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 Protocol Version 3.0: 21 Jul 2015

Sponsor: Astellas Pharma Europe B.V.

Sylviusweg 62
2333 BE Leiden
The Netherlands

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

Version 3.0

Incorporating Substantial Amendment 2 [See Attachment 1]

21 July 2015

EudraCT 2013-000508-40

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

Protocol History:
Version 1.0 [17Sep2013]
Version 1.1 Incorporating Non-Substantial Amendment 1 [05Jun2014]
Version 2.0 Incorporating Substantial Amendment 1 [21Nov2014]

***Investigator**:*
Investigator information is on file at Astellas

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SRC/PAC Approved

I. SIGNATURES

1. SPONSOR'S SIGNATURES

Required signatures (e.g. Protocol authors, Sponsor's reviewers and contributors, etc.) are located in **Section** 14. **Sponsor's Signatures**; e-signatures (when applicable) are located at the end of this document.

2. INVESTIGATOR'S SIGNATURE

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

ISN/Protocol 2819-CL-0202 / Version 3.0

Incorporating Substantial Amendment 2 / 21 July 2015

I have read all pages of this clinical study protocol for which Astellas is the Sponsor. I agree to conduct the study as outlined in the protocol and to comply with all the terms and conditions set out therein. I confirm that I will conduct the study in accordance with ICH GCP guidelines and applicable local regulations. I will also ensure that sub-investigator(s) and other relevant members of my staff have access to copies of this protocol and the ICH GCP guidelines to enable them to work in accordance with the provisions of these documents.

Principal Investigator:

Signature: .....

Date (DD Mmm YYYY)

Printed Name: .....

Address: .....

.....

II. CONTACT DETAILS OF KEY SPONSOR'S PERSONNEL

CRO contact for reporting of Serious Adverse Events (SAEs): (See Section 5.5.5)	**Please send the SAE Worksheet to:** [redacted]
Astellas 24h-Contact for Serious Adverse Events (SAEs)	**Astellas Pharma Europe B.V.** **Astellas Pharma Global Development Europe** **Fax: +31 (0) 71 545 5208** **Email: safety-eu@astellas.com**
Medical Monitor/Medical Expert:	[redacted]
Clinical Research Contacts:	[redacted]

III. LIST OF ABBREVIATIONS AND DEFINITION OF KEY TERMS

List of Abbreviations

Abbreviations	Description of abbreviations
AE	Adverse event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase (GPT)
APEB	Astellas Pharma Europe BV
ATC	Anatomical Therapeutic Chemical
AST	Aspartate Aminotransferase (GOT)
AUC	Area under the curve
BI	Epidemic hypervirulent *C. difficile* strain
CA	Competent Authorities
CDAD	Clostridium Difficile Associated Diarrhea
CDI	Clostridium Difficile Infection
CIOMS	Council for International Organizations of Medical Sciences
C_{max}	Maximum concentration
CRO	Contract Research Organization
DILI	Drug-induced Liver Injury
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eCTD	Electronic Common Technical Document
EDC	Electronic Data Capture
EMA	European Medicines Agency
EOS	End of Study
EOT	End of Treatment
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	Gastrointestinal
GMP	Good Manufacturing Practices
GGT	Gamma glutamyltransferase
GRAS	Generally Recognized as Safe
HIPAA	The Health Insurance Portability and Accountability Act of 1996
ICD	International Classification of Disease
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
IND	Investigational New Drug
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology

Abbreviations	Description of abbreviations
ITT	Intent To Treat
ISN	International Study Number
IUD	Intrauterine device
IUS	Intrauterine system
KID	Kid's Inpatient Database
LA-CRF	Liver Abnormality Case Report Form
LFT	Liver Function Tests
LLOQ	Lower Limit of Quantification
LS	Least Squares
MAA	Marketing Authorization Application
MedDRA	Medical Dictionary for Regulatory Activities
NAP1	North American Pulsed 1
NDA	New Drug Application
NASH	Non-alcoholic steatohepatitis
NHDS	National Hospital Discharge Survey
OP-1118	Main metabolite of Fidaxomicin
OTC	over-the-counter
PCR	Polymerase Chain Reaction
PHIS	Pediatric Health Information System
PHI	Protected Health Information
PK	Pharmacokinetics
PKAS	Pharmacokinetics Analysis Set
RBC	Red Blood Cell
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reactions
TBL	Total Bilirubin
TC	Telephone call
TEAE	Treatment Emergent Adverse Event
TLF	Tables, Listings, Figures
TMF	Trial Master File
TTROD	Time to resolution of diarrhea
UBM	Unformed Bowel Movement
ULN	Upper Limit of Normal
US	United States
WBC	White Blood Cell
WHODRL	World Health Organization Drug Reference List

Definition of Key Study Terms

Terms	Definition of terms
Baseline	Observed values/findings which are regarded observed starting point for comparison.
Clinical response for subjects aged from birth to < 2 years	Absence of watery diarrhea for 2 consecutive days during treatment and subjects remain well until the time of study drug discontinuation (initial clinical response). In addition, subjects 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 subject/parent/legal guardian supplemented by a review of the subject's personal records for the day (if hospitalized), and the presence of watery diarrhea.
Clinical response for subjects 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 subjects remain well until the time of study drug discontinuation (initial clinical response). In addition, subjects 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 subject/parent/legal guardian, supplemented by a review of the subject's personal records for the day (if hospitalized), and the number of UBMs.
Enroll	To register or enter into a clinical trial. NOTE: Once a subject has been enrolled, the clinical trial protocol applies to the subject.
End of Study	The end of the study is defined as the date of the last subject's last visit/TC.
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).
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 subject, and continues until the last assessment after completing administration of the test drug or comparative drug.
Post investigational period	Period of time after the last assessment of the protocol. Follow-up observations for sustained adverse events and/or survival are done in this period.
Randomization	The process of assigning trial subjects to treatment or control groups using an element of chance to determine assignments in order to reduce bias.
Recurrence for subjects aged 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 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.
Recurrence for subjects aged ≥ 2	The re-establishment of diarrhea after confirmed clinical response to an extent (as measured by the frequency of UBMs) that is greater than that noted on the last day of study drug with positive direct or indirect testing for

Terms	Definition of terms
years < 18 year	the presence of toxigenic *C.difficile* in stool and that, in the investigator's opinion, would require retreatment with CDAD anti-infective therapy.
Screening	A process of active consideration of potential subjects for enrollment in a trial.
Screen failure	Potential subject 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 subject.
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 above.
Time to resolution of diarrhea (TTROD) for subjects aged from birth < 2 years	The time elapsing (in hours rounded up from minutes $\geq$ 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).
Time to resolution of diarrhea (TTROD) for subjects aged ≥ 2 years to < 18 years	The time elapsing (in hours rounded up from minutes $\geq$ 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 are sustained through EOT).
Variable	Any quantity that varies; any attribute, phenomenon or event that can have different qualitative or quantitative values.

IV. SYNOPSIS

Date and Version # of Protocol Synopsis:	21 July 2015 / Version 3.0
Sponsor: Astellas Pharma Europe BV (APEB)	**Protocol Number:** 2819-CL-0202
Name of Study Drug: Fidaxomicin	**Phase of Development:** 3

Title of Study:
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

Planned Study Period:
From 3Q 2014 to 2Q 2017

Study Objective(s):
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 subjects with *Clostridium difficile*-associated diarrhea (CDAD) from birth to < 18 years of age.

Planned Total Number of Study Centers and Location(s):
Approximately 65-80 centers in North America and Europe.

Study Population:
Male and female subjects from birth to < 18 years of age, diagnosed with CDAD confirmed by a positive *C. difficile* toxin test in stool or positive detection of toxigenic *C. difficile* in stool.

Number of Subjects to be Enrolled:
144 subjects from birth to < 18 years of age will be enrolled with at least 24 subjects in each of the following age categories: birth to < 24 months, ≥ 2 years to < 6 years, ≥ 6 years to < 12 years, and ≥ 12 years to < 18 years (the remaining 48 subjects can be enrolled in any of the age groups).

Study Design Overview:
This multicenter, investigator-blind, randomized parallel group study will 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 subjects from birth to < 18 years of age with confirmed CDAD. Note that in the United States of America subjects can only be included if aged ≥ 6 months to < 18 years.

One hundred forty four subjects, stratified by age at enrollment (birth to < 24 months, ≥ 2 years to < 6 years, ≥ 6 years to < 12 years, and ≥ 12 years to < 18 years) will be enrolled. A minimum of 24 subjects will be enrolled into each age group.

Subjects must meet all inclusion criteria, no exclusion criteria, and have been diagnosed with CDAD.

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

Subjects from birth to < 6 years of age will be randomized to receive weight based doses of either fidaxomicin oral suspension (32 mg/kg/day with a maximum dose of 400 mg/day, divided in 2 doses) 2 times daily for 10 days, or vancomycin oral liquid (40 mg/kg/day with a maximum dose of 500 mg/day divided in 4 doses) 4 times daily for 10 days.

Study Design Overview continued**:**

Subjects aged ≥ 6 years to < 18 years of age will be randomized to receive a 200 mg fidaxomicin tablet 2 times daily for 10 days, or a 125 mg vancomycin capsule 4 times daily for 10 days. If a subject aged ≥ 6 years to <18 years is unable to swallow tablets or capsules, the investigator can decide to give fidaxomicin oral suspension, at a dose of 400 mg/day, or vancomycin oral liquid at a dose of 500 mg/day.

Plasma and stool samples will be analyzed for fidaxomicin and its main metabolite OP-1118 concentrations. For subjects 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. For all subjects a stool sample will be taken between Day 5 and 10 inclusive, within 24 hours of a dose.

At End of Treatment (EOT), subjects will be evaluated for initial clinical response (see Definition of Key Study Terms section) and two days thereafter for confirmed clinical response. Clinical responses will be based on the investigator's assessment of clinical parameters, most importantly resolution of diarrhea and the need for further treatment for CDAD.

Subjects without initial clinical response at EOT will enter the Follow-up period for safety (adverse events) and will be contacted (visit or telephone call [TC]) at EOS (EOT+30 days).

Subjects without confirmed clinical response at EOT + 2 days will continue in the Follow-up period for safety (adverse events) and will be contacted (visit or TC) at EOS.

Subjects who have a confirmed clinical response will be followed for recurrence and sustained clinical response (see Definition of Key Study Terms section) throughout the Follow-up period, with weekly visits or TCs. At the end of the 30 day Follow-up period the EOS TC / visit will take place.

If diarrhea recurs during the Follow-up period an Unscheduled visit will take place for reassessment of CDAD recurrence. If recurrence is confirmed, subjects will continue in the Follow-up period for safety (adverse events) and will be contacted (visit or TC) at the EOS.

In case of discontinuation of study drug before completion of the full 10-day treatment course, the subject should complete the EOT visit as soon as possible after the last drug administration. If at this visit, subject has an initial clinical response, the subject will continue in the Follow-up period for safety and efficacy unless consent has been withdrawn.

CDAD status will be assessed by interviews with the subject/parent/legal guardian (or hospital staff e.g. when hospitalized). These interviews will be conducted in the morning, daily during the treatment period through the 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).

Palatability will be assessed for all subjects receiving fidaxomicin oral suspension and vancomycin oral liquid.

Site and Sponsor staff involved in dispensing, administering or collecting the study drug will be unblinded as well as the subject and parents/legal guardians. They will be instructed not to discuss the study drug with the blinded staff.

A Data and Safety Monitoring Board (DSMB) will be established for this study.

Inclusion/Exclusion Criteria:

Inclusion:

Subject is eligible for the study if all of the following apply:

1. Institutional Review Board (IRB)-/Independent Ethics Committee (IEC)-approved written Informed Consent/ assent (if applicable) and privacy language as per national regulations (e.g., HIPAA Authorization for U.S. sites) must be obtained from the subject or legally authorized representative prior to any study-related procedures (including withdrawal of prohibited medication, if applicable).
2. Male and female subjects aged from birth to < 18 years. **Note that in the United States of America subjects can only be included if aged ≥ 6 months to < 18 years.**
3. Subject is diagnosed with CDAD according to local diagnostic criteria. As a minimum there must be positive detection, within 72 hours prior to randomization, of either toxin A and/or toxin B in stool or positive detection of toxigenic *C. difficile* in stool and:
    a. Subject from birth to < 2 years: watery diarrhea in the 24 hours prior to screening.
    b. Subject ≥ 2 years to < 18 years: ≥ 3 unformed bowel movements in the 24 hours prior to screening.
4. For subjects < 5 years: Negative rotavirus test.
5. Female subject of childbearing potential:
    a. must have a negative urine pregnancy test at Screening, and
    b. must abstain from sexual activity for the duration of the study, or
    c. must use two forms of birth control* (at least one of which must be a barrier method) starting at Screening and throughout the study period and for 28 days after the final study drug administration.
6. Female subject must not be breastfeeding at Screening or during the study period, and for 28 days after the final study drug administration.
7. Female subject must not donate ova starting at Screening and throughout the study period, and for 28 days after the final study drug administration.
8. Subject agrees not to participate in another interventional study while in the study (with the exception of studies as described in exclusion criteria 6).

Waivers to the inclusion criteria will **NOT** be allowed.

*Acceptable forms of birth control include:

- Established use of oral, injected or implanted hormonal methods of contraception.
- Placement of an intrauterine device (IUD) or intrauterine system (IUS).
- Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository.

Exclusion:

Subject will be excluded from participation if any of the following apply:

1. Concurrent use of metronidazole, oral vancomycin or any other antibiotic treatments for CDAD. If the investigator feels the clinical imperative is to begin treatment before knowing the laboratory result for 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.

2. Subject has pseudomembranous colitis, fulminant colitis, toxic megacolon or ileus.
3. Subject has a history of inflammatory bowel disease (e.g., ulcerative colitis or Crohn's disease etc.).
4. Subject has diarrhea caused by an agent other than *C. difficile* (e.g. infections, infestations, drugs etc.).
5. Subject has known hypersensitivity to fidaxomicin, vancomycin or their excipients or to teicoplanin.
6. Subject has received an investigational therapy within 28 days, prior to Screening, with the exception of studies with primary treatment for cancer without novel Investigational Medicinal Product (IMP) and which do not affect the assessment of diarrhea.
7. Subject has a condition which, in the investigator's opinion, makes the subject unsuitable for study participation.

Waivers to the exclusion criteria will **NOT** be allowed.

Investigational Product(s):
Fidaxomicin oral suspension and fidaxomicin 200 mg tablets

Dose(s):
From birth to < 6 years of age: fidaxomicin oral suspension, 32 mg/kg/day with a maximum daily dose of 400 mg, divided in 2 doses per day.

Ages ≥ 6 years to < 18 years: fidaxomicin 200 mg tablet, two times daily.

If a subject aged ≥ 6 years to < 18 years is unable to swallow tablets, fidaxomicin oral suspension at a dose of 200 mg, two times daily can be given.

Mode of Administration:
Oral

Comparative Drug(s):
Vancomycin oral liquid and vancomycin 125 mg capsules.

Dose(s):
From birth to < 6 years of age: vancomycin oral liquid 40 mg/kg/day with a maximum daily dose of 500 mg, divided in 4 doses per day.

Ages ≥ 6 years to < 18 years: vancomycin 125 mg capsule, four times daily.

If a subject aged ≥ 6 years to <18 years is unable to swallow capsules, vancomycin oral liquid at a dose of 125 mg, four times daily can be given.

Mode of Administration:
Oral

Rescue Therapy:
Standard of care

Concomitant Medication Restrictions or Requirements:
No other antibacterial drugs potentially useful in the treatment of CDAD (e.g., metronidazole, oral vancomycin, oral bacitracin, fusidic acid, rifaximin, nitazoxanide) or fecal transplantation should be given during the trial unless they are specifically given because of a primary treatment failure or suspected CDAD recurrence after initial clinical response.

Drugs to control diarrhea (e.g., loperamide) should also be withheld during the study period. Whenever possible, drugs which could affect peristalsis should be avoided. Subjects receiving opioids for pain prior to enrollment may continue to receive the same opioid and dose during the treatment phase if required.

Duration of Treatment:
10 days

Definitions:

Clinical response for subjects aged from birth to < 2 years is defined as: Absence of watery diarrhea for 2 consecutive days during treatment and subjects remain well until the time of study drug discontinuation (initial clinical response). In addition, subjects 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 subject/parent/legal guardian supplemented by a review of the subject's personal records for the day (if hospitalized), and the presence of watery diarrhea.

Clinical response for subjects aged ≥ 2 years to < 18 years is defined as: 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 subjects remain well until the time of study drug discontinuation (initial clinical response). In addition, subjects 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 subject/parent/legal guardian, supplemented by a review of the subject's personal records for the day (if hospitalized), and the number of UBMs.

Time to resolution of diarrhea (TTROD) for subjects aged from birth to < 2 years is defined as: 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).

Time to resolution of diarrhea (TTROD) for subjects aged ≥ 2 years to < 18 years is defined as: 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 are sustained through EOT).

Recurrence for subjects aged from birth to < 2 years is defined as: 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.

Recurrence for subjects aged ≥ 2 years < 18 years is defined as: 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.

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

Sustained clinical response is defined as: Confirmed clinical response (EOT + 2 days) without CDAD recurrence until the time of assessment during the Follow-up period.

Endpoints for Evaluation:

Primary:

Efficacy

Confirmed clinical response based on the assessment by the investigator (at EOT+2 days)

Secondary:

Efficacy

- Sustained clinical response at the EOS (EOT +30 days)
- Sustained clinical response 14 days after Confirmation Clinical Response (EOT +16 days)
- Time to resolution of diarrhea (TTROD)
- Recurrence of CDAD during or at the end of the Follow-up period
- Time to recurrence during or at the end of the Follow-up period

Safety

The safety evaluation will include adverse events, clinical laboratory tests (hematology, biochemistry and urinalysis), vital signs and ECGs.

Drug concentration measurement

- Plasma concentrations of fidaxomicin and its main metabolite (OP-1118) within 30 minutes pre-dose and 1 to 5 hours post-dose taken between Day 5 and 10, inclusive.
- Fecal concentration of fidaxomicin and its main metabolite (OP-1118) within 24 hours of a dose taken between Day 5 and 10, inclusive.

Palatability

Acceptance of formulation at first administration of study drug and at Day 7 (± 1 day) in all subjects receiving fidaxomicin oral suspension or vancomycin oral liquid.

Exploratory:

[redacted]

Statistical Methods:

Sample Size Justification:

The sample size for this study is based on clinical and practical considerations. One hundred forty four subjects, stratified by age at enrollment (from birth to < 24 months, ≥ 2 years to < 6 years, ≥ 6 years to < 12 years, and ≥ 12 years to < 18 years) will be enrolled. Eligible subjects will be randomized to fidaxomicin or vancomycin in a 2:1 ratio, stratified by age group. At least 24 subjects will be enrolled into each age group (i.e., a minimum of 16 randomized to fidaxomicin and 8 to vancomycin).

Efficacy

Efficacy data will be summarized for the Full Analysis Set (FAS), defined as all subjects who were randomized and received at least one dose of the study drug. In general, all summaries will be provided by treatment arm and age group.

The proportion of subjects with confirmed clinical response (primary efficacy endpoint) at EOT+2 days will be summarized within each treatment arm by age group along with exact 95% confidence intervals (CIs). In addition, 95% CIs will be presented for the adjusted difference in confirmed clinical response between treatment arms, where adjusted difference will be calculated using stratified CMH (Cochran-Mantel-Haenszel) method using age group as the stratified variable.

The secondary efficacy endpoints recurrence of CDAD and sustained clinical response (at 16 days after EOT and at EOS) will be summarized in the same manner as the primary efficacy endpoint.

For the endpoints TTROD and time to recurrence of CDAD, Kaplan-Meier survival functions will be generated and graphically displayed (with 95% CIs) by treatment arm. Quartile estimates for the time to event and corresponding 95% CIs will be computed for each treatment arm.

Other analyses may be done as deemed appropriate.

Drug Concentration Measurement

Descriptive statistics will be provided for plasma concentrations of fidaxomicin and its main metabolite OP-1118 by time point (pre-dose and 1 to 5 hours post-dose) and for the fecal concentration of fidaxomicin and OP-1118 , overall and by age group (only for subjects treated with fidaxomicin).

Pharmacodynamics

Not applicable.

Safety

All safety parameters will be summarized descriptively for the whole safety population. Summaries will be grouped by treatment; further stratification by age group might be done where deemed appropriate.

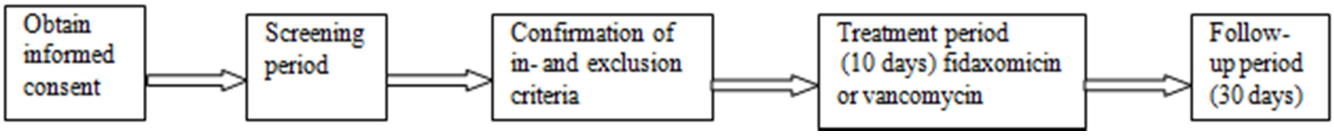
Interim Analyses

Not applicable.

V. FLOW CHART AND SCHEDULE OF ASSESSMENTS

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 subject's last visit (End of Study).

In case of premature withdrawal or failure during the treatment period, the subject 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 subject 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					+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]
Fecal 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					+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) Subjects 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 subject is eligible, the subject 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 subject/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) Subjects who discontinue study drug prematurely should complete the EOT visit as soon as possible after the final dose.

Footnotes continued on next page

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

h) Two days after EOT, a telephone contact with the subject/parent/legal guardian or a visit (if the subject is still in the hospital) will take place for all subjects with an initial clinical response at EOT to confirm the clinical response. All subjects will continue in the 30-day Follow-up period. Subjects 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 subjects who had confirmed clinical response; the subject/parent/legal guardian will be contacted by phone.

j) For subjects 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). Subjects 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 subjects 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 subjects 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 subjects 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 subjects a stool sample will be taken between Day 5 and 10 inclusive, within 24 hours of a dose.

p) For subjects 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 4, section 5.4.3. A historical/standard of care samples without parameter(s) indicated with * in the table is acceptable.

t) For subjects < 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.

