22 September 2011
EMA/857570/2011
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Dificlir

fidaxomicin

Procedure No.: EMEA/H/C/2087

Note

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

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Table of contents

List of abbreviations

AE	Adverse event
AUC	Area under the curve
BI	An epidemic hypervirulent *C. difficile* strain
b.i.d	Two times daily
CDAD	*Clostridium difficile*-associated diarrhoea
CDI	*Clostridium difficile* infection
cGMP	current Good Manufacturing Practice
C_{max}	Maximum plasma concentration
eCCL	Estimated creatinine clearance
ECG	Electrocardiogram
EOT	End of therapy
ESCMID	European Society of Clinical Microbiology and Infectious Diseases
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	Gastrointestinal
IC_{50}	Half maximal inhibitory concentration
IDSA	Infectious Disease Society of America
i.v.	Intravenously
LC-MS/MS	Liquid chromatography tandem mass spectrometry
LFT	Liver function test
LLOQ	Lower limit of quantification
MIC	Minimum inhibitory concentration
mITT	Modified Intent-to-Treat
MedDRA	Medical Dictionary for Regulatory Activities
MRSA	Methicillin-resistant *Staphylococcus aureus*
NAP1	North America PFGE pulsotype 1
OP-1118	Primary metabolite of fidaxomicin
OPT-80	Code name for fidaxomicin drug product
PAR-101	Old name for fidaxomicin drug product
PD	Pharmacodynamic

P-gp	P-glycoprotein
PIP	Paediatric Investigation Plan
PK	Pharmacokinetic
PP	Per protocol
PT	MedDRA preferred term
QTcB	Bazett's corrected QT interval
QTcF	Fridericia corrected QT interval
REA	Restriction endonuclease analysis
RP-HPLC	Reversed-phase high performance liquid chromatography
SAE	Serious adverse event
SmPC	Summary of Product Characteristics
SOC	MedDRA System Organ Class
TEAE	Treatment-emergent adverse event
t.i.d	Three times daily
TTROD	Time-to-resolution of diarrhoea
UBM	Unformed bowel movements
VRE	Vancomycin-resistant Enterococcus
WBC	White blood cells

1. Background information on the procedure

1.1. Submission of the dossier

The applicant FGK Representative Service GmbH submitted on 16 July 2010 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Dificlir, through the centralised procedure under Article 3 (2) (a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 03 June 2009.

The applicant applied for the following indication: "Treatment of *Clostridium difficile* infections (CDI) also known as *C. difficile*-associated disease (CDAD) and prevention of recurrences (see Section 5.1)."

The legal basis for this application refers to:

A - Centralised / Article 8(3) / New active substance.

Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/98/2010 on the agreement of a paediatric investigation plan (PIP)

At the time of submission of the application, the PIP was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Not applicable.

Market Exclusivity

Not applicable.

New active Substance status

The applicant requested the active substance fidaxomicin contained in the above medicinal product to be considered as a new active substance in itself.

Scientific Advice

The applicant received Scientific Advice from the CHMP on 01 June 2006. The Scientific Advice pertained to clinical aspects of the dossier.

Licensing status

Fidaxomicin has been given a Marketing Authorisation in USA on 27 May 2011

The product was not licensed in any country at the time of submission of the application.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Kristina Dunder Co-Rapporteur: Philippe Lechat

- The application was received by the EMA on 16 July 2010.
- The procedure started on 18 August 2010.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 4 November 2010. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 12 November 2010.
- During the meeting on 13-16 December 2010, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 20 December 2010.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 26 April 2011.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 7 June 2011.
- During the CHMP meeting on 20-23 June 2011, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the list of outstanding issues on 18 August 2011.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the list of outstanding issues to all CHMP members on 5 September 2011.
- The Rapporteurs circulated an updated Overview to all CHMP members on 19 September 2011.
- During the meeting on 19-22 September 2011, 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 22 September 2011.

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Clostridium difficile infection (CDI), also known as *C. difficile*-associated disease or diarrhoea (CDAD) is one of the leading courses of nosocomial infections with disease severity ranging from mild diarrhoea to fulminant colitis. The disease is caused by infection of the inner lining of the colon by *C. difficile* bacteria, which produces toxins that cause inflammation of the colon, severe diarrhoea and, in the most serious cases, death. CDI accounts for approximately 15-35% of cases of antibiotic-associated diarrhoea, and for 95% of cases of antibiotic-associated pseudomembranous colitis. Over the last 10-20 years the incidence and severity of CDI has increased, particularly in elderly, with a substantial number of cases being described also outside healthcare settings. A potential cost of CDI per year in the EU of €3 billion has been estimated, assuming an EU population of 457 million.

Clostridium difficile is a spore-forming, anaerobic, gram-positive rod. CDI is caused by an overgrowth of *C. difficile* in the colon most commonly associated with previous antibiotic use which eradicates or disrupts the gut flora, allowing *C. difficile* to proliferate. Antibiotics commonly linked to CDI include cephalosporins, fluoroquinolones, clindamycin, ampicillin, and amoxicillin, but almost any antibiotic can cause CDI. Proliferating *C. difficile* produces toxins that cause a variety of complications, including pseudomembranous colitis, toxic megacolon, perforations of the colon, and sepsis. *C. difficile* can also persist as spores in the stools leading to frequent recurrences after successful initial treatment.

Outbreaks of CDI with increased morbidity and mortality have increasingly been reported the last decade. These outbreaks are generally associated with the emergence and dissemination of a more virulent strain characterized variously as restriction endonuclease analysis (REA) type BI, PFGE pulsotype 1 (NAP1), PCR ribotype 027, and toxinotype III. This NAP1/BI/027 strain is known to be resistant to fluoroquinolone-class antibiotics and has been shown to produce amounts of toxins A and B that are 16-23 times greater than those produced by control strains from toxinotype 0; this hypervirulent strain also produces binary toxin. To date, these hypervirulent strains of *C. difficile* have been identified in the US, Canada, and 16 European Union (EU) countries, as well as Switzerland.

Mild cases of CDI may recover after stopping the causative antibiotic therapy, although this approach is often not sufficient for more severe cases and targeted antibiotic therapy has to be instituted. The two most commonly used and approved therapies are oral vancomycin and metronidazole. Both agents are in most cases effective in treating CDI but approximately one third of patients who initially respond to metronidazole or vancomycin suffer a clinical recurrence, probably due to disruption of the normal gut flora by these agents and persistence of the spore form of *C. difficile*. Orally administered metronidazole is almost completely absorbed and the systemic exposure is associated with significant adverse effects. Vancomycin is one of very few alternatives of antibiotics used to treat some serious and life-threatening infections caused by multi-drug resistant bacteria such as methicillin-resistant *Staphylococcus aureus* (MRSA). There is evidence of emerging resistance to vancomycin among various important pathogens such as MRSA and vancomycin-resistant Enterococcus (VRE). In order to slow the continuing emergence of glycopeptide-resistant strains, the medical community discourages the use of vancomycin except when necessary. Thus an alternative drug with similar or better activity and safety profile as metronidazole or vancomycin against CDI is urgently needed.

2.1.2. About the product

Fidaxomicin (also known as OPT-80 and PAR-101) is a novel antibiotic agent and the first representative of a new class of antibacterials called macrocycles. It has a narrow spectrum antibacterial profile mainly directed against *Clostridium difficile* and exerts a moderate activity against some other gram-positive species. Fidaxomicin is bactericidal and acts via inhibition of RNA synthesis by bacterial RNA polymerase at a distinct site from that of rifamycins. The drug product is poorly absorbed and exerts its activity in the gastrointestinal (GI) tract, which is an advantage when used in the applied indication, treatment of *C. difficile* infection (CDI) (also known as *C. difficile*-associated disease or diarrhoea [CDAD]).

Proposed indication (from the applicant):

Dificlir (fidaxomicin) is indicated for the treatment of *Clostridium difficile* infections (CDI) also known as *C. difficile*-associated disease (CDAD) and prevention of recurrences (see Section 5.1).

Proposed posology and method of administration (from the applicant):

Dificlir is for oral administration.

Adults and Elderly (≥ 65 years of age):

The recommended dose for Dificlir is 200 mg administered twice daily (q12h) for 10 days.

Paediatric Population:

The safety and efficacy of Dificlir in children has not yet been established.

2.2. Quality aspects

2.2.1. Introduction

Dificlir is presented as film-coated tablets containing 200 mg of fidaxomicin as active substance. The other ingredients are microcrystalline cellulose, pregelatinised starch, hydroxypropyl cellulose, butylated hydroxytoluene, sodium starch glycollate and magnesium stearate.

The ingredients of the coating are polyvinyl alcohol, titanium dioxide, talc, macrogol and lecithin.

The medicinal product is packaged in HDPE bottles with tamper-evident, induction-sealed, polypropylene child-resistant caps and desiccants or is packaged in aluminum/aluminum blister strips with paper backing.

2.2.2. Active Substance

Fidaxomicin is a white to off-white powder, practically insoluble in water. It is also freely soluble in tetrahydrofuran, dimethyl sulfoxide and methanol, soluble in acetone, sparingly soluble in ethanol, acetone, ethyl acetate, dichloromethane and acetonitrile, slightly soluble in isopropanol. Figure 1 describes the absolute stereochemistry of fidaxomicin as determined by x-ray. It was noted that this active substance has fourteen chiral centres. Only one polymorph form (polymorph form A) is routinely produced by the synthetic process described in the dossier and is used in the manufacture of the finished product.

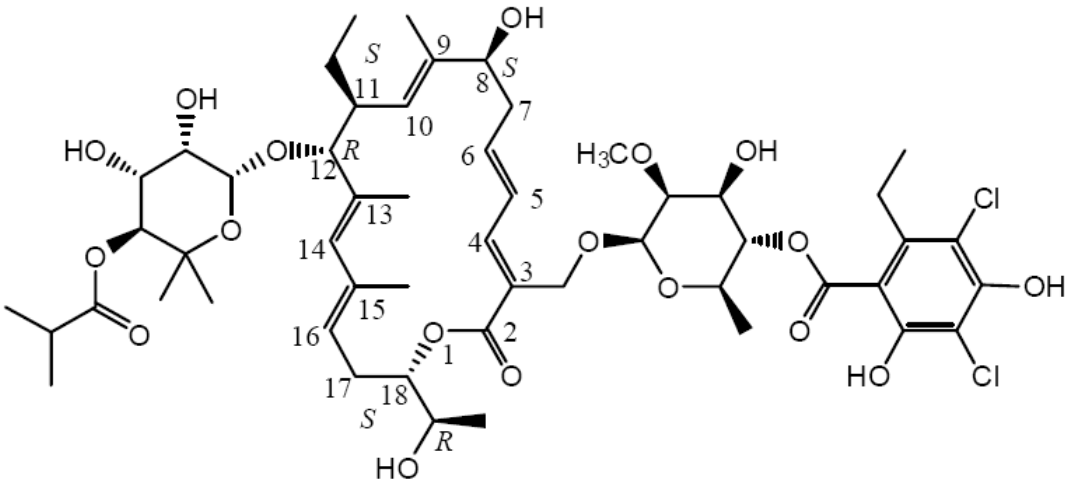


Figure 1: Fidaxomicin

Manufacture

Fidaxomicin drug substance is a purified fermentation product produced by the organism *Dactylosporangium aurantiacum*. The manufacturing process consists of inoculum expansion, production fermentation, isolation and purification. A full description of the manufacturing process was provided. Adequate controls of critical steps and intermediates are sufficient to ensure the quality of the active substance, and adequate specifications for starting materials, reagents, and solvents have been provided. The purified active substance is packed in low density polyethylene (LDPE) bags. Inner and outer LDPE bags with a silica gel sachet are placed inside a triple laminated aluminium bag which is placed inside of an HDPE container. The chemical structure of fidaxomicin has been confirmed by spectroscopy (IR, 1H-NMR, 13C-NMR, Raman and x-ray).

Specification

The specification of the active substance complies with ICH Q3A and includes tests for appearance (visual), identification, (HPLC & TLC), assay (HPLC), impurities (HPLC), residual solvents (GC), acetic acid (HPLC), sulphated ash (Ph.Eur.), heavy metals (Ph.Eur.), particle size distribution, microbiology test (Ph.Eur.) specific optical rotation (Ph.Eur.), form identity (XRPD) and water content (Ph.Eur.). A detailed description for all analytical methods was provided. Full method validation data was provided for the in-house analytical methods and are in accordance with the relevant ICH Guidelines. In general analytical methods proposed are suitable to control the quality of the active substance. The impurity limits are acceptable and there is no concern from the point of view of safety. Batch analysis data have been provided and show consistent compliance with the predefined active substance specification.

Stability

Stability data for three batches of fidaxomicin, stored for 48 months at 2 to 8°C were provided. Furthermore stability results from long-term (25°C/60%RH) and accelerated studies (40°C/75%RH) for three production scale batches were completed according to ICH guidelines demonstrated adequate stability of the active substance. The following parameters were monitored during the stability studies: assay, impurities (HPLC), appearance (visual) and water content. The microbiology test (Ph.Eur.) is

conducted annually. It was noticed that the test methods applied are those used for release of the active substance. It can be concluded that the proposed re-test is justified based on the stability results when the active substance is stored in the original packing material.

2.2.3. Finished Medicinal Product

Pharmaceutical Development

All information regarding the choice of the active substance and the excipients are sufficiently justified. The main aim of the pharmaceutical development was to formulate a conventional film-coated tablet, with a relatively rapid drug release containing 200 mg of fidaxomicin as active substance.

The initial dosage form to be developed for phase IA of the clinical studies was a hard gelatin capsule. Due to long-term stability concerns, a capsule containing 50 mg of fidaxomicin and microcrystalline cellulose was thus developed for evaluation in subsequent phases 1B and 2A. Based on the results of the phase 2A study, the 200 mg dosage strength of fidaxomicin was selected for further clinical development. An immediate release uncoated tablet containing 200 mg of fidaxomicin was developed for the first phase 3 clinical trial. During phase 3 the immediate release tablet was further optimized for longer shelf life. This optimized formulation was used in the second phase 3 clinical trial.

Manufacture of the product

The proposed commercial manufacturing process for the film-coated tablets involves standard technology and it is divided into the following steps: mixing, wet granulation, drying, milling, blending, compression, film coating, and packaging. The equipment used is commonly available in the pharmaceutical industry. The manufacturing process has been adequately described and granulation process has been identified as critical and optimised during the drug development. The validation protocol proposed for the full scale batches has been provided and the quality of the production batches will be evaluated through the results of in process testing as well as the results of finished product testing.

Product Specification

The product specification is standard for film-coated tablets and contains tests with suitable limits for appearance, identification (HPLC & UV), assay (HPLC), impurities (HPLC), uniformity of dosage (Ph.Eur), dissolution, residual solvent (GC), disintegration (Ph.Eur.), BHT Assay and microbiological purity (Ph.Eur). Impurities and degradation products have been evaluated and found to be acceptable from the point of view of safety. No impurities are caused by the interaction with the excipients used in the formulation. All analytical procedures that were used for testing the finished product were properly described and satisfactorily validated in accordance with the relevant ICH guidelines. The batch analysis data for eight pilot batches confirm that the film-coated tablets can be manufactured reproducibly according to the agreed finished product specifications.

Stability of the product

Stability results from long-term (25°C/60%RH) and accelerated studies (40°C/75%RH) for three production scale batches were completed according to ICH guidelines demonstrated adequate stability of the active substance. Furthermore, stability data were also provided at refrigerated at 5°C up to 24 months. The following parameters were monitored during the stability studies: assay, impurities, BHT assay, appearance, dissolution and water content. The microbiology test (Ph.Eur.) is conducted annually and hardness testing was performed at 24 month. It was noted that the test methods applied are those used for release of the finished product. All the results remained well within the specification limits during all the stability studies. A photostability testing programme was conducted in accordance with the recommendations of ICH guideline Q1B. The results were found to meet the specifications and the finished product does not require any special light protection. Forced degradation test were performed under thermal, acidic, basic, and oxidative conditions. Based on the results, it was noted that these stress conditions (thermal, basic, acid and oxidative) can affect the specifications of the finished product.

Based on available stability data, the proposed shelf life and storage conditions as stated in the SmPC are acceptable. A stability study of the finished product under ICH conditions prepared from different intermediates that had been stored in bulk, for the maximum holding time has been recommend to be conducted as a post-authorisation measure.

2.2.4. Discussion on chemical, and pharmaceutical aspects

The pharmaceutical development of the formulation, the manufacturing process, control of the active substance and the finished product have been presented in a satisfactory manner and justified in accordance with relevant CHMP and ICH guidelines. The manufacturing flow-chart was provided with suitable in-process controls. The validation protocol proposed for the full scale batches has been provided and the quality of the production batches will be evaluated through the results of in process testing as well as the results of finished product testing. The routine specifications and tests methods proposed for the active substance and finished product will adequately control the quality of the active substance and finished product. Analytical methods were well described and validated in agreement with relevant guidelines.

Batch analyses were presented and the results showed that the finished product meets the specifications proposed.

The container-closure system was found to be suitable to ensure the quality of the finished product as shown by the stability data.

The conditions used in the stability studies comply with the ICH stability guideline. The control tests and specifications for finished were adequately established.

The proposed holding times of the different intermediate products stored in bulk, an ICH stability study of the finished product, prepared from the different intermediates that had been stored for the maximum holding time, has been recommended.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

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

conclusion that the medicinal product should have a satisfactory and uniform performance in the clinic. All other quality issues have been resolved.

2.2.6. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following point for investigation:

2.3. Non-clinical aspects

2.3.1. Introduction

Pivotal non-clinical studies on the pharmacology and toxicology of fidaxomicin were conducted in accordance with principles of GLP.

However, it was noted that some studies or part of studies were performed by test facilities where the GLP inspection results by the US FDA indicated that objectionable conditions or practices were found: it concerns genotoxicity studies and the 28-day oral toxicity and toxicokinetics in Cynomolgus Monkeys. In the Cynomolgus study, an amendment to the report was issued about 7 years after the end of the last bioanalytical results without any clear explanation.

Furthermore, an ethical concern should be noted in the 3-month repeated-dose oral toxicity study in Beagle dogs: for the highest dose, dogs were dosed up to 48 capsules/day.

2.3.2. Pharmacology

Primary pharmacodynamic studies

Fidaxomicin is active against Gram-positive strains only, in particular *Clostridium difficile*. The mode of action is bactericidal and both parent compound and the major metabolite, OP-1118 have antimicrobial activity. Fidaxomicin is an inhibitor of the enzyme ***RNA polymerase.*** The site of action is different from that of rifamycins.

In vitro microbiological data is further detailed in the clinical pharmacology report.

In vivo studies

- Hamster studies

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 fidaxomicin (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 ED_{50} 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 fidaxomicin 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 fidaxomicin 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.

In summary, preclinical *in vivo* studies using clindamycin sensitised hamsters showed that fidaxomicin was effective in protecting animals from lethal infections with an ED_{50} of less than 0.3 mg/kg. Overall, the non-clinical pharmacology of fidaxomicin has been acceptably characterised and is consistent with expected clinical activity.

Secondary pharmacodynamic studies

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

Safety pharmacology programme

Table 1: Overview of studies

Organ system	Species (#)	Dose/Duration	Major findings
Cardiovascular hERG *in vitro*	*In vitro*	Fidaxomicin and OP-1118= 0.01-10 µg/mL	Actual max conc fidaxomicin=7.85 µg/mL, OP-1118=8.37 µg/mL. No significant effect on hERG current. Positive control cisapride caused 90% inhibition.
Cardiovascular, PO	Dog (4 M+4F)	1000, 3200, 9600 mg/kg	No effects on blood pressure, body temp, PR interval QRS complex, QTc interval. Lower pulse pressure but small magnitude of change.
Cardiovascular, IV	Dog (3M+3F)	0, 1, 4, 7.5 mg/kg	Study terminated at 1 mg/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.)
Respiratory, IV	Rat (8M)	0, 1, 4, 7.5 mg/kg	Data collected up to 5 hr post dose. NOEL=7.5 mg/kg.
CNS (FOB), IV	Rat (6 M)	0, 1, 4, 7.5 mg/kg	Positive control=chlorpromazine HCl. Assessment up to 8 hr post dose. NOEL= 7.5 mg/kg.

IV vehicle=solutol HS-15/phosphate buffered saline, FOB=functional observational battery

In an intravenous cardiac telemetry study in dog, transient hypotension was observed immediately after dosing of fidaxomicin in Solutol HS 15. However, the excipient was the probable cause of this finding. In another cardiovascular study, also performed in dog, where fidaxomicin was given orally at a dose which produced systemic levels in excess of those observed in the intravenous cardiovascular study, no effects were seen. Neither fidaxomicin nor its main metabolite OP-1118 had an inhibitory effect on the hERG channel current (IC50 greater than the highest doses tested; nominal, 10 µg/mL; actual, 7.85 µg/mL for fidaxomicin and 8.37 µg/mL for OP-1118). Studies to assess potential effects of fidaxomicin on the respiratory and CNS systems in rats were also negative for an effect. 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 fidaxomicin have been acceptably characterised and has not revealed any unexpected effects.

Pharmacodynamic drug interactions

Studies to determine the potential synergy/antagonism of fidaxomicin and main metabolite OP-1118 with other antimicrobials are presented in the clinical pharmacology summary. No other pharmacodynamic drug interaction studies were performed.

2.3.3. Pharmacokinetics

Table 2: Overview of pharmacokinetics of fidaxomicin

Absorption	Low systemic availability after oral administration.
Distribution	Mainly the gastrointestinal tract after oral administration.
Metabolism	Main metabolite OP-1118, a desisobutyryl hydrolysis product is an active metabolite. Acyl migration to form tiacumicins C and F has been observed. OP-1118 has a potential to inhibit CYP3A4 dependent hydroxylation of midazolam and testosterone (time and metabolism dependent inhibition).
Excretion	Primarily in the faeces.

Pharmacokinetic and/or toxicokinetic studies with fidaxomicin were performed in rat, rabbit and dog and monkey. Validated bioanalytical methods for plasma (rat, rabbit, dog, monkey) and faeces (dog) were used.

In *in vitro* studies on transit of fidaxomicin and its main metabolite OP-1118 across Caco-2 cell monolayers the ratio between basolateral to apical (B-A) transit and apical to basolateral (A-B) transit was 73.9 for fidaxomicin at a concentration of 5 µM, and 15.7 for OP-1118 at a concentration of 125 µM. Both cyclosporine A and ketoconazole (known unspecific inhibitors of P-gp) decreased the (B-A)/(A-B)-ratio indicating that fidaxomicin and OP-1118 are substrates for P-gp.

Following oral administration of fidaxomicin in rat, plasma concentrations were low (< LLOQ; 0.5 µg/mL) and very little fidaxomicin (< 0.01 mg/g) was detected in colon or caecum at any time point through 24 hours. In an oral study in dogs the fate of ^{3}H-fidaxomicin after administration at 6.47 mg/kg, or 245.6 µCi per animal were explored. Radioactivity was not detectable in any plasma sample. LC-MS/MS analysis detected low levels (~20 ng/mL) of the metabolite OP-1118 in only two samples, at 1 and 2 hours post-dose.

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 increase with dose, except in dog where saturation was seen at high doses.

A 3-month repeated dose study in beagle dogs, using the clinical tablet formulation and oral dose levels of 0, 1, 3.2, and 9.6 g/day showed that the extent of exposure for both fidaxomicin and OP-1118 increased with increasing dose, in a nonlinear fashion: $AUC_{0\text{-tlast}}$ increased greater than proportionally across the dosing range, while C_{max} increased greater than proportionally between the 1 g and 3.2 g doses and usually proportionally between the 3.2 g and 9.6 g doses. A large interanimal variability was found, possibly due to differences in local gut pH. Male and female cynomolgous monkeys (3/sex/group) were dosed for 28 days with 0, 10, 30, and 90 mg/kg/day of fidaxomicin. Plasma levels (C_{max} and AUC) increased approximately proportionately between the doses. It is worthwhile to compare these results with those observed in dogs receiving 90 mg/kg fidaxomicin in Labrasol where plasma levels were approximately 5-6×higher than those observed in monkeys (C_{max},~0.15 µg/mL), supporting the use of dogs in assessments of toxicity following oral administration.

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 fidaxomicin, 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).

Fidaxomicin 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 catalyzed 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, also described in the section on oral absorption, was conducted in which dogs were orally administered (gavage) 6.47 mg/kg of [3H]-fidaxomicin, to deliver 245.6 µCi/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 fidaxomicin (400 mg/kg as tablets) less than 1% of the administered drug was recovered in the bile as either fidaxomicin or OP-1118. The overall recovery in faeces and bile for fidaxomicin 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.

Fidaxomicin show mild inhibition of certain CYP enzymes at levels (10 µg/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 fidaxomicin and OP-1118 are substrates for efflux pumps, and this efflux is inhibited by cyclosporine A and ketoconazole, inhibitors of P-glycoprotein. Fidaxomicin is also an inhibitor of P-glycoprotein, with an IC50 of 2.59 µM (2.74 µg/mL), while OP-1118 is a much weaker inhibitor (IC50 > 125 µM, or 123 µg/mL). The inhibitory effect of fidaxomicin and OP-1118 on other intestinal transporters has not been investigated and the applicant is now planning to investigate the effect of fidaxomicin on MRPs, OATPs and BCRP in vitro and in addition attempt to analyse possible signs of DDI involving transporters in the clinical studies already performed by analysis of co-medications and possible signs of reduced or increased absorption. However, it seems unlikely that screening for reduced effect or increased adverse events of co-administered medications that are substrates for MRPs, OATPs and BCRP will generate data that can lead to any firm conclusion regarding potential for fidaxomicin to interact with these transporters. It is therefore considered sufficient with an *in vitro* study investigating the effect of fidaxomicin on MRPs, OATPs and BCRP. If this study shows a risk for significant interaction further *in vivo* evaluation may be needed.

2.3.4. Toxicology

Fidaxomicin has a low bioavailability, partly due to a low solubility and several different vehicles have therefore been explored in order to increase the systemic exposure. Difficulties in obtaining high enough plasma levels in rat and rabbit led to the use of intravenous administration in these species. Low plasma levels after oral administration was also seen in monkeys. Only one species, the dog for which oral administration was possible, was therefore used in a 3 month repeat dose study. In the pivotal studies either intravenous administration using Solutol (PEG stabiliser) as vehicle (reproductive

and developmental toxicity studies in rat and rabbit, and in vivo genotoxicity in rat) or oral administration of tablets in capsules (3 month study in dog) were used. All pivotal studies were performed according to GLP.

Except for histamine like reactions, possibly due to a toxic interaction between fidaxomicin and some of the vehicles investigated, no adverse effects were generally seen in any of the studies performed, except for soft and coloured faeces, diarrhoea and emesis at high doses. Exposure margins were generally high for fidaxomicin and its major metabolite. In several studies the margins were greater than 20-100x (AUC) compared to levels found in healthy volunteers, although some species variations occurred, e.g. with a margin of 4-6x (AUC) for OP-1118 in the dog. However, it is pointed out that taking the 3 and 6 times higher exposure levels for fidaxomicin and OP-1118 in CDI patients into account the exposure margins are significantly reduced and results in approximately only similar levels of OP-1118 being reached in the 3 month dog study as what might be seen in the clinic. In addition the lack of complete PK-data from CDI patients together with the possibility of future exposure of CDI patients with more severely affected GI-tract (and thus possibly higher absorption of fidaxomicin) as compared to patients studied, create an uncertainty in the establishment of "true" exposure margins. This uncertainty is addressed in the RMP by a suggested thorough monitoring of this group of patients.

