Clinical trial results:
A Phase 2A, Multi-Center, Open-Label, Uncontrolled Study to Determine the Safety, Tolerability, and Pharmacokinetics of fidaxomicin Oral Suspension or Tablets in Pediatric Subjects With Clostridium difficile-associated Diarrhea

Summary

EudraCT number	2013-001448-75
Trial protocol	Outside EU/EEA
Global end of trial date	07 March 2014

Results information

Result version number	v1
This version publication date	01 June 2016
First version publication date	13 June 2015

Trial information

Trial identification

Sponsor protocol code	OPT-80-206

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01591863
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Optimer Pharmaceuticals (a Cubist company)
Sponsor organisation address	4747 Executive Dr. Ste 1100, San Diego, CA, United States, 92121
Public contact	Clinical Trial Disclosure, Astellas Pharma Global Developmnet, Inc., Astellas.resultsdisclosure@astellas.com
Scientific contact	Clinical Trial Disclosure, Astellas Pharma Global Development, Inc., Astellas.resultsdisclosure@astellas.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000636-PIP01-09
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	07 March 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	07 March 2014
Global end of trial reached?	Yes
Global end of trial date	07 March 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to investigate the safety, tolerability, and pharmacokinetics of fidaxomicin oral suspension or tablets in pediatric subjects, aged 6 months to 17 years, 11 months, with Clostridium difficile-associated diarrhea (CDAD), following the administration of doses given every 12 hours for 10 consecutive days. Both plasma and fecal PK analyses were performed.

Protection of trial subjects:

This clinical study was written, conducted and reported in accordance with the protocol, ICH GCP Guidelines, and applicable local regulations, including the European Directive 2001/20/EC, on the protection of human rights, and with the ethical principles that have their origin in the Declaration of Helsinki.

Astellas ensures that the use and disclosure of protected health information (PHI) obtained during a research study complies with the federal, national and/or regional legislation related to the privacy and protection of personal information.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	12 October 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 3
Country: Number of subjects enrolled	United States: 35
Worldwide total number of subjects	38
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	9

Children (2-11 years)	17
Adolescents (12-17 years)	12
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Participants diagnosed with CDAD, defined by (1) a positive stool C.difficile Toxin A and/or Toxin B assay result within 48 hours of enrollment; (2) in the 24 hours prior to enrollment: participants 6-23 months: >3 episodes of watery diarrhea; participants 2 years-17 years 11 months: A change in bowel habits, with >3 unformed bowel movements.

Period 1

Period 1 title	Overall study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Fidaxomicin 6-23 Months

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Fidaxomicin
Investigational medicinal product code	OPT-80, ASP2819
Other name	Dificid, Dificlir
Pharmaceutical forms	Oral suspension
Routes of administration	Oral use

Dosage and administration details:

Participants aged 6 months to 23 months were dosed with weight-based doses of open-label fidaxomicin oral suspension 32 mg/kg/day, with a maximum dose of 400 mg/day, divided into 2 doses (every 12 hours), with or without food each day for 10 days.

Arm title	Fidaxomicin 2-5 Years, 11 Months

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Fidaxomicin
Investigational medicinal product code	OPT-80, ASP2819
Other name	Dificid, Dificlir
Pharmaceutical forms	Oral suspension
Routes of administration	Oral use

Dosage and administration details:

Participants aged 2-5 years, 11 months were dosed with weight-based doses of open-label fidaxomicin oral suspension 32 mg/kg/day, with a maximum dose of 400 mg/day, divided into 2 doses (every 12 hours), with or without food each day for 10 days.

Arm title	Fidaxomicin 6-11 Years, 11 Months

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Fidaxomicin
Investigational medicinal product code	OPT-80, ASP2819
Other name	Dificid, Dificlir
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants aged 6 years to 11 years, 11 months were dosed with open-label fidaxomicin 200 mg tablets by mouth every 12 hours, with or without food, each day for 10 days. Participants aged 6 years to 11 years, 11 months who were unable to swallow tablets received fidaxomicin oral suspension, with a maximum dose of 400 mg/day, divided in 2 doses of 200 mg, with approval by the sponsor on a case-by-case basis and after consultation with the medical monitor.

Arm title	Fidaxomicin 12-17 Years, 11 Months
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Fidaxomicin
Investigational medicinal product code	OPT-80, ASP2819
Other name	Dificid, Dificlir
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants aged 12 years to 17 years, 11 months were dosed with open-label fidaxomicin 200 mg tablets by mouth every 12 hours, with or without food, each day for 10 days. Participants aged 12 years to 17 years, 11 months who were unable to swallow tablets received fidaxomicin oral suspension, with a maximum dose of 400 mg/day, divided in 2 doses of 200 mg, with approval by the sponsor on a case-by-case basis and after consultation with the medical monitor.

Number of subjects in period 1	Fidaxomicin 6-23 Months	Fidaxomicin 2-5 Years, 11 Months	Fidaxomicin 6-11 Years, 11 Months
Started	9	8	9
Completed	5	3	7
Not completed	4	5	2
Consent withdrawn by subject	-	1	-
Treatment failure	1	-	-
Adverse event	1	2	-
Recurrence	2	2	2

Number of subjects in period 1	Fidaxomicin 12-17 Years, 11 Months
Started	12
Completed	9
Not completed	3
Consent withdrawn by subject	-
Treatment failure	-
Adverse event	-
Recurrence	3

Baseline characteristics

Reporting groups	
Reporting group title	Fidaxomicin 6-23 Months
Reporting group description: -	
Reporting group title	Fidaxomicin 2-5 Years, 11 Months
Reporting group description: -	
Reporting group title	Fidaxomicin 6-11 Years, 11 Months
Reporting group description: -	
Reporting group title	Fidaxomicin 12-17 Years, 11 Months
Reporting group description: -	

Reporting group values	Fidaxomicin 6-23 Months	Fidaxomicin 2-5 Years, 11 Months	Fidaxomicin 6-11 Years, 11 Months
Number of subjects	9	8	9
Age categorical Units: Subjects			
Age continuous Units: months			
arithmetic mean	15.2	50.5	116.8
standard deviation	± 3.6	± 10.8	± 18.7
Gender categorical Units: Subjects			
Female	6	1	3
Male	3	7	6

Reporting group values	Fidaxomicin 12-17 Years, 11 Months	Total	
Number of subjects	12	38	
Age categorical Units: Subjects			
Age continuous Units: months			
arithmetic mean	182.2		
standard deviation	± 19.3	-	
Gender categorical Units: Subjects			
Female	6	16	
Male	6	22	

End points

End points reporting groups

Reporting group title	Fidaxomicin 6-23 Months
Reporting group description: -	
Reporting group title	Fidaxomicin 2-5 Years, 11 Months
Reporting group description: -	
Reporting group title	Fidaxomicin 6-11 Years, 11 Months
Reporting group description: -	
Reporting group title	Fidaxomicin 12-17 Years, 11 Months
Reporting group description: -	

Primary: Safety as assessed by incidence of adverse events (AEs), clinical laboratory test results, vital sign measurements, physical examinations, and electrocardiogram (ECG) results

End point title	Safety as assessed by incidence of adverse events (AEs), clinical laboratory test results, vital sign measurements, physical examinations, and electrocardiogram (ECG) results[1]

End point description:

An AE is any untoward medical occurrence in a subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE may be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not it is considered related to the medicinal product. A serious AE (SAE) is any untoward medical occurrence that at any dose: Was fatal; Was life threatening; Required inpatient hospitalization or prolongation of existing hospitalization; Resulted in persistent or significant disability/incapacity; Was a congenital anomaly/birth defect. A treatment-emergent adverse event (TEAE) is an adverse event with an onset date/time on or after first dose date/time of study drug. The analysis population was the safety analysis set, which included all patients with any evaluable safety data who have received at least one dose of study drug.

End point type	Primary

End point timeframe:

From first dose of study drug to 30 days after last dose of study drug (up to 41 days)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This study was written with no planned statistical analyses (statistical hypothesis testing) to be performed for any endpoints due to the simple design and purposes of the study.