1 INTRODUCTION

1.1 Background

Fidaxomicin is a macrolide (18-membered macrocycle) antibacterial drug produced by *Dactylosporangium aurantiacum*, and has a highly potent yet narrow-spectrum bactericidal activity against *Clostridium difficile*. Fidaxomicin was approved by the Food and Drug Administration (FDA) in May 2011 for the United States (US) and in December 2011 by the European Committee for the European Union (EU) for the treatment of *C. difficile* infection (CDI) also known as *C. difficile*-associated diarrhea (CDAD) in adults, and is now being developed for use in pediatric patients with the same condition.

CDAD is the most common cause of nosocomial diarrhea in developed countries. The disease accounts for approximately 20% of cases of antibiotic-associated diarrhea, and for the majority of cases of antibiotic-associated pseudomembranous colitis [Blanckaert et al, 2008; Calfee 2008; Monaghan et al, 2008; Mylonakis et al, 2001]. Although typically associated with hospitals and long-term care facilities, CDAD may also be acquired in the community. While not nearly as common as hospital-acquired CDAD, community-acquired CDAD is afflicting otherwise healthy people with no recent history of hospital admission or antibiotic use [Monaghan et al, 2008; Bartlett, 2006; Kuijper et al, 2006; Mylonakis et al, 2001]. One study reported that approximately 50% of patients with CDAD who visited a general practitioner in 2006 acquired the disease outside of a healthcare setting [Weil et al, 2007]

C. difficile is a spore-forming, anaerobic, gram-positive bacillus. CDAD is caused by an overgrowth of *C. difficile* in the colon often resulting from antibiotic use that disrupts the beneficial microflora found in the gut, allowing *C. difficile* to proliferate. The rising incidence of CDAD has been attributed to the frequent prescription of broad-spectrum antibiotics to hospitalized patients, the increasing incidence of virulent strains (such as the North American PFGE pulse-field gel electrophoresis type 1 [NAP1]/restriction endo-nuclease analysis type BI (Epidemic hypervirulent *C. difficile* strain)/Polymerase Chain Reaction ribotype 027 or NAP1/BI/027),[Kuijper et al, 2006; Kuijper et al, 2008] or less commonly to cancer chemotherapy [Fekety, 1997]. Antibiotics commonly linked to CDAD include ampicillin, amoxicillin, clindamycin, fluoroquinolones, and cephalosporins, [Wistrom et al, 2001; Fekety, 1997] but almost all antibiotics can induce CDAD. Once overgrown, *C.difficile* produces harmful toxins that can cause a variety of complications, including pseudomembranous colitis, toxic megacolon, perforations of the colon, and sepsis, and can cause or contribute to death in up to 14.4% of cases [Loo et al, 2005]. Recent reports mostly in adults suggest that CDAD is evolving into a more severe disease. Outbreaks of CDAD with increased morbidity and mortality have been described in North America and in the EU [Ackermann et al, 2004]. These outbreaks were associated with the emergence and dissemination of a hypervirulent strain characterized as toxinotype III, NAP1/BI/027. The NAP1/BI/027 strain has been reported in the US, Canada, and Northern Europe [Blanckaert et al, 2008; Calfee 2008; Kuijper et al, 2006]. This strain is thought to be responsible for increasing morbidity and mortality. It contains an 18-base pair tcdC deletion, and has been shown in vitro to produce 16 to 23 times more toxins A and B than other strains [Monaghan

et al, 2008; Credito & Appelbaum, 2004].To date, hypervirulent strains of *C. difficile* have been identified in the US, Canada, Japan, and many other countries, and are of increasing concern [Kuijper et al, 2008].

CDAD has long been considered a disease of adults and not a clinical problem in children [McFarland et al, 2000; Larson et al, 1982]. It is unclear whether typical CDAD occurs in children under 2 years of age. Even in older children, CDAD is associated with variable diarrheal symptoms, with some reports stating that CDAD rarely causes severe diarrhea in children [Vernacchio et al, 2006; Spivack et al, 2003]. However, other studies have shown the presence of *C. difficile* in a significant number of older children presenting with diarrhea; 27.3% of hospitalized children with diarrhea had a positive *C. difficile* test in a study in the US [Kader et al, 1998].

Recently, the disease has been recognized to be increasing in children and younger adults with a significant proportion of these cases exhibiting the onset of symptoms in the community [DuPont et al, 2008; Benson et al, 2007]. These observations along with the emergence of a more virulent and possibly more transmissible strain (NAP1/BI/027) prompted the initiation of population-based surveillance systems for CDAD. The preliminary data now emerging from these surveillance systems, as well as data from hospital discharge records confirm that prevalence of CDAD in pediatric populations is much lower than in adults, but is steadily increasing. The most recent data indicate that the incidence/prevalence of CDAD in children in the US has likely reached a rate of approximately 20,000 cases annually [Kuijper et al, 2008].

The most recent data on population-based surveillance of CDAD in children in the US were reported by Kast and colleagues at the recent 2010 International Conference on Emerging Infectious Diseases [Kast et al, 2010].

The investigators reported the incidence of CDAD in 2009 from 2 distinct catchment areas: five metropolitan counties in Colorado and four rural counties in Minnesota. The analysis captured both healthcare facility-onset disease and community-onset disease. The overall incidence of CDAD in individuals aged 1-17 years was similar between the two areas. In the urban centers in Colorado, the rate was 16 per 100,000, whereas in the rural counties, the rate was 21 per 100,000. Adjusting for the regional differences in CDAD prevalence described by Elixhauser and Jhung [Elixhauser & Jhung, 2011], the rates in each surveillance area closely approximate to 20 per 100,000.[a] The inclusion of both rural and metropolitan populations and the similarity of the results across populations support the generalizability of the data to the general US pediatric population. Thus, using current US census data for individuals under 18 years of age (i.e., 74,548,215 persons aged under 5 years through 17 years) yields a national incidence of approximately 15,000 cases per year based on both the rural and metropolitan data.

[a] When regional CDAD rates (all ages combined) were evaluated, the rate in the Midwest (including Minnesota) was slightly higher than the overall national rate (83 versus 79.3 per 100,000; 5% higher) whereas the rate in the West (including Colorado) was somewhat lower than the national rate (62 versus 79.3 per 100,000; 20% lower). Adjusting the rate of 21 per 100,000 from Minnesota by 5% results in a rate of 20 per 100,000. Adjusting the rate of 16 per 100,000 from Colorado upward by 20% also results in a rate of 20 per 100,000.

Lower national CDAD rates were obtained by McDonald and colleagues based on data on discharges from short-stay hospitals from a period approximately 10 years prior to that covered by Kast and colleagues [Kast et al, 2010; McDonald, 2006]. In the McDonald study, diagnoses of intestinal infection due to *Clostridium difficile* (ICD-9 code 8.45) between 1996 and 2003 from the National Hospital Discharge Survey (NHDS) database were used to estimate national rates. The NHDS consists of diagnosis and demographic data collected from a national probability sample of patient discharge records from approximately 500 hospitals. An algorithm (SUDAAN™) was used to estimate national rates. Although this study included adults as well as children, rates were analyzed by age groups. The point estimate rate for patients <15 years was 9/100,000 (95% CI 5-9 per 100,000). Using US census data on individuals <15 years (61,882,854 persons aged under 5 years through 14 years[b]), the point estimate of the national rate in the years between 1993 and 2003 is 5,570 cases/year.

The increase in the incidence of pediatric CDAD between time periods covered by the McDonald and Kast studies is supported by an analysis of pediatric hospitalization data by Zilberberg [Zilberberg, 2009]. Using the Kid's Inpatient Database (KID) and the NHDS database, the incidence of CDAD diagnoses between 1997 and 2006 was evaluated. The KID database represents 3,789 hospitals from 38 states and the NHDS database covers discharges from about 5000 non institutional, nonfederal, short-stay hospitals in the US. The most recent data from this study (2006 data) indicated that the rate of CDAD among hospitalized children in the US was 12.8 per 10,000 hospitalizations based on KID data and 14.03 per 10,000 hospitalizations based on the NHDS database.

The actual number of cases calculated by Zilverberg does not deviate greatly from the national estimates calculated in the McDonald study [McDonald et al, 2006] using data from 1996 to 2003.

Relatively recent multi-hospital rates of CDAD in pediatric populations were also reported by Kim [Kim et al, 2008]. This study examined the rate of CDAD at 22 free-standing children's hospitals from major metropolitan areas in the US from 2001 to 2006 using data from the Pediatric Health Information System (PHIS) database. During the study period, investigators identified a total of 4,895 pediatric patients with CDAD at the children's hospitals. Based on this data they report rates of 4.4 cases per 10,000 patient days in 2001 and 6.5 cases per 10,000 patient days in 2006. The annual incidence density per 1,000 admissions was 2.6 in 2001 and 4.0 in 2006. Insufficient data are available on the denominator used in this study to estimate the annual number of cases nationwide based on these findings. The same study showed a mortality rate of 3.8% in children with CDAD.

Although community-onset disease is an impetus for the development of population-based surveillance, it is likely that hospital discharge data capture the majority of this segment of the CDAD population because community-onset disease is most typically diagnosed in conjunction with a visit to the hospital emergency room. The extent to which re-infection accounts for potential double-counting is unknown.

[b] US census distribution. < 5 years: 21,299,656; 5 to 9 years: 20,609,634; 10 to 14 years: 19,973,564.

The etiology in children is the same as in adults with one major difference: children, particularly those < 2 years of age, frequently harbor *C. difficile* while being clinically asymptomatic. In addition, unlike in adults and older children with CDAD, the exclusion of other causes of diarrhea is not as conclusive in neonates and young babies < 6 months because children often have underlying gastrointestinal or immunologic diseases and children are more susceptible to infection by viral diarrhea agents, for example rotavirus, many of which cannot be cultured at all or only in sophisticated research labs.

Several studies have been carried out to determine the culture rates in feces of *C. difficile* in children with and without diarrhea, with these studies showing variable culture rates and no apparent association between a positive culture and clinical diagnosis. In newborn infants in particular (i.e., < 1 month old), the occurrence of positive cultures varied widely, from 4% in Sweden, 11% in France, 25% in the Netherlands, 31% in the US, 67% in Belgium, and 71% in the UK [Penders et al, 2006; Enad et al, 1997; Collignon et al, 1993; Delmee et al, 1988; Al-Jumaili et al, 1984; Holst et al, 1981]. It should be noted that these results were seen in all newborns, with no direct correlation to the presence of diarrhea.

A 1989 study demonstrated that *C. difficile*-positive cultures were obtained at a similar frequency from infants of less than 1 year of age both with and without diarrhea (32.5% compared to 27.9%, difference not significant, p=0.44) [Karsch et al, 1989]. Similarly, Vernacchio and colleagues demonstrated that 3.5% of healthy children (aged 6 to 36 months) had positive *C. difficile* cultures, whereas the proportion of children with positive *C. difficile* cultures plus diarrhea was only 1.9% (p=0.12) [Vernacchio et al, 2006]. In a Finnish study, the prevalence of positive cultures was compared between hospitalized children with diarrhea (21.1%) to any hospitalized children (32.7%) [Vesikari et al, 1984]. In this study newborns and infants were included (i.e., patients of 0 to 2 years).

Taken together, it is clear that young children of all age groups frequently harbor *C. difficile* and tolerate the presence of *C. difficile,* but can be clinically asymptomatic and not develop CDAD. The presence of intestinal colonization with *C. difficile* does not necessarily correlate with diarrhea in this age group.

As a possible scientific rationale for the differences in colonization and incidence of CDAD seen in young children compared to adults, it has been suggested that neonates and infants do not respond to clostridial toxins in the same way as adults do [Tullus et al, 1989]. Though the mechanism for this difference is unclear, hypotheses include the inability of immature receptors to bind or respond to the toxins, transference of protective maternal antibodies, and the inability of the infant's immune system to mount an effective immune response.

Patients are currently treated by discontinuation of the offending medication, as well as supportive therapy, but antimicrobial therapy is required if these measures fail to control the infection (Kelly, 1994; Fekety, 1997). The two most commonly utilized specific therapies are vancomycin and metronidazole, the latter being used off-label.

Vancomycin is recommended for first-line treatment of CDAD in severe cases, but not in mild to moderate cases, which represent the majority of CDAD patients (Bauer, 2009). Increasing

use of vancomycin has caused some concern as it is the only antibiotic active against some serious life-threatening, multi-drug resistant bacteria [Hospital Infection Control Practices Advisory Committee (HICPAC), 1995; Watanabe, 1997].

Metronidazole is the recommended treatment for patients with mild to moderate disease experiencing a first episode of CDI [American Society of Health-System Pharmacists (ASHP), 1998; Bauer, 2009]. Metronidazole is effective in these subgroups of patients, and can be used either orally or intravenously. However, it is near-fully absorbed in the absence of diarrhea, and oral absorption is associated with significant adverse effects including nausea, neuropathy, leukopenia, seizures, and a toxic reaction to alcohol [Kelly, 1994; Fekety, 1984, Fekety, 1997].

Furthermore, its use is discouraged in young children and pregnant women [Yassin, 2001]. Finally, several reports have shown a lower clinical response rate in severe cases when treated with metronidazole treatment compared to vancomycin [Zar, 2007; Louie, 2007]. The current recommendations for CDAD treatment in The Medical Letter and Up-To-Date, and endorsed by the recent guidelines of the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) [Bauer, 2009] and the Society for Healthcare Epidemiology of America and the Infectious Disease Society of America (SHEA-IDSA) [Cohen, 2010] state that vancomycin, but not metronidazole, should be used to treat severe cases of CDAD.

Although current CDI treatment options are effective in treating the acute symptoms, none of the available treatments is without significant problems. In the case of vancomycin, these problems include high recurrence rate, high risk of acquiring resistant organisms, especially VRE. Therapy with metronidazole presents the following problems high recurrence rate, higher rate of failures in severe cases compared to vancomycin, frequent adverse effects.

A major shortcoming of currently available antimicrobial treatments for CDI is the typical recurrence rate of approximately 20% to 50% [Kyne, 1999; Kyne, 2001; Aslam, 2005; Louie, 2007; Louie, 2006; Musher, 2006]. A new agent that effectively treats CDI and markedly reduces recurrence would be a significant therapeutic advance.

Fidaxomicin tablets are approved for use in the US and other countries to treat adult subjects with CDAD. Also due to the need for a liquid formulation for pediatric patients, an oral suspension formulation of fidaxomicin has been developed.

Data from the recent pediatric PK study with fidaxomicin tablets and oral suspension suggest a pharmacokinetic profile that is generally similar to that observed in adults. The safety observations were consistent with both the underlying conditions of the subjects and with data from prior studies in the adult CDAD population, and suggest that fidaxomicin is well tolerated in this population. Fidaxomicin showed strong efficacy in treating the initial disease, but higher recurrence percentage than observed in prior adult studies. The pharmaco-kinetic, safety, and efficacy results observed in this study support the continuation of pediatric development of fidaxomicin.

1.2 Non-clinical and Clinical Data

1.2.1 Non-Clinical Data

The pharmacology, toxicology and pharmacokinetics of fidaxomicin have been studied in different animal species and in in vitro studies, and have demonstrated the safety of fidaxomicin for human use.

Juvenile nonclinical studies have been conducted to study the effect of fidaxomicin on the growth and development of major organ systems in order to allow clinical studies to be performed in pediatric patients with CDAD, ranging from birth to 18 years. The 4-week oral repeated-dose toxicity study in juvenile Beagle dogs showed no target organ for toxicity and fidaxomicin was well tolerated in dogs from Post Natal Day 4, which is the age equivalent a newborn child, onwards. Furthermore, no adverse effects were seen on development of any organ system evaluated after 28 days of dosing up to 200 mg/kg/day fidaxomicin. Although GI tracts were considered to be the most susceptible organ due to the expected high local concentrations of fidaxomicin, no histological changes were observed in the GI tract of juvenile animals. Fidaxomicin was shown to have the same safety profile in young animals as in adult animals. There are no indications for target organs or differences in sensitivity. In summary, long term dosing of fidaxomicin up to 200 mg/kg/day does not show adverse effects on any of the developing organ systems in juvenile animals and does not indicate any safety concern for pediatric patients from birth and older.

Full details can be found in the current version of the Investigator's Brochure (IB) version 9.3.

1.2.2 Clinical Data

The safety and efficacy of fidaxomicin have been evaluated in 8 phase 1 studies in healthy adult subjects, a phase 2A study conducted in adults with CDAD, 2 phase 3 studies conducted in adults with CDAD and a recent phase 2A study conducted in children with CDAD. All studies have been completed and the data have been analyzed. Full details can be found in the current version of the IB addendum 1 version 9.3. A summary of the studies is provided in Table 2

Table 2: Summary of Fidaxomicin Clinical Studies

Study Number	Title	Duration and Dose of Fidaxomicin	Comparator	Number of Subjects Treated
OPT-80-005 Phase 1	A single center, open-label, randomized, two-period, cross-over study to determine the pharmacokinetics and the effect of food on the bioavailability of OPT-80 in healthy subjects and the pharmacokinetics of a lead-in single arm of 200 mg OPT-80 in healthy subjects	Single dose: 200 mg or 400 mg	None	34
OPT-80 1A-SD Phase 1	A phase 1A, single dose-escalating safety study of OPT-80 in healthy volunteers	Single dose: 100 mg, 200 mg, 300 mg, 450 mg	Placebo	16

Table continued on next page

Study Number	Title	Duration and Dose of Fidaxomicin	Comparator	Number of Subjects Treated
OPT-80 1B-MD Phase 1	A phase 1B, multiple dose-escalating safety study of OPT-80 in healthy volunteers	10 days: 150 mg, 300 mg, 450 mg	Placebo	24
OPT-80-007 Phase 1	A phase 1, open-label, two-period, randomized crossover study to evaluate the effect of a single dose of cyclosporine on the single-dose pharmacokinetic profile of fidaxomicin (OPT-80) in healthy male subjects	Single dose: 200 mg	Fidaxomicin 200 mg with Cyclosporine (Neoral®) 200 mg	14
OPT-80-008 Phase 1	A phase 1, open-label, monosequence crossover study to evaluate the effect of steady-state fidaxomicin (OPT-80) tablets on the single-dose pharmacokinetic profile of digoxin in healthy subjects	11 days: 400 mg (200 mg q12h)	Digoxin 0.5 mg, with or without fidaxomicin	14
OPT-80-009 Phase 1	A phase 1, open-label, monosequence crossover study to evaluate the potential for cytochrome P450-mediated drug interactions with fidaxomicin (OPT-80) in healthy male subjects	7 days: 400 mg (200 mg q12h)	Warfarin 10 mg; Omeprazole 40 mg; Midazolam 5 mg; with or without fidaxomicin	24
2819-CL-2003 Phase 1	A Phase 1, Open-label, Randomized, Two-way Crossover Study to Evaluate the Effect of Multiple Doses of Fidaxomicin on the Single Dose Pharmacokinetics of Rosuvastatin in Healthy Male Subjects	5 days: 400 mg (200 mg q12h)	10 mg rosuvastatin, with or without fidaxomicin	26
2819-CL-3001 Phase 1	A Phase 1, Randomized, Double-Blind, Placebo-Controlled, Dose Escalation Study to Assess the Safety, Tolerability and Pharmacokinetics of Single and Multiple Ascending Doses of Fidaxomicin in Healthy Male Japanese and Caucasian Subjects	100 mg or 200 mg given as a single dose with 5 day washout, then twice daily for 9 days with a final dose on the 10th day	Placebo	36
OPT-80 Phase 2A	An open-label, dose ranging, randomized clinical evaluation of OPT-80 in patients with *Clostridium difficile*-associated diarrhea (CDAD)	10 days: 100 mg, 200 mg, 400 mg (each as split dose, q12h)	None	48
101.1.C.003 Phase 3	A multi-national, multicenter, double-blind, randomized, parallel group study to compare the safety and efficacy of 200 mg PAR-101 taken Q12h with 125 mg vancomycin taken Q6h for ten days in subjects with *Clostridium difficile*-associated diarrhea	10 days: 400 mg (200 mg q12h)	Vancomycin 500 mg (125 mg q6h)	623
101.1.C.004 Phase 3	A multi-national, multicenter, double-blind, randomized, parallel group study to compare the safety and efficacy of 200 mg PAR-101 taken Q12h with 125 mg vancomycin taken Q6h for ten	10 days: 400 mg (200 mg q12h)	Vancomycin 500 mg (125 mg q6h)	524

Study Number	Title	Duration and Dose of Fidaxomicin	Comparator	Number of Subjects Treated
	days in subjects with *Clostridium difficile*-associated diarrhea			
OPT-80-206 Phase 2A in pediatrics	A Phase 2A, Multi-Center, Open-Label, Uncontrolled Study to Determine the Safety, Tolerability, and Pharmacokinetics of fidaxomicin Oral Suspension or Tablets in Pediatric Subjects With Clostridium difficile-associated Diarrhea (CDAD)	10 days: Fidaxomicin oral suspension, 32 mg/kg/day with a maximum dose of 400 mg/day, divided in 2 doses (ages 6 months–5 years 11 months) every 12 hours. Fidaxomicin 200 mg tablets, PO. (ages 6 years–17 years 11 months) every 12 hours.	None	38

1.2.2.1 Phase 1 Studies

In two ascending dose studies (Studies OPT-80 1A-SD and OPT-80 1B-MD), following single oral doses of 100 to 450 mg and multiple oral doses of 150 to 450 mg of fidaxomicin to healthy adult volunteers, plasma levels of fidaxomicin were near the lower limit of quantification [LLOQ]=5 ng/mL, showing a dose-proportional increase over the dose range studied. Plasma elimination half-lives ranged from 0.94 to 2.77 hours. In contrast, normalized to the 150 mg dose, fecal concentrations of fidaxomicin reached a mean of 916.0 µg/g (range 138.4 to 1768.9 µg/g) after 10 days of dosing. The high fecal concentrations and low systemic level are consistent with the therapeutic properties of fidaxomicin, which is indicated for local, bactericidal effects in the gastrointestinal tract. Overall, fidaxomicin was well tolerated by all subjects at doses up to 450 mg. The adverse events (AEs) were comparable between active and placebo over the dose range studied. There were no clinically significant abnormalities or drug-related changes in serum chemistry, hematology, and urinalysis throughout the study period. There were no clinically significant abnormalities in hemodynamic or electrocardiographic data collected throughout the study.

