Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for Fidaxomicin

Proprietary Product Name: Dificid

Sponsor: Specialist Therapeutics Australia Pty

Date of first round CER August 2012

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TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <http://www.tga.gov.au>.

About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

Contents

1. Clinical rationale

Clostridium difficile is a gram-positive, spore-forming, obligate anaerobic bacterium. It is the leading cause of nosocomial diarrhoea in patients undergoing antibiotic treatment and sometimes chemotherapy. The *Clostridium difficile*-Associated Disease (CDAD) is the result colonisation and production of enterotoxins A and B by this organism in large intestine. The severity of disease can range from mild diarrhoea to fulminant pseudomembranous colitis with complication like toxic megacolon and intestinal perforation. The reported mortality rates range from 6 to 30%. Community acquired CDAD is also recognised, which case may not be associated with known antibiotic use.

The term *Clostridium difficile* Infection (CDI) is used interchangeably with CDAD. However, CDAD is preferred in this report as it is unambiguous with respect to intestinal colonisation and disease.

In North America and the European Union, outbreaks of CDAD associated with the emergence of a hypervirulent strain have occurred. The strain is variously known as Toxinotype III, North American Pulsed-field type 1 (NAP1), Restriction Endonuclease Analysis (REA) type BI or Polymerase Chain Reaction ribotype 027 (NAP1/BI/027). This strain has been shown, *in vitro*, to produce 16 to 23 times more toxins A and B than other strains. It also produces a binary toxin.

The current treatment options in management of CDAD include discontinuation of the offending medication, supportive measures and antimicrobials. The two most commonly used antibiotics to treat CDAD are oral vancomycin and metronidazole. Both are associated with a high rate of clinical recurrence. Oral vancomycin is the only antibiotic approved for use in the treatment of CDAD in Australia and acts locally unlike metronidazole which is absorbed well acts systemically after oral administration.

The rationale put forward for investigation of fidaxomicin for use in CDAD include the need for a narrow spectrum bactericidal agent against *Clostridium difficile* with low potential for development of resistance or cross resistance and minimal systemic absorption.

Guidance

The TGA adopted guidelines include 'Points to consider on Pharmacokinetics and Pharmacodynamics in the development of antibacterial medicinal products' accessible from <http://www.tga.gov.au/pdf/euguide/ewp265599en.pdf>.

2. Contents of the clinical dossier

2.1. Scope of the clinical dossier

The clinical studies supporting this application comprise 1 food study, 1 single dose pharmacokinetics (PK) study and 1 multiple dose PK study. There are 3 drug-drug PK interaction studies. All PK studies were in healthy adult volunteers.

There is one Phase II dose selection study and two Phase III pivotal clinical trials. These three studies were carried out in adult patients with CDAD.

A study to ascertain absolute bioavailability of fidaxomicin has not been performed. A justification for included in the dossier. The factors supporting this course of action included local (non-systemic) mode of action, localised pathology for which usage is being sought, well-characterised and simple metabolic fate.

2.2. Paediatric data

This submission does not contain paediatric data.

2.3. Good clinical practice (GCP)

The clinical studies included in this submission are stated to have complied with the GCP and the applicable ethical standards of human research.

3. Pharmacokinetics

3.1. Pharmacokinetics in healthy subjects and food effect

3.1.1. Study OPT-80-005

This was a study of investigation of relative bioavailability of oral fidaxomicin when taken with food compared to administration in fasted state.

The food study was preceded by a lead-in group of 6 healthy adult volunteers for assessment of single dose pharmacokinetics of fidaxomicin (Group 1), followed by randomised, open-label, 2 treatment periods, crossover study for the assessment of food effect on systemic bioavailability of fidaxomicin in healthy adult volunteers (Group 2).

The primary objective was to ascertain whether systemic bioavailability of fidaxomicin was influenced by its oral administration with or without food in healthy adult volunteers. The pharmacokinetic parameters of fidaxomicin (OPT-80) and its major metabolite (OP-1118) were both assessed in plasma. A secondary objective was to analyse levels of fidaxomicin and OP-1118 in urine and faeces.

Group 1

This was a lead-in group in which a single 200 mg oral dose of fidaxomicin was initially administered to 6 healthy adult volunteers (3 males, 3 females) in fasting state. The mean age of the group was 35 years.

The plasma samples were collected before dosing (predose/baseline) and at 0.25, 0.5, 1, 1.5, 2, 4, 6, 8, 12, and 24 h after the dose. Urine was collected at baseline and at 0-4, 4-8, 8-12, and 12-24 h post-dose. Faecal samples were collected at baseline and for 5 days post-dose.

Group 2

This was a randomised, 2 treatment periods, 2 way crossover study of a single 400 mg oral dose of fidaxomicin in healthy adult volunteers. The dose was doubled to 400 mg compared to the lead-in group in order to ensure sufficient data points for pharmacokinetic analyses.

A total of 28 healthy volunteers were randomised and completed the study. The mean age of the group was 32 years with equal number of men and women.

The participants in Group 2 received the treatment in the two periods in a randomised manner as follows:

Period 1 (**Treatment A =** 400 mg fidaxomicin administered orally in fasting state.

Period 2 (**Treatment B =** 400 mg fidaxomicin administered orally with food (high fat meal).

There was a washout interval of 7 days between the two treatment periods. The pharmacokinetic blood samples were collected prior to dosing and at 0.25, 0.5, 1, 1.5, 2, 4, 6, 8, 12, and 24 h after dosing.

Urine samples were collected at baseline and at 0-4, 4-8, 8-12, and 12-24 h post-dose in Period 1 only. Faecal samples were collected at baseline and for 5 days post-dose in Period 1 only.

The reported results were as follows:

- Following oral administration of 200 mg fidaxomicin in lead-in group (Group 1) under fasting conditions, the T_{max} ranged from 1 to 8 h for both OPT-80 and its metabolite OP-1118. There were insufficient data to calculate $AUC_{0-¥}$ and half-life ($t_{1/2}$) for OPT-80. The mean (SD)[1] $t_{1/2}$ of OP-1118 was 8.36 (2.03) hours.
- Following oral administration of 400 mg fidaxomicin in Group 2 under fasting conditions (Treatment A), the T_{max} ranged from 5-8 h for OPT-80 with a median of 1 hour and 1-8 h for OP-1118 with a median of 1 hour. The mean $t_{1/2}$ was 9.64 (2.56) h and 10.1 (1.9) h for OPT-80 and OP-1118 respectively.
- The increase in OPT-80 dose level under fasting conditions from 200 mg (Group 1) to 400 mg (Group 2) did not result in proportional increase in OPT-80 C_{max} (9.88 versus 10.6 ng/mL) and AUC_{0-t} (69.5 versus 81.2 ng.h/mL) levels or OP-1118 C_{max} (17.6 versus 25.5 ng/mL) or AUC_{0-t} (136 versus 172 ng.h/mL).
- Following oral administration of 400 mg fidaxomicin in Group 2 under fed conditions (Treatment B), OPT-80 C_{max} was 21.5% lower (7.52 versus 10.6 ng/mL) and OP-1118 C_{max} was 33.4% lower (15.7 versus 25.5 ng/mL) in fed state compared to fasting state. The median T_{max} was prolonged in fed state compared to the fasted state (2 versus 1 hour respectively) for both OPT-80 and OP-1118. The total systemic exposures (AUC_{0-t}) to OPT-80 (78.6 versus 81.2 ng.h/mL) and OP-1118 (156 versus 172 ng.h/mL) were somewhat lower under fed state compared to fasting state.

The statistical comparison gave the following results:

- The fed/fasted (test/reference) ratio for OPT-80 C_{max} (peak systemic exposure) was 78.5% (90%CI 67% to 92%) indicating breach on the lower side of the conventionally accepted equivalence margin of 80-125%.
- The fed/fasted ratio for OPT-80 $AUC_{0-\infty}$ (total systemic exposure) was 87.5% (90%CI 69% to 111%) indicating similar failure on the lower side of the accepted equivalence margin. The comparison using AUC_{0-t} was within both equivalence limits.
- The fed/fasted ratio for OP-1118 C_{max} was 66.6% (90%CI 58% to 76%) indicating breach on the lower side of the conventionally accepted equivalence margin of 80-125%.
- The fed/fasted ratio for OP-1118 $AUC_{0-\infty}$ was 78.1%% (90%CI 63% to 98%) indicating similar failure on the lower side of the equivalence margin. The comparison using AUC_{0-t} was within both equivalence limits.
- In urine, fidaxomicin was not measureable in any sample from any participant. The metabolite OP-1118 was measurable but < 25 ng/mL at all timepoints. Thus the urinary excretion represented a minor route of elimination that is, up to 1.23% of administered drug as its metabolite OP-1118.
- Faecal route was the dominant route of excretion. The peak faecal concentrations of fidaxomicin measured after a single dose of 200 mg ranged from 391 to 1240 µg/g. Peak faecal concentrations of OP-1118 ranged from 229 to 947 µg/g. Faecal levels following 400 mg dose were higher with peak fidaxomicin levels frequently exceeding 2000µg/g in both fed and fasting states.

[1] SD = standard deviation.

- The mean faecal recovery of fidaxomicin was 62% (± 33%) in Group 1 and 51% (± 35%) in Group 2. A secondary analysis which removed 3 participants with a single faecal sample increased the mean recovery to 75 (± 14%) and (55 ± 37%) in Groups 1 and 2 respectively.

Evaluator's comment

The justification for not conducting an absolute bioavailability study is considered acceptable.

The systemic exposure to drug (peak and total) following oral administration appears to very small (ng range for both the drug and its metabolite) and administration with food does not increase it. Absence of fidaxomicin in urine sample and high recovery (~75%) in faeces support any biotransformation limited mainly to the gastrointestinal tract.

Based on these data, the proposed recommendation that fidaxomicin can be administered regardless of food intake is considered acceptable.

3.1.2. Study OPT-80 1A-SD

This was a Phase I, trial to study the pharmacokinetic of single doses of oral fidaxomicin in 16 healthy volunteers. The design was randomised, double-blind, placebo-controlled involving dose escalation. The mean age of the participants was 49 years (range 31 to 62 years) and included both males and females.

The four single escalating doses of OPT-80 (fidaxomicin) were 100 mg, 200 mg, 300 mg and 400 mg administered orally after morning breakfast.

Each patient received two escalating doses (100 mg and 300 mg in Group 1 and 200 mg and 450 mg in Group 2) in a crossover manner with 1-2 weeks washout period in between the two treatment periods. At each dose level, 6 volunteers were randomized to receive active drug and 2 received placebo.

The reported results were as follows:

- There were insufficient OPT-80 plasma levels data points above the lower limit of quantification in 100, 200 and 300 mg dose groups to allow pharmacokinetic analysis.
- Four participants in the 450 mg dose group had evaluable plasma OPT-80 data showing T_{max} from 0.5 to 3 h (Mean ± SD, 1.4 ± 1.1) with mean (± SD) C_{max} of 26.5 ± 7.8 ng/mL. The apparent half-life of OPT-80 ranged from 0.94 to 2.77 h (Mean ± SD, 1.62 ± 0.84). The mean $AUC_{0-¥}$ was 76.18 ± 29.60 hr-ng/ml (range 52.24 to 116.42).
- No urine data were available in this study.
- Over 26% drug (200 and 300 mg dose groups) was recovered unchanged in the faeces over 120 hour collection period. Over 66% of the administered dose was excreted as OPT-80 product of hydrolysis metabolite designated M1 (OP-1118; molecular weight 988). The total faecal drug recovery (OPT-80 plus OP-1118) approximated 92.6% (± 42.0%) of the administered single doses.
- The peak faecal concentrations ranged from 158.4 to 480.7 µg/g. When normalized to 100 mg dose, the peak concentrations ranged from 52.8 to 160.2 µg/g (mean ± SD 104.39 ± 34.94 µg/g).
- Approximately 7.1% (1.1% to 37.1%) of single oral dose (100 and 450 mg dose groups) was excreted in faeces as unchanged OPT-80 over the 120 hour collection period. Measurement of M1 (OP-1118) for the 100 mg and 450 mg dose groups was could not be done due to incomplete collection of faecal samples. Therefore, the total recovery for these 2 dosing groups could not be calculated.

3.1.3. Study OPT-80 1B-MD

This was a Phase I, multiple-dose study to assess pharmacokinetics of fidaxomicin in 24 healthy volunteers. The design was randomised, double-blind, placebo-controlled with dose escalation.

Following on from the previous single dose study, this study aimed to investigate pharmacokinetics of OPT-80 in healthy volunteers after administration of oral doses for 10 consecutive days that is, steady state pharmacokinetics.

A total of 24 healthy volunteers participated in the study in 3 groups of 8 subjects each. The doses of OPT-80 evaluated were 150 mg, 300 mg and 450 mg administered orally (once daily) after morning breakfast on 10 consecutive days.

At each dose level, 6 volunteers were randomised to receive fidaxomicin (150, 300 or 450 mg) and 2 to receive placebo. The dosing was started in the 150 mg group followed by 300 mg and 450 mg groups on subsequent days. Continued once daily dosing to a total of 10 days of was completed at home.

The mean age of the participants was 52 years (range 38 - 62 years) and included both males and females.

The results were reported as follows:

- After multiple dose oral administrations, plasma concentrations of OPT-80 were mostly below the limit of quantification across the studied dose range (150 – 450 mg). Detectable plasma concentrations were found in 12 samples from 6 subjects.
- Of the 12 detectable concentrations, two were significantly above the lower limit of quantification (LLOQ), while others were around the LLOQ (5 ng/mL). The two significant plasma levels (11.1 ng/mL and 48.0 ng/mL) observed in the same subject were on Day 1/Hour 1 and pre-dose on Day 10 respectively.
- The multiple dose study yielded much lower plasma concentrations compared to the single dose study. The sponsor commented that this could be due to the use of formulations that possess different absorption characteristics. The current study used powder filled capsules that contained OPT-80 and microcrystalline cellulose as the bulking agent, whereas a liquid filled capsule that contained OPT-80 dissolved in labrasol was used in the single dose study.
- Due to low OPT-80 plasma levels across the dose range, there were insufficient plasma data points above LLOQ for pharmacokinetic analysis. Therefore, no pharmacokinetic parameters could be defined from this study.
- Intact OPT-80 was not detected in any urine sample.
- Normalised to 150 mg dose, the mean faecal OPT-80 was 916 µg/g (138 – 1769 µg/g), and mean faecal OP-1118 was 267 µg/g (51 – 571 µg/g).

3.2. Overall Absorption, Distribution, Metabolism and Excretion (ADME) features

Fidaxomicin is locally acting in the gastrointestinal tract. There is minimal systemic absorption (C_{max} 5-10ng/mL) based on reports in clinical studies in human healthy volunteers.

The metabolic fate of fidaxomicin is well accounted for and does not possess complicated pharmacokinetic features.

