Clinical trial results:
Open Label Study to Evaluate the Pharmacokinetics of Fidaxomicin in Inflammatory Bowel Disease (IBD) Subjects with Clostridium Difficile Infection (CDI)

Summary

EudraCT number	2014-003002-32
Trial protocol	CZ DE AT GR PL IT
Global end of trial date	24 October 2016

Results information

Result version number	v1
This version publication date	28 October 2017
First version publication date	28 October 2017

Trial information

Trial identification

Sponsor protocol code	2819-MA-1003

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02437591
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Astellas Pharma Europe Ltd.
Sponsor organisation address	2000 Hillswood Drive, Chertsey, United Kingdom, KT16 0RS
Public contact	Clinical Trial Disclosure, Astellas Pharma Europe Ltd., astellas.resultsdisclosure@astellas.com
Scientific contact	Clinical Trial Disclosure, Astellas Pharma Europe Ltd., astellas.resultsdisclosure@astellas.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	24 October 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	24 October 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the trial was to investigate the plasma pharmacokinetics of fidaxomicin and its primary metabolite OP-1118, in participants with inflammatory bowel disease (IBD) and clostridium difficile infection (CDI).

Protection of trial subjects:

This clinical study was written, conducted and reported in accordance with the protocol, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (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	13 August 2015
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	Greece: 3
Country: Number of subjects enrolled	France: 2
Country: Number of subjects enrolled	Italy: 2
Country: Number of subjects enrolled	Poland: 9
Country: Number of subjects enrolled	Russian Federation: 7
Country: Number of subjects enrolled	Austria: 1
Country: Number of subjects enrolled	United Kingdom: 1
Worldwide total number of subjects	25
EEA total number of subjects	18

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)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	22
From 65 to 84 years	3
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled at 28 clinical sites across 9 European countries and regions.

Pre-assignment

Screening details:

Male or female participants of at least 18 years of age with confirmed diagnosis or history of IBD for at least 3 months and a positive local standard CDI test for the presence of C. difficile. A CDI stool test had to be confirmed positive within 48 hours prior to enrollment.

Period 1

Period 1 title	Overall Study (Treatment & Follow Up) (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Fidaxomicin

Arm description:

Participants received 200 mg of fidaxomicin from day 1 to day 10, twice daily.

Arm type	Experimental
Investigational medicinal product name	Fidaxomicin
Investigational medicinal product code	OPT-80, PAR-101, ASP2819
Other name	Dificlir TM, Dificid, Difimicin
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received 200 mg of fidaxomicin orally, twice a day (every 12 hours) starting on day 1 for 10 treatment days.

Number of subjects in period 1	Fidaxomicin
Started	25
Completed	21
Not completed	4
Consent withdrawn by subject	3
Lost to follow-up	1

Baseline characteristics

Reporting groups	
Reporting group title	Overall Study (Treatment & Follow Up)
Reporting group description:	
Treatment Period & Follow Up Period	

Reporting group values	Overall Study (Treatment & Follow Up)	Total	
Number of subjects	25	25	
Age categorical Units: Subjects			
18 to 64	22	22	
65 to 74	1	1	
> 74	2	2	
Age continuous Units: years			
arithmetic mean	38.9		
standard deviation	± 16.5	-	
Gender categorical Units:			
Male	13	13	
Female	12	12	
Baseline CDI Severity by European Society of Clinical Microbiology and Infectious Disease Score Units: Subjects			
Severe	7	7	
Non severe	18	18	
Colonoscopy or Sigmoidoscopy Units: Subjects			
Pseudomembranous colitis -Yes	2	2	
Pseudomembranous colitis -No	23	23	
Laboratory Examinations- Marked Leucocytosis Units: Subjects			
Marked leucocytosis - Yes	4	4	
Marked leucocytosis - No	21	21	
Number of Previous CDI Episodes Units: Subjects			
= 0	20	20	
= 1	5	5	
≥ 2	0	0	
Use of Antibiotics for CDI Within 90 Days Prior to Enrollment Units: Subjects			
Yes	5	5	
No	20	20	
Laboratory Examinations - Marked Left Shift			

Units: Subjects			
Marked left shift – No	24	24	
Marked left shift – Missing	1	1	
Laboratory Examinations - Rise in Serum Creatinine Units: Subjects			
Rise in Serum Creatinine - No	25	25	
Laboratory Examinations - Elevated Serum Lactate Units: Subjects			
Elevated Serum Lactate - No	10	10	
Elevated Serum Lactate - Missing	15	15	
Laboratory Examinations - Markedly Reduced Serum Albumin Units: Subjects			
Markedly Reduced Serum Albumin - Yes	3	3	
Markedly Reduced Serum Albumin - No	21	21	
Markedly Reduced Serum Albumin - Missing	1	1	
Body Mass Index (BMI) Units: kg/m^2			
arithmetic mean	21.76		
standard deviation	± 4.87	-	
Charlson Co-Morbidity Index Score Units: Year			
arithmetic mean	1.3		
standard deviation	± 2	-	
Study Drug Average Daily Dose Units: Milligrams			
arithmetic mean	398.5		
standard deviation	± 7.27	-	
Duration of Exposure to Study Drug			
Duration of exposure to study drug was defined as (the date of last dosing) – (the date of first dosing) + 1.			
Units: Days			
arithmetic mean	10.1		
standard deviation	± 0.28	-	