Fidaxomicin and its main metabolite, OP-1118, showed maximum plasma concentration (C_{max}) values that were 21.5% and 33.4% lower, respectively, in the fed versus the fasted states, while extents of exposure (AUC_{0-t}) were equivalent (Study OPT-80-005). The frequency, types and severities of AEs following the administration of either 200 or 400 mg fidaxomicin indicated that it was generally well tolerated under both fasted and fed conditions.

In a study comparing the pharmacokinetics of 200 mg fidaxomicin in Japanese and Caucasian healthy male adults (Study 2819-CL-3001), C_{max} of fidaxomicin and OP-1118 was higher in the Japanese group by 70% and 62%, respectively, while AUC_{0-last} was increased by 28% and 31% respectively, following a single dose (and similar results were observed after repeated administration). As these increases are within the range of exposures observed following dosing

with fidaxomicin (200 mg) in clinical studies, and these exposure levels were demonstrated to be safe, the increases are not considered clinically significant. Coadministration of the P-glycoprotein inhibitor cyclosporine with fidaxomicin (Study OPT-80-007) increased the least squares (LS) mean C_{max} of fidaxomicin and main metabolite OP-1118 by approximately 4-fold and 10-fold, respectively, compared to fidaxomicin alone. AUC_{0-t} for fidaxomicin and OP-1118 were also increased by cyclosporine, but to a lesser extent (approximately 2-fold and 4-fold, respectively). Despite these increases in systemic exposure with cyclosporine, plasma fidaxomicin concentrations remained low (< 27 ng/mL) and the drug was safe and well tolerated. Therefore, the increases in fidaxomicin concentrations that may occur during concomitant treatment with cyclosporine are unlikely to be clinically meaningful as systemic exposure is not relevant to the safety or efficacy of fidaxomicin which is used for CDAD, infections that are confined to the gastrointestinal (GI) tract.

In study OPT-80-008, subjects received a single oral dose of 0.5 mg digoxin tablets on Days 1 and 13. All subjects also received oral fidaxomicin tablets (200 mg, q12h) on Days 8 to 18. When digoxin was administered 1 hour after a dose of 200 mg fidaxomicin, the LS mean C_{max} and $AUC_{0-\infty}$ values for digoxin were increased by approximately 14% and 12%, respectively, on Day 13 as compared to Day 1. Other pharmacokinetic parameters were generally similar between Days 1 and 13. These data suggested that 200 mg fidaxomicin q12h had little or no effect on the pharmacokinetics of digoxin.

When a probe cocktail of R- and S-warfarin, omeprazole, and midazolam was administered as a single dose with steady-state 200 mg fidaxomicin (Study OPT-80-009), no statistically significant drug-drug interactions (DDI) were observed between fidaxomicin and warfarin isomers, omeprazole and its metabolite 5-hydroxyomeprazole, or with midazolam.

Following coadministration of rosuvastatin with fidaxomicin (Study 2819-CL-2003), a substrate for transporters BCRP, MRP2, and OATP2B1, with fidaxomicin (200 mg twice daily) in healthy volunteers, the rosuvastatin C_{max} increased by 17% and $AUC_{0-\infty}$ by 9.7%. This effect of fidaxomicin on rosuvastatin exposure is not considered clinically relevant and no dose adjustment is necessary.

1.2.2.2 Phase 2A Study

In the phase 2A study, fidaxomicin administered to subjects with CDAD twice daily for 10 days at total daily doses of 100, 200 and 400 mg showed dose-dependent relief of CDAD symptoms by the end of therapy. Almost 90% of subjects receiving 400 mg/day (200 mg q12h) showed total relief of symptoms at the end of treatment. There were no treatment-emergent adverse events (TEAE) that were considered to be drug-related. An analysis of time-to-resolution of diarrhea provided additional evidence that higher doses were more efficacious than lower doses.

At the dose of 200 mg q12h (400 mg/day), observable plasma fidaxomicin concentrations from Day 1 and Day 10 ranged from 5.32 to 84.9 ng/mL, while stool concentrations averaged over 1,400 µg/g. At the same dose, stool concentrations of fidaxomicin were approximately

2-3 fold higher than OP-1118, the active metabolite, but plasma levels of OP-1118 remained well below the µg/mL range (maximum value 402 ng/mL).

Microbiological evaluation of the stool samples from this study alongside stools from vancomycin-treated subjects showed that by comparison with vancomycin treated subjects, subjects treated with fidaxomicin had: (i) undiminished fecal titers of *Bacteroides fragilis* and other major phylogenetic groups; (ii) lower post-treatment *C. difficile* spore counts; (iii) less frequent post-therapy expression of toxin.

1.2.2.3 Phase 3 Studies

Two randomized, double-blind, parallel group, multicenter phase 3 studies Studies 101.1.C.003 and 101.1.C.004) were conducted to compare the safety and efficacy of 400 mg/day fidaxomicin (taken orally as 200 mg tablet q12h) with 500 mg/day vancomycin capsule (taken orally as 125 mg q6h) for 10 days in subjects with CDAD. Comparing fidaxomicin to vancomycin, clinical response rates at the EOT were similar (Study 101.1.C.003: 92.2% versus 89.6%; Study 101.1.C.004: 91.7% versus 90.6%, fidaxomicin versus vancomycin, per protocol population). Fidaxomicin was superior to vancomycin for sustained clinical response at 30 days follow-up (Study 101.1.C.003: 74.4% versus 64.2%, p=0.007; Study 101.1.C.004: 76.7% versus 63.3%, p=0.001, Full Analysis Set (FAS) population). Recurrence rates were significantly lower with fidaxomicin compared to vancomycin (Study 101.1.C.003: 15.7% versus 25.1%, p=0.008; Study 101.1.C.004: 12.6% versus 27.0%, p<0.001, FAS population).

In pooled results, fidaxomicin was well-tolerated with a safety profile similar to that of vancomycin. Only 5.9% of subjects treated with fidaxomicin withdrew from trials due to AEs. The primary cause leading to discontinuation was vomiting, occurring at an incidence of 0.5% in both fidaxomicin and vancomycin treatment groups.

1.2.2.4 Phase 2A Pediatric Study

A single arm phase 2A study (OPT-80-206) in subjects with CDAD aged 6 months to 17 years and 11 months to assess the safety, tolerability and pharmacokinetics of fidaxomicin tablets and suspension was conducted. Subjects below 6 years of age received weight-based doses of fidaxomicin oral suspension (32 mg/kg/day with a maximum dose of 400 mg/day, divided into two doses) every 12 hours for 10 days. Subjects 6 years–17 years 11 months received 200 mg fidaxomicin tablets every 12 hours for 10 days.

Clinical response rates were high overall, with 92.1% of subjects experiencing a clinical cure. Recurrence rates were 28.6% overall, and higher than observed in prior adult studies. This is likely reflective of high number of pediatric patients enrolling with prior episodes of CDAD, which is a strong risk factor for further recurrence [McFarland, 1999].

This study was conducted in children with underlying CDAD, and frequently severe underlying diseases such as neoplasms (24%). Overall, the safety observations were consistent with both the underlying conditions of the subjects and with data from prior studies in the adult CDAD population, and suggest that fidaxomicin is well tolerated in this population.

Fecal concentrations were in excess of the MIC_{90} of the organism in all age groups. There was a trend toward higher fecal concentrations of fidaxomicin in the lowest age group. Higher fecal concentrations in the lowest age group or in individuals in other age groups are not related to AEs.

As observed previously in adults, plasma concentrations were generally in the low ng/mL range, with a mean fidaxomicin concentration across the age strata that ranged from 9.8 ng/mL to 15.2 ng/mL, at 3-5 hours post-dose. As in adults, metabolite concentrations in the plasma were typically higher than parent concentrations, though still in the ng/mL range, with mean values from 28.5 ng/mL to 122 ng/mL across the age strata. There appeared to be no age-related trends in systemic exposures.

The observed plasma levels were not found to be above the levels observed in the main juvenile dog oral toxicity study (2819-TX-0004).

For further study results details reference is made to the Investigator's Brochure addendum 1 version 9.3.

1.3 Summary of Key Safety Information for Study Drugs

1.3.1 Fidaxomicin

The safety of fidaxomicin has been evaluated in 8 phase 1 studies in healthy adult subjects, one phase 2A dose-finding study conducted in adults with CDAD, 2 phase 3 studies conducted in adults with CDAD in which oral vancomycin was a comparator and one recent phase 2A pediatric study. In addition, there is post-marketing pharmacovigilance data. The full safety information of fidaxomicin is described in the Investigator's Brochure (IB) version 9.3.

1.3.2 Vancomycin

The safety profile of oral vancomycin has been established through extensive post-marketing experience and clinical studies. For safety information of vancomycin reference is made to the SmPC vancomycin capsules.

1.4 Risk-Benefit Assessment

CDAD in adults is associated with significant mortality and morbidity, particularly in those infected with highly virulent strains. Loo showed that deaths attributable to CDAD occurred in 6.9% of patients [Loo et al, 2005], while all cause mortality in the fidaxomicin phase 3 studies was 5.3% to 7.6%. In an observational study the mortality in children with CDAD was 3.8% [Kim et al, 2008]. The risks of any treatment should therefore be assessed in the context of the seriousness of the underlying condition. The currently recommended treatments, metranidazole and vancomycin, have limitations such as disruption of intestinal flora, cross resistance with other agents and a high rate of recurrence. Fidaxomicin has low systemic absorption and a narrow spectrum of antimicrobial activity and therefore represents a potentially useful treatment for CDAD in children.

Non-clinical safety pharmacology, repeat dose toxicity, genotoxicity and reproductive toxicity studies of fidaxomicin did not identify any hazard for humans.

Although systemic bioavailability is low in humans (C_{max} 9.88 ng/mL after a 200 mg dose), the elderly and those with CDAD appear to have higher exposure, as do patients with hepatic impairment.

Common AEs observed in the adult phase 3 studies were nausea, vomiting, and constipation. Uncommon AEs were rash, pruritis, decreased appetite, dizziness, headache, dysgeusia, abdominal distension, flatulence, dry mouth and alanine aminotransferase increased (SmPC Dificlir). Acute hypersensitivity reactions have been reported during post marketing such as rash, pruritis, angioedema and dyspnea. [reference IB version 9.3].

In the phase 2 and 3 studies in adults, the deaths were mainly due to respiratory disorders, sepsis and malignancy, and all were considered unrelated or unlikely to be related to fidaxomicin or vancomycin.

Given the limited experience with fidaxomicin to date, lack of efficacy should also be considered a possibility. However, the results of phase 3 studies in adults showed that one of the standard treatments for CDAD, vancomycin, was comparable in terms of clinical response and safety and may be associated with higher rates of recurrence compared with fidaxomicin treatment.

The results of the phase 2A pediatric study (age: > 6 months - < 18 years: see section 1.2) showed a safety profile consistent with that seen in adults, with gastrointestinal disorders and infections/infestations the commonest AEs. Six subjects developed AEs considered related to study drug none of which were serious. These were tachycardia, constipation, diarrhea, nausea, vomiting, increased body temperature, urticaria, and elevated liver enzymes. There were no safety signals detected by analysis of vital signs, ECG or laboratory data. Fidaxomicin has not been used in children < 6 months. A 4-week oral repeated-dose toxicity study in juvenile beagle dogs showed no target organ for toxicity after 28 days of dosing up to 200 mg/kg/day fidaxomicin from Post Natal Day 4 (see section 1.2.1), which is the age equivalent to a newborn child.

Fidaxomicin is the first representative in the novel antibacterial class of macrocycles. The current safety data-base consists of a total of 798 patients with mild to moderately severe CDI treated up to 10 days. Based on post-marketing experience since July 2011, the safety profile of fidaxomicin has slightly changed relative to that seen in the Phase III studies. Some patients with hypersensitivity reactions reported a history of allergy to macrolides. Fidaxomicin should be used with caution in patients with a known macrolides allergy (SmPC Dificlir). The available data suggest that fidaxomicin will have an acceptable benefit-risk balance in the treatment of CDAD in children.

2 STUDY OBJECTIVE(S), DESIGN, AND ENDPOINTS

2.1 Study Objectives

2.1.1 Primary

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 subjects with *Clostridium difficile*-associated diarrhea (CDAD) from birth to < 18 years of age.

2.1.2 Secondary

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

2.2 Study Design and Dose Rationale

2.2.1 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 subjects from birth to < 18 years of age with confirmed CDAD. Note that in the United States of America subjects 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 investigator-blinded only.

The study will be conducted in North America and Europe across ~65 to 80 sites. A target of one hundred forty four subjects, stratified by age at enrollment (from birth to < 24 months, ≥ 2 years to < 6 years, ≥ 6 years to < 12 years, and ≥ 12 years to < 18 years) will be enrolled. A minimum of 24 subjects will be enrolled into each age group.

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

CDAD status will be assessed by interviews with the subject/parent/legal guardian (or hospital staff e.g. when hospitalized). These interviews will be conducted in the morning, daily during the treatment period through the 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). During the interviews a standardized questionnaire will be used to collect the following information, number, date and time of the last episode of watery diarrhea or unformed bowel movements since the last contact and if the subject has been hospitalized. The

subjects/parent/ legal guardian/hospital staff will receive a leaflet with instructions what information is to note.

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

At EOT, the initial clinical response will be assessed. All subjects will continue in the Follow-up period. Subjects that have no initial clinical response will only be contacted at EOS for safety (adverse events).

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

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

For subjects with a recurrence of diarrhea during the Follow-up period, an Unscheduled visit as soon as possible 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). Subjects with recurrence of CDAD will after the Unscheduled visit, continue in the Follow-up period and will only be contacted at EOS for safety (adverse events).

Thirty days after EOT, the EOS TC/visit will take place. For subjects 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 subjects a telephone call (TC) will be done for recording of safety information (adverse events).

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. (For subjects with a recurrence of diarrhea during the Follow-up period, a stool sample for reassessment of CDAD, see above.)

For subjects receiving fidaxomicin, plasma and stool samples will be analyzed fidaxomicin and its main metabolite OP-1118 concentrations. Palatability will be assessed for all subjects receiving fidaxomicin oral suspension or vancomycin oral liquid.

A Data and Safety Monitoring Board (DSMB) will be established for this study.

2.2.2 Dose Rationale

Subjects aged ≥ 6 years to < 18 years will be randomized to receive either 400 mg daily dose of fidaxomicin or 500 mg daily dose of vancomycin and subjects from birth to < 6 years of age will be randomized to receive weight based doses of either fidaxomicin oral suspension or vancomycin oral liquid.

Vancomycin will be given at a dose of 40 mg/kg/day up to a maximum of 500 mg/day, either as an oral liquid (Vancomycin Hospira powder for oral solution and for solution for infusion, Hospira SpA, Italian SmPC), or oral capsules. This dose of vancomycin is considered standard for children (SmPC vancomycin capsules). Please refer to section 5.1.1 Table 3B weight based dosing instruction of the vancomycin oral liquid.

The standard total daily dose of vancomycin in adults is 500 mg/day, while that for fidaxomicin is 20% lower at 400 mg/day. Neither drug undergoes appreciable systemic absorption when administered orally, both are considered effective and have an acceptable risk/benefit balance.

The total daily dose of fidaxomicin for children in the current study was therefore chosen to be 20% lower than the standard dose of vancomycin as follows:

Fidaxomicin will be given at a dose of 32 mg/kg/day up to a maximum of 400 mg/day, either as an oral suspension, or oral tablets. Please refer to section 5.1.1 Table 3A weight based dosing instruction of the fidaxomicin oral suspension.

Both treatments will be given for 10 days, a duration demonstrated to result in an acceptable cure rate of 85.7% to 88.2% in the adult phase 3 studies.

The results of the Phase 2A pediatric study (OPT-80-206) suggest a pharmacokinetic profile that is generally similar to that observed in adults, with low ng/mL concentrations of fidaxomicin and its metabolite observed in the plasma, while concentrations in the feces are in the µg/g range, well above the MIC90 of the target organism. Overall, the safety observations were consistent with both the underlying conditions of the subjects and with data from prior studies in the adult CDAD population, and suggest that fidaxomicin is well tolerated in this population. The pharmacokinetic, safety, and efficacy results observed in this study support the continuation of pediatric development of fidaxomicin with the same dose.

2.3 Endpoints

2.3.1 Primary Endpoint

Efficacy

- Confirmed clinical response based on the assessment by the investigator (at EOT+2 days).

Definitions

Clinical response for subjects aged from birth to < 2 years is defined as:
Absence of watery diarrhea for 2 consecutive days during treatment and subjects remain well until the time of study drug discontinuation (initial clinical response). In addition, subjects 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 subject/parent/ legal guardian supplemented by a review of the subject's personal records for the day (if hospitalized), and the presence of watery diarrhea.

Clinical response for subjects aged ≥ 2 years to < 18 years is defined as: 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 subjects remain well until the time of study drug discontinuation (initial clinical response). In addition, subjects 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 subject/parent/legal guardian, supplemented by a review of the subject's personal records for the day (if hospitalized), and the number of UBMs.

2.3.2 Secondary Endpoints

Efficacy

- Sustained clinical response at the EOS (EOT +30 days)
- Sustained clinical response 14 days after Confirmation Clinical Response (EOT +16 days)
- Time to resolution of diarrhea (TTROD)
- Recurrence of CDAD during or at the end of the Follow-up period.
- Time to recurrence during or at the end of the Follow-up period.

Definitions:

Sustained clinical response is defined as: Confirmed clinical response (EOT + 2 days) without CDAD recurrence until the time of assessment during the Follow-up period.

Time to resolution of diarrhea (TTROD) for subjects aged from birth to < 2 years is defined as: 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).

Time to resolution of diarrhea (TTROD) for subjects aged ≥ 2 years to < 18 years is defined as: 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 are sustained through EOT).

Recurrence for subjects aged from birth to < 2 years is defined as: 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.

Recurrence for subjects aged ≥ 2 years < 18 years is defined as: the re-establishment of diarrhea 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 after confirmed clinical response 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.

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

Safety

- AEs
- Vital signs: systolic and diastolic blood pressure, pulse rate and body temperature
- Laboratory tests: hematology, biochemistry, urinalysis
- Electrocardiogram (ECG) assessment

Drug concentration

- Plasma concentrations of fidaxomicin and its main metabolite (OP-1118) within 30 minutes pre-dose and 1 to 5 hours post-dose taken on any day between Day 5 and 10 inclusive.
- Fecal concentration of fidaxomicin and its main metabolite (OP-1118) within 24 hours of a dose taken between Day 5 and 10 inclusive.

Palatability

- Acceptance of formulation at first administration of study drug and at Day 7 (± 1 day) in all subjects receiving fidaxomicin oral suspension and vancomycin oral liquid.

2.3.3 Exploratory Endpoints

[redacted]

3 STUDY POPULATION

3.1 Selection of Study Population

Male and female subjects from birth to < 18 years of age, diagnosed with CDAD confirmed by a positive *C. difficile* toxin test in stool or positive detection of toxigenic *C. difficile* in stool.

3.2 Inclusion Criteria

Subject is eligible for the study if all of the following apply:

1. Institutional Review Board (IRB)-/Independent Ethics Committee (IEC)-approved written Informed Consent/assent (if applicable) and privacy language as per national regulations (e.g., HIPAA Authorization for US sites) must be obtained from the subject or legally authorized representative prior to any study-related procedures (including withdrawal of prohibited medication, if applicable).
2. Male and female subjects aged from birth to < 18 years. **Note that in the United States of America subjects can only be included if aged ≥ 6 months to < 18 years.**
3. Subject is diagnosed with CDAD according to local diagnostic criteria. As a minimum there must be positive detection, within 72 hours prior to randomization, of either toxin A and/or toxin B in stool or positive detection of toxigenic *C. difficile* in stool and:
    a. Subject from birth to < 2 years: watery diarrhea in the 24 hours prior to screening.
    b. Subject ≥ 2 years to < 18 years: ≥ 3 unformed bowel movements in the 24 hours prior to screening.
4. For subjects < 5 years: Negative rotavirus test.
5. Female subject of childbearing potential:
    a. must have a negative urine pregnancy test at Screening, and
    b. must abstain from sexual activity for the duration of the study, or
    c. must use two forms of birth control* (at least one of which must be a barrier method) starting at Screening and throughout the study period and for 28 days after the final study drug administration.
6. Female subject must not be breastfeeding at Screening or during the study period, and for 28 days after the final study drug administration.
7. Female subject must not donate ova starting at Screening and throughout the study period, and for 28 days after the final study drug administration.
8. Subject agrees not to participate in another interventional study while in the study (with the exception of studies as described in exclusion criteria 6).

    *Acceptable forms of birth control include:

    - Established use of oral, injected or implanted hormonal methods of contraception.
    - Placement of an intrauterine device (IUD) or intrauterine system (IUS).
    - Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository.

Waivers to the inclusion criteria will **NOT** be allowed.

3.3 Exclusion Criteria

Subject will be excluded from participation if any of the following apply:

1. Concurrent use of metronidazole, oral vancomycin or any other antibiotic treatments for CDAD. If the investigator feels the clinical imperative to begin treatment before knowing the laboratory result for 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.
2. Subject has pseudomembranous colitis, fulminant colitis, toxic megacolon or ileus.
3. Subject has a history of inflammatory bowel disease (e.g., ulcerative colitis or Crohn's disease etc.).
4. Subject has diarrhea caused by an agent other than *C. difficile* (e.g., infections, infestations, drugs etc.).
5. Subject has known hypersensitivity to fidaxomicin, vancomycin or their excipients or to teicoplanin.
6. Subject has received an investigational therapy within 28 days, prior to Screening, with the exception of studies with primary treatment for cancer without novel Investigational Medicinal Product (IMP) and which do not affect the assessment of diarrhea.
7. Subject has a condition which, in the investigator's opinion, makes the subject unsuitable for study participation.

