12 December 2019
EMA/4852/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report on group of an extension of marketing authorisation and an extension of indication variation

Dificlir

International non-proprietary name: fidaxomicin

Procedure No. EMEA/H/C/002087/X/0034/G

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted

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List of abbreviations

ADR	Adverse Drug Reaction
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine aminotransferase
AST	Aspartate transaminase
BCS	Biopharmaceutics classification system
BR	Benefit-Risk
CCR	Confirmed Clinical Response
CDAD	C. difficile-associated diarrhoea
CDI	Clostridium difficile infection
CFU	Colony forming unit
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CMA	Critical Material Attribute
CQA	Critical Quality Attributes
CMA	Critical Material Attribute
DEHP	Bis(2-ethylhexyl) phthalate
DoE	Design of experiments
EC	European Commission
EFD	Embryo-foetal development (study)
EOS	End of Study
EOT	End of Treatment
ERA	Environmental risk assessment
ESCMID	European Society of Clinical Microbiology and Infectious Diseases
EU	European Union
FAS	Full Analysis Set
FDA	Federal Drug Administration
FMEA	Failure Mode and Effect Analysis
Fpen	Market penetrance for PEC estimate
FXM	Fidaxomicin
GCP	Good Clinical Practice
GGT	Gamma-glutamyltransferase
GI	Gastrointestinal
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GVP	Good pharmacovigilance practice
HPLC	High performance liquid chromatography
ICR	Initial Clinical Response
IMP	Investigational medicinal product
INR	International Normalised Ratio
IRT	Interactive response technology
ITT	Intention to Treat
LOQ	Limit of Quantification
LoQ	List of Questions
MAA	Marketing Authorisation Application

MIC	Minimum Inhibitory Concentration
mITT	Modified Intention to Treat
NLT	Not less than
NMT	Not more than
NOAEL	No Observed Adverse Effect Level
NOEC	No Observe Effect Concentration (used in ecotoxicology studies)
NOEL	No Observed Effect Level (used in toxicology studies)
OP-1118	Major active metabolite to fidaxomicin
PD	Pharmacodynamic
PDA	Photo diode array
PDCO	Paediatric Committee
PECSW	Predicted environmental concentration in surface water
Ph.Eur.	European Pharmacopoeia
PIP	Paediatric Investigation Plan
PK	Pharmacokinetic
PKAS	Pharmacokinetic Analysis Set
PL	Package Leaflet
PND	Postnatal day
PP	Per protocol
PSUR	Periodic Safety Update Report
PT	Preferred Term
PUR	Polyurethane
PVC	Polyvinyl chloride
RMP	Risk Management Plan
RQ	Environmental risk quotient
RRT	Relative retention time
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SCR	Sustained clinical response
SD	Standard deviation
SHEA-IDSA	Society for Healthcare Epidemiology of America and the Infectious Disease Society of America
SLS	Sodium lauryl sulfate
SmPC	Summary of Product Characteristics
SOC	System Organ Class
TBL	Total bilirubin
TEAE	Treatment Emergent Adverse Event
TP	Transformation product (in environment)
TTROD	Time to resolution of diarrhoea
UBM	Unformed bowel movement
ULN	Upper limit of normal
US	United States
UV	Ultraviolet
WBC	White Blood Count

1. Background information on the procedure

1.1. Submission of the dossier

Astellas Pharma Europe B.V. submitted on 14 January 2019 a group of variation(s) consisting of extensions of the marketing authorisation and the following variation(s):

Variation(s) requested		**Type**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

Extension application to introduce a new pharmaceutical form associated with new strength (40 mg/ml granules for oral suspension) for paediatric use of Dificlir in children from birth to less than 18 years of age. This is grouped with a type II variation (C.I.6.a) for the film-coated tablet formulation, to include paediatric use of Dificlir in children with body weight of at least 12.5 kg.

The RMP (version 11.0), the labelling and the package leaflet (PL) are updated accordingly.
The PL is also being amended to include a statement that Dificlir is essentially 'sodium-free', in accordance with the Annex to the European Commission guideline on 'Excipients in the labelling and package leaflet of medicinal products for human use'. The details of the local representative of the MAH in the Czech Republic are also updated.

The legal basis for this application refers to:

Article 7.2 of Commission Regulation (EC) No 1234/2008 – Group of variations

Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0062/2018 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0062/2018 was completed.

The PDCO issued an opinion on compliance for the PIP EMEA-000636-PIP01-09-M07

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The MAH did not seek Scientific advice at the CHMP.

The paediatric development programme generally follows the guideline on the evaluation of medicinal products indicated for treatment of bacterial infections addresses paediatric-specific clinical data requirements (EMA/CHMP/187859/2017).

The agreed PIP measures include the development of an age-appropriate oral suspension formulation, three juvenile toxicity studies, and two clinical studies in paediatric patients with *Clostridium difficile* infection. All measures were complete at the time of this submission. The clinical study reports for paediatric clinical studies OPT-80-206 and 2819-CL-0202 (SUNSHINE) have previously been submitted via Article 46 procedures; EMEA/H/C/2087/P46 022 (submitted 10 Sep 2014, CHMP adoption 10 Nov 2014) and EMEA/H/C/2087 P46 024 (submitted 31 Aug 2018, CHMP adoption 15 Nov 2018).

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Filip Josephson Co-Rapporteur: N/A

The application was received by the EMA on	14 January 2019
The procedure started on	30 January 2019
The Rapporteur's first Assessment Report was circulated to all CHMP members on	23 April 2019
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	N/A
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	23 April 2019
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	16 May 2019
The CHMP agreed on the consolidated List of Questions to be sent to the MAH during the meeting on	29 May 2019
The MAH submitted the responses to the CHMP consolidated List of Questions on	15 August 2019
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	17 September 2019
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	03 October 2019
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the MAH on	17 October 2019
The MAH submitted the responses to the CHMP List of Outstanding Issues on	12 November 2019
The Rapporteurs circulated the Joint Assessment Report on the responses to	18 November 2019

the List of Outstanding Issues to all CHMP members on	
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Dificlir on	12 December 2019

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The proposed indication for the granule formulation is treatment of *Clostridium difficile* infections (CDI), also known as *C. difficile*-associated diarrhoea (CDAD), in paediatric patients from birth to < 18 years of age.

In addition, the existing indication for the film-coated tablet formulation is proposed to be modified, to include paediatric patients with a body weight of at least 12.5 kg.

Clostridium difficile has recently been re-classified and the organism officially renamed as *Clostridioides difficile*, which should be used in the indication.

2.1.2. Epidemiology

CDAD is one of the leading courses of nosocomial infections, accounting for approximately 15-35% of cases of antibiotic-associated diarrhoea and 95% of cases of antibiotic-associated pseudomembraneous colitis. A potential cost of CDI per year in the EU of €3 billion has been estimated, assuming an EU population of 457 million.

2.1.3. Aetiology and pathogenesis

C. difficile is a spore-forming, anaerobic, gram-positive rod that produces toxins that cause inflammation of the colon with severe diarrhoea and, in the most serious cases, pseudomembranous colitis, toxic megacolon, perforations of the colon, sepsis and even death.

CDAD is caused by an overgrowth of *C. difficile* in the colon and is the leading cause of infectious nosocomial diarrhoea in industrialized countries. The disease accounts for approximately 20% of cases of antibiotic-associated diarrhoea, 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). Antibiotics commonly linked to CDAD include cephalosporins, fluoroquinolones, clindamycin, ampicillin, and amoxicillin, but almost any antibiotic can cause CDAD. In addition to antibiotics, a number of other risk factors have been identified for CDAD in the paediatric population, including solid organ transplant, gastrostomy tube placement, chronic inflammatory gastrointestinal disease/motility disorders, cystic fibrosis, immunosuppression and previous *C. difficile* infection (Cooperstock, 2013; Sandora et al, 2011).

2.1.4. Clinical presentation and diagnosis

CDAD has historically been considered a disease of adults and not a clinical problem in the paediatric population. The disease has been recognized to be increasing in children and younger adults with a growing proportion of these cases exhibiting the onset of symptoms in the community.

It is unclear whether typical CDAD occurs in children <24 months of age. Infants and young children may harbour and tolerate the presence of *C. difficile* whilst remaining clinically asymptomatic, and may not develop CDAD (Sammons et al, 2013; Khalaf et al, 2012; Jangi & Lamont, 2010; Cerquetti et al, 1995). In neonates the occurrence of positive cultures varies widely, from 4% in Sweden, 11% in France, 25% in the Netherlands, 31% in the United States, 67% in Belgium and 71% in the United Kingdom, with no direct correlation to the presence of diarrhoea (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).

As a possible scientific rationale for the differences in colonization and incidence of CDAD seen in young children compared with 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.

In older children, CDAD is associated with variable diarrheal symptoms. Studies to determine the culture rates of *C. difficile* in faeces in paediatric patients with and without diarrhoea have detected *C. difficile* in up to 27.3% of hospitalized children (Kader et al, 1998), but no apparent association between a positive culture and clinical diagnosis has been established.

Diagnosis of CDAD requires both, clinical signs and symptoms and the detection of *C. difficile* toxin A and/or B in faeces. The definitive diagnosis of CDAD in paediatric patients, in particular young children and infants who are more likely to carry the organism with symptoms, may be complicated by physiological differences in normal stool habit and a high frequency of diarrheal illnesses caused by other pathogens, e.g. rotavirus, which can be incorrectly attributed to *C. difficile* infection. Nor can CDAD diagnosis in the paediatric population be confirmed as correct on the basis of response to treatment, as illness caused by many of these other pathogens will often spontaneously resolve within the same timeframe as the treatment course for CDAD.

2.1.5. Management

Mild cases of CDI may recover after stopping the causative antibiotic therapy, although this approach is often not sufficient for more severe cases.

Oral vancomycin and metronidazole are both approved for the treatment of CDAD in adult and paediatric patients in the EU by oral administration. Both are available in liquid formulations. Orally administered metronidazole is almost completely absorbed, and systemic exposure is associated with adverse effects. Meanwhile, there is growing concern over emerging resistance to vancomycin among other important target pathogens, such as MRSA, with increasing clinical use. The current recommendations for CDAD treatment, endorsed by the recent guidelines of the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and the Society for Healthcare Epidemiology of America and the Infectious Disease Society of America (SHEA-IDSA) state that vancomycin, but not metronidazole, should be used to treat severe cases of CDAD.

C. difficile can persist as spores in the stools leading to frequent recurrences after successful initial treatment in 20-50% of patients.

Fidaxomicin 200 mg tablet PO BD was authorised in the EU for the treatment of CDAD in adults in 2011 (EMEA/H/C/002087). The 200-mg tablet formulation demonstrated non-inferiority to vancomycin in clinical response and superiority in recurrence and sustained clinical response and a similar safety profile to vancomycin in adult Phase 3 studies.

About the product

- A07AA12 Antidiarrheals, intestinal antiinflammatory/antiinfective agents, antibiotics.

  Fidaxomicin is a macrocyclic (macrolide) antibacterial with narrow-spectrum bactericidal activity against *Clostridioides difficile*. Fidaxomicin is bactericidal and acts via inhibition of RNA synthesis by bacterial RNA polymerase at a distinct site from that of other RNA polymerase inhibitors. After oral administration, it is poorly absorbed systemically and therefore exerts its activity in the gastrointestinal tract, which is an advantage in the treatment of CDAD.

  This submission provides data supporting extension of the approved indication to the paediatric population <18 years of age, and extension of the MAA to add a new age-appropriate pharmaceutical form and strength (granules for oral suspension, 40 mg/ml) for use in paediatric patients. The tablet formulation can also be administered to adolescents and older children able to tolerate tablets.

- *Proposed indication:*

  DIFICLIR granules for oral suspension is indicated for the treatment of *Clostridium difficile* infections (CDI) also known as *C. difficile*-associated diarrhoea (CDAD) in paediatric patients from birth to < 18 years of age.

- *Proposed posology: Paediatric population*

  For appropriate dosing in the paediatric population, DIFICLIR granules for oral suspension or DIFICLIR film-coated tablets may be used.

  The recommended dose in paediatric patients weighing at least 12.5 kg is 200 mg (one tablet or 5 ml oral suspension) administered twice daily (once every 12 hours) for 10 days.

  The recommended dose of the oral suspension in paediatric patients, by body weight, to be administered twice daily (once every 12 hours) for 10 days, is presented in the table below.

  Dosing instructions for the oral suspension

Weight band of patient	**Mg per dose (every 12 hours)**	**Volume of fidaxomicin oral suspension (every 12 hours)**
< 4.0 kg	40 mg	1.0 mL
4.0 - < 7.0 kg	80 mg	2.0 mL
7.0 - < 9.0 kg	120 mg	3.0 mL
9.0 - < 12.5 kg	160 mg	4.0 mL
≥ 12.5 kg	200 mg	5.0 mL

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as granules for oral suspension containing 40 mg/ml of fidaxomicin as active substance.

Other ingredients are as follows: cellulose, microcrystalline, sodium starch glycollate, xanthan gum, citric acid, sodium citrate, sodium benzoate (E211), sucralose, and mixed berry flavour

The product is available in an amber glass bottle with a polypropylene child-resistant cap in an aluminium pouch as described in section 6.5 of the SmPC.

2.2.2. Active Substance

Fidaxomicin is a fermentation product produced by the organism *Dactylosporangium aurantiacum*, along with other related substances. The major chemical component is an unsaturated 18-membered macrocycle.

The active substance fidaxomicin has already been assessed in connection with the marketing authorization of Dificlir 200 mg tablets in the centralised procedure (EU/1/11/733/003). The active substance information provided in this application is identical to that approved for Dificlir 200 mg tablets.

2.2.3. Finished Medicinal Product

The finished product is formulated as white to yellowish white granules and is supplied in a 150 mL amber glass bottle with a polypropylene child resistant cap. Each bottle is filled with 7.7 g of the granule formulation that contains 4.4 g of the active ingredient.

The content of the bottle will be reconstituted with 105 mL of water for injection to obtain an oral suspension of 200 mg/5 mL fidaxomicin. The total volume of suspension in the bottle after reconstitution with water for injection is 110 mL. This provides a sufficient volume of the suspension for the period of 10 days of dosing at 200 mg fidaxomicin twice a day with one-day additional dosing.

The finished product is developed as a granule formulation.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards except mixed berry flavour which complies with an in-house specification. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report.

Regarding the finished product, the critical quality attributes (CQAs) were established based on the target product profile. A criterion was set for each CQA as a basis for evaluation for the impact of the attributes of each formulation component on the pharmaceutical properties of the fidaxomicin granules.

A risk assessment was carried out using failure mode effects analysis (FMEA), applying subject matter expertise and prior knowledge to identify potential failure modes for each component in the proposed formulation. In the FMEA, the risks of each component quantity on product CQAs were analysed and evaluated.

This product is an immediate release oral suspension dosage form and a dissolution test method has been developed. As the product is an oral suspension formulation, the basket method (apparatus 1) is not applicable. Therefore, paddle method (apparatus 2), which is commonly used for evaluating dissolution of oral dosage forms, is selected. The dissolution profile is achieved a complete dissolution. Based on the results, the selected paddle method (apparatus 2) is considered suitable for the dissolution test of fidaxomicin oral suspension. The method has been confirmed to have a sufficient discriminatory power regarding different granulation conditions of the finished product. In conclusion, the developed method is deemed suitable for quality control for fidaxomicin oral suspension.

The finished product is manufactured using the unit operations of sizing, granulation, wet sizing, drying, dry sizing and blending. The manufacturing process for the finished is developed to ensure that granules meet the quality specifications and consequently can be manufactured reproducibly and consistently.

A risk analysis based on manufacturing experience was performed using Failure Mode and Effect Analysis (FMEA) to systematically identify processing parameters and their interrelations that could potentially impact with CQAs.

Extensive manufacturing process development studies have indicated that process parameters may impact the CQAs based on risk assessment. It was confirmed that CQAs can be within product specification.

The primary packaging is amber glass bottle with a polypropylene child-resistant cap. The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

The feasibility of administering through an enteral feeding tube was investigated according to the *Quality of medicines questions and answers: Part 2* presented by the European Medicines Agency. This study addressed ease of administration, tube blocking, dose recovery, flush volumes and physicochemical compatibility. The study showed positive results by using 4-8 Fr tubes with flush volumes of 1-4 mL purified water. This study was performed using tubes made of PVC (DEHP free) or PUR and each material showed sufficient physicochemical compatibility. It was concluded that administration of the oral suspension through an enteral feeding tube is feasible

Manufacture of the product and process controls

The manufacturing process consists of 7 main steps: sizing, granulation, wet sizing, drying, dry sizing, blending, and bottle filling. The process is considered to be a standard manufacturing process.

A process validation scheme has been provided and considered satisfactory. All the relevant manufacturing steps will be validated before commercial launch. The in-process controls are adequate for this type of manufacturing process.

Product specification

The finished product will be delivered in a bottle with the granules, which will be suspended before use with purified water to an oral suspension.

The finished product release and shelf life specifications include appropriate tests for this kind of dosage form: Granules: appearance (visual), identification (HPLC, UV), related substances (HPLC), microbial limit (Ph. Eur.), assay of fidaxomicin (HPLC). Suspension: appearance (visual), resuspension time (visual), pH (Ph. Eur.), dissolution (Ph. Eur.), assay of sodium benzoate (HPLC), and uniformity of dosage units.

The potential presence of elemental impurities in the finished product has been assessed on a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. As the result of the risk assessment, additional controls are not required for elemental impurities for this finished product. In addition, total mass of elemental impurities calculated from typical value of active substance and excipients is sufficiently below the 30% of option 1 limits. Therefore, an elemental impurity specification and associated limit are not proposed.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. No additional reference standards are used for analysis of finished product beyond those described for the active substance.

Batch analysis results are provided for 2 commercial scale batches in the proposed manufacturing site, these batches have equivalent quality as the batches manufactured at other manufacturing site for clinical study and for primary stability studies. Therefore, it is confirmed the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

The finished product is released on the market based on the above release specifications, through traditional final product release testing.

Stability of the product

Stability data from 3 pilot scale batches of finished product stored for up to 36 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for characteristics granules, characteristics suspension, assay of fidaxomicin, assay of sodium benzoate, related substances, dissolution, water content, pH, viscosity, dose uniformity of suspension, and microbial limits.

The analytical procedures used are stability indicating. No significant changes were observed in any of the monitored parameters through 36 months and 6 months of storage at 25°C/60%RH and 40°C/75%RH, respectively, compared to the initial values.

In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. The results demonstrated that the finished product without the primary packaging configuration did not meet the acceptance criteria after light exposure. Therefore, a light protective package is proposed.

A bulk holding study was conducted using one batch of pilot scale final blend. The results demonstrated no significant change.

Three primary stability batches were used for an in-use stability study. The in-use stability testing was conducted using the oral suspension dispersed with water after the storage of the primary stability studies. The in-use stability study was conducted according to the guideline, "In-use Stability Testing of Human Medicinal Products" (CPMP/QWP/2934/99). The results demonstrated that the suspension prepared from the fidaxomicin granules (which are stored for 36 months at long term condition) is stable for at least 12 days when the suspension is stored in refrigerator.

Based on available stability data, the proposed shelf-life of 36 months without any special temperature storage conditions and stored in the original package in order to protect from light, as stated in the SmPC (section 6.3), are acceptable. The reconstituted suspension is stable for 12 days in a refrigerator (2° C – 8° C).

Adventitious agents

No excipients derived from animal or human origin have been used.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

The applicant has applied QbD principles in the development of the finished product and its manufacturing process. However, no design space were claimed for the manufacturing process of the finished product

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendation(s) for future quality development

No applicable

2.3. Non-clinical aspects

2.3.1. Introduction

Only three non-clinical toxicology studies (using the oral suspension formulation) have been submitted for this application. These are addressed in the toxicological section. An overview of additional non-

clinical pharmacology, pharmacokinetics and toxicology data generated for oral capsule administration in adults is derived from the EPAR for Dificlir (original procedure EMEA/H/C/2087 from 2011).

2.3.2. Pharmacology

Fidaxomicin (FXM) is a small molecular weight molecule that has been developed for the treatment of Gram-positive bacteria; in particular *C. difficile* infections. The mode of action is bactericidal and both parent compound and the major metabolite, OP-1118 have antimicrobial activity. FXM is an inhibitor of the enzyme RNA polymerase. The site of action is different from that of rifamycins.

Primary and secondary pharmacodynamic studies

Two primary pharmacodynamics studies were reported for Hamster. In the first of these studies, BIO070503A, hamsters were infected with *C. difficile* ATCC 43255 (passaged once through a mouse host), and mortality was compared between animals treated for 7 days with three dose levels of FXM (0.3, 0.8, and 2.5 mg/kg/day), vancomycin (5 mg/kg) or metronidazole (100 mg/kg). In order to avoid cross-contamination, animals were housed singly in microisolator cages. The 50% protective dose was lower than the lowest dose tested, 0.3 mg/kg (the animal that died due to non-*C. difficile* related causes is excluded from the ED50 calculation), and no animals died during the treatment phase in any of the other groups excluding control. As expected from this model, in which hamsters can redevelop infection following treatment removal, some animals (1 per group) died after treatment withdrawal. A second study, BIO120203A, investigated the impact of different formulations of FXM on efficacy in the hamster model. In this study, hamsters were infected with a clinical isolate of *C. difficile* (TTU614) and the relative efficacies of FXM suspended in water, xanthan gum, lecithin, and Labrasol were compared. The efficacies appeared similar, with 0/6 animals surviving in the untreated controls, and 1-2 animals dying in each of the treated groups, more often in the weeks following the end of treatment (as is common for this model, in which some animals will redevelop *C. difficile* infection.) This study therefore showed that the formulation is relatively unimportant to the efficacy of the compound.

Pharmacological effects outside of the primary target have not been identified, and thus no mechanistic studies of this nature have been conducted.

In summary, preclinical in vivo studies using clindamycin sensitised hamsters showed that FXM was effective in protecting animals from lethal infections with an ED50 of less than 0.3 mg/kg. Overall, the non-clinical pharmacology of FXM has been acceptably characterised and is consistent with expected clinical activity.