Subject analysis sets

Subject analysis set title	IBD type - Crohn’s Disease
Subject analysis set type	Safety analysis
Subject analysis set description:	
Participants with Crohn’s Disease with positive CDI test for the presence of C. difficile who received 200 mg of fidaxomicin from day 1 to day 10, twice daily.	
Subject analysis set title	IBD type - Ulcerative Colitis
Subject analysis set type	Safety analysis
Subject analysis set description:	
Participants with Ulcerative Colitis with positive CDI test for the presence of C. difficile who received 200 mg of fidaxomicin from day 1 to day 10, twice daily.	

Reporting group values	IBD type - Crohn's Disease	IBD type - Ulcerative Colitis	
Number of subjects	14	11	
Age categorical Units: Subjects			
18 to 64	14	8	
65 to 74	0	1	
> 74	0	2	
Age continuous Units: years			
arithmetic mean	35.4	43.3	
standard deviation	± 10.9	± 21.6	
Gender categorical Units:			
Male	8	5	
Female	6	6	
Baseline CDI Severity by European Society of Clinical Microbiology and Infectious Disease Score Units: Subjects			
Severe	2	5	
Non severe	12	6	
Colonoscopy or Sigmoidoscopy Units: Subjects			
Pseudomembranous colitis -Yes	0	2	
Pseudomembranous colitis -No	14	9	
Laboratory Examinations- Marked Leucocytosis Units: Subjects			
Marked leucocytosis - Yes	2	2	
Marked leucocytosis - No	12	9	
Number of Previous CDI Episodes Units: Subjects			
= 0	12	8	
= 1	2	3	
≥ 2	0	0	
Use of Antibiotics for CDI Within 90 Days Prior to Enrollment Units: Subjects			
Yes	1	4	
No	13	7	
Laboratory Examinations - Marked Left Shift Units: Subjects			
Marked left shift – No	14	10	
Marked left shift – Missing	0	1	
Laboratory Examinations - Rise in Serum Creatinine Units: Subjects			
Rise in Serum Creatinine - No	14	11	
Laboratory Examinations - Elevated Serum Lactate Units: Subjects			
Elevated Serum Lactate - No	7	3	

Elevated Serum Lactate - Missing	7	8	
Laboratory Examinations - Markedly Reduced Serum Albumin Units: Subjects			
Markedly Reduced Serum Albumin - Yes	1	2	
Markedly Reduced Serum Albumin - No	13	8	
Markedly Reduced Serum Albumin - Missing	0	1	
Body Mass Index (BMI) Units: kg/m^2			
arithmetic mean	22.09	21.35	
standard deviation	± 5.88	± 3.39	
Charlson Co-Morbidity Index Score Units: Year			
arithmetic mean	0.9	1.7	
standard deviation	± 1.2	± 2.6	
Study Drug Average Daily Dose Units: Milligrams			
arithmetic mean	397.4	400.0	
standard deviation	± 9.72	± 0.00	
Duration of Exposure to Study Drug			
Duration of exposure to study drug was defined as (the date of last dosing) – (the date of first dosing) + 1.			
Units: Days			
arithmetic mean	10.1	10.1	
standard deviation	± 0.27	± 0.30	

End points

End points reporting groups

Reporting group title	Fidaxomicin
Reporting group description:	
Participants received 200 mg of fidaxomicin from day 1 to day 10, twice daily.	
Subject analysis set title	IBD type - Crohn's Disease
Subject analysis set type	Safety analysis
Subject analysis set description:	
Participants with Crohn's Disease with positive CDI test for the presence of C. difficile who received 200 mg of fidaxomicin from day 1 to day 10, twice daily.	
Subject analysis set title	IBD type - Ulcerative Colitis
Subject analysis set type	Safety analysis
Subject analysis set description:	
Participants with Ulcerative Colitis with positive CDI test for the presence of C. difficile who received 200 mg of fidaxomicin from day 1 to day 10, twice daily.	