Waivers to the exclusion criteria will **NOT** be allowed.

4 TREATMENT(S)

4.1 Identification of Investigational Product(s)

4.1.1 Test Drug(s)

Fidaxomicin granules for oral suspension is supplied as granules in a bottle. A separate box will be provided with ancillaries for preparation of the oral suspension. A pharmacy manual will be provided for the preparation of the fidaxomicin suspension. The prepared bottle is for multiple dosing and sufficient for 10 day treatment.

The fidaxomicin oral suspension contains fidaxomicin, microcrystalline cellulose, sodium starch glycolate, xanthan gum, anhydrous citric acid, sodium citrate, sodium benzoate, sucralose and mixed berry flavor*. All excipients are Generally Recognized as Safe (GRAS) listed.

Administration via nasogastric tube is acceptable and specific material characteristics for specific tubes should be with the information in the pharmacy manual.

If a patient leaves the hospital, instructions will be provided to caregivers on how to store and administer the suspension in a patient information card. The suspension will always be made by or under responsibility of the pharmacy or qualified designee (if allowed as per the local regulations) of the investigational site.

* All flavor ingredients contained in this product are approved for use by the FDA or in a reliable published industry list. All the flavoring ingredients contained in the above mentioned product are listed in Annex I - (EU) No 872/2012 (list of flavouring substances) - to Regulation (EC) No 1334/2008 adopted on October 1, 2012 and that will apply starting 22 April 2013 and are composed of Art. 3.2.D. Flavouring preparations. It also contains modified food starch (E1520), propylene glycol (E1450) and triacetine. The product was not derived from a genetically modified source material.

Fidaxomicin tablets are commercially available as Dificlir 200 mg film-coated tablets (SmPC Dificlir). Each tablet contains 200 mg of fidaxomicin.

4.1.2 Comparative Drug(s)

Vancomycin oral liquid is supplied as powder for oral liquid. A separate box will be provided with ancillaries for preparation of the oral liquid.

Sweet syrups may be added to the liquid to improve the taste of the oral administration. [Vancomycin Hospira powder for oral solution and for solution for infusion, Hospira SpA, Italian SmPC]. SyrSpend will be provided to be used as sweet syrup for the vancomycin oral liquid. A pharmacy manual will be provided for the preparation of the vancomycin oral liquid.

Administration via nasogastric tube is described in the pharmacy manual.

If a subject leaves the hospital, instructions will be provided to caregivers on how to store and administer the liquid in a patient information card. The liquid will always made by or under responsibility of the pharmacy or qualified designee (if allowed as per the local regulations) of the investigational site.

Vancomycin capsules are provided as commercially available 125 mg vancomycin capsules containing 125mg vancomycin (SmPC of vancomycin capsules) .

4.2 Packaging and Labeling

All medication used in this study will be prepared, packaged, and labeled under the responsibility of qualified staff at Astellas Pharma Europe B.V.(APEB) or Sponsor's designee in accordance with APEB or Sponsor's designee Standard Operating Procedures (SOPs), Good Manufacturing Practice (GMP) guidelines, ICH GCP guidelines, and applicable local laws/regulations.

Each patient kit and medicinal parts will bear a label conforming to regulatory guidelines, GMP and local laws and regulations which identifies the contents as investigational drug.

A qualified person of APEB or Sponsor's designee will perform the final release of the medication according to Directive 2003/94/EC annex 13.

4.3 Study Drug Handling

Current ICH GCP Guidelines require the investigator to ensure that study drug deliveries from the Sponsor are received by the investigator/or designee and

- that such deliveries are recorded,
- that study drug is handled and stored according to labeled storage conditions,
- that study drug with appropriate expiry/retest and is only dispensed to study subjects in accordance with the protocol, and
- that any unused study drug is returned to the Sponsor.

As this is an investigator blind study, site and Sponsor staff involved in dispensing, administering or collecting the study drug will be unblinded.

Drug inventory and accountability records for the study drugs will be kept by the investigator/or designee. Study drug accountability throughout the study must be documented and reconciled. The following guidelines are therefore pertinent:

- The investigator agrees not to supply study drugs to any persons except the eligible subjects in this study in accordance with the protocol.
- The investigator or designee will keep the study drugs in a pharmacy or other locked and secure storage facility under controlled storage conditions, accessible only to those authorized by the investigator to dispense these test drugs.
- A study drug inventory will be maintained by the investigator or designee. The inventory will include details of material received and a clear record of when they were dispensed and to which subject.
- At the conclusion or termination of this study, the investigator or designee agrees to conduct a final drug supply inventory and to record the results of this inventory on the Drug Accountability Record. It must be possible to reconcile delivery records with those of used and/or returned medication. Any discrepancies must be accounted for and documented. Appropriate forms of deliveries and returns must be signed by the site staff delegated this responsibility.
- The site must return study drug to the Sponsor or designee at the end of the study or upon expiration.

4.4 Blinding

This is an investigator-blind study. Subjects will be randomized to receive fidaxomicin or vancomycin in an investigator-blind fashion such that the investigator, Sponsor's or designee's study management team, and clinical staff will not know which agent is being administered. However, site and Sponsor or designee staff involved in dispensing, administering or collecting the study products and drug concentration blood sampling will be unblinded, as well as subjects and the parents/legal guardians. In case of questions, subjects and parents/legal guardians can discuss with the unblinded staff. Subjects, parents/legal

guardians and unblinded staff will be instructed not to discuss the treatment (appearance, frequency of dosing, times of individual doses, palatability etc) and drug concentration blood sampling with the blinded staff. Blinded staff will be instructed not to discuss the study treatment with unblinded staff, subjects and parents/legal guardians.

Given the complexity of maintaining the blind because of the charactaristics of the study medication and the pediatric population, accidental unblinding is a risk. Every effort will be taken to maintain the blind. In the event of accidental unblinding of blinded site, CRO or sponsor staff, this will be documented. Accidental unblinding is not a reason to discontinue study drug, even if the unblinding occurs before the start of treatment. Subjects should not be re-randomized for any reason, even if accidental unblinding occurs. Further details will be described in the blinding instructions.

4.4.1 Unblinding for Subject Safety Reasons

Unblinding of the study drug should only be considered for subject safety or when critical therapeutic decisions are contingent upon knowing the blinded study drug assignment. Any unblinding by the investigational staff must be reported immediately to the Sponsor and must include an explanation of why the treatment allocation was disclosed. If possible, the Sponsor should be contacted prior to unblinding of the study drug.

4.4.2 Blinding Method

The medication will be provided in a blinded outer carton to prevent accidental unblinding by the investigator. The content of the provided medication will be unblinded hence medication will only be prepared and handled by unblinded care givers and site staff.

4.4.3 Retention of the Assignment Schedule and Procedures for Treatment Code Breaking

The randomization list and study drug blind will be maintained by the Interactive Response Technology (IRT) system.

The DSMB will be provided access to the treatment assignment for periodic review of the data as documented in the DSMB Charter.

4.4.4 Breaking the Treatment Code for Emergency

The treatment code for each randomized subject will be provided by the IRT in the event of a medical emergency requiring knowledge of the treatment assigned to the subject. The time, date, subject number and reason for obtaining any of these codes, and therefore breaking the blind, must be documented in the study file. They must only be requested by the investigator or other persons designated as sub-investigators.

4.4.5 Breaking the Treatment Code by the Sponsor

The Sponsor may break the treatment code for subjects who experience a Suspected Unexpected Serious Adverse Reaction (SUSAR), in order to determine if the individual case or a group of cases requires expedited regulatory reporting. Individual Emergency Codes will

be provided to the limited staff that is responsible to break the codes for all SUSAR cases for reporting purposes.

4.5 Assignment and Allocation

Randomization will be performed via IRT. 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.

5 TREATMENTS AND EVALUATION

5.1 Dosing and Administration of Study Drug(s) and Other Medication(s)

5.1.1 Dose/Dose Regimen and Administration Period

At the end of Screening, eligible subjects will be randomized to the fidaxomicin or vancomycin treatment arm. The subject will take the study drug for 10 days.

Subjects randomized to the fidaxomicin treatment arm, from birth to < 6 years of age will be administered fidaxomicin oral suspension, 32 mg/kg/day with a maximum dose of 400 mg/day, divided in 2 doses/day for 10 days (see Table 3A below) and subjects aged ≥ 6 years to < 18 years will receive a fidaxomicin 200 mg tablet, 2 times daily, for 10 days.

Table 3A: Weight-based Dosing Instruction of the Fidaxomicin Oral Suspension

Weight band of patient	Dose in mg/day (twice daily dosing)	mg/dose	Volume of fidaxomicin oral suspension to administer
≤ 3.9 kg	80 mg	40 mg	1.0 mL
4.0-6.9 kg	160 mg	80 mg	2.0 mL
7.0-8.9 kg	240 mg	120 mg	3.0 mL
9.0-12.4 kg	320 mg	160 mg	4.0 mL
≥ 12.5 kg	400 mg	200 mg	5.0 mL

Subjects randomized to the vancomycin treatment arm, from birth to < 6 years of age will be administered a vancomycin oral liquid 40 mg/kg/day with a maximum dose of 500 mg/day, divided in 4 doses/day, for 10 days (see Table 3B below) and subjects aged ≥ 6 years to < 18 years will be administered a vancomycin 125 mg capsule, 4 times daily, for 10 days.

Table 3B: Weight-based Dosing Instruction of the Vancomycin Oral Liquid

Weight band of patient	Dose in mg/day (four times daily dosing)	mg/dose	Volume of vancomycin oral liquid to administer
≤ 3.9 kg	100 mg	25 mg	1.0 ml
4.0-6.9 kg	200 mg	50 mg	2.0 ml
7.0-8.9 kg	300 mg	75 mg	3.0 ml
9.0-12.4 kg	400 mg	100 mg	4.0 ml
≥ 12.5 kg	500 mg	125 mg	5.0 ml

For subjects aged ≥ 6 years to < 18 years prior to randomization the ability for the subject to swallow tablets or capsules needs to be determined. If a subject aged ≥ 6 years to < 18 years cannot swallow tablets or capsules, fidaxomicin oral suspension or vancomycin oral liquid can be given as per the subject's treatment allocation. During the treatment period, a change of formulation for a subject is not allowed.

Subjects and parents/legal guardians/unblinded study staff will be instructed not to discuss the treatment (appearance, frequency of dosing, palatability, times of individual doses etc.) with the blinded study staff.

5.1.2 Increase or Reduction in Dose of the Study Drug(s)

Increases and reductions of study drug are not permitted because the aim of the study is to investigate fixed weight based dose of fidaxomicin and vancomycin.

5.1.3 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. The most recent use of fidaxomicin or any macrolide antibiotic should be recorded in the eCRF, regardless of how long ago it was taken.

Concomitant medication includes relevant therapies prescribed by the study doctor, other doctors and over the counter drugs taken from Day 1 until the EOS (EOT + 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. This also includes drugs used on a chronic and as-needed basis. Subjects 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.

5.1.3.1 Prohibited Medication and Restricted Medication

No other antibacterial agents potentially useful in the treatment of CDAD (e.g., metronidazole, oral vancomycin, oral bacitracin, fusidic acid, rifaximin, nitazoxanide) or fecal 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.

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.

Drugs to control diarrhea (e.g., loperamide) should also be withheld during the study period. Whenever possible, drugs which could affect peristalsis should be avoided. Subjects receiving opioids for pain prior to enrollment may continue to receive the same opioid and dose during the treatment phase if required.

See Appendix 12.1 Excluded Concomitant Medications for additional details on prohibited medications and medications permitted with restrictions.

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.

5.1.4 Treatment Compliance

Study subjects and/or legal guardian (as applicable) should be counseled on the need to meet 100% treatment compliance. The unblinded investigator or designee should ensure that subjects meet this goal. The quantity of study drug dispensed will be counted or measured and recorded in the eCRF at EOT.

Treatment compliance will be based on the weight of the oral liquid/oral suspension used or count of tablets/capsules used during the treatment period (whatever applies), which will be recorded in the eCRF. Subjects will be regarded as compliant if the calculated amount of oral liquid/oral suspension used or of tablets/capsules used (as applicable) is between 80% and 120% (inclusive) of the expected amount for the number of days on treatment.

Site and Sponsor staff involved in dispensing, administering or collecting the study drug will be unblinded.

The study drug will not be dispensed to any persons not enrolled in the study.

5.2 Demographics and Baseline Characteristics

5.2.1 Demographics

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

5.2.2 Medical History

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

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

A detailed diarrhea history for each subject 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 enrollment. The following risk factors will be collected in the eCRF: Antibiotics/ Cancer/ Other, if applicable.

5.2.4 Rotavirus

For subjects < 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.

5.3 Efficacy Assessment

The following efficacy variables will be assessed:

- Confirmed clinical response based on the assessment by the investigator (at EOT+2 days).
- Sustained clinical response at the End of Study (EOT +30 days).
- Sustained clinical response 14 days after Confirmation Clinical Response (EOT +16 days).
- Time to resolution of diarrhea (TTROD).
- Recurrence of CDAD during or at the end of the Follow-up period.
- Time to recurrence of CDAD during or at the end of the Follow-up period.

Definitions are described in sections 2.3.1 and 2.3.2

During the treatment period (until EOT) the subject/parent/legal guardian (or hospital staff e.g. when hospitalized) will be contacted daily in the morning for interviews. These interviews will also take place at EOT+2; thereafter weekly at 9, 16 and 23 days after the EOT, and at End of Study (EOS) EOT + 30 days. These interviews may be conducted by telephone (e.g. when not hospitalized). During the interviews a standardized questionnaire will be used to collect the following information, number, date and time of the last episode of watery diarrhea or unformed bowel movements since the last contact and if the subject has been hospitalized. The subjects/parent/legal guardian/hospital staff will receive a leaflet with instructions what information is to note.

Resolution of diarrhea is to be assessed by the investigator based on these interviews, supplemented by review of the subject's personal records for the day (if subject is hospitalized), and the number of UBMs/presence of watery diarrhea (as applicable).

The assessment of initial clinical response will take place at EOT; 2 days thereafter the assessment of confirmed clinical response will be done.

Sustained clinical response and recurrence will only be assessed in subjects having confirmed clinical response at EOT +2 days. For this, the subject/parent/legal guardian will be contacted weekly after EOT (at EOT + 9, +16 and +23 days) until recurrence or the EOS TC/visit (EOT + 30 days), whichever comes first. (If an Unscheduled visit occurs, recurrence will be assessed). The subject/parent/legal guardian will be instructed to note the date in the event of recurrence. The assessment of recurrence will be done by the investigator.

5.4 Safety Assessment

5.4.1 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 subject 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.

5.4.2 Adverse Events

See Section 5.5 Adverse Events and Other Safety Aspects for information regarding adverse event collection and data handling.

5.4.2.1 Adverse Events of Possible Hepatic Origin

See Appendix 12.2 Liver Safety Monitoring and Assessment for detailed information on liver abnormalities, monitoring and assessment, if the AE for a subject enrolled in a study and receiving study drug is accompanied by increases in liver function testing (LFT) e.g., AST, ALT, bilirubin, etc. or is suspected to be due to hepatic dysfunction.

5.4.3 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 4 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 subjects are fasting prior to blood sampling for these assessments. Please refer to 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 4. A historical/standard of care samples without parameter(s) indicated with * in the table is acceptable.

Every effort will be made to reduce anxiety and discomfort due to blood tests. A topical anesthetic will be offered to minimize discomfort associated with venipuncture.

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 (see Section 5.5.1).

Table 4 Clinical Laboratory Tests to be Performed

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

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

5.4.4 Physical Examination

The subject'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 (see section 5.5.1).

5.4.5 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.

Wherever possible, ECGs will be taken with the subject in the supine position, after the subject has been lying quietly for 5 minutes.

ECGs will be recorded at a speed of 25 mm/sec and all leads have to include at least 4 complexes. The original ECG traces will include the subject number, date and visit number and must be kept with the source documents. If the ECG traces are printed on thermal paper, a photocopy must be made and kept with the source documents.

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.

Any clinically significant adverse changes on the ECG will be reported as AEs in the eCRF (see section 5.5.1).

5.4.6 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, abdominal tenderness) will be recorded at Screening. Abdominal discomfort and abdominal tenderness will be recorded at End of Treatment. Any clinically relevant adverse change will be recorded as an AE in the eCRF (see section 5.5.1).

5.5 Adverse Events and Other Safety Aspects

The reference safety information for fidaxomicin to be used for this study is the IB. The reference safety information for vancomycin to be used for this study is the SmPC vancomycin capsules.

5.5.1 Definition of Adverse Events (AEs)

An AE is defined as any untoward medical occurrence in a subject administered a study drug or has undergone study procedures and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

An abnormality identified during a medical test (e.g., laboratory parameter, vital sign, ECG data, physical exam) should be defined as an AE only if the abnormality meets one of the following criteria:

- Induces clinical signs or symptoms.
- Requires active intervention.
- Requires interruption or discontinuation of study drug.
- The abnormality or investigational value is clinically significant in the opinion of the investigator.

All subjects will remain in the study until EOS for safety assessment. All AEs occurring between signing informed consent and EOS TC/visit should be recorded.

The specified AEs / findings of interest for this study are shown below and may require more extensive collection of information which will be collected in targeted questionnaires:

- Development of microbial resistance to fidaxomicin
- Hypersensitivity to fidaxomicin
- GI hemorrhage
- Decreases in WBC, neutrophil and lymphocyte counts
- Hepatic laboratory value abnormalities
- Renal laboratory value abnormalities
- QT-interval prolongation
- Lack of efficacy / lack of effect / treatment failure

Some countries may have additional local requirements for events that are required to be reported as AEs or in an expedited manner similar to an SAE. In these cases, it is the investigator's responsibility to ensure these AEs or other reporting requirements are followed and the information is appropriately recorded in the (e)CRF accordingly.

In addition, if any of these events meet the criteria for a Serious Adverse Event (SAE), the SAE reporting requirements in section 5.5.5 will apply.

5.5.2 Definition of Serious Adverse Events (SAEs)

An adverse event is considered "serious" if, in the view of either the investigator or Sponsor, it results in any of the following outcomes:

- Results in death
- Is life threatening (an adverse event is considered "life-threatening" if, in the view of either the investigator or Sponsor, its occurrence places the subject at immediate risk of

death. It does not include an adverse event that, had it occurred in a more severe form, might have caused death)
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Results in congenital anomaly, or birth defect
- Requires inpatient hospitalization or leads to prolongation of hospitalization (hospitalization for treatment/observation/examination caused by AE is to be considered as serious)
- Other medically important events

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These events, including those that may result in disability/incapacity, should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Special situation events relevant to the medicinal products administered to the subject as part of the study (e.g., study drug, comparator, background therapy) that may require expedited reporting and/or safety evaluation include, but are not limited to:

- Overdose of the medicinal product(s)
- Suspected abuse/misuse of the medicinal product(s)
- Inadvertent or accidental exposure to the medicinal product(s)
- Medication error involving the medicinal product(s) (with or without subject/patient exposure to the Sponsor medicinal product, e.g., name confusion)
- Drug-drug interaction
- Lack of efficacy

All special situations listed above should be especially monitored and reported on a SAE form, even if considered non-serious and regardless whether or not an (S)AE occurred. The above special situation will not be captured on the AE form in the eCRF, instead they will be captured in the dosing and accountability forms within the eCRF.

As fidaxomicin is orally administered, for this study, there is no risk of occupational exposure and risk of transmission of infectious agents is limited, therefore the Sponsor do not expect these events to be reported.

The Sponsor has a list of events that they classify as “always serious” events. If an adverse event is reported that is considered to be an event per this classification as “always serious”, additional information on the event may be requested.

If a subject becomes pregnant during treatment, this should be reported as if it were an SAE. Refer to section 5.5.8 Procedure in Case of Pregnancy.

5.5.3 Criteria for Causal Relationship to the Study Drug

Adverse events that fall under either "Possible" or "Probable" should be defined as "adverse events whose relationship to the study drugs could not be ruled out".

Causal relationship to the study drug	Criteria for causal relationship
Not Related	A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and/or in which other drugs, chemicals or underlying disease provide plausible explanations.
Possible	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.
Probable	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on re-administration (rechallenge) or withdrawal (dechallenge).

5.5.4 Criteria for Defining the Severity of an Adverse Event

The following standard with 3 grades is to be used to measure the severity of AEs, including abnormal clinical laboratory values:

- Mild: No disruption of normal daily activities
- Moderate: Affect normal daily activities
- Severe: Inability to perform daily activities

5.5.5 Reporting of Serious Adverse Events (SAEs)

In the case of a serious adverse event (SAE), the investigator must contact the delegated CRO by telephone or fax immediately (within 24 hours of awareness).

The investigator should complete and submit an SAE Worksheet containing all information that is required by the Regulatory Authorities to the delegated CRO by fax immediately (within 24 hours of awareness). If the faxing of an SAE Worksheet is not possible or is not possible within 24 hours, the local drug safety contact should be informed by phone.

The SAE Worksheet should be sent to the delegated CRO:

[redacted]

(Toll-free fax numbers will be provided for each country; the country-specific fax number

can be found on the SAE Worksheet fax cover sheet)
[redacted]

If there are any questions, or if clarification is needed regarding the SAE, please contact the Sponsor's Medical Monitor/Expert or his/her designee (see Section II Contact Details of Key Sponsor's Personnel).

Follow-up information for the event should be sent promptly (within 7 days of the initial notification.

Full details of the SAE should be recorded on the medical records and on the eCRF. The investigator must ensure that information on the SAE Worksheet is reconciled with the information on the AE pages within the eCRF.

The following minimum information is required:

- ISN/Study number 2819-CL-0202,
- Subject number, sex and age,
- The date of report,
- A description of the SAE (event, seriousness of the event), and
- Causal relationship to the study drug.