Safety pharmacology programme

A total of five safety pharmacology studies (four in-vivo studies and one in-vitro hERG study) were conducted. The in-vivo studies were conducted in rat (two studies for respiration and FOB-CNS effects using iv administration) and dog (two studies for cardiovascular effects). In the hERG study, there were no significant effects on hERG current (IC_{50} greater than max conc. FXM 7.85µg/mL, OP-1118 8.37µg/mL). In an oral cardiovascular dog study, there were no effects on blood pressure, body temp, PR interval QRS complex, QTc interval (max dose 9600mg/kg). Lower pulse pressure was measured but with a small magnitude of change. In an intravenous route study in dog, the study was terminated at 1mg/kg due to tolerability problems (monitored up to 20 hours post dose). Transient pronounced drop in blood pressure and transient histamine like effects (red eyes, skin discoloration, salivation, prostration, twitching of paws) were observed. The excipient for the iv administration (solutol HS15) was likely the cause of the hypotension finding. In the oral cardiovascular dog study, where systemic

levels more than those observed in the intravenous cardiovascular study were reached, no similar effects were seen. In the respiratory and CNS rat studies, there we no adverse effects (NOEL 7.5mg/kg for both studies). No specific safety pharmacology studies on the renal/urinary system or the gastrointestinal system were conducted but data from toxicity studies in dog showed that high doses (9600 mg/kg) may produce gastrointestinal effects such as emesis and diarrhoea. Overall, the non-clinical pharmacology and safety pharmacology of FXM have been acceptably characterised and has not revealed any unexpected effects.

2.3.3. Pharmacokinetics

Pharmacokinetic and/or toxicokinetic studies with fidaxomicin (FXM) have been performed in rat, rabbit and dog and monkey using validated bioanalytical methods for plasma (rat, rabbit, dog, monkey) and faeces (dog). FXM has poor aqueous solubility, especially at low pH. This is likely linked to the overall low systemic bioavailability in all species observed after oral capsule administration. The rat seems to have a rapid intestinal metabolism of FXM, as little FXM was detected in colon and caecum (< 0.01mg/g). This indicates that the rat is less suitable to use in oral toxicology studies. Following oral administration of FXM in dog, measurable plasma concentrations were achieved. A 3-month repeated dose study in beagle dogs, using the clinical tablet formulation and oral dose levels of 0, 1, 3.2, and 9.6g/day showed that the extent of exposure for both FXM and OP-1118 increased with increasing dose, in a nonlinear fashion: AUC0-tlast increased greater than proportionally across the dosing range, while Cmax increased greater than proportionally between the 1 g and 3.2g doses and usually proportionally between the 3.2g and 9.6g doses. A large inter-animal variability was found, possibly due to differences in local gut pH. Depending on vehicle used, bioavailability was at the most 3%. Male and female cynomolgus monkeys were dosed for 28 days with 0, 10, 30, and 90mg/kg/day of FXM. Plasma levels (Cmax and AUC) increased approximately proportionately between the doses. Overall, exposure in monkey after oral doses was lower than in dog, supporting the choice of dog as the best animal model (compared to rat and monkey) to use in toxicity studies.

A greater than proportional increase in plasma levels with dose was recorded in rat and dog given intravenous doses and the metabolite OP-1118 exhibited similar greater than proportional increases with dose, except in dog where saturation was seen at high doses. Exposure to the metabolite OP-1118 appeared saturated at 4mg/kg (iv.) and no further increase was seen with the high dose of 7.5mg/kg (iv.).

The volume of distribution was generally less than total body water, indicating that the small amount of drug absorbed is not preferentially partitioned out of total body water and that the ng/mL plasma concentrations observed are an appropriate measure of systemic exposure. Studies on protein binding in plasma from rats, rabbits, dogs, and humans showed no large differences between species. For FXM, the plasma protein binding in rats, rabbits, dogs, and humans was 96.8%, 98.5%, 97.5%, and 97.8%, and for OP-1118, 93.5%, 97.7%, 92.0%, and 96.1%, respectively, over the concentration ranges tested (0.1-100 µg/mL).

FXM was hydrolysed to the active major metabolite OP-1118 (desisobutyryl fidaxomicin) in rat, dog, monkey and human (not studied in vivo in monkey). OP-1118 was the major species produced in rabbit (molar AUC ratio 6.55-10.75) but was detected at modest levels in rat (data from pregnant animals) and dog (molar AUC ratios of 0.28-0.41 in rat and 0.09-0.33 in dog). The transformation was not CYP or NADPH dependent and is likely to be catalysed via an esterase. Other minor pathways identified in vitro include monohydroxylation, sulphation, and glucuronidation. Among these metabolites, only acyl migration and hydrolysis products were detected in plasma, urine, and faeces from dogs. The half-life for both parent compound and major metabolite was less than one hour in rat and rabbit and somewhat longer in dog.

A study with radiolabelled compound in dogs was conducted in which dogs were orally administered (gavage) 6.47 mg/kg of [^{3}H]-FXM, to deliver 245.6µCi/dog. Total recovery of radioactivity was 87%; of this, over 99% was recovered in the faeces, while < 1% was recovered in the urine. In bile duct cannulated Beagle dogs administered FXM (400mg/kg as tablets) less than 1% of the administered drug was recovered in the bile as either FXM or OP-1118. The overall recovery in faeces and bile for FXM and OP-1118 was 92.1% ± 9.32% in male and 92.3% ± 11.7% in female dogs. Based upon the observation that a second concentration peak was observed in the plasma of some dogs following oral administration, hepatic recirculation is possible, although the extent is likely to be low.

FXM has demonstrated mild inhibition of certain CYP enzymes at levels (10µg/mL) near the solubility limit at physiological pH. OP-1118 is, however, an inhibitor of CYP3A4, at concentrations achievable in the gastrointestinal tract. Thus, the potential for inhibition of gut CYP3A4 cannot be ruled out. Both FXM and OP-1118 are substrates for efflux pumps, and this efflux is inhibited by cyclosporine A and ketoconazole, inhibitors of P-glycoprotein. FXM is also an inhibitor of P-glycoprotein, with an IC50 of 2.59µM (2.74µg/mL), while OP-1118 is a much weaker inhibitor (IC50 > 125µM, or 123µg/mL). The inhibitory effect of FXM and OP-1118 on other intestinal transporters has not been investigated.

In summary, based on pharmacokinetic considerations, the best toxicological animal model for FXM of those tested is the dog. FXM has low systemic availability after oral administration and the distribution after uptake seems to mainly be in the gastrointestinal tract. FXM has one main metabolite OP-1118 which is also present in humans. The excretion of FXM is mainly via the faeces.

2.3.4. Toxicology

Three new non-clinical toxicology studies in Beagle dog using the oral suspension formulation (one adult repeat-dose toxicity study and two juvenile toxicity studies) have been submitted in order to fulfil PIP requirements (last modification EMEA/000636/PIP01-09-M07). The toxicological assessment for this Paediatric Line Extension will primarily concern itself with the novel non-clinical submitted studies with the focus being on the oral suspension usage in juvenile animals. Toxicological data from the already conducted non-clinical assessment of oral capsules will be mentioned depending on their relevance to the new studies.

Choice of animal models

FXM has a low bioavailability, partly due to a low solubility, in all its tested oral formulations (see below). Among tested animal models (rat, dog, cynomolgus, rabbit), and based on pharmacokinetic considerations, the dog was considered the best toxicological animal model for oral administration (only dog was used for long term 3-month repeat-dose toxicity assessment; monkey was only used in a single 28d study - high plasma exposure levels were not possible to reach despite repeated dosing). FXM has one major metabolite with antibiotic activity, OP-1118, that is present in rats, dog, cynomolgus and human. The newly submitted non-clinical studies in the present procedure are all in Beagle dog.

Single dose toxicity

No acute toxicity was seen in Beagle dog after a single oral dose of up to 120mg/kg. If FXM is given in a single iv. dose to dog, gastrointestinal problems are seen at 1mg/kg and clinical signs (e.g. decreased activity, tremor, difficulty breathing) are seen at 4 and 7.5mg/kg.

Repeat dose toxicity

Dogs were exposed to FXM for 14d or 3-months. In the 14d-studies (n=2-3 animals per dose and sex), doses up to 6400mg/dog did not generate toxicity and 9600mg/dog gave some gastrointestinal problems (pale faeces, soft faeces and yellow faeces observed). In the pivotal 3-month + 28d recovery dog study (n=4-7 animals per dose and sex; 1000 to 9600mg/day corresponding to 101 to 942mg/kg in males, 121 to 1190mg/kg in females), there were no test-article related effects on body weights, food consumption, clinical or anatomic pathology parameters, ECG or any ophthalmic lesions. The main effects of FXM administration were limited to the GI-system, as evidenced by clinical signs of pale/yellow faeces and white emesis. The GI-effects were considered to be a localized effect caused by the high number of tablets administered per day to the dogs (total administered drug product was equivalent to approximately 5-7% of the daily food intake) rather than an indicator of test article-related toxicity. The NOEL was defined as 5 tablets/day (1000 mg/animal/day) and the NOAEL as 48 tablets/day (9600 mg/animal/day, corresponding to 942 mg/kg/day in males and 1190mg/kg/day in females, based on average body weights), the highest dose administered. At the NOAEL dose, the lowest average Cmax values measured at either time point (day 0 or day 86) for either sex was 3010ng/mL for FXM and 361ng/mL for the metabolite OP-1118, which are ~100-fold and ~4-fold higher than peak concentrations seen in CDI patients. The lowest average AUC0-tlast values measured at either time point for either sex were 8160ngxhr/mL for FXM and 945ngxhr/mL for OP-1118, which are ~20-fold and ~0.6-fold, respectively, compared to what might be seen in patients at the therapeutic dose.

In an 7d repeat-dose toxicity dog study for oral formulation comparison (oral capsule vs. oral suspension; dose: 200mg/kg; n=2-4 animals per group), there was no observed toxicity and the mean exposure to FXM and OP-1118 in plasma and faeces was generally higher with oral capsule compared to oral suspension (inter-animal variability was generally high and precluded rigorous comparisons between genders, dosage forms or other studies). This would indicate that there is even less bioavailability for the oral suspension.

Genotoxicity

Neither FXM nor OP-1118 were mutagenic in the bacterial reverse mutation assay, while an increased frequency of cells with chromosomal aberrations was observed in Chinese Hamster Ovary (CHO) cells after treatment with FXM in absence of metabolic activation at concentrations ≥100 ug/mL. In order to reflect the high concentrations of FXM in the GI-tract as opposed to low systemic exposure and to evaluate the possible local clastogenic effect of this drug an in vivo comet analysis of liver and duodenal cells has been performed. Rats were treated with oral capsule FXM up to 2000mg/kg/day (~150-fold over the human daily dose when scaled by small intestinal surface area) for two days and the comet analysis showed no difference in liver cells while a dose dependent trend in decreased Tail DNA was shown in duodenal cells. However, there was no significant difference in Tail DNA between treated and control (vehicle treated) rats at any of the doses used and no significant effect on Tail Migration or Tail Moment. In addition, only two animals had a Tail DNA % outside the historical vehicle control range (2.00-9.25%), 1 out of 6 rats in each of the 1000 and 2000mg/kg/day dose groups, 1.60% and 1.19%, respectively. Overall, the biological relevance of the decreased trend in %Tail DNA is considered highly questionable.

Carcinogenicity

Considering the established and proposed short treatment period (10d for adults and children), carcinogenicity studies were not conducted with FXM in the original application and no new carcinogenicity studies have been submitted for the paediatric extension.

Local tolerance

No local tolerance studies have been performed.

Other toxicity studies

Phototoxicity

FXM is unlikely to be phototoxic as it has very low absorbance in the 290-700 nM range, combined with the low bioavailability and low expected systemic exposure.

Impurities

Based on a rat Comet assay study (2000mg/kg), the exposure margins for a total of 11 specified impurities in the oral suspension have been estimated (and adjusted for average small intestine surface area in rat and human) for the specification. This gave a margin estimate range between 12x and 90x which is considered acceptable considering the short treatment period (10d).

2.3.5. Ecotoxicity/environmental risk assessment

Fidaxomicin (CAS #873857-62-6) is a macrolide antibiotic that has formula $C_{52}H_{74}Cl_2O_{18}$ and a molecular weight of 1058.04g/mol. It has a log Kow of 4.4 at pH7. A default estimate of surface water predicted environmental concentration (PEC_{SW}) gives 2ug/L (400mg dose, Fpen 1%; triggering a Phase II assessment) and a 10d adjusted treatment regime gives 0.055ug/L. The present extension that extends the indication to the 0-18year age group, is estimated to generate a maximum environmental exposure increase of 2.4%. FXM has a moderate potential for binding to soils/sludges and rapidly moves from surface waters to sediments with a water DT_{50} 2.8-3.4d and sediment DT_{50} 26.9-63.3d at 20◦C and 57.1-134 at 12◦C. As such, FXM can be considered persistent in sediment (>120d).

FXM degrades into several transformation products (TPs) whereof three being major TPs (>10% applied radioactivity in sediment). Out of those TPs, one was OP-1118 ('component 17'; also seen in animals and humans) and another ('component 15') was an isomer of OP-1118. Considering that OP-1118 is an active metabolite to FXM, this would indicate that these TPs also have antibiotic activity to some, likely lesser, extent. In an aquatic toxicity assessment, cyanobacteria (*Anabaena*) were found to be the most sensitive model organism with a growth rate NOEC of 5.82mg/L and a biomass NOEC of 1.62mg/L (EC_{10} of 2.7mg/L). Sludge bacteria were second most sensitive at a NOEC of 5.9mg/L (similar in sensitivity to algae based on growth rate and less sensitive based on biomass endpoint). No effects were seen in Daphnia, developing fathead minnow (*P. promelas*) or developing harlequin fly (*C. riparus*). None of the effects gave rise to a risk quotient (RQ) over 1 (or 0.1 for microorganisms based on cyanobacteria or sludge bacteria).

Table 1. Summary of main study results

Substance (INN/Invented Name): Fidaxomicin (FXM)			
CAS-number (if available): 873857-62-6			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD TG107	5.2 (pH 5) 4.4 (pH 7) 1.9 (pH 9)	Potential PBT (N)
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	4.4	Possible B at >3
	BCF	?	Unlikely B considering the large diameter (2.4nm) & size of the molecule (1058g/mol).
Persistence	DT50 or ready biodegradability	Water DT50 < 40d Sediment DT50 > 120d	P based on 12C adjusted DT50 in sediment?
Toxicity	NOEC or CMR	1.62 mg/L (algae biomass) to 5.82mg/L (algae growth rate)	not T (>0.01mg/L)
PBT-statement :	The compound is not considered as PBT		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surface\text{-}water}$, default or refined (e.g. prevalence, literature)	2	µg/L	> 0.01 threshold (Y); Phase IIA trigger
Other concerns (e.g. chemical class)	Antibiotic drug		(Y) Antibiotic resistance
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-Desorption	OECD TG106	<u>*Soil*</u> K_f (soil 1) = 7.52 K_f (soil 2) = 96.4 K_f (soil 3) = 11.3 K_{foc} (soil 1) = 215 K_{foc} (soil 2) = 3710 K_{foc} (soil 3) = 869 <u>*Sludge*</u> K_f (sludge 1) = 366 K_f (sludge 2) = 424 K_{foc} (sludge 1) = 818 K_{foc} (sludge 2) = 870	<u>Study OFM0048</u> Soil 1: sandy clay loam (3.5% OC) Soil 2: Clay loam (2.6% OC) Soil 3: Sandy loam (1.3% OC)
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD TG308	<u>*FXM system 1*</u> $DT_{50,\ water}$ = 2.8d / 5.9d $DT_{50,\ sediment}$ = 63.3d / 134d $DT_{50,\ whole\ system}$ = 4.3d / 9.1d <u>*FXM system 2*</u> $DT_{50,\ water}$ = 3.4d / 7.2d $DT_{50,\ sediment}$ = 26.9d / 57.1d $DT_{50,\ whole\ system}$ = 4.6d / 9.8d <u>*Comp15 system*</u> $DT_{50,\ water}$ = 2.2-9.3d $DT_{50,\ whole\ system}$ = 53.9d	<u>Study OFM0044</u> DT50 values calculated using SFO. Based on 20◦C. Recalculated to 12◦C (20C / 12C) FXM is proposed to degrade to isomer of OP-1118 ("component 15"). Up to 19 minor transformation products were detected.

		AR% shifting to sediment: ~30 to 50% at 14d			Persistent in sediment at >120d. Sediment-tox study triggered.
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test, 72h	OECD TG201	<u>*Biomass*</u> NOEC LOEC EC10 EC50 <u>*Growth rate*</u> NOEC LOEC EC10 EC50 <u>*Yield*</u> NOEC LOEC EC10 EC50	 1.62 5.82 2.70 >18.4 5.82 18.4 >18.4 >18.4 5.82 18.4 7.41 >18.4	 mg/L mg/L mg/L mg/L mg/L mg/L mg/L mg/L mg/L mg/L mg/L mg/L	<u>Study OFM0046</u> *Anabaena (Cyanobacteria)* Most sensitive endpoint: Biomass NOEC 1.62mg/L. Most relevant sensitive endpoint: growth rate NOEC 5.82mg/L
Daphnia sp. Reproduction Test, 21d	OECD TG211	<u>*Growth*</u> NOEC <u>*Repro*</u> NOEC	 19.6 19.6	 mg/L mg/L	<u>Study OFM0051</u> *Daphnia sp.* Overall NOEC 19.6 and LOEC > 19.6mg/L.
Fish, Early Life Stage Toxicity Test/*Fathead minnow*	OECD TG210	<u>*Hatching*</u> NOEC <u>*Survival*</u> NOEC <u>*Length*</u> NOEC <u>*Weight*</u> NOEC	 8.91 8.91 8.91 8.91	 mg/L mg/L mg/L mg/L	<u>Study OFM0045</u> *Pimephales promelas* Overall NOEC 8.91 and LOEC > 8.91mg/L.
Activated Sludge, Respiration Inhibition Test, 3h.	OECD TG209	NOEC EC20	5.90 8.10	mg/L mg/L	<u>Study OFM0047</u>
Phase IIb Studies					
Sediment dwelling organism	OECD TG218	<u>*Emergence*</u> NOEC <u>*Dev. Rate*</u> NOEC <u>*Sex ratio*</u> NOEC	 82.8 82.8 82.8	 mg/kg mg/kg mg/kg	<u>Study OFM0043</u> *Chironomus riparius* *Overall NOEC 82.8 and LOEC > 82.8mg/kg.* *The $NOEC_{OC10}$ is 290.5mg/kg*

2.3.6. Discussion on non-clinical aspects

The MAH for Dificlir has submitted three non-clinical toxicology studies (using the oral suspension formulation), thereby fulfilling the PIP requirements for this paediatric line extension. All TK measurements conducted came with uncertainties due to low levels of target in samples (often <LOQ) and high inter-animal variation in combination with a relatively limited group size (common in dog studies). No exact quantification was possible between the oral capsule and oral suspension uptake in adult dogs, but the data indicates that the already low bioavailability with oral capsules is even lower with the oral suspension and that the uptake in very early life in dog (PND4) is greater than when older (PND31).

Beside a more general assessment, the juvenile toxicity studies were conducted to investigate if FXM would affect gastrointestinal properties and/or development if given at a very early age. While the dose-range finding study observed some minor clinical GI-signs (i.e. liquid/yellow material in faeces) at the high dose (200mg/kg), no such effects were detected in the pivotal study (also max dose of 200mg/kg). Both studies started at PND4 (the dose-range finding study ending exposure at PND17 and the pivotal study ending at PND31). As such, there are no clear signs that FXM has any GI-toxicity at an early age in dog.

As the log Kow is > 3 for FXM, an OECD TG305 bioaccumulation study is generally required but the physicochemical properties of 2.4nm diameter and a molecular weight of nearly 1100g/mol (1058g/mol) indicates that the likelihood for bioaccumulation is reduced (considered lowered at >1.7nm average diameter and >1100g/mol), making it less likely that an OECD TG305 study data is necessary. Overall, with regard to the ERA for FXM, while FMX is persistent in sediment, there are no indications that FXM is an environmental risk or a PBT substance.

2.3.7. Conclusion on the non-clinical aspects

Overall, the toxicological program for the oral suspension formulation did not reveal any fidaxomicin hazards to consider. There are no objections to an approval of the Paediatric line extension of Dificlir from a non-clinical point of view.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies **(Table 2)**

Type of Study	Study Identifier (Country)	Primary objective(s) of the Study	Study Design and Type of Control	Dosage Regimen	Number of Subjects	Subjects	Duration of Treatment	Sex Age Median (Min, Max) (Months)
Phase 2a	OPT-80-206 11 sites in the US and Canada	Safety, tolerability and pharmacokinetics of fidaxomicin oral suspension (powder formulation for reconstitution) or tablets	Open-label, uncontrolled	Oral fidaxomicin 200 mg tablets or 32 mg/kg per day oral suspension twice daily (every 12 hours) beginning day 1, for 10 treatment days	Enrolled: 38 Treated: 36 Completed: 24	Paediatric subjects ≥ 6 months to < 18 years of age with CDAD	10-day treatment period 28-day follow-up period	22M/16F 101.5 (11 - 206)
Phase 3	2819-CL-0202 "SUNSHINE" 74 sites in North America and Europe in 11 countries (USA, Canada, PL, FR, DE, RO, HU, ES, IT, BE, SK)	Clinical response (at EOT+2d) to fidaxomicin oral suspension (granule formulation for reconstitution) or tablets and vancomycin oral liquid or capsules	Single-blind, randomised (2:1), parallel-group, active-controlled	Oral fidaxomicin 200 mg tablets or 32 mg/kg per day oral suspension twice daily (every 12 hours) beginning day 1, for 10 treatment days	Enrolled and randomised: 148 Treated: 142 Completed: 137	Paediatric subjects birth ≥ 1 month to < 18 years of age with CDAD	10-day treatment period 30-day follow-up period	82M/60F 60.0 (1 - 204)

CDAD: *Clostridium difficile*-associated diarrhoea.

Source: Applicant's submission 2.7.6. Synopses of individual studies.

2.4.2. Pharmacokinetics

The product is intended for local action in the GI-tract. The pharmacokinetics is therefore mainly of interest for systemic safety evaluations. Efficacy conclusions based on PK data are not valid given that the site of action is prior to plasma.

Different oral suspension formulations were used in the two studies. A powder formulation was investigated for reconstitution in OPT-80-206 and a granule formulation in SUNSHINE. The granule formulation used in SUNSHINE is the to-be-marketed-formulation.

The plasma and faecal concentrations of fidaxomicin and its main metabolite, OP-1118, were measured in both studies. The plasma sampling time points were selected based on the expected time of maximal concentration in adults, which is typically between 1 and 5 hours post-dose at steady state at day 5 for both fidaxomicin and OP-1118.

Study OPT-80-206

Plasma samples were collected 0 to 2 hours pre-dose and at 1 to 2 hours and 3 to 5 hours post-dose on any day between days 5 and 10. Faecal samples were collected within 24 hours post-dose on day 10 (or at the end of therapy, if sooner than day 10). In total, 36 patients were included in the plasma pharmacokinetic analysis set and 30 patients in the faecal pharmacokinetic analysis set. The mean plasma concentrations of fidaxomicin and OP-1118 are shown in table 3 below.