Single dose toxicity

Table 3: Single dose toxicity study performed with Fidaxomicin in rat and dog

Species/Sex	Route of administration	Dose (mg/kg) /observation period	Observed Maximum Nonlethal dose [mg/kg]	Approximate Lethal Dose (mg/kg)	Major findings	GLP status
Rat / Crl:CD® (SD) (IGS)BR [5/se/group]	Oral (Labrasol®)	0, 167, 500, 1000	1000	> 1000	- No deaths occurred. **At 167 mg/kg** - Hair loss on forelegs; few or no faeces, coloured material around nose and eyes **At ≥ 167 and 500 mg/kg** - Staining of fur, yellow (concentrated) urine	Yes
Rat / Crl:CD® (SD) (IGS)BR [5-6/sex/ group 3/sex for add-on TK group]	Intravenous (10% dimethyl acetamide, 20% ethanol, 70% PEG 400) Injection in tail vein	0, 20, 62.5, 200	62.5	200	**At 0-62.5 mg/kg** - Sore on tail (slight to moderate) - discoloured urine (red, red/brown, red/yellow) **At ≥ 62.5 mg/kg** - Anogenital staining, tail changes (biting slight to moderate/severe sore); bright yellow urine **At 200 mg/kg** - **Mortality:** 3 M, 2 F - Laboured breathing, hunched posture, cold to touch, tail changes (blue or black in colour, end missing)	Yes
Pilot study Rat / Sprague Dawley [0, 75, 100 mg/kg : 2-3M/ group 75,	Intravenous (10% dimethyl acetamide, 20% ethanol, 70% PEG 400) Injection in tail vein or femoral vein	0, 75, 100 (tail vein), single dose 75, 85 (femoral vein), 2 doses (Days 1 and	85	100	**At 0, 75 and 85 mg/kg** - Darkening of the tail (blue colour) - Transient findings of slight to moderate decrease in activity, slight uncoordinated gait, recumbancy, eyes partially closed, limited use of hindlimbs and animal repeatedly opening and closing mouth	SOP of LAB

85 mg/kg: 3F/group]		3)			**At 100 mg/kg** - Both animals died within 3 minutes post-dose	
Dog, Beagle [3/sex]	Oral (LT-2[b])	10, 30, 120[c] Each dose was separated by a 7-Day wash out period.	120	> 120	**At all doses** - No mortality. **At ≥ 10 mg/kg**: - **Food consumption** decreases that occurred on Days 0-1 were deemed unrelated to treatment due to the absence of a dose-relationship	No
Dog, Beagle [3/sex]	Intravenous (1% Solutol® HS 15 in PBS)	1, 4, 7.5 Each dose was separated by a 7-Day washout period	7.5	≥ 7.5	**At all doses** - No mortality. **At 1 mg/kg**: - Mucoid faeces, swelling, skin warm to touch, discoloured skin **At ≥ 1 mg/kg**: - Decreased activity, difficult breathing, salivation, tremors, lacrimation, stereotypy, discoloured skin	No

M = male F = female SOP = Standard Operating Procedures

No treatment-related effects were seen at any dose level up to 1000 mg/kg in rats when administered as a single oral dose or at doses up to 200 mg/kg intravenously. Fidaxomicin at 200 mg/kg via intravenous injection to rats resulted in 50% mortality but this was considered likely to be due to the poor solubility and precipitation of fidaxomicin in vasculature at high plasma concentrations. The NOAEL for a single i.v. fidaxomicin dose in the rat was 62.5 mg/kg. At this NOAEL dose, a peak plasma level of 3000-10200 ng/mL fidaxomicin was noted at 30 minutes after dose, at least ~100-fold higher than the Cmax that might be seen in CDI patients.

Repeat dose toxicity

Table 4: Oral and intravenous toxicity studies performed with Fidaxomicin in rat

Species/ Sex/ type of study	Route of administration	Doses (mg/kg/day)	Duration	NOAEL (mg/kg)	Major findings	GLP status
Pivotal study Crl:CD(SD) (IGS)BR rats [10/sex/group] (potential toxicity study)	Oral (gavage)	0 (Labrasol) 10, 30, 90	28 days	**90**	**At all doses** - No drug related deaths **At 90 mg/kg** - By week 4, the mean body weight of M rats was approximately 9% less than the control group (2 out of 10 rats).	**Yes**
Crl:CD(SD) rats [3/sex/group] (Tolerability study)	Intravenous	0 and 4 (nominal) 0 and 0.45 – 1.1 (actual)	14 days	**0.45 to 1.1**	- No drug related deaths - Minimal ↑ for the thymus organ weights	**No**
Sprague Dawley rats [10-14/sex/group] (non pivotal TK and tolerability study)	Bolus Intravenous	0 (vehicle) 4, 20, 75	14 days	**ND**	**At all doses** - High mortality occurred in all group including control. - Severe ↓ in activity, laboured respiration, severe ↓ in respiration, gasping, hunchback recumbancy, partially closed eyes, uncoordination, moderate amounts of red urine/liquid, salivation (males only), and paleness.	-

Sprague Dawley rats [5/sex/group]	Intravenous infusion	0 (*0.2% Tween-80 and 5% dextrose solution*) 19.2	14 days	**ND**	- No mortality - No macroscopic or microscopic changes - Slight ↓ in body weight gain.	**-**

F = female; M = male MTD = Maximum tolerated dose ↑ = increase ↓ = decrease ND = not determined TK = toxicokinetic

Table 5: Oral toxicity studies performed with Fidaxomicin in dogs

Species/ Sex/ type of study	Route of administration	Doses (mg/kg/ day)	Duration	NOAEL (mg/kg)	Major findings	GLP status
Pilot study Beagle dogs [3/sex/dose] (non pivotal potential toxicity)	Oral (gavage)	30, 60, 120	14 days	**120**	- No mortality - No effects on food consumption or body weights. **<u>At 60 and 120 mg/kg</u>** - Abnormal excreta (soft faeces, mucoid faeces, faeces containing white material and/or diarrhoea) and/or emesis. - No effects on food consumption or body weights.	-
Pilot study Beagle dogs [2/sex/dose] (non pivotal toxicity and TK)	Oral (gavage)	0, 54, 140, 436 (M) 0, 62, 165, 516 (F)	14 days	**NOEL = 436 to 516**	- No mortality - No test article-related clinical observations or changes	No
Pilot study Beagle dogs [2/sex/dose]	Oral (gavage)	0, 810, 1200 (M) 0, 965, 1378 (F)	14 days	**1200 (M) 1378 (F)**	- No mortality - pale faeces, soft faeces and yellow faeces, and sporadic incidents of emesis in a dose-dependent manner - Food consumption was slightly lower for both males and females	No
Pivotal study Beagle dogs [4-7/sex/dose]	Oral (gavage)	0, 10, 30, 120	3-month	**-**	- Anaphylactoid reactions noted in 1 animal in the control group, 3 animals in the 10 mg/kg/day group, and 2 animals in the 120 mg/kg/day group were either euthanized in extremis or found dead + macroscopic findings (reddening of mucosa of duodenum, ileum, jejunum, colon, cecum, and rectum, and dark red discoloration of the lungs and lymph nodes). - No test article-related effects in the surviving dogs **<u>At 120 mg/kg</u>** - Soft faeces, mucoid faeces, and diarrhoea in M and F. - Emesis containing white material in F.	**Yes**
Pivotal study Beagle dogs [4-7/sex/dose]	Oral (gavage)	0, 101, 324, 942 (M) 0, 121, 400, 1190 (F)	3-month	**942 (M) 1190 (F)**	- No mortality - pale/yellow faeces and faeces containing white/yellow material - sporadic observations of emesis of white material	Yes

NOEL= no-observable-effect level NOAEL = the no-observable-adverse-effect level M = male F = female TK = toxicokinetic

Table 6: Oral toxicity studies performed with Fidaxomicin in monkeys

Species/ Sex/ type of study	Route of administration	Doses	Duration	NOEL (mg/kg)	Major findings	GLP status

Pivotal study Cynomolgus Monkeys (12 (12M, 12F) [3/sex/dose]	Oral (capsule)	10, 30, 90	28 days	**90**	**<u>At all doses</u>** - No drug related mortality, but procedure-related accidental death at 90 mg/kg/day (1 M and 1 F) (severe hypoactivity, hypothermia, red material on mouth and nose, ptosis and pallor, presence of red foamy material in the trachea, multiple areas of dark discoloration on all lobes of the lungs). - No other drug related adverse effects at any dose level.	Yes

M = male F = female NOEL= no-observable-effect level

Fidaxomicin neither showed any adverse effects following multiple dosing when administered orally to rats, cynomolgus monkeys or dogs. In rats and monkeys the toxicity of fidaxomicin was evaluated at oral doses up to 90 mg/kg for 28 days; and in dogs, at oral doses up to 9600 mg/day for 3 months. Following 28 days of repeated dosing with up to 90 mg/kg fidaxomicin (in Labrasol) in rats, there were no drug related deaths or effects on clinical observations. The NOEL was 90 mg/kg/day.

Following 28 days of repeated dosing with up to 90 mg/kg fidaxomicin (in Labrasol) in Cynomolgous monkeys no treatment-related effects were observed at any dose level. The highest dose level (90 mg/kg/day, Cmax 131-417 ng/mL, AUC0-tlast 288-1180 ng-hr/mL) was considered to be the NOEL.

The pivotal toxicity study was a 3 month repeated-dose study in dogs dosed orally with fidaxomicin at doses of up to 9600 mg/day. There were no test-article related effects on body weights, food consumption, clinical or anatomic pathology parameters, ECG or any ophthalmic lesions. Effects of fidaxomicin administration were limited to GI effects, as evidenced by clinical observations of pale/yellow faeces and white emesis which was 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. (Tablets were administrated in capsules. Control group received the same number of empty capsules as the high dose group.) 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 1190 mg/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 were 3010 ng/mL for fidaxomicin and 361 ng/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 8160 ng-hr/mL for fidaxomicin and 945 ng-hr/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.

Genotoxicity

Table 7: *In vitro* genotoxicity study performed with in Fidaxomicin and metabolite OP-1118

Study Type	Test article	Species (Gender)	Doses	Results	GLP status
Ames reverse-mutation	Fidaxomicin	4 strains of Salmonella typhimurium (TA1535, TA1537, TA98, TA100) + E. coli strain WP2 uvrA	0, 1.5, 5.0, 15, 50, 150, 500, 1500, 5000 µg/plate +/-S-9	Negative	Yes
	OP-1118		0, 1.5, 5.0, 15, 50, 150, 500, 1500, 5000 µg/plate +/-S9	Negative	Yes
Mammalian chromosome aberration test	Fidaxomicin	CHO cells	*First experiment* 12.5 to 200 µg/mL (-S9) 3.125 to 100 µg/mL (+S9) *Repeat assay* 3.125 to 150 µg/mL (+S9) 50 to 140 µg/mL (-S9)	- Positive for the induction of structural chromosome aberrations without S9. - Negative for the induction of structural chromosome aberrations with S9. - Negative for the induction of numerical chromosome aberrations.	Yes
	OP-1118		Substantial toxicity at 5000 µg/mL (–S9, 4 hr exposure group), and at ≥ 1500 µg/mL (+S9 4 hr and –S9 20 hr continuous exposure group). Based on these findings, the doses chosen ranged from 500 to 4000 µg/mL for the -S9 (4 hr exposure groups), and from 100 to 1200 µg/mL for the +S9 (4 hr and –S9 (20 hr continuous exposure group).	The % of cells with numerical aberrations in the –S9 was statistically increased relative to solvent control at 900 µg/mL ($p \geq 0.05$). However, 2.5% of cells with numerical aberrations were within the historical solvent control range of 0.0% to 7.5%. *Conclusion* Therefore, this finding was not considered to be biologically significant. OP-1118 was concluded to be negative for the induction of structural and numerical chromosome aberrations in CHO cells in both the non-activated and the S9-activated test systems.	Yes

% = percentage ↑ = *increase* *hr = hour*

Table 8: *In vivo* genotoxicity study performed with in Fidaxomicin

Study Type	Test article	Species (Gender)	Route of administration	Doses (mg/kg)	Results	GLP status
Mammalian Erythrocyte micronucleus Test	Fidaxomicin	5 Rat/ Sprague Dawley	Intravenous	0, 18.75, 37.5, 75	A statistically significant ↑ in micronucleated PCEs at 37.5 mg/kg group 24 hours post dose relative to the control group ($p \leq 0.05$). *Conclusion* The number of micronucleated PCEs in all animals in this group was within the range of historical control values and therefore was not considered to be biologically significant.	Yes

PCE = polychromatic erythrocytes

Neither fidaxomicin 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 fidaxomicin in absence of metabolic activation at concentrations ≥ 100 µg/mL. Fidaxomicin was administered to rats intravenously with the top dose selected as the maximum tolerated dose (75 mg/kg). A statistically significant increase in micronucleated PCEs was observed in the 37.5 mg/kg group 24 hours post dose relative to the control group ($p \leq 0.05$). However, since there was no dose response and the number of MPCEs in all animals in the positive medium dose were within the historical range of 0-2.0 MPCE/2000 PCE from 1997-2002 the result of this test is considered to be negative. Since fidaxomicin was found to induce structural aberrations in vitro. a second in vivo test was also performed in response to a major objection raised by the CHMP. In order to reflect the high concentrations of fidaxomicin 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 up to 2000 mg/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 2000 mg/kg/day dose groups, 1.60% and 1.19%, respectively.

Possible mechanisms behind the decrease in %Tail DNA discussed by the applicant are cross-linking, tissue processing, cytotoxicity, antioxidant properties, and biological and assay variability. The standard protocol used in the present Comet study has been shown to be sufficient for detecting cross-linkers in primary cells from the GI-tract and kidney, suggesting that the protocol used may be regarded as appropriate (although not optimal) for detecting a cross-linker in intestinal cells. The absence of toxicity in actively proliferating tissues in the performed in vivo studies (e.g. no evidence of histopathological changes seen in the gastrointestinal tract in the 3 month study in dog), which would have been expected if fidaxomicin were acting via a cross-linking mechanism, together with the fact that no statistically significant effects were seen between control or treated animals or in any other parameter in the Comet assay clearly support the conclusion that a cross-linking mechanism for fidaxomicin is highly unlikely. This conclusion is further supported by the negative findings in the bacterial reverse mutation assays performed.

An effect due to tissue processing would be expected to occur in all samples regardless of dose group and is therefore not seen as a likely explanation. On the other hand cytotoxicity and an effect via possible antioxidant properties cannot be ruled out at present and are thus considered to be possible mechanisms for the decrease in %Tail DNA seen. Biological and assay variability might also be a possible explanation. The variability in the present study, which was similar to that reported by others, make interpretation of data difficult especially since the decreased trend in %Tail DNA appears to be driven by data from a single animal. The impact of a single value on the statistical significance of the decrease in %Tail DNA seen in the present study strongly indicates that variability is a likely explanation for the response seen. The biological relevance of the decreased trend in %Tail DNA is thus highly questionable.

Carcinogenicity

Considering the short (10 days) planned duration of dosing, carcinogenicity studies were not conducted with fidaxomicin.

Reproduction Toxicity

Fidaxomicin did not induce any maternal toxicity and had no toxic effects on fertility or early embryonic development at the highest dose tested in rats (6.3 mg/kg/day actual dose given). The lowest AUC0-last value measured for fidaxomicin for either sex, at any time point, was 2620 ng-hr/mL, 6-fold higher than the AUC that might be expected in CDI patients.

Maternal, reproductive or embryo-foetal developmental toxicity of fidaxomicin was neither detected at the highest dose tested in rats (15 mg/kg/day) nor rabbits (7.5 mg/kg/day). The lowest mean AUC0-tlast values measured for fidaxomicin at these dose levels (measurements made on the first and last days of dosing) were 9350 ng-hr/mL in the rat and 2280 ng-hr/mL in the rabbit, which are 22-fold and 6-fold higher, respectively, than the AUC that might be expected in CDI patients. At the same doses, the lowest measured OP-1118 AUC0-tlast values were 6320 and 21,600 ng-hr/mL in the rat and rabbit, which are 4-fold and 13-fold higher respectively. It should be noted that exposure levels equal to or higher than those seen in healthy volunteers where generally only achieved during 2-8 hours in rats and rabbits. Since a 24 hour exposure is expected in humans and an even higher exposure is expected in CDI patients, there is an uncertainty in the interpretation of the negative findings reported and the significance for the human situation. However, since the systemic levels of fidaxomicin and OP-1118 are in the ng/mL levels (~100 nM and below) and both compounds are substrates for Pgp and thus likely to be largely excluded from the foetus due to the high expression of P-gp in the placenta the exposure of the foetus at therapeutic doses is expected to be low. The remaining uncertainty is reflected in the suggested text for section 4.6 of the SmPC.

Local Tolerance

No local tolerance studies were performed.

The primary site of exposure in humans is the gut. At the highest doses in the 3 month dog study emesis and soft stools were observed but these effects were not exacerbated with continued dosing and were neither associated with changes in food consumption or weight gain or any histological changes. This suggests that high faecal levels of fidaxomicin up to mg/g levels are not associated with gastrointestinal toxicity.

Other toxicity studies

Phototoxicity

Possible phototoxicity of fidaxomicin is not necessary to be explored based on the UV spectra presented for this compound, with no or very low absorbance in the 290-700 nM range, together with a low bioavailability and low expected systemic exposure

Evaluation of Impurities and Degradation Products

Several impurities of fidaxomicin remain in the drug product after the fermentation based development process and eleven impurities are included in the proposed specification together with four additional degradation products. Exposure margins for the defined impurities have been calculated by comparing expected exposures based on analysis of the fidaxomicin lots used in the key qualifying studies (in vivo genotoxicity test and 3 month repeated dose in dog) with theoretical maximum exposure levels in humans based on a 400 mg daily dose. Data on degradation products has been presented and in order to evaluate the impurities at levels higher than those found in clinical batches, genotoxicity studies have been conducted using an aged batch of fidaxomicin (approximately 3.5 years). The use of the 3 month dog study and the two in vivo genotoxicity studies performed (see above) for qualification of impurities is considered to be acceptable. In addition the use of the second in vivo assay together with

an in vitro gene mutation bacterial assay which was performed using an aged batch of fidaxomicin for qualification of degradation products is also considered to be acceptable.

2.3.5. Ecotoxicity/environmental risk assessment

The log Kow for fidaxomicin is shown to be below the threshold of 4.5 and there is thus likely no need to investigate the persistence, bioaccumulation or toxicity of fidaxomicin (additional log Kow determination is part of the planned Tier A evaluation). The calculated PECsurface water is concluded to be over the trigger limit and a Tier A evaluation of fidaxomicin will be performed. The applicant has provided timelines for the studies necessary to evaluate the environmental fate and effect of fidaxomicin including timelines for the Phase II Tier A environmental fate and effect analysis and submission of the report.

2.3.6. Discussion on non-clinical aspects

Fidaxomicin showed low acute toxicity and the only mortalities reported were after intravenous administration of 200 mg/kg to rats, which might have been due to a precipitation of fidaxomicin in the vasculature (solubility is 18 µg/mL at pH 7 and 104 µg/mL at pH 8). No serious adverse effects were either seen after repeat doses of fidaxomicin even though high exposure levels of fidaxomicin and its major metabolite OP-1118 were achieved, in rat and rabbit (after intravenous administration of fidaxomicin) and in dog (after oral administration of large amounts of tablets). In the pivotal toxicity study, a 3 month repeated-dose study in dogs dosed orally with fidaxomicin at doses of up to 9600 mg/day, there were no test-article related effects. Effects of fidaxomicin were limited to the gastrointestinal tract, as evidenced by clinical observations of pale/yellow faeces and white emesis. The NOAEL was 9600 mg/animal/day.

The genotoxic potential of fidaxomicin and the major metabolite OP-1118 is concluded to be non-significant, based on the overall results from in vitro and *in vivo* studies (erythrocyte micronucleus test and comet analysis of liver and duodenal cells in rat).

Fidaxomicin had no reproductive, maternal or embryo-foetal developmental toxic effects. The conclusion made by the applicant that the exposure margins are sufficient is generally accepted. The low systemic exposure combined with the shown affinity of both fidaxomicin and OP-1118 for Pgp, which is highly expressed in placenta, is likely to reduce exposure and thus the risk for the foetus at therapeutic doses. The remaining uncertainty is reflected in the suggested text for section 4.6 of the SmPC.

Eleven impurities of fidaxomicin are included in the proposed specification of drug substance together with four additional degradation products. Exposure margins for the defined impurities have been calculated by comparing estimates of exposures based on analysis of the fidaxomicin lots used in the key qualifying studies and theoretical maximum exposures in humans. Even though there are uncertainties regarding the expected exposure levels in patients (discussed below) the use of the 3 month dog study together with the two in vivo genotoxicity studies performed for qualification of the impurities is considered acceptable. The suggested limit of NMT 0.5% for the degradation products is also considered to be justified.

There are uncertainties regarding exposure levels in CDI patients and especially patients with more severely affected GI-tract as compared to patients included in the Phase III studies performed. This has also been taken into consideration when exposure margins have been calculated. In addition the remaining uncertainty has been addressed in the RMP as well as in recommendations made in the SmPC.

The value of the calculated PECsurface water is over the trigger limit.

As a result of the above considerations, the available data do not allow to conclude definitively on the potential risk of fidaxomicin to the environment. In the context of the obligation of the MAH to take due account of technical and scientific progress, the CHMP recommends the following points for further investigation to be addressed:

TierA evaluation of fidaxomicin to be initiated (including an additional determination of log Kow). (Timelines have been defined and a final ERA report is expected to be submitted in Q3 2012).

2.3.7. Assessment of paediatric data on non-clinical aspects

No prenatal or postnatal development studies were performed. This is considered acceptable based on the reported limited systemic exposure of fidaxomicin and OP-1118 in man and the lack of adverse effects on fertility/early embryonic development and embryo-foetal development. Studies in juvenile animals were neither performed but will be conducted prior to clinical investigations in paediatric populations.

2.3.8. Conclusion on the non-clinical aspects

The non-clinical aspects of fidaxomicin have been properly addressed.

With respect to the ERA, a TierA evaluation of fidaxomicin will be initiated.

2.4. Clinical aspects

2.4.1. Introduction

GCP

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

The applicant 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

The clinical development programme for Dificlir (fidaxomicin, also referred to as OPT-80), 200 mg film-coated tablets consists of three phase 1 studies, one phase 2A study and two phase 3 studies:

Table 9:

Study ID	Design; Control Type	Number of Study Centers Enrolling Subjects (Locations)	Subjects by Arm; Treated/ Completed	Indication Studied	Gender M/F Mean Age (Range) Race[1]	Duration	Study and Control Drugs Dose, Route, Regimen	Frequency of Dosing
OPT-80 1A-SD	Single dose, double-blinded, randomized, placebo-controlled, dose escalation study Placebo control	Single center, USA	16/15	Healthy subjects	8/8 Age: 49.3 (31-62) 15H/1W	Single dose	Fidaxomicin 100mg, 200mg, 300mg, 450mg Oral	Single dose
OPT-80 1B-MD	Multiple dose, double-blind, randomized, placebo-controlled, dose escalation study Placebo control	Single center, USA	24/23	Healthy subjects	12/12 Age: 51.6 (38-62) 19H/5W	10 days	Fidaxomicin 150mg, 300mg, 450mg Oral	Once daily dosing
OPT-80-005	Group 1: single-dose, 1-period PK study Group 2: randomized, single-dose, 2-period, 2-way crossover, fed/fasting study No control	Single center, USA	Group 1: 6/6 Group 2: 28/28	Healthy subjects	Group 1: 3/3 Age: 35 (18-44) 1W/5B Group 2: 14/14 Age: 32 (18-48) 23W/5B	Group 1: single dose Group 2: single dose on two occasions	Group 1: fidaxomicin 200 mg single dose Group 2: fidaxomicin 400 mg single dose Oral	Single dose
OPT-80 Phase 2A	Open-label, randomized study No control	4 sites (2 USA, 2 Canada)	48/41 50 mg q12h 16/12 100 mg q12h 16/13 200 mg q12h 16/16	CDI	18/30 Age 54.9 (18-90) 43W/2B/ 1A/2O	10 days	Fidaxomicin 50 mg q12h 100 mg q12h 200 mg q12h Oral	Twice daily dosing
101.1.C. 003	Randomized, double-blind, comparative study Vancomycin control	68 sites (52 USA, 16 Canada)	Fidaxomicin 300/280 Vancomycin 323/295	CDI	263/333 Age 61.6 (18-94) 519W/63B/ 11A/3O	10 days	Fidaxomicin 200 mg q12h Vancomycin 125 mg q6h Oral	Fidaxomicin: twice daily dosing Vancomycin: four times daily
101.1.C. 004	Randomized, double-blind, comparative study Vancomycin control	86 sites (30 USA, 12 Belgium, 11 Canada, 6 France, 8 Germany, 3 Italy, 5 Spain, 2 Sweden, 9 UK)	Fidaxomicin 264/233 Vancomycin 260/234	CDI	199/310 Age 63.4 (18-94) 470W/34B/ 3A/2O	10 days	Fidaxomicin 200 mg q12h Vancomycin 125 mg q6h Oral	Fidaxomicin: twice daily dosing Vancomycin: four times daily

Based on safety population in studies OPT-80 1A-SD, OPT-80 1B-MD, OPT-80-005 and OPT-80 Phase 2A, and on Modified Intention-to-Treat (mITT) population in studies 101.1.1.C.003 and 101.1.C.004**.** A = Asian, B = Black, H = Hispanic, O = Other, W = White

2.4.2. Pharmacokinetics

The product is intended for local action but regardless of its physiochemical properties (poor solubility, poor permeability and high molecular weight) the parent drug and its main metabolite OP1118 reach plasma concentrations in the 30 and 100 ng/ml range after oral administration. The PK of fidaxomicin and OP-1118 was characterized in (above tabled) 6 clinical studies. OP-1118 has a narrow spectrum of activity comparable to that of fidaxomicin, although with lower activity. Across studies, approximately 2-fold higher plasma levels of OP-1118 than for those of the parent compound are seen.

Several in vitro studies with human biomaterials were also performed to characterize the efflux transport and metabolism of fidaxomicin, with the aim of ascertaining the potential for concomitantly administered drugs to alter the disposition of fidaxomicin. Conversely, in vitro studies were also performed to assess if fidaxomicin (and its main metabolite OP-1118) have the ability to inhibit the efflux transport or metabolism of other drugs.

Several adequately validated bioanalytical methods have been used during the development programme.

Absorption

There is no estimate of absolute bioavailability in humans but it was determined in several nonclinical dog studies, using different formulations with various solubility enhancers, with estimates around 0.2-3%.

In a caco-2-assay, the efflux ratio values were markedly in excess of 2 for both fidaxomicin and OP-1118 (the efflux ratios of fidaxomicin were 44.9 and 24.7 at 5 and 10 µM. For OP-1118, the efflux ratio of was 6.36 at 125 µM.), indicating that active transport via efflux proteins was involved. A marked decrease on the efflux ratio was seen in the presence of cyclosporin A and ketoconazole indicating that fidaxomicin and OP-1118 are P-gp substrates.