The Sponsor or Sponsor's designee will submit expedited safety reports (i.e. CIOMS, IND Safety Reports) to the regulatory agencies (i.e. EMA, FDA) as necessary, and will inform the investigators of such regulatory reports. Investigators must submit safety reports as required by their local Institutional Review Board (IRB)/Independent Ethics Committee (IEC) within timelines set by regional regulations (i.e. EU, (e)CTD, FDA). Documentation of the submission to and receipt by the IRB/IEC of expedited safety reports should be retained by the site.

The delegated CRO will notify all investigators responsible for ongoing clinical studies with the study drug of all SAEs which require submission per local requirements to IRB/IEC.

The investigators should provide written documentation of IRB/IEC notification for each report to the Sponsor.

You may contact the Sponsor's Medical Monitor/Expert for any other problem related to the safety, welfare, or rights of the subject.

For Suspected Unexpected Serious Adverse Reactions (SUSARs) from a blinded trial, unblinded CIOMS-I reports will be submitted to the authorities and central IRB/IEC where required.

5.5.6 Follow-up of Adverse Events

All AEs occurring during or after the subject has discontinued the study are to be followed up until resolved or judged to be no longer clinically significant, or until they become chronic to the extent that they can be fully characterized.

If during AE follow-up, the adverse event progresses to an ″SAE″, or if a subject experiences a new SAE, the investigator must immediately report the information to the Sponsor.

Please refer to Appendix 12.2 Liver Safety Monitoring and Assessment for detailed instructions on DILI.

5.5.7 Monitoring of Common Serious Adverse Events

For this protocol, there are no SAEs that are exempted from expedited safety reporting.

5.5.8 Procedure in Case of Pregnancy

If a female subject or partner of a male subject becomes pregnant during the treatment period or Follow-up period, the investigator should report the information to the delegated CRO as if it is an SAE. The expected date of delivery or expected date of the end of the pregnancy, last menstruation, estimated conception date, pregnancy result and neonatal data etc., should be included in this information.

The investigator will follow the medical status of the mother, as well as the fetus, as if the pregnancy is an SAE and will report the outcome to the Sponsor.

When the outcome of the pregnancy falls under the criteria for SAEs [spontaneous abortion, induced abortion, stillbirth, death of newborn, congenital anomaly (including anomaly in a miscarried fetus)], the investigator should respond in accordance with the report procedure for SAEs. Additional information regarding the outcome of a pregnancy (which is categorized as an SAE) is mentioned below.

- "Spontaneous abortion" includes miscarriage, abortion and missed abortion
- Death of an infant within 1 month after birth should be reported as an SAE regardless of its relationship with the study drug
- If an infant dies more than 1 month after the birth, it should be reported if a relationship between the death and intrauterine exposure to the study drug is judged as "possible" by the investigator
- In the case of a delivery of a living newborn, the "normality" of the infant is evaluated at the birth
- Unless a congenital anomaly is identified prior to spontaneous abortion or miscarriage, the embryo or fetus should be assessed for congenital defects by visual examination. If during the conduct of a clinical trial, a male subject makes his partner pregnant, the subject should report the pregnancy to the investigator. The investigator will report the pregnancy to the Sponsor/delegated CRO as an SAE.

5.5.9 Emergency Procedures and Management of Overdose

Fidaxomicin: In the event of suspected overdose, the subject should receive supportive care and monitoring. The Medical Monitor/Expert should be contacted as applicable.

Vancomycin: In the event of suspected overdose, guidance in the local product labeling is to be followed at the investigator's discretion. The Medical Monitor/Expert should be contacted as applicable.

5.5.10 Supply of New Information Affecting the Conduct of the Study

When new information becomes available necessary for conducting the clinical study properly, the Sponsor will inform all investigators involved in the clinical study as well as the regulatory authorities. Investigators should inform the IRB/IEC of such information when needed.

5.6 Test Drug Concentration

Plasma and stool samples will be analyzed for fidaxomicin and its main metabolite OP-1118 concentrations.

For subjects 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.

Blood samples will be collected via an intravenous cannula or by direct venipuncture. Whole blood will be collected at each sampling time point into an appropriately labeled blood collection tube. A 1 mL blood tube containing EDTA as anticoagulant will be collected. Plasma will be prepared and stored in pre labeled polypropylene vials at nominal -70 C, according to procedures specified in the laboratory operations manual.

For all the subjects, one stool sample will be taken on any day between Day 5 and 10 inclusive, within 24 hours of a dose for drug concentration analysis.

Stool samples will be collected in containers provided by the central laboratory according to the instructions provided in the laboratory operations manual.

Information on the pre-printed sample tube labels should contain at a minimum:

- Study number 2819-CL-0202
- Subject number
- “Plasma” or “feces”
- Unique sample number
- Protocol Day and time

All samples for a subject will be stored and shipped as a package for that subject as organized by the central laboratory. Samples will be shipped under appropriate dry-ice conditions by a courier to the central laboratory and analyzed under responsibility of Astellas Bioanalysis-Europe section of Astellas in Europe for subsequent determination of fidaxomicin and OP-1118 concentrations. Bioanalysis of fidaxomicin and OP-1118 in plasma and faeces will be performed using validated liquid chromatography with tandem mass spectrometry (LC MS/MS) methods.

Further details will be specified in the laboratory operations manual.

The actual date and time of each blood and stool sample collection will be recorded in the eCRF, as well as if the stool sample is taken from the diaper.

5.7 Other Measurements, Assessments or Methods

5.7.1 Stool Samples for Toxigenic *C.difficile* and Microbiological Testing

Stool samples will be obtained at Screening, at the End of Treatment visit and in case of recurrence at the Unscheduled visit. Stool samples will be split into two aliquots; one for local (direct or indirect) testing for presence of toxigenic *C.difficile* at the study site and one for microbiological testing at the reference laboratory.

For assessment of inclusion criteria for Screening, a routinely performed local rapid test that was taken after the onset of CDAD and within 72 hours prior to randomization is acceptable. This sample may be a pre-consent sample taken as standard of care. In this situation an additional stool sample (for possible microbiological and biochemistry testing) for the reference laboratory needs to be taken as part of Screening, even if on antibiotic treatment.

Microbiological testing will be performed on stool samples collected pre-treatment and post-treatment and in case of recurrence. Results from relevant microbiological and biochemical assays may be used for an exploratory evaluation of efficacy or to further increase knowledge on the investigational product.

Stool samples for microbiology testing at the reference laboratory will be frozen at -70 C and stored at the site until sent batch-wise to a central laboratory for further characterization. Stool samples will be analyzed in order to confirm the presence of toxigenic *C. difficile* and where sufficient sample allows, also confirm the presence of toxin in the stool sample. *C. difficile* will be cultured from all confirmed positive samples and additional tests may be carried out on these isolates including, but not limited to PCR ribotyping and antimicrobial susceptibility profile evaluation. The samples will be stored for no longer than 5 years after the completion of the study. A decision on the exact analyses to be performed will be taken at a later stage and may be dependent on the results of the toxin tests or ribotyping. Assessments will be limited to any microbiological marker present in the stool sample or its derived culture.

Results from the central laboratory will not be returned to the investigator.

Details for processing and shipping the stool samples will be described in the laboratory manual, to be provided before the start of the study.

5.7.2 Palatability Testing

Palatability will be assessed for all subjects receiving fidaxomicin oral suspension and vancomycin oral liquid (i.e. subjects from birth to ≤ 6 years of age and subjects > 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 subject/parents/legal guardian when at home.

Details will be provided in the palatability assessment instructions.

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

5.8 Total Amount of Blood

The following blood volume limits for sampling are recommended (although are not evidence-based). If an investigator decides to deviate from these, this should be justified. Per individual, the trial-related blood loss (including any losses in the manoeuvre) should not exceed 3% of the total blood volume during a period of four weeks and should not exceed 1% at any single time. In the rare case of simultaneous trials, the recommendation of 3% remains the maximum. The total volume of blood is estimated at 80 to 90 mL/kg body weight; 3% is 2.4 mL blood per kg body weight. (Ethical Considerations for Clinical Trials on Medicinal Products Conducted with the Paediatric Population, European Medicines Agency, 2008).

Examples of the total amount of blood collected per subject during the course of the study are shown in Table 5.

Table 5: Examples of the total amount of blood collected per subject during the course of the study

Assessment	Volume of Blood per Sample [mL]	Volume of Blood per Sample Pediatric tubes [mL]	Number of Assessments	Total Volume of Blood (mL)	Total Volume of Blood using pediatric tubes (mL)
Drug concentration measurement	1	1	2	2	2
Safety Laboratory					
Hematology (Sample volumes are estimated)	2.7	1*	2	5.4	2
Biochemistry	5	1*	2	10	2
Total Maximum Amount per Subject				17.4	6

* Example only

Age appropriate pediatric sampling tubes should be used, in order to comply with the guidelines of maximum blood volume above.

An historical or standard of care sample may be acceptable (see section 5.4.3).

6 DISCONTINUATION

6.1 Discontinuation of Individual Subject(s)

A discontinuation is a subject who was enrolled in the study and for whom study treatment is permanently discontinued prematurely for any reason.

The subject is free to withdraw from the study treatment and/or study for any reason and at any time without giving reason for doing so and without penalty or prejudice. The investigator is also free to terminate a subject's involvement in the study at any time if the subject's clinical condition warrants it.

If a subject is discontinued from the study with an ongoing adverse event or an unresolved laboratory result that is significantly outside of the reference range, the investigator will attempt to provide follow-up until the condition stabilizes or no longer is clinically significant.

Examples for Discontinuation Criteria for Individual Subjects:

- Adverse event(s)
- Lack of efficacy
- Subject lost to follow up
- Protocol deviation

A clear and concise reason for discontinuation should be recorded in the eCRF.

In case of discontinuation of study drug before completion of the full 10-day treatment course, the subject should complete the EOT visit as soon as possible after the last drug administration. If at this visit, subject has an initial clinical response, the subject will continue in the Follow-up period for safety and efficacy unless consent has been withdrawn.

6.2 Discontinuation of the Site

If an investigator intends to discontinue participation in the study, the investigator must immediately inform the Sponsor.

6.3 Discontinuation of the Study

The Sponsor may terminate this study prematurely, either in its entirety or at any study site, for reasonable cause provided that written notice is submitted in advance of the intended termination. Advance notice is not required if the study is stopped due to safety concerns. If the Sponsor terminates the study for safety reasons, the Sponsor will immediately notify the investigator and subsequently provide written instructions for study termination.

7 STATISTICAL METHODOLOGY

The statistical analysis will be coordinated by the responsible biostatistician of Astellas. A Statistical Analysis Plan (SAP) will be written to provide details of the statistical analysis along with specifications for tables, listings and figures (TLFs) to be produced. The SAP will be finalized before the database soft lock at the latest.

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

Any deviation from the SAP will be described and justified in the Clinical Study Report.

In general, all data will be summarized with descriptive statistics (number of subjects, mean, standard deviation, minimum, median and maximum) for continuous endpoints, and frequency and percentage for categorical endpoints.

In general, data summaries will be presented within each treatment arm, by age group (and overall) and time point (as applicable), using the following classifications:

Treatment arm:	fidaxomicin or vancomycin
Age group:	from birth to < 24 months ≥ 2 years to < 6 years ≥ 6 years to < 12 years ≥ 12 years to < 18 years and overall

7.1 Sample Size

One hundred forty four eligible subjects will be enrolled and randomized to either fidaxomicin or vancomycin in a 2:1 ratio (96 randomized to fidaxomicin and 48 to vancomycin), stratified by age at enrollment (from birth to < 24 months, ≥ 2 years to < 6 years, ≥ 6 years to < 12 years, and ≥ 12 years to < 18 years). At least 24 subjects will be enrolled into each age group (i.e., a minimum of 16 randomized to fidaxomicin and 8 to vancomycin).

The sample size for this study was agreed on 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.

7.2 Analysis Sets

The following analysis sets, defined in the following subsections, will be used in the analysis and reporting of this study:

- Full Analysis Set (FAS).
- Safety Analysis Set (SAF).
- Pharmacokinetic Analysis Set (PKAS).
- Intent to Treat (ITT)

Detailed criteria for the analysis sets will be laid out in the SAP and the Classification Specifications. The allocation of subjects to analysis sets will be determined prior to database hard-lock.

7.2.1 Full Analysis Set (FAS)

The FAS will consist of all subjects who were randomized and who received at least one dose of study medication (treatment allocation as randomized). In the FAS, subjects will be allocated to the treatment arm corresponding to the study medication that were randomized to (treatment allocation as randomized). The FAS will be used for primary and secondary efficacy analyses, as well as selected demographic and baseline characteristics.

7.2.2 Safety Analysis Set (SAF)

The SAF will consist of all subjects who were randomized and who received at least one administration of study medication. In the SAF, a subject will be allocated to the treatment

arm corresponding to the study medication that was first administered, even if it differs from the treatment arm the subject was randomized to.

7.2.3 Pharmacokinetic Analysis Set (PKAS)

The PKAS will consist of all subjects randomized to fidaxomicin, having received at least one dose of fidaxomicin and having at least one valid measurement of plasma concentration or fecal concentration of fidaxomicin or its main metabolite OP-1118.

7.2.4 Intent to Treat Analysis Set (ITT)

The intent-to-treat (ITT) set consists of all randomized subjects, irrespective of a subject having received a study drug (fidaxomicin or vancomycin) or not. In the ITT, subjects will be allocated to the treatment arm corresponding to the study medication that were randomized to (treatment allocation as randomized). The ITT will be used for efficacy analyses, as well as selected demographic and baseline characteristics when necessary.

7.3 Demographics and Other Baseline Characteristics

Demographics and other baseline characteristics will be summarized for the FAS, stratified by treatment arm (and overall) and age group. Gender, race and other categorical baseline characteristics will be summarized using frequency tables. Continuous variables, such as age, height and weight, will be summarized using descriptive statistics. Data will be listed as appropriate.

7.4 Analysis of Efficacy

The definitions for the terms confirmed clinical response, recurrence and sustained clinical response used in this section are given in section 2.3

7.4.1 Analysis of Primary Endpoint

The primary endpoint will be the assessment of confirmed clinical response assessed by the investigator at EOT+2. A missing assessment of the primary endpoint will be imputed according to the rules and methods in section 7.10

7.4.1.1 Primary Analysis

The analysis of the primary efficacy endpoint, confirmed clinical response (see definition in section 2.3.1) at EOT+2 days will be conducted for the FAS.

The proportion of subjects with confirmed clinical response at EOT+2 days will be summarized within each treatment arm by age group along with exact 95% confidence intervals (CIs). In addition, 95% CIs will be presented for the adjusted difference in confirmed clinical response between treatment arms, where adjusted difference will be calculated using stratified CMH (Cochran-Mantel-Haenszel) method using age group as the stratified variable.

7.4.1.2 Subgroup Analysis

In general, efficacy data will be summarized by treatment group and age group using the classifications given in section 7

The proportion of subjects with confirmed clinical response at EOT+2 days and the associated exact 95% CIs will further be provided by treatment arm within age group. Further subgroup analyses, if deemed appropriate, will be described in the SAP.

7.4.2 Analysis of Secondary Endpoints

In general, summaries for the secondary efficacy endpoints will be provided for the FAS population overall and by age group. Definition of secondary efficacy endpoints can be found in section 2.3.2

For the secondary efficacy variables,

- Sustained clinical response 14 days after Confirmation Clinical Response (EOT +16 days)
- Sustained clinical response at the EOS (EOT +30 days)

the response rates and their difference between the two treatments will be calculated along with corresponding 95% CIs in the same manner as for the primary efficacy endpoint.

For the variable,

- Recurrence of CDAD

the incidence rate of recurrence in subjects with confirmed clinical response at EOT+2 days and the difference in incidence rates between treatments will be calculated along with 95% CIs in the same manner as for the primary efficacy endpoint.

For the variables,

- Time (hours) to resolution of diarrhea, measured from first dose of study medication,
- Time (days) to recurrence of CDAD (only for subjects with confirmed clinical response)

descriptive statistics by treatment arm will be provided and the survival functions in both treatment arms will be estimated using the Kaplan-Meier method and displayed graphically (with 95% CIs). Quartile estimates for the time to event and corresponding two-sided 95% CIs will be computed for both treatment arms. For these two time-to-event variables, no further stratification by age group is intended but may be done if deemed appropriate.

7.4.2.1 Other Analyses - Palatability

Results from the assessments of palatability in subjects receiving fidaxomicin oral suspension on Day 1 and on Day 7 (±1 day) will be summarized by means of a frequency table, stratified by treatment arm, age group and study day.

7.5 Analysis of Safety

Safety data will be summarized in a descriptive manner for the SAF, generally grouped by treatment arm. Stratification by age group might be done where deemed appropriate.

7.5.1 Adverse Events

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). An AE starting or a condition existing pre-treatment that worsens after first study drug intake

will be considered as treatment emergent AE (TEAE). The number and percentage of TEAEs, SAEs, TEAEs leading to discontinuation, and TEAEs related to study drug will be summarized by system organ class, preferred term and treatment arm. The number and percentage of TEAEs by severity will also be summarized. All AEs will be listed.

Further details will be provided in the SAP.

7.5.2 Laboratory Assessments

For quantitative laboratory measurements descriptive statistics will be used to summarize results and change from baseline by treatment arm and time point. Shifts relative to normal ranges from baseline to each time point during treatment period in lab tests will also be tabulated. Laboratory data will be displayed in listings.

7.5.3 Vital Signs

Descriptive statistics will be used to summarize vital sign results and changes from baseline (change only for blood pressure and pulse rate) by treatment arm and time point (visit). Vital signs data will be displayed in listings.

7.5.4 ECGs

The 12-lead ECG results (from the central readings) will be summarized by treatment arm and time point (visit).

7.6 Analysis of Pharmacokinetics

7.6.1 Test Drug Concentration

Descriptive statistics (incl. numbers of values below level of quantification) will be provided for plasma concentrations of fidaxomicin and its main metabolite OP-1118 by time point (pre-dose and 1 to 5 hours post dose [the morning or evening dose]) and for the fecal concentration of fidaxomicin and OP-1118 (assessed on Day 5 or after).

These summaries will be provided for the PKAS (only for treatment arm fidaxomicin), overall and by age group and once by formulation with nesting of the two strata being done when deemed reasonable.

7.7 Analysis of Pharmacodynamics

Not applicable.

7.8 Protocol Deviations and Other Analyses

7.8.1 Protocol Deviations

Protocol deviations as defined in Section 8.1.6. Protocol Deviations will be summarized for all randomized subjects by treatment arm and total as well as by site. A data listing will be provided by site and subject.

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.

Further details will be provided in the SAP.

7.8.2 Medical History

Medical history will be summarized coded using MedDRA and summarized by system organ class and preferred term.

7.8.3 Previous and Concomitant Medication

Previous and concomitant medication will be coded using World Health Organization Drug Reference List (WHODRL) and Anatomical Therapeutic Chemical (ATC) classification system and will be summarized by ATC 2nd and 4th levels.

7.8.4 Diagnosis of the Target Disease

Appropriate descriptive summaries will be provided for the data collected in context of diagnosis of the target disease. Details will be provided in the SAP.

7.8.5 Analysis of Exploratory Endpoints

7.8.5.1 [redacted]

[redacted]

7.8.6 Treatment Compliance

Treatment compliance rates and number (%) of subjects who were treatment compliant (as defined in section 5.1.4 will be summarized by treatment arm and age group.

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

No formal interim analysis is planned. If required for regulatory submissions, interim analyses may be carried out (e.g. to present the results of some age strata while recruitment is ongoing in other strata). If so, details of the analysis and for preserving the blind will be included in the analysis plan.

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

Every effort should be made to follow-up subjects and to obtain data – especially on the important endpoints of confirmed clinical response (EOT+2) and recurrence/sustained clinical response (to EOS).

The following imputation of missing information for the assessment of clinical response and recurrence/sustained response is foreseen (taking into consideration applicable visit windows):

- Missing information for efficacy variables of confirmed clinical response and sustained clinical response will be estimated using the multiply imputation procedure which will replace each missing value with a set of plausible values as predictions from logistic regression based on bowel movement data, and previous CDAD experience. Each multiply imputed data set will then be analyzed and the methodology combines the results from all datasets to give a single final analysis that takes into account the uncertainty of the imputed values.

Sensitivity analyses for efficacy endpoints will be described in the SAP.

As a general principle, no imputation of other missing data will be done (e.g. labs, vital signs, ECGs, etc). Exceptions are the start and stop dates of AEs and concomitant medication. The imputed dates will be used to allocate the concomitant medication and AEs to a study period, in order 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.

Visit windows for the assessments planned after the EOT are defined in the Schedule of Assessments.

8 OPERATIONAL AND ADMINISTRATIVE CONSIDERATIONS

8.1 Procedure for Clinical Study Quality Control

8.1.1 Data Collection

The investigator or designee will enter data collected using an Electronic Data Capture (EDC) system. All data on each subject generated according to the protocol must be recorded continuously in an eCRF designed according to the protocol**.** The investigator or site designee is responsible to ensure that all data in the eCRFs and queries are accurate and complete and that all entries are verifiable with source documents. These documents should be appropriately maintained by the site.

For data that can potentially unblind staff (e.g., drug dispensing, drug intake, drug returned, palatability, drug concentration blood samples) a separate database will be set up, only accessible for unblinded site staff and the unblinded monitor.

The monitor should verify the data in the eCRFs with source documents and confirm that there are no inconsistencies between them.

Laboratory tests are performed at local laboratory. The data will be entered in the eCRF.

The ECGs are done locally at site and all original ECG traces are to be shipped to central ECG reader for central ECG reading. Central ECG read data will be transferred electronically to the Sponsor.

For Screen failures the demographic data, reason for failing, informed consent, inclusion and exclusion criteria and AEs will be collected in the eCRF.

Palatability scale will be completed by the subject/parent/legal guardian on paper. Unblinded site staff should review the scale data while the subject/parent legal guardian is at the site. The unblinded site staff will enter the subject questionnaire data directly into the EDC system.

8.1.2 Specification of Source Documents

Source data must be available at the site to document the existence of the study subjects and to substantiate the integrity of study data collected. Source data must include the original documents relating to the study, as well as the medical treatment and medical history of the subject.