Table 3. Summary of observed plasma levels of fidaxomicin (OPT-080) and OP-1118

	Plasma Level, ng/mL									
	6–23 Mo (N = 8)		2–5 Y, 11 Mo (N = 7)		6–11 Y, 11 Mo (N = 9)		12–17 Y, 11 Mo (N = 12)		All Subjects (N = 36)	
Time, Days 5–10	OPT-080	OP-1118	OPT-080	OP-1118	OPT-080	OP-1118	OPT-080	OP-1118	OPT-080	OP-1118
Predose										
Mean	13.171	133.376	9.236	30.624	10.081	38.838	7.836	22.312	9.853	51.019
SD	23.494	316.127	3.546	27.326	6.437	36.677	8.638	22.035	12.133	143.617
Median	3.310	15.000	9.070	26.000	8.730	20.500	6.580	15.200	7.095	19.500
Minimum	1.180	4.230	4.460	0.445	1.150	5.540	1.750	4.240	1.150	0.445
Maximum	65.800	850.000	13.200	82.200	18.700	106.000	31.700	71.300	65.800	850.000
1–2 Hours postdose										
Mean	13.364	130.235	16.618	51.725	12.363	47.321	8.874	27.476	11.993	60.739
SD	21.030	323.276	10.900	31.296	11.704	44.274	6.604	18.101	12.776	158.866
Median	5.695	17.000	13.300	41.700	8.710	29.000	7.265	28.150	8.795	27.600
Minimum	1.75	5.66	7.77	26.70	1.89	6.99	1.86	4.62	1.75	4.62
Maximum	64.70	930.00	35.00	96.80	39.90	129.00	22.90	56.90	64.70	930.00
3–5 Hours postdose										
Mean	15.217	121.946	14.606	45.825	15.590	53.341	9.830	28.465	13.363	60.016
SD	29.310	307.181	5.411	20.034	10.059	62.232	6.083	20.645	15.472	152.196
Median	4.925	14.550	14.400	44.750	14.925	25.300	8.400	24.100	8.725	24.100
Minimum	0.563	2.370	7.530	22.700	3.550	5.870	3.130	2.880	0.563	2.370
Maximum	87.400	882.000	22.400	71.100	28.900	193.000	22.800	74.300	87.400	882.000

Source: Table 14.2.7.1.
PK = pharmacokinetics; SD = standard deviation.

The overall mean concentration of fidaxomicin and OP-1118 in faecal samples were 3228 and 865 µg/g, respectively.

SUNSHINE

Plasma samples were collected within 30 minutes pre-dose and 1 to 5 hours post-dose on any day between days 5 and 10 but not necessarily on the same day. Faecal samples were collected within 24 hours post-dose on any day between days 5 and 10. The mean plasma concentrations for fidaxomicin and its main metabolite OP-1118 approximately doubled post-dose relative to pre-dose. The mean plasma concentration of fidaxomicin in the paediatric population is shown in table 4 below.

Table 4. Observed Plasma Concentrations of Fidaxomicin and OP-1118 on Days 5 to 10

Statistic	Plasma Concentration (ng/mL)				
	<24 Months	≥2 to <6 Years	≥6 to <12 Years	≥12 to <18 Years	All Patients
Fidaxomicin					
Predose					
n	18	24	22	18	82
Mean (SD)	9.52 (7.46)	21.31 (28.86)	15.42 (19.36)	35.09 (75.18)	20.17 (40.16)
Median (min, max)	7.69 (2.5, 29.0)	9.86 1.2, 121.0	9.14 (2.1, 93.8)	11.10 (2.2, 326.0)	9.19 (1.2, 326.0)
1 to 5 hours postdose					
n	19	22	24	16	81
Mean (SD)	33.29 (46.06)	41.22 (78.38)	31.76 (32.06)	55.69 (86.30)	39.41 (62.15)
Median (min, max)	18.40 (3.0, 208.0)	14.05 (2.2, 367.0)	21.55 7.0, 154.0	32.65 (3.9, 359.0)	21.00 (2.2, 367.0)
OP-1118					
Predose					
n	18	24	22	18	82
Mean (SD)	34.52 (22.37)	57.25 (113.56)	32.88 (41.09)	136.16 (336.35)	63.04 (171.97)
Median (min, max)	30.50 (8.8, 81.6)	22.70 (5.4, 560.0)	20.05 (6.7, 203.0)	29.25 (7.4, 1410.0)	23.90 (5.4, 1410.0)
1 to 5 hours postdose					
n	19	22	24	16	81
Mean (SD)	100.26 (126.60)	134.53 (362.91)	66.80 (67.66)	186.23 (370.75)	116.64 (259.10)
Median (min, max)	71.90 (9.8, 459.0)	33.75 (9.4, 1720.0)	47.65 (16.9, 337.0)	57.30 (11.3, 1500.0)	47.80 (9.4, 1720.0)

Source: SUNSHINE, Table 12.4.1.1; Table 12.4.1.2; Table 12.4.1.4 and Table 12.4.1.5

The mean (SD) fecal concentration of fidaxomicin was 2685.56 (2476.92) µg/g and 889.23 (817.83) µg/g for OP-1118.

Pre- and post-dose plasma concentration values were higher for tablets as compared to oral suspension for both fidaxomicin and its metabolite OP-1118, see table 5 below. The mean (SD) post-dose faecal concentrations for oral suspension (2969.87 [2713.58]) were higher compared to tablets (2190.63 [1948.68]); however, for its metabolite OP-1118, post-dose faecal concentrations for oral suspension (789.15 [728.58]) were lower as compared to tablets (1059.73 [941.04]).

Table 5. Observed Plasma Concentrations of Fidaxomicin and OP 1118 on Days 5 to 10 by Formulation

Statistic	Plasma Concentration (ng/mL)	
	Oral Suspension (Granules)	Tablets
Fidaxomicin		
Predose		
n	55	27
Mean (SD)	15.26 (20.43)	30.16 (63.27)
Median (min - max)	9.05 (1.2 - 121.0)	9.26 (2.5 - 326.0)
1 to 5 hours postdose		
n	53	28
Mean (SD)	34.60 (57.79)	48.53 (69.85)
Median (min - max)	15.30 (2.2 - 367.0)	26.75 (3.9 - 359.0)
OP-1118		
Predose		
n	55	27
Mean (SD)	42.18 (76.76)	105.54 (277.67)
Median (min - max)	24.30 (5.4 - 560.0)	22.90 (6.7 - 1410.0)
1 to 5 hours postdose		
n	53	28
Mean (SD)	102.38 (245.19)	143.63 (286.31)
Median (min - max)	47.20 (9.4 - 1720.0)	57.25 (11.3 - 1500.0)

Source: SUNSHINE, Table 12.4.1.7 and Table 12.4.1.8

2.4.3. Pharmacodynamics

Primary and Secondary pharmacology

The primary pharmacology of fidaxomicin was previously described and discussed in detail in the original marketing authorisation application for the adult indication in 2011 (EMEA/H/C/002087). No new data are presented in this application. No clinically significant differences in pharmacodynamics are expected between adult and paediatric subjects with CDAD, given the similarity of the pathophysiology of the disease.

Preclinical studies and adult clinical studies with fidaxomicin do not indicate any signals on cardiac safety, as discussed in the original marketing authorisation application in 2011 (EMEA/H/C/002087). Given poor absorption from the GI tract, a thorough QT study in healthy volunteers exposed for high doses of the study drug was not considered feasible as part of the clinical development programme, and this was previously accepted by CHMP considering the absence of preclinical signal.

In the paediatric studies OPT-80-206 and SUNSHINE, no safety signal was observed relating to an effect of fidaxomicin on QTc.

2.4.4. Discussion on clinical pharmacology

Pharmacokinetics

There are limited pharmacokinetic data available for the paediatric population. Of the two submitted studies only OPT-80-206 had investigation of PK as an objective, but due to sparse PK sampling limited pharmacokinetic parameters were obtained. In SUNSHINE the PK sampling was even more sparse. No modelling of plasma concentrations to obtain PK parameters (maximum plasma drug concentration, area under the time-concentration curve, etc) was planned for either study. Descriptive statistics were presented for all summarized data. In SUNSHINE one subject below 6 months of age was included, however there is only one post-dose concentration available for this subject (no pre-dose or faecal concentration). In OPT-80-206 the youngest subject enrolled was 11 months. There is thus in practice no PK-data for the youngest population (< 6 months).

From the studies in adults it was concluded that the systemic absorption of fidaxomicin is low. Although there is no estimate of absolute bioavailability in humans it was determined in several nonclinical dog studies, using different formulations with various solubility enhancers, with estimates around 0.2- 3%.

From the submitted studies systemic absorption appears low also in the paediatric population. Systemic exposure is relevant to the assessment of clinical safety. From the presented data no clear correlation of systemic exposure to age could be observed in either paediatric study.

In the SUNSHINE study, the actual administered dose (of oral suspension) varied from < 15 mg/kg/day to ≥ 30 mg/kg/day. An analysis of the plasma concentration of fidaxomicin by planned dosing groups was performed revealing no relevant difference in fidaxomicin concentration between the groups.

The MAH has provided a comparison of the paediatric and adult plasma PK-data for both fidaxomicin and OP-1118. The analysis is limited by the small subset of the data from the SUNSHINE study available for the cross-study comparison (12 of 81 post-dose measurements were used). Overall there is however no indication that the plasma concentrations of fidaxomicin or the metabolite OP-1118 are higher in the paediatric patients than in the adult patients. The MAH states that they have not been able to develop a stable population PK model due to the low systemic concentrations of fidaxomicin. This limits the possibilities for further analysis of the data. In summary the systemic concentrations of fidaxomicin and OP-1118 are low and appear in general to be similar between the adult and paediatric population.

It is conceivable that altered systemic exposure might arise due to disrupted intestinal mucosa in the most severely unwell subjects. The MAH has discussed the impact of severity of disease on the systemic exposure of fidaxomicin. The median plasma concentration values for fidaxomicin were different for the two groups of paediatric patients (with non-severe or severe disease) indicating that higher plasma concentrations are possibly achieved for the patients with severe disease compared to those with non-severe disease. However, the difference was not large and most patients' plasma concentrations, irrespective of severity of the disease, were below 50 ng/ml.

The faecal fidaxomicin concentrations appear somewhat higher in the paediatric population compared to the adult population although the variability was high. There is a trend of higher mean concentrations in the youngest age group. According to the Applicant these samples would typically be collected from diapers, which may dehydrate the sample and contribute a positive bias to the concentration measured. Faecal concentrations of fidaxomicin were well over the MIC of the organism across the weight/age range in the paediatric population.

Comparisons between the fidaxomicin oral suspension and tablets indicate that the systemic absorption is lower for the oral suspension compared to the tablets (both pre- and post-dose plasma concentrations are lower). The same trend is seen in non-clinical studies in dogs (see separate non-clinical AR). High inter-subject variability precludes rigorous comparisons between dosage forms in both human and animal data.

Pharmacodynamics

The primary pharmacology of fidaxomicin was previously described and discussed in detail in the original marketing authorisation application for the adult indication in 2011 (EMEA/H/C/002087). No new data are presented in this application.

2.4.5. Conclusions on clinical pharmacology

Several of the cross-study comparisons of the plasma PK-data are limited by the fact that a different sampling schedule was used in the SUNSHINE study resulting in only a small subset of all PK-data being available for the comparisons. The lack of a population PK-model limits the possibilities of further analysis of the data. Fidaxomicin is locally acting and the PK-data thus only relevant for assessing the safety. Overall, there is no indication that the systemic exposures of fidaxomicin and OP-1118 are higher in the paediatric population compared to the adult population.

The Applicant has provided acceptable responses to all pharmacokinetic issues. There are no objections to an approval of the Paediatric line extension of Dificlir from a pharmacokinetic point of view.

2.5. Clinical efficacy

2.5.1. Dose response studies

No dose-response studies were performed with paediatric subjects. The approach to paediatric dosing was agreed with PDCO and is captured in the Key Binding Elements of the PIP.

The adult fidaxomicin dose of 400 mg/day was selected from a Phase 2 study of 100, 200 and 400 mg/day, in which the highest dose was associated with the most favourable response (no primary failures, shortest time to diarrhoea resolution, highest proportion of subjects entirely free of CDI symptoms at EOT).

The paediatric weight-based dosing regimen for fidaxomicin, used in the paediatric studies, was selected by scaling from the vancomycin dose authorised in children for CDAD. The standard dose of vancomycin in adults is 500 mg/day, while that for fidaxomicin is 20% lower at 400 mg/day. Therefore, the total daily dose of fidaxomicin for paediatric subjects was chosen to be 20% lower (32 mg/kg) than the standard daily dose of vancomycin (40 mg/kg). Correspondingly, above a weight cut-off of ≥12.5 kg, the adult dose of 200 mg q12h (administered either as tablet or oral suspension) can be used. Scaling against vancomycin was considered appropriate by the MAH because neither drug is significantly absorbed from the gastrointestinal tract.

A 10-day treatment duration was selected for the paediatric population, as for adults, because clinical cure rates of 85.7% to 88.2% for fidaxomicin were seen in adult phase 3 studies with a 10-day treatment period.

2.5.2. Main studies

The single arm Phase 2 study OPT-80-206 used a different formulation than the to-be-marketed granules for suspension. Therefore, the main support for efficacy in the paediatric population comes from the randomised, single-blind, active comparator SUNSHINE study.

Study OPT-80-206

A Phase 2A, Multicentre, Open-label, Uncontrolled Study to Determine the Safety, Tolerability, and Pharmacokinetics of Fidaxomicin Oral Suspension or Tablets in Paediatric Subjects with *Clostridium difficile*–associated Diarrhoea

Methods

Study Participants

The study was conducted at 11 sites in the US and Canada.

Key inclusion criteria:

1) Male or female subjects 6 months to < 18 years of age diagnosed with CDAD, which was defined by a positive stool *C. difficile* toxin A and/or toxin B assay result within 48 hours of enrolment and:
    a) Subjects 6 to 23 months: >3 episodes of watery diarrhoea in the 24 hours prior to enrolment.
    b) Subjects 2 years to < 18 years: A change in bowel habits, with >3 unformed bowel movements (UBMs) in the 24 hours prior to enrolment.

Key exclusion criteria:

1) Need for concurrent use of oral vancomycin, metronidazole, or any other effective treatments for CDAD during therapy with fidaxomicin.
2) Fulminant colitis.
3) A history of inflammatory bowel disease (ulcerative colitis or Crohn's disease).
4) Need for concurrent use of the following P-glycoprotein inhibitors during therapy with fidaxomicin: cyclosporine, itraconazole, and ketoconazole; erythromycin, azithromycin, and clarithromycin; verapamil, dronedarone and amiodarone, captopril, carvedilol, conivaptan, diltiazem, felodipine, lopinavir and ritonavir, quercetin, quinidine, and ranolazine. Topical ointments were not excluded, nor were administration of any P-glycoprotein inhibitors during the follow up period.

No other antibacterials potentially effective against CDAD were permitted during the study unless specifically given because of primary treatment failure or recurrence. Anti-diarrhoeal medicines and drugs affecting peristalsis were to be avoided.

Treatments

Subjects aged 6 months to <6 years received weight-based doses of fidaxomicin oral suspension 32 mg/kg/day (maximum 400 mg/day), divided into 2 doses taken q12h. The amount of oral suspension was calculated based on the subject's weight and was calculated at enrollment and remained consistent throughout the treatment period. There was no further adjustment for changes in weight during the treatment period.

Subjects aged 6 years to <18 years received fidaxomicin 200 mg tablets, PO q12h.

The protocol was amended to allow a subject aged 6 years and older who could not swallow a tablet to receive a crushed tablet (if the oral suspension was not available), and to allow a subject to receive the full adult dose of 400 mg/day (either as oral suspension or tablets) if the weight requirement (≥ 12.5 kg) was met.

During the treatment period, a change of formulation or change in dosing was not allowed.

The subject received study medication administered orally with or without food each day for 10 days (20 doses; q12h regimen).

Objectives

The primary objective of this study was to investigate the safety, tolerability, and PK of fidaxomicin oral suspension or tablets in paediatric subjects, with CDAD, following the administration of doses given every 12 hours (q12h) for 10 consecutive days.

The secondary objective of the study was to evaluate the clinical outcome (clinical response at EOT and sustained clinical response through EOT + 28 days).

Outcomes/endpoints

Efficacy Variables included:

- Initial clinical response (ICR) rate at End of Treatment (EOT).

In subjects <2 years, positive clinical response was defined as absence of watery diarrhoea for two consecutive days with no requirement of further CDAD therapy within 2 days after completion of study drug.

In subjects between 2 and < 18 years, positive clinical response was defined as ≤3 unformed bowel movements (UBM) for two consecutive days with no requirement of further CDAD therapy during treatment and subjects remain well until the time of study drug discontinuation.

Clinical response was assessed at Day 10 or the last day of dosing if a positive clinical response was achieved before Day 10. Confirmation of a positive clinical response was assessed 2 to 3 days after the end of therapy.

Treatment failures were not evaluated further for clinical efficacy beyond the point of failure. Only subjects who achieved positive ICR were monitored for SCR and recurrence.

- Sustained clinical response (defined as no recurrence between EOT and EOT +28 days).
- Recurrence and time to recurrence (defined between EOT and EOT +28 days).
- Time to resolution of diarrhoea (defined from first study drug dose to last UBM before 2 consecutive days of ≤ 3 UBMs).
- Stool sample microbiology at pre-enrolment (Day 1), EOT, early termination and any unscheduled visit for recurrence, including susceptibility of screening isolates to reference antibiotics (fidaxomicin, vancomycin, metronidazole, rifaximin).

Safety Variables included:

Adverse Events, Vital signs, Laboratory parameters.

Toxin A/B testing was repeated at early termination visit for subjects who did not have a clinical response and at any unscheduled visit for recurrence, but not otherwise routinely after Day 1.

Sample size

The sample size was based on clinical and practical considerations, not on formal statistical power calculation. Up to 35 subjects were planned to be enrolled, stratified by age at enrolment:

- 6–23 months;
- 2 years to <6 years;
- 6 years to <12 years;
- 12 years to <18 years.

Statistical methods

Descriptive statistics were presented for all summarized data. Analyses of clinical outcome (except for recurrence) were performed using the mITT and PP populations.

The *safety population* included all subjects with any evaluable safety data who had received at least one dose of fidaxomicin. This population was the primary analysis set used in all safety summaries.

The *modified intent-to-treat (mITT) population* included all subjects with CDAD confirmed by a positive toxin assay within 24 hours before enrolment who received at least one dose of study medication. This population was one analysis set used in efficacy summaries.

The *per-protocol (PP) population* was another analysis set used in efficacy summaries. It consisted of subjects in the mITT population who met the following criteria:

- Met all of the inclusion criteria and met none of the exclusion criteria (unless deviations to either of these were documented and approved by the sponsor).
- Were exposed to a sufficient course of therapy: subjects required at least 3 complete days (6 active doses of fidaxomicin) to be considered treatment failures and 8 complete days (16 active doses of fidaxomicin) to be considered as having a positive clinical response.
- Had an end-of-therapy clinical evaluation.
- Did not have significant protocol violations, including use of concomitant CDAD therapy or other drugs that could have confounded the assessment of efficacy.

The *mITT population for recurrence and the PP population for recurrence* included subjects in the mITT and PP populations, respectively, who achieved a positive clinical response.

Subjects with the investigator's assessment of clinical response missing, as well as those who died before investigator assessed clinical response, were treated as clinical failures. Missing values in the investigator's classification of recurrence prior to EOT + 28 days were treated as recurrence. Missing dates and times were imputed.

For clinical response rate, recurrence, and sustained response, 2-sided 95% CIs were summarized for each age group and for all age groups combined. For time to recurrence, the survival function (in days) was estimated using the Kaplan-Meier method. For TTROD, subjects were censored at time of discontinuation, except for those subjects who completed the end-of-therapy visit and did not have resolution of diarrhoea, who were censored at 240 hours.

Results

Participant flow

A total of 38 subjects were enrolled.

Table 6. Subject Disposition, All Enrolled Subjects (SUNSHINE)

	Number of Subjects (%)				
	6–23 Mo (N=9)	2–5 Y, 11 Mo (N=8)	6–11 Y, 11 Mo (N=9)	12–17 Y, 11 Mo (N=12)	All Subjects (N=38)
Enrolled[a]	9	8	9	12	38
Completed end of therapy visit	9	5	9	12	35
Had recurrence visit or completed follow-up visit	8	6	9	12	35
Withdrawn during treatment period	0	3	0	0	3
Reason for withdrawal					
Adverse event	0	2 (25.0)	0	0	2 (5.3)
Withdrawal by subject	0	1 (12.5)	0	0	1 (2.6)
Protocol deviation	0	0	0	0	0
Treatment failure	0	0	0	0	0
Lost to follow-up	0	0	0	0	0
Other	0	0	0	0	0
Withdrawn during follow-up period	4	2	2	3	11
Reason for withdrawal					
Adverse event	1 (11.1)	0	0	0	1 (2.6)
Withdrawal by subject	0	0	0	0	0
Protocol deviation	0	0	0	0	0
Recurrence	2 (22.2)	2 (25.0)	2 (22.2)	3 (25.0)	9 (23.7)
Treatment failure	1 (11.1)[b]	0	0	0	1 (2.6)
Lost to follow-up	0	0	0	0	0
Other	0	0	0	0	0
Completed entire study	5 (55.6)	3 (37.5)	7 (77.8)	9 (75.0)	24 (63.2)

Source: Table 14.1.1.

[a]Two additional subjects (016-005 and 022-001) were enrolled but did not receive study medication; therefore, age category was not defined for these subjects.

[b]Subject 010-006 was determined to be a treatment failure at Day 10 of dosing and therefore was designated as completing therapy, but the primary disposition remained treatment failure.

Most subjects completed EOT and few were withdrawn during the treatment period, but only two-thirds of subjects completed the entire study. During the follow-up period (EOT to EOT + 28 days), the major reason for withdrawals was recurrence, occurring in almost a quarter of the subjects (n=9, 24 %). The lowest EOT and study completion rates were seen amongst subjects aged ≥2 to <6 years, unfortunately the age sub-group that also started with the smallest number of enrolled subjects.

Baseline data

Baseline disease severity categories were defined as follows:

- Mild: 4 to 5 UBMs/day or WBC count ≤12,000/mm³.
- Moderate: 6 to 9 UBMs/day or WBC count 12,001/mm3 to 15,000/mm³.
- Severe: ≥10 UBMs/day or WBC count ≥15,001/mm³.

Either of the defining characteristics (UBMs/day or WBC count) assigned a subject to a category, with a default to the more severe category when signs/symptoms overlapped.

Table 7. Demographics and Disease Characteristics, all enrolled subjects (OPT-80-206)

Parameter Category/Statistics	Number (%) of Subjects				
	≥ 6 to < 24 Months (n = 9)	≥ 2 to < 6 Years (n = 8)	≥ 6 to < 12 Years (n = 9)	≥ 12 to < 18 Years (n = 12)	All Subjects (n = 38)
Age (months)					
Mean (SD)	15.2 (3.6)	50.5 (10.8)	116.8 (18.7)	182.2 (19.3)	99.4 (68.9)
Median	14.0	47.0	127.0	189.0	101.5
Minimum - maximum	11 - 22	38 - 71	81 - 136	145 - 206	11 - 206
Sex					
Male	3 (33.3)	7 (87.5)	6 (66.7)	6 (50.0)	22 (57.9)
Female	6 (66.7)	1 (12.5)	3 (33.3)	6 (50.0)	16 (42.1)
Race					
White	9 (100.0)	5 (62.5)	8 (88.9)	11 (91.7)	33 (86.8)
Black or African American	0	1 (12.5)	1 (11.1)	0	2 (5.3)
Asian	0	1 (12.5)	0	0	1 (2.6)
American Indian or Alaska Native	0	0	0	1 (8.3)	1 (2.6)
Multiple	0	1 (12.5)	0	0	1 (2.6)
Baseline weight (kg)					
Mean (SD)	9.97 (1.16)	15.39 (3.53)	29.06 (8.96)	58.04 (21.70)	30.81 (23.63)
Median	9.70	16.20	28.40	55.85	25.25
Minimum - maximum	8.7 - 12.0	10.4 - 19.6	10.8 - 43.2	28.3 - 103.7	8.7 - 103.7
Body mass index (kg/m^2)					
Mean (SD)	16.74 (2.55) †	15.68 (1.29)	17.33 (3.72)	21.25 (3.80)	18.16 (3.80)
Median	15.80	15.25	17.30	21.75	17.15
Minimum - maximum	14.2 - 21.9	14.5 - 18.1	10.6 - 25.2	15.7 - 27.6	10.6 - 27.6
Baseline disease severity ‡					
Mild	4 (44.4)	4 (50.0)	6 (66.7)	9 (75.0)	23 (60.5)
Moderate	3 (33.3)	3 (37.5)	1 (11.1)	2 (16.7)	9 (23.7)
Severe	2 (22.2)	1 (12.5)	2 (22.2)	1 (8.3)	6 (15.8)
Number of UBMs 24 hours before therapy					
Mean (SD)	7.6 (5.4)	5.9 (1.7)	6.0 (2.3)	5.6 (2.2)	6.2 (3.2)
Median	6.0	5.5	5.0	5.0	5.0
Maximum - minimum	4 - 20	4 - 9	4 - 10	4 - 12	4 - 20

mITT: Modified Intent-to-Treat; UBM: unformed bowel movement; WBC: white blood cell.

† n = 7

‡ Baseline disease severity categories were defined as: mild = 4 to 5 UBM/day or WBC count ≤ 12000/mm^3; moderate = 6 to 9 UBM/day or WBC count 12001/mm^3 to 15000/mm^3; severe = ≥ 10 UBM/day or WBC count ≥ 15001/mm^3.

Source: OPT-80-206, Table 14.1.2.1

Medical history

Conditions reported by >10% of subjects at baseline included, as expected, gastrointestinal disorders (abdominal pain, constipation, diarrhoea, gastroesophageal reflux disease, nausea, and vomiting) and gastrointestinal-related infections and infestations (clostridial infection and *C. difficile* colitis), but also anaemia, gastrostomy tube insertion, pyrexia, otitis media, thrombocytopenia, failure to thrive, dehydration, esophagogastric fundoplasty, cerebral palsy, hypertension, sepsis, sinusitis, and tachycardia.

Overall, 23.7% of subjects had a history of neoplasms (benign, malignant, and unspecified).

Prior and concomitant medications

Prior to the study 36.8% of subjects had taken metronidazole and 23.7% had received oral vancomycin as an antidiarrheal/anti-inflammatory. Prior use of antidiarrheal and intestinal anti-inflammatory drugs was reported by 39.5% of subjects. Prior use of systemic antibiotics (not including those effective in the treatment of CDAD) was reported by 26.3% of subjects, including cephalosporins (13.2%), clindamycin (5.3%), and fluoroquinolones (2.6%), which have historically been considered to put adults at high risk for CDAD.

Overall, 18.4% of subjects received systemic antibiotics concomitantly with study medication, ranging from 11.1% to 25.0% across age groups. Piperacillin/tazobactam was the most frequently used concomitant antibiotic (13.2% of subjects). Metronidazole and vancomycin were each used concomitantly by 5.3% of subjects.

During the follow-up period, 26.3% of subjects received systemic antibiotics (not including those effective in the treatment of CDAD). Piperacillin/tazobactam was the most frequently used antibiotic (10.5% of subjects) during this period.

Compliance

A 100.0% compliance rate was reported for 84.2% of all subjects (Safety analysis set). All subjects with a compliance <100.0% were in the ≥2 to <6 years age category (4 subjects achieving between <20% and 80-<100% compliance).

Numbers analysed

Table 8. Analysis sets (OPT-80-206)

Analysis Set	Number (%) of Subjects				
	≥ 6 to < 24 Months (n = 9)	≥ 2 to < 6 Years (n = 8)	≥ 6 to < 12 Years (n = 9)	≥ 12 to < 18 Years (n = 12)	All Subjects (n = 38)
Enrolled	9 (100.0)	8 (100.0)	9 (100.0)	12 (100.0)	38 (100.0)
Safety analysis set	9 (100.0)	8 (100.0)	9 (100.0)	12 (100.0)	38 (100.0)
Plasma pharmacokinetic	8 (88.9)	7 (87.5)	9 (100.0)	12 (100.0)	36 (94.7)
Fecal pharmacokinetic	8 (88.9)	4 (50.0)	9 (100.0)	9 (75.0)	30 (78.9)
Modified Intent-to-Treat	9 (100.0)	8 (100.0)	9 (100.0)	12 (100.0)	38 (100.0)
Per Protocol	9 (100.0)	6 (75.0)	9 (100.0)	12 (100.0)	36 (94.7)
Modified Intent-to-Treat for recurrence	8 (88.9)	6 (75.0)	9 (100.0)	12 (100.0)	35 (92.1)
Per Protocol for recurrence	7 (77.8)	5 (62.5)	9 (100.0)	12 (100.0)	33 (86.8)
Completed EOT	9 (100.0)	5 (62.5)	9 (100.0)	12 (100.0)	35 (92.1)
Completed study	5 (55.6)	3 (37.5)	7 (77.8)	9 (75.0)	24 (63.2)

EOT: end-of-treatment (day 10)

Source: OPT-80-206, Table 14.1.1 and Table 14.1.3

Outcomes and estimation

Efficacy outcomes

Table 9. Efficacy Parameters for Fidaxomicin by Age Category, mITT (OPT-80-206)

	Number (%) of Subjects				
Table E1.	≥ 6 to < 24 Months (n = 9)	≥ 2 to < 6 Years (n = 8)	≥ 6 to < 12 Years (n = 9)	≥ 12 to < 18 Years (n = 12)	All Subjects (n = 38)
Clinical response at EOT					
Yes	8 (88.9)	6 (75.0)	9 (100.0)	12 (100.0)	35 (92.1)
95% confidence interval †	(68.4, 100.0)	(45.0, 100.0)	(100.0, 100.0)	(100.0, 100.0)	(83.5, 100.0)
Sustained clinical response at EOT + 28 days					
Yes	6 (66.7)	4 (50.0)	7 (77.8)	8 (66.7)	25 (65.8)
95% confidence interval †	(35.9, 97.5)	(15.4, 84.7)	(50.6, 100.0)	(40.0, 93.3)	(50.7, 80.9)
Time to resolution of diarrhoea					
50^{th} percentile (hours)	121	18	49	22	49
Recurrence by EOT + 28 days					
n	8	6	9	12	35
Yes	2 (25.0)	2 (33.3)	2 (22.2)	4 (33.3)	10 (28.6)
95% confidence interval †	(0.0, 55.0)	(0.0, 71.1)	(0.0, 49.4)	(6.7, 60.0)	(13.6, 43.5)

EOT: end-of-treatment (day 10); mITT: modified intent-to-treat

† Two-sided 95% point estimate confidence interval surrounding the sustained response rate.

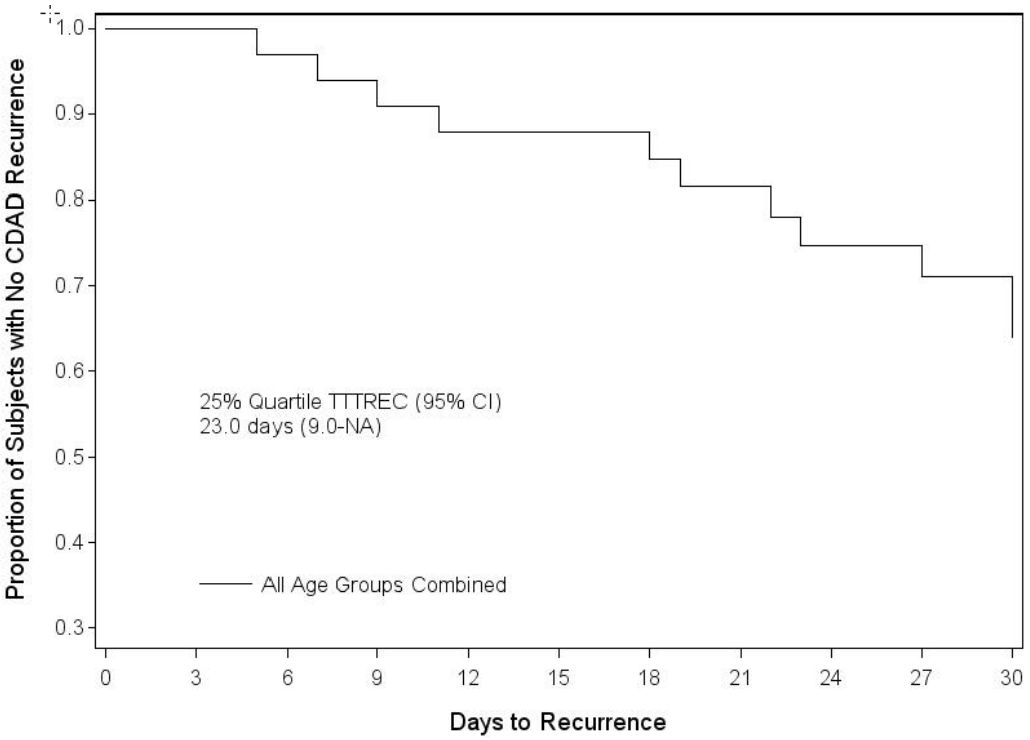
Source: Adapted from OPT-80-206, Table 14.2.1; Table 14.2.2; and Table 14.2.3.

Numerically lower clinical response (75%) and sustained clinical response (50%) rates were observed in the ≥2 to <6 years age group vs other age groups, but small sub-groups make this difficult to interpret. Lower compliance and lower EOT and study completion rates in this age group, which was already the smallest in size at study start, may be partly responsible for this finding.

The denominator used for SCR appears to be the mITT population rather than only the sub-group of subjects with clinical response at EOT (this differs from SUNSHINE). This is despite the fact the protocol states that only subjects who achieved positive ICR were monitored for SCR and recurrence, whereas treatment failures were not evaluated further for clinical efficacy beyond the point of failure. When the number of positive clinical responses is instead used as denominator, the overall SCR amongst responding subjects is 71.4%.

The median time to resolution of diarrhoea varied considerably between age groups.

Figure 1. Time to Recurrence of CDAD, All Age Groups, mITT (OPT-80-206)



The overall recurrence rate (28.6%) was consistent across the age sub-groups and is notably higher than that observed for fidaxomicin in SUNSHINE (11.8%), and also higher that that observed in Phase 3 studies of fidaxomicin in adults (14% pooled fidaxomicin subjects, mITT population). As seen in adult subjects, recurrence rate on fidaxomicin was approximately stable throughout the four weeks following EOT. Of the 10 paediatric subjects with recurrence, 9 subjects had one or more prior episode of CDAD or prior treatment for CDAD.

Microbiology

Table 10. Susceptibility of Screening Isolates by Clinical Response and Antibiotic, mITT (OPT-80-206)

Outcome	Antibiotic	Geometric Mean (µg/mL)	Range (µg/mL)	MIC_{50} (µg/mL)	MIC_{90} (µg/mL)
Cure (n = 28)	Fidaxomicin	0.45	0.020–1.00	0.500	1.000
	Vancomycin	1.13	0.500–4.00	1.000	2.000
	Metronidazole	0.64	0.250–2.00	0.500	1.000
	Rifaximin	0.05	0.015–33.00	0.030	33.00
Failure (n = 3)	Fidaxomicin	0.11	0.020–0.500	0.125	0.500
	Vancomycin	1.00	1.000–1.000	1.000	1.000
	Metronidazole	0.50	0.500–0.500	0.500	0.500
	Rifaximin	0.02	0.015–0.060	0.015	0.060

Source: Table 14.2.8.15.
mITT = modified intent to treat; MIC = minimum inhibitory concentration.

The MIC values of screening isolates associated with clinical failure were actually lower (MIC90 0.5 µg/mL) than those associated with clinical cure (MIC90 1 µg/mL). This suggests that clinical failure was not due to lack of susceptibility to fidaxomicin, and other factors such as concurrent infection with other GI pathogens, and tolerability and compliance of the treatment, may be involved.

Study 2819-CL-0202 ("SUNSHINE")

A phase 3, multicentre, investigator-blind, randomised, parallel-group study to investigate the safety and efficacy of a 10-day course of fidaxomicin oral suspension or tablets taken every q12h as compared to vancomycin oral liquid or capsules taken every q6h for 10 days in paediatric subjects with *Clostridium difficile*-associated diarrhoea.

Methods

Study Participants

The study was conducted in North America (23 sites) and Europe (Poland (9 sites), France (7 sites), Germany (7 sites), Romania (6 sites), Hungary (5 sites), Spain (5 sites), Italy (4 sites), Belgium (3 sites), Canada (3 sites) and Slovakia (2 sites).

Key inclusion criteria:

1. Male and female subjects from birth to < 18 years of age (US-only: aged ≥ 6 months to < 18 years) diagnosed with CDAD according to local diagnostic criteria. As a minimum there was to 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. difficil*e in stool and:
    a. Subject from birth to < 2 years of age: watery diarrhoea in the 24 hours prior to screening
    b. Subject ≥ 2 years to < 18 years of age: > 3 UBMs in the 24 hours prior to screening
2. For subjects < 5 years of age: negative rotavirus test (a pre-consent SOC test within 3 days of randomisation and after onset of diarrhoea was accepted).

The following Exclusion criteria applied:

1. Concurrent use of metronidazole, oral vancomycin or any other antibiotic treatments for CDAD. If the investigator felt the clinical imperative to begin treatment before knowing the laboratory result for toxigenic *C. difficile*, up to 4 doses but no more than 24 hours of treatment with metronidazole, oral vancomycin or any other effective treatment for CDAD were allowed.
2. Pseudomembranous colitis, fulminant colitis, toxic megacolon or ileus.
3. History of inflammatory bowel disease (e.g., ulcerative colitis or Crohn's disease).
4. Diarrhoea caused by an agent other than *C. difficile* (e.g., infections, infestations, drugs).
5. Known hypersensitivity to fidaxomicin, vancomycin or their excipients or to teicoplanin.
6. Subject had 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 diarrhoea.
7. Subject had a condition which, in the investigator's opinion, made the subject unsuitable for study participation.
8. France only: subject had a weight of < 2.5 kg (Amendment 4).

Treatments

Eligible subjects were randomised 2:1 to fidaxomicin or vancomycin groups. Subjects aged <6 years received oral liquid, while subjects ≥6 years received tablets. During the treatment period, a change of formulation or change in dosing was not allowed.

The subject received study medication administered orally with or without food each day for 10 days (20 doses; q12h regimen).

Table 11. Weight-based Dosing Instruction of the Fidaxomicin Oral Suspension (SUNSHINE)

Weight band of subject	Dose in mg/day (twice daily dosing)	mg/dose	Dose in mg/kg/day	Volume of fidaxomicin oral suspension to administer
< 3.9 kg	80 mg	40 mg	At least 20 mg/kg/d	1.0 mL
4.0-6.9 kg	160 mg	80 mg	22.9 to 40 mg/kg/d	2.0 mL
7.0-8.9 kg	240 mg	120 mg	26.7 to 34.3 mg/kg/d	3.0 mL
9.0-12.4 kg	320 mg	160 mg	25.6 to 35.6 mg/kg/d	4.0 mL
≥ 12.5 kg	400 mg	200 mg	Adult dose (max 32 mg/kg/d)	5.0 mL

Source: Adapted from Study Protocol 2819-CL-0202, Version 3.0, Table 3A.

If a subject aged ≥6 years could not swallow tablets or capsules, fidaxomicin oral suspension or vancomycin oral liquid could be given as per the subject's treatment allocation. During the treatment period, a change of formulation or change in dosing was not allowed.

Antimicrobial agents potentially useful in the treatment of CDAD (e.g., metronidazole, oral vancomycin, oral bacitracin, fusidic acid, rifaximin, nitazoxanide) or faecal transplantation were not permitted during the study, unless they were specifically given because of a primary treatment failure or suspected CDAD recurrence after a positive initial response. There were a number of drugs that were to be avoided during the study e.g. drugs which could affect peristalsis, loperamide.

Objectives

The primary objective of the study was to investigate the clinical response to fidaxomicin granules for oral suspension or tablets and vancomycin oral liquid or capsules of paediatric subjects with CDAD.

The secondary objectives of this study were to investigate the recurrence/sustained clinical response to and safety of fidaxomicin and vancomycin in paediatric subjects with CDAD, as well as palatability of the fidaxomicin oral suspension formulation.

Outcomes/endpoints

Primary efficacy variable

Confirmed Clinical Response (CCR) based on the assessment by the investigator at end of treatment (EOT) + 2 days in the Full Analysis Set (FAS) population, in subjects with a documented positive Initial Clinical Response (ICR). Subjects with no ICR were expected to have no CCR.

In subjects <2 years, CCR was defined as absence of watery diarrhoea for two consecutive days with no requirement of further CDAD therapy within 2 days after completion of study drug.

In subjects between 2 and < 18 years, CCR was defined as <3 unformed bowel movements (UBM) for two consecutive days with no requirement of further CDAD therapy during treatment.

Subjects who did not achieve positive ICR with CCR at EOT + 2 days were contacted again only at End of Study (EOS) for safety follow-up.

Secondary efficacy variables included:

- Initial clinical response (EOT).
- Sustained clinical response (defined as no recurrence at EOT + 9, 16, 23 and 30 days in a subject with CCR at EOT + 2 days).
- Global cure (defined as no recurrence at EOT + 9, 16, 23 and 30 days in a subject regardless of outcome at EOT + 2 days).
- Time to resolution of diarrhoea (defined from first study drug dose to last UBM before resolution of diarrhoea).
- Recurrence and time to recurrence (defined between EOT+2 days and EOT + 9, 16, 23 and 30 days), with recurrence of diarrhoea defined as reestablishment of diarrhoea to an extent that was greater than note on the last day of study drug.
- Stool sample microbiology at pre-enrolment (Day 1), EOT, early termination and any unscheduled visit for recurrence, including positivity for other pathogens, and susceptibility of screening *C. difficile* isolates to reference antibiotics (fidaxomicin, vancomycin, metronidazole, rifaximin).
- Palatability (subjects receiving the fidaxomicin oral suspension) on a 5-point rating svale (awful, poor, fair, good, excellent) on Day 1 and Day 7 ±1 of treatment.

Safety Variables included:

Adverse Events, Vital signs, Laboratory parameters.

Adverse Events of Special Interest (AESI) were pre-defined:

- Development of microbial resistance to fidaxomicin
- Hypersensitivity to fidaxomicin
- Gastrointestinal haemorrhage
- Haematological AEs: decreases in white blood cell (WBC), neutrophil and lymphocyte counts
- Hepatic laboratory value abnormalities
- Renal laboratory value abnormalities
- QT interval prolongation
- Lack of efficacy/lack of effect/treatment failure

Toxin A/B testing was repeated at EOT, early termination visit for subjects who did not have a clinical response and at any unscheduled visit for recurrence, but not otherwise routinely after Day 1.

Sample size

The sample size was for this study was agreed on with the Paediatric Development Committee (PDCO) as part of the PIP and was based on clinical and practical considerations, as the prevalence of the target disease amongst paediatric subjects is low. The study was not powered for hypothesis testing.

A total of 144 eligible subjects were planned to be randomised to either fidaxomicin or vancomycin in a 2:1 ratio (96 randomised to fidaxomicin and 48 to vancomycin), stratified by age at screening with at least 24 subjects in each age group:

- From birth to < 24 months (2 years) of age (6 months to < 24 months at US sites),
- ≥ 2 to < 6 years of age,
- ≥ 6 to < 12 years of age, and
- ≥ 12 to < 18 years of age.

Randomisation

Randomization 2:1, stratified by age group.

Blinding (masking)

The content of medication was unblinded to caregivers and delegated site staff members.

Statistical methods

The *full analysis set (FAS)*, was the primary analysis population, consisting of all randomised subjects who received at least 1 dose of study drug. This population was the analysis set used in demographic, baseline disease characteristic and efficacy summaries.

The *safety analysis set (SAF)* consists of all randomised subjects who received at least one dose of study drug (fidaxomicin or vancomycin). This population was the analysis set used in safety summaries.

The *intent-to-treat (ITT)* analysis set consists of all randomised subjects, irrespective of a subject having received a study drug (fidaxomicin or vancomycin) or not. In the ITT analysis set, subjects were allocated to the treatment group corresponding to the study medication they were randomised to (treatment allocation as randomised). This population was the analysis set used for sensitivity analysis of the efficacy summaries.

The *pharmacokinetics analysis set (PKAS)* consists of all subjects randomised to fidaxomicin, having received at least 1 dose of fidaxomicin and having at least 1 valid measurement of plasma concentration or faecal concentration of fidaxomicin or its main metabolite OP-1118.