Primary: Maximum Plasma Concentration (Cmax) for Fidaxomicin

End point title	Maximum Plasma Concentration (Cmax) for Fidaxomicin[1]
End point description:	
The analysis population was the pharmacokinetic analysis set (PKAS All Patients), which consisted of all participants from the subset of the safety analysis set (SAF). The safety analysis set (SAF) consisted of all participants who received at least 1 dose of study drug. The PKAS population contained at least 1 blood plasma measurement of fidaxomicin and its metabolite OP-1118, regardless of whether the value of the measurement was above or below lower limit of quantification and whether the participant had a full pharmacokinetic sampling profile or a limited pharmacokinetic sampling profile. For participants with limited PK sampling, Cmax on Days 5 and 10 was estimated by value from scheduled time window for tmax (2 hours ± 30 minutes). Sampling for participants with reduced PK profile was completed on Day 1 (Predose, 0.5, 1, 1.5, 2, 3, 4, 5 and 10 hours postdose) and Day 5 & 10 (Predose and tmax). N represents number of participants with the available data.	
End point type	Primary
End point timeframe:	
Day 1, Day 5 and Day 10 (Predose, 0.5, 1, 1.5, 2, 3, 4, 5 and 10 hours postdose)	

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: Statistical analysis for this endpoint was not completed.

End point values	Fidaxomicin			
Subject group type	Reporting group			
Number of subjects analysed	24			
Units: ng/mL				
arithmetic mean (standard deviation)				
Day 1 [N=23]	14.61 (± 16.10)			
Day 5 [N=23]	20.33 (± 31.80)			
Day 10	16.25 (± 15.06)			
Maximum Across Days	22.57 (± 30.42)			

Statistical analyses

No statistical analyses for this end point

Primary: Maximum Plasma Concentration (Cmax) for OP-1118

End point title	Maximum Plasma Concentration (Cmax) for OP-1118[2]

End point description:

The analysis population was the pharmacokinetic analysis set (PKAS All Patients). For participants with limited PK sampling, Cmax on Days 5 and 10 was estimated by value from scheduled time window for tmax (2 hours ± 30 minutes). Sampling for participants with reduced PK profile was completed on Day 1 (Predose, 0.5, 1, 1.5, 2, 3, 4, 5 and 10 hours postdose) and Day 5 & 10 (Predose and tmax). N represents number of participants with the available data.

End point type	Primary

End point timeframe:

Day 1, Day 5 and Day 10 (Predose, 0.5, 1, 1.5, 2, 3, 4, 5 and 10 hours postdose)

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: Statistical analysis for this endpoint was not completed.

End point values	Fidaxomicin			
Subject group type	Reporting group			
Number of subjects analysed	24			
Units: ng/mL				
arithmetic mean (standard deviation)				
Day 1 [N=23]	45.26 (± 67.48)			
Day 5 [N=23]	70.28 (± 116.7)			
Day 10	53.10 (± 43.54)			
Maximum Across Days	78.50 (± 111.58)			

Statistical analyses

No statistical analyses for this end point

Primary: Area Under the Curve from 0 to 12 hrs (AUC12) for Fidaxomicin

End point title	Area Under the Curve from 0 to 12 hrs (AUC12) for Fidaxomicin[3]

End point description:

The analysis population was the pharmacokinetic analysis set (PKAS All Patients). Sampling for participants with reduced PK profile was completed on Day 1 (Predose, 0.5, 1, 1.5, 2, 3, 4, 5 and 10 hours postdose) and Day 5 & 10 (Predose and tmax).

End point type	Primary

End point timeframe:

Day 1 (Predose to 12 hours postdose)

Notes:

[3] - 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: Statistical analysis for this endpoint was not completed.

End point values	Fidaxomicin			
Subject group type	Reporting group			
Number of subjects analysed	14			
Units: h*ng/mL				
arithmetic mean (standard deviation)				
Day 1	77.70 (± 79.77)			

Statistical analyses

No statistical analyses for this end point

Primary: Area Under the Curve from 0 to 12 hrs (AUC12) for OP-1118

End point title	Area Under the Curve from 0 to 12 hrs (AUC12) for OP-1118[4]

End point description:

The analysis population was the pharmacokinetic analysis set (PKAS All Patients). Sampling for participants with reduced PK profile was completed on Day 1 (Predose, 0.5, 1, 1.5, 2, 3, 4, 5 and 10 hours postdose) and Day 5 & 10 (Predose and tmax).

End point type	Primary

End point timeframe:

Day 1 (Predose to 12 hours postdose)

Notes:

[4] - 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: Statistical analysis for this endpoint was not completed.

End point values	Fidaxomicin			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: h*ng/mL				
arithmetic mean (standard deviation)	283.5 (± 400.8)			

Statistical analyses

No statistical analyses for this end point

Primary: Time of Maximum Concentration (tmax) for Fidaxomicin

End point title	Time of Maximum Concentration (tmax) for Fidaxomicin[5]

End point description:

The analysis population was the pharmacokinetic analysis set (PKAS All Patients). Sampling for participants with reduced PK profile was completed on Day 1 (Predose, 0.5, 1, 1.5, 2, 3, 4, 5 and 10 hours postdose) and Day 5 & 10 (Predose and tmax). N represents number of participants with the available data.

End point type	Primary

End point timeframe:

Day 1, Day 5 and Day 10 (Predose, 0.5, 1, 1.5, 2, 3, 4, 5 and 10 hours postdose)

Notes:

[5] - 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: Statistical analysis for this endpoint was not completed.

End point values	Fidaxomicin			
Subject group type	Reporting group			
Number of subjects analysed	24			
Units: hours				
median (full range (min-max))				
Day 1 [N=23]	1.500 (0.450 to 11.5)			
Day 5 [N=13]	1.033 (0.500 to 3.00)			
Day 10 [N=14]	1.750 (0.00 to 5.35)			

Statistical analyses

No statistical analyses for this end point

Primary: Time of Maximum Concentration (tmax) for OP-1118

End point title	Time of Maximum Concentration (tmax) for OP-1118[6]

End point description:

The analysis population was the pharmacokinetic analysis set (PKAS All Patients). Sampling for participants with reduced PK profile was completed on Day 1 (Predose, 0.5, 1, 1.5, 2, 3, 4, 5 and 10 hours postdose) and Day 5 & 10 (Predose and tmax). N represents number of participants with the available data.

End point type	Primary

End point timeframe:

Day 1, Day 5 and Day 10 (Predose, 0.5, 1, 1.5, 2, 3, 4, 5 and 10 hours postdose)

Notes:

[6] - 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: Statistical analysis for this endpoint was not completed.

End point values	Fidaxomicin			
Subject group type	Reporting group			
Number of subjects analysed	24			
Units: hours				
median (full range (min-max))				
Day 1 [N=23]	1.500 (0.450 to 11.5)			
Day 5 [N=13]	1.033 (0.500 to 5.00)			
Day 10 [N=14]	2.042 (0.00 to 5.35)			

Statistical analyses

No statistical analyses for this end point

Primary: Metabolite-to-Parent Ratio (MPR) for OP-1118

End point title	Metabolite-to-Parent Ratio (MPR) for OP-1118[7]

End point description:

The analysis population was the pharmacokinetic analysis set (PKAS All Patients). Sampling for participants with reduced PK profile was completed on Day 1 (Predose, 0.5, 1, 1.5, 2, 3, 4, 5 and 10 hours postdose) and Day 5 & 10 (Predose and tmax). N represents number of participants with the available data.

End point type	Primary

End point timeframe:

Day 1, Day 5 and Day 10 (Predose, 0.5, 1, 1.5, 2, 3, 4, 5 and 10 hours postdose)

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: Statistical analysis for this endpoint was not completed.

End point values	Fidaxomicin			
Subject group type	Reporting group			
Number of subjects analysed	24			
Units: Ratio				
arithmetic mean (standard deviation)				
Day 1 [N=10]	2.912 (± 0.8492)			
Day 5 [N=10]	3.883 (± 1.127)			
Day 10 [N=11]	3.471 (± 0.9172)			

Statistical analyses

No statistical analyses for this end point

Primary: Area Under the Concentration Time Curve From the Time of Dosing to the Start of the Next Dosing Interval (AUCtau) for Fidaxomicin

End point title	Area Under the Concentration Time Curve From the Time of Dosing to the Start of the Next Dosing Interval (AUCtau) for Fidaxomicin[8]

End point description:

The analysis population was the pharmacokinetic analysis set (PKAS All Patients). Sampling for participants with reduced PK profile was completed on Day 1 (Predose, 0.5, 1, 1.5, 2, 3, 4, 5 and 10 hours postdose) and Day 5 & 10 (Predose and tmax). N represents number of participants with the available data.

End point type	Primary

End point timeframe:

Day 5 and Day 10 (Predose, 0.5, 1, 1.5, 2, 3, 4, 5 and 10 hours postdose)

Notes:

[8] - 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: Statistical analysis for this endpoint was not completed.

End point values	Fidaxomicin			
Subject group type	Reporting group			
Number of subjects analysed	24			
Units: h*ng/mL				
arithmetic mean (standard deviation)				
Day 5 [N=11]	155.6 (± 150.9)			
Day 10 [N=11]	129.1 (± 115.0)			

Statistical analyses

No statistical analyses for this end point

Primary: Area Under the Concentration Time Curve From the Time of Dosing to the Start of the Next Dosing Interval (AUCtau) for OP-1118

End point title	Area Under the Concentration Time Curve From the Time of Dosing to the Start of the Next Dosing Interval (AUCtau) for OP-1118[9]

End point description:

The analysis population was the pharmacokinetic analysis set (PKAS All Patients). Sampling for participants with reduced PK profile was completed on Day 1 (Predose, 0.5, 1, 1.5, 2, 3, 4, 5 and 10 hours postdose) and Day 5 & 10 (Predose and tmax). N represents number of participants with the available data.

End point type	Primary

End point timeframe:

Day 5 and Day 10 (Predose, 0.5, 1, 1.5, 2, 3, 4, 5 and 10 hours postdose)

Notes:

[9] - 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: Statistical analysis for this endpoint was not completed.

End point values	Fidaxomicin			
Subject group type	Reporting group			
Number of subjects analysed	24			
Units: h*ng/mL				
arithmetic mean (standard deviation)				
Day 5 [N=10]	668.7 (± 726.0)			
Day 10 [N=10]	389.1 (± 364.7)			

Statistical analyses

No statistical analyses for this end point

Primary: Concentration Immediately Prior to Dosing at Multiple Dosing (Ctrough) for Fidaxomicin

End point title	Concentration Immediately Prior to Dosing at Multiple Dosing (Ctrough) for Fidaxomicin[10]

End point description:

The analysis population was the pharmacokinetic analysis set (PKAS All Patients). Sampling for participants with reduced PK profile was completed on Day 1 (Predose, 0.5, 1, 1.5, 2, 3, 4, 5 and 10 hours postdose) and Day 5 & 10 (Predose and tmax). N represents number of participants with the available data.

End point type	Primary

End point timeframe:

Day 5 and Day 10 (Predose, 0.5, 1, 1.5, 2, 3, 4, 5 and 10 hours postdose)

Notes:

[10] - 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: Statistical analysis for this endpoint was not completed.

End point values	Fidaxomicin			
Subject group type	Reporting group			
Number of subjects analysed	24			
Units: ng/mL				
arithmetic mean (standard deviation)				
Day 5 [N=23]	6.183 (± 6.521)			
Day 10 [N=22]	4.414 (± 3.173)			

Statistical analyses

No statistical analyses for this end point

Primary: Concentration Immediately Prior to Dosing at Multiple Dosing (Ctrough) for OP-1118

End point title	Concentration Immediately Prior to Dosing at Multiple Dosing (Ctrough) for OP-1118[11]

End point description:

The analysis population was the pharmacokinetic analysis set (PKAS All Patients). Sampling for participants with reduced PK profile was completed on Day 1 (Predose, 0.5, 1, 1.5, 2, 3, 4, 5 and 10 hours postdose) and Day 5 & 10 (Predose and tmax). N represents number of participants with the available data.

End point type	Primary

End point timeframe:

Day 5 and Day 10 (Predose, 0.5, 1, 1.5, 2, 3, 4, 5 and 10 hours postdose)

Notes:

[11] - 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: Statistical analysis for this endpoint was not completed.

End point values	Fidaxomicin			
Subject group type	Reporting group			
Number of subjects analysed	24			
Units: ng/mL				
arithmetic mean (standard deviation)				
Day 5 [N=23]	22.08 (± 22.21)			
Day 10 [N=23]	18.24 (± 15.63)			

Statistical analyses

No statistical analyses for this end point

Primary: Apparent Total Systemic Clearance After Single or Multiple Extra-Vascular Dosing (CL/F) for Fidaxomicin

End point title	Apparent Total Systemic Clearance After Single or Multiple Extra-Vascular Dosing (CL/F) for Fidaxomicin[12]

End point description:

The analysis population was the pharmacokinetic analysis set (PKAS All Patients). Sampling for participants with reduced PK profile was completed on Day 1 (Predose, 0.5, 1, 1.5, 2, 3, 4, 5 and 10 hours postdose) and Day 5 & 10 (Predose and tmax). N represents number of participants with the available data.

End point type	Primary

End point timeframe:

Day 1, Day 5 and Day 10 (Predose, 0.5, 1, 1.5, 2, 3, 4, 5 and 10 hours postdose)

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: Statistical analysis for this endpoint was not completed.

End point values	Fidaxomicin			
Subject group type	Reporting group			
Number of subjects analysed	24			
Units: L/h				
arithmetic mean (standard deviation)				
Day 1 [N=14]	2460 (± 1458)			
Day 5 [N=11]	2306 (± 1556)			
Day 10 [N=11]	3228 (± 3037)			

Statistical analyses

No statistical analyses for this end point

Primary: Apparent Total Systemic Clearance After Single or Multiple Extra-Vascular Dosing (CL/F) for OP-1118

End point title	Apparent Total Systemic Clearance After Single or Multiple Extra-Vascular Dosing (CL/F) for OP-1118[13]

End point description:

The analysis population was the pharmacokinetic analysis set (PKAS All Patients). Sampling for participants with reduced PK profile was completed on Day 1 (Predose, 0.5, 1, 1.5, 2, 3, 4, 5 and 10 hours postdose) and Day 5 & 10 (Predose and tmax). N represents number of participants with the available data.

End point type	Primary

End point timeframe:

Day 1, Day 5 and Day 10 (Predose, 0.5, 1, 1.5, 2, 3, 4, 5 and 10 hours postdose)

Notes:

[13] - 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: Statistical analysis for this endpoint was not completed.

End point values	Fidaxomicin			
Subject group type	Reporting group			
Number of subjects analysed	24			
Units: L/h				
arithmetic mean (standard deviation)				
Day 1 [N=13]	1293 (± 1311)			
Day 5 [N=10]	630.1 (± 541.0)			
Day 10 [N=12]	1083 (± 1072)			

Statistical analyses

No statistical analyses for this end point

Secondary: Stool Concentrations of Fidaxomicin Throughout Fidaxomicin Treatment on Day 1, Day 5, Day 10 and at Any Unscheduled Failure Visit

End point title	Stool Concentrations of Fidaxomicin Throughout Fidaxomicin Treatment on Day 1, Day 5, Day 10 and at Any Unscheduled Failure Visit

End point description:

The analysis population was the pharmacokinetic analysis set (PKAS All Patients). Concentrations below the limit of quantification (10 ng/mL of diluted fecal homogenate or about 2 mcg/g fecal concentrations) were set to zero. Sampling for participants with reduced PK profile was completed on Day 1 (Predose, 0.5, 1, 1.5, 2, 3, 4, 5 and 10 hours postdose) and Day 5 & 10 (Predose and tmax). Day 1 as per protocol data excludes fecal samples taken less than 12-hours after the first dose. N represents number of participants with the available data.

End point type	Secondary

End point timeframe:

Day 1, Day 5 and Day 10

End point values	IBD type - Crohn's Disease	IBD type - Ulcerative Colitis		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	14	10		
Units: mcg/g				
arithmetic mean (standard deviation)				
Day 1 As Per Protocol [N=5;2]	348.80 (± 341.17)	196.90 (± 253.29)		
Day 1 [N=10;7]	174.40 (± 292.45)	94.11 (± 158.07)		
Day 5 [N=12;9]	840.50 (± 397.55)	628.79 (± 418.57)		

Day 10 [N=13;9]	894.23 (± 687.71)	772.71 (± 520.85)		

Statistical analyses

No statistical analyses for this end point

Secondary: Stool Concentrations of Metabolite OP-1118 Throughout Fidaxomicin Treatment on Day 1, Day 5, Day 10 and at Any Unscheduled Failure Visit

End point title	Stool Concentrations of Metabolite OP-1118 Throughout Fidaxomicin Treatment on Day 1, Day 5, Day 10 and at Any Unscheduled Failure Visit

End point description:

The analysis population was the pharmacokinetic analysis set (PKAS All Patients). Concentrations below the limit of quantification (10 ng/mL of diluted fecal homogenate or about 2 mcg/g fecal concentrations) were set to zero. Sampling for participants with reduced PK profile was completed on Day 1 (Predose, 0.5, 1, 1.5, 2, 3, 4, 5 and 10 hours postdose) and Day 5 & 10 (Predose and tmax). Day 1 as per protocol data excludes fecal samples taken less than 12-hours after the first dose. N represents number of participants with the available data.

End point type	Secondary

End point timeframe:

Day 1, Day 5 and Day 10

End point values	IBD type - Crohn's Disease	IBD type - Ulcerative Colitis		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	14	10		
Units: mcg/g				
arithmetic mean (standard deviation)				
Day 1 As Per Protocol [N=5;2]	143.54 (± 134.04)	85.00 (± 120.21)		
Day 1 [N=10;7]	71.77 (± 117.08)	40.86 (± 71.50)		
Day 5 [N=12;9]	618.08 (± 492.88)	331.51 (± 234.82)		
Day 10 [N=13;9]	496.29 (± 558.32)	424.58 (± 241.24)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Clinical Response of CDI at Day 12 Test of Cure (TOC) after End of Treatment (EoT)

End point title	Percentage of Participants with Clinical Response of CDI at Day 12 Test of Cure (TOC) after End of Treatment (EoT)

End point description:

The analysis population was the modified full analysis set (mFAS), which consisted of all participants with confirmed CDI who received at least 1 dose of study treatment and had a valid assessment of TOC. The CDI clinical response (ToC) was based on the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) criteria. Treatment response was present when either stool frequency decreased or stool consistency improved and parameters of disease severity (clinical, laboratory, radiological) improved and there were no new signs of severe disease developed. In all other cases, treatment was considered a failure. Treatment response was observed daily and evaluated after at least three days, assuming that the participant was not worsening on treatment.

End point type	Secondary

End point timeframe:

Day 12 (48-72 hours after EoT)

End point values	Fidaxomicin	IBD type - Crohn's Disease	IBD type - Ulcerative Colitis	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	25	14	11	
Units: Percentage of Participants				
number (confidence interval 95%)	80.0 (60.9 to 91.1)	64.3 (38.8 to 83.7)	100.0 (74.1 to 100.0)	

Statistical analyses

No statistical analyses for this end point

Secondary: Health Economic and Resource Variables by CDI Response at ToC on Day 12 – Overall Length of Hospital Stay

End point title	Health Economic and Resource Variables by CDI Response at ToC on Day 12 – Overall Length of Hospital Stay

End point description:

The analysis population was modified full analysis set (mFAS). Health economic and resource variables were stratified by clinical response of CDI at ToC on day 12 (yes/no/total). Responders/nonresponders were participants assessed as cured/not cured for clinical response for CDI at day 12. N represents number of participants with the available data.

End point type	Secondary

End point timeframe:

Day 1 to Day 180

End point values	Fidaxomicin			
Subject group type	Reporting group			
Number of subjects analysed	25			
Units: Days				
arithmetic mean (standard deviation)				
Overall Length of Hospital Stay Responder [N=17]	34.8 (± 41.6)			
Overall Length of Hospital Stay Nonresponder [N=4]	21.5 (± 13.2)			

Overall Length of Hospital Stay Total [N=21]	32.2 (± 37.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Health Economic and Resource Variables by CDI Response at ToC on Day 12 – Length of Stay on Isolated Ward

End point title	Health Economic and Resource Variables by CDI Response at ToC on Day 12 – Length of Stay on Isolated Ward

End point description:

The analysis population was modified full analysis set (mFAS). Health economic and resource variables were stratified by clinical response of CDI at ToC on day 12 (yes/no/total). Responders/nonresponders were participants assessed as cured/not cured for clinical response for CDI at day 12. N represents number of participants with the available data.

End point type	Secondary

End point timeframe:

Day 1 to Day 180

End point values	Fidaxomicin			
Subject group type	Reporting group			
Number of subjects analysed	25			
Units: Days				
arithmetic mean (standard deviation)				
Isolated Ward Responder [N=3]	19.3 (± 8.4)			
Isolated Ward Nonresponder [N=1]	3 (± 0)			
Isolated Ward Total [N=4]	15.3 (± 10.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Health Economic and Resource Variables by CDI Response at ToC on Day 12 – Length of Hospital Stay With Reason CDI Recurrence

End point title	Health Economic and Resource Variables by CDI Response at ToC on Day 12 – Length of Hospital Stay With Reason CDI Recurrence

End point description:

The analysis population was modified full analysis set (mFAS). Health economic and resource variables were stratified by clinical response of CDI at ToC on day 12 (yes/no/total). Responders/nonresponders were participants assessed as cured/not cured for clinical response for CDI at day 12. N represents number of participants with the available data.

End point type	Secondary

End point timeframe:

Day 1 to Day 180

End point values	Fidaxomicin			
Subject group type	Reporting group			
Number of subjects analysed	25			
Units: Days				
arithmetic mean (standard deviation)				
CDI Recurrence Responder [N=2]	6 (± 0)			
CDI Recurrence Nonresponder [N=0]	0 (± 0)			
CDI Recurrence Total [N=2]	6 (± 0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Health Economic and Resource Variables by CDI Response at ToC on Day 12 – Hospital Admissions

End point title	Health Economic and Resource Variables by CDI Response at ToC on Day 12 – Hospital Admissions

End point description:

The analysis population was modified full analysis set (mFAS). Health economic and resource variables were stratified by clinical response of CDI at ToC on day 12 (yes/no/total). Responders/nonresponders were participants assessed as cured/not cured for clinical response for CDI at day 12. N represents number of participants with the available data.

End point type	Secondary

End point timeframe:

Day 1 to Day 180

End point values	Fidaxomicin			
Subject group type	Reporting group			
Number of subjects analysed	25			
Units: Participants				
arithmetic mean (standard deviation)				
Hospital Admissions Responder [N=17]	2.3 (± 1.8)			
Hospital Admissions Nonresponder [N=4]	2.5 (± 1.3)			
Hospital Admissions Total [N=21]	2.3 (± 1.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Health-Related Quality of Life (HRQoL) as Measured by the Short Inflammatory Bowel Disease Questionnaire (SIBDQ) Score

End point title	Health-Related Quality of Life (HRQoL) as Measured by the Short Inflammatory Bowel Disease Questionnaire (SIBDQ) Score

End point description:

The HRQoL total score results are based on the SIBDQ that consisted of 10 items covering 4 dimensions and 7 levels: Bowel dimension, Systemic dimension, Emotional dimension and the Social dimension. The Short IBDQ questionnaire consisted of 10 questions, each was graded on a scale from 1 (worst case) to 7. All scores were averaged by dividing each score by its number of items so that all score ranges are from 1 to 7, with one being poor and 7 optimum health related quality of life. The analysis population was the modified full analysis set (mFAS). N represents number of participants with the available data.

End point type	Secondary

End point timeframe:

Day 10, Day 26, Day 40,Day 90 and Day 180 (EOS)

End point values	Fidaxomicin			
Subject group type	Reporting group			
Number of subjects analysed	25			
Units: Units on a Scale				
arithmetic mean (standard deviation)				
SIBDQ: total score Day 10 [N=24]	3.68 (± 1.08)			
SIBDQ: total score Day 26 [N=24]	4.28 (± 1.16)			
SIBDQ: total score Day 40 [N=23]	4.64 (± 1.06)			
SIBDQ: total score Day 90 [N=23]	4.87 (± 1.21)			
SIBDQ: total score Day 180 [N=20]	4.98 (± 1.32)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Treatment-Emergent Adverse Events (TEAEs) up to 30 days after End of Treatment (EOT)

End point title	Number of Participants with Treatment-Emergent Adverse Events (TEAEs) up to 30 days after End of Treatment (EOT)

End point description:

A TEAE was defined as an AE starting, or an existing condition that worsened, after first drug intake and until 30 days after the EoT visit on day 10. The analysis population was safety analysis set (SAF) and it consisted of all participants who received at least 1 dose of study drug.

End point type	Secondary

End point timeframe:

From first dose of study drug up to 30 days after the EOT visit (Day 10)

End point values	Fidaxomicin			
Subject group type	Reporting group			
Number of subjects analysed	25			
Units: Participants				
TEAE	15			
Drug-related TEAE	10			
Serious TEAE	6			
Drug-related serious TEAEs	2			
TEAEs leading to death	0			
Drug-related TEAE leading to death	0			
TEAE leading to withdrawal of treatment	0			
Drug-related TEAEs leading to withdrawal of treat	0			
Death	0			

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 up to 7 days after EOS (up to 187)

Adverse event reporting additional description:

An adverse events (AE) was defined as any untoward medical occurrence in a participants administered a study drug or who had undergone study procedures and did not necessarily have a causal relationship with this treatment. All participants remained in the study until end of study (EoS) visit 8 (day 180) for safety assessments.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	14.1

Reporting groups

Reporting group title	Fidaxomicin

Reporting group description:

Participants received 200 mg of fidaxomicin orally, twice a day (every 12 hours) on day 1 for 10 treatment days.

Serious adverse events	Fidaxomicin		
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 25 (24.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Colitis ulcerative			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Crohn's disease			

subjects affected / exposed	2 / 25 (8.00%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Hypoxia			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Skin ulcer			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Clostridial infection			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Fidaxomicin		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 25 (40.00%)		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	3 / 25 (12.00%)		
occurrences (all)	3		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	3 / 25 (12.00%)		
occurrences (all)	3		
Flatulence			
subjects affected / exposed	2 / 25 (8.00%)		
occurrences (all)	3		

Inflammatory bowel disease subjects affected / exposed occurrences (all)	2 / 25 (8.00%) 3		
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all)	2 / 25 (8.00%) 2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 August 2015	-The phase of study was amended from phase 4 to phase 3b/4. As fidaxomicin was not an approved drug within the Russian Federation, this study was to be regarded as a phase 3b study. -To maximize the probability of enrolling the required number of participants within the stipulated enrollment period, 3 sites in the Russian Federation were added to the study. -The time point changed from 12 to 10 hours postdose of fidaxomicin and acceptable time window (changed from within 24 hours of first dose to not earlier than 12 hours) for the last pharmacokinetic sampling was updated to introduce some flexibility to assist the logistical challenges faced by the clinical sites. -In the protocol text it was clarified when to take stool samples. -In the protocol text it was clarified that the review of pharmacokinetic data was ongoing throughout the study. -In the protocol text it was clarified that the enrollment was interrupted after the first 3 patients. -Definitions of activity of IBD were updated in the inclusion criteria. New recommendations for 'active IBD' have been discussed among authorities and IBD specialists and will assist with the analyses of efficacy, as discussed with the protocol Steering Committee. -As some medication on the list had to be used in case of failure and/or recurrence of CDI, the protocol terminology was amended from 'prohibited medication' to 'medication to be avoided'. -Independent' was added in the text before Data Monitoring Committee (DMC), to clarify that the external DMC was independent. -The information regarding the stool sample taken for enrollment was updated. As it could take time to retrieve the results from CDI testing, the wording in the text was changed to 'the time of confirmation of CDI diagnosis' rather than 'the time of sample taken' so participantscould be enrolled within 48 hours after receiving the diagnosis of CDI.
19 August 2015	-In the protocol text it was clarified when screening samples for safety laboratory assessment were to be taken. -The SmPC was added as reference safety information for AEs for countries where fidaxomicin was an approved drug. -For the AEs of special interest, the ranges for hepatic laboratory abnormalities were updated as clarified by the global pharmacovigilance department. -The information regarding the collection of treatment-emergent adverse events (TEAEs) was updated. As this study was continuous for a long period after the stop of study drug, a distinction was made between 'TEAEs' and 'other AEs'. -As endoscopic findings were not part of the Mayo Score, the information regarding endoscopic findings was removed and the summary of score was updated. -The CDI clinical assessment and severity score was deleted from visit 4. This assessment could not be performed as this visit was conducted over the telephone. -To improve the evaluation of outcomes of IBD during the study, definitions were added for the response and flare of both 'ulcerative colitis' and 'Crohn's disease'. -As requested by the IEC in the UK, the number of mucosal samples taken during the study was maximized to 4. -Contact details of sponsor's personnel were updated to reflect the change of role of the medical expert and changes to European and regional study management.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The study was on hold after first 3 participants PK results were examined to ensure maximum plasma concentrations were not high and to minimize the safety risks.The Microbiological Response endpoint data was not available, it will be reported later.

Notes: