EUROPEAN MEDICINES AGENCY
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Committee for Medicinal Products for Human Use (CHMP)

# Dificlir

(fidaxomicin)

Procedure No. EMEA/H/C/002087/P46 022

# CHMP assessment report for paediatric use studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

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

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# 1. Introduction

On 10 September 2014, the MAH submitted a completed paediatric study for Dificlir, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

# 2. Scientific discussion

## *2.1. Information on the development program*

The MAH stated that study OPT-80-206, A Phase 2A, Multicenter, Open-label, Uncontrolled Study to Determine the Safety, Tolerability, and Pharmacokinetics of Fidaxomicin Oral Suspension or Tablets in Pediatric Subjects With *Clostridium difficile*-associated Diarrhea, is part of a Paediatric Investigation Plan (PIP) that has been agreed with the European Medicines Agency (EMA) for the development of fidaxomicin for the treatment of CDAD in the paediatric population (EMA PIP Number: EMEA-000636-PIP01-09-M02, EMA Decision Number: P/0063/2014).

The results of the safety/pharmacokinetics study OPT-80-206 will be used to comply with the agreed measures for Study 5 of the PIP.

## *2.2. Information on the pharmaceutical formulation used in the study*

The existing authorized fidaxomicin 200 mg film-coated tablets are considered as a suitable formulation for children from 6 years onwards.

For study OPT-80-206, a liquid formulation was developed for paediatric subjects up to 6 years or subjects unable to swallow the tablets. The liquid formulation in this study was a powder formulation to be reconstituted prior to use to obtain an oral suspension. The maximum dosing regimen for the oral suspension formulation was the same as for the fidaxomicin tablets, i.e. 200 mg twice daily. The goal was to provide 200 mg of fidaxomicin in 5 ml of suspension, and have enough suspension in one bottle to supply 10 days of dosing (110 ml of suspension).

A final liquid formulation (granules for oral suspension) is currently under development and will be used in the safety/efficacy study in paediatric subjects (2819-CL-0202; Study 6 of agreed PIP).

***Assessor's comment***

In the present study both tablets and an experimental suspension (in the two lowest age groups) has been used. The relative bioavailability between tablet and suspension was not stated by the MAH.
This issue will not be further pursued since formulation development is on-going and a final formulation will be used in the safety and efficacy study.

## *2.3. Clinical aspects*

### 2.3.1. Introduction

The MAH submitted a final report for:

- OPT-80-206, A Phase 2A, Multicenter, Open-label, Uncontrolled Study to Determine the Safety, Tolerability, and Pharmacokinetics of Fidaxomicin Oral Suspension or Tablets in Pediatric Subjects With *Clostridium difficile*-associated Diarrhea

## 2.3.2. Clinical study

OPT-80-206, A Phase 2A, Multicenter, Open-label, Uncontrolled Study to Determine the Safety, Tolerability, and Pharmacokinetics of Fidaxomicin Oral Suspension or Tablets in Pediatric Subjects With *Clostridium difficile* – associated Diarrhea

## Description

OPT-80-206 is a multi-centre, open-label trial study to investigate the safety, tolerability and pharmacokinetics of a 10-day course of fidaxomicin oral suspension or tablets given every 12 hours, in pediatric subjects with CDAD.

## Methods

### *Objective(s)*

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

The secondary objective of the study was to evaluate the clinical outcome. An assessment of clinical response of CDAD at Day 10 was conducted and sustained clinical response was evaluated at 28 days post-treatment.

### *Study design*

This was a multicenter, open-label uncontrolled study conducted in the United States (10 sites) and Canada (1 site).

### *Study population /Sample size*

The following inclusion criteria were used:

1. Male or female subjects 6 months to < 18 years of age, inclusive. Female subjects of childbearing potential must have been using an adequate and reliable method of contraception (eg, abstinence, barrier with additional spermicide foam or jelly, intrauterine device, hormonal contraception). Subjects (both male and female) must have agreed to avoid conception during treatment and for 4 weeks following the end of study treatment.
2. Diagnosed with CDAD, which was defined by a positive stool *C. difficile* toxin A and/or toxin B assay result within 48 hours of enrollment and:
    a. Subjects 6 to 23 months: >3 episodes of watery diarrhea in the 24 hours prior to enrollment.
    b. Subjects 2 years to < 18 years: A change in bowel habits, with >3 unformed bowel movements (UBMs) in the 24 hours prior to enrollment.
3. Informed consent/assent was provided.