Table 10: Efflux Ratios of Fidaxomicin, OP-1118, and Digoxin (Positive Control) in the Presence of P-gp Inhibitors, Cyclosporin A (CsA) and Ketoconazole

Test Compound Identification	In the Presence of CsA		In the Presence of Ketoconazole	
	Corrected Efflux Ratio	Efflux decrease (%)	Corrected Efflux Ratio	Efflux decrease (%)
5 µM Fidaxomicin	0.883	98.8	7.52	89.8
125 µM OP-1118	8.21	44.2	1.67	88.6
10 µM Digoxin	~ 0	100	0.205	98.9

There have been numerous changes in the formulations and manufacturers over the development programme.

The initial dosage form evaluated in a Phase 1A clinical trial (OPT-80 1A-SD) was a hard gelatin capsule filled with a solution of 50 mg of fidaxomicin in Labrasol. Due to long-term stability concerns, a capsule containing 50 mg of fidaxomicin and microcrystalline cellulose, NF (Avicel PH-102) was developed for evaluation in subsequent Phase 1B (OPT-80 1B-MD) and 2A (OPT-80 Phase 2A) trials. Based upon the results of the Phase 2A trial, the 200 mg dosage strength of fidaxomicin was selected for further clinical development; an immediate release uncoated tablet containing 200 mg of fidaxomicin was developed for Phase 3 clinical trial (101.1.C.003).

In the Phase 3 study 101.1.C.003, a modification of the solvent used for crystallization of the drug substance was made, and butylated hydroxytoluene (BHT) was added to the finished drug product with the goal of improving stability and extending product shelf-life. In order to evaluate whether this change affected the pharmacokinetics of the active drug, the plasma levels were compared between the two formulations (Table below). In study 101.1.C.003 the formulation of fidaxomicin was changed after approximately the first 100 subjects.

Table 11: Phase 3 Fidaxomicin Plasma and Faecal Concentrations by Formulation

Sample		Formulation 1 (200 mg film coated tablets)		Formulation 2 (200 mg uncoated tablets)	
		Fidaxomicin	OP-1118	Fidaxomicin	OP-1118
Plasma (Day 1, 3-5 hours), ng/mL	N	107	106	57	57
	Mean (SD)	21.78 (27.22)	39.51 (46.71)	24.66 (25.21)	49.68 (58.87)
	Range	[0.4, 185.0]	[0.3, 321.0]	[1.1, 102.0]	[1.9, 363.0]
Plasma (Day 10, 3-5 hours), ng/mL	N	38	38	21	21
	Mean (SD)	25.28 (33.25)	68.99 (83.10)	28.40 (27.16)	72.68 (77.36)
	Range	[2.4, 191.0]	[3.0, 370.0]	[1.9, 99.70]	[4.7, 264.0]
Faecal (Day 10, 0-24 hours), ng/mL	N	65	63	37	36
	Mean (SD)	1344.55 (853.36)	711.59 (473.42)	1015.16 (500.70)	980.13 (861.55)
	Range	[31.7, 4640.0]	[63.4, 3140.0]	[102, 1960.0]	[93.7, 4170.0]

The to-be-marketed formulation (formulation 1, - 200 mg film coated tablet) was used in the phase III studies [exclusively for the C.004 and for a high majority of patients in the C.003 (90/287 patients were not receiving the formulation 1 in this latter study)]. No bioequivalence studies have been performed to bridge between different formulations. The submitted dissolution studies do not constitute a sufficiently discriminative bridge between formulations. This has to be kept in mind when looking at PK data from early studies with different formulations. However, within-study comparisons of factors which do not involve absorption may however be performed. Fidaxomicin tablets and Vancocin® capsules were over-encapsulated for blinding purposes during the Phase 3 clinical trials. The possible impact of over-encapsulation on efficacy was questioned. As both products met the preset criteria of >85% of API released within 30 min and as the drugs are locally acting in the lower GI tract, over-encapsulation is not expected to have any effect on the efficacy of the fidaxomicin tablet or Vancocin® capsule.

The formulation with BHT was also used in the food effect study (OPT-80-005).

Study OPT-80-005 was a single centre, open-label, randomised, two-period, crossover study to determine the pharmacokinetics and the effect of food on the bioavailability of fidaxomicin in healthy subjects.

This study also included a lead-in group of six subjects who received a single 200 mg dose of fidaxomicin. The purpose of the lead-in group was to ensure sufficient sensitivity for the bioanalytical assessment with the tablet formulation to ensure that the food effect portion of the study would provide meaningful data for comparison between the fasted and fed arms of the study. Based on the results of the lead-in group, the doses for the main study were increased to a supra-therapeutic dose of 400 mg.

The food-effect portion of the study was a randomised, single-dose, two-period (7-day washout), two-way crossover study of healthy volunteers (N = 28), with safety and PK analysis of plasma after a single oral 400 mg dose of study medication during fasting, or within 30 minutes of a high-fat breakfast.

Pharmacokinetic blood samples were collected on Day 1 and Day 8. Faecal collection for PK analysis occurred at baseline (first sample on Day -1) and continued for 5 days post-dose in Period 1 only. Urine was collected at baseline (first voided sample on Day 1 prior to dosing) up to 24 hours post-dose of Period 1 only.

The calculated PK parameters and statistical analyses are shown in the tables below:

Table 12: Summary of the Mean (SD) PK Parameter Data for Fidaxomicin and OP-1118

		Fidaxomicin		OP-1118	
		400 mg OPT-80[b]	400 mg OPT-80[b]	400 mg OPT-80[b]	400 mg OPT-80[b]
Parameter	Units	Fasted	Fed	Fasted	Fed
C_{max}	ng/mL	10.6 (6.47)	7.52 (2.89)	25.5 (15.5)	15.7 (5.86)
T_{max}[a]	hr	1.00 (0.500, 8.02)	2.00 (0.500, 8.00)	1.00 (1.00, 8.05)	2.00 (0.500, 8.00)
AUC_{0-24}	ng-hr/mL	81.7 (37.0)	78.6 (35.6)	172 (53.0)	156 (55.6)
AUC_{0-t}	ng-hr/mL	81.2 (36.4)	78.6 (35.6)	172 (52.0)	156 (55.6)
$AUC_{0-\infty}$	ng-hr/mL	75.9 (33.2)	89.7 (50.8)	206 (57.8)	184 (77.3)
$t_{1/2}$	hr	9.64 (2.56)	9.56 (3.28)	10.1 (1.90)	9.47 (2.53)

a Median (min, max) presented for T_{max}

b Positive predose values (Subject 017) that are greater than 5% of C_{max} are excluded

Table 13: Statistical Analysis of OPT-80 Pharmacokinetic Data (400 mg OPT-80 Fed Relative to 400 mg OPT-80 Fasted)

Analyte	Parameter(Units)	N[a]	Test Mean[b] 400 mg OPT-80 (Fed)	N[a]	Reference Mean[b] 400 mg OPT-80 (Fasted)	Test/ Reference[c] (%)	90% Confidence Interval[d] (%)
OPT-80	C_{max} (ng/mL)	27	7.02	28	8.94	78.5	(67.26 , 91.69)
	AUC_{0-t} (ng*hr/mL)	27	70.6	28	73.0	96.7	(87.04 , 107.43)
	$AUC_{0-\infty}$ (ng*hr/mL)	10	68.2	5	77.9	87.5	(68.94 , 111.16)

Table 14: Statistical Analysis of OPT-1118 Pharmacokinetic Data (400 mg OPT-80 Fed Relative to 400 mg OPT-80 Fasted)

Analyte	Parameter(Units)	N[a]	Test Mean[b] 400 mg OPT-80 (Fed)	N[a]	Reference Mean[b] 400 mg OPT-80 (Fasted)	Test/ Reference[c] (%)	90% Confidence Interval[d] (%)
OP-1118	C_{max} (ng/mL)	27	14.9	28	22.4	66.6	(58.37 , 75.97)
	AUC_{0-t} (ng*hr/mL)	27	146	28	162	89.7	(82.46 , 97.65)
	$AUC_{0-\infty}$ (ng*hr/mL)	11	169	10	217	78.1	(62.56 , 97.58)

Fidaxomicin and OP-1118 Cmax values were 22% and 33% lower in the fed state compared to the fasted state. The AUC0-t for both moieties was equivalent in the fed state compared to the fasted state. Urine data and faecal data did not contribute to the assessment of the food interaction due to urine levels of fidaxomicin being undetectable in all samples collected in this study and very variable faecal data, respectively.

No specific food-recommendations were given in the subsequent clinical phase III studies. Due to the disease, large meals are not expected and also due to the occurrence of diarrhoea, the potential importance of food is likely small. In conclusion, the recommendation to take the product regardless of meals is in accordance with the phase III trial recommendations and is considered supported.

Distribution

Fidaxomicin has not been administered to humans intravenously as its low aqueous solubility makes it extremely difficult to solubilise in a formulation acceptable for human use. However, in intravenous studies in non-clinical species (e.g., rat, rabbit and dog) where high volumes (10 mL/kg) of dilute solution was used, the volume of distribution at steady state was found to be less than or equal to body water, suggesting that fidaxomicin does not extensively distribute away from body water.

Elimination

The main components of the elimination of systemically available fidaxomicin have not been identified. There are however indications of hepatic elimination of some kind, such as biliary excretion (increased systemic exposure in patients with signs of hepatic impairment as well as secondary peaks observed in the plasma – concentration time curve).

Most of a 200-300 mg oral dose (93%±42%) is excreted as drug related compounds in faeces (study OPT-80-1A-SD). Approximately 26% of a single oral dose is recovered as unchanged drug in faeces and over 66% of the dose is found as OP-1118. Peak concentrations in the faeces are generally observed at least 24 hours after single oral doses and concentrations remain detectable in the faeces for up to 5 days. Less than 1 % of the dose is excreted in the urine. Fidaxomicin's half life is approximately 8-10 h.

The metabolism of fidaxomicin has been studied in multiple in vitro systems including phosphate buffer solution, human intestinal and liver microsomes, human hepatocytes, and human plasma. A hydrolysis reaction (plausibly mediated by esterases) appears to be the main route of metabolism of fidaxomicin in vitro. Based on the presented data, it is not possible to say whether OP-1118 has been formed in the GI tract or following absorption of fidaxomicin.

No mass balance study has been conducted. Hence, there was concern regarding an insufficient characterisation of the elimination pathways, formation of metabolites and plasma exposure of metabolites other than OP-1118. The applicant has provided some additional information regarding known and expected metabolites in dog and human plasma, faeces and urine samples and dog bile. Monohydroxylated metabolites were not detectable in any of the in vivo samples examined. Glucuronidated and/or sulphated metabolites were not detectable in any matrix except for dog bile. Additional analyses of human and dog plasma showed that concentrations of the acyl migration product Tiacumicin F were higher in dog than in human plasma. Based on these data it cannot be completely excluded that there may be any unknown metabolites formed with exposure greater than 10% of total drug-related exposure. However, in vitro data do not suggest any difference in metabolic profile between human and dog. Furthermore, the absorption is low and Dificlir is to be used only for 10 days. The lack of characterisation of the human metabolism can therefore be accepted.

Variability

Inter-individual variability in systemic exposure to fidaxomicin was generally > 25 % in healthy volunteers. There is no valid estimate from patients given the sparse PK sampling applied. No estimate of intra-individual variability has been provided.

Pharmacokinetics of main metabolite

The PK-characteristics of OP-1118 is fairly well described. The elimination of OP-1118 seems formation rate limited as the terminal half life is similar to fidaxomicin's. The approximately 2-fold higher plasma levels of OP-1118 than for those of the parent compound indicate that OP-1118 have a smaller volume of distribution than fidaxomicin or/and that OP-1118 to some extent is formed pre-systemically.

Target population

There is some degree of uncertainties on to what extent the systemic exposure might increase in case of severe degree of inflammatory bowel in CDI patients. Based on very variable data and a between study comparison, the maximum plasma concentrations of fidaxomicin and OP-1118 in patients was in average 2 times higher than the C_{max} values measured in healthy volunteers. The difference is likely larger given that only one PK sample was used in the patient study, which makes the estimation of Cmax more uncertain.

The range of plasma concentrations observed in CDI patients could rise up to 237 ng/mL for fidaxomicin and 871 ng/mL for the metabolite OP-1118 whereas in healthy individuals in OPT-80-005 the highest plasma concentrations observed are approximately 10 times lower, at 28.9 ng/mL for fidaxomicin and 77.4 ng/mL for OP-1118 (fasted – group 2). This increased absorption is likely due to the inflammatory state of the bowels resulting from the infection.

The levels of fidaxomicin in faecal samples are approximately 2-fold higher than those of the metabolite.

Based on available data faecal concentration does not appear to be predictive of outcome. As a matter of fact, regardless the outcome (success, failure) the concentrations are far in excess of MIC (up to> 30 000 x). Consequently faecal fidaxomicin level/MIC ratio does not appear to be predictive of cure.

Dose proportionality and time dependencies

Regarding dose proportionality, increasing the dose from 200 to 400 mg did not result in a proportional increase in fidaxomicin or OP-1118 C_{max} or AUC_{0-t} values.

The applicant has not discussed the reason for this finding, however, solubility problems is likely one part of the explanation. As fidaxomicin is given as a fixed dose, 200 mg, there is no need to follow up on this issue. There is no pronounced accumulation of fidaxomicin or OP-1118 following multiple doses.

Special populations

Pharmacokinetics in special populations has been investigated using data generated by sparse sampling (one sample around predicted Cmax) from the phase III studies.

Impaired hepatic function

Hepatic status, based on the Canadian NCI toxicity criteria, seems to affect the elimination of fidaxomicin and even more so OP-1118. In the two Phase III clinical studies in patients with CDI, there were 12 patients with hepatic impairment, as determined by the finding of at least one liver function test at baseline of toxicity grade 2 or higher where PK data was available. PK data from these patients show mean fidaxomicin and OP-1118 levels approximately 2 times higher than those observed in patients with liver function test results of toxicity grade 1 or lower.

Table 15: Fidaxomicin Plasma Concentrations in Patients with Hepatic Impairment (Pooled Phase 3 Studies)

Sample		Toxicity Grade ≤ 1		Toxicity Grade ≥ 2	
		Fidaxomicin	OP-1118	Fidaxomicin	OP-1118
Plasma (Day 1, 3-5 hours), ng/mL	N	301	297	12	11
	Mean (SD)	21.59 (22.62)	41.97 (46.48)	38.95 (57.93)	95.52 (100.53)
	Range	[0.669, 145]	[0.982, 363]	[0.364, 185]	[0.283, 321]
Plasma (Day 10, 3-5 hours), ng/mL	N	114	115	4	4
	Mean (SD)	27.28 (34.85)	79.23 (133.17)	34.65 (27.91)	200.18 (141.36)
	Range	[0.305, 191]	[1.09, 871]	[14.2, 75.9]	[40.7, 370]

The degree of hepatic impairment is uncertain since the validated Child Pugh score was not used. In response to CHMP's request, the applicant has presented concentrations in patients with chronic hepatic cirrhosis and compared these to levels for subjects without this history.

Table 16: Plasma Drug Levels (3-5 hours post-dose) in Subjects with and without Hepatic Cirrhosis

Hepatic Cirrhosis	Plasma levels, 3-5h post-dose	FDX, ng/mL		OP-1118, ng/mL	
		Day 1	EOT	Day 1	EOT
Yes	N >LLOQ	10	3	7	3
	N <LLOQ	-	-	-	-
	Mean	48.06	52.27	122.36	247.33
	SD	60.77	25.58	104.36	123.00
	Median	24.10	55.80	96.10	248.00
	Min, Max	0.40, 185	25.1, 75.9	0.50, 321	124, 370
No	N >LLOQ	302	97	309	100
	N <LLOQ	13	2	14	2
	Mean	21.98	27.81	42.73	80.71
	SD	24.53	33.44	47.40	128.81
	Median	13.65	15.70	26.20	41.40
	Min, Max	0.36, 197	0.31, 191	0.28, 363	1.09, 871

Amongst the cirrhotic subjects, plasma levels for fidaxomicin and OP-1118 were also presented based upon total bilirubin at baseline: <34, 34-50 and >50 µmol/L. The data suggest increased exposure in patients with chronic hepatitis and cirrhosis, approximately 2-fold increase in fidaxomicin and 3-fold increase in OP-1118.

Data are very limited but also suggest an increased exposure with increased bilirubin suggesting increased fidaxomicin and OP-1118 exposure in subjects with cholestasis. The applicant suggests caution in patients with severe hepatic impairment. Given the limited data and the difficulty in drawing conclusions regarding different stages of hepatic impairment caution should be advised also in patients with moderate hepatic impairment.

Elderly

Plasma levels also appear to be elevated in the elderly (age > 65 years). When phase III data is stratified for age over and under 65 years, fidaxomicin and OP-1118 levels are approximately 2 times higher for patients > 65 years compared to patients < 65 years.

Impaired renal function

Further, there is no strong signal towards renal function influencing the elimination of fidaxomicin or OP-1118.

Gender, weight, race

There is also no influence of gender on the PK of fidaxomicin or OP-1118.

Subgroup analyses by gender were carried out in the Phase 3 studies 101.1.C.003 and 101.1.C.004, there is no sign that gender would influence PK parameters. Limited data suggest that weight and race do not have any major influence on the plasma concentration of fidaxomicin or OP-1118.

Paediatric population

The safety and efficacy of Dificlir in children has not been established. A deferral on the obligation to submit studies from the paediatric population has been granted.

Pharmacokinetic interaction studies

The applicant has performed an ambitious *in vitro* programme concluding that systemic interactions due to CYP inhibition or induction are not likely given the presented data.

However, the data from *in vitro* CYP inhibition studies cannot rule out that fidaxomicin and OP-1118 inhibit gut CYP3A4 (which is present at significant levels) due to the locally high concentrations of fidaxomicin and OP-1118. In order to assess the magnitude of this interaction, the applicant was asked by CHMP to perform a clinical pharmacokinetic study assessing the interaction of fidaxomicin on a CYP3A4 probe substrate (e.g. oral midazolam). Further, the available *in vitro data* did also not rule out that fidaxomicin and OP-1118 may inhibit gut P-gp given the same argumentation as above. The inhibitory effect of fidaxomicin and OP-1118 on other intestinal transporters has not been investigated. The applicant is investigating the effect of fidaxomicin on MRPs, OATPs and BCRP transporters *in vitro*. Timelines have been provided, with final reporting scheduled for 4Q2011.

During assessment of the dossier, the applicant also submitted three additional interaction studies. Co-administration with a single dose of cyclosporine resulted in a 4.2- and 1.9-fold increase in fidaxomicin Cmax and AUC and 9.5- and 4.1-fold increase in OP-1118 Cmax and AUC. Half-life was not affected. Hence, the mechanism of the interaction seems to be increased absorption due to inhibition of transporter proteins, most likely P-gp, at intestinal level.

Co-administration of the P-gp substrate digoxin with Dificlir (200 mg twice daily) in healthy volunteers resulted in an increase in digoxin Cmax of 14% and AUC of 12%.

A cocktail interaction study was performed to assess the potential of fidaxomicin to alter the CYP-mediated metabolism of S-warfarin, omeprazole, and midazolam which are probe substrates for CYP2C9, CYP2C19, and CYP3A4/5, respectively. The study results suggest that fidaxomicin has no clinically relevant effect on CYP2C9, CYP2C19 and CYP3A4.

2.4.3. Pharmacodynamics

Mechanism of action

Fidaxomicin is a novel antibiotic agent representing a new class of 18-membered macrocyclic antibacterial drugs. It acts via inhibition of RNA synthesis by bacterial RNA polymerase at a distinct site from that of the currently used RNA polymerase inhibitors. Inhibition of the clostridial RNA polymerase occurs at a concentration 20-fold lower than that for the *E. coli* enzyme (1 µM vs. 20 µM), partly

explaining the significant specificity of fidaxomicin activity. Its mechanism of action is distinct from that of any other class of antimicrobials.

Primary and Secondary pharmacology

Fidaxomicin is a narrow spectrum antibacterial agent with almost no activity against gram-negative organisms (MIC50 and MIC90 values universally above 100 µg/mL) and moderate to good activity against gram-positive organisms, but with marked variation between genera.

Table 17: MICs (mg/mL) of Fidaxomicin against some Gram-positive Species

Organism (n)	**MIC Range, mg/L**	**MIC_{90}, mg/L**
Clostridium difficile (791)	0.003-1	0.25
Clostridium perfringens (35)	≤ 0.016-0.06	0.03
Gram positive aerobic/facultative		
Enterococcus faecium (40)	1-8	4
Enterococcus faecalis (40)	2-4	4
Enterococcus spp. (21)	2-16	8
Staphylococcus aureus (75)	2-16	8
Coagulase-negative *Staphylococcus (60)*	0.5-8	4
Gram Positive Anaerobes		
Anaerobic gram-positive cocci (49)	0.06-1024	2
Anaerobic gram-positive nonsporeforming rods (20)	≤ 0.016-16	16

The main metabolite, OP-1118 has a narrow spectrum of activity comparable to that of fidaxomicin, although with lower activity, with an MIC against *C. difficile* of 8 µg/mL. Given the high faecal concentrations of the metabolite, the activity versus *C. difficile*, and the low activity against other organisms, it can be concluded that the metabolite probably plays a role in the microbiologic activity of fidaxomicin.

Data from a recent study, Tannock et al (2010), demonstrate that fidaxomicin's sparing of flora is not limited to Gram-negative bacteria but is also sparing the predominant Gram-positive commensals. Using molecular methods, Day 1 and End of treatment faecal samples from 23 CDI subjects, who were recruited for the Phase 2 dose-ranging fidaxomicin clinical trial (50 mg, 100 mg, and 200 mg twice a day for 10 days), and a control group of 8 patients that received vancomycin (125 mg four times daily for 10 days) were analysed for the presence of various phylogenetic microbiota (*Bacteroides-Prevotella*; *Bifidobacterium*; *Atopobium*; enterobacteria, clostridal clusters XIV and IV, and lactobacilli-enterococci). As these subjects entered the study with *C. difficile* infection (and thus abnormal flora at entry), day 365 stool samples were also analyzed to reflect the composition of the normal bowel flora and found to be similar to the composition of flora in the stools of eight healthy, untreated volunteers. Their data demonstrated little effect by fidaxomicin on the composition of the faecal microbiota in terms of its major phylogenetic clusters, which progressed during and after treatment toward a composition similar to that observed at day 365. In addition, vancomycin treatment resulted in disruption of the major phylogens.

Out of 248 patients tested for vancomycin-resistant *Enterococcus* (VRE) colonization before and after treatment in the 101.1.C.003 trial, patients treated with fidaxomicin had a lower likelihood of new colonization with VRE than patients treated with vancomycin (7% for fidaxomicin versus 31% for vancomycin, $p < 0.001$) [Nerandzic, 2009]. Among patients with pre-existing VRE, the mean concentration of VRE in their stool decreased significantly after 10 days of treatment in the fidaxomicin (5.9 versus 3.8 $\log_{10}$ VRE/g stool; P =0.01) but not the vancomycin group (5.3 versus 4.2 $\log_{10}$ VRE/g stool; P =0.20).

In vitro testing showed that fidaxomicin had a low level of spontaneous resistance rate, and cross-resistance testing of fidaxomicin with other antibiotics showed a lack of cross-resistance towards other antibiotics tested, including macrolides, β-lactams, fluoroquinolones, rifamycins, vancomycin or metronidazole. Sequencing of laboratory-generated mutants with reduced fidaxomicin susceptibility has identified mutations in the target enzyme (RNA polymerase) similar to those identified in *Bacillus* strains with low susceptibility to lipiarmycin, a related compound.

This microbiological activity covers the BI/027/NAP1 isolates which are epidemic hypervirulent *C. difficile* strains, while these bacteria are globally less susceptible to antibiotics. No difference between MICs according to serotypes, in particular BI, is observed.

Regarding bactericidal kinetics, fidaxomicin and its metabolite have a bactericidal activity. The killing is time-dependant. Bactericidal activity is obtained in 6 to 24 hours for concentrations from 4 to 32 x MIC.

Bactericidal activity for metronidazole is faster and more complete than this observed for fidaxomicin. Considering speed and degree of bactericidal activity, fidaxomicin is placed between metronidazole and vancomycin.

In vitro, the inoculum, the presence of different concentrations of cations and the use of several collections of media have no impact on MICs. The only factors decreasing the in vitro fidaxomicin activity regarding *C. difficile*, are increased pH (> 7.2 to 7.9) and the faecal material, factors increasing MIC values up to 8-fold. But these findings should be considered regarding fidaxomicin faecal concentrations (up to 5 000 x MIC90 for *C. difficile*).

Of interest, the applicant has tested the interaction between the excipients of the to-be-marketed formulation and the *in vitro* microbiological activity. There is a lack of drug-excipient interaction (same MICs or a difference of one dilution between presence and absence of excipients).

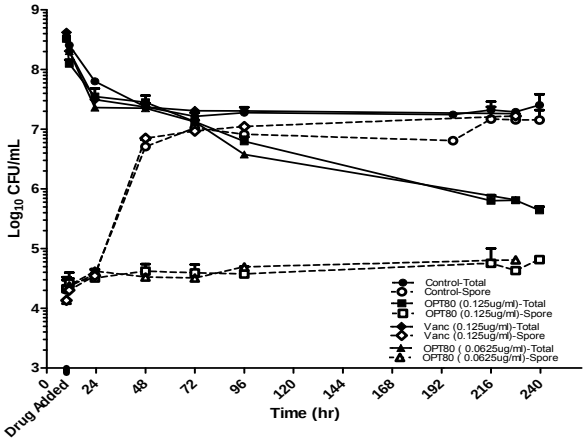
Fidaxomicin and its main metabolite were demonstrated to have a significant post-antibiotic effect (PAE) against *C. difficile*. At 4 times the MIC, the post-antibiotic effect is approximately 10 hours for fidaxomicin and 3 hours for OP-1118.

Genotypically distinct strains of *C. difficile* have been shown to demonstrate a propensity to hypersporulate and have been reported to be responsible for outbreaks. The BI/NAP1 strain, like other outbreak strains, has demonstrated the capacity to hypersporulate compared with other non-outbreak strains.

The action of fidaxomicin regarding recurrences is important taking into account the high rate of recurrences known with vancomycin and metronidazole (both drugs being known as favouring sporulation).

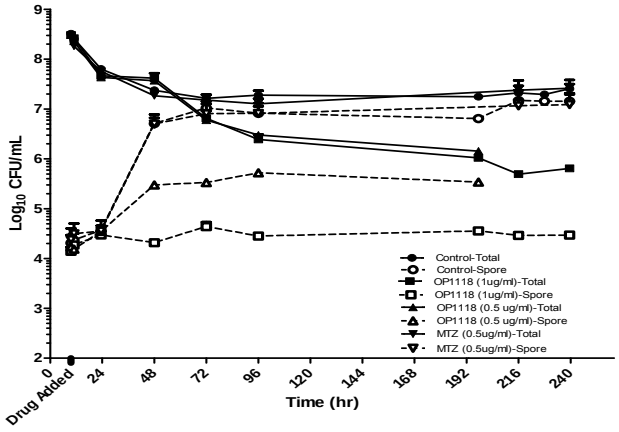
In vitro sporulation inhibition studies have been conducted in hypervirulent *C. difficile* REA BI strain. Sub-MIC concentrations of fidaxomicin, OP-1118, vancomycin, or metronidazole were added to the culture 12 hours after inoculation (end of the log-phase growth period), and samples were collected at various time points thereafter and plated to quantify both total CFUs and spores. Sub-MIC concentrations of fidaxomicin (Figure 2) and its major metabolite (OP-1118, Figure 3) inhibit spore formation in *C. difficile*. In contrast, vancomycin and metronidazole do not inhibit sporulation.