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

Analysis of the secondary efficacy endpoints were based on both the FAS and ITT analysis sets, except for SCR (positive CCR subjects only), recurrence of CDAD (positive CCR subjects only) and palatability (subjects receiving oral liquid formulation of either study drug). Sustained clinical response, recurrence of CDAD and Global cure were analysed using the same statistical methods as outlined for the primary analysis.

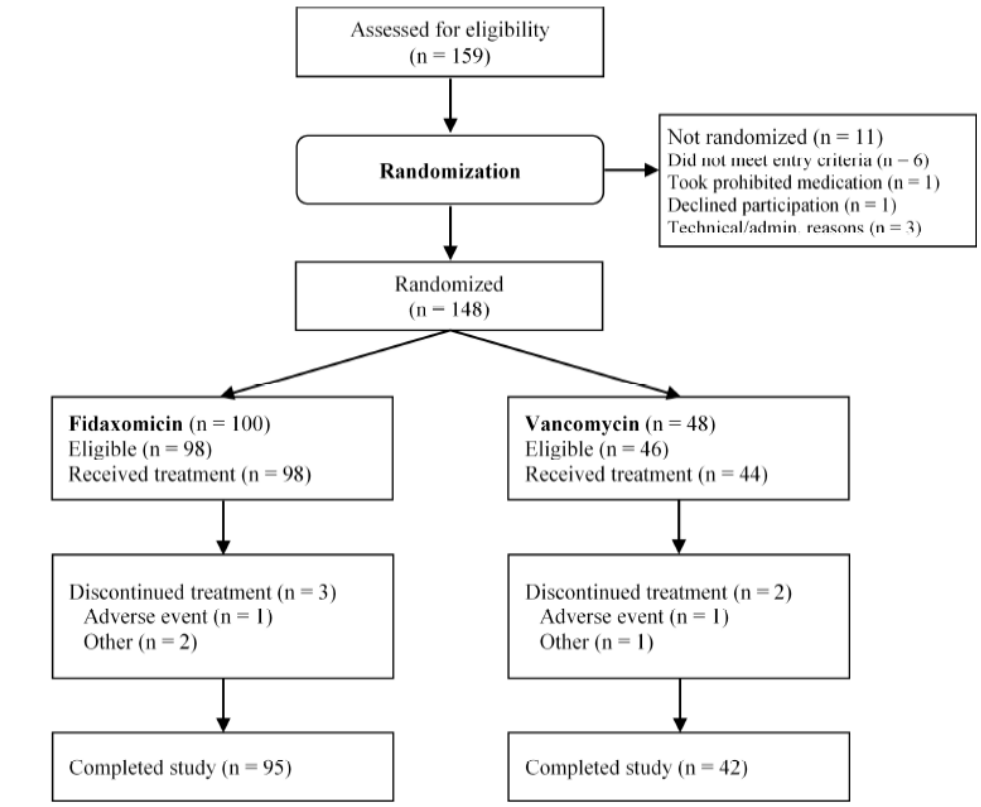
For TTROD and Time to recurrence, the survival functions in both treatment groups were estimated using the Kaplan-Meier method and displayed graphically. Comparison of the survival curves of the 2 treatment groups were done using log-rank test. Quartile estimates (25th, 50th [median], and 75th) along with 80th and 90th percentile estimates for the time to event and corresponding 2-sided 95%

CIs were computed for both treatment groups. For subjects in the ITT analysis set who did not receive any study drug (possibly received another drug for diarrhoea), day 10 was used as EOT date for the TTROD analysis. Subjects with CCR at EOT + 2 days who completed the follow-up period but did not experience a recurrence of CDAD were censored at EOT + day 30.

Summary tables for acceptability and palatability categories day 1 vs day 7 were presented for each treatment group for the total population as well as by age group.

Results

Participant flow



Source: Tables 12.1.1.1, 12.1.1.2, 12.1.1.3.1, Appendices 13.1.7.1, 13.2.1.1 and 13.2.2.2

The rate of study completion was good, at 97% for fidaxomicin, 91.3% for vancomycin, 95% overall.

Conduct of the study

A total of 4 amendments were made to the study protocol. The most clinically important are summarised below:

Amendment 2 (21-11-14): change to the study population to enrol paediatric subjects from birth; removal of visit/physical examination from EOS timepoint; change in timeframe for positive detection of CDAD from within 48 hours prior to randomisation to within 72 prior to randomisation.

Amendment 4 (6-11-15, therefore after subject enrolment had started): exclusion of subjects weighing <2.5 kg at the request of ANSM, on the grounds that dosing would be higher than recommended (>32 mg/kg).

Baseline data

Table 12. Demographics and disease characteristics, FAS (SUNSHINE)

Parameter	Number (%) of Subjects									
	< 24 Months		≥ 2 to < 6 Years		≥ 6 to < 12 Years		≥ 12 to < 18 Years		All Subjects	
Category/Statistic	Fidaxomicin (n = 20)	Vancomycin (n = 10)	Fidaxomicin (n = 32)	Vancomycin (n = 16)	Fidaxomicin (n = 26)	Vancomycin (n = 10)	Fidaxomicin (n = 20)	Vancomycin (n = 8)	Fidaxomicin (n = 98)	Vancomycin (n = 44)
Age (months)										
Mean (SD)	15.1 (6.0)	16.9 (4.5)	39.8 (12.0)	39.8 (12.9)	102.5 (23.1)	102.0 (21.4)	180.0 (19.1)	178.5 (13.5)	80.0 (62.2)	73.9 (60.0)
Median	15.0	18.0	36.0	36.0	102.0	102.0	180.0	180.0	60.0	48.0
Min - max	1 - 23	8 - 23	24 - 60	24 - 60	72 - 132	72 - 132	144 - 204	156 - 204	1 - 204	8 - 204
Sex										
Male	11 (55.0)	6 (60.0)	20 (62.5)	10 (62.5)	18 (69.2)	6 (60.0)	8 (40.0)	3 (37.5)	57 (58.2)	25 (56.8)
Female	9 (45.0)	4 (40.0)	12 (37.5)	6 (37.5)	8 (30.8)	4 (40.0)	12 (60.0)	5 (62.5)	41 (41.8)	19 (43.2)
Race										
White	14 (70.0)	9 (90.0)	25 (78.1)	13 (81.3)	24 (92.3)	7 (70.0)	18 (90.0)	6 (75.0)	81 (82.7)	35 (79.5)
Black/ African American	1 (5.0)	0	2 (6.3)	0	2 (7.7)	0	1 (5.0)	2 (25.0)	6 (6.1)	2 (4.5)
Asian	1 (5.0)	0	1 (3.1)	0	0	0	0	0	2 (2.0)	0
Other	2 (10.0)	0	2 (6.3)	1 (6.3)	0	0	0	0	4 (4.1)	1 (2.3)
Missing	2 (10.0)	1 (10.0)	2 (6.3)	2 (12.5)	0	3 (30.0)	1 (5.0)	0	5 (5.1)	6 (13.6)
Weight (kg)										
Mean (SD)	9.14 (2.42)	10.28 (2.28)	15.80 (4.29)	15.55 (3.29)	29.13 (9.08)	30.13 (9.76)	60.88 (16.85)	44.60 (4.81)	27.18 (20.71)	22.95 (13.62)
Median	8.85	10.45	14.05	14.50	26.70	28.60	55.20	44.65	19.15	17.90
Min - max	4.3 - 13.3	5.8 - 13.8	9.9 - 30.8	10.8 - 22.3	17.0 - 54.0	18.0 - 46.3	35.3 - 100.0	38.6 - 52.1	4.3 - 100.0	5.8 - 52.1
Body mass index (kg/m^2)										
Mean (SD)	15.76 (1.59)	15.93 (2.49)	15.88 (2.19)	15.71 (1.63)	16.15 (3.03)	17.13 (2.82)	22.96 (6.64)	17.41 (2.88)	17.33 (4.55)	16.39 (2.41)
Median	15.56	15.93	15.55	15.48	15.29	17.00	19.68	16.23	16.07	16.17
Min - max	13.1 - 18.3	12.4 - 20.8	12.6 - 24.1	13.2 - 19.1	12.4 - 24.1	12.6 - 21.4	16.5 - 38.2	14.5 - 22.9	12.4 - 38.2	12.4 - 22.9
Number of subjects with diarrhea due to confirmed CDAD within 3 months before screening										
1 episode	4 (20.0)	1 (10.0)	9 (28.1)	3 (18.8)	4 (15.4)	1 (10.0)	4 (20.0)	2 (25.0)	21 (21.4)	7 (15.9)
2 episodes	1 (5.0)	1 (10.0)	3 (9.4)	1 (6.3)	0	0	1 (5.0)	0	5 (5.1)	2 (4.5)
≥ 3 episodes	0	1 (10.0)	2 (6.3)	0	0	0	0	0	2 (2.0)	1 (2.3)
Unknown	1 (5.0)	1 (10.0)	0	1 (6.3)	1 (3.8)	0	1 (5.0)	1 (12.5)	3 (3.1)	3 (6.8)
Number of UBMs 24 hours before therapy †										
n	-	-	32	16	26	9	20	8	78	33
Mean (SD)	-	-	6.3 (5.7)	6.6 (6.3)	7.5 (8.7)	5.3 (3.7)	5.1 (2.5)	6.8 (7.1)	6.4 (6.3)	6.3 (5.8)
Median	-	-	4.0	4.0	6.0	4.0	4.0	4.5	5.0	4.0
Min - max	-	-	3 - 30	3 - 24	3 - 48	3 - 15	3 - 12	3 - 24	3 - 48	3 - 24

UBM: unformed bowel movement. † Only recorded for subjects ≥ 24 months of age. Watery diarrhea was reported for all subjects < 24 months of age.

Source: SUNSHINE, Table 12.1.2.1.1; Table 12.1.2.1.4; Table 12.1.2.2.1.1.1; Table 12.1.2.2.1.1.2; Table 12.1.2.2.2.1.1 and Table 12.1.2.2.2.1.2

There was only one subject included below the age of 6 months (fidaxomicin group, enrolled in Italy). The lowest bodyweight enrolled was 4.3 kg.

Two subjects received a single dose of metronidazole day one of the study treatment period most likely prior to the start of study drug. Two subjects received intravenous vancomycin which is not considered effective against CDI, one subject for a single day (day 12) and one subject for approximately 4 days, prior and concomitant to study medication. The administration of metronidazole and vancomycin in these subjects did likely not have an impact on the outcome of the CDI episodes.

At screening only 31 (36.5%) subjects randomised to fidaxomicin and 19 (48.7%) subjects randomised to vancomycin were tested positive for *C. difficile* toxin by the central laboratory ELISA, while all subjects were positive according to local laboratory. The differences noted may be attributable to differences between techniques. In addition, the lack of positive testing at the central laboratory may be that the cause of GI symptoms was not *C. difficile* in all cases but other GI organisms or non-infectious causes of diarrhoea, given the uncertainties regarding the definitive diagnosis of CDAD especially in the youngest children, who may carry *C. difficile* without apparent disease, and who also commonly suffer diarrheal illnesses secondary to other pathogens.

A substantial proportion of subjects (43.9% fidaxomicin, 50% vancomycin) tested positive at Screening for GI organisms other than *C. difficile*. The toxins detected in the study population were a mix of bacterial and viral, and several subjects had more than 1 pathogen.

Medical history

Risk factors that contributed to the current episode of *C. difficile* infection were recorded for 79.6% subjects overall, most importantly the use of antibiotics in 51.0% subjects in the fidaxomicin group and 65.9% subjects in the vancomycin group. Cancer as a risk factor was recorded in around 40% of subjects overall, with a similar percentage of subjects affected in both treatment groups. (Around a third of adult subjects in the Phase 3b/4 adult clinical study also had a medical history of neoplasm).

In the 3 months prior to screening, 40% had experienced prior diarrhoea episodes (treated with antibacterial medications in 25%) and 27% had had prior diarrhoea episodes with confirmed CDAD (treated with antibiotics in 22%). All these characteristics of diarrhoea history were found in a greater proportion of subjects in the fidaxomicin group compared with those in the vancomycin group, e.g., prior diarrhoea episodes in 43% and 34% subjects, respectively. Multiple previous CDAD recurrences were also reported in some subjects in the previous 3 months; 2 episodes in around 5% of subjects and ≥3 episodes in around 2% of subjects (similar between treatment groups).

Most subjects (61%) had mild CDAD, as defined by 4 to 5 unformed bowel movements (UBMs) per day or a white blood cell count ≤ 12000/mm^3. All subjects except one (result missing) were positive at screening for one or both *C. difficile* toxins A and B, and all subjects except one (not tested) <5 years of age had a negative rotavirus test.

Prior and concomitant medications

Previous medications were used by 98.6% subjects, most frequently antibacterials for systemic use (88.7%) and ophthalmological medicines (75.4%). Of note, a greater proportion of subjects in the fidaxomicin group compared with the vancomycin group had previously taken antidiarrhoeals, intestinal antiinflammatory/ antiinfective agents (69.4% vs 56.8%), antiemetics and antinauseants (43.9% vs 31.8%), mineral supplements (33.7 vs 18.2%) and drugs for constipation (34.7% vs 13.6%). Notably, 39.4% of subjects had received vancomycin and 40.8% metronidazole as previous medications.

The most frequently recorded concomitant medications (by therapeutic subgroup) were antibacterials for systemic use (71.1%) and ophthalmological medicines (71.1%), antidiarrheals, intestinal anti-

inflammatory /anti-infective agents (62.0% subjects), stomatological preparations (59.2% subjects), drugs for acid related disorders (51.4% subjects) and analgesics (56.3% subjects). Low and similar proportions of subjects in both treatment groups took prohibited medications during the study (6.1% vs 4.5%).

A difference between the treatment groups was reported in the use of the following relevant concomitant medications: antidiarrhoeals, intestinal anti-inflammatory/anti-infective agents (67.3% in the fidaxomicin group versus 50.0% in the vancomycin group), drugs for constipation (34.7% versus 22.7%) and mineral supplements (31.6% versus 22.7%).

Compliance

The total volume of liquid dosing administered for fidaxomicin (mean 88.4 g, median 96.1 g) was approximately half that for vancomycin (mean 177.2 g, median 186.7 g). Meanwhile the total number of tablets/capsules administered for fidaxomicin (mean 19.9, median 20) was approximately half that for vancomycin (mean 38.1, median 40). This may impact the tolerability in paediatric subjects. Compliance was similar between tablets/capsules and granules for oral suspension/oral liquid, with both treatments.

Treatment compliance calculated as the actual amount of drug received as percentage of planned amount of drug was high, with a mean of 98.0% in the fidaxomicin group and 95.8% in the vancomycin group. A lower percentage of subjects in the fidaxomicin group had a compliance of <80% than in the vancomycin group (4.4% versus 12.9%), which the Applicant notes could have contributed to the numerically lower efficacy of vancomycin.

The median duration of treatment was 11.0 days in both treatment groups and mean (SD) duration 10.6 (1.0) days for fidaxomicin and 10.5 (1.1) days for vancomycin.

Numbers analysed

Table 13. Subject disposition, all randomised subjects (SUNSHINE)

Analysis Set	Number (%) of Subjects									
	< 24 Months		≥ 2 to < 6 Years		≥ 6 to < 12 Years		≥ 12 to < 18 Years		All Subjects	
	Fidaxomicin (n = 20)	Vancomycin (n = 10)	Fidaxomicin (n = 33)	Vancomycin (n = 16)	Fidaxomicin (n = 27)	Vancomycin (n = 13)	Fidaxomicin (n = 20)	Vancomycin (n = 9)	Fidaxomicin (n = 100)	Vancomycin (n = 48)
Randomised	20 (100.0)	10 (100.0)	33 (100.0)	16 (100.0)	27 (100.0)	13 (100.0)	20 (100.0)	9 (100.0)	100 (100.0)	48 (100.0)
Intent-to-Treat	20 (100.0)	10 (100.0)	33 (100.0)	16 (100.0)	27 (100.0)	13 (100.0)	20 (100.0)	9 (100.0)	100 (100.0)	48 (100.0)
Full analysis set	20 (100.0)	10 (100.0)	32 (97.0)	16 (100.0)	26 (96.3)	10 (76.9)	20 (100.0)	8 (88.9)	98 (98.0)	44 (91.7)
Safety	20 (100.0)	10 (100.0)	32 (97.0)	16 (100.0)	26 (96.3)	10 (76.9)	20 (100.0)	8 (88.9)	98 (98.0)	44 (91.7)
Pharmacokinetic	20 (100.0)	0	30 (90.9)	0	25 (92.6)	0	20 (100.0)	0	95 (95.0)	0

Source: SUNSHINE, Table 12.1.1.2

Table 14. Protocol deviations (SUNSHINE)

Type of Deviation	Fidaxomicin (n = 98)	Vancomycin (n = 44)	Total (n = 142)
Any deviation	11 (11.2)	9 (20.5)	20 (14.1)
Entered into the study even though they did not satisfy entry criteria (PD1)	1 (1.0)	2 (4.5)	3 (2.1)
Developed withdrawal criteria during the study and was not withdrawn (PD2)	0	0	0
Received wrong treatment or incorrect dose (PD3)	2 (2.0)	5 (11.4)	7 (4.9)
Received excluded concomitant treatment (PD4)	8 (8.2)	2 (4.5)	10 (7.0)

PD: protocol deviation.

The table gives the number (percentage) of patients.

One patient randomized to fidaxomicin entered the study without satisfying all entry criteria. The patient was included in the ITT analysis set and excluded from the FAS.

Source: Table 12.1.1.5.1, Appendix 13.2.2.1

The rate of protocol deviations in the vancomycin group was nearly double that in the fidaxomicin group. The nature of the protocol deviations is relevant given the imbalance between treatment groups and the small overall size of the study was discussed by the MAH during the procedure.

Outcomes and estimation

Primary efficacy analysis

Table 15. Confirmed Clinical Response at EOT + 2 Days by Age, FAS (SUNSHINE)

Outcome	Number (%) of Subjects									
	< 24 Months		≥ 2 to < 6 Years		≥ 6 to < 12 Years		≥ 12 to < 18 Years		All ages	
	Fidax (n = 20)	Vanc (n = 10)	Fidax (n = 32)	Vanc (n = 16)	Fidax (n = 26)	Vanc (n = 10)	Fidax (n = 20)	Vanc (n = 8)	Fidax (n = 98)	Vanc (n = 44)
Confirmed clinical response at EOT + 2 days#										
Yes	13 (65.0)	9 (90.0)	25 (78.1)	12 (75.0)	23 (88.5)	5 (50.0)	15 (75.0)	5 (62.5)	76 (77.6)	31 (70.5)
95% CI†	(40.8, 84.6)	(55.5, 99.7)	(60.0, 90.7)	(47.6, 92.7)	(69.8, 97.6)	(18.7, 81.3)	(50.9, 91.3)	(24.5, 91.5)	(68.0, 85.4)	(54.8, 83.2)
Missing	0	0	0	1	2 (7.7)	0	1 (5.0)	0	3	1
Difference between treatment groups in the confirmed clinical response										
Difference	-25.0		3.1		38.5		12.5		7.5 †*	
95% CI†	(-53.0, 3.0)		(-22.5, 28.7)		(5.1, 71.8)		(-26.0, 51.0)		(-7.4, 23.9)	

EOT: end-of-treatment (day 10).

Results without imputation of missing CCR.

† Based on exact binomial distribution, presented for treatment proportion and treatment difference for each age category.

* Adjusted difference calculated using a stratified Cochran-Mantel-Haenszel. The stratification levels correspond to the age categories defined for randomization purposes.

Source: Adapted from SUNSHINE, Tables 12.3.1.1 and 12.3.1.7.1

The overall rate of CCR (77.6% fidaxomicin, 70.5% vancomycin) is lower than that observed in Phase 3 studies of fidaxomicin in adults (88% pooled fidaxomicin subjects, 86% pooled vancomycin subjects, mITT population) and also lower than the rate of clinical response at EOT observed in OPT-80-206 (92%).

Analysis of the primary efficacy endpoint (CCR) using the ITT population was consistent with primary analysis: 76.0% vs 64.6%, adjusted difference 11.3% (95% CI: -4.0%, 27.3%).

Sensitivity analysis of the primary efficacy endpoint (CCR) excluding 2 subjects (both fidaxomicin) from site 10014, following early termination of the study at the site due to procedural non-compliance, was also consistent with primary analysis.

A numerically lower CCR rate was observed for fidaxomicin in the <2 years age group (65.0% vs 90.0%), but small sub-group size makes this difficult to interpret. The Applicant states that efficacy of fidaxomicin may have been impacted by the deaths of 3 subjects in this treatment group due to complications of prior disease. However, 2 subjects in the vancomycin group also died due to complications of prior disease. Furthermore, all deaths reported in the study occurred during the follow-up period, after CCR had already been determined.