The following information should be included in the source medical records:

- Demographic data (age, sex, race, ethnicity (if permitted), height and body weight)
- Inclusion and exclusion criteria details
- Participation in study and original signed and dated informed consent forms
- Visit dates
- Medical history and physical examination details
- Key efficacy and safety data, if applicable (as specified in the protocol)
- AEs and concomitant medication
- Results of relevant examinations (e.g., ECG charts, X-ray films etc.)
- Laboratory printouts (if applicable)
- Reason for premature discontinuation (if applicable)
- Randomization number (if applicable)
- Dispensing and return of study drug details

Source documents related to the study drug or treatment allocation will be stored in a separate binder, only accessible for unblinded study staff.

8.1.3 Clinical Study Monitoring

The Sponsor or delegated CRO is responsible for monitoring the clinical study to ensure that subject's human rights, safety, and well-being are protected, that the study is properly conducted in adherence to the current protocol and GCP, and study data reported by the investigator/sub-investigator are accurate and complete and that they are verifiable with study-related records such as source documents. The Sponsor is responsible for assigning study monitor(s) to this study for proper monitoring. They will monitor the study in accordance with planned monitoring procedures.

8.1.4 Direct Access to Source Data/Documents

The investigator and the study site must accept monitoring and auditing by the Sponsor or delegated CRO as well as inspections from the IRB/IEC and relevant regulatory authorities. In these instances, they must provide all study-related records, such as source documents (refer to section 8.1.2 "Specification of Source Documents") when they are requested by the

Sponsor monitors and auditors, the IRB/IEC, or regulatory authorities. The confidentiality of the subject's identities shall be well protected consistent with local and national regulations when the source documents are subject to direct access.

8.1.5 Data Management

Data Management will be coordinated by the Global Data Science department of the Sponsor in accordance with the SOPs for data management. All study specific processes and definitions will be documented by Data Management. eCRF completion will be described in the eCRF instructions. Coding of medical terms and medications will be performed using MedDRA and World Health Organization (WHO) Drug Dictionary respectively.

8.1.6 Protocol Deviations

A protocol deviation is generally an unplanned excursion from the protocol that is not implemented or intended as a systematic change. The investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol and must protect the rights, safety, and welfare of subjects. The investigator should not implement any deviation from, or changes of, the protocol, unless it is necessary to eliminate an immediate hazard to trial subjects.

A protocol waiver is a documented prospective approval of a request from an investigator to deviate from the protocol. Protocol waivers are strictly prohibited.

For the purposes of this protocol, deviations requiring notification to Sponsor are defined as any subject who:

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

When a deviation from the protocol is identified for an individual subject, the investigator or designee must ensure the Sponsor is notified. The Sponsor will follow-up with the investigator, as applicable, to assess the deviation and the possible impact to the safety and / or efficacy of the subject to determine subject continuation in the study.

If a deviation impacts the safety of a subject, the investigator must contact the Sponsor immediately.

The investigator will also assure that deviations meeting IRB/IEC and applicable regulatory authorities' criteria are documented and communicated appropriately. All documentation and communications to the IRB/IEC and applicable regulatory authorities will be provided to the Sponsor and maintained within the Trial Master File (TMF).

NOTE: Other deviations outside of the categories defined above that are required to be reported by the IRB/IEC in accordance with local requirements will be reported, as applicable.

8.1.7 End of Trial in All Participating Countries

The end of trial in all participating countries is defined as the Last Subject's Last visit.

8.2 Ethics and Protection of Subject Confidentiality

8.2.1 Institutional Review Board (IRB) / Independent Ethics Committee (IEC) / Competent Authorities (CA)

Good Clinical Practice (GCP) requires that the clinical protocol, any protocol amendments, the Investigator's Brochure, the informed consent and all other forms of subject information related to the study (e.g., advertisements used to recruit subjects) and any other necessary documents be reviewed by an IEC/IRB. The IEC/IRB will review the ethical, scientific and medical appropriateness of the study before it is conducted. IEC/IRB approval of the protocol, informed consent and subject information and/or advertising, as relevant, will be obtained prior to the authorization of drug shipment to a study site.

Any substantial amendments to the protocol will require IEC/IRB approval prior to implementation of the changes made to the study design at the site. The investigator will be required to submit, maintain and archive study essential documents according to ICH GCP.

Any serious adverse events that meet reporting criteria, as dictated by local regulations, will be reported to both responsible Ethics Committees and Regulatory Agencies, as required. During the conduct of the study, the investigator should promptly provide written reports (e.g., ICH Expedited Reports, and any additional reports required by local regulations) to the IEC/IRB of any changes that affect the conduct of the study and/or increase the risk to subjects. Written documentation of the submission to the IEC/IRB should also be provided to Sponsor.

If required by local regulations, the investigator shall make accurate and adequate written progress reports to the IEC/IRB at appropriate intervals, not exceeding one year. The investigator shall make an accurate and adequate final report to the IRB/IEC within one year after last subject out (LSO) or termination of the study.

8.2.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, ICH guidelines, applicable regulations and guidelines governing clinical study conduct and the ethical principles that have their origin in the Declaration of Helsinki.

8.2.3 Informed Consent of Subjects

8.2.3.1 Subject Information and Consent

The investigator or his/her representative will explain the nature of the study to the subject or his/her guardian(s) or legal representative(s), and answer all questions regarding this study. For this pediatric study next to Information Sheets and Consent Forms, Assent forms for subjects (according to applicable local regulations) will be prepared. Prior to any study-related screening procedures being performed on the subject, the informed consent statement will be reviewed

and signed and dated by the subject or his/her guardian(s) or legal representative(s), the person who administered the informed consent and any other signatories according to local requirements. A copy of the signed informed consent/assent form will be given to the subject or his/her guardian(s) / legal representative(s) and the original will be placed in the subject's medical record. An entry must also be made in the subject's dated source documents to confirm that informed consent was obtained prior to any study-related procedures and that the subject / his/her guardian(s) / legal representative(s) received a signed copy.

The signed consent/assent forms will be retained by the investigator and made available (for review only) to the study monitor and auditor regulatory authorities and other applicable individuals upon request.

8.2.3.2 Supply of New and Important Information Influencing the Subject's Consent and Revision of the Written Information

The investigator or his/her representative will immediately inform the subject/his/her guardian(s)/legal representative(s) orally whenever new information becomes available that may be relevant to the subject's consent or may influence the subject's/his/her guardian(s)/ legal representative(s) willingness to continue to participate in the study (e.g., report of serious drug adverse drug reaction). The communication must be documented in the subject's medical records and must document whether the subject/his/her guardian(s)/legal representative(s) is willing to remain in the study or not.

The investigator must update their ICF/assent and submit it for approval to the IRB/IEC. The investigator or his/her representative must obtain written informed consent from the subject/ his/her guardian(s)/legal representative(s) on all updated ICFs throughout their participation in the study. The investigator or his/her designee must re-consent subjects with the updated ICF/assent even if relevant information was provided orally. The investigator or his/her representative who obtained the written informed consent and the subject/his/her guardian(s)/ legal representative(s) should sign and date the informed consent form. A copy of the signed informed consent/assent form will be given to the subject/his/her guardian(s)/legal representative(s) and the original will be placed in the subject's medical record. An entry must be made in the subject's records documenting the re-consent process.

8.2.4 Subject Confidentiality

Individual subject medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited. Such medical information may be given only after approval of the subject to the subject's physician or to other appropriate medical personnel responsible for the subject's well-being.

The Sponsor shall not disclose any confidential information on subjects obtained during the performance of their duties in the clinical study without justifiable reasons.

The Sponsor affirms the subject's right to protection against invasion of privacy. Only a subject identification number and/or initials will identify subject data retrieved by the Sponsor. However, the Sponsor requires the investigator to permit the Sponsor, Sponsor's

representative(s), the IRB/IEC and when necessary, representatives of the regulatory health authorities to review and/or to copy any medical records relevant to the study.

The Sponsor will ensure that the use and disclosure of protected health information (PHI) obtained during a research study complies with the federal and/or regional legislation related to the privacy and protection of personal information (i.e. HIPAA).

8.3 Administrative Matters

8.3.1 Arrangement for Use of Information and Publication of the Clinical Study

Information concerning the study drug, patent applications, processes, unpublished scientific data, the Investigator's Brochure and other pertinent information is confidential and remains the property of the Sponsor. Details should be disclosed only to the persons involved in the approval or conduct of the study. The investigator may use this information for the purpose of the study only. It is understood by the investigator that the Sponsor will use the information obtained during the clinical study in connection with the development of the drug and therefore may disclose it as required to other clinical investigators or to regulatory agencies. In order to allow for the use of the information derived from this clinical study, the investigator understands that he/she has an obligation to provide the Sponsor with all data obtained during the study.

Publication of the study results is discussed in the Clinical Study Agreement.

8.3.2 Documents and Records Related to the Clinical Study

The investigator will archive all study data (e.g., Subject Identification Code List, source data, eCRFs, and Investigator's File) and relevant correspondence. These documents are to be kept on file for the appropriate term determined by local regulation (for US sites, two years after approval of the NDA or discontinuation of the IND). The Sponsor will notify the site/investigator if the NDA/MAA is approved or if the IND/IMPD is discontinued. The investigator agrees to obtain the Sponsor's agreement prior to disposal, moving, or transferring of any study-related records. The Sponsor will archive and retain all documents pertaining to the study according to local regulations.

Data generated by the methods described in the protocol will be recorded in the subjects' medical records and/or study progress notes. All data will be entered on the eCRFs supplied for each subject.

The documents of the DSMB shall be retained by the Sponsor.

8.3.3 Protocol Amendment and/or Revision

Any changes to the study that arise after approval of the protocol must be documented as protocol amendments: substantial amendments and/or non-substantial amendments. Depending on the nature of the amendment, IRB/IEC, Competent Authority (CA) approval or notification may be required. The changes will become effective only after the approval of the Sponsor, the investigator, the regulatory authority, and the IRB/IEC (if applicable).

Amendments to this protocol must be signed by the Sponsor and the investigator. Written verification of IRB/IEC approval will be obtained before any amendment is implemented which affects subject safety or the evaluation of safety, and/or efficacy. Modifications to the protocol that are administrative in nature do not require IRB/IEC approval, but will be submitted to the IRB/IEC for their information, if required by local regulations.

If there are changes to the Informed Consent, written verification of IRB/IEC approval must be forwarded to the Sponsor. An approved copy of the new Informed Consent must also be forwarded to the Sponsor.

8.3.4 Insurance of Subjects and Others

The Sponsor has covered this study by means of an insurance of the study according to national requirements. The name and address of the relevant insurance company, the certificate of insurance, the policy number and the sum insured are provided in the Investigator's File.

8.3.5 Signatory Investigator for Clinical Study Report

ICH E3 guidelines recommend and EU Directive 2001/83/EC requires that a final study report which forms part of a marketing authorization application be signed by the representative for the Coordinating Investigator(s) or the Principal Investigator(s). The representative for the Coordinating Investigator (s) or the Principal Investigator(s) will have the responsibility to review the final study results to confirm to the best of his/her knowledge it accurately describes the conduct and results of the study. The representative for Coordinating Investigator(s) or the Principal Investigator(s) will be selected from the participating investigators by the Sponsor prior to database lock.

9 QUALITY ASSURANCE

The Sponsor is implementing and maintaining quality assurance and quality control systems with written SOPs to ensure that trials are conducted and data are generated, documented, recorded, and reported in compliance with the protocol, GCP, and applicable regulatory requirement(s).

The Sponsor or Sponsor's designee may arrange to audit the clinical study at any or all investigational sites and facilities. The audit may include on-site review of regulatory documents, case report forms, and source documents. Direct access to these documents will be required by the auditors.

10 STUDY ORGANIZATION

10.1 Data and Safety Monitoring Board (DSMB)

A DSMB will be set up for this study in order to monitor on periodic basis the safety of the study subjects. The board for this study will consist of members independent of the Sponsor and the conduct of the study. The board will advise the Sponsor on safety aspects of the study and based on this information, continuation of the trial. The procedures and scope of the board are defined in a separate document, the DSMB Charter.

10.2 Other Study Organization

Not applicable.

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12 APPENDICES

12.1 List of Excluded Concomitant Medications

Part A
Prohibited Medications

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.

This list is not exhaustive. In case of doubt, the investigator should contact the local study monitor.

CDAD treatment
Oral vancomycin
Metronidazole
Oral bacitracin
Fusidic acid
Rifaximin
Nitazoxanide
Linezolid
Rifampicin
Fecal transplantation

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 subject has been taking this medication on a long-term basis on the same dose and will continue with the same dose during the study.

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

This list is not exhaustive. In case of doubt, the investigator should contact the local study monitor.

Drugs to that could affect peristalsis
Loperamide
Codeine
Morphine
Pethidine
Fentanyl
Methadone
Tramadol
Other opioids

12.2 Liver Safety Monitoring and Assessment

Any subject enrolled in a clinical study with active drug therapy and reveals an increase of serum aminotransferases (AT) to > 3 × ULN, or bilirubin > 2 × ULN, should undergo detailed testing for liver enzymes (including at least ALT, AST, ALP, and Total Bilirubin [TBL]). Testing should be repeated within 48-72 hours of notification of the test results. Subjects should be asked if they have any symptoms suggestive of hepatobiliary dysfunction.

Definition of Liver Abnormalities

Confirmed abnormalities will be characterized as moderate and severe where ULN:

	ALT or AST		Total Bilirubin
Moderate	> 3× ULN	Or	> 2× ULN
Severe*	> 3× ULN	and	> 2× ULN

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

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

The investigator may determine that abnormal liver function results, other than as described above, may qualify as moderate or severe abnormalities and require additional monitoring and follow-up.

Follow-up Procedures

Confirmed moderate and severe abnormalities in hepatic functions should be thoroughly characterized by obtaining appropriate expert consultations, detailed pertinent history, physical examination and laboratory tests. The site should complete the Liver Abnormality Case Report Form (LA-CRF) that has been developed globally and can be activated for any study or an appropriate document. Subjects with confirmed abnormal liver function testing should be followed as described below.

Confirmed moderately abnormal LFTs should be repeated 2-3 times weekly then weekly or less if abnormalities stabilize or the study drug has been discontinued and the subject is asymptomatic.

Severe hepatic liver function abnormalities as defined above, in the absence of another etiology, may be considered an important medical event and may be reported as a Serious Adverse Event (SAE). The Sponsor should be contacted and informed of all subjects for whom severe hepatic liver function abnormalities possibly attributable to study drug are observed.

To further assess abnormal hepatic laboratory findings, the investigator is expected to:

- Obtain a more detailed history of symptoms and prior or concurrent diseases. Symptoms and new onset-diseases should be recorded as 'adverse events' on the AE page of the (e)CRF. Illnesses and conditions such as hypotensive events, and decompensated cardiac disease that may lead to secondary liver abnormalities should be noted. Non-alcoholic steatohepatitis (NASH) is seen in obese hyperlipoproteinemic, and/or diabetic patients and may be associated with fluctuating aminotransferase levels. The investigator should ensure that the medical history form captures any illness that pre-dates study enrollment that may be relevant in assessing hepatic function.
- Obtain a history of concomitant drug use (including non-prescription medication, complementary and alternative medications), alcohol use, recreational drug use, and special diets. Medications, including dose, should be entered on the concomitant medication page of the (e)CRF. Information on alcohol, other substance use, and diet should be entered on the LA-CRF or an appropriate document.
- Obtain a history of exposure to environmental chemical agents.
- Based on the subject's history, other testing may be appropriate including:
    - acute viral hepatitis (A,B, C, D, E or other infectious agents)
    - ultrasound or other imaging to assess biliary tract disease
    - other laboratory tests including INR, direct bilirubin
- Consider gastroenterology or hepatology consultations.
- Submit results for any additional testing and possible etiology on the LA-CRF or an appropriate document.

Study Discontinuation

In the absence of an explanation for increased LFT's, such as viral hepatitis, pre-existing or acute liver disease or exposure to other agents associated with liver injury, the subject may be discontinued from the study. The investigator may determine that it is not in the subject's best interest to continue study enrollment. Discontinuation of treatment should be considered if:

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

In addition, if close monitoring for a subject with moderate or severe hepatic laboratory tests is not possible, drug should be discontinued.

*Hy's Law Definition-Drug-induced jaundice caused by hepatocellular injury, without a significant obstructive component, has a high rate of bad outcomes, from 10–50% mortality (or transplant)." The two "requirements" for Hy's Law are: 1) Evidence that a drug can cause hepatocellular-type injury, generally shown by an increase in transaminase elevations higher 3 times the upper limit of normal ("2 x ULN elevations are too common in treated and untreated patients to be discriminating"). 2) Cases of increased bilirubin (at least 2 x ULN) with concurrent transaminase elevations at least 3x ULN and no evidence of intra- or extra-hepatic

bilirubin obstruction (elevated alkaline phosphatase) or Gilbert's syndrome. [Temple R. Hy's law: predicting serious hepatotoxicity. *Pharmacoepidemiol Drug Saf* 2006 Apr;15(4):241-3.]

Reference

Guidance for Industry titled "Drug-Induced Liver Injury: Premarketing Clinical Evaluation" issued by FDA on July 2009.

12.3 Common Serious Adverse Events

For this protocol, there are no SAEs that are exempted from expedited safety reporting.

13 ATTACHMENTS

13.1 Attachment 1: Substantial Amendment 2

I. The purpose of this amendment is:

Substantial Changes
1. Update Inclusion Criteria
DESCRIPTION OF CHANGE:
Inclusion Criteria #2 has been amended to specify that in the United States of America subjects can only be included if aged ≥ 6 months to < 18 years.
RATIONALE:
Following the submission of Substantial Amendment 1 protocol version 2.0, dated 21 November 2014, related to the widening of the inclusion criteria to open the study for inclusion of children from birth onwards, the FDA raised concerns regarding the inclusion of children younger than 6 months. The FDA is concerned that the extension of enrollment to children younger than 6 months of age will result in inclusion of subjects who are colonized rather than infected with *C. difficile*. Because the FDA has granted a waiver for the development of fidaxomicin for children from birth to 6 months due to the concern around diagnosis in this age group, subjects from birth to less than 6 months cannot be included in the 2819-CL-0202 US study sites.

Non-Substantial Changes
1. Update Safety Reporting
DESCRIPTION OF CHANGE:
Removal of safety reporting to delegated CRO for North American sites.
RATIONALE:
Unify the safety reporting process for European and North American sites by using the same delegated CRO.
2. Update Contact Details of Key Sponsor Personnel
DESCRIPTION OF CHANGE:
Update contact details for the clinical research contact.
RATIONALE:
Study manager has been replaced.

3. Update Planned Study Period
DESCRIPTION OF CHANGE:
Planned study period is extended.
RATIONALE:
Planned study period has been extended based on expected recruitment rate.
4. Update Study Design
DESCRIPTION OF CHANGE:
1) Revision is made to investigate subjects from birth instead of ≥ 6 months, with the exception of the USA. 2) Revision is made to subjects aged ≥ 6 years instead from birth to receive fidaxomicin tablets.
RATIONALE:
1) Subjects from birth to < 18 years of will be investigated, with the exception of the USA. 2) Only subjects aged ≥ 6 years to < 18 years will be randomized to receive fidaxomicin tablets. Error was identified and corrected.
5. Update Concomitant Treatments
DESCRIPTION OF CHANGE:
To include the most recent use of fidaxomicin or any macrolide antibiotic to be recorded in the eCRF.
RATIONALE:
Previous exposure to fidaxomicin or any macrolide antibiotic is considered important information in the event of hypersensitivity to fidaxomicin during the study, irrespective of how long ago the prior exposure occurred.
6. Update Discontinuation of Individual Subject(s)
DESCRIPTION OF CHANGE:
Protocol violation is revised to protocol deviation.
RATIONALE:
Update language to align with current process for protocol deviation.
7. Include instructional text related to reporting certain events as adverse events (AEs) based on local requirements.
DESCRIPTION OF CHANGE:

Include statement related to reporting certain events as AEs based on local requirements in Section 5.5.1, Definition of an Adverse Event (AE).
RATIONALE:
Based on local requirements, certain events that occur during a subject's participation in the clinical trial may be reported as adverse events or expedited as serious adverse events. Investigators will be responsible for reporting these events as required in the eCRFs as applicable.

8. Include other minor administrative-type corrections
DESCRIPTION OF CHANGE:
Corrections of mis-spellings, format, etc. through-out the protocol.
RATIONALE:
For accuracy throughout the protocol.

II. Amendment Summary of Changes: Substantial

IV Synopsis and 3 Study Population *Inclusion/Exclusion Criteria, Inclusion & 3.2 Inclusion Criteria*
WAS:
2. Male and female subjects aged from birth to < 18 years.
IS AMENDED TO:
2. Male and female subjects aged from birth to < 18 years. **Note that in the United States of America subjects can only be included if aged ≥ 6 months to < 18 years.**

IV Synopsis *Study Design Overview*
WAS:
This multicenter, investigator-blind, randomized parallel group study will 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 subjects aged ≥ 6 months to < 18 years with confirmed CDAD.
IS AMENDED TO:
This multicenter, investigator-blind, randomized parallel group study will 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 subjects **from birth** ~~aged ≥ 6 months~~ to < 18 years **of age** with confirmed CDAD. **Note that in the United States of America subjects can only be included if aged ≥ 6 months to < 18 years.**

Study Design Overview
WAS:
Subjects from birth to < 18 years of age will be randomized to receive a 200 mg fidaxomicin tablet 2 times daily for 10 days, or a 125 mg vancomycin capsule 4 times daily for 10 days. If a subject aged ≥ 6 years to <18 years is unable to swallow tablets or capsules, the investigator can decide to give fidaxomicin oral suspension, at a dose of 400 mg/day, or vancomycin oral liquid at a dose of 500 mg/day.
IS AMENDED TO:
Subjects **aged ≥ 6 years** ~~from birth~~ to < 18 years will be randomized to receive a 200 mg fidaxomicin tablet 2 times daily for 10 days, or a 125 mg vancomycin capsule 4 times daily for 10 days. If a subject aged ≥ 6 years to <18 years is unable to swallow tablets or capsules, the investigator can decide to give fidaxomicin oral suspension, at a dose of 400 mg/day, or vancomycin oral liquid at a dose of 500 mg/day.
2.2 Study Design and Dose Rationale *2.2.1 Study Design*
ADDED:
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 subjects from birth to < 18 years of age with confirmed CDAD. **Note that in the United States of America subjects can only be included if aged ≥ 6 months to < 18 years.**

IIb Amendment Summary of Changes: Non-Substantial

II. CONTACT DETAILS OF KEY SPONSOR'S PERSONNEL *CRO Contact for Reporting of Serious Adverse Events (SAEs)*
DELETED:
Please send the SAE Worksheet to: ~~European sites:~~ [redacted] (Toll-free fax numbers will be provided for each country; the country-specific fax number can be found on the SAE Worksheet fax cover sheet) [redacted] ~~North American sites:~~ [redacted]

5.5 Adverse Events and Other Safety Aspects
5.5.5 Reporting of Serious Adverse Events (SAEs)

DELETED:

The SAE Worksheet should be sent to the delegated CRO:

~~European sites~~

[redacted]

(Toll-free fax numbers will be provided for each country; the country-specific fax number can be found on the SAE Worksheet fax cover sheet)

[redacted]

~~North American sites~~

[redacted]

II. CONTACT DETAILS OF KEY SPONSOR'S PERSONNEL
Clinical Research Contacts

WAS:

[redacted]

Astellas Pharma Europe B.V.

[redacted]

[redacted]

Astellas Pharma Europe B.V.

[redacted]

IS AMENDED TO:

[redacted]

Astellas Pharma B.V.

[redacted]

[redacted]
~~Astellas Pharma Europe B.V.~~
[redacted]
Astellas Pharma Europe B.V.
[redacted]

IV Synopsis *Planned Study Period*
WAS:
Planned Study Period: From 3Q 2014 to 1Q 2016
IS AMENDED TO:
Planned Study Period: From 3Q 2014 to ~~1Q 2016~~ **2Q 2017**

5 TREATMENTS and EVALUATION *5.1.3 Previous and Concomitant Treatment*
ADDED:
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. **The most recent use of fidaxomicin or any macrolide antibiotic should be recorded in the eCRF, regardless of how long ago it was taken.**

5.5.1 Definition of Adverse Events
ADDED:
Some countries may have additional local requirements for events that are required to be reported as AEs or in an expedited manner similar to an SAE. In these cases, it is the investigator's responsibility to ensure these AEs or other reporting requirements are followed and the information is appropriately recorded in the (e)CRF accordingly.

6 DISCONTINUATION *6.1 Discontinuation of Individual Subjects(s)*
WAS:
• Protocol violation
IS AMENDED TO:
• Protocol ~~violation~~**deviation**

13.2 Attachment 2: Substantial Amendment 1 [21Nov2014]

I. The purpose of this amendment is:

To describe substantial change to the study population following the EMA decision (P/0264/2014) dated 03 Oct 2014 on the acceptance of a modification of the agreed Paediatric Investigational Plan (PIP) for fidaxomicin to open the study for subjects from birth onwards.

To include non-substantial changes (e.g., administrative changes, clarifications, additions). This amendment is considered substantial. The non-substantial changes however, will be implemented once submitted.

Substantial Changes
1. Update of Age Ranges to Include Subjects from birth onwards
DESCRIPTION OF CHANGE:
Throughout the protocol, the age ranges '< 6 months of age' are changed to 'from birth'.
RATIONALE:
The age ranges are updated following the EMA decision (P/0264/2014) dated 03 Oct 2014 on the acceptance of a modification of the agreed Paediatric Investigational Plan (PIP) for fidaxomicin.

The non-substantial changes mentioned below do not meet any of the criteria for a substantial amendment, as they have no impact on the safety, or physical or mental integrity of the clinical trial participants or the scientific value of the study.

Non-Substantial Changes
2. Update Contact Details of Key Sponsor Personnel
DESCRIPTION OF CHANGE:
1) CRO contact for reporting of Serious Adverse Events was updated 2) Updated contact details of Clinical Research Contact
RATIONALE:
1) Information is updated to reflect the SAE reporting process in European and North American sites 2) New study manager was added to the study team
3. Update List of Abbreviations
DESCRIPTION OF CHANGE:
1) Removed abbreviation for Astellas Bioanalysis-Europe 2) Added abbreviation for Intent To Treat

RATIONALE:
1) Abbreviation for Astellas Bioanalysis-Europe is no longer used 2) Statistical methodology section has been updated
4. Update Definition of Key Study Terms
DESCRIPTION OF CHANGE:
TC is added to End of Study definition
RATIONALE:
Addition is made to align with Table 1 Schedule of Assessments
5. Update Study Objectives
DESCRIPTION OF CHANGE:
The term palatability is added
RATIONALE:
Palatability is added for clarification and consistency
6. Update Study Design / Planned Total Number of Study Centers and Location(s)
DESCRIPTION OF CHANGE:
Number of study sites is updated to ~65 to 80 sites
RATIONALE:
Number of study sites is updated according to the current situation
7. Update Secondary Endpoints
DESCRIPTION OF CHANGE:
1) Palatability is moved from exploratory endpoint to secondary endpoint 2) [redacted]
RATIONALE:
1) Palatability is moved from exploratory endpoint to secondary endpoint, to align with protocol study objectives and protocol consistency. 2) [redacted]
8. Update Statistical Methodology
DESCRIPTION OF CHANGE:
1) Intent to Treat (ITT) added to the analysis sets

2) Full Analysis Set (FAS) text updated 3) Added wording to Analysis of Primary Endpoint 4) Method changed to exact 5) The primary analysis method is modified 6) Subgroup Analysis is modified 7) Additional Efficacy Analyses is added 8) Palatability is removed from the Analysis of Exploratory Endpoints and added to the Analysis of Secondary Endpoints 9) Interim Analysis section is updated 10) Handling of missing data has been updated
RATIONALE:
1) Intent to Treat (ITT) is added to analysis sets, as recommended by the FDA 2) Full Analysis Set (FAS) text updated for clarification 3) Wording added for clarification 4) Method changed to exact to be more accurate 5) The primary analysis method is modified to take into account the stratification to ensure statistical correctness and clarification. 6) Subgroup Analysis is modified to ensure statistical correctness and clarification 7) Additional Efficacy Analyses is added to include and explain ITT analysis 8) Palatability is removed from the Analysis of Exploratory Endpoints and added to the Analysis of Secondary Endpoints, to align with protocol study objectives and protocol consistency 9) Interim Analysis section is updated to allow interim reporting according to regulatory requirements, as it may be necessary to report data for some age groups earlier than others 10) The imputation of missing values has changed to make better use of available data. It uses multiple imputation to make better estimates of the differences between the treatments and the associated variability. Additional changes to the text have been made for clarification
9. Update Schedule of Assessments
DESCRIPTION OF CHANGE:
Table 1 - Schedule of Assessments ‘Follow-up visit’ has been changed to ‘Follow-up TC’
RATIONALE:
Change is made for clarification that this is normally a phone call instead of a visit

10. Update Timeframe for Positive Detection of CDAD
DESCRIPTION OF CHANGE:
Timeframe of a positive detection of CDAD is changed from within 48 hours to within 72 hours prior to randomization
RATIONALE:
The time frame is aligned with the Inclusion criteria of the protocol
11. Update on Concomitant Treatments / Prohibited Medication
DESCRIPTION OF CHANGE:
1) Text on the coadministration of PgP inhibitor is added 2) Section title has been changed to Prohibited Medication and Restricted Medication, and Restricted therapies has been changed to medications permitted with restrictions
RATIONALE:
1) Addition is made to align protocol with the fidaxomicin SmPC 2) Change is made to cover section content and align with Appendix 12.1
12. Update Risk-Benefit Assessment
DESCRIPTION OF CHANGE:
1) Addition made to include text on children < 6 months 2) Text added on hypersensitivity reactions
RATIONALE:
1) Addition is made to make reference to the included age range from birth to < 6 months 2) Addition is made to align protocol with the fidaxomicin SmPC
13. Dose Regimen
DESCRIPTION OF CHANGE:
Weight based dosing instruction of the fidaxomicin oral suspension and the vancomycin oral liquid have been added
RATIONALE:
Weight band dosing is included in the protocol to further clarify weight based dosing based on pragmatic ranges related to comparable safe adult dosages

[redacted]
[redacted]
[redacted]
15. Update Comparative Drug(s)
DESCRIPTION OF CHANGE:
Vancomycin oral solution has been changed to Vancomycin oral liquid
RATIONALE:
Change is made for consistency throughout protocol
16. Update Laboratory Assessments
DESCRIPTION OF CHANGE:
1) Table number has been updated 2) Asterisk has been removed from creatinine 3) Asterisk has been removed from Albumin
RATIONALE:
1) Table number has been updated as new tables were inserted 2) Creatinine is to be measured as Clinical Laboratory test as reporting of Renal laboratory value abnormalities is requested by PRAC assessment of PSUR4 with DLP 26-Nov-2013 3) Change is made to better characterize the severity of the CDAD at baseline
17. Definition of Adverse Events (AEs) / Definition of Serious Adverse Events (SAEs)
DESCRIPTION OF CHANGE:
1) The specified AEs of interest have been updated 2) Lack of efficacy has been added to the special situation events
RATIONALE:
1) Additions are made to align with PBEBR5 of JUL2014, PRAC assessment of PSUR4 with DLP 26-Nov-2013, and for clarification. 2) Lack of efficacy has been added to the special situation events as Lack of efficacy is related to the potential risk of Development of resistance to fidaxomicin and narratives have been requested by PRAC on PSUR4 assessment.

II Amendment Summary of Changes:

Update Contact Details of Key Sponsor Personnel
Page 9, CRO Contact for Reporting of Serious Adverse Events (SAEs), Page 57, 61 Section 5.5.5: Reporting of Serious Adverse Events
ADDED:
Please send the SAE Worksheet to: **European sites:** [redacted] (Toll-free fax numbers will be provided for each country; the country-specific fax number can be found on the SAE Worksheet fax cover sheet) [redacted] **North American sites:** [redacted]
Page 9, Clinical Research Contact:
ADDED:
[redacted] **Astellas Pharma Europe B.V.** [redacted]

Update List of Abbreviations	
Page 10, List of Abbreviations	
DELETED	
~~DDR/DMRL/BA EU~~	~~Drug Discovery Research / Drug Metabolism Research Laboratory / BioAnalysis~~
Page 11, List of Abbreviations	
ADDED:	
ITT Intent to Treat	

Update Definition of Key Study Terms
Page 12, page 13 Definition of Key Study Terms, Page 18 Synopsis, page 40 section 2.3.1, page 41 section 2.3.2
WAS:
Clinical response for subjects aged ≥ 6 months to < 2 years

IS AMENDED TO:
Clinical response for subjects aged **from birth** ~~≥ 6 months~~ to < 2 years
WAS:
Recurrence for subjects aged ≥ 6 months to < 2 years
IS AMENDED TO:
Recurrence for subjects aged **from birth** ~~≥ 6 months~~ to < 2 years
WAS:
Time to resolution of diarrhea (TTROD) for subjects aged ≥ 6 months to < 2 years
IS AMENDED TO:
Time to resolution of diarrhea (TTROD) for subjects aged **from birth** ~~≥ 6 months~~ to < 2 years

Update Definition of Key Study Terms
Page 12 Definition of Key Study Terms
ADDED:
The end of the study is defined as the date of the last subject's last visit**/TC**.

Update Study Objectives
Page 14 Synopsis, Page 38 2.1.1 Study Objectives - Primary
WAS:
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 subjects with Clostridium difficile-associated diarrhea (CDAD) aged ≥ 6 months to < 18 years.
IS AMENDED TO:
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 subjects with Clostridium difficile-associated diarrhea (CDAD) ~~aged~~ **from birth**~~≥ 6 months~~ to < 18 years **of age**.
Page 38 2.1.2 Study Objectives - Secondary
WAS:
The secondary objectives of this study are to investigate the recurrence/sustained clinical response to and safety of fidaxomicin and vancomycin in pediatric subjects with Clostridium difficile-associated diarrhea (CDAD) aged ≥ 6 months to < 18 years, as well as acceptance of the fidaxomicin oral suspension formulation.
IS AMENDED TO:

The secondary objectives of this study are to investigate the recurrence/sustained clinical response to and safety of fidaxomicin and vancomycin in pediatric subjects with Clostridium difficile-associated diarrhea (CDAD) ~~aged~~ **from birth**~~≥ 6 months~~ to < 18 years **of age**, as well as **palatability (**acceptance**)** of the fidaxomicin oral suspension formulation.

Update Study Population
Page 14 Synopsis, Page 43 3.1 Selection of Study Population
WAS:
Male and female subjects aged ≥ 6 months to < 18 years, diagnosed with CDAD confirmed by a positive C. difficile toxin test in stool or positive detection of toxigenic C. difficile in stool.
IS AMENDED TO:
Male and female subjects ~~aged~~ **from birth**~~≥ 6 months~~ to < 18 years **of age**, diagnosed with CDAD confirmed by a positive C. difficile toxin test in stool or positive detection of toxigenic C. difficile in stool.

Update Subjects to be Enrolled
Page 14 Synopsis
WAS:
144 subjects aged ≥ 6 months to < 18 years will be enrolled with at least 24 subjects in each of the following age categories: ≥ 6 months to < 24 months, ≥ 2 years to < 6 years, ≥ 6 years to < 12 years, and ≥ 12 years to < 18 years (the remaining 48 subjects can be enrolled in any of the age groups).
IS AMENDED TO:
144 subjects ~~aged~~ **from birth**~~≥ 6 months~~ to < 18 years **of age** will be enrolled with at least 24 subjects in each of the following age categories: ~~≥ 6 months~~**birth** to < 24 months, ≥ 2 years to < 6 years, ≥ 6 years to < 12 years, and ≥ 12 years to < 18 years (the remaining 48 subjects can be enrolled in any of the age groups).

Update Study Design
Page 14 Synopsis
WAS:
One hundred forty four subjects, stratified by age at enrollment (≥ 6 months to < 24 months, ≥ 2 years to < 6 years, ≥ 6 years to < 12 years, and ≥ 12 years to < 18 years) will be enrolled. Subjects aged ≥ 6 months to < 6 years will be randomized to receive weight based doses of either fidaxomicin oral suspension (32 mg/kg/day with a maximum dose of 400 mg/day, divided in 2 doses) 2 times daily for 10 days, or vancomycin oral liquid (40 mg/kg/day with a maximum dose of 500 mg/day divided in 4 doses) 4 times daily for 10 days. Subjects aged ≥ 6 years to < 18 years will be randomized to receive a 200 mg fidaxomicin tablet 2 times daily for 10 days, or a 125 mg vancomycin capsule 4 times daily for 10 days. If a subject aged ≥ 6 years to <18 years is unable to swallow tablets or capsules, the

investigator can decide to give fidaxomicin oral suspension, at a dose of 400 mg/day, or vancomycin oral liquid at a dose of 500 mg/day.
IS AMENDED TO:
One hundred forty four subjects, stratified by age at enrollment (**birth**~~≥ 6 months~~ to < 24 months, ≥ 2 years to < 6 years, ≥ 6 years to < 12 years, and ≥ 12 years to < 18 years) will be enrolled. Subjects **from birth** ~~aged ≥ 6 months~~ to < 6 years **of age** will be randomized to receive weight based doses of either fidaxomicin oral suspension (32 mg/kg/day with a maximum dose of 400 mg/day, divided in 2 doses) 2 times daily for 10 days, or vancomycin oral liquid (40 mg/kg/day with a maximum dose of 500 mg/day divided in 4 doses) 4 times daily for 10 days. Subjects ~~aged~~ **from birth** ~~≥ 6 years~~ to < 18 years **of age** will be randomized to receive a 200 mg fidaxomicin tablet 2 times daily for 10 days, or a 125 mg vancomycin capsule 4 times daily for 10 days. If a subject aged ≥ 6 years to <18 years is unable to swallow tablets or capsules, the investigator can decide to give fidaxomicin oral suspension, at a dose of 400 mg/day, or vancomycin oral liquid at a dose of 500 mg/day.
Page 38, section 2.2.1
WAS:
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 subjects aged ≥ 6 months and < 18 years with confirmed CDAD. The study will be conducted in North America and Europe across ~50 to 70 sites. A target of one hundred forty four subjects, stratified by age at enrollment (≥ 6 months to < 24 months,
IS AMENDED TO:
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 subjects ~~aged~~ **from birth to** ~~≥ 6 months and~~ < 18 years **of age** with confirmed CDAD. The study will be conducted in North America and Europe across ~**65**~~50~~ to **80**~~70~~ sites. A target of one hundred forty four subjects, stratified by age at enrollment (**from birth**~~≥ 6 months~~ to < 24 months,

Update Inclusion Criteria
Page 16 Synopsis, Page 43 3.2 Inclusion Criteria
WAS:
2. Male and female subjects aged ≥ 6 months to < 18 years. 3. Subject is diagnosed with CDAD according to local diagnostic criteria. As a minimum there must be positive detection, within 72 hours prior to randomization, of either toxin A and/or toxin B in stool or positive detection of toxigenic C. difficile in stool and:

a. Subject ≥ 6 months to < 2 years: watery diarrhea in the 24 hours prior to screening.
IS AMENDED TO:
2. Male and female subjects aged **from birth**~~≥ 6 months~~ to < 18 years. 3. Subject is diagnosed with CDAD according to local diagnostic criteria. As a minimum there must be positive detection, within 72 hours prior to randomization, of either toxin A and/or toxin B in stool or positive detection of toxigenic C. difficile in stool and: a. Subject **from birth**~~≥ 6 months~~ to < 2 years: watery diarrhea in the 24 hours prior to screening.

Update Dose Rationale / Dose Regimen
Page 17 Synopsis, Investigational Product(s)
WAS:
Dose(s): Ages ≥ 6 months to < 6 years: fidaxomicin oral suspension, 32 mg/kg/day with a maximum daily dose of 400 mg, divided in 2 doses per day.
IS AMENDED TO:
Dose(s): ~~Ages~~ **From birth** ~~≥ 6 months~~ to < 6 years **of age**: fidaxomicin oral suspension, 32 mg/kg/day with a maximum daily dose of 400 mg, divided in 2 doses per day.
Page 17 Synopsis, Comparative Drug(s)
WAS:
Dose(s): Ages ≥ 6 months to < 6 years: vancomycin oral liquid 40 mg/kg/day with a maximum daily dose of 500 mg, divided in 4 doses per day.
IS AMENDED TO:
Dose(s): ~~Ages~~ **From birth** ~~≥ 6 months~~ to < 6 years **of age**: vancomycin oral liquid 40 mg/kg/day with a maximum daily dose of 500 mg, divided in 4 doses per day.
Page 40, section 2.2.2
WAS:
Subjects aged ≥ 6 years to < 18 years will be randomized to receive either 400 mg daily dose of fidaxomicin or 500 mg daily dose of vancomycin and subjects aged ≥ 6 months to < 6 years will be randomized to receive weight based doses of either fidaxomicin oral suspension or vancomycin oral liquid.
IS AMENDED TO:

Subjects aged ≥ 6 years to < 18 years will be randomized to receive either 400 mg daily dose of fidaxomicin or 500 mg daily dose of vancomycin and subjects ~~aged~~ **from birth**~~≥ 6 months~~ to < 6 years of age will be randomized to receive weight based doses of either fidaxomicin oral suspension or vancomycin oral liquid.
Page 40, section 2.2.2
ADDED:
Please refer to 5.1.1 Table 3B weight based dosing instruction of the vancomycin oral liquid.
Page 40, section 2.2.2
ADDED:
Please refer to 5.1.1 Table 3A weight based dosing instruction of the fidaxomicin oral suspension.
Page 45, section 4.1.2
WAS:
Vancomycin oral liquid is supplied as powder for oral solution. A separate box will be provided with ancillaries for preparation of the oral solution. Sweet syrups may be added to the solution to improve the taste of the oral administration. [Vancomycin Hospira powder for oral solution and for solution for infusion, Hospira SpA, Italian SmPC]. SyrSpend will be provided to be used as sweet syrup for the vancomycin oral liquid. A pharmacy manual will be provided for the preparation of the vancomycin oral solution.
IS AMENDED TO:
Vancomycin oral liquid is supplied as powder for oral ~~solution~~**liquid**. A separate box will be provided with ancillaries for preparation of the oral ~~solution~~**liquid**. Sweet syrups may be added to the ~~solution~~ **liquid** to improve the taste of the oral administration. [Vancomycin Hospira powder for oral solution and for solution for infusion, Hospira SpA, Italian SmPC]. SyrSpend will be provided to be used as sweet syrup for the vancomycin oral liquid. A pharmacy manual will be provided for the preparation of the vancomycin oral ~~solution~~**liquid**.
Page 48, section 5.1.1
WAS:
Subjects randomized to the fidaxomicin treatment arm, aged ≥ 6 months to < 6 years will be administered fidaxomicin oral suspension, 32 mg/kg/day with a maximum dose of 400 mg/day, divided in 2 doses/day for 10 days and subjects aged ≥ 6 years to < 18 years will receive a fidaxomicin 200 mg tablet, 2 times daily, for 10 days.

IS AMENDED TO:

Subjects randomized to the fidaxomicin treatment arm, ~~aged~~ **from birth**~~≥ 6 months~~ to < 6 years **of age** will be administered fidaxomicin oral suspension, 32 mg/kg/day with a maximum dose of 400 mg/day, divided in 2 doses/day for 10 days **(see Table 3A below)** and subjects aged ≥ 6 years to < 18 years will receive a fidaxomicin 200 mg tablet, 2 times daily, for 10 days.