The following exclusion criteria applied:

1. Need for concurrent use of oral vancomycin, metronidazole, or any other effective treatments for CDAD during therapy with fidaxomicin.
2. Pregnant or breastfeeding an infant.

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

The sample size was based on clinical and practical considerations, not on formal statistical power calculation. Thirty-eight evaluable subjects, stratified by age at enrollment (6–23 months; 2 years-< 6 years; 6 years–< 12 years, and 12 years–< 18 years) were enrolled. The goal was to enroll equal numbers of subjects in each age stratum.

***Treatments***

The dose of 32 mg/kg/day in divided doses q12h (maximum 400 mg/day) was selected in order to achieve local and systemic exposures that were comparable to but did not exceed those observed in adults.

The weight-based dosing was selected by scaling from the vancomycin dose administered to children for CDAD; scaling against vancomycin was considered appropriate because neither drug is significantly absorbed from the gastrointestinal tract.

The subject received study medication administered orally with or without food each day for 10 days (20 doses; q12h regimen). Subjects aged 6 months to < 6 years received weight-based doses of fidaxomicin oral suspension 32 mg/kg/day, with a maximum dose of 400 mg/day, divided into 2 doses taken q12h.

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

***Outcomes/endpoints***

Pharmacokinetic variables

Plasma and fecal samples were obtained and analyzed for concentrations of fidaxomicin and its main metabolite OP-1118 using validated methods. A PK visit occurred between Days 5 and 10, during which 3 blood samples were collected, at 0 to 2 hours before dosing and then 1 to 2 hours and 3 to 5 hours after dosing. Fecal collection for PK assessments occurred on Day 10 within 24 hours after dosing (or at the end of therapy if sooner than Day 10).

Primary Efficacy Variable

The primary efficacy variable was clinical response rate day 10 or the last day of dosing.

Positive clinical response (cure) was determined as follows:

- Subjects aged 6 to 23 months who no longer had watery diarrhea for 2 consecutive days during treatment, who remained well before the time of study medication discontinuation, and who did not require further CDAD therapy within 2 days after completion of study medication were considered to have a positive clinical response.
- Subjects 2 years to < 18 years who had improvement in the number and character of bowel movements as determined by 3 or fewer UBMs for 2 consecutive days during treatment, who remained well before the time of study medication discontinuation, and who did not require further CDAD therapy within 2 days after completion of study medication were considered to have a positive clinical response.

Assessment of clinical response: symptoms of CDAD were fever >38° C (100.4° F), white blood cell (WBC) count >13,000/mm3, abdominal discomfortt, and abdominal tenderness.

Secondary Efficacy Variables included:

Recurrence rate and time to recurrence
Sustained clinical response (assessed 28 days post-treatment)
Safety variables

### *Statistical Methods*

Descriptive statistics were presented for all summarized data.

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

The *modified intent-to-treat (mITT) population* included all subjects with CDAD confirmed by a positive toxin assay within 24 hours before enrollment who received at least one dose of study medication.

The *per-protocol (PP) population* consisted of subjects in the mITT population who met the following criteria:

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

Analyses of clinical outcome (except for recurrence) were performed using the mITT and PP populations.

The sample size was based on clinical and practical considerations and not formal statistical power calculation.

## Results

### *Recruitment / Number analysed*

**Table 1. Summary of Subject Enrollment and Disposition (All Enrolled Subjects)**

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

Source: Table 14.1.1.

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

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

***Assessor's comment***

During the follow-up period, the major reason for withdrawals was recurrence that occurred in almost a quarter of the patients (n=9, 24 %).

***Baseline data***

*Demographic data*

**Table 2. Summary of Demographic and Baseline Characteristics (mITT Population)**

| | 6–23 Mo (N=9) | 2–5 Y, 11 Mo (N=8) | 6–11 Y, 11 Mo (N=9) | 12–17 Y, 11 Mo (N=12) | All Subjects (N=38) |
|---|---|---|---|---|---|
| Age (months) | | | | | |
| Mean (SD) | 15.2 (3.6) | 50.5 (10.8) | 116.8 (18.7) | 182.2 (19.3) | 99.4 (68.9) |
| Median | 14.0 | 47.0 | 127.0 | 189.0 | 101.5 |
| Min, max | 11, 22 | 38, 71 | 81, 136 | 145, 206 | 11, 206 |
| Sex, n (%) | | | | | |
| Male | 3 (33.3) | 7 (87.5) | 6 (66.7) | 6 (50.0) | 22 (57.9) |
| Female | 6 (66.7) | 1 (12.5) | 3 (33.3) | 6 (50.0) | 16 (42.1) |
| Race, n (%) | | | | | |
| White | 9 (100.0) | 5 (62.5) | 8 (88.9) | 11 (91.7) | 33 (86.8) |
| Black or African American | 0 | 1 (12.5) | 1 (11.1) | 0 | 2 (5.3) |
| Asian | 0 | 1 (12.5) | 0 | 0 | 1 (2.6) |
| American Indian or Alaska Native | 0 | 0 | 0 | 1 (8.3) | 1 (2.6) |
| Multiple | 0 | 1 (12.5) | 0 | 0 | 1 (2.6) |
| Ethnicity, n (%) | | | | | |
| Hispanic or Latino | 1 (11.1) | 0 | 0 | 3 (25.0) | 4 (10.5) |
| Not Hispanic or Latino | 8 (88.9) | 8 (100.0) | 9 (100.0) | 9 (75.0) | 34 (89.5) |
| Subject status, n (%) | | | | | |
| Inpatient | 2 (22.2) | 4 (50.0) | 2 (22.2) | 6 (50.0) | 14 (36.8) |
| Outpatient | 7 (77.8) | 4 (50.0) | 7 (77.8) | 6 (50.0) | 24 (63.2) |
| Baseline disease severity, n (%)[a] | | | | | |
| Mild | 4 (44.4) | 4 (50.0) | 6 (66.7) | 9 (75.0) | 23 (60.5) |
| Moderate | 3 (33.3) | 3 (37.5) | 1 (11.1) | 2 (16.7) | 9 (23.7) |
| Severe | 2 (22.2) | 1 (12.5) | 2 (22.2) | 1 (8.3) | 6 (15.8) |
| *C. difficile* toxin, n (%) | | | | | |
| Positive | 9 (100.0) | 8 (100.0) | 9 (100.0) | 12 (100.0) | 38 (100.0) |
| No. of UBMs 24 hours before CDI therapy | | | | | |
| Mean (SD) | 7.6 (5.4) | 5.9 (1.7) | 6.0 (2.3) | 5.6 (2.2) | 6.2 (3.2) |
| Median | 6.0 | 5.5 | 5.0 | 5.0 | 5.0 |
| Min, max | 4, 20 | 4, 9 | 4, 10 | 4, 12 | 4, 20 |
| Grouping of UBMs, n (%) | | | | | |
| 4–5 | 4 (44.4) | 4 (50.0) | 6 (66.7) | 9 (75.0) | 23 (60.5) |
| 6–9 | 3 (33.3) | 4 (50.0) | 1 (11.1) | 2 (16.7) | 10 (26.3) |
| ≥10 | 2 (22.2) | 0 | 2 (22.2) | 1 (8.3) | 5 (13.2) |
| Baseline weight (kg) | | | | | |
| Mean (SD) | 9.97 (1.16) | 15.39 (3.53) | 29.06 (8.96) | 58.04 (21.70) | 30.81 (23.63) |
| Median | 9.70 | 16.20 | 28.40 | 55.85 | 25.25 |
| Min, max | 8.7, 12.0 | 10.4,19.6 | 10.8, 43.2 | 28.3, 103.7 | 8.7, 103.7 |
| BMI ($kg/m^2$) | | | | | |
| Mean (SD) | 16.74 (2.55)[b] | 15.68 (1.29) | 17.33 (3.72) | 21.25 (3.80) | 18.1 (3.80) |
| Median | 15.80 | 15.25 | 17.30 | 21.75 | 17.15 |
| Min, max | 14.2, 21.9 | 14.5, 18.1 | 10.6, 25.2 | 15.7, 27.6 | 10.6, 27.6 |

Source: Table 14.1.2.1.

BMI = body mass index; CDI = *Clostridium difficile* infection; max = maximum; min = minimum; mITT = modified intent to treat; SD = standard deviation; UBMs = unformed bowel movements; WBC = white blood cell.

[a]Baseline disease severity categories are defined as: mild = 4 to 5 UBM/day or WBC count ≤12,000/$mm^3$; moderate = 6 to 9 UBM/day or WBC count 12,001/$mm^3$ to 15,000/$mm^3$; severe = ≥10 UBM/day or WBC count ≥15,001/$mm^3$. [b]n = 7.

***Assessor's comment***

All patients were positive at baseline for one or both *C. difficile* toxins A and B.

*Medical history*

At baseline > 10 % of the subjects reported a number of health conditions. In addition to gastrointestinal disorders (abdominal pain, constipation, diarrhea, gastroesophageal reflux disease, nausea, and vomiting) and gastrointestinal-related infections and infestations (clostridial infection and *C. difficile* colitis), conditions reported by >10% of subjects overall included anemia, gastrostomy tube insertion, pyrexia, otitis media, thrombocytopenia, failure to thrive, dehydration, esophagogastric fundoplasty, cerebral palsy, hypertension, sepsis, sinusitis, and tachycardia. Overall, 23.7% of subjects had a history of neoplasms (benign, malignant, and unspecified).

*Prior and concomitant medications*

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

Previous treatment with antineoplastic agents ranged from 8.3% to 25.0% among the age groups and was reported for 13.2% of subjects overall.

There were 18.4% of subjects receiving systemic antibiotics concomitantly with study medication, ranging from 11.1% to 25.0% across age groups. Piperacillin/tazobactam was the most frequently used concomitant antibiotic (13.2% of subjects). Metronidazole and vancomycin were each used concomitantly by 5.3% of subjects. During the follow-up period, 26.3% of subjects received systemic antibiotics (not including those effective in the treatment of CDAD).

***Pharmacokinetic results***

The plasma and faecal concentration levels of fidaxomicin and its metabolite, OP-1118, are shown in tables below.

The mean plasma concentrations of fidaxomicin across the age groups ranged from 8.9 to 16.6 ng/mL at 1 to 2 hours after dosing and 9.8 ng/mL to 15.6 ng/mL at 3 to 5 hours after dosing. For the metabolite OP-1118 mean plasma levels ranged from 27.5 to 130 ng/mL at 1 to 2 hours after dosing, and 28.5 to 122 ng/mL at 3 to 5 hours after dosing. One subject in the youngest age group showed much higher plasma OP-1118 levels than the other subjects, Fidaxomicin concentration was also high in this subject and was possibly due to a poor gastrointestinal integrity in this individual.

**Table 3. Summary of Observed Plasma Levels of Fidaxomicin (OPT-080) and Its Metabolite (OP-1118)**

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

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

The overall mean of fidaxomicin and OP-1118 in fecal samples were 3228 and 865 µg/g, respectively. The MAH points out that there was a trend toward higher mean concentrations in the youngest age group and a point to consider in evaluating the variability in the youngest stratum is that these samples would typically be collected from diapers, which may dehydrate the sample and contribute a positive bias to the concentration measured.

**Table 4. Summary of Observed Fecal Levels of Fidaxomicin (OPT-080) and Its Metabolite (OP-1118) at End-of-Therapy Visit**

| | Fecal Level, µg/g | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 6–23 Mo (N = 8) | | 2–5 Y, 11 Mo (N = 4) | | 6–11 Y, 11 Mo (N = 9) | | 12–17 Y, 11 Mo (N = 9) | | All Subjects (N = 30) | |
| | OPT-080 | OP-1118 | OPT-080 | OP-1118 | OPT-080 | OP-1118 | OPT-080 | OP-1118 | OPT-080 | OP-1118 |
| > LLOQ, n | 8 | 7 | 4 | 3 | 9 | 9 | 9 | 9 | 30 | 28 |
| < LLOQ, n | 0 | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 2 |
| Mean | 5406.88 | 758.83 | 1404.75 | 250.67 | 2980.44 | 1147.22 | 2348.89 | 871.67 | 3227.93 | 865.49 |
| SD | 3859.37 | 548.67 | 1312.93 | 100.27 | 1800.64 | 817.16 | 1239.11 | 368.64 | 2668.08 | 614.15 |
| Median | 4700.00 | 942.00 | 1040.50 | 280.00 | 2280.00 | 897.00 | 1950.00 | 743.00 | 2425.00 | 758.00 |
| Minimum | 848.0 | 75.8 | 268.0 | 139.0 | 844.0 | 166.0 | 1010.0 | 378.0 | 268.0 | 75.8 |
| Maximum | 11500 | 1610.0 | 3270.0 | 333.0 | 6660.0 | 2540.0 | 4400.0 | 1490.0 | 11500 | 2540.0 |

Source: Table 14.2.7.3.
LLOQ = lower limit of quantification; PK = pharmacokinetics; SD = standard deviation.

***Assessor's comment***

The selection of post-dose time-points for plasma PK of parent and metabolite and the grouping of time interval 1-2 h and 3-5 h are somewhat unclear. According to the MAH the time-points were selected based on the expected time of maximal concentration in adults, which is typically between 1 and 5 hours post-dosing in adults for both the parent drug and OP-1118. However the plasma concentration time profile has been shown in adults to be relatively flat, particularly at the 3-5 h time-interval, which is used to compare with adult exposure.

Although no formal statistical analysis was performed for the paediatic plasma PK data no clear correlation of obtained exposure to age could be detected.

***Efficacy results***

*Clinical response rate*

**Table 5. Summary of Clinical Response Rates at End of Therapy**

| | Positive Clinical Response Rate (%) | | | | |
|---|---|---|---|---|---|
| Population | 6–23 Mo | 2–5 Y, 11 Mo | 6–11 Y, 11 Mo | 12–17 Y, 11 Mo | All Subjects |
| Modified intent-to-treat | 8/9 (88.9) | 6/8 (75.0) | 9/9 (100.0) | 12/12 (100.0) | 35/38 (92.1) |
| 95% Confidence interval[a] | 68.4, 100.0 | 45.0, 100.0 | 100.0, 100.0 | 100.0, 100.0 | 83.5, 100.0 |
| Per protocol | 8/9 (88.9) | 5/6 (83.3) | 9/9 (100.0) | 12/12 (100.0) | 34/36 (94.4) |
| 95% Confidence interval[a] | 68.4, 100.0 | 53.5, 100.0 | 100.0, 100.0 | 100.0, 100.0 | 87.0, 100.0 |

Source: Table 14.2.1.
[a]Two-sided 95% point estimate confidence interval surrounding the cure rate.

***Assessor's comment***

Clinical response evaluated day 10 or the last day of dosing was 92 % for the mITT population.

*Recurrence rate and time to recurrence*

There were 28.6% of subjects in the mITT population (n = 35) and 30.3% of subjects in the PP population (n = 33) had recurrence of CDAD during the follow-up period. The proportions of subjects experiencing recurrence were generally similar across age groups.

The 20th percentile for time to recurrence ranged from 7 to 27 days and was 22 days overall.

*Sustained clinical response*

Overall, 65.8% of subjects in the mITT population and 66.7% of subjects in the PP population had a sustained response (response at end of treatment and through day 28 post-treatment).

***Assessor's comment***

Approximately 29-30 % of the patients had a recurrence of CDAD during the follow-up period.

***Safety results***

*Exposure*

**Table 6. Summary of Extent of Exposure (Safety Population)**

| | 6–23 Mo (N=9) | 2–5 Y, 11 Mo (N=8) | 6–11 Y, 11 Mo (N=9) | 12–17 Y, 11 Mo (N=12) | All Subjects (N=38) |
|---|---|---|---|---|---|
| Days on treatment[a] | | | | | |
| Mean (SD) | 10.4 (0.7) | 7.1 (3.9) | 10.0 (0.0) | 10.2 (0.6) | 9.6 (2.2) |
| Median | 10.0 | 9.5 | 10.0 | 10.0 | 10.0 |
| Minimum, maximum | 10, 12 | 1, 10 | 10, 10 | 10, 12 | 1, 12 |
| Formulation, n (%) | | | | | |
| Oral suspension | 9 (100.0) | 6 (75.0) | 5 (55.6) | 4 (33.3) | 24 (63.2) |
| Tablets | 0 | 2 (25.0) | 4 (44.4) | 8 (66.7) | 14 (36.8) |
| Assigned dose, n (%) | | | | | |
| 80 mg | 0 | 0 | 0 | 0 | 0 |
| 120 mg | 2 (22.2) | 0 | 0 | 0 | 2 (5.3) |
| 160 mg | 7 (77.8) | 2 (25.0) | 1 (11.1) | 0 | 10 (26.3) |
| 200 mg | 0 | 6 (75.0) | 8 (88.9) | 12 (100.0) | 26 (68.4) |

Source: Table 14.3.1.
SD = standard deviation.
[a]Calculated as [(last dose date time – first dose date time)/24].

*Adverse events*

**Table 7. Overall Incidence of Adverse Events (Safety Population9**

| | Number of Subjects (%) | | | | |
|---|---|---|---|---|---|
| | 6–23 Mo (N=9) | 2–5 Y, 11 Mo (N=8) | 6–11 Y, 11 Mo (N=9) | 12–17 Y, 11 Mo (N=12) | All Subjects (N=38) |
| Subjects with any TEAE | 7 (77.8) | 7 (87.5) | 6 (66.7) | 8 (66.7) | 28 (73.7) |
| Subjects with any severe TEAE | 1 (11.1) | 1 (12.5) | 0 | 1 (8.3) | 3 (7.9) |
| Subjects with any treatment-related TEAE | 0 | 3 (37.5) | 2 (22.0) | 1 (8.3) | 6 (15.8) |
| Subjects with any SAE | 4 (44.4) | 3 (37.5) | 1 (11.1) | 1 (8.3) | 9 (23.7) |
| Subjects with an AE leading to discontinuation | 0 | 3 (37.5) | 0 | 0 | 3 (7.9) |
| Subjects with an AE leading to death | 1 (11.1) | 0 | 0 | 0 | 1 (2.6) |

Sources: Tables 14.3.2.1, 14.3.2.2, 14.3.2.3, 14.3.2.4, and 14.3.2.6; Listings 16.2.7.4 and 16.2.7.3.
AE = adverse event; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

**Table 8. Treatment-Emergent Adverse Events Occurring in ⩾2 Subjects Overall (Safety Population)**

| MedDRA Preferred Term | Number of Subjects (%) | | | | |
|---|---|---|---|---|---|
| | 6–23 Mo (N=9) | 2–5 Y, 11 Mo (N=8) | 6–11 Y, 11 Mo (N=9) | 12–17 Y, 11 Mo (N=12) | All Subjects (N=38) |
| Pyrexia | 3 (33.3) | 0 | 0 | 1 (8.3) | 4 (10.5) |
| Vomiting | 0 | 2 (25.0) | 1 (11.1) | 1 (8.3) | 4 (10.5) |
| Abdominal pain upper | 0 | 2 (25.0) | 0 | 1 (8.3) | 3 (7.9) |
| *Clostridium difficile* colitis | 2 (22.2) | 0 | 1 (11.1) | 0 | 3 (7.9) |
| Chest pain | 0 | 0 | 1 (11.1) | 1 (8.3) | 2 (5.3) |
| Constipation | 0 | 1 (12.5) | 1 (11.1) | 0 | 2 (5.3) |
| Dehydration | 0 | 2 (25.0) | 0 | 0 | 2 (5.3) |
| Diarrhoea | 0 | 0 | 2 (22.2) | 0 | 2 (5.3) |
| Headache | 0 | 0 | 0 | 2 (16.7) | 2 (5.3) |
| Hypertension | 1 (11.1) | 0 | 0 | 1 (8.3) | 2 (5.3) |
| Nasopharyngitis | 2 (22.2) | 0 | 0 | 0 | 2 (5.3) |
| Nausea | 0 | 2 (25.0) | 0 | 0 | 2 (5.3) |
| Oesophagitis | 0 | 1 (12.5) | 0 | 1 (8.3) | 2 (5.3) |
| Urticaria | 0 | 1 (12.5) | 0 | 1 (8.3) | 2 (5.3) |

Source: Table 14.3.2.1.
MedDRA = *Medical Dictionary for Regulatory Activities*.

The majority of TEAEs were mild (44.7% of subjects, 76/102 events) or moderate (21.1% of subjects, 20/102 events) in severity. Three subjects (7.9%) experienced evere TEAEs: 1 subject each in the 6 to 23 months, 2 years to <6 years, and the 12 years to <18 years age groups.

*Serious adverse event**s***

A total of 9 subjects (23.7%) experienced at least 1 SAE (overall 13 SAEs). Greater proportions of subjects in the younger age groups had SAEs. Ten events resolved with sequelae, 2 were resolving and resulted in death. SAEs reported from more than one subject were *C. difficile* colitis and vomiting. The subject who died was in the 6 to 23 months age group, suffered from infant acute lymphocytic leukemia and was undergoing chemotherapy. The patient developed bacteremia, septic shock and respiratory failure. None of the SAEs were considered related to the study drug.

*Discontinuations due to TEAEs*

Three subjects (7.9%) were discontinued from study medication or withdrawn from the study due to TEAEs (urticaria, flatulence, increased body temperature and tachycardia).

## 2.3.3. Discussion on clinical aspects

The bioavailability for the tablets was not determined in the initial MAA for the product. From animals studies the bioavailability has been estimated to be in the range 0.2-3%, which is consistent with a locally acting agent.

In phase III studies of fidaxomicin in adults with CDAD, plasma levels 3 to 5 hours after a 200-mg dose (given twice daily) averaged 28.5 ±26.7 ng/mL on Day 10 of dosing, and OP-1118 averaged 85.6 ± 131 ng/mL. The plasma levels seen in children are comparably low, with an average fidaxomicin concentration across all strata of 13.4 ±15.5 ng/mL at 3 to 5 hours post-dose and OP-1118 of 60 ±152.2 ng/mL. Although no formal statistical analysis was performed for the paediatic PK data no clear correlation of obtained exposure to age could be detected.

Feaces samples collected within 24 hours of the last dose had a mean concentration of 3228 µg/g (range 268 to 11,500) and 865 µg/g (range 76 to 2540) for fidaxomicin and OP-1118, respectively. In phase III studies of fidaxomicin in adults with CDAD (global cure) the corresponding figures was >1000 µg/g and >800 µg/g for fidaxomicin and OP-1118, respectively.

After a 10-day treatment period, the clinical response was 92 % and approximately one third of the patients had a relapse during the follow-up period.

The safety profile seems to be similar to that seen in adult patients with CDAD.

However, no firm conclusion can be drawn from the limited data of this open-labeled study, although data support further development of fidaxomicin in children in accordance with the PIP.

The MAH is of the opinion that further data is required to confirm the safety and efficacy in the pediatric population. The results of this study do not alter the benefit/risk of Dificlir in adults. Further, the MAH believe that the data is not sufficient to support changes in the product information.

# 3. Rapporteur's overall conclusion and recommendation

## Overall conclusion

The MAH's conclusions are supported.

Although no firm conclusions can be drawn regarding PK, efficacy and safety of fidaxomicin in children based on the limited data from this open-labelled study, data support the further development in accordance with the PIP.

## Recommendation

### x Fulfilled:

No regulatory action required.

### ☐ Not fulfilled:

# Additional clarifications requested

Not applicable