Secondary efficacy analyses

Table 16. Secondary Efficacy Parameters for Fidaxomicin by Age, FAS (SUNSHINE)

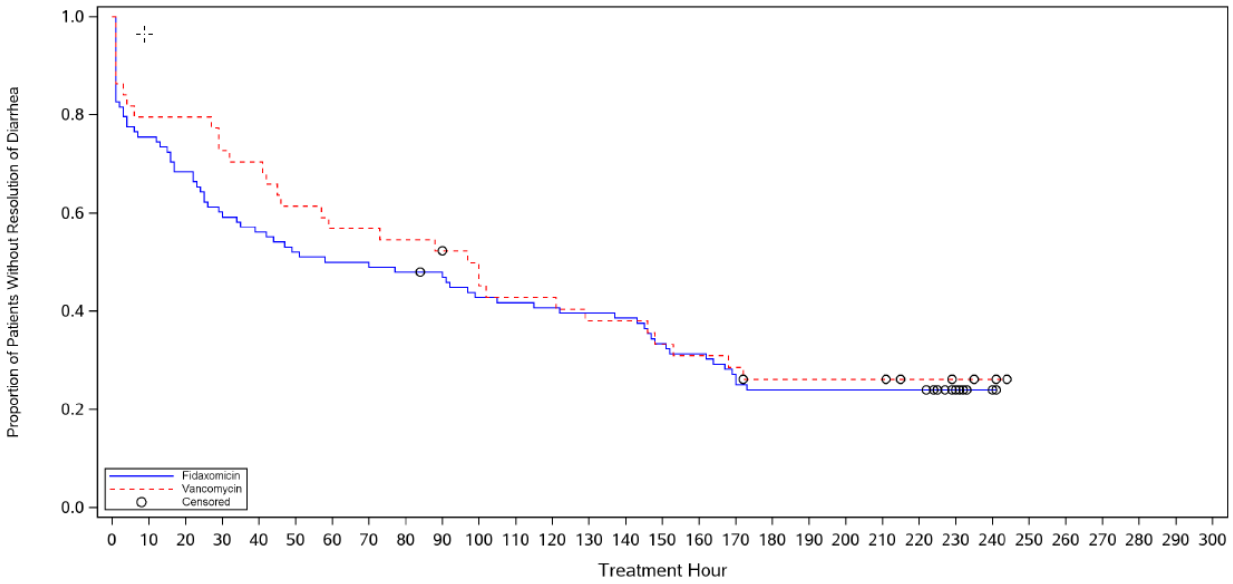
	< 24 Months		≥ 2 to < 6 Years		≥ 6 to < 12 Years		≥ 12 to < 18 Years		All Subjects	
	Fidax (n=20)	Vanc (n=10)	Fidax (n=32)	Vanc (n=16)	Fidax (n=26)	Vanc (n=10)	Fidax (n=20)	Vanc (n=8)	Fidax (n=98)	Vanc (n=44)
Initial clinical response at EOT										
Number (%) of subjects	13 (65.0)	9 (90.0)	26 (81.3)	13 (81.3)	24 (92.3)	8 (80.0)	16 (80.0)	6 (75.0)	79 (80.6)	36 (81.8)
Global cure at EOT + 30 days										
Number (%) of subjects	11 (55.0)	7 (70.0)	21 (65.6)	8 (50.0)	22 (84.6)	5 (50.0)	13 (65.0)	5 (62.5)	67 (68.4)	22 (50.0)
95% confidence interval	(31.5, 76.9)	(34.8, 93.3)	(46.8, 81.4)	(24.7, 73.5)	(65.1, 95.6)	(12.2, 73.8)	(40.8, 84.6)	(8.5, 75.5)	(58.2, 77.4)	(34.6, 65.4)
Difference (%)									18.8	
95% CI									(1.5, 35.5)	
Sustained clinical response at EOT + 30 days										
n*	13	9	25	12	23	5	15	5	76	31
Number (%) of subjects	11 (84.6)	7 (77.8)	21 (84.0)	8 (66.7)	21 (91.3)	4 (80.0)	12 (80.0)	3 (60.0)	65 (85.5)	22 (71.0)
95% confidence interval	(54.6, 98.1)	(40.0, 97.2)	(63.9, 95.5)	(34.9, 90.1)	(72.0, 98.9)	(28.4, 99.5)	(51.9, 95.7)	(14.7, 94.7)	(75.6, 92.5)	(52.0, 85.8)
Difference (%)									15.8	
95% CI									(-0.5, 34.5)	
Recurrence at EOT + 30 days										
n*	13	9	25	12	23	5	15	5	76	31
Number (%) of subjects	2 (15.4)	2 (22.2)	3 (12.0)	4 (33.39	2 (8.7)	1 (20.0)	2 (13.3)	2 (40.0)	9 (11.8)	9 (29.0)
95% confidence interval	(1.9, 45.4)	(2.8, 60.0)	(2.5, 31.2)	(9.9, 65.1)	(1.1, 28.0)	(0.5, 71.6)	(1.7, 40.5)	(5.3, 85.3)	(5.6, 21.3)	(14.2, 48.0)
Difference (%)									-15.8	
95% CI									(-34.5, 0.5)	
Time to resolution of diarrhoea										
n*	13	9	25	12	23	5	15	5	76	31
Mean (hours)	77.6	68.1	61.0	73.1	43.7	37.4	47.3	74.7	55.1	63.2
Median (hours)	35.0	44.0	27.5	78.0	24.0	15.0	19.5	52.0	25.5	45.5
Time to Recurrence										
n*	13	9	25	12	23	5	15	5	76	31
Mean (hours)	13.0	6.0	6.0	8.3	17.0	6.0	14.5	15.5	11.9	9.1
Median (hours)	13.0	6.0	7.0	7.5	17.0	6.0	14.5	15.5	11.0	7.0

EOT: end-of-treatment (day 10)

* Subjects with CCR only.

Source: Adapted from SUNSHINE, Table 12.3.1.1; Table 12.3.1.7.1; Table 12.3.2.1; Table 12.3.2.5.1; Table 12.3.4.1; Table 12.3.3.5; Table 12.3.4.5.1; Tables 12.3.6.2 to 12.3.6.5.

Figure 2. Time to Resolution of Diarrhoea, All Age Groups, FAS (SUNSHINE)

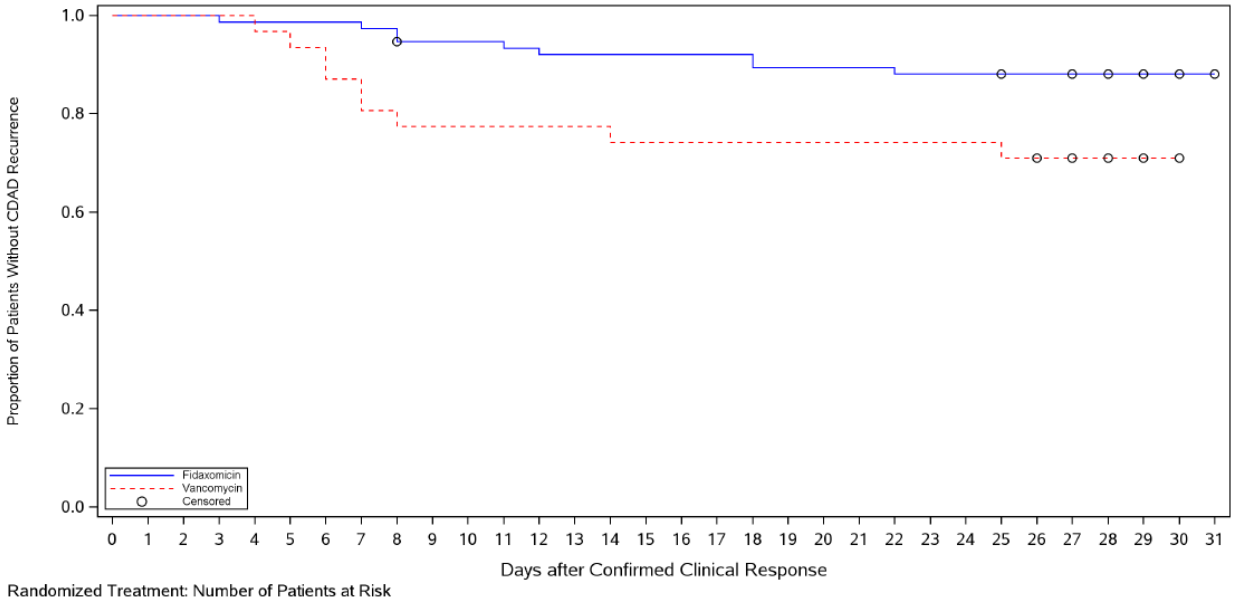


Randomized Treatment: Number of Patients at Risk

Fidaxomicin	98	74	67	59	55	51	49	49	47	46	41	40	39	38	37	32	30	26	23	23	23	23	23	9	2	0	0	0	0	0	0
Vancomycin	44	35	35	32	31	27	25	25	24	23	21	18	18	16	16	14	13	12	10	10	10	10	8	7	2	0	0	0	0	0	0

EOT: End of Treatment.
Patients who completed the 10 day treatment period but did not show resolution of diarrhea until EOT were censored at Day 10 (240 hours).
Patients who did not complete the 10 day treatment period, discontinued treatment earlier but did not show resolution of diarrhea until day of discontinuation, were censored at day of discontinuation (days converted to hours).
Patients whose diarrhea did not continue after the first dose are included with a time to resolution to diarrhea of 1 hour.

Figure 3. Time to Recurrence of CDAD, All Age Groups, FAS (SUNSHINE)



Randomized Treatment: Number of Patients at Risk

Fidaxomicin	76	76	76	76	75	75	75	75	74	71	71	71	70	69	69	69	69	69	69	67	67	67	67	66	66	66	65	65	52	35	4	1
Vancomycin	31	31	31	31	31	30	29	27	25	24	24	24	24	24	24	23	23	23	23	23	23	23	23	23	23	23	22	20	17	12	1	0

EOT: End of Treatment.
Patients with confirmed clinical response at EOT+2 days, who completed the Follow-up period but did not experience a recurrence of CDAD were censored at EOT+30 days and those who did not complete the Follow-up period and discontinued during this period and did not experience a recurrence of CDAD were censored at day of discontinuation.

Numerically lower initial clinical response and global cure rates were observed with fidaxomicin in the <2 years age group vs other age groups. However, the rate of SCR was comparable across age sub-groups and consistently higher for fidaxomicin than vancomycin, indicating that subjects with successful CCR from fidaxomicin at EOT + 2 days tended to remain clinically cured rather than experience recurrence, regardless of age group. Note that the denominator used for SCR is the sub-group of subjects who demonstrated positive CCR (this differs from OPT-80-206).

The overall recurrence rate amongst fidaxomicin subjects (11.8%) was comparable to that observed in Phase 3 studies of fidaxomicin in adults (14% pooled fidaxomicin subjects, mITT population), while the recurrence rate amongst vancomycin subjects was higher than for fidaxomicin subjects (29%), which is also consistent with that observed in adults (26% pooled vancomycin subjects, mITT population). Most recurrences on vancomycin (7/9) had occurred by EOT + 9 days, whereas recurrences on fidaxomicin occurred at a more stable rate during three weeks after EOT. All reported recurrences in both treatment groups had occurred by EOT + 23 days. This pattern reflects what was observed in the adult clinical programme, where the effect of fidaxomicin on recurrence rates was most pronounced in the initial two weeks after completing therapy.

Microbiology

While 69% of fidaxomicin and 79.5% of vancomycin subjects were confirmed positive for *C. difficile* on Screening culture, just 1.2% and 6.1%, respectively, remained positive at EOT. Interestingly, only 33.3% of clinical recurrences on fidaxomicin and 50% on vancomycin were positive again for *C. difficile* on culture at the time of recurrence.

Fidaxomicin MIC90 for *C. difficile* was ≤0.25 µg/mL for Screening, EOT and Recurrence isolates. The geometric mean fidaxomicin MIC was 0.1 µg/mL for recurrences. This suggests that recurrence was not due to lack of susceptibility to fidaxomicin.

Palatability

For FAS subjects receiving fidaxomicin granules for oral suspension (n=67), the palatability was assessed as "good" in 19/55 (34.5%) subjects and "excellent" in 13/55 (23.6%) subjects on day 1 and as "good" in 21/52 (40.4%) subjects and "excellent" in 16/52 (30.8%) subjects on day 7. These results were numerically slightly better than for FAS subjects receiving vancomycin oral liquid at both time points (28% and 16% Day 1, 36% and 12% Day 7). Assessments were missing for fidaxomicin in 12/67 (18%) and 15/67 (22%) at Day 1 and 7, respectively, and for vancomycin in 5/30 (17%) at both timepoints.

Summary of main study

The following tables summarise the efficacy results from the phase III study supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 17. Summary of efficacy for SUNSHINE trial

<table>
<tr><td colspan="4"><u>Title:</u> A phase 3, multicentre, investigator-blind, randomised, parallel-group study to investigate the safety and efficacy of a 10-day course of fidaxomicin oral suspension or tablets taken every q12h as compared to vancomycin oral liquid or capsules taken every q6h for 10 days in paediatric subjects with Clostridium difficile-associated diarrhoea</td></tr>
<tr><td>Study identifier</td><td colspan="3">Study 2819-CL-0202 (SUNSHINE)</td></tr>
<tr><td rowspan="2">Design</td><td colspan="3">Single-blind, 2:1 randomisation fidaxomicin : vancomycin, inpatient/outpatient, multicentre (US and Europe), subjects ≥6 months to <18 years,</td></tr>
<tr><td colspan="2">Treatment period:
Follow-up period:</td><td>10 Days
30 Days</td></tr>
<tr><td>Hypothesis</td><td colspan="3">Descriptive</td></tr>
<tr><td rowspan="2">Treatments groups</td><td colspan="2">Fidaxomicin</td><td><u>Birth to <6 years</u>: Oral suspension, 32 mg/kg/d (max 400 mg/day) in 2 doses 10 days
<table>
<tr><th>Weight band</th><th>BD dose</th></tr>
<tr><td>< 3.9 kg</td><td>40 mg</td></tr>
<tr><td>4.0-6.9 kg</td><td>80 mg</td></tr>
<tr><td>7.0-8.9 kg</td><td>120 mg</td></tr>
<tr><td>9.0-12.4 kg</td><td>160 mg</td></tr>
<tr><td>≥ 12.5 kg</td><td>200 mg</td></tr>
</table>
<u>≥6 years to <18 years</u>: Tablets, 200 mg BD, 10 days</td></tr>
<tr><td colspan="2">Vancomycin</td><td><u>Birth to <6 years</u>: Oral liquid, 40 mg/kg/day (max. 500 mg/day) in 4 doses, 10 days

<u>≥6 years to <18 years</u>: Capsules, 125 mg QDS, 10 days</td></tr>
<tr><td>Endpoints and definitions</td><td>Primary efficacy variable</td><td>Confirmed Clinical Response (CCR) at End of Therapy (EOT) + 2 days (FAS)</td><td><u><2 years</u>: absence of watery diarrhoea for 2 consecutive days.
<u>2 to <18 years</u>: <3 unformed bowel movements (UBM) for 2 consecutive days.
No requirement of further CDAD therapy within 2 days of EOT.</td></tr>
</table>

	Key secondary efficacy variable	Recurrence within EOT + 30 days (in subjects with positive CCR)	Reestablishment of diarrhoea to an extent that was greater than note on the last day of study drug.
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Full Analysis Set (all randomised subjects who received at least 1 dose of study drug)		
Descriptive statistics and estimate variability	**Treatment group**	**Fidaxomicin**	**Vancomycin**
	Number of subjects	98	44
	CCR at EOT + 2 days (%Yes)	77.6%	70.5%
	95% Confidence Interval	68.0, 85.4	54.8, 83.2
	Comparison	Adjusted* % difference	7.5%
		Adjusted* 95% Confidence Interval	-7.4, 23.9
Analysis description	**Key secondary efficacy analysis**		
Analysis population and time point description	FAS subjects with positive CCR		
	Number of subjects	76	31
	Recurrence by EOT + 30 days (%Yes)	11.8%	29.0%
	95% Confidence Interval	5.6, 21.3	14.2, 48.0
	Comparison	Adjusted* % difference	-15.8%
		Adjusted* 95% Confidence Interval	-34.5, 0.5
* Adjusted treatment difference of proportions was calculated using a stratified Cochran-Mantel-Haenszel method. The stratification levels correspond to the age groups defined for randomization purposes. Binomial exact 95% CIs are presented for treatment proportion and treatment difference, while Newcombe 95% CIs presented for adjusted treatment difference.			

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The paediatric clinical studies were designed in accordance with the agreed Paediatric Investigation Plan. Although not powered for statistical testing, the objectives, definitions (disease, cure, failure, recurrence), inclusion and exclusion criteria, comparator (for SUNSHINE) and clinical endpoints generally reflected those applied in the adult clinical development programme. The clinical data generated is therefore intended to support extrapolation of the previously established positive B/R balance for fidaxomicin tablets in adults.

OPT-80-206 enrolled paediatric subjects in N. America, while SUNSHINE was representative of paediatric subjects from both Europe and N. America.

As for the adult clinical programme, subjects with life-threatening disease and requiring surgery were not enrolled in the paediatric studies, and this is already reflected in the SmPC, which states that, due to limited clinical data, fidaxomicin should be used with caution in subjects with pseudomembranous colitis, fulminant or life-threatening CDI.

Subjects in the paediatric studies tended to have mild CDAD, whereas approximately one-third of subjects in the adult clinical programme had moderate disease, and one-third severe disease.

In SUNSHINE, in the 3 months prior to screening, 27% of subjects had had prior diarrhoea episodes with confirmed CDAD. Multiple previous CDAD recurrences in the previous 3 months were reported in some subjects; 2 previous episodes in around 5% of subjects and ≥3 previous episodes in around 2% of subjects (similar between treatment groups). The Applicant states that over half of the OPT-80-206 study population also had prior episodes of documented *C. difficile* infection in their medical history, but this could not be confirmed from tabulated data in the CSR. The Applicant has clarified that in most cases the number of individual prior CDI episodes cannot be counted, since recurrent CDI was most frequently captured as "recurrent CDI" over the duration of the recurrent episodes, without individual episodes listed.

While prior use of vancomycin or metronidazole was permitted in OPT-80-206, in SUNSHINE (as in the adult clinical studies) this was limited to no more than 1 days' prior therapy. Detection of *C. difficile* A or B toxin was required within 48 hours of randomisation for OPT-80-206, as for the adult clinical programme, but 72 hours for SUNSHINE. Two subjects in OPT-80-206 received a single dose of metronidazole day one of the study treatment period most likely prior to the start of study drug. Two subjects received intravenous vancomycin which is not considered effective against CDI, one subject for a single day (day 12) and one subject for approximately 4 days, prior and concomitant to study medication. The administration of metronidazole and vancomycin in these subjects did likely not have an impact on the outcome of the CDI episodes.

The paediatric studies used different formulations. OPT-80-206 used a powder for oral suspension, which was then further improved to produce the to-be-marketed granules for oral suspension used in SUNSHINE. While in OPT-80-206 the amount of oral suspension was calculated based directly on the subject's weight (32 mg/kg/d, max 400 mg/d) at enrolment, in SUNSHINE an amount in whole mL was determined by the weight bracket an enrolment (delivering in practice between 20 and 32 mg/kg/d to those receiving less than adult dose). Furthermore, an amendment to OPT-80-206 allowed subjects who could not tolerate tablets to receive a crushed tablet if the oral suspension "was not available".

The study population for OPT-80-206 was slightly older (mean and median age 8 years) than the SUNSHINE study population (median age 5 years, mean age 6.7 years). Subjects were stratified by age in both studies. OPT-80-206 enrolled subjects 6 months and older. Although SUNSHINE was in

principle open to the entire paediatric population from birth, only 1 subject <6 months of age were actually enrolled in the entire paediatric programme (SUNSHINE study, fidaxomicin group, enrolled in Italy). Across both studies, no subject was enrolled in the lowest weight category of the proposed paediatric dosing regimen.

Efficacy data and additional analyses

The key efficacy endpoints for this application are initial/ confirmed clinical response and recurrence.

The clinical response rate to fidaxomicin was high in both paediatric studies. The point estimates for rates of CCR and recurrence, as well as other secondary efficacy endpoints, were comparable between fidaxomicin and vancomycin groups in SUNSHINE, albeit with wide confidence intervals as expected for this small sized study, which was not powered for statistically testing.

The rate of clinical response at EOT was higher for fidaxomicin in OPT-80-206 (92%) than the rate of CCR at EOT + 2 days in SUNSHINE (77.6% fidaxomicin, 70.5% vancomycin). For comparison, the rate of CCR observed in Phase 3 studies of fidaxomicin in adults was 88% for pooled fidaxomicin subjects and 86% for pooled vancomycin subjects (mITT population).

Numerically lower response rates were observed in the ≥2 to <6 years age group in OPT-80-206, and in the <2 years age group in SUNSHINE, but small sub-groups make these findings difficult to interpret. When the studies are compared, no clear efficacy trends can be observed across age groups.

The overall recurrence rate for fidaxomicin in OPT-80-206 (28.6%) was consistent across the age sub-groups and is higher than that observed for fidaxomicin in SUNSHINE (11.8%), and also higher that that observed in Phase 3 studies of fidaxomicin in adults (14% pooled fidaxomicin subjects, mITT population). Meanwhile, the recurrence rate amongst vancomycin subjects (29%) in SUNSHINE was consistent with that observed in adult studies (26% pooled vancomycin subjects, mITT population). As seen in adult studies, recurrence rate on fidaxomicin was approximately stable throughout the four weeks following EOT in both OPT-80-206 and SUNSHINE, while vancomycin recurrences tended to occur within the first two weeks.

The differences between rates observed across the paediatric and adult studies may reflect differences between the study populations in terms of patient characteristics including immune response, geographic distribution, difficulty diagnosing CDAD in paediatric subjects, the nature and severity of subjects' underlying conditions, and the burden and contribution of other GI pathogens. Furthermore, subjects with multiple occurrences of CDI (defined as more than 1 prior occurrence within the past 3 months and known to be a risk factor for recurrence following successful initial treatment) were excluded from the adult clinical studies, but not from the paediatric studies.

Microbiology data obtained from the paediatric studies is consistent with that observed in the adult clinical programme and the established wild-type MIC distribution for *C. difficile*. There does not appear to be a relationship between MIC and clinical outcome.

The palatability of fidaxomicin appears to be acceptable on the basis of the presented data.

2.5.4. Conclusions on the clinical efficacy

The paediatric clinical programme is not independently powered to demonstrate efficacy in CDAD across the paediatric population from birth to <18 years, but instead is designed to support extrapolation of the previously established positive benefit-risk balance for fidaxomicin tablets in

adults. The overall results support, at least descriptively, both cure and recurrence rates with fidaxomicin that are comparable to those achieved with an authorised comparator, vancomycin, and comparable to those seen in adult studies.

The CHMP concluded that studies provided sufficient efficacy support for an extended indication, for use of Dificlir in paediatric patients, indicated for the treatment of *Clostridioides difficile* infections (CDI).

2.6. Clinical safety

The clinical safety of fidaxomicin tablets and granules for oral suspension in the paediatric population is supported by safety data from the two paediatric clinical studies described in detail. Overall, the paediatric clinical programme treated 136 paediatric subjects with CDAD with fidaxomicin, and 44 paediatric subjects with CDAD with vancomycin.

Patient exposure

In OPT-80-206, the safety analysis set comprised all 38 subjects enrolled in the study (including 2 subjects who did not receive any dose fidaxomicin). In SUNSHINE, the safety analysis set comprised 98 subjects in the fidaxomicin group and 44 subjects in the vancomycin group.

The follow-up period was 28 days in Study OPT 80 206 and 30 days in SUNSHINE. Long term data are not available.

The two studies used different formulations (powder vs granules) for the oral suspension, therefore the data are not fully integrated, but are presented side-by-side where possible to enable comparison.

Exposure to different formulations

Table 18. Exposure to Each Formulation, Safety Analysis Set (OPT-80-206 and SUNSHINE)

Age Category	Number of Subjects					
	OPT-80-206		SUNSHINE			
	Fidaxomicin (n = 38)		Fidaxomicin (n = 98)		Vancomycin (n = 44)	
	Oral Suspension (Powder)	Tablet	Oral Suspension (Granules)	Tablet	Oral Liquid	Capsule
Total	**24 (63.2%)**	**14 (36.8%)**	**67 (68.4%)**	**31 (31.6%)**	**30 (68.2%)**	**14 (31.8%)**
<6 months	0	0	1	0	0	0
≥6 to < 24 months	9	0	19	0	10	0
≥ 2 to < 6 years	6	2	32	0	16	0
≥ 6 to < 12 years	5	4	12	14	3	7
≥ 12 to < 18 years	4	8	3	17	1	7

Source: Adapted from Applicant's Clinical Overview; original source Module 2.7.3, Table 17.

Duration of exposure

Table 19. Duration of Exposure and Dose, Safety Analysis Set (OPT-80-206)

Parameter Category/Statistics	Number (%) of Subjects				
	≥ 6 to < 24 Months (n = 9)	≥ 2 to < 6 Years (n = 8)	≥ 6 to < 12 Years (n = 9)	≥ 12 to < 18 Years (n = 12)	All Subjects (n = 38)
Days on treatment					
Mean (SD)	10.4 (0.7)	7.1 (3.9)	10.0 (0.0)	10.2 (0.6)	9.6 (2.2)
Median	10.0	9.5	10.0	10.0	10.0
Minimum - maximum	10 - 12	1 - 10	10 - 10	10 - 12	1 - 12
Assigned dose (in mg)					
120	2 (22.2)	0	0	0	2 (5.3)
160	7 (77.8)	2 (25.0)	1 (11.1)	0	10 (26.3)
200	0	6 (75.0)	8 (88.9)	12 (100.0)	26 (68.4)

Source: Adapted from OPT-80-206, Table 14.3.1

Table 20. Duration of Exposure and Dose, Safety Analysis Set (SUNSHINE)

Parameter Category/Statistics	Suspension/Liquid		Tablet/Capsule		All Formulations	
	Fidaxomicin (n = 67)	Vancomycin (n = 30)	Fidaxomicin (n = 31)	Vancomycin (n = 14)	Fidaxomicin (n = 98)	Vancomycin (n = 44)
Days on treatment †						
Mean (SD)	10.5 (1.1)	10.6 (0.7)	10.7 (0.5)	10.5 (1.7)	10.6 (1.0)	10.5 (1.1)
Median	11.0	11.0	11.0	11.0	11.0	11.0
Minimum - maximum	5 - 12	8 - 11	10 - 11	5 - 12	5 - 12	5 - 12
Total drug administered (in mg) ‡						
n	64	25	26	14	90	39
Mean (SD)	3536.7 (728.1)	4429.7 (836.0)	3984.6 (54.3)	4758.9 (804.8)	3666.1 (646.3)	4547.9 (829.8)
Median	3845.4	4667.6	4000.0	5000.0	3942.5	4932.3
Minimum - maximum	1234 - 5142	2406 - 5774	3800 - 4000	2000 - 5125	1234 - 5142	2000 - 5774
Drug administered per weight unit per day (in mg/kg/day) ‡						
n	64	25	26	14	90	39
Mean (SD)	23.5 (6.6)	30.9 (9.4)	8.6 (3.7)	12.8 (4.2)	19.2 (9.0)	24.4 (11.8)
Median	25.8	32.4	7.6	11.3	20.0	23.8
Minimum - maximum	6 - 34	10 - 56	4 - 16	8 - 22	4 - 34	8 - 56
Average daily dose (in mg) ‡						
n	64	25	26	14	90	39
Mean (SD)	334.9 (67.7)	420.3 (69.1)	371.9 (14.7)	451.5 (18.0)	345.6 (59.9)	431.5 (57.9)
Median	354.9	445.9	363.6	454.5	363.6	454.5
Minimum - maximum	123 - 514	241 - 525	364 - 400	400 - 475	123 - 514	241 - 525

† Duration was defined as the date of last administration - the date of first administration + 1.

‡ Only calculated for subjects who returned all unused study drug.

Source: Adapted from SUNSHINE, Table 12.2.1.2

Adverse events

Treatment-emergent adverse events

The treatment-emergent adverse events (TEAEs) reported in OPT-80-206 were coded according to the MedDRA Version 15.0 and in SUNSHINE according to Version 17.0.

At least one TEAE was reported for >70% of subjects in all treatment groups (fidaxomicin in OPT-80-206, fidaxomicin in SUNSHINE and vancomycin in SUNSHINE). The proportion of subjects experiencing a TEAE was not considerably different between age sub-groups.

Numerical differences in the incidence of PTs between the treatment groups in SUNSHINE must be interpreted with caution given the small sample size.

The TEAEs most frequently reported across the paediatric studies were pyrexia and vomiting. These overlap with the most frequent PTs in the pooled adult analysis (nausea, hypokalaemia, vomiting, abdominal pain and headache), and are consistent with signs and symptoms of the underlying disease.

Table 21. Overview of Treatment-emergent Adverse Events, Safety Analysis Set (OPT-80-206 and SUNSHINE)

	Number (%) of Subjects		
	OPT-80-206	SUNSHINE	
	Fidaxomicin (n = 38)	Fidaxomicin (n = 98)	Vancomycin (n = 44)
Any TEAE	28 (73.7)	72 (73.5)	33 (75.0)
Drug-related TEAEs †	6 (15.8)	7 (7.1)	5 (11.4)
Any serious TEAEs	9 (23.7)	24 (24.5)	12 (27.3)
Drug-related serious TEAEs †	0	0	0
TEAE leading to death	1 (2.6)	3 (3.1)	0*
TEAE leading to withdrawal of treatment	3 (7.9)	1 (1.0)	1 (2.3)
Severe TEAEs	3 (7.9)	16 (22.2)	7 (21.2)

TEAE: treatment-emergent adverse event.

† A drug-related TEAE was defined as a TEAE considered by the investigator to be definitely or possibly related to fidaxomicin in OPT-80-206 and probably or possibly related to fidaxomicin or vancomycin in SUNSHINE.

*An additional 2 deaths, both in the vancomycin group, were reported after study completion (days 43 and 47, respectively).

Source: Adapted from OPT-80-206, Table 17 and Table 14.3.2.5, SUNSHINE, Table 12.6.1.1.1 and Table 12.6.1.4.1

Table 22. Common (≥ 5%) TEAEs, Safety Analysis Set (OPT-80-206)

MedDRA (v15.0) Preferred Term	Number (%) of Subjects
	Fidaxomicin (n = 38)
Any treatment-emergent adverse event	**28 (73.7)**
Pyrexia	4 (10.5)
Vomiting	4 (10.5)
Abdominal pain upper	3 (7.9)
Clostridioides difficile colitis	3 (7.9)
Headache	2 (5.3)
Diarrhoea	2 (5.3)
Constipation	2 (5.3)
Nasopharyngitis	2 (5.3)
Dehydration	2 (5.3)
Urticaria	2 (5.3)
Hypertension	2 (5.3)
Nausea	2 (5.3)
Chest pain	2 (5.3)
Oesophagitis	2 (5.3)

Source: OPT-80-206, Table 14.3.2.1

Table 23. Common (≥ 5%) TEAEs, Safety Analysis Set (SUNSHINE)

MedDRA (v17.0) Preferred Term	Number (%) of Subjects	
	Fidaxomicin (n = 98)	Vancomycin (n = 44)
Any treatment-emergent adverse event	**72 (73.5)**	**33 (75.0)**
Pyrexia	13 (13.3)	10 (22.7)
Headache	8 (8.2)	0
Vomiting	7 (7.1)	6 (13.6)
Diarrhoea	7 (7.1)	5 (11.4)
Abdominal pain	5 (5.1)	9 (20.5)
Constipation	5 (5.1)	1 (2.3)
Pruritus	3 (3.1)	3 (6.8)
Oral candidiasis	3 (3.1)	3 (6.8)

Source: SUNSHINE, Table 12.6.1.2.1

Severity of TEAEs

The majority of TEAEs were mild (44.7% of subjects, 76/102 events) or moderate (21.1% of subjects, 20/102 events) in severity.

Only 3 subjects (7.9%) in OPT-80-206 experienced severe TEAEs: 1 subject each in the 6 to 23 months, 2 years to <6 years, and the 12 years to <18 years age groups. The rate of severe TEAEs was similar between fidaxomicin and vancomycin in SUNSHINE.

The incidences of severe AEs were similar with Fidaxomicin and control, and the events not likely ADRs of the study product, but are linked to severe background disease and co-medicines for these diseases.

Drug-related treatment-emergent adverse events

A drug-related TEAE was defined as a TEAE considered by the investigator to be definitely or possibly related to fidaxomicin in OPT-80-206 and probably or possibly related to fidaxomicin or vancomycin in SUNSHINE.

Overall, 13.2% of subjects (14/102 events) had TEAEs considered possibly related to study medication and only 1 subject (2.6%) (2 years to <6 years age group) had a TEAE considered definitely related to study medication.

Table 24. Drug-related TEAEs, Safety Analysis Set (OPT-80-206)

MedDRA (v15.0) Preferred Term	Number (%) of Subjects
	Fidaxomicin (n = 38)
Any definitely or possibly related TEAE	**6 (15.8)**
Urticaria	2 (5.3)
Vomiting	2 (5.3)
Constipation	1 (2.6)
Diarrhoea	1 (2.6)
Alanine aminotransferase increased	1 (2.6)
Body temperature increased	1 (2.6)
Aspartate aminotransferase increased	1 (2.6)
Gamma-glutamyltransferase increased	1 (2.6)
Nausea	1 (2.6)
Tachycardia	1 (2.6)

TEAE: treatment-emergent adverse event.

Source: OPT-80-206, Table 14.3.2.3

Table 25. Drug-related TEAEs, Safety Analysis Set (SUNSHINE)

MedDRA (v17.0) Preferred Term	Number (%) of Subjects	
	Fidaxomicin (n = 98)	Vancomycin (n = 44)
Any probably or possibly related TEAE	**7 (7.1)**	**5 (11.4)**
Constipation	2 (2.0)	0
Oral candidiasis	1 (1.0)	1 (2.3)
Diarrhoea	1 (1.0)	0
Alanine aminotransferase increased	1 (1.0)	0
Pyrexia	1 (1.0)	0
Irritability	1 (1.0)	0
Vomiting	0	1 (2.3)
Abdominal pain	0	1 (2.3)
Vulvovaginal mycotic infection	0	1 (2.3)
Hypotension	0	1 (2.3)

TEAE: treatment-emergent adverse event.

Source: SUNSHINE, Table 12.6.1.3.1

Adverse Events of Special Interest

OPT-80-206

Adverse events of special interest (AESIs) were not defined in OPT 80 206.

SUNSHINE

Table 26. Treatment-emergent Adverse Events of Special Interest, Safety Analysis Set (SUNSHINE)

MedDRA V17.0 SMQ	Fidaxomicin (n = 98)		Vancomycin (n = 44)	
	n (%)	E	n (%)	E
Decreases in WBC, neutrophil and lymphocyte counts (hematological events)†	12 (12.2)	43	4 (9.1)	6
Hypersensitivity‡	9 (9.2)	12	4 (9.1)	4
Hepatic laboratory value abnormalities (potential DILI)§	5 (5.1)	7	1 (2.3)	1
Renal laboratory value abnormalities (renal events)¶	5 (5.1)	5	1 (2.3)	1
Gastrointestinal hemorrhage‡	1 (1.0)	1	0	0
QT prolongation¶	0	0	0	0

DILI: drug-induced liver injury; E: includes each occurrence of an event; SAF: safety analysis set; SMQ: standardized MedDRA query; WBC: white blood cell.

Sorting order: descending order of frequency (total).

† Identified via medical review

‡ SMQ narrow

§ Refer to the SAP [Appendix 13.1.9, Section 6.2.2]

¶ SMQ broad

Source: Table 12.6.1.12.1

One subject (3400210008) in the fidaxomicin group experienced a TEAE of anaphylactic reaction. The serious TEAE was reported to start on day 28 and resolved on the following day. In the investigator's opinion, the event was assessed as not related to study drug.

A trend for low WBC, neutrophil and lymphocyte counts, were more prevalent in the fidaxomicin group in the phase 3 study and this was discussed during the procedure. While lymphopenia was slightly more common with fidaxomicin than with control (25.3% vs. 20.5%), the opposite was in fact true for low values of leukocytes and neutrophils. Of note, the fidaxomicin arm had a higher incidence of pre-existing blood and lymphatic system disorders (40.8% versus 29.5% respectively) and more fidaxomicin subjects anti-neoplastic/immunomodulating agents (43.9% vs. 36.4%, respectively). Further, there are no pre-clinical data to support a negative impact on lymphocytes or other haematology, even at very high exposures and the systemic exposure in the both adults and children is rather minimal. In summary, lymphopenia is not considered an ADR of fidaxomicin.

ALT increases were numerically more common in the fidaxomicin group, where ALT increase is listed as an ADR in section 4.8 on the basis of prior studies in adults. The issue of ALT increase and causality was discussed during the procedure, re-addressing the findings in adults and those reported in the paediatric studies. Also, in the adult studies, ALT increases were only numerically different from that seen with control. As mentioned, the frequency of severe background disease and associated co-medicines (with great potential for ALT increases) were not balanced between fidaxomicin arms and control, favouring control in both the adult and paediatric studies. When looking at ALT increases in shift table analysis, there was no relevant difference in ALT increases by treatment arm, Table below. For cases of clinically significant ALT values reported in the SUNSHINE study (n=8 for fidaxomicin, 3 for vancomycin), there was 1 single case (2 events) reported as related to fidaxomicin by the investigator. That conclusion was not supported by the applicant and is not supported by the Rapporteur either. The two events occurred in an 11-year old girl undergoing heavy chemotherapy for a medulloblastoma, where the second event (more pronounced) occurred some 10 days after end of fidaxomicin treatment.

Table 27. Shift Table for ALT Results, Biochemistry (Sunshine CSR)

Treatment	EOT	Baseline				
		Low	Normal	High	Total	No data
Fidaxomicin	Low	2 (100.0%)	2 (2.7%)	0	4	0
	Normal	0	59 (80.8%)	7 (36.8%)	66	1
	High	0	12 (16.4%)	12 (63.2%)	24	1
	Total	2	73	19	94	2
	No Data	0	1	1	2	4
Vancomycin	Low	0	0	1 (7.1%)	1	0
	Normal	2 (100.0%)	22 (81.5%)	5 (35.7%)	29	0
	High	0	5 (18.5%)	8 (57.1%)	13	1
	Total	2	27	14	43	1
	No Data	0	0	0	0	1

In summary, when re-addressing ALT increases as a potential ADR of fidaxomicin, it is very clear that the evidence for causality is very weak. Of note, non-clinical studies indicated no effect on liver function, even at very high oral doses (9600 mg) delivered to dogs for 3 months. Further, the systemic exposure in humans treated with the approved dose is minimal. The CHMP therefore suggests that ALT increases should no longer be considered an ADR of fidaxomycin.

Three (3.1%) subjects in the fidaxomicin group experienced acute renal failure of moderate intensity (SAE in 2 of those subjects), and 1 (2.3%) subject in the vancomycin group developed renal failure of severe intensity, an SAE. None of the renal events observed in 6 subjects were assessed as related to study drug.

One SAE of moderate rectal haemorrhage was reported on day 11 in a subject in the fidaxomicin group and was not considered to be drug-related.

Serious adverse event/deaths/other significant events

Serious adverse events

At least one serious TEAE was reported in approximately 25% of subjects in all treatment groups (fidaxomicin in OPT-80-206, fidaxomicin in SUNSHINE and vancomycin in SUNSHINE). None of the SAEs reported in the paediatric studies were known adverse drug reactions of fidaxomicin based on adult data. According to the investigator, none of the serious TEAEs were related to study drug.

Table 28. Serious AEs, Safety Analysis Set (OPT-80-206)

MedDRA (v15.0) System Organ Class Preferred Term	**Number (%) of Subjects** **Fidaxomicin (n = 38)**
Any serious adverse event	**9 (23.7)**
Infections and Infestations	**6 (15.8)**
Clostridioides difficile colitis	3 (7.9)
Adenovirus infection	1 (2.6)
Clostridial infection	1 (2.6)
Septic shock	1 (2.6)
Gastrointestinal Disorders	**2 (5.3)**
Vomiting	2 (5.3)
Haematemesis	1 (2.6)
Blood and Lymphatic System Disorders	**1 (2.6)**
Febrile neutropenia	1 (2.6)
Respiratory, Thoracic and Mediastinal Disorders	**1 (2.6)**
Respiratory failure	1 (2.6)
Injury, Poisoning and Procedural Complications	**1 (2.6)**
Gastrostomy failure	1 (2.6)

Source: OPT-80-206, Table 14.3.2.4

Table 29. Serious AEs, Safety Analysis Set (SUNSHINE)

MedDRA (v17.0) System Organ Class Preferred Term	**Number (%) of Subjects**	
	Fidaxomicin (n = 98)	**Vancomycin (n = 44)**
Any serious adverse event †	**24 (24.5)**	**12 (27.3)**
Infections and Infestations	**10 (10.2)**	**3 (6.8)**
Sepsis	2 (2.0)	0
Bacterial sepsis	1 (1.0)	0
Bacterial diarrhoea	1 (1.0)	0
Clostridioides difficile infection	1 (1.0)	0
Herpes simplex meningoencephalitis	1 (1.0)	0
Klebsiella bacteraemia	1 (1.0)	0
Pneumonia	1 (1.0)	0
Respiratory syncytial virus infection	1 (1.0)	0
Respiratory tract infection	1 (1.0)	0
Staphylococcal sepsis	1 (1.0)	0
Clostridium difficile colitis	0	1 (2.3)
Fungal sepsis	0	1 (2.3)
Influenza	0	1 (2.3)
Scedosporium infection	0	1 (2.3)
Blood and Lymphatic System Disorders	**5 (5.1)**	**1 (2.3)**
Febrile neutropenia	3 (3.1)	1 (2.3)
Febrile bone marrow aplasia	1 (1.0)	0
Thrombocytosis	1 (1.0)	0
Gastrointestinal Disorders	**4 (4.1)**	**4 (9.1)**
Abdominal pain lower	1 (1.0)	0
Pancreatitis	1 (1.0)	0
Rectal haemorrhage	1 (1.0)	0
Small intestinal obstruction	1 (1.0)	0
Colitis	0	1 (2.3)
Diarrhoea	0	1 (2.3)
Gastrointestinal necrosis	0	1 (2.3)
Ileus paralytic	0	1 (2.3)
Intestinal obstruction	0	1 (2.3)
General Disorders and Administration Site Conditions	**3 (3.1)**	**2 (4.5)**
Pyrexia	2 (2.0)	2 (4.5)
Mucosal inflammation	1 (1.0)	0
Pain	1 (1.0)	0
Metabolism and Nutrition Disorders	**3 (3.1)**	**0**
Dehydration	2 (2.0)	0
Acidosis	1 (1.0)	0

MedDRA (v17.0) System Organ Class Preferred Term	Number (%) of Subjects	
	Fidaxomicin (n = 98)	Vancomycin (n = 44)
Renal and Urinary Disorders	**2 (2.0)**	**1 (2.3)**
Renal failure acute	2 (2.0)	0
Renal failure	0	1 (2.3)
Neoplasms Benign, Malignant and Unspecified	**2 (2.0)**	**1 (2.3)**
Acute myeloid leukaemia	1 (1.0)	0
Leukaemia	1 (1.0)	0
Malignant ascites	0	1 (2.3)
Nervous System Disorders	**2 (2.0)**	**0**
Amnesia	1 (1.0)	0
Convulsion	1 (1.0)	0
Headache	1 (1.0)	0
Immune System Disorders	**2 (2.0)**	**0**
Anaphylactic reaction	1 (1.0)	0
Food allergy	1 (1.0)	0
Respiratory, Thoracic and Mediastinal Disorders	**1 (1.0)**	**1 (2.3)**
Respiratory distress	1 (1.0)	0
Respiratory failure	0	1 (2.3)
Congenital, Familial and Genetic Disorders	**1 (1.0)**	**0**
Mitochondrial encephalomyopathy	1 (1.0)	0
Psychiatric Disorders	**1 (1.0)**	**0**
Abnormal behaviour	1 (1.0)	0
Surgical and Medical Procedures	**1 (1.0)**	**0**
Radiotherapy	1 (1.0)	0
Investigations	**0**	**1 (2.3)**
Heart rate irregular	0	1 (2.3)

† Includes any serious adverse events upgraded by the sponsor based on review of the list of "Always Serious" terms. The complete list of "Always Serious" terms is available on request.

Source: SUNSHINE, Table 12.6.1.6.1

Most of the SAEs were in the SOC Infections and infestations, which is not unexpected given the underlying comorbidities in the study population. Three of the 9 SAEs reported in OPT-80-206, and two of the 59 SAEs reported in SUNSHINE, relate to persistence or recurrence of CDAD despite study drug treatment, which were considered not drug-related by the Investigator but may represent failure of the treatment.

Deaths

One subject died in OPT-80-206 and 5 subjects in SUNSHINE (3 allocated to fidaxomicin, 2 allocated to Vancomycin), all during the follow up period (non-related). The 3 deaths in the children treated with fidaxomicin (all < 2 years of age) concerned Klebsiella sepsis following stem cell transplant, worsening of AML and suspected metabolic encephalopathy (Leigh Syndrome). All 3 had fulfilled the 10 days treatment with fidaxomicin.

Table 30. Deaths, Safety Analysis Set (OPT-80-206 and SUNSHINE)

Study	Age	Day	Preferred Term	Comorbid/concomitant conditions	Relationship to Study Drug According to Investigator	Clinical response to fidax/vanc**
Fidaxomicin						
OPT-80-206	17 m	13	Respiratory failure	Palliative chemotherapy for lymphoblastic leukaemia and lymphohistiocytosis, disseminated infection, septic shock	Not related	
SUNSHINE	16 m	22	Sepsis	Acute megakaryoblastic leukaemia, haematopoietic stem cell transplant, aspiration pneumonia	Not related	
		28	Leukaemia		Not related	
		40	*Klebsiella* bacteraemia		Not related	
	14 m	17	Acute myeloid leukaemia	Acute myeloid leukaemia	Not related	
	7 m	30	Mitochondrial encephalomyopathy (Leigh syndrome)	Suspected metabolic encephalopathy since birth	Not related	
Vancomycin						
SUNSHINE	7 y*	13	Fungal sepsis	Leukaemia, bone marrow aplasia	Not related	
		13	*Scedosporium* infection		Not related	
	13 y*	46	Abdominal desmoplastic tumor	Desmoplastic abdominal cancer, malignant ascites, pancytopenia	Not related	

* Both deaths in the vancomycin group occurred after study end. **Not provided by Applicant in discussion.

Source: Adapted from OPT-80-206, Table 14.3.2.6 and Section 12.3.2; and SUNSHINE, Table 12.6.1.2.1; Appendix 13.2.7.1; Appendix 13.2.7.3 and Section 9.1.2.1.

Laboratory findings

OPT-80-206

Few subjects shifted from normal baseline values to abnormal values for any haematology, chemistry or urinalysis parameters over the course of the study. TEAEs related to the isolated abnormalities were reported for 1 subject each (total 11).

TEAEs of increased blood pressure and tachycardia were reported for 1 subject each; 1 subject had a TEAE of increased body temperature, 2 subjects had hypertension, and 4 subjects experienced TEAEs of pyrexia.

No relevant changes in urinalysis results were reported in OPT 80 206.

Three subjects had a change in QTcB interval from baseline of >30 msec. Two subjects had a QTcB interval >450 msec at the end of therapy. None of the subjects had QTcB intervals that met the higher thresholds, and none of the changes were recorded as AEs.

SUNSHINE

Haematology

Slight decreases in mean neutrophils from baseline to EOT in both groups were noted, likely consistent with a positive response to CDAD treatment. None of the changes from baseline to EOT in both studies and the differences between fidaxomicin and vancomycin in SUNSHINE were considered clinically relevant in this population, many subjects had a medical history of neoplasms and were being treated with antineoplastic and immunomodulating agents during the study.

Biochemistry

ALT increases are discussed in section 3.3.8.2 (Adverse events events).

Vital Signs

There were no clinically relevant changes in vital signs from baseline to EOT in either study and there were no relevant differences between fidaxomicin and vancomycin in SUNSHINE.

Urinalysis

The proportion of subjects in the fidaxomicin group who tested positive for occult blood increased from 11.8% to 13.2%, for urine glucose from 1.2% to 3.9% and for urine protein from 8.2% to 11.7%. In the vancomycin group, there was a decrease in positive test results for occult blood from 11.4% to 8.3% and an increase for urine protein from 8.6% to 13.9%.

Electrocardiograms

ECG results were assessed by the investigator as clinically significantly abnormal in 1 (1.0%) fidaxomicin subject during the treatment period (day 9: right ventricular hypertrophy related to organ failure due to Leigh syndrome).

Prolonged QTc interval was observed in 11 subjects of the fidaxomicin group (baseline: 11.6%, day 5 to 10: 11.8%) and 6 subjects in the vancomycin group (baseline: 14.0%, day 5 to 10: 14.3%). No QTc interval was above 500 ms. None of the changes were recorded as TEAEs.

Safety related to drug-drug interactions and other interactions

Potential drug interactions are described in the prescribing information. No drug-drug interaction studies have been performed in the paediatric population.

Discontinuation due to adverse events

OPT-80-206

Overall, 4 TEAEs leading to permanent discontinuation of study drug and withdrawal from the study were reported in 3 (8%) subjects: drug-related moderate urticaria on day 3; mild flatulence (not drug-related) on day 6; and possibly drug-related mild tachycardia (100 bpm) with mild increased body temperature on day 2.

SUNSHINE

TEAEs leading to permanent discontinuation of study drug were reported for 2 (1.4%) subjects: notably moderate colitis in a subject treated with fidaxomicin and severe vomiting in a subject receiving vancomycin. Both TEAEs were assessed by the investigator as not related to study drug. Both subjects were in the age group ≥ 2 to < 6 years.

Post marketing experience

Ten Periodic Safety Update Reports are available. Approximately 248,320 patient courses of therapy of marketed fidaxomicin have been dispensed since the International Birth Date on 27 May 2011 up to

26 May 2018, and approximately 1529 subjects received fidaxomicin in clinical studies sponsored by the Marketing Authorization Holder.

During the reporting interval of the latest Periodic Safety Update Report (covering the period from 27 May 2017 to 26 May 2018), warnings and special precautions for subjects with moderate to severe hepatic impairment, severe renal impairment, inflammatory bowel disease, and pseudomembranous colitis were removed from the Company Core Data Sheet based on the results of completed post-approval safety studies. No new safety concerns or a substantial change in the identified (and potential) risks were identified and no significant actions related to safety were taken.

2.6.1. Discussion on clinical safety

The paediatric studies were conducted in accordance with the agreed Paediatric Investigation Plan.

The safety profile in paediatric subject is based on data from 136 paediatric subjects exposed to fidaxomicin. Using the "Rule of 3", only ADRs with a frequency of greater than 1 in 45.3 could be detected from this safety database. There are data available on the safety of a treatment duration greater than 10 days in paediatric subjects (mean exposure 9.6 days in OPT-80-206 and 10.6 days in SUNSHINE, range 1 – 12 days). Additionally, follow up in these studies was limited to 30 days after the end of therapy.

Although fidaxomicin is intended for treatment only up to 10 days' duration, some subjects experience recurrence of CDAD requiring further treatment, and the safety of repeated courses of fidaxomicin in paediatric subjects is not known. A post-marketing safety study of repeated use in adults was initially agreed with CHMP following the original authorisation in adults, however it was later accepted that the availability of published data indicating a low rate of recurrence following fidaxomicin treatment and the availability and use of alternative treatments made such a study unfeasible, and as such Repeated fidaxomicin treatment courses was removed from RMP v7 as Missing Information in 2017. It seems reasonable that the safety of repeated treatment courses should not differ between paediatric and adult subjects.

Only subjects in SUNSHINE were exposed to the to-be-marketed granules for oral suspension formulation. Only one subject <6 months old (fidaxomicin group, SUNSHINE), and no subject in the lowest bodyweight category of the paediatric dosing regimen proposed in the SmPC for the granules for suspension, were included in the paediatric clinical programme.

Neither OPT-80-206 nor SUNSHINE explicitly excluded subjects with renal or hepatic dysfunction at screening, or multiple recurrences of CDAD in the previous 3 months, as the adult Phase 3 studies did. The currently authorised SmPC includes warnings in section 4.4 regarding the lack of data in such subjects.

Fidaxomicin was generally well tolerated by paediatric subjects, in line with the low systemic exposure of this orally administered drug. The safety profile was generally similar between the fidaxomicin and vancomycin groups in SUNSHINE, and the most commonly reported TEAEs reflect the underlying disease. The TEAEs most frequently reported across the paediatric studies were pyrexia (10.5% OPT-80-206, 13.3% SUNSHINE) and vomiting (10.5% OPT-80-206, 7.1% SUNSHINE). The only drug-related TEAEs by PT reported for ≥3 subjects across all the treatment groups were constipation and vomiting.

No clear patterns are seen when comparing overall TEAEs, drug-related TEAEs or AESIs between the different age categories in OPT-80-206 and SUNSHINE. All deaths occurred in the <24 months age category and, correspondingly, there were also slightly more SAEs in this category. Deaths, un-related

to study treatment in all cases, occurred during follow-up, in children with other severe disease conditions.

From the safety database all the adverse reactions reported in clinical trials and post-marketing have been included in the Summary of Product Characteristics.

2.6.2. Conclusions on the clinical safety

The data generated are reassuring. The paediatric clinical programme is not extensive enough to provide a complete safety dataset for the paediatric population from birth to <18 years, but instead is designed to support extrapolation of the previously established positive BR balance for fidaxomicin tablets in adults. This is fully in line with the CHMP Guidance for Industry, where it is stated that both efficacy and safety may be based on study results obtained in adults, provided similar exposure. In the case of fidaxomicin, the systemic exposure is minimal in both adults and children, side effects linked to systemic exposure are in fact very unlikely. Using the same dose in children as in adults, which is the case here, would likely yield a higher local intestinal exposure and there is no reason to expect a lower efficacy on true *C. difficile* infections. The frequency and to some extent type of GI side effects, generated by the local exposure, may likely differ in children and adults, also with the same local exposure, where for example vomiting is frequently more often reported in paediatric studies. However, the overall GI AE profile was similar to that seen in adults, and also similar or slightly more favourable than with control (Vancomycin) in the phase 3 study.

2.7. Risk Management Plan

Safety concerns

No safety concerns are currently identified in the Dificlir RMP.

Pharmacovigilance plan

Not applicable, as no safety concerns are currently identified in the Dificlir RMP.

Risk minimisation measures

Not applicable, as no safety concerns are currently identified in the Dificlir RMP.

Conclusion

The CHMP and PRAC considered that the risk management plan version 13.0 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the MAH fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.9. Product information

2.9.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Xtandi 40 mg and 80mg film-coated tablets. The bridging report submitted by the MAH has been found acceptable.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

C. difficile is a spore-forming, anaerobic, gram-positive rod that produces toxins that cause inflammation of the colon with severe diarrhoea and, in the most serious cases, pseudomembranous colitis, toxic megacolon, perforations of the colon, sepsis and even death.

CDAD is caused by an overgrowth of *C. difficile* in the colon and is the leading cause of infectious nosocomial diarrhoea in industrialized countries. The disease accounts for approximately 20% of cases of antibiotic-associated diarrhoea, 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). Antibiotics commonly linked to CDAD include cephalosporins, fluoroquinolones, clindamycin, ampicillin, and amoxicillin, but almost any antibiotic can cause CDAD. In addition to antibiotics, a number of other risk factors have been identified for CDAD in the paediatric population, including solid organ transplant, gastrostomy tube placement, chronic inflammatory gastrointestinal disease/motility disorders, cystic fibrosis, immunosuppression and previous *C. difficile* infection (Cooperstock, 2013; Sandora et al, 2011).

3.1.2. Available therapies and unmet medical need

Oral vancomycin and metronidazole are both approved for the treatment of CDAD in adult and paediatric patients in the EU by oral administration. Both are available in liquid formulations. Orally administered metronidazole is almost completely absorbed, and systemic exposure is associated with adverse effects. Meanwhile, there is growing concern over emerging resistance to vancomycin among other important target pathogens, such as MRSA, with increasing clinical use.

CDAD has historically been considered a disease of adults, and not a significant problem amongst the paediatric population. A clear link between carriage of the organism and development of symptoms has not been established. The definitive diagnosis of CDAD in paediatric patients, in particular young children and infants who are more likely to carry the organism without symptoms, may also be complicated by physiological differences in normal stool habit and a high frequency of diarrheal

illnesses caused by other pathogens, e.g. rotavirus, which can be incorrectly attributed to *C. difficile* infection.

3.1.3. Main clinical studies

This application is supported by data from two paediatric studies agreed as part of the Paediatric Investigation Plan (P/0062/2018).

Study OPT-80-206 was an open-label, single-arm, Phase 2 study of 10 days' 32 mg/kg/d oral fidaxomicin tablets or powder for oral suspension (not the final formulation) in paediatric subjects (n=38) in N. America from 6 months to <18 years old with CDAD.

Study 2819-CL-0202 (SUNSHINE) was a randomised, single-blind, active-comparator controlled Phase 3 study of 10 days' weight-based oral fidaxomicin tablets or granules for oral suspension (the final formulation) in paediatric subjects (n=148) in N. America and Europe from birth to <18 years old with CDAD.

Although not powered for statistical testing, the objectives, definitions (disease, cure, failure, recurrence), inclusion and exclusion criteria, comparator (for SUNSHINE) and clinical endpoints generally reflected those applied in the adult clinical development programme.

Subjects in the paediatric studies tended to have mild CDAD, and subjects with life-threatening disease and requiring surgery were excluded. Unlike in the adult clinical programme, subjects with multiple recurrences of CDAD in the previous 3 months could enrol.

3.2. Favourable effects

The primary efficacy endpoint, the rate of CCR at EOT + 2 days, in SUNSHINE was comparable between treatment arms (77.6% fidaxomicin, 70.5% vancomycin, adjusted difference = 7.5, 95%CI [-7.4 to 23.9]). For comparison, the rate of CCR observed in Phase 3 studies of fidaxomicin in adults was 88% for pooled fidaxomicin subjects and 86% for pooled vancomycin subjects (mITT population). The rate of clinical response at EOT was higher in OPT-80-206 (92%, 95%CI 83.5 to 100).

The recurrence rate for the fidaxomicin group in SUNSHINE was lower than that for the vancomycin group (11.8% vs 29%, adjusted difference -15.8, 95%CI -34.5, 0.5), and this was comparable to Phase 3 studies of fidaxomicin in adults (14% pooled fidaxomicin subjects, 26% pooled vancomycin subjects, mITT population). The recurrence rate for fidaxomicin was higher in OPT-80-206 (28.6%, 95%CI 13.6 to 43.5). As seen in adult studies, recurrence rate on fidaxomicin was approximately stable throughout the four weeks following EOT in both OPT-80-206 and SUNSHINE, while vancomycin recurrences tended to occur within the first two weeks.

Microbiology data obtained from the paediatric studies is consistent with that observed in the adult clinical programme and the established wild-type MIC distribution for *C. difficile*. There does not appear to be a relationship between MIC and clinical outcome.

The palatability of fidaxomicin appears to be acceptable in the paediatric population and compliance was generally high across all the formulations.

3.3. Uncertainties and limitations about favourable effects

Only SUNSHINE used the final, to-be-marketed formulation.

The confidence intervals for the point estimates of the key efficacy endpoints are wide in both studies, as is to be expected given the small study sizes.

Numerically lower response rates were observed in the ≥2 to <6 years age group in OPT-80-206, and in the <2 years age group in SUNSHINE, but small sub-groups make these findings difficult to interpret. When the studies are compared, no clear efficacy trends can be observed across age groups.

The numerical differences between rates observed across the paediatric and adult studies may reflect differences between the study populations in terms of patient characteristics including immune response, geographic distribution, difficulty diagnosing CDAD in paediatric subjects, the nature and severity of subjects' underlying conditions, and the burden and contribution of other GI pathogens. Furthermore, subjects with multiple occurrences of CDI (defined as more than 1 prior occurrence within the past 3 months and known to be a risk factor for recurrence following successful initial treatment) were excluded from the adult clinical studies, but not from the paediatric studies.

Difficulty in definitively diagnosing CDAD in the paediatric population means it is likely these studies enrolled a less homogenous target population than the adult clinical programme. A substantial proportion of subjects (43.9% fidaxomicin, 50% vancomycin) tested positive at Screening for GI organisms other than *C. difficile*. The toxins detected in the study population were a mix of bacterial and viral, and several subjects had more than 1 pathogen. It is likely that a proportion of enrolled subjects were treated for diarrhoea incorrectly attributed to *C. difficile*. The qualifying diagnosis cannot be confirmed as correct on the basis of successful clinical cure, as many of these other causes of diarrheal illness spontaneously resolve within the same time frame as the study treatment. However, this is considered to be representative of the "real life" population expected to be treated with fidaxomicin.

Due to the nature of fidaxomicin, an antibiotic with very little systemic absorption intended to act locally in the gastrointestinal lumen; it is not possible to provide PK/PD support for efficacy of the proposed dose in the usual way. The faecal PK parameters appear somewhat higher for children compared to adults although with high inter-subject variability. The down scaling of dose is based on that approved for vancomycin, also an antibiotic with next to none systemic uptake; the approach is considered reasonable.

3.4. Unfavourable effects

The safety profile was generally similar between the fidaxomicin and vancomycin groups in SUNSHINE, and the most commonly reported TEAEs reflect the underlying disease. The TEAEs most frequently reported across the paediatric studies were pyrexia (10.5% OPT-80-206, 13.3% SUNSHINE) and vomiting (10.5% OPT-80-206, 7.1% SUNSHINE). The only drug-related TEAEs by PT reported for ≥3 subjects across all the treatment groups were constipation and vomiting.

The majority of TEAEs were mild (44.7% of subjects, 76/102 events) or moderate (21.1% of subjects, 20/102 events) in severity.

At least one serious TEAE was reported in approximately 25% of subjects in all treatment groups (fidaxomicin in OPT 80 206, fidaxomicin in SUNSHINE and vancomycin in SUNSHINE). According to the investigator, none of the serious TEAEs were related to study drug. Most of the SAEs were in the SOC

Infections and infestations, which is not unexpected given the underlying comorbidities in the study population.

3.5. Uncertainties and limitations about unfavourable effects

The safety profile in paediatric subject is based on data from 136 paediatric subjects exposed to fidaxomicin. Using the "Rule of 3", only ADRs with a frequency of greater than 1 in 45.3 could be detected from this safety database. However, there are data available on the safety of a treatment duration greater than 10 days in paediatric subjects. Additionally, follow up in these studies was limited to 30 days after the end of therapy.

Only 1 subject <6 months of age (SUNSHINE study, fidaxomicin group), and no subject in the lowest weight category of the proposed paediatric dosing regimen, were enrolled in the entire paediatric programme. Of note, CDAD is a very infrequent disease in the youngest.

Trends in decreased haematological parameters and increased hepatic parameters, although not dramatic, mirror those seen in the adult development programme. In both the adult and paediatric studies, alternative aetiologies related to background disease and concomitant medications are deemed a more likely cause of these effects, which are not considered to be ADRs.

Systemic exposure is relevant to the assessment of clinical safety. There are very limited pharmacokinetic data available for the paediatric population. No modelling of plasma concentrations to obtain PK parameters (maximum plasma drug concentration, area under the time-concentration curve, etc) was planned for either study. Only limited data on systemic exposures from the paediatric patients can be compared to levels obtained in adults (i.e. where drug levels were tested within the same time frames from intake). The exposures are similar or lower, with a couple of outliers. When discussing these uncertainties of systemic exposures (outliers included) one should notice that pre-clinical toxicology studies were in practice free from any findings (rats, dogs, monkeys); that includes 14 days studies in beagle dogs, where the exposures were fairly extreme. Hence, in fact there is no safety margin to discuss, but rather exposure margins (to no findings). It should also be remembered that this concerns a treatment of 10 days, not chronic medication. The uncertainties are therefore considered acceptable and results re-assuring.

3.6. Effects Table

Table 31. Effects Table for Dificlir, proposed as treatment of *Clostridioides difficile* infections (CDI), also known as *C. difficile*-associated diarrhoea (CDAD), in paediatric patients from birth to < 18 years of age.

Effect	Short Description	Unit	Treatment (Fidax)	Control (Vanc)	Uncertainties/ Strength of evidence	References
Favourable Effects						
Clinical response at EOT (Day 10)	Resolution of diarrhoea and no further need for CDAD treatment	%	92.1	N/A	95%CI 83.5, 100.0	OPT-80-206
CCR at EOT + 2 days (Day 12)	Resolution of diarrhoea and no further need for CDAD treatment	%	77.6	70.5	Difference 7.5 95%CI -7.4, 23.9	SUNSHINE
Recurrence within EOT + 30 days	Recurrence of CDAD requiring treatment	%	28.6	N/A	95%CI 13.6, 43.5	OPT-80-206
			11.8	29.0	Difference -15.8 95%CI -34.5, 0.5	SUNSHINE
Unfavourable Effects						
Drug-related TEAEs affecting ≥2 subjects	Urticaria	%	5.3	N/A	Due to study sizes, only ADRs with a frequency of greater than 1 in 45.3 could be detected	OPT-80-206
	Constipation Diarrhoea Vomiting	%	2 1 0	0 0 2.3		SUNSHINE

Abbreviations: ALT = alanine aminotransferase, CCR = Confirmed Clinical Response, CDAD = C. difficile-associated diarrhoea, CI = Confidence Interval, EOT = End of Treatment, Fidax = fidaxomicin, Vanc = vancomycin.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The paediatric clinical programme is not independently powered to demonstrate efficacy in CDAD across the paediatric population from birth to <18 years, but instead is designed to support extrapolation of the previously established positive BR balance for fidaxomicin tablets in adults. The overall results support, at least descriptively, clinically meaningful cure and recurrence rates with fidaxomicin, which are comparable to those achieved with an authorised comparator, vancomycin, and comparable to those seen in adult studies.

The data generated are generally reassuring that fidaxomicin is well tolerated in paediatric subjects, in line with results in adults and similar to that seen with the control agent vancomycin, with an acceptable side effect profile considering the seriousness of the target condition.

3.7.2. Balance of benefits and risks

Efficacy has been established in adults, where efficacy with fidaxomicin is similar to that with vancomycin. Results are in line with that have now been shown in paediatric patients.

Efficacy has been established in adults, where efficacy with fidaxomicin is similar to that with vancomycin. Results in line with that have now been shown in paediatric patients.

The safety of fidaxomicin in adults was shown to be favourable, in line with that of vancomycin. Again, with current extension application, likewise observation is made for use of Dificlir in paediatric patients. At present no relevant risks have been identified, apart from rash/urticaria (infrequent) which is common to all antibiotics.

The favourable efficacy results outweigh the risks.

3.7.3. Additional considerations on the benefit-risk balance

The CHMP considered that the oral suspension has not been evaluated in adults and no bioequivalence study has been performed. However, the absorption of fidaxomicin is minimal, and therefore the omission of such a study could be considered acceptable. Hence, following discussion, CHMP recommended that the adult population be included in the indication of Dificlir Granules for oral suspension, with choice of formulation be differentiated under Posology, section 4.2.

A statement to this effect is introduced in section 4.2 of the film-coated tablet formulation that Dificlir oral suspension may be an alternative for adult patients with difficulties to swallow; likewise, the same section of SmPC states that for paediatric patients with a body weight of less than 12.5 kg, reduced doses are recommended, referring to use of Dificlir 40 mg/ml granules for oral suspension.

3.8. Conclusions

The overall B/R of fidaxomicin in the paediatric population is positive, and a line extension (Dificlir granules for oral suspension 40mg /ml) can be recommended. In addition, for this formulation, the indication is broadened to allow use in adult population. Further on, the extension of the existing indication for Tablet formulation includes the paediatric population with a body weight of at least 12.5 kg.

4. Recommendations

Outcome

Based on the CHMP review of data on quality and safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Dificlir 40 mg/ml granules for oral suspension and of the already approved Dificlir presentations is favourable in the following indications:

DIFICLIR film-coated tablets is indicated for the treatment of *Clostridioides difficile* infections (CDI) also known as *C. difficile*-associated diarrhoea (CDAD) in adult and paediatric patients with a body

weight of at least 12.5 kg (see section 4.2 and 5.1).

Consideration should be given to official guidelines on the appropriate use of antibacterial agents.

DIFICLIR granules for oral suspension is indicated for the treatment of *Clostridioides difficile* infections (CDI) also known as *C. difficile*-associated diarrhoea (CDAD) in adults and paediatric patients from birth to < 18 years of age (see section 4.2 and 5.1).

Consideration should be given to official guidelines on the appropriate use of antibacterial agents
The CHMP therefore recommends the extension(s) of the marketing authorisation for Dificlir subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Additional risk minimisation measures

Not applicable

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0062/2018 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

No significant studies in the agreed paediatric investigation plan P/0062/2018 have been completed, in accordance with Article 45(3) of Regulation (EC) No 1901/2006, after the entry into force of that Regulation.