Figure 2: Sub-MIC Concentrations of Fidaxomicin



Total and spore count of *C. difficile* strain REA BI group exposed to no drug (● and □), fidaxomicin at 0.25xMIC (□ and ▫), fidaxomicin at 0.125x MIC (□ and Δ) and 1x MIC vancomycin (♦ and ◊). Total count is represented by solid lines and filled symbols. Spore counts are presented with dashed lines and open symbols.

Figure 3: Sub-MIC Concentrations of Metabolite (OP-1118)



Total and spore count of *C. difficile* strain REA BI group exposed to no drug (● and □), OP-1118 at 0.25xMIC (□ and ▫), OP-1118 at 0.125x MIC (□ and Δ) and metronidazole at 0.25x MIC (□ and ▽). Total count is represented by solid lines and filled symbols. Spore counts are presented with dashed lines and open symbols.

The applicant also provided data showing that in contrast to vancomycin or metronidazole, fidaxomicin does inhibit production of toxins. It has been demonstrated that fidaxomicin is able to inhibit toxin production in both hypervirulent UK1 strain (an epidemic 027 strain) and the VPI 10463 strain (ATCC 43255, a high level toxin producing isolate). Production of both Toxin A and Toxin B, measured via an ELISA method, was shown to be inhibited in the presence of sub-MIC concentrations of fidaxomicin. In contrast, vancomycin or metronidazole did not inhibit production of either toxins. In this study, fidaxomicin or other drugs were added at the beginning of stationary phase (24 hours after inoculation) and exposure continued through the following 7 days. Samples were collected at timepoints following drug addition and assayed for toxins A and B via ELISA. The drug concentrations used were 0.125 to 0.25 times the MIC, concentrations far below the fidaxomicin concentrations found

in the faeces following treatment. Despite this, toxin production was nearly completely suppressed in the presence of fidaxomicin, even following 1 week of culture.

The above findings were confirmed via examination of RNA transcripts in presence of fidaxomicin.

However, the mechanism behind the inhibitory effect on toxins would deserve being elucidated through further investigation.

Breakpoints

Susceptibility patterns on baseline isolates from the clinical studies indicated the same range of MIC values as in published in vitro data. Since fidaxomicin in the treatment of CDI can be considered a topical agent and no clear relationship between exposure and efficacy has been demonstrated, it is agreed with the Applicant that clinical breakpoints seem not relevant. However, in order to be able to monitor any development of resistance, epidemiological breakpoints should be applied. Based on wild-type distributions MIC data on fidaxomicin and *C. difficile*, an epidemiological cut-off value of 1.0 mg/L seems appropriate.

Secondary pharmacology

Fidaxomicin does not appear to have any significant effect on QTc intervals, which is in line with preclinical data. A trend for a dose related increase in QTc might be suspected from phase IIA study. Data from phase 3 studies did not indicate any clinical relevant effect on cardiac function.

2.4.4. Discussion on clinical pharmacology

The PK data presented in support of the application does not allow a full *in vivo* characterisation of the PK properties of fidaxomicin and its metabolites. Parts lacking for a full characterisation are mass balance data, absolute bioavailability data and protein binding data.

As fidaxomicin is intended to act locally, it is not possible to draw any firm conclusions on the effect of food on other aspects than safety due to systemic exposure based on the food effect study. From this perspective, the difference between fasting and fed states is not clinically relevant.

Plasma protein binding and binding within blood has not been studied. This is considered acceptable.

As no mass balance study has been performed, it is not possible to conclude that OP-1118 is the only major metabolite formed *in vivo*. In response to CHMP request, the applicant has provided some additional information regarding known and expected metabolites in dog and human plasma, faeces and urine samples and dog bile. Based on these data it cannot be completely excluded that there may be any unknown metabolites formed with exposure greater than 10% of total drug-related exposure. However, *in vitro* data do not suggest any difference in metabolic profile between human and dog. Furthermore, the absorption is low and Dificlir is to be used only for 10 days. The lack of characterisation of the human metabolism can therefore be accepted

Limited data suggest increased exposure in patients with chronic hepatitis cirrhosis, approximately 2-fold increase in fidaxomicin and 3-fold increase in OP-1118. Very limited data also suggest an increased exposure with increased bilirubin suggesting increased fidaxomicin and OP-1118 exposure in subjects with cholestasis. Given the limited data and the difficulty in drawing conclusions regarding different stages of hepatic impairment, caution is advised in patient with moderate or severe hepatic impairment. The correlation between PK and age, where exposure is increased in the elderly, is likely not clinically relevant given the large inter individual variability in PK. Further, a considerable number of elderly patients were included in the phase III studies (median age was 63 years and 66 years in the two studies, respectively).

There is a risk for interaction with P-gp inhibitors. Co-administration with a single dose of cyclosporine resulted in a 4.2- and 1.9-fold increase in fidaxomicin Cmax and AUC and 9.5- and 4.1-fold increase in OP-1118 Cmax and AUC. The applicant considers this increase in exposure not clinically meaningful as

adverse events were mild and mainly of gastrointestinal nature. However, it is difficult to draw conclusion regarding safety of increased exposure from an interaction study with a low number of subjects. Hence, co-administration of potent inhibitors of P-gp should be avoided. This is addressed in the RMP as important missing information and the applicant has included an appropriate statement in the SmPC.

Co-administration of the P-gp substrate digoxin with Dificlir (200 mg twice daily) in healthy volunteers resulted in an increase in digoxin Cmax of 14% and AUC of 12%. The effect on digoxin is small and not considered clinically relevant. However, given the fairly high bioavailability of digoxin (about 60%), this is not a very sensitive substrate to evaluate the effect on P-gp in the intestine. A larger effect on more sensitive substrates with lower bioavailability such as dabigatranetexilat cannot be excluded. The observed interaction with digoxin is however very small. Based on this data, fidaxomicin is *in vivo* at most a mild to moderate P-gp inhibitor.

Regarding PD, the narrow-spectrum *in vitro* activity of fidaxomicin and its high activity against the target pathogen *C. difficile* make this drug suitable for the treatment of CDI. Lack of cross-resistance with other classes of antimicrobial agents indicates a unique mode of action that is different from known RNA polymerase inhibitors. Since resistance against fidaxomicin seems primarily be due to single or multiple mutations in target genes, the rate of development of clinical significant resistance is hard to predict. Reassuringly, the high intestinal concentrations of fidaxomicin and the large marginal to inhibitory concentrations also against *C. difficile* first step mutants, may provide a sufficient mutant prevention concentration during the treatment period. However, susceptibility pattern of *C. difficile* to fidaxomicin should be closely monitored in the future. A post-marketing surveillance programme collecting clinical isolates from centres in Europe is planned to monitor strains of *C. difficile* for changes in antimicrobial resistance patterns.

The Applicant has provided data supporting that treatment with fidaxomicin is less likely to cause intestinal colonization or overgrowth with VRE compared to treatment with vancomycin in CDI patients.

The PK/PD parameter predictive of clinical success is suggested to be time over MIC value and not to be concentration dependent. Duration of a specific antibiotic concentration in the gastrointestinal tract may be very variable due to the character of diarrheal diseases, in which rapid intestinal transit may hasten faecal excretion of drug. The feature of a significant post-antibiotic effect is favourable, indicating that the anti-clostridial activity of fidaxomicin persists also after its removal, which would be beneficial in *C. difficile* infection.

The superiority over vancomycin in early recurrences, mainly during the first two weeks after EOT, as demonstrated in the clinical studies indicates that fidaxomicin also exerts a spore-killing effect, which was further supported by *in vitro* data.

Susceptibility patterns on baseline isolates from the clinical studies indicated the same range of MIC values as in published *in vitro* data. Since fidaxomicin in the treatment of CDI can be considered a topical agent and no clear relationship between exposure and efficacy has been demonstrated, it is agreed with the Applicant that clinical breakpoints seem not relevant. However, in order to be able to monitor any development of resistance, epidemiological breakpoints should be applied. Based on wild-type distributions MIC data on fidaxomicin and *C. difficile*, an epidemiological cut-off value of **1.0 mg/L** seems appropriate. The planned surveillance study will provide further information.

It is reassuring that the quantitative counts of *Bacteroides* group during fidaxomicin treatment appear rather unaffected. This finding is in line with the spectrum of activity of fidaxomicin and its main metabolite (very low activity against *Bacteriodes* spp.). By using molecular methods to monitor alterations in the bowel microflora during and after fidaxomicin and vancomycin administration, fidaxomicin was shown to have a less marked effect also on major gram-positive phylogenetic clusters, such clostridia and bifidobacteria, compared to vancomycin.

Fidaxomicin does not appear to have any significant effect on QTc intervals, which is in line with preclinical data. A trend for a dose related increase in QTc might be suspected from phase IIA study. Data from phase 3 studies did not indicate any clinical relevant effect on cardiac function.

2.4.5. Conclusions on clinical pharmacology

The pharmacokinetic documentation is considered sufficient.

Regarding pharmacodynamics, fidaxomicin is a new anti-*C. difficile* agent with a unique bactericidal mechanism of action. Its pharmacodynamic properties are considered interesting for the treatment of patients with CDI, in particular due to the narrow-spectrum activity, spore-killing activity, post-antibiotic effect and lack of cross-resistance to other classes of antibacterial drugs.

In contrast to vancomycin or metronidazole, it is interesting to observe that fidaxomicin does inhibit production of toxins.

The CHMP considers the following issues related to pharmacology:

The applicant should provide the final reports for the *in vitro* studies investigating the effect of fidaxomicin on MRP2, OATP2B1 and BCRP by 4Q 2011 (RMP measure).

The mechanism behind the inhibitory effect on toxins would deserve being elucidated through further investigation (Recommendation)

2.5. Clinical efficacy

2.5.1. Dose response study

The Phase 2 A dose-finding study (OPT-80 Phase 2A) was an open-label, dose-ranging, randomised, safety and clinical evaluation of fidaxomicin tablets in patients with CDI. Fidaxomicin tablets were administered to patients at doses of 100 mg/day (50 mg q12h), 200 mg/day (100 mg q12h), and 400 mg/day (200 mg q12h) for 10 days. The objective was to select the schedule regimen to be used in the Phase 3 studies. This study was conducted in mild to moderate CDI patients, with the following definition:

- Diarrhoea (defined as a change in bowel habits, with 3 or more unformed bowel movements [UBMs] in 24 hours, or more than 6 loose or watery stools within 36 hours), and
- Presence of either toxin A or B of *C. difficile* in the stool.

Regarding the primary study endpoints, results are as following:

Table 18: Clinical Cure and Relief of Symptoms of CDI in Study OPT-80 Phase 2A (mITT Population)

	Fidaxomicin 100 mg/day N = 16		Fidaxomicin 200 mg/day N = 16		Fidaxomicin 400 mg/day N = 15	
	n	%	n	%	n	%
Clinical cure	12	(75.0)	13	(81.3)	15	(100.0)
Relief of symptoms						
Relief	6	(37.5)	8	(50.0)	13	(86.7)
No Relief	9	(56.3)	6	(37.5)	2	(13.3)
Unknown	1	(6.3)	2	(12.5)	0	(0.0)

Note: Clinical cure was imputed to failure for subjects who discontinued the study during treatment.
Relief of symptoms of CDI was defined as ≤3 bowel movements per day without other associated signs and symptoms such as fever, abdominal pain and elevated white blood cells (WBC) by Day 10 of the study. Patients with any of these symptoms remaining by Day 10 were considered No Relief.

Taking into account the limits of this study (critical methodology with an open-label trial, low number of patients-16 patients evaluated in each dose level-, different formulation as that used in Phase 3 studies and in marketing), 400 mg/day (200 mg q 12h) has been considered as the most appropriate dose for the treatment of CDI in adults for the following reasons: the dose response for the relief of CDI was the most favourable response seen in the 400 mg/day treatment group. This treatment group showed no primary failures, shortest time to diarrhoea resolution, and highest percentage of patients totally free of CDI symptoms at EOT.

2.5.2. Main studies

The efficacy of fidaxomicin is supported by two multi-centre, double-blind, randomised, parallel group studies that used a non-inferiority design to compare the safety and efficacy of 400 mg/day fidaxomicin (200 mg q12h) with 500 mg/day vancomycin (125 mg q6h) for 10 days in patients with CDI (confirmed with positive toxin test).

Table 19:

Study ID	Title	Treatment duration; Dose of fidaxomicin per day	Comparator	Number of treated patients
101.1.C.0**03** Phase 3	A Multi-National, Multi-Centre, Double-Blind, Randomized, Parallel Group Study To Compare The Safety And Efficacy Of Fidaxomicin In Patients With *Clostridium difficile*-Associated Diarrhoea	10 days: 200 mg q 12 h	Vancomycin 125 mg q 6 h	623
101.1.C.0**04** Phase 3	A Multi-National, Multi-Centre, Double-Blind, Randomized, Parallel Group Study To Compare The Safety And Efficacy Of Fidaxomicin In Patients With *Clostridium difficile*-Associated Diarrhoea	10 days: 200 mg q 12 h	Vancomycin 125 mg q 6 h	524

Methods

The designs of the two phase 3 studies were almost identical. Study 04 included study sites from Europe and North America while study 03 only included sites from USA and Canada. Both studies

tested a non inferiority hypothesis with a 10% non inferiority margin (assumed to preserve 50% of the vancomycin absolute efficacy based on clinical trials in the setting).

The selected dose of fidaxomicin, 200mg q12h, used in these phase 3 studies is supported by results observed with the Phase 2A study: no primary failures, shortest time to diarrhoea resolution, highest percentage of subjects totally free of CDI symptoms at EOT and is further reinforced by the reassuring microbiological finding on the bowel flora (with *Bacteroides* counts being used as a marker).

Vancomycin served as comparator in both phase 3 studies which is endorsed since vancomycin is recommended for moderate to severe CDI and for recurrent episodes in many countries. The selected dose of vancomycin is in line with current recommendations and clinical practice.

Study Participants

Inclusion criteria included male or female adult inpatients or outpatients, who had CDI as defined by:

- Diarrhoea : defined as a change in bowel habits, with > 3 unformed bowel movements (UBMs; or > 200ml unformed stool for subjects having rectal collection devices) in the 24 hours before randomisation, and
- Presence of either toxin A or B of *C.difficile* in the stool within 48 hours of randomisation.
- ≤24 hours pre-treatment with CDI therapy.

By the time of the original protocol there was a lack of validated severity scale for CDI. However, with the publication of results for the Phase 3 trial of tolevamer versus vancomycin and metronidazole (Louie 2007), it was decided to adopt a modified severity score based on the published CDI disease severity index, i.e.:

- -Mild CDI : 4-5 UBMs or WBC < 12,000/mm3
- -Moderate CDI : 6-9 UBMs or WBC > 12,001-15,000/mm3
- -Severe CDI :10+ UBMs or WBC > 15,001/mm3

Any one of the 2 defining characteristics could have assigned a subject to a category, with a default to the more severe category when signs overlapped.

Patients with life threatening or fulminant CDI (white blood cell [WBC] count >30 x109/L; temperature >40°C; or evidence of hypotension [systolic blood pressure less than 90 mmHg], and septic shock, peritoneal signs, or significant dehydration) or toxic megacolon were excluded from the study. Patients with multiple occurrences of CDI (defined as more than 1 prior occurrence within the past 3 months) and those suffering Crohn's disease were also excluded.

Treatments

Patients were randomised to receive either fidaxomicin or vancomycin. Subjects allocated to fidamoxicin received either a 200-mg capsule fidamoxicin BID with intermittent matching placebo doses also administered BID for a total of 4 capsules per day. Vancomycin subjects received 125-mg capsules QID.

Objectives

The primary objectives of the phase 3 studies were to

- Demonstrate that the cure rate of CDI following treatment with fidaxomicin is non-inferior to that following treatment with vancomycin.

- Evaluate the safety and tolerability of fidaxomicin in subjects with CDI.

The secondary objective was to

- Evaluate the rate of recurrence and global cure rates of CDI following treatment of fidaxomicin compared with vancomycin.

Subjects were randomised and stratified at each site on the basis of either having a single prior episode within 3 months or having no prior occurrence within the last 3 months.

Outcomes/endpoints

Definition of the analysis populations

The mITT Population for Cure was the group of subjects with CDI confirmed by positive toxin assay and who received at least 1 dose of study medication.

The mITT Population for Recurrence was the group of subjects in the mITT Population for Cure who were classified as cured at the end of therapy.

The PP Population for Cure was the group of subjects included in the mITT population who met the following criteria (referred to as the Microbiologically Evaluable Population in the protocol and SAP):

- Met all inclusion criteria and no exclusion criteria
- Subjects required at least 3 complete days for failures and 8 complete days for cures
- Had an EOT clinical evaluation
- Did not have significant protocol violations

The PP Population for Recurrence was the group of subjects in the PP Population for Cure who:

- Were cured at EOT
- Were followed for recurrence up to the post-study visit or experienced a recurrence ≤30 days post treatment and
- Did not use concomitant CDI therapy or other drugs which could have confounded the assessment of recurrence.

Primary efficacy variable

- The primary cure rate in the PP population and mITT populations.

Secondary efficacy variables

- The recurrence rate in the PP and mITT populations (studies 03 and 04).
- Global cure rate in the PP and mITT populations (study 04).

Explorative variables

- Global cure rate in the PP and mITT populations (study 03).
- Time-to-resolution of diarrhoea (TTRD) (studies 03 and 04).

Cure was defined as:

Subjects who, in the opinion of the Investigator required no further CDI therapy 2 days after completion of study medication.

Subjects who had 3 or fewer unformed stools for 2 consecutive days and remained well before the time of study medication discontinuation were considered cured. Subjects who were considered cured based on stabilization and improvement in CDI signs and symptoms were evaluated 2 to 3 days after the end of therapy. If they remained stable and were not considered to require further CDI therapy to maintain their stable state, they were to be followed for recurrence as cures.

Subjects who had rectal collection devices were considered to have resolution of diarrheal when the volume (over a 24-hour period) was decreased by 75% compared with the volume observed at admission or when the subject was no longer passing liquid stools.

Failure was defined as:

Subjects who in the opinion of the Investigator required additional CDI therapy were considered failures.

The Investigator based clinical impressions of the need for additional CDI therapy on subjects' CDI status, inclusive of the presence of diarrhoea and other signs and symptoms of CDI including:

Fever >38.0°C, not attributable to another clear aetiology (e.g., pneumonia)

Elevated WBC count >13,000/µL not attributable to another clear aetiology (e.g., pneumonia)

Abdominal pain of moderate or greater severity lasting 1 hour or more and/or abdominal tenderness of at least moderate severity, including any peritoneal signs.

Recurrence was defined as

A re-establishment of diarrhoea within 30 days post treatment, to an extent that was greater than the frequency noted on the last day of study medication with the demonstration of either toxin A or B (or both) of *C. difficile*. The recurrence also must have, in the Investigator's opinion, required retreatment with CDI anti-infective therapy. Among recurrence, relapse and re-infection could not be distinguished, apart indirectly from time of occurrence (re-infection being more likely when occurring beyond 14 days post treatment).

Global cure rate was defined as

The number of subjects in each treatment group who had been evaluated as cured and who did not have a recurrence within 30 days after discontinuation of treatment.

Time-to-resolution of diarrhoea (TTROD) was defined as
The time elapsing (days and hours) from start of treatment to resolution of diarrhoea (first of 2 consecutive days of ≤3 UBMs that are then sustained through EOT).

The primary endpoint and definition of clinical cure is considered clinically relevant and has been previously used in large CDI studies and are in accordance with the recent ESCMID guidance document for CDI (2009). No biological or microbiological endpoint has yet been shown to correlate sufficiently well with clinical outcome. TTROD is an interesting endpoint since the anticipated cure rate at day 10 is expected to be very high (>90%) meaning that time to resolution may be discriminatory between treatments. The endpoint global cure is considered very important since this endpoint may be considered most meaningful for the patient.

Sample size

Studies 03 and 04:

The sample size calculation was based on the non-inferior comparison of fidaxomicin with vancomycin in the cure rate at the EOT visit for the PP population. The calculation assumed power of 90% and

2.5% (1-sided) Type I error rate. A non-inferiority margin of 10% was assumed. It was also assumed that the cure rates of fidaxomicin and vancomycin in a population with confirmed CDI meeting the study's entry criteria were both equal to 85%. The choice of a cure rate of 85% for vancomycin was chosen as the median value of the cure rates from 7 active-comparator studies evaluated in the Cochrane Review of published studies of CDI. A placebo response rate of 10% to 20% is estimated based on limited clinical and historical data.

Study 04:

In study 04, prior to study database lock and unblinding, results from study 03 initiated a blinded sample size re-assessment for this study and the assumptions for cure and evaluability were updated to a 90% cure rate and an 85% evaluability rate. Based on these new assumptions, the sample size needed for assessment of non-inferiority in cure rates was approximately 483 subjects. Hence, study enrolment for study 04 was stopped in November 2009.

Randomisation

Subjects were randomized and stratified at each site on the basis of, either having a single prior episode within 3 months, or having no prior occurrence within the last 3 months.

Blinding (masking)

Throughout the treatment period, each subject took blinded study medication orally q6h (QID; 40 doses). Vancomycin, fidaxomicin, and matching placebo capsules were overencapsulated to appear identical and were packaged in blister cards.

Statistical methods

Methods of analysis for the primary endpoint:

A non-inferiority design was used to demonstrate the efficacy of fidaxomicin compared to vancomycin using a 2-sided 95% CIs for the difference between treatment groups, where the lower limit of the 2-sided 95% CI is -10%.

Secondary and explorative endpoints:

Clinical recurrence: Two-sided 95% CIs were presented in addition to the point estimates of recurrence rates for each treatment group. A time-to-recurrence analysis was also conducted, and defined as the time in days from the last date of dosing to the assessment date of recurrence. This analysis only included patients who were considered cured at the EOT visit.

Global Cure: A similar approach as performed for clinical recurrences was used.

Time to resolution of diarrhoea: Summary statistics for the TTROD were provided for each treatment group, and included the numbers of patients whose diarrhoea resolved, number censored, median time to resolution (50^{th} percentile), and 95% CIs on the median time to resolution. Diarrhoea that did not resolve by Day 10 was censored on Day 10 (last day of bowel movement collection on the diary). In addition, patients who withdrew were censored on Day 10.

Results

Participant flow

In study 03, a total of 629 patients were enrolled, with 623 receiving study drug (323 on vancomycin and 300 on fidaxomicin). Overall 54 patients (22 patients [7.3%] in the fidaxomicin group and 32 patients [9.8%] in the vancomycin group) withdrew from the study.

In study 04, a total of 535 patients were enrolled, with 524 receiving study drug (260 on vancomycin and 264 on fidaxomicin). Overall 79 patients (45 patients [16.7%] in the fidaxomicin group and 34 patients [12.8%] in the vancomycin group) withdrew from the study. Overall, 39.5% of patients who received study drug in this trial were enrolled in European sites.

Reasons for early termination from study participation are listed below:

Table 20: Withdrawals from Study in the Phase 3 Studies (Enrolled Population)

	101.1.C.003		**101.1.C.004**	
	Fidaxomicin (N=302)	**Vancomycin (N=327)**	**Fidaxomicin (N=270)**	**Vancomycin (N=265)**
Total who terminated early	22 (7.3)	32 (9.8)	45 (16.7)	34 (12.8)
Reason for early termination				
Adverse event	12 (4.0)	15 (4.6)	15 (5.6)	16 (6.0)
Patient choice	6 (2.0)	7 (2.1)	10 (3.7)	10 (3.8)
Clinical failure	0	0	8 (3.0)	3 (1.1)
Effective Concomitant CDI Therapy	0	5 (1.5)	0	0
Protocol violation	0	3 (0.9)	3 (1.1)	2 (0.8)
Non-compliance	2 (0.7)	1 (0.3)	8 (3.0)	3 (1.1)
Lost to follow-up	1 (0.3)	1 (0.3)	0	0
Treatment failure (less than 3 days of therapy)	1 (0.3)	0	0	0
Not having a robust enough response	0	0	1 (0.4)	0

NOTE: A patient can have multiple reasons for study termination.
Reference: 101.1.C.003 CSR, Table 3; 101.1.C.004 CSR, Table 10

Conduct of the study

Table 21: Time and event schedule for studies 03 and 04

Assessments	Pre-Randomization/ Randomization Day 1[a]	Treatment Period[a] Days 2-9	End-of-Therapy Visit Day 10-11	Contact[b] Days 12-31	Unscheduled Visit for Recurrence[c]	Early Termination	Post-study Visit[b,c] Days 36-40
Informed Consent	X						
Inclusion/Exclusion	X						
Medical history	X						
Physical examination	X		X		X	X	X
ECG[k,l]	X	X[k]	X[l]			X[k]	
Vital signs[d]	X		X		X	X	X
Clinical laboratory tests	X		X			X	
PK blood samples[e,j]	X[e]	X[e]	X[e,j]			X[f,k]	
Stool sample[f,g,h]	X[f]		X[h]		X[f,g]	X[f,g,h]	
Adverse events	X	X	X	X	X	X	X
Concomitant medication	X	X	X	X	X	X	X
Pregnancy test[i]	X						
Investigator evaluation of signs & symptoms of CDI	X	X	X	X[n]	X	X	X
Determine clinical response			X	X		X	
Assess outcome regarding recurrence					X		X
Study medication administration	X[m]	X	X				
Subject interview (CDI status)[b]	X	X	X	X	X	X	X

General Protocol Amendments

Study 03:

There were 4 amendments of the protocol. All changes were implemented during enrolment before the breaking of the blind. Only the most important changes are listed below.

Amendment 1 (30 April 2006):

- Modified efficacy criteria to reflect stabilization and improvement in CDI signs and symptoms.
- Modified definition of SAEs.
- Modified the time period for observation of AEs such that the observation period for AEs now started at the time informed consent was obtained and lasted through 7 days after the last dose of study drug or until the last protocol-specified study visit, whichever occurred later.

Amendment 2 (20 December 2006):

- Modified inclusion criterion 1 to include the presence of either toxin A or B of *C. difficile* in the stool within 48 hours of randomization.
- Added two additional inclusion criteria: permitting use of opiates if the subject was on a stable dose at randomization, and permitting enrolment if subject had failed a full course of metronidazole yet continued to experience diarrhoea as defined in the protocol while remaining toxin positive.

Amendment 3 (14 February 2008):

- Revised the definition of diarrhoea to add a definition for subjects using a rectal collection device. The revised definition was a change in bowel habits, with >3 UBM (or >200 mL of unformed stool for subjects having rectal collection devices) in the 24 hours before randomization.

Amendment 4 (5 June 2008):

- Added procedures to follow in the event of an increase in QTc interval ≥60 msec above baseline or >500 msec after treatment to Safety Evaluations.

Study 04:

There were 5 protocol amendments for German sites and 4 for other sites. All changes were implemented during enrolment before the breaking of the blind. Only important changes not already listed for study 03 are listed below.

Amendment 2 (German sites) 29 May, 2007):

- Inclusion criterion 1 was changed to indicate that subjects had to be 18 years of age or older.

Important amendments to SAP (studies 03 and 04)

- Added baseline disease severity as a summary variable within demographics and baseline characteristics; added additional subgroups to summaries of cure rates.
- Added categorization of strains (BI/NAP1 versus non-BI/NAP1); added baseline severity and MIC to the analysis and added a diagnostics analysis to examine correlation of variables in the logistic regression model; updated subgroups for the logistic regression model.

Study 04 (3 December 2009): Changed global cure from an exploratory endpoint to a secondary efficacy endpoint.

Baseline data

The treatment groups were generally comparable for demographic characteristics within each study. A considerable number of elderly patients were included, median age was 63 years and 66 years in the two studies, respectively.

Compliance in both the phase 3 studies was high with at least 91% of prescribed doses taken in both studies and treatment groups.

In both studies a reasonably limited number of patients prematurely withdrew the study (around 10%).

The reasons for non evaluable patients for the PP analysis were not given. However, this should have been displayed especially in the light of the apparent imbalance between the two treatment arms in study C004 (20% in the fidaxomicin arm vs. 11% in the vancomycin arm). This issue was raised by CHMP. It was finally admitted that given the small imbalance and the confidence intervals for cure rates and recurrence rates, the results are unlikely to be affected.

Table 22: Demographic Characteristics in the Phase 3 Studies (mITT Population)

	101.1.C.003			101.1.C.004		
	Fidaxomicin (N=287)	**Vancomycin (N=309)**	**All patients (N=596)**	**Fidaxomicin (N=252)**	**Vancomycin (N=257)**	**All patients (N=509)**
Sex, n (%)						
Female	164 (57.1)	169 (54.7)	333 (55.9)	148 (58.7)	162 (63.0)	310 (60.9)
Male	123 (42.9)	140 (45.3)	263 (44.1)	104 (41.3)	95 (37.0)	199 (39.1)
Race, n (%)						
White	252 (87.8)	267 (86.4)	519 (87.1)	232 (92.1)	238 (92.6)	470 (92.3)
Black	30 (10.5)	33 (10.7)	63 (10.6)	17 (6.7)	17 (6.6)	34 (6.7)
Asian	4 (1.4)	7 (2.3)	11 (1.8)	2 (0.8)	1 (0.4)	3 (0.6)
Other[a]	1 (0.3)	2 (0.6)	3 (0.5)	1 (0.4)	1 (0.4)	2 (0.4)
Age (yrs)						
N	287	309	596	252	257	509
Mean±SD	60.3±16.9	62.9±16.9	61.6±16.9	64.3±17.9	62.5±18.4	63.4±18.1
Median	61.0	64.0	63.0	67.5	65.0	66.0
Range	18, 94	19, 94	18, 94	18, 94	19, 93	18, 94
Weight (kg)						
N	287	308	595	251	257	508
Mean±SD	78.1±24.2	76±21.3	77±22.8	71.44±20.65	70.88±19.78	71.15±20.20
Median	74.1	73.0	74.0	68.00	67.00	68.00
Range	36.36, 230.6	36, 242.3	36, 242.3	32.0, 231.6	32.8, 181.4	32.0, 231.6
Height (cm)						
N	287	308	595	251	256	507
Mean±SD	167.1±11.1	166.9±12.1	167±11.6	167.07±9.68	165.76±10.94	166.41±10.35
Median	167.0	167.6	167.6	166.00	165.00	165.10
Range	124, 193	129.54, 198	124, 198	146.0, 195.6	114.0, 208.0	114.0, 208.0
BMI[b]						
N	287	308	595	251	256	507
Mean±SD	27.9±8.1	27.3±7.4	27.6±7.8	25.48±6.30	25.74±6.26	25.61±6.28
Median	26.3	26.0	26.2	24.22	24.88	24.49
Range	15.9, 79.6	15.4, 83.6	15.4, 83.6	12.5, 63.8	12.8, 51.9	12.5, 63.8

Baseline characteristics were generally comparable for patients enrolled in the two phase 3 studies, although the patients in study 04 tended to have more severe CDI than those in study 03 on the basis of more inpatients. The prior use of antibiotics in study 04 was twice the rate as compared to study 03.

Table 23: Summary of Baseline Characteristics in the Phase 3 Studies (mITT Population)

	101.1.C.003			**101.1.C.004**		
	Fidaxomicin (N=287)	Vancomycin (N=309)	All patients (N=596)	Fidaxomicin (N=252)	Vancomycin (N=257)	All patients (N=509)
Patient status, n (%)						
Inpatient	167 (58.2)	187 (60.5)	354 (59.4)	174 (69.0)	173 (67.3)	347 (68.2)
Outpatient	120 (41.8)	122 (39.5)	242 (40.6)	78 (31.0)	84 (32.7)	162 (31.8)
Stratum, n (%)						
No Prior Episode	239 (83.3)	255 (82.5)	494 (82.9)	212 (84.1)	221 (86.0)	433 (85.1)
Single Prior Episode	48 (16.7)	54 (17.5)	102 (17.1)	40 (15.9)	36 (14.0)	76 (14.9)
Daily Bowel Movements						
N	287	309	596	251	257	508
Mean ±SD	8.1±4.2	8.3±5.4	8.2±4.8	7.5±4.4	7.5±4.3	7.5±4.3
Median	7.0	6.0	7.0	6.0	6.0	6.0
Min, Max	4, 32	4, 50	4, 50	4, 30	4, 30	4, 30
Baseline disease severity, n (%)						
Mild	64 (22.3)	80 (25.9)	144 (24.2)	77 (30.6)	95 (37.0)	172 (33.8)
Moderate	111 (38.7)	106 (34.3)	217 (36.4)	82 (32.5)	73 (28.4)	155 (30.5)
Severe	112 (39.0)	123 (39.8)	235 (39.4)	90 (35.7)	88 (34.2)	178 (35.0)
Missing	0	0	0	3 (1.2)	1 (0.4)	4 (0.8)
C. difficile Toxin, n (%)						
Positive	287 (100)	309 (100)	596 (100)	252 (100)	257 (100)	509 (100)
Negative	0	0	0	0	0	0
CDI Indication, n (%)						
Diarrhoea Alone	49 (17.1)	68 (22.0)	117 (19.6)	188 (74.6)	192 (74.7)	380 (74.7)
Diarrhoea and Other Symptoms	238 (82.9)	241 (78.0)	479 (80.4)	64 (25.4)	65 (25.3)	129 (25.3)
Prior Use of CDI Antibiotics, n (%)						
Prior Use	128 (44.6)	139 (45.0)	267 (44.8)	225 (89.3)	220 (85.6)	445 (87.4)
No Prior Use	159 (55.4)	170 (55.0)	329 (55.2)	27 (10.7)	37 (14.4)	64 (12.6)
Metronidazole Failure, n (%)						
Yes	13 (4.5)	17 (5.5)	30 (5.0)	12 (4.8)	8 (3.1)	20 (3.9)
No	274 (95.5)	292 (94.5)	566 (95.0)	240 (95.2)	249 (96.9)	489 (96.1)

The applicant was asked to further characterize the degree of severity of the enrolled population, notably to specify the number of patients with pseudomembranous colitis. The applicant stated that only 8 patients had pseudomembranous colitis (5 in the fidaxomicin and 3 in the vancomycin arms respectively). Moreover, it was clarified that CDI requiring ICU hospitalisation was not recorded in the trials. Overall, the relatively limited experience in severely ill patients, including subjects with pseudomembranous colitis is added to the SmPC. This population will have to be closely monitored through the RMP.

Numbers analysed

Table 24: Study 03: Summary of Data Analysis Sets

Study Population	Vancomycin (N=327) n (%)	OPT-80 (N=302) n (%)	Overall Total (N=629) n (%)
Enrolled			629
Randomized	327 (100.0)	302 (100.0)	629 (100.0)
Safety	323 (98.8)	300 (99.3)	623 (99.0)
mITT for Cure	309 (94.5)	287 (95.0)	596 (94.8)
Per Protocol for Cure	283 (86.5)	265 (87.7)	548 (87.1)
mITT for Recurrence	265 (81.0)	253 (83.8)	518 (82.4)
Per Protocol for Recurrence	221 (67.6)	211 (69.9)	432 (68.7)

Table 25: Study 04: Summary of Data Analysis Sets

Study Population	Vancomycin (N=265) n (%)	OPT-80 (N=270) n (%)	Overall Total (N=535) n (%)
Enrolled			535
Randomized	265 (100.0)	270 (100.0)	535 (100.0)
Safety	260 (98.1)	264 (97.8)	524 (97.9)
MITT for Cure	257 (97.0)	252 (93.3)	509 (95.1)
Per Protocol for Cure	235 (88.7)	216 (80.0)	451 (84.3)
MITT for Recurrence	223 (84.2)	221 (81.9)	444 (83.0)
Per Protocol for Recurrence	182 (68.7)	180 (66.7)	362 (67.7)

Abbreviations: MITT = modified-intent-to-treat

Outcomes and estimation

Primary endpoint

The clinical cure rates in both the PP and mITT populations were similar in both phase 3 studies. The 95% CI lower limit was well above the non-inferiority margin of -10%, demonstrating the non-inferiority of fidaxomicin relative to vancomycin. For both studies, the point estimate consistently favours the fidaxomicin arm whatever the population. Similar results were seen in sensitivity analyses using a modified endpoint based strictly on the objective measure of resolution of diarrhoea (i.e., ≤ 3 UBMs during treatment that was sustained to the EOT visit), with a difference of 1.86 in favour of fidaxomicin (95% CIs -2.94, 6.62) being seen in the PP population.

Table 26: Summary of Clinical Cure Rates at End of Therapy for the Pooled Phase 3 Studies

	101.1.C.003			101.1.C.004			Pooled 003 and 004		
	Fidaxo-micin n/N (%)	Vancomycin n/N (%)	Difference 95% CI[1] n/N (%)	Fidaxo-micin n/N (%)	Vancomycin n/N (%)	Difference 95% CI[1] n/N (%)	Fidaxo-micin n/N (%)	Vancomycin n/N (%)	Difference 95% CI[3] n/N (%)
PP population	244/265 (92.1)	254/283 (89.8)	2.3	198/216 (91.7)	213/235 (90.6)	1.0	**442/481 (91.89)**	**467/518 (90.15)**	1.74
95% CI[2]	(88.1, 94.8)	(85.6, 92.8)	(-2.6, 7.1)	(87.1, 94.7)	(86.1, 93.8)	(-4.3, 6.3)	(89.02, 94.07)	(87.20, 92.49)	**(-1.84, 5.28)**
mITT population	253/287 (88.2)	265/309 (85.8)	2.4	221/252 (87.7)	223/257 (86.8)	0.9	**474/539 (87.94)**	**488/566 (86.22)**	1.72
95% CI[2]	(83.8, 91.4)	(81.4, 89.2)	(-3.1, 7.8)	(83.0, 91.2)	(82.0, 90.4)	(-4.9, 6.7)	(84.84, 90.48)	(83.06, 88.87)	**(-2.25, 5.67)**

[1] The lower bound of the 2-sided 95% CI is equivalent to the lower bound of the planned 1-sided 97.5% CI for the difference in cure rates.
[2] 2-sided 95% point estimate confidence interval surrounding the cure rate.
[3] 2-sided 95% CI around the difference in response rates.

Secondary endpoints

In both studies the recurrence rate was significantly lower in the fidaxomicin groups compared to the vancomycin groups. The 95% CIs did not contain the value of zero, indicating superiority of fidaxomicin over vancomycin in the risk of recurrence. Analysis of time to recurrence showed that patients treated with fidaxomicin experienced recurrence of CDI later than patients treated with vancomycin (estimated 10% of vancomycin-treated patients had recurrence by Day 8 post-dose versus 20 days for fidaxomicin-treated patients p = 0.003).

Table 27: Summary of CDI Recurrence Rates in the Phase 3 Studies

	101.1.C.003			101.1.C.004			Pooled 003 and 004		
	Fidaxo-micin n/N (%)	Vanco-mycin n/N (%)	Difference 95% CI n/N (%)	Fidaxo-micin n/N (%)	Vanco-mycin n/N (%)	Difference 95% CI n/N (%)	Fidaxo-micin n/N (%)	Vanco-mycin n/N (%)	Difference 95% CI n/N (%)
mITT population	39/253 (15.4)	67/265 (25.3)	-9.9	28/221 (12.7)	60/223 (26.9)	-14.2	67/474 (14.14)	127/488 (26.02)	-11.89
95% CI	(11.5, 20.4)	(20.4, 30.9)	(-16.6, -2.9)	(8.9, 17.8)	(21.5, 33.1)	(-21.4, -6.8)	(11.22, 17.65)	(22.25, 30.19)	(-16.83, -6.84)
P-value			0.005			<0.001			<0.001
PP population	28/211 (13.3)	53/221 (24.0)	-10.7	23/180 (12.8)	46/182 (25.3)	-12.5	51/391 (13.04)	99/403 (24.57)	-11.52
95% CI	(9.3, 18.6)	(18.8, 30.1)	(-17.9, -3.3)	(8.6, 18.5)	(19.5, 32.1)	(-20.3, -4.4)	(9.99, 16.85)	(20.53, 29.10)	(-16.83, -6.09)
P-value			0.004			0.002			<0.001

In line with this, the global cure rate in patients treated with fidaxomicin was statistically and clinically superior to patients treated with vancomycin.

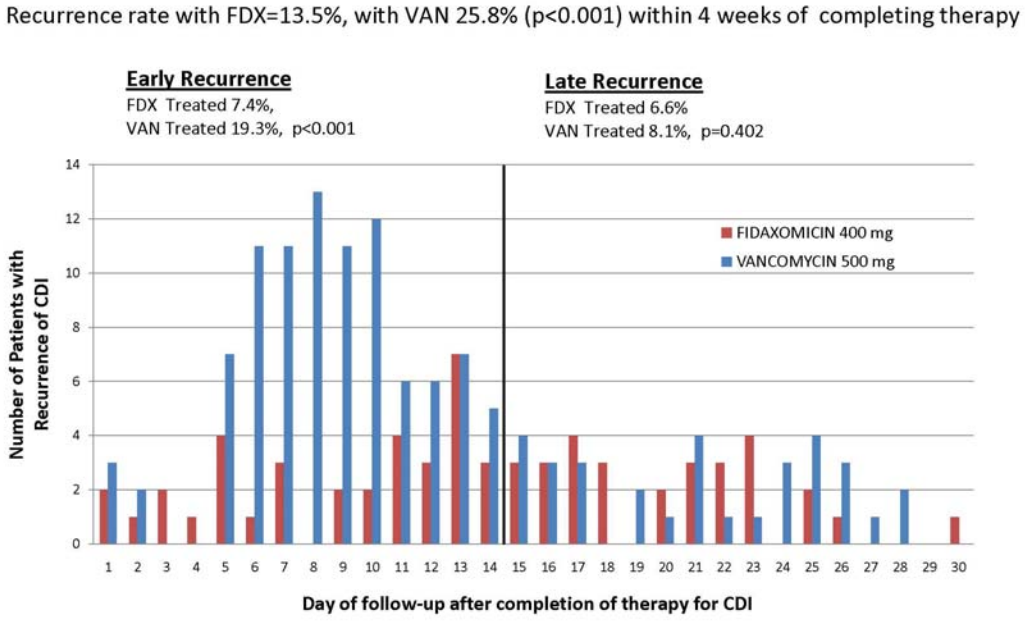
Table 28: Summary of Global Cure Rates in the Phase 3 Studies

	101.1.C.003			101.1.C.004			Pooled 003 and 004		
	Fidaxo-micin n/N (%)	Vanco-mycin n/N (%)	Difference 95% CI[1]	Fidaxo-micin n/N (%)	Vanco-mycin n/N (%)	Difference 95% CI[1]	Fidaxo-micin n/N (%)	Vanco-mycin n/N (%)	Difference 95% CI[1]
mITT population 95% CI[2] P-value	214/287 (74.6) (69.2, 79.3)	198/309 (64.1) (58.6, 69.2)	10.5 (3.1, 17.7) 0.006[3]	193/252 (76.6) (71.0, 81.4)	163/257 (63.4) (57.4, 69.1)	13.2 (5.2, 20.9) 0.001[4]	407/539 (75.51) (71.62, 79.02)	361/566 (63.78) (59.66, 67.71)	11.73 (6.32, 17.04) <0.001[4]
PP population 95% CI[2] P-value	206/265 (77.7) (72.3, 82.3)	190/283 (67.1) (61.5, 72.3)	10.6 (3.1, 17.9) 0.006[3]	172/216 (79.6) (73.7, 84.5)	154/235 (65.5) (59.2, 71.3)	14.1 (5.9, 22.1) <0.001[4]	378/481 (78.59) (74.61, 82.09)	344/518 (66.41) (62.15, 70.42)	12.18 (6.66, 17.59) <0.001[4]

[1] 2-sided 95% CI around the difference (fidaxomicin minus vancomycin) in global cure rates.
[2] 2-sided 95% point estimate CI surrounding the global cure rate.
[3] 2-tailed z-Test for two population proportions based on the normality assumption.
[4] p-value from Chi-square test of difference in global cure rates between fidaxomicin and vancomycin.
Note: The global cure rate was defined as the percentage of patients who achieved cure and did not have a recurrence at any time up to the post-study visit.

The activity of fidaxomicin on recurrence was most pronounced in the initial two weeks after completing therapy, when only 7.4% of patients treated initially with fidaxomicin experienced a recurrence compared with 19.3% of those treated initially with vancomycin (p<0.001). In the following two-week period, the recurrence rates were similar: 6.6% for those originally treated with fidaxomicin compared with 8.1% for those treated with vancomycin (p=0.402). Thus, these results indicate that fidaxomicin reduces the risk for relapses (early recurrence, < 2 weeks from EOT) while there was a similar rate of late recurrences (probable re-infections) in both treatment arms.

Figure 4:



There was no significant difference in time to resolution of diarrhoea (TTROD) between the treatment groups.

Subgroup analyses

Subgroup analyses indicated an association with cure rate in a number of subgroup variables, such as age (worse outcome for the elderly), baseline severity of disease, concomitant systemic antibiotic therapy (worse outcome if yes), status of patients (worse outcome in inpatients) as well as type of initial *C. difficile* strain (worse outcome for BI strains). These observations were generally as expected based on clinical experience and were observed in both treatment groups. For each of these subgroup variables, there did not appear to be any marked difference between treatment groups in observed cure rates. Regarding countries where patients were included, United States sites combined had a lower cure rate than those in Canada. This difference is likely explained by the predominance of outpatients treated at the Canadian sites. Fidaxomicin treated patients were generally associated with a numerically higher cure rate than vancomycin in the pooled analysis in most of the subgroups, including age ≥ 65 and inpatient status.

Subgroup analyses of recurrences and global cure rates indicated consistent numerical superior outcome for fidaxomicin treated patients also in subgroups generally associated with inferior cure rates, including advanced age, prior episode of CDI, CDI antibiotic within 24 hours of study initiation, concomitant systemic antibiotic and inpatient status. In the pooled analyses of the phase 3 studies, patients with BI strain at baseline had numerically fewer recurrences if treated with fidaxomicin compared to vancomycin.

Microbiological outcome

No relationship between MIC and outcome was identified in fidaxomicin treated patients. The hypervirulent BI strain which is associated with outbreaks of severe disease was included as a subgroup in the outcome analyses. The BI strain trend was towards poorer outcomes and higher MIC values. However, even at the same MIC value as for non-BI strains, BI strains performed worse, thus the difference in outcome with the BI strain does not appear to be an MIC effect.

Table 29: Outcomes by Strain Type in Studies 101.1.C.003 and 101.1.C.004 (mITT Population)

Outcome	Study	Strain type	Vancomycin n/N (%)	Fidaxomicin n/N (%)	Total n/N (%)
Clinical cure					
	101.1.C.003	BI	67/83 (80.7)	59/75 (78.7)	126/158 (79.7)
	101.1.C.003	Non-BI	121/132 (91.7)	117/125 (93.6)	238/257 (92.6)
	101.1.C.004	BI	47/57 (82.5)	54/65 (83.1)	101/122 (82.8)
	101.1.C.004	Non-BI	108/123 (87.8)	120/131 (91.6)	228/254 (89.8)
Recurrence					
	101.1.C.003	BI	14/67 (20.9)	16/59 (27.1)	30/126 (23.8)
	101.1.C.003	Non-BI	34/121(28.1)	12/117 (10.3)	46/238 (19.3)
	101.1.C.004	BI	18/47 (38.3)	12/54 (22.2)	30/101 (29.7)
	101.1.C.004	Non-BI	30/108 (27.8)	11/120 (9.2)	41/228 (18.0)
Global cure					
	101.1.C.003	BI	53/83 (63.9)	43/75 (57.3)	96/158 (60.8)
	101.1.C.003	Non-BI	87/132 (65.9)	105/125 (84.0)	192/257 (74.7)

	101.1.C.004	BI	29/57 (50.9)	42/65 (64.6)	71/122 (58.2)
	101.1.C.004	Non-BI	78/123 (63.4)	109/131 (83.2)	187/254 (73.6)

In all but one of the 31 fidaxomicin-treated patients with strains isolated post-treatment at failure or recurrence the final strain had the same MIC as the baseline strain (or was within a dilution of the baseline strain). One patient in study 04 had a baseline isolate with MIC 0.06 µg/mL. The subject was a cure but culture was positive at EOT with unchanged MIC. Later the subject recurred with a strain with a MIC of 16 µg/mL. REA typing methods could not discriminate whether this was the initial strain (recrudescence) or an infection with a new strain.

Based on available data from the phase 3 studies no correlation between faecal concentrations, MIC and outcome could be demonstrated. Thus faecal concentration/MIC does not appear to be a predictive pharmacodynamic parameter. However due to limited number of faecal samples at EOT, especially in patients with failure and large variations between individuals, these data is not considered conclusive.

Ancillary analyses

Additional analysis was carried out using the ESCMID categories of severe and non-severe CDI using the pooled data from the two phase 3 studies. The ESCMID definitions of severe CDI used in the analysis were based on: fever (core body temperature > 38.5°C); marked leucocytosis (leukocyte count >15x109/L) and rise in serum creatinine (≥ 1.5 mg/dL). According to the ESCMID criteria approximately 25% of the mITT patient population were classified as severe CDI. The results in the severe and non-severe categories reflected the same trends as seen for the main analysis. Patients with non-severe CDI responded better for clinical cure rates than patients with severe CDI, regardless of treatment group. For recurrence rates in the fidaxomicin group, similar percentages of patients in the severe and non-severe CDI groups had a recurrence of infection, while in the vancomycin group patients with severe CDI were more likely to have a recurrence of infection.

Table 30: Analysis of Efficacy Endpoints by Severe and Non-Severe CDI (Based on ESCMID criteria) in the pooled Phase 3 Studies (mITT Population)

	Fidaxomicin		**Vancomycin**		**95% CI[a]**
	N	**n (%)**	**N**	**n (%)**	
Clinical Cure Rates					
Overall	539	474 (87.9)	566	488 (86.2)	(-2.3, 5.7)
Severe CDI	135	102 (75.6)	144	108 (75.0)	(-9.5, 10.6)
Non-severe CDI	404	372 (92.1)	422	380 (90.0)	(-1.9, 5.9)
Recurrence Rates					
Overall	474	67 (14.1)	488	127 (26.0)	(-16.8, -6.8)
Severe CDI	102	**14 (13.7)**	108	**33 (30.6)**	**(-27.4, -5.6)**
Non-severe CDI	372	53 (14.2)	380	94 (24.7)	(-16.0, -4.8)
Global Cure Rates					
Overall	539	407 (75.5)	566	361 (63.8)	(6.3, 17.0)
Severe CDI	135	**88 (65.2)**	144	**75 (52.1)**	**(1.6, 24.2)**
Non-severe CDI	404	319 (79.0)	422	286 (67.8)	(5.2, 17.1)

[a] 2-sided 95% CI around the difference (fidaxomicin minus vancomycin) in response rates

Summary of main studies

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 31: Summary of Efficacy for trial 101.1.C.003

Title: A Multi-National, Multi-Centre, Double-Blind, Randomized, Parallel Group Study to Compare the Safety and Efficacy of 200 mg PAR-101 Taken q12h with 125 mg Vancomycin Taken q6h for Ten Days in Subjects with *Clostridium difficile*-Associated Diarrhoea			
Study identifier	101.1.C.003		
Design	Multi-National, Multi-Centre, Double-Blind, Randomized, Parallel Group		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		First Subject Enrolled – Last Subject Last Visit: 09 May 2006 - 21 August 2008 Not applicable Not applicable
Hypothesis	Non-inferiority – A lower limit of the two-sided 95% confidence interval (CI) for the difference in treatment cure rates (fidaxomicin - vancomycin) greater than -10% would demonstrate non-inferiority and the efficacy of fidaxomicin in the treatment of *Clostridium difficile* infection (CDI).		
Treatments groups	Fidaxomicin		Fidaxomicin, PO, 200 mg capsules (q12h), with intermittent matching placebo doses, for 10 days. Randomized N=302.
	Vancomycin		Vancomycin, PO, 125 mg capsules (q6h), for 10 days. Randomized N=327.
Endpoints and definitions	Primary endpoint	Cure rate	The cure rate for Per Protocol (PP) population. Definition: Cure • Subjects who, in the opinion of the Investigator, required no further CDI therapy 2 days after completion of study medication were considered cured. Subjects who had 3 or fewer unformed stools for 2 consecutive days and remained well before the time of study medication discontinuation were considered cured. • Alternatively, subjects who at the end of treatment had a marked reduction in the number of unformed stools but who had residual and mild abdominal discomfort interpreted as recovering bowel by the Investigator could be considered cured at that time providing no new anti-infective CDI therapy was required. Subjects who were considered cured based on stabilization and improvement in CDI signs and symptoms were evaluated 2 to 3 days after the end of study medication. In the event that their signs or symptoms of CDI worsened, subjects were to be designated primary failures. If they remained stable and were not considered to require further CDI therapy to maintain their stable state, they were to be followed for recurrence as cures.
	Co-primary endpoint	Cure rate	The cure rate for modified Intent-to-treat (mITT) population.

	Secondary endpoint	Recurrence rate	The recurrence rate of CDI by 28 days ±2 days after the last dose of study therapy was computed for both PP and mITT populations. Definition: Recurrence • The re-establishment of diarrhoea to an extent (frequency of passed unformed stools) that was greater than that noted on the last day of study medication with the demonstration of either toxin A or B or both of *C. difficile* and that, in the Investigator's opinion, required retreatment with CDI anti-infective therapy. Subjects being considered for recurrence must have had positive toxin demonstrated in the stool. If a rapid screening test was used and failed to demonstrate toxin, a confirmatory test using a non-rapid kit method was to be used.
	Secondary endpoint	Global cure rate	The global cure rate (percent of subjects who were cured and did not experience a recurrence) was computed for both PP and mITT populations. Definition: Global cure • Subject who had been evaluated as cured at the end of therapy (EOT) and did not have recurrence at any time up to the post-study visit.
Database lock	3 November 2008		

Results and Analysis

Analysis description	**Primary Analysis – Cure rate at EOT**		
Analysis population and time point description	**Analysis population**: • PP population for cure: subjects included in the mITT population (see description below) who met the following criteria: – Confirmed CDI clinical diagnosis as stated above – Met all inclusion criteria and no exclusion criteria (unless failures to meet the former and meeting any of the latter were documented and approved by the sponsor) – Received a sufficient course of therapy – Had an EOT clinical evaluation – Did not have significant protocol violations including: • Use of concomitant CDI therapy or other drugs which could have confounded the assessment of efficacy • Other significant protocol violations as judged by a blinded assessment before study unblinding **Time Point**: EOT visit		
Descriptive statistics and estimate variability	Treatment group	Fidaxomicin	Vancomycin
	Number of subjects – PP population	265	283
	Clinical cure rate at EOT - PP population	92.1% (244/265)	89.8% (254/283)
	Standard Error	1.66%	1.80%

Effect estimate per comparison	Clinical cure rate at EOT - PP population	Comparison groups	fidaxomicin vs. vancomycin
		The difference in treatment cure rates (fidaxomicin - vancomycin)	2.3%
		Standard Error	2.45%
		95% CI†‡	(-2.6%, 7.1%)
Notes	P-value is not reported since the non-inferiority comparison was based on 95% CI. † The lower bound of the 2-sided 95% CI is equivalent to the lower bound of the planned 1-sided 97.5% CI for the difference in cure rates. ‡ Two-sided 95% point estimate CI surrounding the cure rate.		
Analysis description	**Co-Primary Analysis – Cure rate at EOT**		
Analysis population and time point description	**Analysis population**: • mITT population for cure: subjects with CDI confirmed by positive toxin assay and who received at least 1 dose of study medication. **Time Point**: EOT visit		
Descriptive statistics and estimate variability	Treatment group	Fidaxomicin	Vancomycin
	Number of subjects – mITT population	287	309
	Clinical cure rate at EOT - mITT population	88.2% (253/287)	85.8% (265/309)
	Standard Error	1.91%	1.99%
Effect estimate per comparison	Clinical cure rate at EOT - mITT population	Comparison groups	fidaxomicin vs. vancomycin
		The difference in treatment cure rates (fidaxomicin - vancomycin)	2.4%
		Standard Error	2.76%
		95% CI†‡	(-3.1%, 7.8%)
Notes	P-value is not reported since the non-inferiority comparison was based on 95% CI. † The lower bound of the 2-sided 95% CI is equivalent to the lower bound of the planned 1-sided 97.5% CI for the difference in cure rates. ‡ Two-sided 95% point estimate CI surrounding the cure rate.		
Analysis description	**Secondary analysis –Recurrence rate**		
Analysis population and time point description	**Analysis population(s)**: • PP population for recurrence: subjects in the PP for cure who: – Were cured at EOT – Were followed for recurrence for more than 25 days after treatment or experienced a recurrence ≤30 days post treatment and – Did not use concomitant CDI therapy or other drugs which could have confounded the assessment of recurrence. • mITT population for recurrence: subjects in the mITT population for cure who were classified as cured at the EOT. **Time Point**: 28 days ±2 days after the last dose of study therapy.		
Descriptive statistics and estimate variability	Treatment group	Fidaxomicin	Vancomycin
	Number of subjects – PP population	211	221
	Recurrence rate - PP population	13.3% (28/211)	24.0% (53/221)
	Standard Error	2.34%	2.87%

Effect estimate per comparison	Recurrence rate - PP population	Comparison groups	fidaxomicin vs. vancomycin
		The difference in recurrence rates (fidaxomicin - vancomycin)	-10.7%
		Standard Error	3.70%
		95% CI†‡	(-17.9%, -3.3%)
		P-value§	0.004
Descriptive statistics and estimate variability	Treatment group	Fidaxomicin	Vancomycin
	Number of subjects – mITT population	253	265
	Recurrence rate - mITT population	15.4% (39/253)	25.3% (67/265)
	Standard Error	2.27%	2.67%
Effect estimate per comparison	Recurrence rate - mITT population	Comparison groups	fidaxomicin vs. vancomycin
		The difference in recurrence rates (fidaxomicin - vancomycin)	-9.9%
		Standard Error	3.50%
		95% CI†‡	(-16.6%, -2.9%)
		P-value§	0.005
Notes	† Two-sided 95% CI around the difference (fidaxomicin minus vancomycin) in clinical recurrence rates. ‡ Two-sided 95% point estimate CI surrounding the recurrence rate. § Two-tailed z-Test for two population proportions based on the normality assumption.		
Analysis description	**Secondary analysis – Global cure rate**		
Analysis population and time point description	**Analysis population(s)**: • PP population for cure (see description above) • mITT population for cure (see description above) **Time Point**: The end of study visit		
Descriptive statistics and estimate variability	Treatment group	Fidaxomicin	Vancomycin
	Number of subjects – PP population	265	283
	Global cure rate – PP population	77.7% (206/265)	67.1% (190/283)
	Standard Error	2.56%	2.79%
Effect estimate per comparison	Global cure rate – PP population	Comparison groups	fidaxomicin vs. vancomycin
		The difference in global cure rates (fidaxomicin - vancomycin)	10.6%
		Standard Error	3.79%
		95% CI†‡	(3.1%,17.9%)
		P-value§	0.006
Descriptive statistics and estimate variability	Treatment group	Fidaxomicin	Vancomycin
	Number of subjects – mITT population	287	309
	Global cure rate – mITT population	74.6% (214/287)	64.1% (198/309)
	Standard Error	2.57%	2.73%
Effect estimate per comparison	Global cure rate – mITT population	Comparison groups	fidaxomicin vs. vancomycin
		The difference in global cure rates (fidaxomicin - vancomycin)	10.5%
		Standard Error	3.75%
		95% CI†‡	(3.1%, 17.7%)
		P-value§	0.006
Notes	† Two-sided 95% CI around the difference (fidaxomicin minus vancomycin) in global cure rates. ‡ Two-sided 95% point estimate CI surrounding the global cure rate. § Two-tailed z-Test for two population proportions based on the normality assumption.		

Table 32: Summary of Efficacy for trial 101.1.C.004

Title: A Multi-National, Multi-Centre, Double-Blind, Randomized, Parallel Group Study to Compare the Safety and Efficacy of 200 mg PAR-101 Taken q12h with 125 mg Vancomycin Taken q6h for Ten Days in Subjects with *Clostridium difficile*-Associated Diarrhoea			
Study identifier	101.1.C.004		
Design	Multi-National, Multi-Centre, Double-Blind, Randomized, Parallel Group		
	Duration of Main phase:		First Subject Enrolled – Last Subject Last Visit: 19 Apr 2007 – 11 Dec 2009
	Duration of Run-in phase:		Not applicable
	Duration of Extension phase:		Not applicable
Hypothesis	Non-inferiority – A lower limit of the two-sided 95% confidence interval (CI) for the difference in treatment cure rates (fidaxomicin - vancomycin) greater than -10% would demonstrate non-inferiority and the efficacy of fidaxomicin in the treatment of *Clostridium difficile* infection (CDI).		
Treatments groups	Fidaxomicin		Fidaxomicin, PO, 200 mg capsules (q12h), with intermittent matching placebo doses, for 10 days. Randomized N=270.
	Vancomycin		Vancomycin, PO, 125 mg capsules (q6h), for 10 days. Randomized N=265.
Endpoints and definitions	Primary endpoint	Cure rate	The cure rate for Per Protocol (PP) population. Definition: Cure • Subjects who, in the opinion of the Investigator, required no further CDI therapy 2 days after completion of study medication were considered cured. Subjects who had 3 or fewer unformed stools for 2 consecutive days and remained well before the time of study medication discontinuation were considered cured. • Alternatively, subjects who at the end of treatment had a marked reduction in the number of unformed stools but who had residual and mild abdominal discomfort interpreted as recovering bowel by the Investigator could be considered cured at that time providing no new anti-infective CDI therapy was required. Subjects who were considered cured based on stabilization and improvement in CDI signs and symptoms were evaluated 2 to 3 days after the end of study medication. In the event that their signs or symptoms of CDI worsened, subjects were to be designated primary failures. If they remained stable and were not considered to require further CDI therapy to maintain their stable state, they were to be followed for recurrence as cures.
	Co-primary endpoint	Cure rate	The cure rate for modified Intent-to-treat (mITT) population.

	Secondary endpoint	Recurrence rate	The recurrence rate of CDI by 28 days ±2 days after the last dose of study therapy was computed for both PP and mITT populations. Definition: Recurrence • The re-establishment of diarrhoea to an extent (frequency of passed unformed stools) that was greater than that noted on the last day of study medication with the demonstration of either toxin A or B or both of *C. difficile* and that, in the Investigator's opinion, required retreatment with CDI anti-infective therapy. Subjects being considered for recurrence must have had positive toxin demonstrated in the stool. If a rapid screening test was used and failed to demonstrate toxin, a confirmatory test using a non-rapid kit method was to be used.
	Secondary endpoint	Global cure rate	The global cure rate (percent of subjects who were cured and did not experience a recurrence) was computed for both PP and mITT populations. Definition: Global cure • Subject who had been evaluated as cured at the end of therapy (EOT) and did not have recurrence at any time up to the post-study visit.
	Note: Both secondary endpoints used a Chi-square test of difference in proportions to test the superiority of fidaxomicin versus vancomycin, along with 2-sided 95% CIs being reported for the difference in treatment groups. A gate-keeping strategy was employed to maintain overall error rate for testing secondary endpoints.		
Database lock	27 January 2010		

Results and Analysis

Analysis description	**Primary Analysis – Cure rate at EOT**		
Analysis population and time point description	**Analysis population**: • PP population for cure: subjects included in the mITT population (see description below) who met the following criteria: – Had CDI confirmed by positive toxin assay – Met all inclusion criteria and no exclusion criteria (unless failures to meet the former and meeting any of the latter were documented and approved by the sponsor) – Received a sufficient course of therapy – Had an EOT clinical evaluation – Did not have significant protocol violations including: • Use of concomitant CDI therapy or other drugs, which could have confounded the assessment of efficacy • Other significant protocol violations as judged by a blinded assessment before study unblinding **Time Point**: EOT visit		
Descriptive statistics and estimate variability	Treatment group	Fidaxomicin	Vancomycin
	Number of subjects – PP population	216	235
	Clinical cure rate at EOT – PP population	91.7% (198/216)	90.6% (213/235)
	Standard Error	1.88%	1.90%

Effect estimate per comparison	Clinical cure at EOT – PP population	Comparison groups	fidaxomicin vs. vancomycin
		The difference in treatment cure rates (fidaxomicin - vancomycin)	1.0%
		Standard Error	2.67%
		95% CI†‡	(-4.3%, 6.3%)
Notes	P-value is not reported since the non-inferiority comparison was based on 95% CI. † The lower bound of the 2-sided 95% CI is equivalent to the lower bound of the planned 1-sided 97.5% CI for the difference in cure rates. ‡ Two-sided 95% CI for the cure rate.		
Analysis description	**Co-Primary Analysis – Cure rate at EOT**		
Analysis population and time point description	**Analysis population**: • mITT population for cure: - Subjects with CDI confirmed by positive toxin assay and who received at least 1 dose of study medication. **Time Point**: EOT visit		
Descriptive statistics and estimate variability	Treatment group	Fidaxomicin	Vancomycin
	Number of subjects – mITT population	252	257
	Clinical cure rate at EOT – mITT population	87.7% (221/252)	86.8% (223/257)
	Standard Error	2.07%	2.11%
Effect estimate per comparison	Clinical cure rate at EOT – mITT population	Comparison groups	fidaxomicin vs. vancomycin
		The difference in treatment cure rates (fidaxomicin - vancomycin)	0.9%
		Standard Error	2.96%
		95% CI†‡	(-4.9%, 6.7%)
Notes	P-value is not reported since the non-inferiority comparison was based on 95% CI. † The lower bound of the 2-sided 95% CI is equivalent to the lower bound of the planned 1-sided 97.5% CI for the difference in cure rates. ‡ Two-sided 95% CI for the cure rate.		
Analysis description	**Secondary analysis –Recurrence rate**		
Analysis population and time point description	**Analysis population(s)**: • PP population for recurrence: subjects in the PP population for cure who – Were cured at EOT – Were followed for recurrence for more than 25 days after treatment or experienced a recurrence ≤30 days post treatment and – Did not use concomitant CDI therapy or other drugs which could have confounded the assessment of recurrence. • mITT population for recurrence: subjects in the mITT population for cure who were classified as cured at the EOT. **Time Point**: 28 days ±2 days after the last dose of study therapy.		
Descriptive statistics and estimate variability	Treatment group	Fidaxomicin	Vancomycin
	Number of subjects – PP population	180	182
	Recurrence rate – PP population	12.8% (23/180)	25.3% (46/182)
	Standard Error	2.49%	3.22%

Effect estimate per comparison	Recurrence rate – PP population	Comparison groups	fidaxomicin vs. vancomycin
		The difference in recurrence rates (fidaxomicin - vancomycin)	-12.5%
		Standard Error	4.07%
		95% CI†	(-20.3%, -4.4%)
		P-value‡	0.002
Descriptive statistics and estimate variability	Treatment group	Fidaxomicin	Vancomycin
	Number of subjects – mITT population	221	223
	Recurrence rate – mITT population	12.7% (28/221)	26.9% (60/223)
	Standard Error	2.24%	2.97%
Effect estimate per comparison	Recurrence rate – mITT population	Comparison groups	fidaxomicin vs. vancomycin
		The difference in recurrence rates (fidaxomicin - vancomycin)	-14.2%
		Standard Error	3.72%
		95% CI†	(-21.4%, -6.8%)
		P-value‡	<0.001
Notes	† Two-sided 95% CI for the recurrence rate. ‡ P-value from Chi-square test of difference in recurrence rates between fidaxomicin and vancomycin.		
Analysis description	**Secondary analysis – Global cure rate**		
Analysis population and time point description	**Analysis population(s)**: • PP population for cure (see description above) • mITT population for cure (see description above) **Time Point**: The end of study visit		
Descriptive statistics and estimate variability	Treatment group	Fidaxomicin	Vancomycin
	Number of subjects – PP population	216	235
	Global cure rate – PP population	79.6% (172/216)	65.5% (154/235)
	Standard Error	2.74%	3.10%
Effect estimate per comparison	Global cure rate – PP population	Comparison groups	fidaxomicin vs. vancomycin
		The difference in global cure rates (fidaxomicin - vancomycin)	14.1%
		Standard Error	4.14%
		95% CI†‡	(5.9%, 22.1%)
		P-value§	<0.001
Descriptive statistics and estimate variability	Treatment group	Fidaxomicin	Vancomycin
	Number of subjects – mITT population	252	257
	Global cure rate – mITT population	76.6% (193/252)	63.4% (163/257)
	Standard Error	2.67%	3.00%
Effect estimate per comparison	Global cure rate – mITT population	Comparison groups	fidaxomicin vs. vancomycin
		The difference in global cure rates (fidaxomicin - vancomycin)	13.2%
		Standard Error	4.02%
		95% CI†‡	(5.2%, 20.9%)
		P-value§	0.001
Notes	† Two-sided 95% CI around the difference (fidaxomicin minus vancomycin) in global cure rates. ‡ Two-sided 95% point estimate CI surrounding the global cure rate. § P-value from Chi-square test of difference in global rates between fidaxomicin and vancomycin.		

Clinical studies in special populations

There are no studies performed in special populations. Regarding elderly, patients with hepatic or renal impairment, such patients included in Phase 3 studies have been identified and PK results have been observed. Efficacy data depending on age can be observed in efficacy results.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The clinical development programme included two well conducted Phase III clinical trials.

The inclusion and exclusion criteria for the phase 3 studies are considered acceptable and in line with previous CDI studies. The studied patient population was generally representative for the target population, including a high number of elderly patients with almost 50% being 65 years or older. Although more than 70% of included patients were considered by the investigators to have moderate to severe infection, there is a lack experience in seriously ill patients. For example, very few (5) patients of the fidaxomicin treated patients had a diagnosis of pseudomembranous colitis.

The applicant was asked to further characterize the degree of severity of the enrolled population, notably to specify the number of patients with pseudomembranous colitis. In response, the applicant stated that only 8 patients had pseudomembranous colitis (5 in the fidaxomicin and 3 in the vancomycin arms respectively). Moreover, it was clarified that CDI requiring ICU hospitalisation was not recorded in the trials. Overall, the relatively limited experience in severely ill patients, including subjects with pseudomembranous colitis is stated in the SmPC. This population will have to be closely monitored through the RMP

Efficacy data and additional analyses

The two randomised double-blind controlled phase 3 trials in patients with mild to moderately severe *C. difficile* infection demonstrated non-inferiority of fidaxomicin compared to vancomycin in the primary efficacy variable, clinical cure at end of therapy, and superiority in the secondary endpoints recurrence rate and global cure rate within 36 to 40 days after initiation of treatment.

According to subgroup analyses a number of variables showed an association with cure rate in the mITT and PP populations, such as age, baseline severity of disease, inpatient or outpatient status, as well as type of initial *C. difficile* strain. These observations were as expected based on clinical experience and were observed in both treatment groups. For each of these subgroup variables, there did not appear to be any marked difference between treatment groups in observed cure rates and non-inferiority to vancomycin was demonstrated. Gender or ethnicity did not have an impact on the clinical response. There were no significant differences between treatment groups regarding time to resolution of diarrhoea in either of the two phase 3 studies.

The recurrence rates within 30 days post-treatment were consistently significantly higher in the vancomycin groups compared to the fidaxomicin groups in both the PP and mITT populations. Subgroup analyses indicated consistent numerical superior outcome for fidaxomicin treated patients also in subgroups generally associated with inferior cure rates, including high age, prior episode of CDI, concomitant systemic antibiotic and inpatient status. Similar results were obtained regardless of prior antibiotic therapy against CDI (maximum 24 hours). Also global cure rates were significantly more favourable for fidaxomicin treated patients. Global cure is considered a very crucial endpoint since this endpoint may be considered most meaningful for the patient, taking the high recurrence rates after current available therapeutic options into account (20 to 30% recurrence rates have been

reported after initial successful treatment with metronidazole or vancomycin [Aslam S et al. Lancet Infect. Dis. 2005; 5(9); 549-557]). The superiority of fidaxomicin compared to vancomycin regarding recurrences, were mainly due to a reduction of early recurrences (< 2 weeks after EOT). Even if molecular typing were not successful in distinguishing between relapse and reinfection, it is widely acknowledged that relapses with the original strain mainly occur within 14 days after end of treatment. Thus, available study data indicate a significant effect on relapses (recurrence < two weeks), but not on probable re-infections (recurrences > 2 weeks after EOT). This is further supported by the fact that fidaxomicin exerts a limited effect on the normal microflora and also by the probable antispore effect, both features that would minimize relapses

Fidaxomicin may be considered a topical agent and no correlation between baseline MIC values, faecal concentrations and outcome could be demonstrated. The trend for patients infected with the hypervirulent BI (027) strain that is associated with outbreaks of severe disease was towards poorer outcomes and higher MIC values. However, even at the same MIC value as for non-BI strains, BI strains performed worse, thus the difference in outcome with the BI strain does not appear to be an MIC effect. Patients harbouring the BI strain randomised to fidaxomicin performed at least as well for the primary endpoint. The two phase 3 studies are not superimposable as regards the global cure rate. Depending on the study results on BI either favour the vancomycin arm (C003) or the fidaxomicin arm (C004). Some clarifications were requested to better interpret the outcome depending on the BI/non BI strain. In response the applicant underlined that the numbers of patients with BI was small, representing approximately one third of the isolable strains (and one quarter of the subjects in the studies), and sample size of the trials could not allow to reliably detect differences within the BI subgroup. It was acknowledged that within the subset of patients with BI the cure rates were similar between fidaxomicin (FDX) and vancomycin (VAN) arms.

As underlined by the applicant, physicians will not know the strain type at the time of diagnosis and that subjects without non-BI strains represent the majority of strains in Europe [Hensgens, 2009; UK HSC Public Health Agency, 2010] and in this population better outcomes where reported with fidaxomicin vs. vancomycin.

C. difficile associated diarrhoea may manifest from mild disease where termination of ongoing antibiotic therapy will be sufficient for cure, to severe and fulminant cases requiring intensive care. Unfortunately, there is no validated severity index for CDI. In the present study patients were categorized by the investigators as mild, moderate or severe cases. A high number of elderly patients were included. Although not completely standardised, baseline characteristics indicate that a substantial number of patients with severe disease were included, also supported by the post-study analysis according to ESCMID criteria (25% having severe disease in both treatment groups). However, only one of several alternative criteria was to be fulfilled for classification of "severe CDI".

A very important future patient population where current treatment options have clear short-comings is subjects with previous multiple occurrences of CDI. However, patients with multiple occurrences of CDI (defined as more than 1 prior occurrence within the past 3 months) were excluded from the studies, which should be stated in the SmPC. This group of patients currently constitutes a real clinical challenge and there is an urgent need for improved treatment alternatives leading to sustained cure. Data from the present studies indicate that the clinical outcome were similar in patients with one previous CDI episode within 3 months of inclusion compared to those without previous CDI episode within this time frame. Furthermore, no data on repeated treatment with fidaxomicin have been presented.

As part of the RMP, the applicant committed to set up a post-marketing surveillance programme to monitor isolated strains of *C.difficile* for changes in antimicrobial resistance patterns, a post-marketing

clinical study to investigate the (safety and) efficacy of repeated use of fidaxomicin and a post marketing drug utilization study to further assess the use of fidaxomicin in standard clinical practice.

2.5.4. Conclusions on the clinical efficacy

The efficacy of fidaxomicin in the treatment of patients with single episodes of mild to moderately severe non-recurrent *C. difficile* associated disease is considered satisfactorily demonstrated by the submitted data. Based on efficacy data, fidaxomicin seems to have the potential to offer a valuable alternative in the treatment of CDI, in particular considering the favourable effect on relapses and the unique mode of action suggesting a limited potential for promotion of resistance against established antibiotic classes.

2.6. Clinical safety

Patient exposure

The safety of fidaxomicin has been evaluated in three phase 1 studies in healthy subjects, one phase 2A dose-finding study conducted in patients with CDI and two phase 3 studies conducted in patients with CDI. In all studies, the safety population was defined as the patient population that received at least one dose of treatment with the study drug fidaxomicin, or with the comparator vancomycin or placebo. In the phase 1 studies, 64 subjects received at least one dose fidaxomicin. A total of 660 patients with *C. difficile* associated diarrhoea were treated with at least one dose fidaxomicin and up to 10 days. Of the 1195 patients with CDI randomized to treatment (fidaxomicin or vancomycin) 580 (48.5%) were aged ≥ 65 years which are considered appropriate considering the nature of the disease.

Adverse events

Phase 2 study

Fidaxomicin was well tolerated by all patients after 10 days consecutive dosing at 100 to 400 mg/day. Overall, 9 (18.8%) of the patients reported AEs during the study. The proportion of patients reporting AEs was not dose dependent. No subjects withdrew due to AEs. None of the AEs in study OPT-80 Phase 2A was judged related to study drug by the investigator.

Phase 3 studies

In each of the studies and in the pooled data, the overall incidence of treatment-emerging adverse events (TEAEs) was similar between the two treatment groups. When comparing the two individual studies, it appeared that patients enrolled in both groups in trial 04 experienced more TEAEs than patients randomised in 03 study: 62.3 % FID and 60.4 % VAN versus 70.5 % FID and 68.1 % VAN, respectively. This difference in TEAEs rates was noteworthy for gastrointestinal disorders (especially abdominal pain and constipation, abdominal distension and flatulence), fatigue and ECG QT prolonged. In contrast, peripheral oedema, pyrexia and dyspnoea were more frequently reported in study 03 than in study 04.

The most frequent preferred terms in the pooled analysis were nausea, hypokalaemia, vomiting, abdominal pain and headache. The TEAEs which occurred more frequently in patients treated with fidaxomicin than vancomycin in the pooled analysis (i.e., ≥ 2% difference between the treatment groups) were abdominal pain (5.7% versus 3.1%), and constipation (3.7%versus 1.7%). Several of these reported AEs like nausea, abdominal pain and hypokalaemia are symptoms of the underlying disease. Treatment-related adverse events were reported by 11% of the patients, generally equally distributed in the two treatment groups. The most frequent drug-related TEAE in the pooled analysis

was nausea (3.4% vancomycin; 2.7% fidaxomicin). There were no major differences between the fidaxomicin and vancomycin treatment groups in the type of TEAEs considered drug-related by the investigators. The incidence of treatment-related dizziness was higher in the fidaxomicin group compared to the vancomycin group (5 vs. 1), mainly driven by results from study 03. This AE is listed in section 4.8 of the SmPC.

Table 33: Treatment-Related Adverse Events in Patients with CDI in Phase 3 Studies (by SOC and PT) (Safety Population)

	101.1.C.003		101.1.C.004		Pooled 003 and 004	
System Organ Class Preferred Term	**Vancomycin (N=323)**	**Fidaxomicin (N=300)**	**Vancomycin (N=260)**	**Fidaxomicin (N=264)**	**Vancomycin (N=583)**	**Fidaxomicin (N=564)**
Any treatment-related TEAEs	29 (9.0)	29 (9.7)	36 (13.8)	31 (11.7)	65 (11.1)	60 (10.6)
Blood and lymphatic system disorders	0	0	1 (0.4)	0	1 (0.2)	0
Eosinophilia	0	0	1 (0.4)	0	1 (0.2)	0
Cardiac disorders	0	0	2 (0.8)	0	2 (0.3)	0
Torsade de pointes	0	0	1 (0.4)	0	1 (0.2)	0
Ventricular extrasystoles	0	0	1 (0.4)	0	1 (0.2)	0
Ear and labyrinth disorders	1 (0.3)	1 (0.3)	0	0	1 (0.2)	1 (0.2)
Tinnitus	0	1 (0.3)	0	0	0	1 (0.2)
Deafness	1 (0.3)	0	0	0	1 (0.2)	0
Vertigo	0	1 (0.3)	0	0	0	1 (0.2)
Eye disorders	0	0	2 (0.8)	0	2 (0.3)	0
Dry eye	0	0	1 (0.4)	0	1 (0.2)	0
Halo vision	0	0	1 (0.4)	0	1 (0.2)	0
Gastrointestinal disorders	15 (4.6)	13 (4.3)	18 (6.9)	20 (7.6)	33 (5.7)	33 (5.9)
Nausea	10 (3.1)	7 (2.3)	10 (3.8)	8 (3.0)	20 (3.4)	15 (2.7)
Vomiting	4 (1.2)	3 (1.0)	4 (1.5)	4 (1.5)	8 (1.4)	7 (1.2)
Diarrhoea	1 (0.3)	0	0	1 (0.4)	1 (0.2)	1 (0.2)
Abdominal pain	1 (0.3)	0	0	1 (0.4)	1 (0.2)	1 (0.2)
Abdominal pain upper	1 (0.3)	0	1 (0.4)	0	2 (0.3)	0
Constipation	1 (0.3)	4 (1.3)	2 (0.8)	3 (1.1)	3 (0.5)	7 (1.2)
Dyspepsia	0	1 (0.3)	0	0	0	1 (0.2)
Abdominal distension	1 (0.3)	0	0	2 (0.8)	1 (0.2)	2 (0.4)
Painful defecation	1 (0.3)	0	0	0	1 (0.2)	0
Flatulence	0	0	0	2 (0.8)	0	2 (0.4)
Gastritis	0	0	1 (0.4)	0	1 (0.2)	0
Dry mouth	0	0	1 (0.4)	2 (0.8)	1 (0.2)	2 (0.4)
Hematochezia	0	0	1 (0.4)	0	1 (0.2)	0
Regurgitation	0	0	0	1 (0.4)	0	1 (0.2)
Retching	0	0	0	1 (0.4)	0	1 (0.2)
Epigastric discomfort	0	1 (0.3)	0	0	0	1 (0.2)
Tongue disorder	0	0	0	1 (0.4)	0	1 (0.2)
Stomach discomfort	0	1 (0.3)	0	0	0	1 (0.2)
General disorders and administration site conditions	1 (0.3)	3 (1.0)	4 (1.5)	2 (0.8)	5 (0.9)	5 (0.9)
Oedema peripheral	0	1 (0.3)	2 (0.8)	0	2 (0.3)	1 (0.2)
Pyrexia	1 (0.3)	0	1 (0.4)	0	2 (0.3)	0
Fatigue	0	1 (0.3)	0	0	0	1 (0.2)
Pain	0	1 (0.3)	0	0	0	1 (0.2)
Oedema	0	0	1 (0.4)	0	1 (0.2)	0
Asthenia	0	0	0	1 (0.4)	0	1 (0.2)
Chills	0	0	1 (0.4)	0	1 (0.2)	0
Chest discomfort	0	0	0	1 (0.4)	0	1 (0.2)
Hepatobiliary disorders	0	1 (0.3)	0	0	0	1 (0.2)
Hyperbilirubinemia	0	1 (0.3)	0	0	0	1 (0.2)
Immune system disorders	1 (0.3)	0	0	0	1 (0.2)	0
Hypersensitivity	1 (0.3)	0	0	0	1 (0.2)	0
Infections and infestations	1 (0.3)	2 (0.7)	1 (0.4)	2 (0.8)	2 (0.3)	4 (0.7)

	101.1.C.003		101.1.C.004		Pooled 003 and 004	
System Organ Class **Preferred Term**	**Vancomycin (N=323)**	**Fidaxomicin (N=300)**	**Vancomycin (N=260)**	**Fidaxomicin (N=264)**	**Vancomycin (N=583)**	**Fidaxomicin (N=564)**
Vulvovaginal mycotic infection	1 (0.3)	0	0	0	1 (0.2)	0
Fungal infection	0	1 (0.3)	0	0	0	1 (0.2)
Vaginal infection	0	1 (0.3)	0	0	0	1 (0.2)
Clostridium difficile colitis	0	0	0	1 (0.4)	0	1 (0.2)
Candidiasis	0	0	0	1 (0.4)	0	1 (0.2)
Oral candidiasis	0	0	1 (0.4)	0	1 (0.2)	0
Injury, poisoning and procedural complications	0	1 (0.3)	0	0	0	1 (0.2)
Accidental overdose	0	1 (0.3)	0	0	0	1 (0.2)
Investigations	3 (0.9)	4 (1.3)	3 (1.2)	4 (1.5)	6 (1.0)	8 (1.4)
Alanine aminotransferase increased	1 (0.3)	2 (0.7)	0	2 (0.8)	1 (0.2)	4 (0.7)
Aspartate aminotransferase increased	2 (0.6)	1 (0.3)	0	0	2 (0.3)	1 (0.2)
Aspartate aminotransferase abnormal	0	0	0	1 (0.4)	0	1 (0.2)
Blood lactate dehydrogenase increased	1 (0.3)	0	0	0	1 (0.2)	0
Blood alkaline phosphatase increased	1 (0.3)	0	0	0	1 (0.2)	0
Blood uric acid increased	0	1 (0.3)	0	0	0	1 (0.2)
Hepatic enzymes increased	0	1 (0.3)	0	0	0	1 (0.2)
Electrocardiogram QT prolonged	0	0	1 (0.4)	1 (0.4)	1 (0.2)	1 (0.2)
Liver function test abnormal	0	0	1 (0.4)	0	1 (0.2)	0
Neutrophil count decreased	0	0	0 (0.0)	1 (0.4)	0	1 (0.2)
Transaminases increased	0	0	1 (0.4)	0	1 (0.2)	0
Metabolism and nutrition disorders	3 (0.9)	5 (1.7)	5 (1.9)	0	8 (1.4)	5 (0.9)
Hypokalaemia	1 (0.3)	0	3 (1.2)	0	4 (0.7)	0
Dehydration	1 (0.3)	0	0	0	1 (0.2)	0
Hypomagnesaemia	1 (0.3)	0	0	0	1 (0.2)	0
Hyponatraemia	0	1 (0.3)	0	0	0	1 (0.2)
Anorexia	0	4 (1.3)	1 (0.4)	0	1 (0.2)	4 (0.7)
Cachexia	0	0	1 (0.4)	0	1 (0.2)	0
Musculoskeletal and connective tissue disorders	0	0	0	1 (0.4)	0	1 (0.2)
Muscle spasms	0	0	0	1 (0.4)	0	1 (0.2)
Nervous system disorders	6 (1.9)	8 (2.7)	3 (1.2)	1 (0.4)	9 (1.5)	9 (1.6)
Headache	3 (0.9)	3 (1.0)	1 (0.4)	0	4 (0.7)	3 (0.5)
Dizziness	0	4 (1.3)	1 (0.4)	1 (0.4)	1 (0.2)	5 (0.9)
Dysgeusia	2 (0.6)	2 (0.7)	1 (0.4)	1 (0.4)	3 (0.5)	3 (0.5)
Somnolence	1 (0.3)	0	0	0	1 (0.2)	0
Psychiatric disorders	2 (0.6)	1 (0.3)	0	2 (0.8)	2 (0.3)	3 (0.5)
Agitation	1 (0.3)	0	0	0	1 (0.2)	0
Mental status changes	1 (0.3)	0	0	0	1 (0.2)	0
Hypervigilance	0	1 (0.3)	0	0	0	1 (0.2)
Insomnia	0	0	0	1 (0.4)	0	1 (0.2)
Hallucination	0	0	0	1 (0.4)	0	1 (0.2)
Renal and urinary disorders	0	1 (0.3)	0	1 (0.4)	0	2 (0.4)
Renal failure	0	1 (0.3)	0	0	0	1 (0.2)
Urinary tract pain	0	0	0	1 (0.4)	0	1 (0.2)
Reproductive system and breast disorders	0	0	1 (0.4)	1 (0.4)	1 (0.2)	1 (0.2)
Vulvovaginal pruritus	0	0	0	1 (0.4)	0	1 (0.2)
Vulvovaginal discomfort	0	0	1 (0.4)	0	1 (0.2)	0
Respiratory, thoracic and mediastinal disorders	0	0	1 (0.4)	0	1 (0.2)	0
Acute respiratory failure	0	0	1 (0.4)	0	1 (0.2)	0

	101.1.C.003		101.1.C.004		Pooled 003 and 004	
System Organ Class Preferred Term	**Vancomycin (N=323)**	**Fidaxomicin (N=300)**	**Vancomycin (N=260)**	**Fidaxomicin (N=264)**	**Vancomycin (N=583)**	**Fidaxomicin (N=564)**
Skin and subcutaneous tissue disorders	2 (0.6)	1 (0.3)	6 (2.3)	1 (0.4)	8 (1.4)	2 (0.4)
Pruritus	1 (0.3)	0	4 (1.5)	1 (0.4)	5 (0.9)	1 (0.2)
Erythema	0	0	2 (0.8)	0	2 (0.3)	0
Alopecia	0	0	0	1 (0.4)	0	1 (0.2)
Rash macular	0	0	1 (0.4)	0	1 (0.2)	0
Night sweats	0	0	1 (0.4)	0	1 (0.2)	0
Petechiae	0	0	1 (0.4)	0	1 (0.2)	0
Pruritus generalised	0	1 (0.3)	0	0	0	1 (0.2)
Dermatitis allergic	1 (0.3)	0	0	0	1 (0.2)	0
Vascular disorders	0	0	1 (0.4)	0	1 (0.2)	0
Hot flush	0	0	1 (0.4)	0	1 (0.2)	0

Serious adverse event/deaths/other significant events

There were no deaths or serious adverse events (SAE) among the healthy subjects in the phase 1 studies. In study OPT-80 Phase 2A, one patient died during the study due to a staphylococcal sepsis and a cerebral haemorrhage on Day 10, leading to death on Day 16. These events were considered by the investigator to be unrelated to study drug. Five patients were reported as having SAEs during the phase 2 study. In the 100 mg/day treatment group, one patient had diarrhoea (subsequently diagnosed as nephrolithiasis) of moderate severity and another had severe exacerbation of congestive heart failure. In the 200 mg/day treatment group, one patient had a GI haemorrhage of moderate severity, and another patient had chest pain of moderate severity. No patients in the 400 mg treatment group had an SAE. All SAEs reported in the phase 2 study were considered to be unrelated to study drug.

In the pooled phase 3 studies, a total of 38 and 36 deaths occurred among patients treated with vancomycin and fidaxomicin, respectively. The most common cause of death was sepsis, which was the cause of death for 7 patients (4 in the vancomycin group and 3 in the fidaxomicin group): followed by respiratory failure in 6 patients (2 versus 4), and pneumonia in 5 patients (2 versus 3). None of the deaths were considered to be related to administration of the study drug.

The overall incidence of SAEs in both studies was similar between the two treatment groups. About one quarter of patients experienced SAEs in both groups. FID-patients tended to experience more blood disorders (especially neutropenia, leucopenia), vascular disorders (1.8 % versus 0.7 %), AEs related to the SOC "Investigations" (blood uric acid increased and lymphocyte count), hyponatraemia, hypophosphataemia and hyperkalaemia. Only a low number of SAEs was considered as treatment-related: 4 patients in the FID-group. A causal relationship cannot be firmly excluded although patients' history and the concomitant/underlying medical conditions appeared as important confounding factors.

Regarding GI bleedings, regardless of causal relationship, 7 (1.2 %) cases of haematochezia were reported in FID-patients [versus 1 (0.2 %) in the VAN-group], 5 (0.9 %) cases of gastrointestinal haemorrhage [versus 1 (0.2 %) in the VAN-group], 4 (0.7 %) cases of diarrhoea haemorrhagic [versus none in the VAN-group], 1 case (0.2 %) of rectal haemorrhage [versus 2 (0.3 %) in the VAN-group] and no upper gastrointestinal haemorrhage [versus 1 (0.2 %) in the VAN-group]. An extended safety analysis in patients with gastro-intestinal bleeding events in the pooled data demonstrated that the incidence of all GI bleeding events was comparable between treatment groups, 4.1% in the fidaxomicin group vs. 3.1% in the vancomycin group. More than half of the GI bleeding events in both treatment groups occurred more than 5 days after the last dose of study drug. Amongst the GI bleeding events

that occurred during or closer to the study drug dosing period (i.e., with onset on or before Day 13), 2 of the 11 "early" GI bleeding events (18%) for fidaxomicin subjects were associated with an SAE, compared with 6 of the 10 "early" GI bleeding events (60%) for vancomycin subjects. The two fidaxomicin subjects who had "early" GI bleeding associated with an SAE both had undergone recent bowel resection prior to study enrolment, were on concomitant medications that could contribute to GI bleeding and only received a few doses of study drug.

In addition, despite fidaxomicin has a low absorption level, systemic AEs considered as drug-related were reported (e.g. hallucinations (with positive dechallenge), transaminases increase).

Nevertheless, no specific pattern and major safety concerns arose from these SAEs.

Table 34: SAEs Reported by > 2 Patients in either Treatment Group in the Phase 3 Studies (Safety Population)

	101.1.C.003		101.1.C.004		Pooled 003 and 004	
System Organ Class Preferred Term	**Vancomycin (N=323)**	**Fidaxomicin (N=300)**	**Vancomycin (N=260)**	**Fidaxomicin (N=264)**	**Vancomycin (N=583)**	**Fidaxomicin (N=564)**
Any SAE	78 (24.1)	75 (25.0)	58 (22.3)	70 (26.5)	135 (23.2)	145 (25.7)
Blood and lymphatic system disorders	6 (1.9)	7 (2.3)	2 (0.8)	6 (2.3)	8 (1.4)	13 (2.3)
Anaemia	1 (0.3)	4 (1.3)	1 (0.4)	0	2 (0.3)	4 (0.7)
Leucopenia	1 (0.3)	1 (0.3)	0	3 (1.1)	1 (0.2)	4 (0.7)
Neutropenia	0	0	0	4 (1.5)	0	4 (0.7)
Thrombocytopenia	2 (0.6)	0	0	3 (1.1)	2 (0.3)	3 (0.5)
Lymphopenia	1 (0.3)	1 (0.3)	1 (0.4)	2 (0.8)	2 (0.3)	3 (0.5)
Cardiac disorders	10 (3.1)	7 (2.3)	4 (1.5)	5 (1.9)	14 (2.4)	12 (2.1)
Cardiac failure congestive	2 (0.6)	4 (1.3)	1 (0.4)	1 (0.4)	3 (0.5)	5 (0.9)
Atrial fibrillation	1 (0.3)	3 (1.0)	0	1 (0.4)	1 (0.2)	4 (0.7)
Myocardial infarction	2 (0.6)	0	0	4 (1.5)	2 (0.3)	4 (0.7)
Gastrointestinal disorders	11 (3.4)	13 (4.3)	13 (5.0)	13 (4.9)	24 (4.1)	26 (4.6)
Gastrointestinal haemorrhage	1 (0.3)	4 (1.3)	0	0	1 (0.2)	4 (0.7)
Small intestine obstruction	0	1 (0.3)	3 (1.2)	0	3 (0.5)	1 (0.2)
Vomiting	0	1 (0.3)	3 (1.2)	1 (0.4)	3 (0.5)	2 (0.4)
Intestinal obstruction	0	1 (0.3)	1 (0.4)	3 (1.1)	1 (0.2)	4 (0.7)
Abdominal pain	1 (0.3)	1 (0.3)	0	3 (1.1)	1 (0.2)	4 (0.7)
Diarrhoea	2 (0.6)	2 (0.7)	1 (0.4)	1 (0.4)	3 (0.5)	3 (0.5)
Megacolon	0	2 (0.7)	0	1 (0.4)	0	3 (0.5)
General disorders and administrative site conditions	3 (0.9)	6 (2.0)	5 (1.9)	3 (1.1)	8 (1.4)	9 (1.6)
Pyrexia	1 (0.3)	1 (0.3)	2 (0.8)	2 (0.8)	3 (0.5)	3 (0.5)
Infections and infestations	30 (9.3)	21 (7.0)	20 (7.7)	23 (8.7)	50 (8.6)	44 (7.8)
Clostridium difficile colitis	6 (1.9)	3 (1.0)	3 (1.2)	5 (1.9)	9 (1.5)	8 (1.4)
Pneumonia	5 (1.5)	4 (1.3)	5 (1.9)	4 (1.5)	10 (1.7)	8 (1.4)
Sepsis	3 (0.9)	3 (1.0)	2 (0.8)	4 (1.5)	5 (0.9)	7 (1.2)
Urosepsis	2 (0.6)	1 (0.3)	2 (0.8)	1 (0.4)	4 (0.7)	2 (0.4)
Staphylococcus sepsis	2 (0.6)	1 (0.3)	1 (0.4)	0	3 (0.5)	1 (0.2)
Escherichia sepsis	1 (0.3)	0	2 (0.8)	0	3 (0.5)	0
Investigations	4 (1.2)	14 (4.7)	8 (3.1)	10 (3.8)	11 (1.9)	24 (4.3)
Blood uric acid increased	1 (0.3)	3 (1.0)	0	2 (0.8)	1 (0.2)	5 (0.9)
Lymphocyte count decreased	1 (0.3)	1 (0.3)	0	3 (1.1)	1 (0.2)	4 (0.7)
Metabolism and nutrition disorders	18 (5.6)	11 (3.7)	10 (3.8)	16 (6.1)	28 (4.8)	27 (4.8)
Hypokalaemia	4 (1.2)	0 (0.0)	2 (0.8)	2 (0.8)	6 (1.0)	2 (0.4)
Dehydration	3 (0.9)	0 (0.0)	1 (0.4)	2 (0.8)	4 (0.7)	2 (0.4)
Hyperglycaemia	3 (0.9)	1 (0.3)	3 (1.2)	2 (0.8)	6 (1.0)	3 (0.5)
Hyponatraemia	3 (0.9)	2 (0.7)	0	4 (1.5)	3 (0.5)	6 (1.1)
Hypoglycaemia	0	3 (1.0)	0	0	0	3 (0.5)

System Organ Class Preferred Term	101.1.C.003 Vancomycin (N=323)	 Fidaxomicin (N=300)	101.1.C.004 Vancomycin (N=260)	 Fidaxomicin (N=264)	Pooled 003 and 004 Vancomycin (N=583)	 Fidaxomicin (N=564)
Hypophosphataemia	0	3 (1.0)	0	2 (0.8)	0	5 (0.9)
Hyperkalaemia	1 (0.3)	2 (0.7)	1 (0.4)	3 (1.1)	2 (0.3)	5 (0.9)
Hyperuricaemia	2 (0.6)	1 (0.3)	2 (0.8)	1 (0.4)	4 (0.7)	2 (0.4)
Psychiatric disorders	4 (1.2)	1 (0.3)	1 (0.4)	1 (0.4)	5 (0.9)	2 (0.4)
Mental status changes	3 (0.9)	0 (0.0)	0	0	3 (0.5)	0
Renal and urinary disorders	4 (1.2)	5 (1.7)	3 (1.2)	6 (2.3)	7 (1.2)	11 (2.0)
Renal failure	3 (0.9)	1 (0.3)	1 (0.4)	3 (1.1)	4 (0.7)	4 (0.7)
Renal failure acute	1 (0.3)	4 (1.3)	2 (0.8)	0	3 (0.5)	4 (0.7)
Respiratory, thoracic and mediastinal disorders	13 (4.0)	10 (3.3)	11 (4.2)	8 (3.0)	24 (4.1)	18 (3.2)
Dyspnoea	3 (0.9)	1 (0.3)	0	0	3 (0.5)	1 (0.2)
Respiratory failure	3 (0.9)	2 (0.7)	3 (1.2)	3 (1.1)	6 (1.0)	5 (0.9)
Respiratory distress	0	1 (0.3)	0	2 (0.8)	0	3 (0.5)
Pulmonary oedema	2 (0.6)	1 (0.3)	2 (0.8)	1 (0.4)	4 (0.7)	2 (0.4)
Pneumonia aspiration	2 (0.6)	1 (0.3)	1 (0.4)	0	3 (0.5)	1 (0.2)

Note: SOCs values are representative of all SAEs for that particular SOC

Cardiac safety

There were no clinically significant changes in any vital signs parameters in either of the clinical studies. Preclinical studies on fidaxomicin do not indicate any signals on cardiac safety. Human clinical data on cardiac safety should preferably be based on a thorough QT study in healthy volunteers exposed for high doses of the study drug. Small differences in QTc time will be difficult to detect in patients due to underlying factors that may affect ECG parameters. Since fidaxomicin is poorly absorbed it was not considered feasible to expose healthy volunteers to supra-therapeutic levels needed for such a study. This is considered acceptable considering the lack of preclinical signals on cardiac safety.

In the phase IIA study, a trend might be suspected for increase in QT interval (uncorrected and corrected) with a dose-relationship. Mean change in QTcF for the 400 mg/day-group was 6.7 ± 20.32 ms. In addition, 2 patients (including one with a pacemaker for sick sinus syndrome) presented changes in QTcF ≥ 30 ms or ≥ 60 ms (1 each). The low number of patients in each treatment-group in this phase II study should be kept in mind and precludes any definite conclusions about effects of FID on QT-interval.

In phase III studies, the number of cases of changes of QTc (Bazett's or Fredericia's) and cases of QTc > 450 ms reported with FID were not statistically different from those reported with VAN. The applicant stated that an ad hoc analysis was performed in study 101.1.C.004 according to plasma levels of FID and its main metabolite but no details were provided in the submitted dossier. In response to the D120, the applicant further substantiated this issue. Overall, non-clinical studies did not show any major effect of FID and its main metabolite on QT-interval. Phase 2 study involved a limited number of patients and provided poorly suggestive and informative data. Phase 3 studies did not allow firm conclusions about the risk of inducing QT-interval prolongation of FID or its main metabolite.

The applicant did not perform any specific QTc study since he considers that very low plasma levels seen after FID dosing in healthy subjects makes such a study not feasible, making the necessary supratherapeutic exposure not achievable in volunteers.

Taking account of the poorly suggestive data on QT interval prolongation, no such study appears warranted. However, this issue is worth being closely monitored during postmarketing experience.

An additional subgroup analysis of patients with high plasma levels (fidaxomicin + OP-1118 ≥ 150 ng/ml) using pooled data from studies 03 and 04 showed no association between QTc prolongation and plasma levels of fidaxomicin or its major metabolite. Thus, no correlation between plasma levels of fidaxomicin or its main metabolite and QT-prolongation could be demonstrated.

Figure 5:

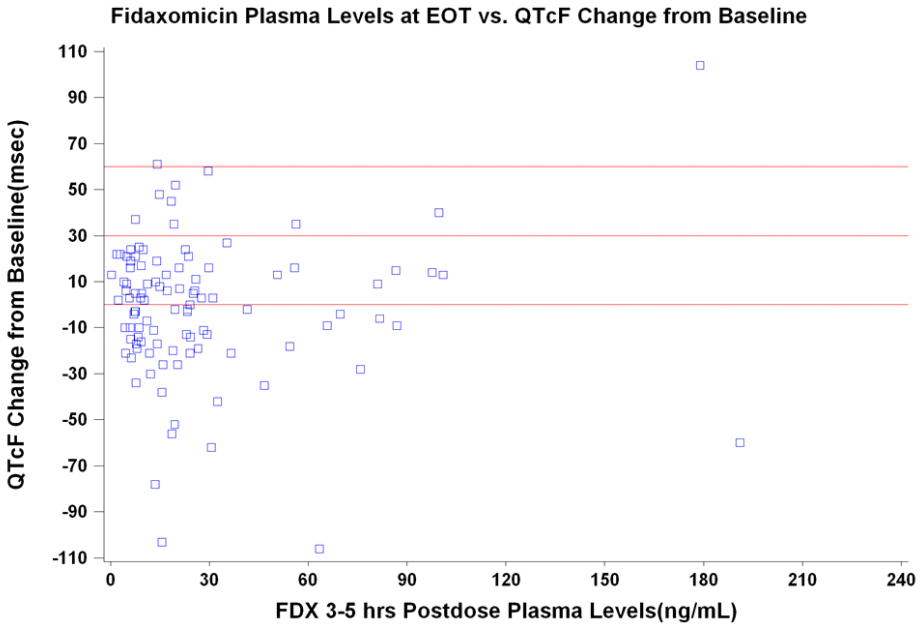
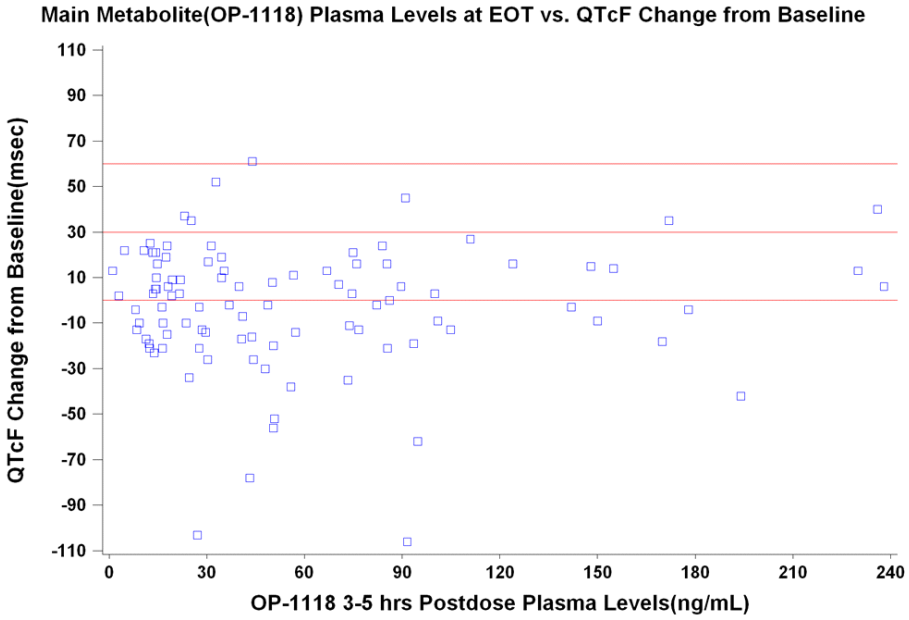


Figure 6:



From the data available, fidaxomicin and its main metabolite at concentrations up to10 µg/ml did not inhibit the hERG current and fidaxomicin had no pharmacologically relevant effect on QT interval, heart rate, blood pressure, PR interval, RR interval, QRS complex in conscious dogs. Thus, QT-interval prolongation does not seem to be a major safety concern with fidaxomicin.

Laboratory findings

There were no clinically significant abnormalities, and no consistent, drug-related changes in the serum chemistry, haematology, or urine analysis parameters throughout the study period in the phase 1 or phase 2 studies.

In the phase 3 studies, mean values were calculated from pre-treatment and end-of treatment measurements. Small changes in clinical laboratory values from baseline to the end of therapy were noted for each treatment. Changes in the WBC count, neutrophils, and electrolytes are consistent with resolving CDI.

Although the number of cases reported remained too low to draw definite conclusions, a trend appeared in both phase III studies for the FID-group for a higher incidence of low neutrophils count, low lymphocytes count, low WBC (some of them also reported as SAEs) and high ASAT/ALAT. The sponsor provided an extended safety analysis of all cases of markedly or clinically significant decreases in WBC, neutrophils or lymphocytes. Adverse events associated with a decrease in white blood cell (WBC) count parameter were more prevalent in the fidaxomicin arm (23 subjects in the fidaxomicin group versus 11 in the vancomycin group). Markedly abnormal low (worsened by two or more grades from the baseline toxicity grade) haematology values occurred at a higher incidence in the fidaxomicin group than the vancomycin group: lymphocytes (3.9% vs. 2.1%), leukocytes (1.6% vs. 0.8%), and neutrophils (1.4% vs. 0.2%). Nearly all of these shifts occurred in subjects with underlying haematological malignancies, recent bone marrow transplantation, and/or ongoing chemotherapy. The fidaxomicin arm had a higher incidence of pre-existing active blood and lymphatic disorders at enrolment compared to vancomycin subjects (38.7% versus 32.6%). The fidaxomicin arm also had a markedly higher prevalence of subjects concomitantly receiving treatment in the medication class of antineoplastic or immunomodulatory agents (67 subjects [11.9%] in the fidaxomicin group versus 48 subjects [8.2%] in the vancomycin group). None of the cases with a serious or markedly abnormal reduction in a WBC parameter in fidaxomicin treated patients were considered as related to the test drug by the investigator. Although it is acknowledged that the reduction in WBC was partly attributed to imbalances in underlying conditions, there was a consistent but small imbalance between treatment groups at fidaxomicin's disadvantage. Adverse events concerning decrease in white blood cell (WBC) count should be closely monitored and cumulatively reported in future PSURs.