Table 3A: Weight-based Dosing Instruction of the Fidaxomicin Oral Suspension

Weight band of patient	**Dose in mg/day (twice daily dosing)**	**mg/dose**	**Volume of fidaxomicin oral suspension to administer**
≤ 3.9 kg	**80 mg**	**40 mg**	**1.0 mL**
4.0-6.9 kg	**160 mg**	**80 mg**	**2.0 mL**
7.0-8.9 kg	**240 mg**	**120 mg**	**3.0 mL**
9.0-12.4 kg	**320 mg**	**160 mg**	**4.0 mL**
≥ 12.5 kg	**400 mg**	**200 mg**	**5.0 mL**

Page 48, section 5.1.1

WAS:

Subjects randomized to the vancomycin treatment arm, aged ≥ 6 months to < 6 years will be administered a vancomycin oral liquid 40 mg/kg/day with a maximum dose of 500 mg/day, divided in 4 doses/day, for 10 days and subjects aged ≥ 6 years to < 18 years will be administered a vancomycin 125 mg capsule, 4 times daily, for 10 days.

IS AMENDED TO:

Subjects randomized to the vancomycin treatment arm, ~~aged~~ **from birth**≥ 6 months to < 6 years **of age** will be administered a vancomycin oral liquid 40 mg/kg/day with a maximum dose of 500 mg/day, divided in 4 doses/day, for 10 days **(see Table 3B below) a**nd subjects aged ≥ 6 years to < 18 years will be administered a vancomycin 125 mg capsule, 4 times daily, for 10 days.

Table 3B: Weight-based Dosing Instruction of the Vancomycin Oral Liquid

Weight band of patient	**Dose in mg/day (four times daily dosing)**	**mg/dose**	**Volume of vancomycin oral liquid to administer**
≤ 3.9 kg	**100 mg**	**25 mg**	**1.0 ml**
4.0-6.9 kg	**200 mg**	**50 mg**	**2.0 ml**
7.0-8.9 kg	**300 mg**	**75 mg**	**3.0 ml**
9.0-12.4 kg	**400 mg**	**100 mg**	**4.0 ml**
≥ 12.5 kg	**500 mg**	**125 mg**	**5.0 ml**

Remove Palatability from Exploratory Endpoints
Page 19 Synopsis
DELETED:
~~**Palatability**~~ • ~~Acceptance of formulation at first administration of study drug and at Day 7 (± 1 day) in all subjects receiving fidaxomicin oral suspension or vancomycin oral liquid.~~
Page 68 Section 7.8.5.2
DELETED:
~~7.8.5.2 Results from the assessments of palatability in subjects receiving fidaxomicin oral suspension on Day 1 and on Day 7 (±1 day) will be summarized by means of a frequency table, stratified by treatment arm, age group and study day.~~

Add Palatability from Exploratory Endpoints to Secondary Endpoints
Page 19 Synopsis
ADDED:
Palatability • **Acceptance of formulation at first administration of study drug and at Day 7 (± 1 day) in all subjects receiving fidaxomicin oral suspension or vancomycin oral liquid.**

[redacted]

Updated Sample Size Justification
Page 20 Synopsis
WAS:
One hundred forty four subjects, stratified by age at enrollment (≥ 6 months to < 24 months, ≥ 2 years to < 6 years, ≥ 6 years to < 12 years, and ≥ 12 years to < 18 years) will be enrolled.
IS AMENDED TO:
One hundred forty four subjects, stratified by age at enrollment (**from birth**~~≥ 6 months~~ to < 24 months, ≥ 2 years to < 6 years, ≥ 6 years to < 12 years, and ≥ 12 years to < 18 years) will be enrolled.

Updated Efficacy
Page 20 Synopsis
WAS:
The proportion of subjects with confirmed clinical response (primary efficacy endpoint) at the confirmation of clinical response (EOT+2 days) will be summarized by treatment arm and age group along with 95% confidence intervals (CIs). In addition, 95% CIs will be presented for the difference in confirmed clinical response between the two treatment arms.
IS AMENDED TO:
The proportion of subjects with confirmed clinical response (primary efficacy endpoint) ~~at the confirmation of clinical response (~~EOT+2 days~~)~~ will be summarized ~~by~~ **within each** treatment arm ~~and~~ **by age group** along with **exact** 95% confidence intervals (CIs). In addition, 95% CIs will be presented for the **adjusted** difference in confirmed clinical response between ~~the two~~ treatment arms, **where adjusted difference will be calculated using stratified CMH (Cochran-Mantel-Haenszel) method using age group as the stratified variable.**
Page 65 section 7.4.1, 7.4.1.1, and 7.4.1.2
WAS:
7.4.1 Analysis of Primary Endpoint 7.4.1.1 Primary Analysis The analysis of the primary efficacy endpoint, confirmed clinical response (see definition in section 2.3.1) will be conducted for the FAS. The proportion of subjects with confirmed clinical response at the confirmation of clinical response (EOT+2 days) will be summarized by treatment arm along with 95% confidence intervals (CIs) according to the Wilson method (without continuity correction). In addition, 95% CIs (according to the Newcombe-Wilson method without continuity correction) will be presented for the difference in clinical response between treatment arms. 7.4.1.2 Subgroup Analysis In general, efficacy data will be summarized by treatment group and age group using the classifications given in section 7. The proportion of subjects with confirmed clinical response and the associated 95% CIs will further be provided by treatment arm within age group. Further subgroup analyses, if deemed appropriate, might be done and will be described in the SAP.
IS AMENDED TO:
7.4.1 Analysis of Primary Endpoint ~~7.4.1~~**The primary endpoint will be the assessment of confirmed clinical response assessed by the investigator at EOT+2. A missing assessment of the primary endpoint will be imputed according to the rules and methods in section 7.10.** 7.4.1.1 Primary Analysis

The analysis of the primary efficacy endpoint, confirmed clinical response (see definition in section 2.3.1) **at EOT+2 days** will be conducted for the FAS.

The proportion of subjects with confirmed clinical response at ~~the confirmation of clinical response (~~EOT+2 days~~)~~ will be summarized ~~by~~ **within each** treatment arm **by age group** along with **exact** 95% confidence intervals (CIs) ~~according to the Wilson method (without continuity correction)~~. In addition, 95% CIs ~~(according to the Newcombe-Wilson method without continuity correction)~~ will be presented for the **adjusted** difference in **confirmed** clinical response between treatment arms**, where adjusted difference will be calculated using stratified CMH (Cochran-Mantel-Haenszel) method using age group as the stratified variable.**

7.4.1.2 Subgroup Analysis

In general, efficacy data will be summarized by treatment group and age group using the classifications given in section 7.

The proportion of subjects with confirmed clinical response **at EOT+2 days** and the associated exact 95% CIs will further be provided by treatment arm within age group. Further subgroup analyses, if deemed appropriate, ~~might be done and~~ will be described in the SAP.

Update Schedule of Assessments
Page 22, 23 Table 1 Schedule of Assessments
WAS:
Follow-up Visit
IS AMENDED TO:
Follow-up ~~Visit~~ **TC**[1]
Page 24 Footnote m
WAS:
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 48 hours prior to randomization, may be used to assess eligibility and a different sample sent to the reference laboratory.
IS AMENDED TO:
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 ~~48~~ **72** hours prior to randomization, may be used to assess eligibility and a different sample sent to the reference laboratory.

Page 61, Section 5.7.1
WAS:
For assessment of inclusion criteria for Screening, a routinely performed local rapid test that was taken after the onset of CDAD and within 48 hours prior to randomization is acceptable.
IS AMENDED TO:
For assessment of inclusion criteria for Screening, a routinely performed local rapid test that was taken after the onset of CDAD and within ~~48~~ **72** hours prior to randomization is acceptable.
Page 25 Footnote s
WAS:
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 3, section 5.4.3. A historical/standard of care samples without parameter(s) indicated with * in the table is acceptable.
IS AMENDED TO:
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 **4**~~3~~, section 5.4.3. A historical/standard of care samples without parameter(s) indicated with * in the table is acceptable.

Update on Concomitant Treatments
Page 34, Section 1.2.2.1
WAS:
Coadministration of cyclosporine with fidaxomicin (Study OPT-80-007) increased the least squares (LS) mean Cmax of fidaxomicin and main metabolite OP-1118 by approximately 4 fold and 10-fold, respectively, compared to fidaxomicin alone. AUC0-t for fidaxomicin and OP-1118 were also increased by cyclosporine, but to a lesser extent (approximately 2-fold and 4-fold, respectively).

IS AMENDED TO:
Coadministration of **the P-glycoprotein inhibitor** cyclosporine with fidaxomicin (Study OPT-80-007) increased the least squares (LS) mean Cmax of fidaxomicin and main metabolite OP-1118 by approximately 4 fold and 10-fold, respectively, compared to fidaxomicin alone. AUC0-t for fidaxomicin and OP-1118 were also increased by cyclosporine, but to a lesser extent (approximately 2-fold and 4-fold, respectively).
Page 50, Section 5.1.3.1 Prohibited Medication and Restricted Medication
ADDED:
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.

Update Risk Benefit Assessment
Page 37, Section 1.4
WAS:
The results of the phase 2A pediatric study (see section 1.2) showed a safety profile consistent with that seen in adults, with gastrointestinal disorders and infections/infestations the commonest AEs. Six subjects developed AEs considered related to study drug none of which were serious. These were tachycardia, constipation, diarrhea, nausea, vomiting, increased body temperature, urticaria, and elevated liver enzymes. There were no safety signals detected by analysis of vital signs, ECG or laboratory data. Fidaxomicin is the first representative in the novel antibacterial class of macrocycles. The current safety data-base consists of a total of 798 patients with mild to moderately severe CDI treated up to 10 days. Based on post-marketing experience since July 2011, the safety profile of fidaxomicin has slightly changed relative to that seen in the Phase III studies.
IS AMENDED TO:
The results of the phase 2A pediatric study **(age: > 6 months- <18 years:** see section 1.2) showed a safety profile consistent with that seen in adults, with gastrointestinal disorders and infections/infestations the commonest AEs. Six subjects developed AEs considered related to study drug none of which were serious. These were tachycardia, constipation, diarrhea, nausea, vomiting, increased body temperature, urticaria, and elevated liver enzymes. There were no safety signals detected by analysis of vital signs, ECG or laboratory data. **Fidaxomicin has not been used in children < 6 months. A 4-week oral repeated-dose toxicity study in juvenile beagle dogs showed no target organ for toxicity after 28 days of dosing up to 200 mg/kg/day fidaxomicin from Post Natal Day 4 (see section 1.2.1), which is the age equivalent to a newborn child.** Fidaxomicin is the first representative in the novel antibacterial class of macrocycles. The current safety data-base consists of a total of 798 patients with mild to moderately severe CDI treated up to 10 days. Based on post-marketing experience since July 2011, the safety profile of fidaxomicin has slightly changed relative to that seen in the Phase III studies. **Some patients with hypersensitivity reactions reported a history of allergy to macrolides.**

Fidaxomicin should be used with caution in patients with a known macrolides allergy (SmPC Dificlir).

Update Prohibited Medication
Page 49, Section 5.1.3.1
WAS:
5.1.3.1 Prohibited Medication See Appendix 12.1 Excluded Concomitant Medications for additional details on prohibited medications and restricted therapies.
IS AMENDED TO:
5.1.3.1Prohibited Medication **and Restricted Medication** See Appendix 12.1 Excluded Concomitant Medications for additional details on prohibited medications and **medications permitted with restrictions**~~restricted therapies~~.

Update Laboratory Assessments
Page 52, Section 5.4.3
WAS:
In Table 3 the laboratory tests that will be performed during the conduct of the study are listed.
IS AMENDED TO:
In Table ~~3~~**4** the laboratory tests that will be performed during the conduct of the study are listed.
Page 53, Table 3, Screening EoT Unscheduled Visit
WAS:
Creatinine*
IS AMENDED TO:
Creatinine~~*~~
Page 54, Section 5.4.3
WAS:
Albumin*
IS AMENDED TO:
Albumin~~*~~

Update Definition of Adverse Events (AEs) / Definition of Serious Adverse Events (SAEs)

Page 55, Section 5.5.1
WAS:
The specified AEs of interest for this study are shown below and will require more extensive collection of information which will be collected in targeted questionnaires: • Development of microbial resistance to fidaxomicin • Hypersensitivity to fidaxomicin • GI hemorrhage • Decreases in WBC, neutrophil counts • Hepatic laboratory value abnormalities • QT-interval prolongation
IS AMENDED TO:
The specified AEs **/ findings** of interest for this study are shown below and ~~will~~ **may** require more extensive collection of information which will be collected in targeted questionnaires: • Development of microbial resistance to fidaxomicin • Hypersensitivity to fidaxomicin • GI hemorrhage • Decreases in WBC, neutrophil **and lymphocyte** counts • Hepatic laboratory value abnormalities • **Renal laboratory value abnormalities** • QT-interval prolongation • **Lack of efficacy / lack of effect / treatment failure**
Page 56, Section 5.5.2
WAS:
Special situation events relevant to the medicinal products administered to the subject as part of the study (e.g., study drug, comparator, background therapy) that may require expedited reporting and/or safety evaluation include, but are not limited to: • Overdose of the medicinal product(s) • Suspected abuse/misuse of the medicinal product(s) • Inadvertent or accidental exposure to the medicinal product(s) • Medication error involving the medicinal product(s) (with or without subject/patient exposure to the Sponsor medicinal product, e.g., name confusion) • Drug-drug interaction All special situations listed above should be especially monitored and reported on a SAE form, even if considered non-serious and regardless whether or not an (S)AE occurred. The above special situation will not be captured on the AE form in the eCRF, instead they will be captured in the dosing and accountability forms within the eCRF. Lack of efficacy will be recorded as part of the study endpoints and will be documented in the clinical study report. Lack of efficacy will not to be recorded/reported as an (S)AE in this study.

IS AMENDED TO:
Special situation events relevant to the medicinal products administered to the subject as part of the study (e.g., study drug, comparator, background therapy) that may require expedited reporting and/or safety evaluation include, but are not limited to: • Overdose of the medicinal product(s) • Suspected abuse/misuse of the medicinal product(s) • Inadvertent or accidental exposure to the medicinal product(s) • Medication error involving the medicinal product(s) (with or without subject/patient exposure to the Sponsor medicinal product, e.g., name confusion) • Drug-drug interaction • **Lack of efficacy** All special situations listed above should be especially monitored and reported on a SAE form, even if considered non-serious and regardless whether or not an (S)AE occurred. The above special situation will not be captured on the AE form in the eCRF, instead they will be captured in the dosing and accountability forms within the eCRF. ~~Lack of efficacy will be recorded as part of the study endpoints and will be documented in the clinical study report. Lack of efficacy will not to be recorded/reported as an (S)AE in this study.~~

Update Naming Astellas Bioanalysis-Europe
Page 60, Section 5.6
WAS:
the Drug Discovery Research / Drug Metabolism Research Laboratory / BioAnalysis (DDR/DMRL/BA)
IS AMENDED TO:
Astellas Bioanalysis-Europe ~~the Drug Discovery Research / Drug Metabolism Research Laboratory / BioAnalysis (DDR/DMRL/BA)~~

Update Palatability Testing
Page 61, Section 5.7.2
WAS:
Palatability will be assessed for all subjects receiving fidaxomicin oral suspension and vancomycin oral liquid (i.e. subjects aged ≥ 6 months to ≤ 6 years
IS AMENDED TO:
Palatability will be assessed for all subjects receiving fidaxomicin oral suspension and vancomycin oral liquid (i.e. subjects from aged**birth** ~~≥ 6 months~~ to ≤ 6 years **of age**

Update Total Amount of Blood
Page 62, Section 5.8
WAS:
Examples of the total amount of blood collected per subject during the course of the study are shown in Table 4. Table 4: Examples of the total amount of blood collected per subject during the course of the study
IS AMENDED TO:
Examples of the total amount of blood collected per subject during the course of the study are shown in Table **5** 4. Table 4 **5**: Examples of the total amount of blood collected per subject during the course of the study

Update Statistical Methodology
Page 64, Section 7
WAS:
In general, data summaries will be presented by treatment arm, by age group (and overall) and time point (as applicable), using the following classifications: Treatment arm: fidaxomicin or vancomycin Age group: ≥ 6 months to < 24 months ≥ 2 years to < 6 years ≥ 6 years to < 12 years ≥ 12 years to < 18 years and overall
IS AMENDED TO:
In general, data summaries will be presented ~~by~~ **within each** treatment arm, by age group (and overall) and time point (as applicable), using the following classifications: Treatment arm: fidaxomicin or vancomycin Age group: **from birth**~~≥ 6 months~~ to < 24 months ≥ 2 years to < 6 years ≥ 6 years to < 12 years ≥ 12 years to < 18 years and overall

Update Sample Size
Page 64, Section 7.1
WAS:
One hundred forty four eligible subjects will be enrolled and randomized to either fidaxomicin or vancomycin in a 2:1 ratio (96 randomized to fidaxomicin and 48 to vancomycin), stratified by age at enrollment (≥ 6 months to < 24 months, ≥ 2 years to < 6 years, ≥ 6 years to < 12 years, and ≥ 12 years to < 18 years).

IS AMENDED TO:
One hundred forty four eligible subjects will be enrolled and randomized to either fidaxomicin or vancomycin in a 2:1 ratio (96 randomized to fidaxomicin and 48 to vancomycin), stratified by age at enrollment (from **birth**~~≥ 6 months~~ to < 24 months, ≥ 2 years to < 6 years, ≥ 6 years to < 12 years, and ≥ 12 years to < 18 years).

Update Analysis Sets
Page 64, Section 7.2
WAS:
The following analysis sets, defined in the following subsections, will be used in the analysis and reporting of this study: • Full Analysis Set (FAS). • Safety Analysis Set (SAF). • Pharmacokinetic Analysis Set (PKAS).
IS AMENDED TO:
The following analysis sets, defined in the following subsections, will be used in the analysis and reporting of this study: • Full Analysis Set (FAS). • Safety Analysis Set (SAF). • Pharmacokinetic Analysis Set (PKAS). • **Intent to Treat (ITT)**
Page 67, Section 7.2.4
ADDED:
7.2.4 Intent to Treat Analysis Set (ITT) **The intent-to-treat (ITT) set consists of all randomized subjects, irrespective of a subject having received a study drug (fidaxomicin or vancomycin) or not. In the ITT, subjects will be allocated to the treatment arm corresponding to the study medication that were randomized to (treatment allocation as randomized). The ITT will be used for efficacy analyses, as well as selected demographic and baseline characteristics when necessary.**

Update Full Analysis Set
Page 66, Section 7.2.1
ADDED:
In the FAS, subjects will be allocated to the treatment arm corresponding to the study medication that were randomized to (treatment allocation as randomized). The FAS will be used for primary and secondary efficacy analyses, as well as selected demographic and baseline characteristics.

Update Analyses
Page 68, Section 7.4.2.1
ADDED:
7.4.2.1 Other Analyses - Palatability **Results from the assessments of palatability in subjects receiving fidaxomicin oral suspension on Day 1 and on Day 7 (±1 day) will be summarized by means of a frequency table, stratified by treatment arm, age group and study day.**

Update Interim Analysis and Handling of Missing Data
Pages 68-69 Section 7.9, Interim Analysis (and Early Discontinuation of the Clinical Study) and 7.10 Handling of Missing Data, Outliers, Visit Windows, and Other Information
WAS:
7.9 Interim Analysis (and Early Discontinuation of the Clinical Study) No formal interim analysis is planned. 7.10 Handling of Missing Data, Outliers, Visit Windows, and Other Information The following imputation of completely missing information for the assessment of clinical response and recurrence is foreseen (taking into consideration applicable visit windows): • Missing information for confirmed clinical response will be classified as clinical failure (no response). • Missing information for sustained clinical response 16 days after the EOT (at Day 26) will be classified as recurrence (= no sustained clinical response), unless data after Day 26 is available that suggests/confirms that clinical response was sustained until Day 26. • Missing information for sustained clinical response 30 days after the EOT (at Day 40) will be classified as recurrence (= no sustained clinical response). Handling of other missing data related to efficacy endpoints will be detailed in the SAP, if deemed appropriate. Sensitivity analyses of efficacy results (with and without imputation) might be necessary and will be described in the SAP. As a general principle, no imputation of other missing data will be done.
IS AMENDED TO:
7.9 Interim Analysis (and Early Discontinuation of the Clinical Study) No formal interim analysis is planned. **If required for regulatory submissions, interim analyses may be carried out (e.g. to present the results of some age strata while recruitment is ongoing in other strata). Is so, details of the analysis and for preserving the blind will be included in the analysis plan.** 7.10 Handling of Missing Data, Outliers, Visit Windows, and Other Information **Every effort should be made to follow-up subjects and to obtain data – especially on the important endpoints of confirmed clinical response (EOT+2) and recurrence / sustained clinical response (to EOS).** The following imputation of ~~completely~~ missing information for the assessment of clinical response and recurrence / **sustained response** is foreseen (taking into consideration

applicable visit windows):

- Missing information for **efficacy variables of** confirmed clinical response **and sustained clinical response** will be **estimated using the multiply imputation procedure which will replace each missing value with a set of plausible values as predictions from logistic regression based on bowel movement data, and previous CDAD experience. Each multiply imputed data set will then be analyzed and the methodology combines the results from all datasets to give a single final analysis that takes into account the uncertainty of the imputed values.** ~~classified as clinical failure (no response).~~
- ~~Missing information for sustained clinical response 16 days after the EOT (at Day 26) will be classified as recurrence (= no sustained clinical response), unless data after Day 26 is available that suggests/confirms that clinical response was sustained until Day 26.~~
- ~~Missing information for sustained clinical response 30 days after the EOT (at Day 40) will be classified as recurrence (= no sustained clinical response).~~

~~Handling of other missing data related to efficacy endpoints will be detailed in the SAP, if deemed appropriate.~~ Sensitivity analyses ~~of~~ **for** efficacy ~~results~~ **endpoints** ~~(with and without imputation) might be necessary and~~ will be described in the SAP.

As a general principle, no imputation of other missing data will be done **(e.g. labs, vital signs, ECGs, etc)**.

14 SPONSOR'S SIGNATURES

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