Fidaxomicin is not metabolised by human cytochrome P450 (CYP) enzymes and does not induce or inhibit these enzymes *in vitro*. Its biotransformation involves hydrolysis of isobutyryl ester to form OP-1118 likely via an esterase, along with a small amount of glucuronidation and sulfation.

In vitro fidaxomicin and its main metabolite OP-1118 are substrates and inhibitors of the efflux transporter P-glycoprotein (P-gp) which is expressed in the gastrointestinal tract. *In vivo* data suggest that fidaxomicin may be a mild to moderate inhibitor of intestinal P-gp.

There do not appear to be any unaccounted metabolites based on pharmacokinetic and mass balance data. More information may be available in the toxicology dossier.

In the Study OPT-80 1A-SD, over 92% of the orally administered drug was accounted for in the faeces as fidaxomicin or its primary metabolite OP-1118. This metabolite has weak antimicrobial activity estimated to be at 32 fold higher MIC_{90} than that of the parent fidaxomicin. Less than 1% of the administered dose is excreted via renal route.

3.3. Pharmacokinetics in target population

The following information is based on pharmacokinetic data collected in the clinical efficacy trials:

3.3.1. Study OPT-80-2A

This was a Phase II dose finding study with the following pharmacokinetic results:

In plasma, observable OPT-80 concentrations from Day 1 and Day 10 ranged from 9.45 to 12.3 ng/mL in the 100 mg/day (50 mg BID) treatment group, 5.12 to 93.7 ng/mL in the 200 mg/day (100 mg BID) treatment group, and 5.32 to 84.9 ng/mL in the 400 mg/day (200 mg BID) treatment group.

The metabolite OP-1118 was present in plasma in measurable concentrations in a greater number of samples than the parent OPT-80. Observable OP-1118 concentrations from Day 1 and Day 10 ranged from 5.23 to 77.2 ng/mL in the 100 mg/day treatment group, 5.12 to 154.3 ng/mL in the 200 mg/day treatment group, and 5.92 to 402.3 ng/mL in the 400 mg/day treatment group.

The faecal OPT-80 and OP-1118 levels ranged from 81.9 to 558.3 µg/g and 140.8 to 1050.6 µg/g respectively in the 100 mg/day group; from 11.7 to 786.7 µg/g and from 16.3 to 937.8 µg/g respectively in the 200 mg/day group, and from 389.0 to 3974.8 µg/g and from 211.0 to 1535.2 µg/g, respectively in the 400 mg/day group.

All faecal concentrations of > 1000 µg/g (8 patients) were found in the 400 mg/day (200 mg BID) fidaxomicin treatment group.

3.3.2. Study 101.1.C.003

This was the first confirmatory clinical efficacy trial.

For each patient, blood samples were obtained pre-dose and between 3 and 5 h post-dose on study Day 1 and again at the end of study treatment of 10 days or at the time of early termination (EOT). A faecal sample for pharmacokinetic measurements was obtained for each patient at end of study therapy or at early termination.

The mean post-dose plasma levels of OPT-80 were 22.8 ± 26.5 ng/mL on Day 1 and 26.4 ± 31.0 ng/mL at EOT. The mean post-dose plasma levels of OP-1118 were 43.1 ± 51.3ng/mL on Day 1 and 70.3 ± 80.5ng/mL at EOT.

The PK results for over 65 years old age groups were provided and indicate somewhat higher mean values than the overall mean values.

The PK results for estimated Creatinine Clearance (eCCL) < 50 mL/minute were similar to the overall results.

At EOT, the mean faecal levels of OPT-80 and OP-1118 in were 1225 ± 759 µg/g and 809 ± 651 µg/g respectively and were noticeably lower in patients who failed to achieve cure as were the resulting OPT-80/MIC ratios.

Evaluator's comment

The stratified results in the > 65 years old population and in patients with impaired renal function with slightly higher values do not indicate clinically significantly higher systemic exposure compared to the overall results.

There is indication that overall systemic exposures obtained in this patient population were somewhat higher than those which have been seen in pharmacokinetic studies in healthy volunteers. However, the systemic exposure is very small and supports the conclusion that the drug principally acts locally with no or negligible systemic absorption.

All post-dose plasma measurements were in ng/mL range. There was no plasma accumulation from baseline to EOT. The average faecal drug levels were nearly 5,000 times higher than the 0.25 µg/mL MIC_{90} against *Clostridium difficile* measured in this study.

3.3.3. Study 101.1.C.004

This was the second confirmatory clinical efficacy trial.

The mean fidaxomicin concentration 3-5 h post-dose at both Day 1 and EOT were between 20 and 30 ng/mL. Plasma levels of the main metabolite OP-1118 were approximately 2 to 3 times that of the parent compound.

As in the previous study (003), the plasma concentrations of fidaxomicin and OP-1118 were mildly elevated in the elderly (age > 65 years) compared to the ≤ 65 age group, though the levels were still in ng/mL range.

Similarly, the plasma concentrations were mildly elevated in patients with impaired renal function with eCCL < 50 mL/min compared to patients with normal renal function with eCCL ≥ 50 mL/min.

At EOT, the mean OPT-80 and OP-1118 levels were 1606 ± 1248 µg/g and 848 ± 567 µg/g, respectively.

Few faecal samples were available from clinical failures, but mean faecal levels and OPT-80/MIC ratios were noted to be similar between cures and failures.

Evaluator's comment

The results were consistent with those obtained in the previous Study 101.1.C.003.

3.4. Pharmacokinetics in other special populations

No dedicated studies were done in special populations. However, pharmacokinetic results from the two pivotal clinical studies were stratified and presented with respect to elderly population (> 65 years of age) and impaired renal function as noted above. These two variables did not appear to cause clinically significant higher systemic exposure to the drug compared to the overall results in these trials.

3.5. Pharmacokinetics related to genetic factors

None investigated.

3.6. Pharmacokinetic interactions

3.6.1. Study OPT-80-007 (cyclosporine interaction study)

This was a randomised, open-label, two-period, crossover study to evaluate the effect of a single dose of cyclosporine on the pharmacokinetics of a single-dose of fidaxomicin (OPT-80) in healthy male volunteers.

Fourteen healthy subjects participated in the study. The subjects were male, with mean age 30 years (range 21 – 40 years), non-smokers and in good health based on clinical assessment.

All subjects received single dose 200 mg oral fidaxomicin alone (Treatment A) and single dose 200 mg oral fidaxomicin in combination with single dose 200 mg oral cyclosporine (Treatment B) in a crossover design with 7 day washout period between the two treatments, according to a randomised schedule under fasting conditions.

The results were as follows:

- Following a single oral dose of 200 mg fidaxomicin alone or in combination with 200 mg cyclosporine (Neoral 2 x 100 mg capsules) in Treatment groups A and B respectively, the median fidaxomicin (OPT-80) T_{max} values of 2.00 and 2.32 h were observed for Treatments A and B respectively. The mean fidaxomicin plasma $t_{1/2}$ was 11.7 and 10.2 h in Treatment A and B groups respectively. The fidaxomicin mean residence time (MRT) was 17.2 and 9.77 h in Treatment A and B groups respectively.
- The (least squares) mean fidaxomicin C_{max} for Treatment B (19.4 ng/mL) was 4.15 fold greater than C_{max} for Treatment A (4.67 ng/mL). The 90% confidence interval (CI) for ratio of test/reference C_{max} was 323% to 532% and was thus entirely outside the 80% to 125% equivalence range.
- The (least squares) mean fidaxomicin $AUC_{0-¥}$ for Treatment B (114 ng.hr/mL) was 1.92 fold greater than $AUC_{0-¥}$ for Treatment A (59.5 ng.hr/mL). The 90%CI for the ratio of test/reference $AUC_{0-¥}$ was 139% to 263% and was also entirely outside of the 80% to 125% equivalence range. Similar result was observed for fidaxomicin AUC_{0-t} test/reference ratio with a 2.45 fold increase in fidaxomicin AUC_{0-t} on co-administration with cyclosporine.

The effect of cyclosporine on the main metabolite of fidaxomicin (OP-1118) was also examined.

- After a single oral dose of 200 mg fidaxomicin alone or in combination with 200 mg cyclosporine in Treatments groups A and B respectively, the median OP-1118 T_{max} of 1.02 and 2.00 h were observed for Treatments A and B respectively. The mean OP-1118 $t_{1/2}$ was 11.2 and 10.4 h and the mean OP-1118 MRT was 14.9 and 8.34 h for Treatments groups A and B respectively.
- The (least squares) mean OP-1118 C_{max} for Treatment B (100 ng/mL) was 9.5 fold higher than C_{max} for Treatment A (10.6 ng/mL). The 90%CI for ratio of test/reference OP-1118 C_{max} was 693% to 1304% and was entirely outside of the 80% to 125% equivalence range.
- The (least squares) mean OP-1118 $AUC_{0-\infty}$ for Treatment B (438 ng.hr/mL) was 4.1 fold greater than $AUC_{0-¥}$ for Treatment A (106 ng.hr/mL). The 90%CI for ratio of test/reference OP-1118 $AUC_{0-¥}$ was 305.97% to 553.21% and was entirely outside of the 80% to 125% equivalence. Similar result was obtained for OP-1118 AUC_{0-t} test/reference value with a 4.27 fold increase in mean value when fidaxomicin was co-administered with cyclosporine.

Evaluator's comment

The study showed statistically and clinically significant pharmacokinetic interaction between fidaxomicin and cyclosporine. The magnitude of higher systemic exposure of OPT-80/OP-1118 in this instance was large although the plasma concentrations remained in ng/mL range.

The study examined one way interaction only as fidaxomicin is a substrate for p-gp. Its effect on cyclosporine was not examined.

In response to a TGA request for information, the sponsor has also provided the following information:

> *'Cyclosporine is a powerful P-glycoprotein (P-gp) inhibitor, and the objective of this study was to determine the impact of P-glycoprotein inhibition on fidaxomicin pharmacokinetics. Fidaxomicin has been poorly characterized, however, as a test substrate for P-glycoprotein, and the importance of P-gp in its intestinal uptake is unclear. While cyclosporine has been reported to be a P-gp substrate, polymorphisms in MDR1 have not been shown to explain differences in pharmacokinetics of cyclosporine and much of the variability is associated instead with polymorphisms in CYP3A4, suggesting that the latter is the major contributor to variability in bioavailability. Substrate-based drug interactions have been reported at the level of the kidney, in terms of increased nephrotoxicity in the presence of P-gp inhibitors in renal epithelial cells. Because fidaxomicin has minimal absorption (ng/mL concentrations in the plasma, well below the µg/mL IC50 for inhibition of P-gp), this interaction is predicted to be irrelevant for fidaxomicin. Cyclosporine is metabolized by CYP3A4, and while fidaxomicin is a very weak inhibitor of CYP3A4, another DDI study (OPT-80-009) demonstrated no impact of fidaxomicin on the pharmacokinetics of CYP3A4 substrate midazolam. Thus, such an interaction was also considered unlikely. Because of the generally conflicting results reported in the literature as to the impact of P-gp on cyclosporine uptake, it was decided to use a more specific test substrate, **digoxin**, to evaluate the potential impact of P-gp inhibition. Administration with fidaxomicin had no clinically relevant impact on digoxin pharmacokinetics. It is worth noting that although cyclosporine pharmacokinetics were not compared in a crossover manner in this study (there was no cyclosporine-only dosing sequence), cyclosporine concentrations were measured in the presence of fidaxomicin dosing. Cyclosporine concentrations measured (C_{max} 395 ± 95ng/mL following a 200 mg dose) were similar to cyclosporine concentrations reported by others using an equivalent assay (LC-MS, rather than ELISA, which can cross-react with metabolites and overestimate concentrations), when adjusted for dose (after a 100 mg dose, C_{max} was 254 ± 85ng/mL).'*

Please also see following studies OPT-80-008 (digoxin) and OPT-80-009 (midazolam).

The sponsor's proposal in the PI is to allow co-administration based on clinical trials in CDAD patients where concomitant P-gp inhibitor use had no attributable effect on safety or efficacy. It is not clear if this is in reference to the two pivotal trials. The sponsor is requested to include a summary of stratified results to which this comment refers in its pre-ACPM response.

3.6.2. Study OPT-80-008 (digoxin interaction study)

This was an open-label, single sequence study to evaluate the effect of steady-state fidaxomicin on pharmacokinetics of a single dose of digoxin in healthy subjects.

The study was carried out in 14 healthy male and female subjects. The mean age of the participants was 31 years (range 21 – 40 years). The participants were non-smokers and in good health based on clinical assessment.

The study was non-randomised as all subjects received all treatments in a sequential manner (mono-sequence crossover design). The study drugs were administered sequentially according to the following treatment schedule:

Period 1: All subjects received a single 0.5mg oral dose of digoxin on Day 1 followed by a 6-day washout period.

Period 2: All subjects received 200 mg fidaxomicin tablets every 12 h for 5 days from Day 8 to 12.

Period 3: On Day 13, a single 0.5mg oral dose of digoxin was administered 1 hour after the morning 200 mg dose of fidaxomicin on that day. Treatment with 200 mg oral fidaxomicin tablets every 12 h continued until the end of Day 18.

The morning dose of study drugs was administered on dosing days after at least a 10 hour fast. No food or water was allowed for 1 hour before or 2 h after the second fidaxomicin dose of the day.

The results were as follows:

- Following a single oral dose of 0.5mg digoxin alone on Day 1 and on co-administration with 200 mg fidaxomicin on Day 13, the median digoxin T_{max} was unchanged (1 hour) and the mean digoxin half-life was 38.8 h and 41.9 h respectively.
- The (least squares) mean digoxin C_{max} was 1.66 ng/mL on co-administration compared to 1.46 ng/mL on administration alone indicating a 14% increase on co-administration with 90%CI for test/reference C_{max} ratio of 98.98% to 131.30%. Thus the upper margin of 90%CI for mean digoxin C_{max} test/reference ratio was outside the upper limit of 125% equivalence.
- The (least squares) mean digoxin $AUC_{0-¥}$ was 12.4 ng.h/mL on co-administration compared to 11.4 ng.h/mL on administration alone indicating a 12% increase on co-administration with 90%CI with test/reference $AUC_{0-¥}$ ratio of 102.67% to 121.58%. Thus the 90%CI for mean digoxin $AUC_{0-¥}$ test/reference ratio was within the 80% to 125% equivalence range.
- The sponsor has provided argument that the 90%CI for AUC_{0-3} ratio was within the 80% to 125% equivalence range and that AUC_{0-3} is a more useful alternative measure of drug exposure in the drug absorption phase and unlike $C_{max,}$ the AUC_{0-3} is not dependent on uncertainty associated with determination at a single point.

Evaluator's comment

Digoxin is P-glycoprotein substrate. The study revealed mild pharmacokinetic interaction between fidaxomicin and digoxin on co-administration (> 10% increase in digoxin C_{max} and AUC).

No dose adjustment is proposed in the PI.

However, a clinically significant interaction in clinical setting that is, CDAD patients with co-morbidities cannot be excluded compared to the results obtained in healthy volunteers in the interaction studies.

Please also see preceding Study OPT-80-007 (cyclosporine) and the following Study OPT-80-009 (midazolam/warfarin/omeprazole).

3.6.3. Study OPT-80-009 (CYP450 interactions)

This was open label, non-randomised, mono-sequence crossover study to evaluate the potential for cytochrome P450 mediated drug interactions with fidaxomicin (OPT-80) in healthy male volunteers.

This was achieved by examining the effect of steady-state fidaxomicin on co-administration with a single-dose of a substrate cocktail of 3 drugs warfarin (CYP2C9), omeprazole (CYP2C19) and midazolam (CYP3A4/5).

Twenty-four healthy male subjects were enrolled and 22 completed the study. The mean age of the participants was 32 years (range 20 – 40 years) and patients were in good health based on clinical examination.

In Treatment Period 1, all participants received a single oral dose of a cocktail of 1 x 10 mg warfarin (Coumadin) tablet, 2 x 20 mg omeprazole (Prilosec OTC) tablets and 5 mg midazolam (Versed midazolam hydrochloride syrup 2mg/mL) on Day 1. This was followed by a washout interval of 16 days.

In Treatment Period 2, all participants received 200 mg oral fidaxomicin tablets every 12 h from study Day 18 to Day 24.

In Treatment Period 3 on study Day 21, all participants also received a single oral dose of a cocktail of 1 x 10 mg warfarin tablet, 2 x 20 mg omeprazole tablets and 5 mg midazolam (2 mg/mL) in co-administration with fidaxomicin. The cocktail was given with the first dose of fidaxomicin tablets of the day. Administration of 200 mg fidaxomicin tablets every 12 h continued through Day 24.

The morning doses of study drugs were administered on dosing days after at least a 10 hour fast. No food or water was allowed for 1 hour before or 2 h after the second fidaxomicin dose of the day.

The results were reported as follows:

Warfarin

- Following a single oral dose of a cocktail of a 10 mg warfarin, 40 mg omeprazole and 5 mg midazolam alone or in combination with oral fidaxomicin tablets 200 mg every 12 h in Periods 1 and 3 respectively that is, on Day 1 and Day 21 respectively, the median R- and S-warfarin T_{max} values ranged from 1.00 to 2.00 h for both Days 1 and 21.
- A mean R-warfarin $t_{1/2}$ of 87.1 h and 102 h and mean R-warfarin MRT of 88.2 h and 94.9 h were observed on Days 1 and 21 respectively.
- A mean S-warfarin $t_{1/2}$ of 91.2 h and 97.3 h and mean S-warfarin MRT of 70.2 h and 71.8 h were observed on Days 1 and 21 respectively.
- The R-warfarin least squares (LS) mean C_{max} on Day 21 was 9.1% higher (661 versus 606ng/mL) than on Day 1.
- The 90%CI for ratio of test/reference LS mean C_{max} for R-warfarin was 104.6% to 113.8% and was thus contained within the 80% to 125% equivalence range.
- The R-warfarin LS mean $AUC_{0-¥}$ on Day 21 was 13.8% higher (40862 versus 35902 ng.hr/mL) than on Day 1.
- The 90%CI for ratio of test/reference LS mean $AUC_{0-¥}$ for R-warfarin was 110.6% to 117.08% and was thus within the 80% to 125% equivalence range.
- The S-warfarin LS mean C_{max} on Day 21 was 9.35% higher (668 versus 611ng/mL) than on Day 1.
- The 90%CI for ratio of test/reference S-warfarin LS mean C_{max} was 104.01% to 114.96%) and was thus within the 80% to 125% equivalence range.
- The S-warfarin LS mean $AUC_{0-¥}$ on Day 21 was 13.06% higher (23171 versus 20495 ng.hr/mL) than on Day 1.
- The 90%CI for ratio of test/reference S-warfarin LS mean $AUC_{0-\infty}$ was 109.53% to 116.7% and was thus contained within the 80% to 125% equivalence range.

Omeprazole

- After a single oral dose of the cocktail alone or in combination with oral fidaxomicin (200 mg every 12 hours) in Periods 1 and 3 that is, on Days 1 and 21 respectively, a median omeprazole and 5-hydroxyomeprazole T_{max} of 2 h was observed on both Days 1 and 21.
- A mean omeprazole $t_{1/2}$ of 1.02 h and 1.18 h and mean omeprazole MRT of 3.01 h and 3.19 h were observed on Days 1 and 21 respectively.

- A mean 5-hydroxyomeprazole $t_{1/2}$ of 1.31 h and 1.47 h and mean MRT of 3.45 h and 3.68 h were observed on Days 1 and 21 respectively. The mean M/P ratios on Days 1 and 21 were 0.893 and 0.929 respectively.
- The omeprazole LS mean C_{max} (561 versus 603 ng/mL) was 6.96% lower on Day 21 compared to Day 1.
- The omeprazole LS mean $AUC_{0-¥}$ (1132 versus 1100 ng.h/mL) was 2.85% higher on Day 21 compared to Day 1.
- The 90%CIs for omeprazole LS mean C_{max} (82.0% to 105.56%) and $AUC_{0-¥}$ (93.0% to 113.74%) ratios (test/reference) were contained within the 80% to 125% equivalence range.
- The 5-hydroxyomeprazole LS mean C_{max} (377 versus 378 ng/mL) was 0.42% lower on Day 21 compared to Day 1.
- The 5-hydroxyomeprazole LS mean $AUC_{0-¥}$ (961 versus 895 ng.h/mL) was 7.43% higher on Day 21 compared to Day 1.
- The 90%CIs for 5-hydroxyomeprazole LS mean C_{max} (91.2% to 108.73%) and $AUC_{0-¥}$ (102.66% to 112.41%) ratios (test/reference) were contained within the 80% to 125% equivalence range.
- INR measurements were taken for 3 consecutive days following each dose of warfarin. Slight elevations (1.2 to 1.5; 1.7 on one case; normal range 0.9-1.1) in the INR were observed in several subjects, there was no trend toward longer INR values when warfarin was taken in combination with fidaxomicin. Of the 14 subjects with an elevated INR at any time following warfarin dosing, 7 had similar elevations after warfarin dosing both with (Period 3) or without (Period 1) fidaxomicin; 6 subjects had elevations only after warfarin was dosed alone (Period 1); and only 1 subject (Subject No. 008) had an elevation (INR 1.2) in Period 3 with no corresponding elevation in Period 1.

Midazolam

- After a single oral dose of the cocktail alone or in combination with oral fidaxomicin (200 mg every 12 hours) in Periods 1 and 3 that is, Days 1 and 21 respectively, a median midazolam and 1-hydroxymidazolam T_{max} of 0.5 h was observed on both Days 1 and 21.
- A mean midazolam $t_{1/2}$ of 5.16 h and 5.27 h and mean MRT of 3.97 h and 4.09 h were observed on Days 1 and 21 respectively.
- A mean 1-hydroxymidazolam $t_{1/2}$ of 6.29 h and 6.72 h and mean MRT of 4.56 h and 5.19 h were observed on Days 1 and 21 respectively. The mean M/P ratios on Days 1 and 21 were 0.469 and 0.551.
- The LS mean midazolam C_{max} (25.1 versus 27.4 ng/mL) was 8.45% lower on Day 21 compared to Day 1.
- The LS mean midazolam $AUC_{0-\infty}$ (63.9 versus 66.2 ng.hr/mL) was 3.52% lower on Day 21 compared to Day 1.
- The 90%CIs for midazolam LS mean C_{max} (82.54% to 101.53%) and $AUC_{0-¥}$ (88.15% to 105.61%) ratios (test/reference) were contained within the 80% to 125% equivalence range.
- The LS mean 1-hydroxymidazolam C_{max} (13.4 versus 13.0 ng/mL) was 2.77% higher on Day 21 compared to Day 1.
- The LS mean 1-hydroxymidazolam $AUC_{0-¥}$ (36.2 versus 31.0 ng.hr/mL) was 16.81% higher on Day 21 than on Day 1.

- The 90%CIs for 1-hydroxymidazolam LS mean C_{max} (90.7% to 116.4%) ratio (test/reference) was within the 80-125% equivalence margin whereas the upper limit of $AUC_{0-¥}$ (106.69% to 127.88%) ratio (test/reference) was outside this margin.

Evaluator's comment

The sponsor has concluded that steady-state administration of 200 mg fidaxomicin did not significantly alter the drug metabolizing capacity of CYP2C9, CYP2C19, and CYP3A4/5 to metabolize S-warfarin, omeprazole, or midazolam respectively. No dose changes are proposed in the PI.

The evaluator is in agreement with these recommendations (no dose change). However, cyclosporine, digoxin and warfarin are all narrow therapeutic drugs and clinical relevant interactions in clinical settings as opposite to results in healthy volunteers cannot be excluded.

It is recommended that a precautionary statement in the PI in relation to these interactions be added. Therapeutic drug monitoring of these drugs before and at the end of 10 day course with fidaxomicin in association with any of these drugs may also need to be considered on individual basis.

3.7. Evaluator's overall conclusions on pharmacokinetics

Fidaxomicin has simple pharmacokinetics and is not absorbed systemically to any clinically significant degree. The excretion is via faecal route as intact parent drug and its metabolite. Given the topical action within the gastrointestinal tract, low systemic bioavailability, absence of clinically relevant interaction for fidaxomicin exposure, the plasma pharmacokinetic features may thus not be critical in clinical practice. There is small food effect (lower bioavailability) which is also not clinically relevant. The effect on cyclosporine, digoxin and warfarin may be clinically important in CDAD patients and although no dose adjustments are recommended based on data, such co-administration should be monitored including measurement of plasma drug levels for these drugs.

4. Pharmacodynamics

4.1. Studies providing pharmacodynamic data

Please also see the associated nonclinical evaluation.

Fidaxomicin is bactericidal against *Clostridium difficile in vitro*, inhibiting RNA synthesis by RNA polymerases (RNAP). It interferes with RNAP at a site distinct from that of rifamycins. Inhibition of the clostridial RNAP occurs at a concentration 20-30 fold lower than that for the *Escherichia coli* enzyme which may partly explain the significant species specific antimicrobial activity of fidaxomicin.

Fidaxomicin has an MIC_{90} of 0.25 µg/mL for *C. difficile*. Gram negative organisms are intrinsically not susceptible to fidaxomicin.

Fidaxomicin acts locally in the gastrointestinal tract on with minimal systemic absorption. Faecal concentrations in colon exceeding MIC_{90} against *C. difficile* are obtained throughout the dosing interval. However, *in vitro* data indicate that fidaxomicin has time-dependent bactericidal activity so that time over minimal inhibitory concentration (MIC) may be the most predictive parameter of clinical efficacy.

In a clinical study, fidaxomicin predominantly affected faecal concentrations of *C. difficile* with little to no effect on microflora such as Bacteroides and other major phylogenetic groups.[2]

Treatment with fidaxomicin also leads to a lower VRE colonisation as compared to treatments with vancomycin and seen in the first Phase III pivotal efficacy study. In vancomycin arm, 31% patients became colonised with VRE during treatment compared with 7% of patients receiving fidaxomicin.[3]

Fidaxomicin has also been shown to inhibit *C. difficile* sporulation *in vitro*. Faecal spore counts (CFU count/g) in fidaxomicin treated patients were found to be 2.3 $\log_{10}$ lower at 21 to 28 days post-therapy than in those patients who received vancomycin.

In vitro, Fidaxomicin was also shown to have a prolonged post-antibiotic effect (6 to 10 hours).

Initial studies showed that fidaxomicin (OPT-80) was at least 2 to 4 fold more active than vancomycin against 15 strains of *C. difficile*. The MIC values of OPT-80 ranged from 0.12 to 0.25 µg/mL. The MIC_{50} and MIC_{90} were both 0.25 µg/mL. The frequency of spontaneous resistance in *C. difficile* ATCC 9689 was low at < $2x10^{-8}$ and OPT-80 achieved faster killing kinetics than vancomycin.

Fidaxomicin is bactericidal, having a minimum bactericidal concentration (MBC) against *C. difficile* American Type Culture Collection (ATCC) 9689 that is equal to its MIC. In comparison, the MBC of vancomycin against *C. difficile* ATCC 9689 is 4 times higher than its MIC.

In another early report, OPT-80 showed only moderate activity against *Staphylococcus aureus*, *Streptococcus pyogenes* and *Enterococcus faecium,* and was inactive against aerobic and anaerobic Gram-negative rods, and *Candida* species.

In a more recent study, the MIC_{90} of OPT-80, vancomycin, and metronidazole against a panel of 207 *C. difficile* strains obtained from patients at two university hospitals in Germany were 0.0078, 0.5 and 0.125 µg/mL, respectively.

A typical MIC_{90} for this organism, tested via Clinical and Laboratory Standards Institute (CLSI) protocol, was 0.125 µg/mL. The same value was obtained in a separate experiment in which 110 genetically distinct strains of *C. difficile* were tested.

Fidaxomicin is 4 and 16 times more potent than metronidazole or vancomycin, respectively, against this species. MIC_{90} values of metronidazole and vancomycin for the same panels of organisms were typically 0.5 and 2 µg/mL respectively.

Amino acid substitutions that confer reduced susceptibility to fidaxomicin have been located within the chromosomally encoded RNAP. Fidaxomicin resistance genes have not been identified on transferable elements.

4.1.1.1. Risk of development of antibiotic resistance

A risk assessment has been provided by the sponsor. The *in vitro* activity of fidaxomicin is as described in the table below.

[2] Louie TJ *et al* (2009). OPT-80 Eliminates Clostridium difficile and Is Sparing of Bacteroides Species during Treatment of C. difficile Infection. Antimicrobial Agents and Chemotherapy 53 (1) p. 261–263

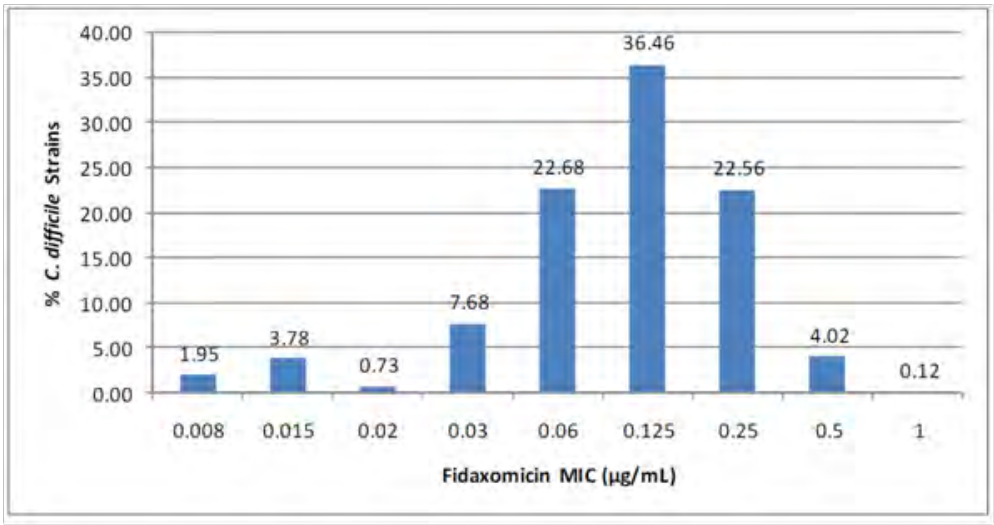
[3] Nerandzic MM *et al* . Acquisition and Overgrowth of Vancomycin-Resistant Enterococci in Patients Treated with Either Fidaxomicin or Vancomycin for C. difficile Infection. Provided as slides among literature references included in Module 5.

Table 1. *In vitro* activity of fidaxomicin

Organism (n)	MIC Range (µg/mL)	MIC_{90} (µg/mL)
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
Gram Positive Anaerobes		
Anaerobic gram-positive cocci (49)	0.06-1024	2
Anaerobic gram-positive nonsporeforming rods (20)	≤0.016-16	16

The distribution of fidaxomicin MIC against *C. difficile* clinical isolates from fidaxomicin Phase III trials (safety population) is shown below in Figure 1.

Figure 1. Distribution of fidaxomicin MIC against *C. difficile* clinical isolates from fidaxomicin Phase III trials (safety population)



Decreased susceptibility to fidaxomicin was observed in only one clinical isolate from a patient enrolled in a Phase III trial. This patient initially achieved clinical cure but later presented with recurrence of CDAD. Day 1 and end of therapy isolates had low MICs (0.06µg/mL) but the recurrence isolate MIC was much higher (16 µg/mL). The typing method used in these clinical studies could not discriminate the strains from each collection (all were "non-specified REA" type), the possibility remains that the strain developed reduced sensitivity to fidaxomicin during the study although it is unclear why this happened once the selective pressure had been removed. An alternate explanation is that there was re-infection with a strain having an innately lower sensitivity to fidaxomicin, although an MIC of > 2 µg/mL has not been seen previously within the wild type population. The recurrence strain did have a mutation identified in the β subunit of RNAP that was not present in the baseline or end of therapy isolates.

In vitro studies with laboratory-generated mutant *C. difficile* strains with reduced susceptibility to fidaxomicin did not show any change in their MIC to other antimicrobial classes, that is, only fidaxomicin MIC values increased in those mutant strains but not their MIC to other antibiotics. Similarly, *C. difficile* strain (ATCC 43597), which is known to be resistant to other class of antibacterial agents was susceptible to fidaxomicin as shown in the table below.

Table 2. *C. difficile* strain MIC

	MIC, µg/mL		
	***C. difficile* ATCC 43255 (wt)**	***C. difficile* ATCC 43255-29C (fidaxomicin-R)**	***C. difficile* ATCC 43597 (macrolide-R)**
Azithromycin	16	8	> 64
Telithromycin	1	0.5	> 64
Ampicillin	4	8	2
Aztreonam	> 64	> 64	> 64
Cefotaxime	64	> 64	64
Ciprofloxacin	16	8	16
Vancomycin	0.5	2	0.5
Metronidazole	0.5	1	1
Rifampin	≤ 0.125	≤ 0.125	≤ 0.125
Fidaxomicin	≤ 0.125	8	≤ 0.125

In a reverse experiment, organisms resistant to other classes of antibiotics were tested for reduced susceptibility toward fidaxomicin. No cross-resistance was found in this manner against the other antibiotics, including macrolides, β-lactams, fluoroquinolones, rifamycins, vancomycin and metronidazole as shown in the table below.

Table 3. Organisms resistant to other classes of antibiotics and the effect of fidaxomicin

	MIC, µg/mL			
	Fidaxomicin	**Rifampin**	**Azithromycin**	**Telithromycin**
Staphylococcus aureus ATCC 29213 (antibiotic sensitive)	4	≤ 0.125	0.5	≤ 0.125
Staphylococcus aureus ATCC BAA-44 (Rifampin resistant)	4	1	> 64	> 64
Staphylococcus aureus 96:11480 (Inducible macrolide resistant, *Erm*)	4	≤ 0.125	> 64	≤ 0.125
Staphylococcus aureus RN4220 E194 (Macrolide resistant, *Msr*A macrolide pump)	4	≤ 0.125	64	2
Staphylococcus aureus ATCC 33591 (methicillin, macrolide resistant)	4	≤ 0.125	>64	> 64
Streptococcus pneumoniae ATCC 49619 (antibiotic sensitive)	> 32	ND	ND	≤ 0.125
Streptococcus pneumoniae 163 (Macrolide resistant, *Mef*A macrolide pump)	64	≤ 0.125	2	≤ 0.125
Enterococcus faecium ATCC 49032 (antibiotic sensitive)	≤ 0.125	ND	ND	4
Enterococcus faecium ATCC 700221 (vancomycin resistant)	4	ND	ND	8

Co-selection of fidaxomicin resistance by other antibiotics has not been studied.

The risk for development of resistant *C. difficile* or transferable resistance genes is considered by the sponsor to be low due to inherent attributes of fidaxomicin including:

1. Narrow spectrum of activity
2. Lack of known transferable elements with fidaxomicin resistance genes
3. Lack of cross-resistance with other classes of antibiotics, and
4. Restricted use of fidaxomicin in humans for treatment of CDAD only.

At present the wild type population of *C. difficile* is fully susceptible to fidaxomicin and the likelihood of exposure to resistant *C. difficile* is low. Use of fidaxomicin for treatment of CDAD overtime can be expected to carry low risk of development of *C. difficile* strains that are

clinically resistant to fidaxomicin. Resistance surveillance is proposed to monitor changes in susceptibility.

Even though fidaxomicin is excreted mainly unchanged in faeces, the environmental impact is considered contained especially in view of the fact that *C. difficile* thrives under anaerobic conditions and is present in environment as dormant spores.

The primary source of uncertainty in this risk assessment is the lack of epidemiological data and resulting reliance on in vitro data along with limited isolates from clinical studies.

4.2. Summary and evaluator's comment on pharmacodynamics

Fidaxomicin has narrow spectrum of antibacterial activity. It is bactericidal against *C. difficile* in vitro inhibiting RNA synthesis by RNA polymerase. Gram negative organisms both aerobic and anaerobic are intrinsically insensitive. It has variable activity against facultative and aerobic Gram positive bacteria. It has variable activity against Gram positive anaerobic bacteria.

Rate of resistance development to fidaxomicin has been shown to be low. It does not exhibit cross resistance to other classes of antibiotics.

The risk of development of bacterial (*C. difficile*) resistance to fidaxomicin is considered low but will require institution of organised resistance surveillance programme if the drug is approved for marketing.

5. Dosage selection for the pivotal studies

5.1. Study OPT-80-2A

This was a Phase II, dose finding study (OPT-80 is also referred to as PAR-101 in documentation for this trial). The design was open-label, randomised, parallel groups study in patients with mild to moderate *Clostridium difficile*-Associated Diarrhoea (CDAD). The study was carried out across four sites in Canada and the US.

The participating patients could be male or female, over 18 years of age and who may have been hospitalised or treated in outpatient setting for mild to moderate CDAD as defined by:

- Diarrhoea - change in bowel habits with 3 or more unformed bowel movements in 24 hours, or more than 6 loose or watery stools within 36 hours; and
- Presence of either Toxin A or B of *Clostridium difficile* toxin in stool.

Patients with a single recurrence episode of recurrent were allowed to enrol but those with multiple recurrences that is, more than one recurrence, of CDAD within the past 3 months were excluded. Patients with inflammatory bowel disease (ulcerative colitis and Crohn's disease) were also excluded. Up to 3 doses of metronidazole and/or vancomycin within 24 h were allowed where the investigator felt clinical imperative to start the treatment before availability of the results for stool toxin. Any other antibiotic or treatment of CDAD was an exclusion criterion.

The patients were randomized into 3 treatment groups as follows:

1. Fidaxomicin 100 mg/day for 10 days that is, 50 mg every 12 hours
2. Fidaxomicin 200 mg/day for 10 days that is, 100 mg every 12 hours
3. Fidaxomicin 400 mg/day for 10 days that is, 200 mg every 12 hours

The route of administration was oral. OPT-80 was provided as an oral capsule containing 50 mg of fidaxomicin formulated in 110 mg of microcrystalline cellulose National Formulary (Avicel PH-102).

The doses for were based on safety and pharmacokinetic data from the preceding Phase I studies in healthy volunteers and on previous animal toxicology studies. Oral doses of up to 450 mg were had been tolerated in these trials. The concentrations of intact OPT-80 were found to be high in faeces and mostly below the limit of quantification in plasma. The pharmacokinetics were linear and when normalized to a 150 mg dose, the average faecal concentration was 916 µg/g. It was thus expected that a faecal concentration (FC) of approximately 1,220 µg/g OPT-80 will be achieved with 200 mg daily dosing. Likewise, for the pharmacokinetics of the metabolite OP-1118 were linear and a 200 mg/day dose was expected to achieve faecal levels of about 356 µg/g of the metabolite. The ratio of the faecal OPT-80 concentration to its MIC_{90} for *C. difficile* is considered predictive of clinical efficacy. For MIC_{90} value of 0.125µg/mL against a panel of 110 genetically distinct *C. difficile* isolates, FC/MIC_{90} ratio for the dose of 200 mg/day was estimated at 9,760. The activity of OP-1118 was 8 to 16 times lower than PAR-101, thus the FC/MIC90 ratio for OP-1118 was estimated at 178 at this dose level.

The patients recorded symptoms on daily diary cards. Laboratory assessments were performed at screening and at End of Treatment (Day 10-12) or withdrawal (whichever was sooner). The clinical assessment and diary card evaluation were performed at End of Treatment (Day 10-12). An interview was conducted on treatment Days 2 through 9, Day 17 and Day 52. The microbiological assessments (stool toxin and culture) were performed at entry and in case of clinical recurrence. The clinical, laboratory, and microbiological assessments were also performed at exit for patients who failed to respond to treatment.

A total of 49 patients were enrolled of which one discontinued before treatment so that there were 16 patients in each of the 3 treatment groups and were included in safety analysis. A total of 41 patients completed the study. Two patients in each groups 100 mg/day and 200 mg/day discontinued due to treatment failure.

There were 47 patients in the modified intent-to-treat (mITT) population (patients who received at least one dose of the study drug) with 16 patients in 100 mg/day treatment group, 16 in 200 mg/day treatment group and 15 in 400 mg/day treatment group. A total of 45 patients were evaluable for clinical cure at end of therapy.

Overall, the sample population consisted of 62.5% females and 37.5% males. The overall mean age of the group was 54.9 (± 19.26) years. The mean number of daily bowl movements was 6.7 (± 2.79) at baseline. The three treatment groups were broadly comparable at baseline.

The primary efficacy variables were as follows:

- *Clinical cure/failure;* the investigator determined the patient response to therapy as a clinical cure or failure based on clinical judgement. The non-responding patients were to be discontinued and placed on conventional therapy. This outcome was the result of a change to the study plan.
- *Relief/No Relief of symptoms ;* relief of symptoms of CDAD was defined as resolution to ≤ 3 bowel movements per day without other associated signs/symptoms such as fever, abdominal pain, and elevated white blood cells by Day 10 of the study. This was the initial outcome of interest in the trial protocol.

The secondary efficacy variables were as follows:

- *Clinical recurrence* ; defined as ≥ 3 unformed stools (loose or watery) in a day and positive stool for *C. difficile* toxin A or B. Recurrence was assessed within 6 weeks after completion of treatment in the trial that is, between Day 17 and Day 52.

- *Time to resolution of diarrhoea;* defined as time (in days) from the first dose of study drug to the resolution of diarrhoea. The day of resolution of diarrhoea was defined as the first day when < 3 unformed stools (watery or loose) within a 24 hour period occurred and was sustained for the duration of treatment up to study Day 10. This was assessed during 10 to 12 day period utilising patient daily diary data.

In addition, the following outcomes were also assessed:

- *Effects on bowel flora;* including *C. difficile* culture and toxin detection in patients who failed to achieve clinical cure or experienced clinical recurrence. This was not a protocol driven assessment.
- *Pharmacokinetic data;*- measurement of faecal and plasma concentrations of OPT-80 and its metabolite OP-1118. Faecal concentrations at different doses were compared to evaluate dose-concentration relationship. Please see above for results.

The efficacy results were reported as follows:

- There were no treatment failures in the 400 mg/day treatment group, that is, all 16 patients treated with fidaxomicin 400 mg/day (200 mg every 12 hours) were considered clinical cures by the investigator.
- Four treatment failures were observed in this study; 2 in each of the fidaxomicin 200 mg/day (100 mg every 12 hours) and fidaxomicin 100 mg/day (50 mg every 12 hours) treatment groups.
- The bowl flora tests in these four patients with clinical failure showed one patient in the 200 mg/day treatment group was positive for *C. difficile* toxin at end of therapy and three (2 patients in the 100 mg/day treatment group and one patient in the 200 mg/day treatment group) were negative for *C. difficile* toxin at end of therapy.
- Based on the mITT population, relief of symptoms of CDAD was observed in 13/15 (86.7%) patients in the 400 mg/day treatment group, 8/16 (50.0%) patients in the 200 mg/day group and 6/16 (37.5%) patients in the 100 mg/day group. A total of 2/15 (13%) patients experienced no relief in the 400 mg/day group compared to 6/16 (37%) in 200 mg/day and 9/16 (56%) patients in 100 mg/day group.
- One patient in 400 mg/day treatment group and one patient in 100 mg/day treatment group experienced clinical recurrence (≥ 3 unformed stools and a positive stool for *C. difficile* toxin A or B) within 6 weeks post-treatment that is, Day 17 to Day 52.
- The bowel flora tests in these 2 patients with recurrence showed *C. difficile* isolated in faeces pre-treatment but negative at Day 10. However, both were positive for *C. difficile* toxin in faeces at recurrence.
- The Time to relief of diarrhoea appeared to decrease with increasing dose. The estimated median time to relief was 5.5 days, 3.5 days, and 3.0 days for the 100 mg/day, 200 mg/day and 400 mg/day treatment groups respectively. The differences among treatment groups were not statistically significant.
- In this trial, nine patients had blood with bowel movements. Four subjects had blood in their stools after Day 4.
- The use of selected prior medications that is, vancomycin and metronidazole was also examined. At total of 9 patients were recorded as taking these medications (8 for metronidazole and 1 vancomycin) for CDAD prior to initiation of treatment with fidaxomicin. These consisted of 2 patients in the 100 mg/day treatment group who took metronidazole 500 mg three times daily for 10 days, one patient for 1 day and one patient for a single dose. Two patients in the 200 mg/day treatment group took either metronidazole 500 mg as 1 dose or vancomycin 500 mg q12h for 1 day (2 doses). Three

patients in the 400 mg/day treatment group took metronidazole 500 mg either three times daily for 10 days (one patient) or as 1 dose (2 patients). Four subjects took prohibited concomitant medications during the course of the study, one patient in the 100 mg/day treatment group, two patients in the 200 mg/day treatment group, and one patient in the 400 mg/day treatment group.

Evaluator's comment

Fidaxomicin administration (at 50, 100, 200 mg BID for 10 days) showed a dose response with clinical cure and relief of symptoms of CDAD increasing with increasing dose. A placebo comparator was not included but is considered appropriate due to the nature of the illness.

The results support the use of 200 mg 12 hourly dose administration for further clinical testing.

6. Clinical efficacy

There were two identically designed pivotal efficacy studies to support the regulatory approval of this product. The studies are summarised below:

6.1. Study 101.1.C.003

This was a Phase III, randomised, double-blind, placebo-controlled, parallel group study of efficacy and safety of 200 mg fidaxomicin orally every 12 h compared with 125 mg vancomycin orally every 6 h for 10 days in patients with *Clostridium difficile*-Associated Diarrhoea (CDAD). The study was carried out across multiple centres in Canada and the United States. The trial was designed as a non-inferiority comparison.

The eligible patients were male or female inpatients or outpatients, who were 16 years of age or older and who had CDAD as defined by:

- Diarrhoea; change in bowel habits, with > 3 unformed bowel movements (UBMs; or > 200 mL unformed stool for patients with rectal collection devices) in 24 h before randomisation; and
- Presence of either toxin A or B of *Clostridium difficile* in the stool within 48 h of randomisation.

Patients who failed at least a full 3-day course of metronidazole but continued to meet the definition of diarrhoea without any significant clinical improvement and remained toxin positive could also be enrolled.

Pre-treatment with metronidazole and/or vancomycin ≤ 24 h of randomisation for less than 4 doses was also allowed. However, use of other antibiotics for CDAD was an exclusion criterion.

Patients with multiple recurrences (> 1 prior occurrence) of CDAD within the past 3 months were excluded. Patients with history of ulcerative colitis and Crohn's disease were also excluded.

Due to ongoing development of the product, two formulations of fidaxomicin were used in this trial.

The sample size was calculated based on known rates of vancomycin efficacy in CDAD from literature which indicated that 530 evaluable patients (265 evaluable patients per group) will be needed to demonstrate non-inferiority of fidaxomicin to vancomycin with a delta of 10% that is, 90% power.

A total of 629 patients were randomised with 302 in fidaxomicin treatment group and 327 in vancomycin treatment group.

The eligible patients underwent stratified randomisation at each trial site on the basis of having experienced (yes/no) a single prior episode of CDAD in the 3 months prior to enrolment. The patients were randomised to the following two treatment groups:

1. Fidaxomicin treatment group – fidaxomicin 200 mg every 12 hours.
2. Vancomycin treatment group – vancomycin 125mg every 6 hours.

Both study drugs were administered by oral route. The duration of treatment was 10 days. Matching placebos were given in both arms to maintain blinding.

As there was no validated measure of severity of CDAD, none was included as part of trial protocol or randomisation. However, a non-validated scale was used as a covariate in the analysis.

The primary efficacy variable was rate of cure at End of Therapy (EOT) visit.

The secondary efficacy variable was recurrence rate at the end of post-study follow-up visit (study Day 36 to 40).

Both clinical outcomes (cure/failure, recurrence) were based on investigators' clinical assessment, most importantly diarrhoea.

For the primary variable, the patients were evaluated clinically during the 10 day treatment phase for assessment of clinical cure or failure.

The patients who, in the opinion of the investigator, required no further treatment 2 days after completion of study medication were considered cured.

The patients who had 3 or fewer unformed stools for 2 consecutive days and who remained well before study medication discontinuation were also considered cured.

The patients 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 also be considered cured at that time provided that no new anti-infective treatment was required for CDAD.

The patients who were considered cured based on stabilisation and improvement in signs and symptoms of CDAD were evaluated 2 to 3 days after the end of study medication. In the event that their signs or symptoms of CDAD worsened, the patients were to be designated primary failures. If they remained stable and were not considered not requiring further CDAD therapy to maintain their stable state, they were considered cured.

For the secondary variable, the cured patients were followed for 28 ± 2 days after the last dose of study medication for assessment of recurrence of CDAD.

The primary operational objective of the study was to show that a 10 day course of fidaxomicin 200 mg orally every 12 h was at least as efficacious as a 10 day course of vancomycin 125 mg orally every 6 h in the treatment of CDAD for achieving clinical cure at the End of Therapy. Two-sided 95% confidence intervals (CI) were computed for the difference in cure rates (fidaxomicin minus vancomycin). A lower limit of the 95%CI, no worse than -10%, was the predefined margin for demonstration of non-inferiority between the 2 drugs.

The secondary efficacy endpoint for this study was recurrence rate of CDI by 28 days ± 2 days after the last dose of study drugs. Two-sided 95% CIs were computed for the difference in treatment recurrence rates.

Two additional exploratory variables of clinical efficacy were assessed as follows:

1. Global Cure; defined as cure without experiencing a recurrence in the follow up period.

2. Time to resolution of diarrhoea (TTROD); defined as the time taken from start of treatment to achieving resolution of diarrhoea which was sustained through to the end-of-therapy (EOT).

All statistical analyses were performed on the modified intent-to treat (mITT) population and the Per Protocol (PP) populations.

As the numbers of centres with a small number of patients was expected to be relatively large, study centre was not included in statistical models, but the consistency of results across centres was evaluated by descriptive review of efficacy results presented by centre.

The subgroup analyses on efficacy endpoints were conducted by age, race, sex, baseline disease severity, country, prior recurrences, inpatient/outpatient status, stratification stratum, metronidazole failure status, and by the use of any antibiotic prescribed for CDAD within 24 h before study treatment. No interim analysis was conducted in this study.

Overall, 95% and 87% patients were included in mITT and PP analyses respectively for assessment of clinical cure and 82% and 69% patients were included in mITT and PP analyses respectively for assessment of recurrence.

The overall mean age of the sample population was 61.6 (± 16.9) years. The over ≥ 75 years old age group comprised 27% of the total. At baseline, the groups were reasonably balanced with respect to demographic and prognostic features including inpatient/outpatient status, number of bowl movements at baseline, baseline disease severity, prior use of antibiotics for CDAD and metronidazole failure.

The results were reported as follows:

- Based on mITT analysis, the proportion of patients judged by the investigator to have achieved clinical cure at the end of 10 day treatment (EOT) was 253/287 (88.2%) in fidaxomicin group compared to 265/309 (85.8%) in vancomycin group. The treatment difference was 2.4% with 95%CI of -3.1% to 7.8%. A similar result was obtained using PP population with cure rates of 92.1% for fidaxomicin and 89.8% for vancomycin (treatment difference 2.3% with 95%CI from -2.6 to 7.1). The non-inferiority was thus successfully demonstrated based on pre-defined criterion of a -10% margin.
- The cure rates for fidaxomicin were numerically higher but not statistically superior to vancomycin.
- A sensitivity analysis to assess the robustness of the primary result, using an alternative definition of cure that is, ≤ 3 unformed bowel movements during treatment sustained to the EOT, supported the primary results.
- Subgroup analyses based on a number of baseline features were carried out and indicated consistent effect across studied strata including the initial strain of *C. difficile* (BI/non-BI) and the 2 formulations used in the trial. The cure rates at most participating centres were similar in both study drugs.
- The secondary efficacy variable of rate of occurrence of recurrence was examined based on follow-up for 28 (±2) days after the last dose of study medications in patients who achieved cure at EOT.
- In mITT population, 39/253 (15.4%) patients in fidaxomicin group compared to 67/265 (25.3%) patients in the vancomycin group experienced clinical recurrence. The treatment difference was -9.9% in favour of fidaxomicin (p = 0.005) with 95%CI for the between groups treatment difference of -16.6% to -2.9%.
- In the PP population, 28/211 (13.3%) patients in fidaxomicin group compared to 53/221 (24.0%) patients in vancomycin group experienced clinical recurrence. The treatment difference was -10.7% with 95%CI from -17.9% to -3.3% (p = 0.004).

A modified recurrence analysis using alternative definition was provided.

A number of subgroup analyses were conducted and showed consistent effect across all studied strata. Notable instances where recurrence rates with fidaxomicin treatment were higher than with vancomycin treatment included Black participants (18.5% versus 11.1%), CDAD antibiotic 24 h prior to study ≥ 4 doses (44.4% versus 27.8% based on small numbers) and initial BI strain (27.1% versus 20.9%). Recurrence rates by centres were generally similar.

The median time to recurrence could not be calculated as recurrence rates were < 50% in both groups.

Global efficacy as judged by global cure rate which aimed to capture patients who achieved clinical cure at EOT without recurrence in the next 4 weeks of follow-up was 74.6% (214/287) in fidaxomicin treated patients compared to 64.1% (198/309) in vancomycin treated patients using mITT population. The treatment difference was 10.5% with 95%CI from 3.1% to 17.7% (p = 0.006). The results were similar using PP population.

The subgroup analyses for global cure rates also showed consistent effect across all strata. As noted earlier for the recurrence rate, the global response rate with fidaxomicin treatment (57.3%) was lower compared to that with vancomycin treatment (63.9%) when the initial strain of *C. difficile* was BI. The global cure rates by study centres were similar between the two groups.

The median time to resolution of diarrhoea (TTROD) in mITT population was 58 h (95%CI from 54 to 73 hours) in fidaxomicin group compared with 78 h (95%CI from 60 to 95 hours) in vancomycin patients. The group difference was not statistically significant.

At baseline, the mean unformed bowel movements (UBMs) were 8.1 (± 4.2) and 8.4 (± 5.4) per day in fidaxomicin and vancomycin groups respectively. On study Day 12, the mean UBMs per were 0.4 (± 1.3) and 0.7 (± 1.6) for fidaxomicin and vancomycin groups respectively.

For plasma pharmacokinetic results, please also see above under the *Pharmacokinetics* section.

At EOT, average OPT-80 faecal levels were in excess of 1000µg/g and OP-1118 levels were about 2/3 of the parent consistent with what has previously seen in the clinical studies. There was an indication of lower faecal levels and lower faecal level/MIC in patients who failed therapy. However, there was broad overlap between the ranges for cures and failures and the faecal levels were far in excess of the MIC in both cures and failures.

With respect to typing, many strains did not fit into an REA group (Non-Sp. REA; 148/415; 35.6%). BI was the most frequently isolated strain (158/415; 38.1%). The OPT-80 MIC_{90} values for all strains ranged between 0.003 and 0.5 µg/mL, with the overall MIC_{90} being 0.25 µg/mL.

Evaluator's comment

The trial successfully demonstrated equivalent efficacy with respect to clinical cure after 10 days of treatment with oral fidaxomicin (200 mg 12 hourly) compared to oral vancomycin (150 mg 6 hourly).

The fidaxomicin treatment was clinically and statistically superior to vancomycin treatment with respect to sustained efficacy that is, prevention of CDAD recurrence within 4 weeks after a 10 day course.

Microbiological examination of clinical isolates from the trial showed no apparent differences between the susceptibility of *C. difficile* strains isolated from clinical cures versus clinical failures.

6.2. Study 101.1.C.004

This was a also a randomised, double-blind, parallel group study to investigate the efficacy and safety of fidaxomicin 200 mg orally every 12 h compared with vancomycin 125mg orally every 6 h for 10 days in patients with *Clostridium difficile*-Associated Diarrhoea (CDAD). The design of the study was similar to the preceding Study 003 including the non-inferiority comparison. The study was carried out at multiple sites in Europe, Canada and the United State.

The eligible patients were male or female, 16 years of age or older, diagnosed with CDAD who had received no more than 24 h of CDAD treatment with vancomycin and/or metronidazole (up to four doses in total) but other antibiotic use for CDAD was an exclusion factor. Individuals who failed at least a full 3 day course of metronidazole but continued to meet the definition of diarrhoea without any significant clinical improvement and remained toxic positive were eligible to participate. Patients with more than 1 episode of CDAD in last 3 months and those with history of inflammatory bowel disease (ulcerative colitis and Crohn's disease were also excluded.

CDAD was defined as:

- Diarrhoea: change in bowel habits with > 3 unformed bowel movements (or > 200mL unformed stool for patients on rectal collection devices) in the 24 h before randomisation;

  and

- Presence of toxin A or B of *Clostridium difficile* in the stool within 48 h of randomisation for metronidazole failures, or within 96 h of randomisation for patients with ≤ 24 h pre-treatment with CDAD therapy.

Based on the results from the previous Study 003 which became available during planning of this study, the assumptions for sample size calculation were updated to 90% cure rate and 85% evaluability rate. The sample size thus required was 483 patients to achieve 90% power at a -10% non-inferiority margin. A total of 535 patients were randomised with 270 to the fidaxomicin treatment group and 265 to the vancomycin treatment group.

At randomisation, the patients were stratified based on having been with or without one episode of CDAD in 3 months preceding enrolment. The two treatment groups were as follows:

1. Fidaxomicin group (200 mg capsule every 12 hours)
2. Vancomycin group (125mg capsule every 6 hours)

The study drugs were administered orally. The duration of treatment was 10 days. The fidaxomicin formulation used in this trial was similar to the formulation 1 in the previous Study 003. The study drugs needed over-encapsulated in both trials and placebo for masking.

The primary efficacy variable was cure rate at end of therapy (EOT). The secondary efficacy variables were rate of recurrence and rate of global cure.

The patients were evaluated clinically during the 10 day course of therapy for clinical cure or failure. The cured patients were followed for 28 ± 2 days after the last dose of study drugs to ascertain recurrence.

Both clinical outcomes (cure/failure, recurrence) were based on investigator assessment of symptoms of CDAD in particular diarrhoea.

All patients in were also evaluated for global cure that is, cure without recurrence at any time up to the post-study follow visit.

The patients who were cured were evaluated for diarrhoea during the post-treatment follow-up from Days 36-40 (post-study visit). The patients with recurring diarrhoea were evaluated for the presence of toxin A and B. The co-administration of any oral or parenteral antibacterial was

captured up to the post-study visit. Toxin A and B assays were also performed at the early termination visit for patients who experienced clinical failure.

The patients who, in the opinion of the investigator, required no further CDI therapy 2 days after completion of study medication were considered cured.

The patients who had three or fewer unformed stools for two consecutive days and who remained well before study medication discontinuation were also considered cured.

The investigator assessment of cure was as follows:

At EOT, the patients with marked reduction in the number of unformed stools and whose residual and mild abdominal discomfort was interpreted by the investigator as recovering bowel could be deemed cured provided that no new anti-infective therapy for CDAD was required, and provided they remained stable for the two subsequent days following completion of study medication.

The patients who were considered cured based on stabilisation and improvement in CDAD signs and symptoms were evaluated 2 to 3 days after the completion of study medication. In the event that signs or symptoms of CDI worsened, patients were to be designated primary failures. If they remained stable and were not considered to have required further CDAD therapy to maintain their stable state, they were followed for recurrence as cures.

Another efficacy variable was time to resolution of diarrhoea (TTROD) defined as the time from start of treatment to resolution of diarrhoea which was sustained to EOT.

The primary statistical objective of the study was to show that a 10 day course of fidaxomicin 200 mg orally every 12 h was non-inferior to a 10 day course of vancomycin 125 mg orally every 6 h in the treatment of CDAD for achieving clinical cure at end of therapy. The primary efficacy endpoint was the cure rate at EOT. The pre-defined non-inferiority margin was -10% with respect to the treatment difference between the two groups.

A gate-keeping strategy was employed to control Type 1 error rate in testing secondary endpoints. If the non-inferiority of fidaxomicin to vancomycin was demonstrated for both the PP and mITT populations at 2-sided alpha 0.05, then the superiority comparison of treatments for recurrence rates was made (2-sided alpha = 0.05). If the treatment comparison for recurrence rates was statistically significant in favour of fidaxomicin for both the mITT and PP populations, then the superiority comparison of treatments for global cure All efficacy analyses was performed (2-sided alpha = 0.05).

All efficacy endpoints were also evaluated across several subgroups including age group, sex, race, prior occurrence of CDAD, country, baseline disease severity. CDAD antibiotic therapy received 24 h prior to study, metronidazole failure before study, concomitant antibacterial therapy, inpatient/outpatient status, and initial strain of *C. difficile* that is, BI strain/non-BI strain.

As the number of centres with a small number of patients was expected to be relatively large, the general consistency of results across centres was also evaluated only by descriptive statistics presented by centre.

Overall, 95% patients were included in the mITT analysis for clinical cure and 83% in the assessment of recurrence. A total of 8 patients (3.0%) patients in fidaxomicin group and 7 patients (2.6%) patients in vancomycin group discontinued due to adverse events.

The overall mean age of the sample population was 63.4 (± 18.1) years. Over 34% patients were in the age group ≥ 75 years. The groups were well balanced with respect to baseline demographic and prognostic features.

The results were as follows:

- In the mITT population at EOT, the clinical cure rate in fidaxomicin group was 87.7% (221/252) compared to 86.8% (223/257) in vancomycin group. The 95% CI for the treatment difference was 0.9% (95%CI -4.9%, 6.7%). Using PP population, the clinical cure rate in fidaxomicin group was 91.7% (198/216) compared to 90.6% (213/235) in vancomycin group. The treatment difference was 1.0% (95%CI -4.3%, 6.3%). The non-inferiority was thus successfully demonstrated based on pre-defined criterion.
- A supplemental analysis using modified definition of clinical cure (≤ 3 unformed bowel movements during treatment sustained to the EOT visit) supported the primary analysis.
- The subgroup analyses were generally consistent with the overall results including baseline BI/non-BI strain type as were results from individual centres.
- An exploratory logistic regression analysis was carried using both mITT and PP datasets to assess predictors of clinical cure. In the mITT population, baseline severity of disease and log-adjusted vancomycin MIC were the two covariates significantly associated with higher clinical cure while adjusting for all other covariates in the model. In PP population, prior CDAD therapy (lower rates if yes) and log-adjusted vancomycin MIC were significant covariates for achieving clinical cure. Prior metronidazole failure was not included in this model due to low numbers for this multiple logistic regression model to work.
- Using mITT population at 28 ± 2 days after EOT, the rate of recurrence of CDAD in fidaxomicin group was 12.7% (28/221) compared to 26.9% (60/223) in vancomycin group. The 95%CI for the treatment difference was -14.2% in favour of fidaxomicin treatment (95%CI -21.4%, -6.8%), $p < 0.001$. Using PP population at 28 ± 2 days after EOT, the rate of recurrence of CDAD in fidaxomicin group was 12.8% (23/180) compared to 25.3% (46/182) in vancomycin group. The 95%CI for the treatment difference was -12.5% in favour of fidaxomicin treatment (95%CI - 20.3%, -4.4%), $p = 0.002$.

A supplemental analysis using modified definition of recurrence supported the above findings.

The subgroup analyses for recurrence were consistent with the overall results including baseline BI/non-BI strain as were the results by individual centres.

An exploratory logistic regression analysis was carried using both mITT and PP datasets to assess predictors of recurrence. In the mITT population, no prior CDAD episode, lack of concomitant systemic antibacterial therapy, mild baseline severity and fidaxomicin treatment were the covariates significantly associated with lower risk of recurrence. In PP population, fidaxomicin treatment, no concomitant systemic antibacterial therapy, not receiving CDAD antibiotic within 24 h prior to study, low baseline severity, and no prior CDAD episode were significantly related to lower recurrence risk.

The median time to recurrence could not be calculated as recurrence rate was below 50% in both groups. The Wilcoxon test was statistically significant ($p < 0.0001$) in favour of fidaxomicin.

Using mITT population, the global efficacy, that is, cure without recurrence in the study in fidaxomicin group was 76.6% (193/252) compared to 63.4% (163/257) in vancomycin group. The 95%CI for the treatment difference was 13.2% in favour of fidaxomicin treatment (95%CI 5.2%, 20.9%), $p = 0.001$. The results were similar using PP population.

The subgroup analyses for global efficacy were consistent with the overall results including baseline BI/non-BI strain.

Exploratory logistic regression modelling indicted fidaxomicin treatment, absence of concomitant systemic antibacterial therapy and mild baseline severity of disease were statistically significantly associated with higher global cure rates in both mITT and PP populations.

In the mITT population, the median TTROD was 50 h (95%CI 30 to 66 hours) for patients in fidaxomicin group compared to 48 h (95%CI 31 to 63 hours) for patients in vancomycin group. The difference was not statistically significant.

At baseline, in the mITT population, the mean daily unformed bowel movements were 7.5 ± 4.4 versus 7.4 ± 4.4 in fidaxomicin and vancomycin groups respectively. On study Day 12, the mean unformed bowel movements were 0.5 ± 1.1 and 0.7 ± 1.6 in the two groups respectively.

Few faecal samples were available from clinical failures, but both mean faecal levels and fidaxomicin faecal level/minimum inhibitory concentration (MIC) ratios were similar between cures and failures, and faecal levels of fidaxomicin were far in excess of MIC. For further results, please see above under Pharmacokinetics section.

Evaluator's comment

The trial successfully demonstrated non-inferiority between fidaxomicin and vancomycin with respect to investigator assessed clinical cure after 10 days of treatment. Fidaxomicin was shown to be statistically superior to vancomycin for reducing recurrences within 4 weeks of treatment.

In consort with the preceding Study 003, the two trials provide reliable confirmatory evidence of efficacy. The trial design, comparator (vancomycin), the doses, the duration and the non-inferiority margin used in the trial are considered appropriate to the objective.

6.3. Evaluator's conclusions on clinical efficacy

The use of 200 mg fidaxomicin every 12 h was appropriate based on Phase II dose finding study. The two pivotal efficacy trials were appropriately designed. The follow up was complete especially with respect to the primary outcomes. The results, repeated in two separate and similarly designed double blind, active controlled studies, are considered reliable demonstration of efficacy of fidaxomicin over vancomycin in the treatment of CDAD.

7. Clinical safety

7.1. Studies providing evaluable safety data

Safety data were collected in all clinical studies included in the dossier and are summarised below by each study.

7.1.1. Study OPT-80-005 (PK and food effect study)

This was food effect study in healthy volunteers in which 6 participants (Group 1) were exposed to a single dose of 200 mg fidaxomicin and 28 participants (Group 2) were exposed to 2 separate single dose administrations of 400 mg fidaxomicin.

In Group 1, 2/6 participants reported headache.

In Group 2, 3/28 participants reported headache.

Overall, 24 treatment emergent adverse events were reported by 13 participants. No adverse events of severe intensity were reported. There were no serious adverse events or deaths or withdrawals due adverse events. No clinically significant changes were reported from laboratory tests, vital signs assessment or from ECGs.

7.1.2. Study OPT-80 1A-SD (single dose PK study)

This was a single dose study in healthy volunteers in which 6 participants were exposed to single 100 mg and 300 mg oral doses in two periods and another 6 participants were exposed to single 200 mg and 450 mg oral doses in two periods.

There was a single report of headache in one subject and report of elevated amylase and lipase in another subject. Both events were reported to have resolved. The amylase and lipase in the affected subject were normal at screen but were elevated at pre-dose.

7.1.3. Study OPT-80 1B-MD (multiple dose PK study)

A total of 18 healthy volunteers were exposed to multiple doses of fidaxomicin in this study. Six participants each received 150 mg or 300 mg or 450 mg once daily oral fidaxomicin for 10 days.

There were 2 reports of headache; one each in 150 mg and 450 mg dose group. There was one report each of weakness, fatigue, dizziness, rash and pruritus. A instance of eosinphilia was reported to be due to lab error.

7.1.4. Study OPT-80-007 (cyclosporine interaction study)

This was a single dose (200 mg fidaxomicin) study with and without cyclosporine in two periods.

Overall 6 adverse events (AEs) were reported comprising of one 1 AE reported after administration of 200 mg fidaxomicin alone and 5 AEs reported after co-administration with cyclosporine. These included 2 cases of abdominal discomfort and 1 case each of diarrhoea, chest discomfort and pain in extremity on co-administration of the two drugs. One case of diarrhoea was reported on fidaxomicin alone administration.

There were no deaths or SAEs.

7.1.5. Study OPT-80-008 (digoxin interaction study)

This was a multiple dose study in which 14 healthy volunteers were administered 200 mg oral fidaxomicin every 12 h for 10-12 days. They also received a single dose of digoxin with and with fidaxomicin (at steady state) during the study.

Overall, a total of 28 AEs were reported by 10 participants. All were of mild or moderate intensity. There were no severe or serious AEs and none led to premature discontinuation.

There was no evidence of higher frequency of adverse events, including headache, on co-administration of the two drugs compared to administration alone.

7.1.6. Study OPT-80-009 (CYP450 probe study)

In this study 25 healthy volunteers received 200 mg oral fidaxomicin every 12 h for one week. They also received cocktail of warfarin, omeprazole and midazolam with and without fidaxomicin.

Overall, a total of 23 AEs were reported by 14 participants with 6 AEs reported following administration of the cocktail, 5 AEs reported following administration of fidaxomicin and 12 AEs reported following co-administration.

The AEs with the highest reported incidence included dizziness (3 AEs), chest discomfort (2 AEs) and diarrhoea (2 AEs). There was one instance of clinically significant increase in eosinophil count (4 x ULN) on Day 21 through to Day 34 in fidaxomicin alone group. This AE led to the subject's discontinuation from the study.

Slight elevations in INR (1.2 to 1.7) were observed in several subjects. However, no trend was evident toward longer INRs when warfarin was taken in combination with fidaxomicin.

7.1.7. Study OPT-80-2A (Phase II dose selection study)

This was a parallel group study in which 48 CDAD patients were treated with oral fidaxomicin (16 patients each with 50 mg or 100 mg or 200 mg every 12 hours) for 10 days.

A total of 9/48 (19%) patients treated reported an AE during the study; 4 patients in the 100 mg/day treatment group, 4 patients in 200 mg/day treatment group and 1 patient in 400 mg/day treatment group.

One death was reported in the study in the 200 mg/day (100 mg every 12 hours) group on Day 10 due to staphylococcal sepsis and cerebral haemorrhage.

A total of five SAEs, including death from cerebral haemorrhage noted above, were reported in 5 patients. These include one case each of gastrointestinal haemorrhage, congestive heart failure, diarrhoea and chest pain.

7.1.8. Study 101.1.C.003 (Phase III Pivotal Efficacy Study 1)

In this pivotal efficacy/safety study 300 and 323 adult CDAD patients were treated with oral fidaxomicin (200 mg 12 hourly) and oral vancomycin (150 mg 6 hourly) respectively for 10 days.

At least one Treatment Emergent AE (TEAE) was reported in 62.3% fidaxomicin treated patients compared to 60.4% vancomycin treated patients.

Gastrointestinal Disorders (25.0% versus 22.3%) followed by General Disorders (15.3% versus 16.7%) and Infections (21.3% versus 19.5%) were the most commonly reported system organ classes in fidaxomicin and vancomycin groups respectively. The incidences of some selected AEs in fidaxomicin versus vancomycin groups were anaemia (3.3% versus 2.2%), arthralgia (2.0% versus 0.6%), headache (6.7% versus 4.3%), dizziness (4.0% versus 1.2%) and rash (3.0% versus 0.6%) respectively.

Incidence of TEAE leading to dose reduction or drug stopping temporarily was 0.7% in fidaxomicin group compared to 0.9% in vancomycin group. Incidence of TEAE leading to permanent drug stopping or discontinuation from study was 7.7% in fidaxomicin group compared to 9.0% in vancomycin group.

SAEs were reported in 25.0% fidaxomicin patients compared to 24.1% vancomycin patients.

All-cause mortality was 5.3% (16/300) for fidaxomicin compared to 6.5% (21/323) in vancomycin group.

There was no definitive trend in mean haematology or mean biochemical changes in either treatment group. Similarly no definitive trend was obvious in assessment of vital signs.

From baseline to end of treatment, the assessment of ECG showed that mean RR interval was increased by 27. 8 ± 153.2 msec in fidaxomicin compared to 6.5 ± 124.0 msec in vancomycin group.

From baseline to the end of treatment, change in QTcF > 30 msec was reported in 4/253 (1.6%) fidaxomicin patients compared to 4/264 (1.5%) vancomycin patients. At the end of treatment QTcF interval > 500 msec was reported in 4/253 (1.6%) fidaxomicin treated patients compared to 5/264 (1.9%) vancomycin treated patients.

There was a report of (multiple) pregnancy in a 19 years old Black patient in fidaxomicin treatment group. The pregnancy was confirmed in this patient on Day 25 with detection of 5 live intrauterine foetuses. The age of pregnancy at this time was approximately 4 weeks. Subsequently, there was one intrauterine death on Day 126. The remaining foetuses were delivered approximately 3.5 months premature with 3 live including one with cleft palate and 1 deceased foetus. The patient had significant and ongoing morbidities and was being treated for precursor B cell lymphocytic leukaemia at the time of developing CDAD and enrolment into the fidaxomicin trial.

A 66 year old male patient in fidaxomicin group reported an anaphylactic reaction. The patient experienced elevated INR and received an injection of vitamin K and frozen plasma for the elevated INR on Day 2 of the study. Approximately 20 minutes later, the patient developed

nausea, vomiting and hypotension. The symptoms resolved after about 3.5 h and the patient completed therapy with fidaxomicin with an outcome of cure and no further reactions.

There was one report of drug overdose in this trial when a 64 years old woman was given full daily dose (400 mg) of fidaxomicin at a single time on Day 3 of the study. No adverse effects were reported. The patient was withdrawn and commenced on vancomycin.

Results of susceptibility testing of clinical isolates at baseline by REA type and by antibiotic and by clinical outcome have been noted elsewhere in the report.

7.1.9. Study 101.1.C.004 (Phase III Pivotal Efficacy Study 2)

In this pivotal efficacy/safety study 264 and 260 adult CDAD patients were treated with oral fidaxomicin (200 mg 12 hourly) and oral vancomycin (150 mg 6 hourly) respectively for 10 days.

At least one Treatment Emergent AE (TEAE) was reported in 70.5% fidaxomicin treated patients compared with 68.1% vancomycin treated patients. Incidence of TEAE leading to dose reduction or drug stopping temporarily was nil in fidaxomicin versus 1.9% in vancomycin group. Incidence of TEAE leading to drug stopping or study discontinuation was 8.3% in fidaxomicin versus 7.7% in vancomycin group.

Gastrointestinal Disorders (32.2% versus 33.8%) followed by General Disorders (14.0% versus 18.1%) and Infections and Infestations (19.7% versus 17.3%) were the most commonly reported system organ classes in fidaxomicin and vancomycin groups respectively. Reported incidences of select AEs were abdominal pain (8.7% versus 4.2%), constipation (4.2% versus 2.3%), abdominal distension (3.4% versus 1.9%), sepsis (2.3% versus 0.8%), ECG QT prolonged (2.7% versus 1.2%) and cough (2.7% versus 0.8%) for fidaxomicin versus vancomycin groups respectively.

All-cause mortality was 7.6% (20/264) in fidaxomicin group compared to 6.5% (17/260) in vancomycin group.

Any SAE was reported in 26.5% fidaxomicin treated patients compared with 22.3% vancomycin groups patients.

Laboratory shifts in haematology variables in provided in Table 4. Marked changes in blood biochemistry and haematology are provided in Table 5.

Table 4. Study 101.1.C.004. Laboratory test shift table. Baseline versus end of therapy. haematology. Safety population.

		Vancomycin				OPT-80		
		End of Therapy Value[1]				End of Therapy Value[1]		
Laboratory Test	n	Low	Normal	High	n	Low	Normal	High
HEMATOCRIT								
Baseline Value								
Low	79	60	19	0	96	77	19	0
Normal	104	12	92	0	111	13	98	0
High	1	0	1	0	0	0	0	0
HEMOGLOBIN								
Baseline Value								
Low	106	88	18	0	117	99	18	0
Normal	91	12	79	0	99	14	85	0
High	1	0	1	0	0	0	0	0
PLATELETS								
Baseline Value								
Low	15	9	6	0	16	8	8	0
Normal	139	3	104	32	156	1	125	30
High	32	0	7	25	26	0	8	18
RBC								
Baseline Value								
Low	97	86	11	0	115	93	22	0
Normal	101	13	88	0	101	16	83	2
High	0	0	0	0	0	0	0	0
WBC								
Baseline Value								
Low	9	8	1	0	16	13	3	0
Normal	133	5	114	14	113	6	98	9
High	56	0	34	22	87	0	57	30

[1] End of therapy or early withdrawal

Note: Only subjects with both baseline and End of Therapy lab test are included in this evaluation.

Abbreviations: RBC = red blood cell; WBC = white blood cell

Table 5. Study 101.1.C.004. Summary of clinically significant, treatment emergent and markedly abnormal laboratory test abnormalities. Safety population.

	End of Therapy or Early Withdrawal[1]	
	Vancomycin	OPT-80
Laboratory Test	(N=260)	(N=264)
Biochemistry		
ALBUMIN		
n[1]	205	225
Low n (%)	1(0.5)	4(1.8)
ALKALINE PHOSPHATASE		
n[1]	221	235
High n (%)	0(0.0)	1(0.4)
ALT (SGPT)		
n[1]	204	223
High n (%)	1(0.5)	5(2.2)
AST (SGOT)		
n[1]	195	217
High n (%)	1(0.5)	2(0.9)
Biochemistry		
BICARBONATE		
n[1]	204	224
Low n (%)	2(1.0)	3(1.3)

Table 5 continued. Study 101.1.C.004. Summary of clinically significant, treatment emergent and markedly abnormal laboratory test abnormalities. Safety Population.

Laboratory Test	End of Therapy or Early Withdrawal[1] Vancomycin (N=260)	OPT-80 (N=264)
Biochemistry		
CALCIUM		
n[1]	221	235
Low n (%)	2(0.9)	3(1.3)
High n (%)	1(0.5)	0(0.0)
CHOLESTEROL		
n[1]	221	235
High n (%)	1(0.5)	2(0.9)
CREATININE		
n[1]	221	235
High n (%)	2(0.9)	2(0.9)
GLUCOSE		
n[1]	203	222
Low n (%)	1(0.5)	1(0.5)
High n (%)	12(5.9)	15(6.8)
PHOSPHORUS		
n[1]	218	231
Low n (%)	4(1.8)	3(1.3)

Laboratory Test	End of Therapy or Early Withdrawal[1] Vancomycin (N=260)	OPT-80 (N=264)
Biochemistry		
POTASSIUM		
n[1]	217	228
Low n (%)	1(0.5)	0(0.0)
High n (%)	4(1.8)	4(1.8)
SODIUM		
n[1]	221	235
Low n (%)	2(0.9)	3(1.3)
High n (%)	0(0.0)	1(0.4)
URIC ACID		
n[1]	221	235
High n (%)	1(0.5)	3(1.3)
Hematology		
HEMOGLOBIN		
n[1]	198	217
Low n (%)	3(1.5)	0(0.0)
LYMPHOCYTES (ABS)		
n[1]	194	211
Low n (%)	6(3.1)	9(4.3)

Table 5 continued. Study 101.1.C.004. Summary of clinically significant, treatment emergent and markedly abnormal laboratory test abnormalities. Safety Population.

	End of Therapy or Early Withdrawal[1]	
	Vancomycin	OPT-80
Laboratory Test	(N=260)	(N=264)
Hematology		
NEUTROPHILS (ABS)		
n[1]	194	211
Low n (%)	0(0.0)	3(1.4)
PLATELETS		
n[1]	186	199
Low n (%)	0(0.0)	1(0.5)
WBC		
n[1]	198	217
Low n (%)	1(0.5)	4(1.8)

[1]Indicates number of subjects with observed data at baseline and End of Therapy or early withdrawal. Subjects are counted only once for markedly abnormal value. The n numbers used for the denominators in calculating percents are the total number of subjects with data for a particular laboratory test for each treatment.

Note: Only laboratory test results where the test results are worse than 2 or more NCI grades from baseline value are summarized in this table. NCI grades are protocol-defined. The criteria for markedly abnormal laboratory tests can be located in the protocol in Attachment 2.

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; WBC = white blood cell

There were no significant changes in vital signs.

From baseline to the end of treatment, change in QTcF > 30msec was reported in 18/229 (7.9%) fidaxomicin treated patients compared to 17/219 (7.8%) vancomycin treated patients. At the end of treatment, QTcF interval > 500msec was reported in 3/229 (1.3%) fidaxomicin treated patients compared to 6/219 (2.7%) vancomycin treated patients. One case of Torsades de Pointes was reported in the vancomycin group.

7.1.10. Pooled data (2 Phase III studies)

A total of 564 CDAD patients were treated with fidaxomicin in the two pivotal clinical trials compared to 583 vancomycin treated patients. AEs were reported in 68.3% and 65.5% patients in the two groups respectively. Notable AEs (incidence ≥ 2%) with frequency higher in fidaxomicin treated group compared to vancomycin treated group respectively were anaemia (2.5% versus 2.1%), vomiting (7.3% versus 6.3%), abdominal pain (5.9% versus 3.9%), constipation (4.4%, 2.1%), hypokalemia (7.3% versus 6.5%), hyperkalemia (2.8% versus 1.7%), headache (6.6% versus 4.6%), dizziness (2.8% versus 2.1%) and dyspnoea (2.5% versus 2.2).

A total of 5.9% patients in fidaxomicin and 6.9% patients in vancomycin groups experienced AEs leading to discontinuation for the study drug. SAEs were reported in 25.7% fidaxomicin treated patients compared to 23.2% vancomycin treated patients. Notable SAEs (≥ 2 patients) with higher occurrence in fidaxomicin treated group compared to vancomycin treated group respectively were anaemia (4 versus 2), leucopenia (4 versus 1), thrombocytopenia (3 versus 2), lymphopenia (3 versus 2), neutropenia (4 versus 0), congestive cardiac failure (5 versus 3), myocardial infarction (4 versus 2), atrial fibrillation (4 versus 1), gastrointestinal hemorrhage (4 versus 1), intestinal obstruction (4 versus 1), abdominal pain (4 versus 1), megacolon (3 versus 0), haemorrhagic diarrhoea (2 versus 0), colitis (2 versus 0), chest pain (2 versus 1), sepsis (7 versus 5), bacteraemia (2 versus 1), hip fracture (2 versus 1), blood uric acid increased (5 versus 1), lymphocyte count decreased (4 versus 1), liver function tests abnormal (2 versus 1), WBC count decreased (2 versus 0), neutrophil count decreased (2 versus 1), hyponatremia (6 versus 3), hyperkalemia (5 versus 2), hypophosphatemia (5 versus 0), hypoglycaemia (3 versus 0), acute renal failure (4 versus 3), respiratory distress (3 versus 0), hypoxia (2 versus 1), chronic obstructive pulmonary disease (2 versus 0) and hypotension (2 versus 1).

Gastrointestinal treatment-emergent adverse events (TEAEs) were reported in 31.4% fidaxomicin treated patients compared with 29.0% vancomycin treated patients. Identified GI bleeding TEAEs were reported in 4.1% fidaxomicin treated patients compared to 3.1% vancomycin treated patients.

Shifts in WBCs (preferred terms of febrile neutropenia, granulocytopenia, leucopenia, lymphopenia, neutropenia, pancytopenia, neutropenic sepsis, WBC disorder, lymphocyte count abnormal, lymphocyte count decreased, neutrophil count decreased, WBC decreased) were more prevalent in fidaxomicin treated group (4.1%) compared to vancomycin treated group (1.9%).

The incidence of increased alanine aminotransferase was 1.6% in fidaxomicin treated group compared to 1.0% in vancomycin treated group.

AEs leading to death were reported in 36/564 (6.4%) fidaxomicin treated patients compared to 38/583 (6.5%) vancomycin treated patients.

7.1.11. Postmarket data

The total exposure estimate for the current aggregate reporting period based on overseas (US and some Canadian exposure) approval (27 May 2011 to 26 November 2011) is approximately 5414 patient-courses of therapy.

A total of 47 individual safety reports were received with a total of 121 reported events including 5 reports with a fatal outcome were received. The reports designated *serious and unlisted* included Infections and Infestations (9; most frequent PT was Clostridial infection [4]), Cardiac disorders (5; all PTs were n=1), Gastrointestinal disorders (5; all PTs were n = 1), and Investigations (5; most frequent PT was WBC count increased [2]). The most frequent serious unlisted PT was Clostridial infection (n=4). The most frequent non-serious unlisted PTs included diarrhoea (n=9), Clostridial infection (n=5) and *C. difficile colitis* (n=4).

Possible hypersensitivity reactions reported in the post-marketing setting and in Phase III trials were also reviewed. Overall, 20 cases of rash were identified searching both the global safety and clinical trial databases: 16/564 (2.8%) fidaxomicin treated patients experienced skin rash and 4 cases of rash were reported in spontaneous post-marketing reports. All 20 cases reported mild to moderate rash events that resolved on discontinuation with or without treatment.

7.2. Evaluator's comment on clinical safety

The safety dataset is limited comprises about 120 healthy adult volunteers exposed to fidaxomicin in pharmacokinetic studies and 52 healthy adult volunteers exposed to fidaxomicin in drug-drug interaction studies. Most of this experience was single dose exposure. A total of 612 adult CDAD patients (260 males; 352 females) including elderly (≥ 65 years old; n = 285) were exposed to fidaxomicin in the 3 Phase II and Phase III studies for treatment up to 10 days.

Another limitation in assessment of the adverse effects profile is the issue of confounding by the underlying disease especially with respect to effects on electrolytes, haematology and gastrointestinal adverse events. Placebo controlled data is not available.

Despite these limitations, it can be concluded due to the controlled nature of the data that the overall adverse effects profile of oral fidaxomicin is similar to oral vancomycin in the treatment of CDAD including deaths and SAEs although the pattern for SAEs is somewhat different in the two groups. For fidaxomicin, the haematological effects especially on white blood cells and effects on hepatic function (enzymes) will need further data for convincing attribution.

8. First round benefit-risk assessment

8.1. First round assessment of benefits

The clinical efficacy of 10 day course of 200 mg oral fidaxomicin every 12 h was found to be similar (non inferior) to 10 day course of 150 mg oral vancomycin every 6 h in the treatment of CDAD with respect to the physician's assessment of clinical cure based on signs and symptoms of disease in particular diarrhoea (88% versus 86% and 88% versus 87% in the two trials).

However, fidaxomicin treatment provided clear advantage and was superior to the comparator vancomycin in preventing recurrence of disease within 4 weeks of completion of therapy (14% versus 26% respectively across both pivotal clinical studies).

The global cure rate which may be interpreted as sustained clinical response, that is, clinical cure without recurrence within 4 weeks was also statistically and clinically higher with fidaxomicin treatment than with vancomycin.

8.2. First round assessment of risks

Neutropenia in association with fidaxomicin may need to be monitored. The risk of development of resistance is considered low.

Please also see the accompanying RMP evaluation.

8.3. First round assessment of benefit-risk balance

Overall, the benefit-risk balance is considered in favour of fidaxomicin use in the treatment of CDAD and provides potentially advantages over the currently approved drug vancomycin in this condition such as lower rate of recurrence within 4 weeks of treatment, narrower spectrum of activity low potential to affect resident gastrointestinal flora, simple pharmacokinetics and easier twice daily dosing regimen.

The fidaxomicin treatment also provides potential benefit of lower risk of contributing to antibiotic resistance since cross resistance with other antibiotic groups has not been observed and a lower risk of colonisation with vancomycin resistant enterococcus (VRE) observed the clinical study.

9. Second round evaluation of clinical data submitted in response to questions

The following further information was sought from the sponsor during course of the evaluation:

> ***Question 1: Study OPT-80-1B-MD: it is not clear why no faecal OPT-80/Op-1118 were detected in 6 out 24 participants even though the samples seem to have been available for all~~participants. The sponsor is requested to provide comment.***

Sponsor's response: No fidaxomicin concentrations were present in the faeces of 6 subjects because each group (3 groups) contained 2 placebo-treated subjects.

TGA response: Noted.

Question 2. Study OPT-80-007 (cyclosporine interaction study): Although fidaxomicin is a substrate for P-gp, given the proposed recommendation that cyclosporine/fidaxomicin co-administration be allowed, has the effect of fidaxomicin on cyclosporine been studied or provide comment why the two way interaction is not considered applicable especially on multiple dosing?

Sponsor's response: Cyclosporine is a powerful P-glycoprotein (P-gp) inhibitor, and the objective of this study was to determine the impact of P-glycoprotein inhibition on fidaxomicin pharmacokinetics. Fidaxomicin has been poorly characterised, however, as a test substrate for P-glycoprotein, and the importance of P-gp in its intestinal uptake is unclear. While cyclosporine has been reported to be a P-gp substrate (Fricker, 1996), polymorphisms in MDR1 have not been shown to explain differences in pharmacokinetics of cyclosporine (Haufroid, 2004) and much of the variability is associated instead with polymorphisms in CYP3A4, suggesting that the latter is the major contributor to variability in bioavailability. Substrate-based drug interactions have been reported at the level of the kidney, in terms of increased nephrotoxicity in the presence of P-gp inhibitors in renal epithelial cells (Anglicheau, 2006). Because fidaxomicin has minimal absorption (ng/mL concentrations in the plasma, well below the μg/mL IC_{50} for inhibition of P-gp), this interaction is predicted to be irrelevant for fidaxomicin. Cyclosporine is metabolised by CYP3A4, and while fidaxomicin is a very weak inhibitor of CYP3A4, another DDI study (OPT-80-009) demonstrated no impact of fidaxomicin on the pharmacokinetics of CYP3A4 substrate midazolam. Thus, such an interaction was also considered unlikely. Because of the generally conflicting results reported in the literature as to the impact of P-gp on cyclosporine uptake, it was decided to use a more specific test substrate, digoxin, to evaluate the potential impact of P-gp inhibition. Administration with fidaxomicin had no clinically relevant impact on digoxin pharmacokinetics. It is worth noting that although cyclosporine pharmacokinetics were not compared in a crossover manner in this study (there was no cyclosporine-only dosing sequence), cyclosporine concentrations were measured in the presence of fidaxomicin dosing. Cyclosporine concentrations measured (C_{max}, 395 ± 95 ng/mL following a 200 mg dose) were similar to cyclosporine concentrations reported by others using an equivalent assay (LC-MS, rather than ELISA, which can cross-react with metabolites and overestimate concentrations), when adjusted for dose (after a 100 mg dose, Cmax was 254 ± 85ng/mL) [Najib, 2003].

TGA response: This reply was also quoted earlier in discussing interaction with cyclosporine. As noted earlier, this interaction (and with digoxin and warfarin) are small in quantitative terms but may be clinically significant in patient population under treatment. Although no dose adjustments are proposed but monitoring including therapeutic drug measurements on individual risk assessment basis may be required when fidaxomicin is given to these patients.

Question 3. Are any other interaction studies being done or planned such as co-administration with dabigatran?

Sponsor's response: No specific DDI studies are planned around P-gp, however, targeted pharmacovigilance activities include aggregate review of patients who are reported to have received concomitant p-gp inhibitors for identification of potential safety signals.

TGA response: Noted.

Question 4. Please confirm whether commercial formulation was used in Phase II and both Phase III trials. If not please outline the differences.

Sponsor's response: The commercial formulation (200 mg film coated tablet) was used in both Phase III studies (101.1.C.003 and 101.1.C.004). Below, see Table 6 for a list of all formulations used during development. A 50 mg powder-filled capsule was used in study, OPT-80 Phase IIA.

Table 6. Batch History of Fidaxomicin Clinical Trial Material

Clinical Study Number	Dosage Strength and Form	Drug Substance Lot(s)	Drug Product Lot	Site of Manufacture	Date of Manufacture
OPT-80 1A-SD	50 mg liquid-filled capsule	92161001	030728	Pharmatek	Jul 2003
OPT-80 1B-MD OPT-80 Phase 2A	50 mg powder-filled capsule	92161901 92161902 92161903	04C12	Stason	Mar 2004
		93161001 93161002 93161901	04J40		Sep 2004
101.1.C.003	200 mg uncoated tablet (Form B Drug Substance)	B-0560065	181338	Par	Feb 2006
		B-0660017	183194		Aug 2006
101.1.C.003 101.1.C.004	200 mg film coated tablet (Form A Drug Substance)	B-0660051	184732	Par	Jan 2007
		B-0660064	R0240001	Patheon	Oct 2007
		B-0660051 B-0660072	R0242001		Oct 2007
		B-0660051 B-0660064	R0242002		Oct 2007

TGA response: Noted.

Question 5. Study 101.1.C.003: It is not clear why a small number of patients had detectable levels of OPT-80 and OP-1118 in plasma prior to dosing on Day 1 of the study. Please provide comments.

Sponsor's response: Seven subjects in Study 003 had "pre-dose" levels above the quantification limit at the start of study. Of these, 1 had the first sampling time point on the second day of dosing, explaining the measurable concentration. The other 6 may be "post-dose" samples placed in "pre-dose" tubes, since:

- In two cases the "post-dose" sample was "missing" and two "pre-dose" tubes were received and analysed,
- In one case only one pre-dose sample was analysed but the post-dose sample was missing (although recorded as having been collected), and the last three are potentially duplicate post-dose samples inadvertently placed in predose tubes, as the fidaxomicin concentrations are virtually identical between the "predose" and "post-dose" samples; this suggests that these were duplicate samples inadvertently placed in pre-and post-dose tubes, rather than both being placed in post-dose tubes.
- While human error cannot be eliminated entirely in sample collection, these events are expected to have been very infrequent based on the rarity of the positive pre-dose samples (only 6 out of 265 pre-dose samples were positive.) Thus, these rare errors would have had no significant impact on the outcomes or conclusions of the pharmacokinetic analysis overall.

TGA response: Noted.

Question 6. Please provide Australian prevalence data for CDAD, if available. Please provide a copy of the Ferguson (2011) paper referred to in the sponsor's assessment of risk of antibiotic resistance development. Has infection with virulent strain (NAP1/BI/027) been reported here? Has any data on epidemiological breakpoints become available?

Sponsor Response: The Ferguson, 2011 reference was provided with the current submission; in general, there are few studies of *C. difficile* incidence in Australia. Although this paper notes that there are limitations to the data captured (that is, reporting was voluntary, one site could not report data, and there was no central control regarding what stools were tested, what criteria were used for select stools for testing, or what tests were used), the estimated incidence they report is 18.0-35.8 cases per 100,000 population. NAP1/BI/027 has been reported in Australia, although the incidence is as yet unknown (Riley, 2009; Richards, 2011). An epidemiological cut off (ECOFF) value of 0.5 µg/mL was set up by EUCAST based on Minimal Inhibitory Concentration (MIC) data from the two fidaxomicin clinical trials and from 5 other independent laboratories as listed below in Table 7.

Table 7. *In vitro* studies of Fidaxomicin MIC distributions against clinical *C. difficile* isolates.

Total	Distribution of MIC (µg/mL) Values											Total	MIC Range	MIC_{50}	MIC_{90}
				0.015	0.03	0.06	0.125	0.25	0.5	1	2				
101.1.C. 004 trial	0	0	9	20	28	75	144	90	24	1	0	391	0.007-1	0.125	0.25
101.1.C. 003 trial	0	2	5	17	37	112	156	95	9	0	0	433	0.004-0.5	0.125	0.25
Karlowsky, 2008	0	0	0	0	0	2	73	65	51	17	0	208	0.06- 1	0.25	0.5
Hecht, 2007	0	0	0	9	11	29	50	11	0	0	0	110	0.015-0.25	0.125	0.125
Finegold, 2004	0	0	0	0	0	7	11	3	1	0	1	23	0.06-2	0.125	0.25
Credito, 2004	-	-	-	12	0	3	2	1	0	0	0	18	≤0.016 - 0.25	≤0.016	0.125
Ackermann, 2004	117	49	21	16	1	3	0	0	0	0	0	207	≤0.0009-0.06	0.0019	0.0078

The rational for choosing 0.5 (in lieu of 1)µg/mL as ECOFF was based on the fact that isolates with MIC of 1 µg/mL were mostly observed in one laboratory in Canada (Karlowsky, 2008). Because of the generally high MIC range at this site (0.06-1 µg/mL) and the nearly exclusive localization of the isolates with an MIC of 1µg/mL to this single site, EUCAST could not rule out the possibility that the MIC values of 1 µg/mL reflected a slight but systematic bias to the MIC values at this site (despite QC results that were within acceptable ranges). Since then, however, *C. difficile* isolates with MIC of 1 µg/mL have also been reported and identified during our ongoing surveillance study. The ongoing surveillance investigation is a post-marketing study that involves participation of six US centres and has so far resulted in testing of over 470 isolates from different geographic locations (Snydman, 2012).

TGA response: The ECOFF is recommended for inclusion in the Australian PI.

Question 7. Please provide comment on surveillance studies of C. difficile that are being planned internationally. Will surveillance program be instituted in Australia? This may have been included in the RMP in refer to RMP should be sufficient.

Optimer has, thus far, implemented surveillance in the US and is setting up surveillance in Canada (to begin in approximately first quarter of 2013), the two regions for which it is the marketing authorization holder, Astellas Pharma Europe Ltd., the MAH in Europe, has initiated surveillance in Europe. STA is evaluating the best method to conduct surveillance in Australia (that is, either arrange for sentinel sites in Australia to submit toxin-positive stool samples/*C. difficile* isolates to an existing program, or alternatively initiate a new local program).

10. Second round benefit-risk assessment

10.1. Second round assessment of benefits

The expected benefits of treating CDAD with 10 day course of fidaxomicin (200 mg every 12 hours) compared to vancomycin (125 mg every 6 hours) remain unaltered that is, non-inferior clinical response at end of therapy (88% versus 86% and 88% versus 87% in the two pivotal trials respectively) and superior sustained efficacy in terms of recurrence at 4 weeks after completion of treatment (15% versus 25% and 13% versus 27% in the two pivotal studies respectively).

10.2. Second round assessment of risks

The expected risks and need for further collection of data such as incidence of neutropenia remain unchanged.

Drug-drug interactions assessed during the development indicate only small magnitude of changes in pharmacokinetic on use with P-gp or CYP substrates. However, these may be meaningful in clinical practice and for narrow therapeutic index drugs such as cyclosporine, digoxin and warfarin, concomitant use with fidaxomicin may need monitoring.

The risk of development of resistance is low but non-negligible and will require systematic surveillance.

10.3. Second round assessment of benefit-risk balance

Overall, the risk-benefit balance is in favour of benefit especially in light of sustained efficacy at 4 weeks compared to vancomycin and the postulated low potential for cross-resistance.

11. Second round clinical summary and conclusion

Vancomycin is the currently only approved antibiotic for use in the treatment of *Clostridium difficile* Associated Diarrhoea (CDAD), although a number of other antibiotics such as metronidazole are used off label in clinical practice. Oral vancomycin acts locally whereas metronidazole is absorbed systemically.

The evidence of clinical efficacy of fidaxomicin presented in this dossier relied on the two pivotal clinical efficacy trials. Both were similarly designed, active (oral vancomycin) controlled, randomised, double blind trials in adult CDAD patients and successfully established non-inferiority of 10 day course of 200 mg oral fidaxomicin every 12 h to 150 mg oral vancomycin every 4 h with respect to clinical cure (physician ascertained resolution of signs and symptoms of CDAD based on clinical examination and patient kept daily diary). The trials were well

planned there were no identifiable critical shortcoming in design or execution. The non-inferiority was tested using both modified ITT (88% versus 86% and 88% versus 87% respectively in fidaxomicin and vancomycin groups in the two trials) and PP statistical populations and the lower side 95% confidence interval for the treatment difference fell safely within the predefined maximum tolerable inferiority margin.

Furthermore, fidaxomicin was statistically and clinically superior to vancomycin with respect to prevention of recurrence of CDAD (relapse within 28 days of competing treatment) of disease and higher global cure (clinical cure without relapse up till 28 days after completion of therapy).

Where the evidence for efficacy is considered reliable and confirmatory, the dataset for safety evaluation is too small (about 565 fidaxomicin treated patients in the 2 pivotal trials) to enable full safety characterisation of the drug. Based on the limited data in this dossier, the adverse effects profile of fidaxomicin treatment was similar to the comparator vancomycin.

Other advantages of fidaxomicin include simple pharmacokinetics, local action without significant systemic absorption, long post antibiotic effect (although its significance is unclear), lack of CYP450 interactions, narrow spectrum of antimicrobial activity, lack cross resistance to other antibiotics and expected low risk of development of resistance.

Fidaxomicin achieves very high faecal levels – many thousands of times it MIC_{90} value against *C. difficile*. However, a relationship between faecal levels, MIC and clinical failures was not established in the clinical efficacy trials.

Based on these findings, the evaluator agreed that a first line indication is appropriate. However, the sponsor's proposed indication which includes '*reducing the risk of recurrence when used for treatment of CDI*' is not supported.

The evaluator agreed that fidaxomicin treatment was satisfactorily shown to have led to lower rate of recurrence within 28 days of completing treatment compared to vancomycin (15% versus 25% and 13% versus 27%) and this is the most important efficacy benefit of fidaxomicin over vancomycin. However, this is more appropriate a measure of sustained efficacy or alternatively more appropriate timepoint for measurement of clinical cure rather than prevention of recurrence.

A comprehensive assessment of risk of development of resistance was provided. The risk appears low but resistance surveillance will need to be instituted if the drug is given marketing approval.

12. Second round recommendation regarding authorisation

It is recommended that the sponsor's submission to register fidaxomicin (200 mg) tablets be approved for the following therapeutic indication and usage guidelines:

> *Fidaxomicin is indicated for the treatment of Clostridium difficile Associated Diarrhoea (CDAD) in adults.*
>
> *To reduce the development of drug-resistant bacteria and maintain the effectiveness of DIFICID and other antibacterial drugs, DIFICID should be used only to treat infections that are diagnosed to be caused by Clostridium difficile.*

The recommended dose is 200 mg administered twice daily for 10 days.

Dificid can be taken before, during or after meals.

No dose adjustment is needed for elderly patients, patients with renal insufficiency, hepatic impairment or patients undergoing dialysis.

Safety and efficacy of fidaxomicin in patients under the age of 18 has not been established. Therefore fidaxomicin is not recommended for use in children.

13. References

Nil listed.

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