The applicant provided a detailed analysis on cases with markedly or clinically significant changes in LFTs. The incidence of AEs involving liver function tests (LFTs; AST, ALT, alkaline phosphatase, and bilirubin) were similar between groups, 17 (3%) of the subjects in the fidaxomicin group and 14 (2.4%) subjects in the vancomycin group had investigations AE related to LFTs. The number of subjects with normal LFTs at baseline but a later LFT at least 3x the upper limit of normal (ULN) was 6 for fidaxomicin and 5 for vancomycin. No subjects in either group met Hy's Law. Five subjects in each group had a reported SAE involving abnormal LFTs. Narratives for these events were submitted, the majority were associated with underlying or concomitant conditions and the LFTs were basically recovered at the end of the investigation period. Due to the limited clinical experience of this novel drug, liver function adverse events shall be closely monitored and cumulatively reported in future PSURs.

Table 35: Summary of Clinically Significant Changes in LFTs in Phase 3 Studies (Safety Population)

Treatment group patient number	Age, sex, race	Study day	AST (U/L)	ALT (U/L)	Alkaline phosphatase (U/L)	Total bilirubin (mg/dL or µmol/L)[1]
101.1.C.003						
Vancomycin						
002050	86, F, W	Day 12	152 High	135 High		
016003	73, F, W	Day 10		125 High		
137006	65, F, W	Day 12			951 High	
Fidaxomicin						
017011	48, F, W	Day 12				38 High
135003	81, F, W	Day 11	202 High	211 High		
144013	75, F, W	Day 10		315 High		
101.1.C.004						
Vancomycin						
055002	74, M, W	Day 4	136 High	613 High		47 High
119002	38, M, B	Day 12	240 High			
200006	27, F, W	Day 12		105 High		
Fidaxomicin						
057010	70, M, W	Day 14		288 High		
069008	36, F, W	Day 10	306 High			
087006	65, M, B	Day 11		174 High		
088025	57, M, W	Day 10			418 High	
088026	58, M, W	Day 5				57 High
140001	77, M, W	Day 11	175 High	340 High	989 High	
146002	29, M, W	Day 10		200 High		
180009	53, F, A	Day 14	121 High	291 High		
180016	77, F, W	Day 4		99 High		
184001	90, F, W	Day 10	138 High	102 High		

Safety in special populations

No analysis of safety data by intrinsic or extrinsic factors was carried out. However, although pharmacokinetics did not appear to be influenced by age, gender and race, and even if the number of patients was low for some subpopulations, it would be relevant to perform a safety analysis by intrinsic factors. According to the applicant, 12 patients with hepatic impairment were enrolled in phase III studies but no specific safety analysis has been provided. Although the number of patients with hepatic or renal impairment will remain too limited to draw definite conclusions and PK parameters did not appear to be influenced by organ impairment, it would be relevant to perform a safety analysis by severity of renal/hepatic impairment. The applicant submitted such an analysis on CHMP request. Regarding renal insufficiency and hepatic insufficiency, the numbers of FID- and VAN-patients in each group are too limited to conclude on a safety profile in these populations (e.g. 63 and 73 for moderate renal insufficiency; 74 and 82 for severe renal insufficiency; 17 and 21 for hepatic insufficiency).

These populations will have to be closely monitored during postmarketing experience (see RMP).

Safety related to drug-drug interactions and other interactions

No drug interaction studies or analyses in relevant patient population have been completed to date.

Discontinuation due to adverse events

No subjects receiving fidaxomicin discontinued participation in the phase 1 studies or phase 2A due to an AE. In the phase 3 studies, compliance to treatment was high for both fidaxomicin and vancomycin with approximately 91% of the overall prescribed doses administered in both treatment groups.

Discontinuation due to adverse events was low in both studies with no apparent difference between treatment groups (< 10% across treatment groups). The TEAEs leading to withdrawal were similar in the two studies, and between the two treatment groups in either study.

Table 36: Treatment Emerging Adverse Events Reported by > 1 Patient in either Treatment Group in Phase 3 Studies for which Drug was Stopped Permanently or the Patient Discontinued From the Study (by SOC and PT) (Safety Population)

	101.1.C.003		101.1.C.004	
System Organ Class Preferred Term	**Vancomycin (N=323) n (%)**	**Fidaxomicin (N=300) n (%)**	**Vancomycin (N=260) n (%)**	**Fidaxomicin (N=264) n (%)**
Any Adverse Event	29 (9.0)	23 (7.7)	20 (7.7)	22 (8.3)
Cardiac disorders	2 (0.6)	0 (0.0)	3 (1.2)	1 (0.4)
Myocardial infarction	2 (0.6)	0 (0.0)	0	1 (0.4)
Cardio-respiratory arrest	0	0	2 (0.8)	0
Gastrointestinal disorders	3 (0.9)	8 (2.7)	7 (2.7)	6 (2.3)
Megacolon	0 (0.0)	2 (0.7)	0	0
Vomiting	0 (0.0)	2 (0.7)	3 (1.2)	1 (0.4)
Nausea	0	0	2 (0.8)	0
Abdominal pain	0	0	0	2 (0.8)
Infections and infestations	7 (2.2)	4 (1.3)	3 (1.2)	5 (1.9)
Sepsis	3 (0.9)	1 (0.3)	0	0
Pneumonia	1 (0.3)	3 (1.0)	1 (0.4)	1 (0.4)
Injury, poisoning and procedural complications	3 (0.9)	1 (0.3)	1 (0.4)	0
Wound dehiscence	2 (0.6)	0 (0.0)	0	0
Metabolism and nutrition disorders	4 (1.2)	0 (0.0)	1 (0.4)	1 (0.4)
Dehydration	2 (0.6)	0 (0.0)	0	1 (0.4)
Psychiatric disorders	4 (1.2)	0 (0.0)	0	1 (0.4)
Confusional state	2 (0.6)	0 (0.0)	0	0
Mental status changes	2 (0.6)	0 (0.0)	0	0
Respiratory, thoracic and mediastinal disorders	5 (1.5)	2 (0.7)	1 (0.4)	2 (0.8)
Respiratory failure	4 (1.2)	1 (0.3)	0	1 (0.4)

Note: SOCs values are representative of all SAEs for that particular SOC

In addition, treatment-emergent AEs leading to dose reduction or temporary medication stoppage were reported in the pooled phase 3 studies by 8 patients in the vancomycin group (bradycardia, arteriovenous fistula thrombosis, nausea and vomiting, anaemia, upper abdominal pain, pyrexia, panic attack, acute respiratory failure and hypotension) and two patients in the fidaxomicin group (nausea and vomiting).

Post marketing experience

There was no post-marketing experience for fidaxomicin at time of Marketing Authorisation application.

2.6.1. Discussion on clinical safety

The current safety data-base consists of a total of 660 patients with mild to moderately severe *C. difficile* associated disease treated up to 10 days with fidaxomicin which may be considered acceptable for single treatment episodes of the study drug. The clinical studies included a large number of elderly patients and a relatively large number of patients with severe disease according to ECMID criteria. Patients with fulminant colitis and patients with inflammatory bowel diseases (ulcerative colitis and Crohn's disease), were excluded from the study.

The clinical studies indicate that both fidaxomicin and vancomycin was well tolerated by the patients, which is in line with the low systemic exposure of these drugs when administered orally. The most frequent drug-related TEAEs in the pooled analysis were nausea, hypokalaemia, headache, vomiting and abdominal pain. The safety profile in general and considering drug-related events was very similar between the treatment groups and between studies.

Adverse events associated with a decrease in white blood cell (WBC) count parameter were more prevalent in the fidaxomicin arm (23 subjects in the fidaxomicin group versus 11 in the vancomycin group). When analysing underlying haematological malignancies, recent bone marrow transplantation, and/or ongoing chemotherapy it was revealed that the difference between the treatment groups can be at least partially explained by underlying comorbidities and by the underlying differences in the proportion of subjects receiving chemotherapeutic agents.

A higher number of patients in the fidaxomicin groups presented with increased transaminases, mainly driven by study 04. A shift from normal values at baseline to high values at a later time point for ALT and AST were seen in approximately 10% of subjects, and was similar in the fidaxomicin and vancomycin groups. Approximately 5% of subjects in each group had a shift from normal to high alkaline phosphatise. The number of subjects with normal LFTs at baseline but a later LFT at least 3x the upper limit of normal (ULN) was 6 for fidaxomicin and 5 for vancomycin. There did not appear to be a correlation with plasma concentrations of fidaxomicin.

Due to the limited clinical experience of this novel drug, close monitoring of laboratory parameter events including haematological and hepatic data should be performed with cumulative reporting in future PSURs.

Safety assessment in acutely-ill patients with severe diarrhoea and a significant degree of co-morbidity is complex and complicated by the fact that the disease itself can induce reactions such as electrolyte disturbances, nausea, abdominal pain, gastrointestinal bleeding and other symptoms. Serious events including death were reported in the phase 3 studies. However these appear to be consistent with the clinical condition of individual patients and were reported by a similar rate in the two treatment arms. The highest frequency of serious adverse events (SAEs) was reported in the SOC Infections and Infestations. The most frequent preferred terms in the pooled analysis were pneumonia, Clostridium difficile colitis, sepsis and respiratory failure. The SAEs neutropenia, blood uric acid increased, hypophosphataemia and gastrointestinal haemorrhage occurred more commonly in the fidaxomicin group, irrespective of relatedness of the study drug. Regarding elevated uric acid levels, an imbalance of underlying conditions (history of gout, hyperuricaemia and/or other serum chemistry abnormities) seem to explain the differences between treatment groups. Fidaxomicin exposure per se, i.e. serum levels of the parent compound or the metabolite, does not seem to have an impact on serum uric acid levels.

All but one of hypophosphataemia reports was demonstrated to be attributable to subject's underlying co-morbidity, such as impaired renal function. There was no clear correlation with CDI severity. However, as a precautionary measure, due to the limited clinical experience of this novel drug, the adverse events blood uric acid increased, hypophosphataemia should be closely monitored with cumulative reporting in future PSURs.

Gastrointestinal bleeding is of specific concern for a drug aimed at treating severe diarrhoea. The extended analysis demonstrated that the incidence of all GI bleeding events was comparable between treatment groups 4.1% vs. 3.1%, respectively. Amongst the GI bleeding events that occurred during or closer to the study drug dosing period (i.e., with onset on or before Day 13), 2 of the 11 "early" GI bleeding events (18%) for fidaxomicin subjects were associated with an SAE, compared with 6 of the 10 "early" GI bleeding events (60%) for vancomycin subjects. Narratives of each GI bleeding event did not raise any increased concerns regarding the role of fidaxomicin as a cause to gastrointestinal

haemorrhage. Although the current data do not indicate any enhanced risk for fidaxomicin to cause GI bleeding, a close monitoring of these advert events with cumulative reports in future PSURs is recommended due to the limited clinical data presently available for this new class of drugs.

There were no clinically significant changes in any vital sign criteria in either of the clinical studies and no significant difference between the treatment groups. No QT study in healthy volunteers was preformed due to the limited absorption of the drug which is considered acceptable considering the lack of preclinical signals on cardiac safety. No clinical significant changes from baseline to EOT in mean ECG parameters were seen in patients participating in the phase 3 studies and no evidence of QTc prolongation by fidaxomicin was identified. However, due to a trend from phase IIA, this issue will have to be monitored in post marketing.

Discontinuation due to adverse events was low in both phase 3 studies with no apparent difference between treatment groups.

Patients with inflammatory bowel diseases were excluded from the studies. As absorption from the gastro-intestinal tract may be increased in these patients, the safety profile may be different in this patient population. This is addressed as important missing information in the RMP and the Applicant should perform close post-marketing surveillance and report cumulatively in future PSURs, in order to generate safety data in this patient group.

Clostridium difficile associated diarrhoea is associated with a high incidence of recurrences. It is reported that up to a third of patients experience recurrences after successful treatment with metronidazole or vancomycin. Some patients suffer of repeated treatment failures and frequent recurrences leading to a substantial impact on the quality of life. The Applicant has committed to perform a post-authorisation clinical study to investigate the safety and efficacy of repeated use of fidaxomicin, in patients subjected to repeated treatment with fidaxomicin.

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

Additional expert consultations

None

2.6.2. Conclusions on the clinical safety

The available safety data, mainly based on two pivotal studies, indicate that fidaxomicin is well tolerated with a safety profile similar with that of vancomycin when used in the treatment of *C. difficile* infection. Fidaxomicin is a new drug with no previous clinical experience to support the safety profile. However, the available non-clinical and clinical safety data indicate that the benefit-risk balance in the applied indication may be considered to be positive.

A post-authorisation clinical study to investigate the safety (and efficacy) of repeated use of fidaxomicin and a post marketing drug utilization study to further assess the use of fidaxomicin in standard clinical practice have been planned (RMP measures).

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management Plan

The applicant submitted a risk management plan

Table 37: Summary of the risk management plan

Safety concern	Agreed pharmacovigilance activities (routine and additional)	Agreed risk minimisation activities (routine and additional)
Important identified risks		
None		
Important potential risks		
Development of resistance to fidaxomicin	A post-marketing surveillance program to monitor isolated strains of *C. difficile* for changes in antimicrobial resistance patterns.	Section 5.1 - Mechanism of Resistance
Important missing information		
Patients with severe renal impairment	Routine pharmacovigilance. Patients with severe renal impairment will be prioritized during signal detection. AEs will be analyzed cumulatively in future periodic safety reports. Additional Pharmacovigilance: Non-interventional study of the use of fidaxomicin in standard clinical practice.	Section 4.4 - Special Warnings and Precautions for use
Patients with severe and moderate hepatic impairment	Routine pharmacovigilance. Patients with severe and moderate hepatic impairment will be prioritized during signal detection. AEs reported will be analyzed cumulatively in future periodic safety reports. Additional Pharmacovigilance: Non-interventional study of the use of fidaxomicin in standard clinical practice.	Section 4.4 - Special Warnings and Precautions for use
Repeated fidaxomicin treatment courses	A post-marketing clinical study to investigate the safety and efficacy of repeated use of fidaxomicin.	Section 4.4 - Special Warnings and Precautions for use
Patients with inflammatory bowel disease (Crohn's disease, ulcerative colitis)	Routine Pharmacovigilance. Patients with IBD will be prioritized during signal detection. AEs reported will be analyzed cumulatively in future periodic safety reports.	Section 4.4 - Special Warnings and Precautions for use

Safety concern	Agreed pharmacovigilance activities (routine and additional)	Agreed risk minimisation activities (routine and additional)
	Additional Pharmacovigilance: Non-interventional study of the use of fidaxomicin in standard clinical practice.	
Patients with life threatening or fulminant CDI, including pseudomembranous colitis	Routine pharmacovigilance. Patients with life threatening or fulminant CDI, including pseudomembranous colitis, will be prioritized during signal detection. AEs reported will be analyzed cumulatively in future periodic safety reports. Additional Pharmacovigilance: Non-interventional study of the use of fidaxomicin in standard clinical practice.	Section 4.4 - Special Warnings and Precautions for use
Data in pregnant patients	Routine pharmacovigilance. Pregnant patients will be prioritized during signal detection. AEs reported will be analyzed cumulatively in future periodic safety reports. Additional Pharmacovigilance: Non-interventional study of the use of fidaxomicin in standard clinical practice.	Section 4.6 - Pregnancy and lactation
Data in paediatric patients	Routine Pharmacovigilance Paediatric patients will be prioritized during signal detection. AEs reported will be analyzed cumulatively in future periodic safety reports. Additional Pharmacovigilance: Paediatric Investigational Plan (PIP)	Section 4.2 – Posology and method of administration
Co-administration of potent inhibitors of P-gp.	Routine pharmacovigilance.	Section 4.4 - Special Warnings and Precautions for use
Impact of fidaxomicin on intestinal efflux transporters (BCRP,	Routine pharmacovigilance	

Safety concern	Agreed pharmacovigilance activities (routine and additional)	Agreed risk minimisation activities (routine and additional)
MRP2, OAP2B1)	Additional Pharmacovigilance: Ongoing in vitro studies; results due Q4 2011	

The CHMP, having considered the data submitted, was of the opinion that the below pharmacovigilance activities in addition to the use of routine pharmacovigilance are needed to investigate further some of the safety concerns:

Description	Due date
In vitro studies on intestinal efflux transporters	4Q2011
Post-marketing surveillance programme to monitor isolated strains of *C.difficile* for changes in antimicrobial resistance patterns	Reports with each PSUR submission
A clinical study to investigate the safety and efficacy of repeated use of fidaxomicin	Progress reports with each PSUR submission.
A drug utilisation study of the use of fidaxomicin in standard clinical practice	Progress reports with each PSUR submission.
Paediatric investigational plan: 1. Open-label study of fidaxomicin oral suspension and tablets in paediatric patients aged 2 to less than 18 years with *C. difficile* associated disease 2. Open-label, parallel group study of fidaxomicin oral suspension and tablets with vancomycin oral suspension and capsules in paediatric patients aged 2 years to less than 18 years with *C. difficile* associated disease 3. Open-label, parallel group study of fidaxomicin oral suspension and tablets with vancomycin oral suspension and capsules in paediatric patients aged 1 to less than 24 months with *C. difficile* associated disease 4. Study to determine the role of *C.difficile* in the pathogenesis of disease observed neonates and to investigate the feasibility of a study to evaluate safety, efficacy and PK of fidaxomicin oral suspension in neonates with *C. difficile* associated disease 5. Study to evaluate safety, efficacy and PK of fidaxomicin oral suspension in neonate with *C. difficile* associated disease	By December 2014

Study protocols including relevant milestones and timelines for the two post-approval studies (repeated use and drug utilisation study) shall be submitted to the CHMP within 3 months after Commission Decision

No additional risk minimisation activities were required beyond those included in the product information.

2.8. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

3. Benefit-Risk Balance

Benefits

Beneficial effects

Fidaxomicin represents a novel class of antibacterials, the 18-membered macrocyclic antibacterial drugs. Due to its unique mechanism of action which is distinct from that of any other class of antimicrobials the potential of cross-resistance to other antibiotic classes is anticipated to be low. The relatively low absorption of fidaxomicin ensures that a high concentration in the entire intestinal tract is maintained after oral administration. Its concentrations in the stool largely exceed the MIC of *C difficile* (up to 5 000 x MIC_{90} for *C. difficile*). In combination with the narrow spectrum of fidaxomicin and its main metabolite directed primarily against Clostridium species, an in vitro demonstrated anti-spore activity and the significant post-antibiotic effect, these features are beneficial characteristics for a drug in the applied indication CDI.

The non-inferiority of fidaxomicin compared to orally administrated vancomycin was demonstrated in two randomized double-blind controlled phase 3 studies in patients with mild to moderately severe *C. difficile* infection. The primary efficacy variable was clinical cure at end of therapy which was achieved for 92% in the fidaxomicin group and in 90% in the vancomycin group, in the PP population (Difference 1.7; 95% CI -1.7 – 5.3). Superiority was shown for secondary endpoints, recurrence rate (14% vs. 26%) and global cure rate (76% vs. 64%) for fidaxomicin and vancomycin, respectively (mITT-population), within 30 days after discontinuation of treatment. These results are considered highly clinically relevant, since recurrence of CDI is an acknowledged challenge with currently available treatments. The reduction in recurrences compared to vancomycin was mainly attributed to fewer recurrences the first two weeks after EOT, thus fidaxomicin appears to be associated with lower rate of relapses (likely with the same strain) while late recurrences (likely re-infection with a new strain) were equally common in both treatment groups. The recurrence rates within 30 days post-treatment were consistently significantly higher in the vancomycin groups compared to the fidaxomicin groups in both the PP and mITT populations. Subgroup analyses indicated consistent numerical superior outcome for fidaxomicin treated patients also in subgroups generally associated with inferior cure rates, including severe disease (as judged by the investigator or using ESCMID criteria), high age, prior episode of CDI, concomitant systemic antibiotic and inpatient status. Also global cure rates were consistently more favourable for the fidaxomicin treated patients. Global cure is considered a crucial endpoint since this endpoint may be considered most meaningful for the patient, taking the high recurrence rates

after current available therapeutic options into account (20 to 30% recurrence rates have been reported after initial successful treatment with vancomycin or metronidazole).

The studied patient population seems to be generally representative for the target population, including a high number of elderly patients with almost 50% of patients ≥ 65 years and approximately 65% being hospitalised and a sufficient number of patients infected with the hypervirulent BI/027 strain (approximately 25%). While study 03 only enrolled patients from North America approximately 40% of patients included in study 04 were from European sites. Gender or ethnicity did not have an impact on the clinical response.

Uncertainty in the knowledge about the beneficial effects

More than 70% of included patients were considered by the investigators to have moderate to severe infection, but there is a lack of validated severity scoring index systems. Patients were generally comparable between treatment groups for reported baseline characteristics. However, data from several important subgroups of patients, such as patients with pseudomembranous colitis, patients with multiple recurrences of CDI, patients with IBD and patients with impaired renal and impaired hepatic function, are missing, which is addressed in the SmPC and in the RMP.

Patients with multiple occurrences of CDI (defined as more than 1 prior occurrence within the past 3 months) were excluded from the studies. This group of patients currently constitutes a real clinical challenge and there is an urgent need for improved treatment alternatives leading to sustained cure. In addition, no data on repeated treatment with fidaxomicin have been presented. The Applicant has committed to perform a post-authorisation study in patients receiving repeated treatment with fidaxomicin, which is addressed in the RMP.

Risks

Unfavourable effects

Fidaxomicin is an NCE and the first representative in this novel antibacterial class of macrocycles, thus no clinical experience of this or similar drugs is available. The current safety data-base may be considered very small and consists of a total of 660 patients with mild to moderately severe *C. difficile* associated diarrhoea treated up to 10 days with fidaxomicin.

The clinical studies indicate that fidaxomicin is well tolerated and has a safety profile in line with that of orally administered vancomycin. The most frequent drug-related TEAEs in the pooled analysis were nausea, hypokalaemia, headache, vomiting and abdominal pain. The safety profile in general and considering drug-related events was very similar between the treatment groups and between studies.

Serious events including death were reported in both phase 3 studies, however these appear to be consistent with the clinical condition of individual patients and were reported by a similar rate in the two treatment arms. The highest frequency of serious adverse events (SAEs) was reported in the SOC Infections and Infestations. The most frequent preferred terms in the pooled analysis were pneumonia, *C. difficile* colitis, sepsis and respiratory failure. The SAEs neutropenia, blood uric acid increased, hypophosphataemia and gastrointestinal haemorrhage occurred more commonly in the fidaxomicin group. Although confounding factors such as underlying conditions and concomitant medications seemed to at least partly contribute to these imbalances between treatment groups, these adverse events should be closely monitored and cumulatively reported in future PSURs.

There was an imbalance in significant changes in liver function tests parameters between treatment groups, with higher number of patients in the fidaxomicin groups presenting increased transaminases, mainly driven by study 04. The majority were associated with underlying or concomitant conditions

and the LFTs were basically recovered at the end of the investigation period. Five subjects in each group had a reported SAE involving abnormal LFTs. There did not appear to be a correlation with plasma concentrations of fidaxomicin.

Uncertainty in the knowledge about the unfavourable effects

Safety assessment in acutely-ill patients with severe diarrhoea and a significant degree of co-morbidity is complex and complicated by the fact that the disease itself can induce reactions such as electrolyte disturbances, nausea, abdominal pain, gastrointestinal bleeding and other symptoms.

Patients with fulminant colitis and patients with inflammatory bowel diseases were excluded from the studies. As absorption from the gastrointestinal tract may be increased in these patients, the safety profile may be different in these patient populations, which is addressed in the RMP as well as in the Product Information. Exposure is also increased in patients with hepatic impairment and in patients with co-administration of P-gp inhibitors. Caution should be advised in patients with moderate to severe hepatic impairment and co-administration of potent P-gp inhibitors should be avoided.

In addition the present uncertainty regarding plasma levels in CDI patients have implications for the evaluation of exposure margins.

Fidaxomicin is a new chemical entity without previous experience in clinical practice and although absorption may be considered relatively low, it cannot be ruled out that levels of systemic exposure may lead to potential safety effects, especially in patients with damaged intestinal mucosa, such as patients with severe CDI and patients with inflammatory intestinal diseases. The presented safety data base is considered very small for an NCE and safety data are currently missing in patients subjected to repeated use of fidaxomicin. Also potential emergence of resistance in the clinical setting is unknown which is addressed in the RMP and in the SmPC. Information on repeated use of fidaxomicin is missing which is addressed in the RMP. The applicant has committed to perform a post-approval study in patients receiving repeated use of fidaxomicin as well as performing a post marketing non-interventional study to further assess the use of fidaxomicin in standard clinical practice. Due to the limited clinical experience of this novel drug, monitoring of adverse events concerning laboratory parameters including haematological and hepatic data should be performed with cumulative reporting in future PSURs.

Benefit Risk Balance

Importance of favourable and unfavourable effects

The fact that fidaxomicin belongs to a novel antibiotic class is considered important from an antibiotic resistance perspective, limiting the risks for cross-resistance. A limited disruption on the normal intestinal flora as well as activity against *C. difficile* spores is considered valuable, since it may contribute to lesser frequency of recurrences. The non-inferiority to vancomycin in clinical cure rates and in particular the superiority in global cure rates, in particular concerning relapses, is very promising, considering the major negative consequences of repeated recurrences, both for the society and for the individual subject.

Data from the current studies indicate that fidaxomicin is well tolerated with a safety profile in line with vancomycin. However, there are several uncertainties remaining, related to potentially increased systemic exposure in patients with impaired hepatic function and in patients with increased absorption of the drug (either due to damage intestinal mucosa or during co-administration of P-gp inhibitors), as well to lack of data in important groups of patients. These uncertainties are stated in the Product information and adequately addressed in the RMP.

Benefit-risk balance

The severity of the disease and the medical need for new agents to treat CDI should be considered along with the unknown risks of this novel drug especially related to seriously ill patients with severely damaged intestinal mucosa. At the present stage, the benefit – risk relationship for fidaxomicin in the treatment of CDI is considered to be favourable.

Discussion on the Benefit Risk Balance

The benefit-risk for fidaxomicin should be weighed to that of currently available treatment options for CDI, vancomycin and metronidazole. Both these drugs are hampered by several drawbacks. CDI is a significant and increasing medical problem, and an effective and safe treatment alternative is urgently needed. The current data base for fidaxomicin may be considered sufficiently demonstrating the benefits of fidaxomicin in the sought indication, provided that adequate post-marketing activities, as guided in the RMP, are adhered to.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Dificlir indicated in adults for the treatment of *Clostridium difficile* infections (CDI) also known as *C. difficile*-associated diarrhoea (CDAD) (see section 5.1) is favourable and therefore recommends the granting of the marketing authorisation 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

Risk Management System and PSUR cycle

The MAH must ensure that the system of pharmacovigilance, presented in Module 1.8.1 of the marketing authorisation, is in place and functioning before and whilst the product is on the market.

The MAH shall perform the pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in the Risk Management Plan (RMP) presented in Module 1.8.2 of the marketing authorisation and any subsequent updates of the RMP agreed by the CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted:

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- at the request of the EMA

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

Not applicable.

Obligation to complete post-authorisation measures

Not applicable.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

New Active Substance Status

Based on the CHMP review of data on the quality, non-clinical and clinical properties of the active substance, the CHMP considers that fidaxomicin is to be qualified as a new active substance.