End point values	Fidaxomicin 6-23 Months	Fidaxomicin 2-5 Years, 11 Months	Fidaxomicin 6-11 Years, 11 Months	Fidaxomicin 12-17 Years, 11 Months
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	9	8	9	12
Units: participants				
With any TEAE	7	7	6	8
With any severe TEAE	1	1	0	1
With any treatment-related TEAE	0	3	2	1
With any SAE	4	3	1	1
With an AE leading to discontinuation	0	3	0	0
With an AE leading to death	1	0	0	0

Statistical analyses

No statistical analyses for this end point

Primary: Pharmacokinetic plasma concentration levels of fidaxomicin

End point title	Pharmacokinetic plasma concentration levels of fidaxomicin[2]

End point description:

The analysis population was the plasma pharmacokinetic (PK) analysis set which included all dosed participants with evaluable plasma PK data, and excluded concentrations for which a problem occurred during sampling or laboratory analysis that invalidates the concentration measurements.

End point type	Primary

End point timeframe:

Days 5-10

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This study was written with no planned statistical analyses (statistical hypothesis testing) to be performed for any endpoints due to the simple design and purposes of the study.

End point values	Fidaxomicin 6-23 Months	Fidaxomicin 2-5 Years, 11 Months	Fidaxomicin 6-11 Years, 11 Months	Fidaxomicin 12-17 Years, 11 Months
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7[3]	5[4]	9[5]	11[6]
Units: ng/mL				
arithmetic mean (standard deviation)				
Pre-dose	13.171 (± 23.494)	9.236 (± 3.546)	10.081 (± 6.437)	7.836 (± 8.638)
1-2 hours postdose	13.364 (± 21.03)	16.618 (± 10.9)	12.363 (± 11.704)	8.874 (± 6.604)
3-5 hours postdose	15.217 (± 29.31)	14.606 (± 5.411)	15.59 (± 10.059)	9.83 (± 6.083)

Notes:

[3] - Participants with plasma concentrations above the lower limit of quantification.

[4] - Participants with plasma concentrations above the lower limit of quantification.

[5] - Participants with plasma concentrations above the lower limit of quantification.

[6] - Participants with plasma concentrations above the lower limit of quantification.

Statistical analyses

No statistical analyses for this end point

Primary: Pharmacokinetic plasma concentration levels of fidaxomicin metabolite OP-1118

End point title	Pharmacokinetic plasma concentration levels of fidaxomicin metabolite OP-1118[7]

End point description:

The analysis population was the PK analysis set.

End point type	Primary

End point timeframe:

Days 5-10

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This study was written with no planned statistical analyses (statistical hypothesis testing) to be performed for any endpoints due to the simple design and purposes of the study.

End point values	Fidaxomicin 6-23 Months	Fidaxomicin 2-5 Years, 11 Months	Fidaxomicin 6-11 Years, 11 Months	Fidaxomicin 12-17 Years, 11 Months
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7[8]	6[9]	9[10]	12[11]
Units: ng/mL				
arithmetic mean (standard deviation)				
Predose	133.376 (± 316.127)	30.624 (± 27.326)	38.838 (± 36.677)	22.312 (± 22.035)
1-2 hours postdose	130.235 (± 323.276)	51.725 (± 31.296)	47.321 (± 44.274)	27.476 (± 18.101)
3-5 hours postdose	121.946 (± 307.181)	45.825 (± 20.034)	53.341 (± 62.232)	28.465 (± 20.645)

Notes:

[8] - Participants with plasma concentrations above the lower limit of quantification.

[9] - Participants with plasma concentrations above the lower limit of quantification.

[10] - Participants with plasma concentrations above the lower limit of quantification.

[11] - Participants with plasma concentrations above the lower limit of quantification.

Statistical analyses

No statistical analyses for this end point

Primary: Pharmacokinetic fecal concentration levels of fidaxomicin

End point title	Pharmacokinetic fecal concentration levels of fidaxomicin[12]

End point description:

The analysis population was the fecal PK analysis set which included all dosed participants with evaluable fecal data, and excluded concentrations for which a problem occurred during collection or laboratory analysis that invalidates the concentration measurements.

End point type	Primary

End point timeframe:

End of therapy (Day 10)

Notes:

[12] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This study was written with no planned statistical analyses (statistical hypothesis testing) to be performed for any endpoints due to the simple design and purposes of the study.

End point values	Fidaxomicin 6-23 Months	Fidaxomicin 2-5 Years, 11 Months	Fidaxomicin 6-11 Years, 11 Months	Fidaxomicin 12-17 Years, 11 Months
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8[13]	4[14]	9[15]	9[16]
Units: µg/g				
arithmetic mean (standard deviation)				
Postdose	5406.88 (± 3859.37)	1404.75 (± 1312.93)	2980.44 (± 1800.64)	2348.89 (± 1239.11)

Notes:

[13] - Participants with fecal concentrations above the lower limit of quantification.

[14] - Participants with fecal concentrations above the lower limit of quantification.

[15] - Participants with fecal concentrations above the lower limit of quantification.

[16] - Participants with fecal concentrations above the lower limit of quantification.

Statistical analyses

No statistical analyses for this end point

Primary: Pharmacokinetic fecal concentration levels of fidaxomicin metabolite OP-1118

End point title	Pharmacokinetic fecal concentration levels of fidaxomicin metabolite OP-1118[17]

End point description:

The analysis population was the fecal PK analysis set.

End point type	Primary

End point timeframe:

End of therapy (Day 10)

Notes:

[17] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This study was written with no planned statistical analyses (statistical hypothesis testing) to be performed for any endpoints due to the simple design and purposes of the study.

End point values	Fidaxomicin 6-23 Months	Fidaxomicin 2-5 Years, 11 Months	Fidaxomicin 6-11 Years, 11 Months	Fidaxomicin 12-17 Years, 11 Months
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7[18]	3[19]	9[20]	9[21]
Units: µg/g				
arithmetic mean (standard deviation)				
Postdose	758.83 (± 548.67)	250.67 (± 100.27)	1147.22 (± 817.16)	871.67 (± 368.64)

Notes:

[18] - Participants with fecal concentrations above the lower limit of quantification.

[19] - Participants with fecal concentrations above the lower limit of quantification.

[20] - Participants with fecal concentrations above the lower limit of quantification.

[21] - Participants with fecal concentrations above the lower limit of quantification.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with clinical response (cure)

End point title	Percentage of participants with clinical response (cure)

End point description:

Positive clinical response (cure) was determined as follows: 6 to 23 months: who no longer had watery diarrhea for 2 consecutive days during treatment, who remained well before the time of study drug discontinuation, and who did not require further CDAD therapy within 2 days after completion of study drug were considered to have a positive clinical response; 2 years to 17 years, 11 months: who had improvement in the number and character of bowel movements as determined by 3 or fewer unformed bowel movements for 2 consecutive days during treatment, who remained well before the time of study drug discontinuation, and who did not require further CDAD therapy within 2 days after completion of study drug were considered to have a positive clinical response. The analysis population was the modified intent-to-treat (mITT) analysis set which included all participants with CDAD confirmed by a positive toxin assay within 24 hours prior to enrollment who received at least one dose of study drug.

End point type	Secondary

End point timeframe:

End of therapy (Day 10)

End point values	Fidaxomicin 6-23 Months	Fidaxomicin 2-5 Years, 11 Months	Fidaxomicin 6-11 Years, 11 Months	Fidaxomicin 12-17 Years, 11 Months
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	9	8	9	12
Units: percentage of participants				
number (confidence interval 95%)	88.9 (68.4 to 100)	75 (45 to 100)	100 (100 to 100)	100 (100 to 100)

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with recurrence of CDAD

End point title	Percentage of participants with recurrence of CDAD

End point description:

Recurrence was defined as the the re-establishment of diarrhea after a positive clinical response, where the number of unformed bowel movements (UBMs) was greater than that noted on the last day of study drug and toxin A and/or B was present, and the investigator considered that retreatment of CDAD was necessary. Only participants who achieved a positive clinical response by end of therapy visit were included. Participants who withdrew from the study during the follow-up period were considered to have a recurrence. The analysis population was the mITT analysis set.

End point type	Secondary

End point timeframe:

From end of therapy to 28 days post-treatment

End point values	Fidaxomicin 6-23 Months	Fidaxomicin 2-5 Years, 11 Months	Fidaxomicin 6-11 Years, 11 Months	Fidaxomicin 12-17 Years, 11 Months
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8	6	9	12
Units: percentage of participants				
number (confidence interval 95%)	25 (0 to 55)	33.3 (0 to 71.1)	22.4 (0 to 49.4)	33.3 (6.7 to 60)

Statistical analyses

No statistical analyses for this end point

Secondary: Time to recurrence of CDAD

End point title	Time to recurrence of CDAD

End point description:

Time to recurrence of CDAD was defined as the time in days from date of cure to the date of recurrence. Only participants who achieved a positive clinical response by end of therapy visit were included. The survival function for time to recurrence (in days) will be estimated using the Kaplan-Meier method using LIFETEST procedure in SAS. Participants who never recurred during the follow-up period were censored at 30 days after last dose. The analysis population was the mITT analysis set. Confidence Interval (CI) limit that could not be calculated is denoted as "99999" as applicable.

End point type	Secondary

End point timeframe:

From end of therapy to 28 days post-treatment

End point values	Fidaxomicin 6-23 Months	Fidaxomicin 2-5 Years, 11 Months	Fidaxomicin 6-11 Years, 11 Months	Fidaxomicin 12-17 Years, 11 Months
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2[22]	2[23]	2[24]	4[25]
Units: days				
number (confidence interval 95%)				
10th percentile	5 (5 to 99999)	9 (9 to 99999)	11 (11 to 99999)	22 (19 to 30)
20th percentile	7 (5 to 99999)	18 (9 to 99999)	27 (11 to 99999)	23 (19 to 99999)

Notes:

[22] - Participants with recurrence.

[23] - Participants with recurrence.

[24] - Participants with recurrence.

[25] - Participants with recurrence.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with sustained clinical response

End point title	Percentage of participants with sustained clinical response

End point description:

Sustained clinical response was defined as positive clinical response at the end of treatment without proven or suspected CDAD recurrence through 28 days post treatment. Only participants who achieved a positive clinical response by end of therapy visit were included.The analysis population was the mITT analysis set.

End point type	Secondary

End point timeframe:

From end of therapy to 28 days post-treatment

End point values	Fidaxomicin 6-23 Months	Fidaxomicin 2-5 Years, 11 Months	Fidaxomicin 6-11 Years, 11 Months	Fidaxomicin 12-17 Years, 11 Months
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	9	8	9	12
Units: percentage of participants				
number (confidence interval 95%)	66.7 (35.9 to 97.5)	50 (15.4 to 84.7)	77.8 (50.6 to 100)	66.7 (40 to 93.3)

Statistical analyses

No statistical analyses for this end point

Secondary: Time to resolution of diarrhea

End point title	Time to resolution of diarrhea

End point description:

Time to resolution of diarrhea was defined as the time elapsed (in hours rounded up from minutes ≥30) from the start of treatment (time of first dose of study drug) to resolution of diarrhea (time of the last UBM the day before the first of 2 consecutive days of ≤3 UBMs that were sustained through the end of therapy). The survival function for time to recurrence (in days) was estimated using the Kaplan-Meier method using LIFETEST procedure in SAS. Participants were censored at time of discontinuation, except for those subjects who completed End of Therapy and did not have resolution of diarrhea were censored at 240 hours. The analysis population was the mITT analysis set. Confidence Interval (CI) limit that could not be calculated is denoted as "99999" as applicable.

End point type	Secondary

End point timeframe:

From first dose of study drug to last dose of study drug (up to Day 10)

End point values	Fidaxomicin 6-23 Months	Fidaxomicin 2-5 Years, 11 Months	Fidaxomicin 6-11 Years, 11 Months	Fidaxomicin 12-17 Years, 11 Months
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8[26]	6[27]	9[28]	12[29]
Units: hours				
number (confidence interval 95%)				
25th percentile	116 (36 to 121)	0 (0 to 36)	0 (0 to 49)	0 (0 to 13)
50th percentile	121 (36 to 240)	18 (0 to 99999)	49 (0 to 99)	22 (0 to 127)
75th percentile	140 (119 to 240)	46 (0 to 99999)	75 (25 to 177)	113 (13 to 147)

Notes:

[26] - Participants with resolved diarrhea.

[27] - Participants with resolved diarrhea.

[28] - Participants with resolved diarrhea.

[29] - Participants with resolved diarrhea.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: From first dose of study drug to 30 days after last dose of study drug	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	15.0

Reporting groups	
Reporting group title	Fidaxomicin 6-23 Months
Reporting group description: -	
Reporting group title	Fidaxomicin 2-5 Years, 11 Months
Reporting group description: -	
Reporting group title	Fidaxomicin 6-11 Years, 11 Months
Reporting group description: -	
Reporting group title	Fidaxomicin 12-17 Years, 11 Months
Reporting group description: -	

Serious adverse events	Fidaxomicin 6-23 Months	Fidaxomicin 2-5 Years, 11 Months	Fidaxomicin 6-11 Years, 11 Months
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 9 (44.44%)	3 / 8 (37.50%)	1 / 9 (11.11%)
number of deaths (all causes)	1	0	0
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Gastrostomy Failure			
subjects affected / exposed	1 / 9 (11.11%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Febrile Neutropenia			
subjects affected / exposed	0 / 9 (0.00%)	1 / 8 (12.50%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Haematemesis			
subjects affected / exposed	0 / 9 (0.00%)	1 / 8 (12.50%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Vomiting			
subjects affected / exposed	0 / 9 (0.00%)	1 / 8 (12.50%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Respiratory Failure			
subjects affected / exposed	1 / 9 (11.11%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Infections and infestations			
Adenovirus Infection			
subjects affected / exposed	0 / 9 (0.00%)	1 / 8 (12.50%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridial Infection			
subjects affected / exposed	0 / 9 (0.00%)	1 / 8 (12.50%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium Difficile Colitis			
subjects affected / exposed	2 / 9 (22.22%)	0 / 8 (0.00%)	1 / 9 (11.11%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic Shock			
subjects affected / exposed	1 / 9 (11.11%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Fidaxomicin 12-17 Years, 11 Months		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 12 (8.33%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Gastrostomy Failure			

subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Febrile Neutropenia			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Haematemesis			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Respiratory Failure			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Adenovirus Infection			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Clostridial Infection			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Clostridium Difficile Colitis			

subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Septic Shock			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Fidaxomicin 6-23 Months	Fidaxomicin 2-5 Years, 11 Months	Fidaxomicin 6-11 Years, 11 Months
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 9 (77.78%)	7 / 8 (87.50%)	6 / 9 (66.67%)
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 9 (11.11%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Pyrexia			
subjects affected / exposed	3 / 9 (33.33%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	3	0	0
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	0 / 9 (0.00%)	2 / 8 (25.00%)	0 / 9 (0.00%)
occurrences (all)	0	2	0
Constipation			
subjects affected / exposed	0 / 9 (0.00%)	1 / 8 (12.50%)	1 / 9 (11.11%)
occurrences (all)	0	1	1
Diarrhoea			

subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	2 / 9 (22.22%)
occurrences (all)	0	0	2
Nausea			
subjects affected / exposed	0 / 9 (0.00%)	2 / 8 (25.00%)	0 / 9 (0.00%)
occurrences (all)	0	2	0
Oesophagitis			
subjects affected / exposed	0 / 9 (0.00%)	1 / 8 (12.50%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Vomiting			
subjects affected / exposed	0 / 9 (0.00%)	2 / 8 (25.00%)	1 / 9 (11.11%)
occurrences (all)	0	4	3
Skin and subcutaneous tissue disorders			
Urticaria			
subjects affected / exposed	0 / 9 (0.00%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	2 / 9 (22.22%)	0 / 8 (0.00%)	0 / 9 (0.00%)
occurrences (all)	2	0	0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 9 (0.00%)	2 / 8 (25.00%)	0 / 9 (0.00%)
occurrences (all)	0	2	0

Non-serious adverse events	Fidaxomicin 12-17 Years, 11 Months		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 12 (66.67%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	3		
General disorders and administration site conditions			

Chest pain subjects affected / exposed occurrences (all) Pyrexia subjects affected / exposed occurrences (all)	 1 / 12 (8.33%) 1 1 / 12 (8.33%) 3		
Gastrointestinal disorders Abdominal pain upper subjects affected / exposed occurrences (all) Constipation subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Oesophagitis subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	 1 / 12 (8.33%) 1 0 / 12 (0.00%) 0 0 / 12 (0.00%) 0 0 / 12 (0.00%) 0 1 / 12 (8.33%) 1 1 / 12 (8.33%) 1		
Skin and subcutaneous tissue disorders Urticaria subjects affected / exposed occurrences (all)	 1 / 12 (8.33%) 1		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	 0 / 12 (0.00%) 0		
Metabolism and nutrition disorders Dehydration subjects affected / exposed occurrences (all)	 0 / 12 (0.00%) 0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 January 2012	Major changes to the conduct of the study are summarized: (1) Revised the timing of the CDAD signs and symptoms evaluation to address redundancy with this assessment and the participant/legal guardian interview (CDAD status); (2) Revised the timing of the investigator's determination of clinical response as was noted in the schedule of events; (3) Revised AE language for clarity and consistency.
04 April 2012	Major changes to the conduct of the study are summarized: (1) Clarified the age limit to 17 years, 11 months; (2) Changed "mother or legal guardian" to "parent or legal guardian"; (3) Updated sponsor contact information; (4) Updated study design to include interviews of the participant/legal guardian on CDAD status to be conducted daily and 2 to 3 days after the last dose of study medication and then weekly through 28 days after treatment; (5) Study assessments were updated to include fecal sample collection at the end of therapy visit to determine concentrations of fidaxomicin and its main metabolite, OP-1118; (6) Clarified that dose preparations and administration based on the participant's weight were calculated at enrollment and remained consistent throughout the treatment period; (7) Updated the facsimile number for AE reports and pregnancy data collection form to be sent; (8) Removed efficacy from data that was to be reviewed by the Safety Moitorig Committee (SMC).
13 June 2012	Major changes to the conduct of the study are summarized: (1) Clarified that dose preparation and administration could not be changed during the course of the 10-day treatment; (2) Updated study evaluations on clinical laboratory tests and pregnancy tests; (3) Updated recording and reporting of AEs.
11 October 2012	Major changes to the conduct of the study are summarized: (1) Added "Informed consent/assent was provided" as an inclusion criterion; (2) Removed exclusion of participants with >24 hours of prior treatment with oral vancomycin and/or metronidazole; (3) Restricted the list of excluded P-glycoprotein inhibitors to cyclosporine, itraconazole and ketoconazole, erythromycin, azithromycin, and clarithromycin, verapamil, dronedarone and amiodarone, captopril, carvedilol, conivaptan, diltiazem, felodipine, lopinavir and ritonavir, quercetin, quinidine, and ranolazine; (4) Updated exclusion criteria to include: (a) Need for concurrent use of oral vancomycin, metronidazole or any other effective treatments for CDAD during therapy with fidaxomicin, (b) pregnant or breast-feeding an infant, (c) Fulminant colitis, (d) a history of inflammatory bowel disease (ulcerative colitis or Crohn's disease), (e) 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 was administration of any P-glycoprotein inhibitors during the follow-up period, (f) updated concomitant therapy for consistency with exclusion criteria for P-glycoprotein inhibitors, (g) updated the protocol to Dificid package insert dated October 2012.

12 December 2013	Major changes to the conduct of the study are summarized: (1) Added that Optimer is now a Cubist company and updated signatory and contact personnel; (2) Updated sample size to at least 32 and up to 35 evaluable subjects and stipulated that with Amendment 5, further enrollment should only consist of subjects in stratum 2 (2 years to 5 years, 11 months); (3) Updated exposure margin in dogs to 117×; (4) Clarified that to be included in the plasma PK population, participants must have had 1 predose and at least 1 of the postdose PK blood samples collected at the PK visit (within the time of maximal concentration window, 1–5 hours after dosing); (5) Updated dose preparation and administration to allow a subject who could not swallow a tablet to receive a crushed tablet if the oral formulation was not available and if the subject met weight requirements to receive the full adult dose of 400 mg/day. Instructions for crushing the tablet were provided in the appendix of the amendment; the following instruction was added: If the subject was not of sufficient weight (12.5 kg) to receive the full adult dose and the oral suspension was no longer available, the subject should not have been enrolled; (6) Clarified that pregnancy tests were only to be conducted in females of childbearing potential; (7) Updated medical monitor and associated contact information; (8) Updated Difficid package insert to current version (March 2013); (9) Added an appendix in protocol, crushed tablet preparation.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported