



Clinical trial results:

A randomized, open label, six sequences, cross-over study in healthy Japanese subjects to evaluate the pharmacokinetic comparability of deferasirox granule formulation with the reference dispersible tablet formulation (Exjade)

Due to EudraCT system limitations, which EMA is aware of, results of crossover studies are not accurately represented in this record. Please go to <https://www.novctrd.com/CtrdWeb/home.nov> for complete trial results.

Summary

EudraCT number	2016-000308-28
Trial protocol	Outside EU/EEA
Global end of trial date	10 August 2015

Results information

Result version number	v1 (current)
This version publication date	11 July 2018
First version publication date	11 July 2018

Trial information

Trial identification

Sponsor protocol code	CICL670F1102
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Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613421111,
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613421111,

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMA-001103-PIP01-10
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
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Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	10 August 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	10 August 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of Part 1 was to evaluate the PK comparability of two different doses of the deferasirox (DFX) granule formulation in comparison to the reference dispersible formulation (Exjade®) in healthy Japanese subjects under fasted conditions. Per amendment, part 2 was added where the primary objective was to evaluate the PK comparability of 900 mg DFX granule formulation in comparison to the reference dispersible formulation (1500 mg) in healthy Japanese subjects under fasted conditions.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	27 June 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Japan: 193
Worldwide total number of subjects	193
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)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	193
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Participants were randomized to 1 of 6 treatment groups in Part 1. In Part 2, participants were randomized to 1 of 2 treatment groups.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Part 1 - Arm A/B/C

Arm description:

On day 1, participants received a single dose of 1500 mg dispersible tablet formulation of deferasirox orally. On day 10, participants received a single dose of 1080 mg of deferasirox granule formulation orally. On day 19, participants received a single dose of 990 mg of deferasirox granule formulation orally.

Arm type	Experimental
Investigational medicinal product name	Treatment A
Investigational medicinal product code	ICL670
Other name	Deferasirox
Pharmaceutical forms	Dispersible tablet
Routes of administration	Oral use

Dosage and administration details:

On day 1, participants received a single dose of 1500 mg dispersible tablet formulation of deferasirox orally.

Investigational medicinal product name	Treatment B
Investigational medicinal product code	
Other name	Deferasirox
Pharmaceutical forms	Granules
Routes of administration	Oral use

Dosage and administration details:

On day 10, participants received a single dose of 1080 mg of deferasirox granule formulation orally.

Investigational medicinal product name	Treatment C
Investigational medicinal product code	
Other name	Deferasirox
Pharmaceutical forms	Granules
Routes of administration	Oral use

Dosage and administration details:

On day 19, participants received a single dose of 990 mg of deferasirox granule formulation orally.

Arm title	Part 1 - Arm A/C/B
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Arm description:

On day 1, participants received a single dose of 1500 mg dispersible tablet formulation of deferasirox orally. On day 10, participants received a single dose of 990 mg of deferasirox granule formulation orally. On day 19, participants received a single dose of 1080 mg of deferasirox granule formulation orally.

Arm type	Experimental
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Investigational medicinal product name	Treatment A
Investigational medicinal product code	ICL670
Other name	Deferasirox
Pharmaceutical forms	Dispersible tablet
Routes of administration	Oral use

Dosage and administration details:

On day 1, participants received a single dose of 1500 mg dispersible tablet formulation of deferasirox orally.

Investigational medicinal product name	Treatment C
Investigational medicinal product code	
Other name	Deferasirox
Pharmaceutical forms	Granules
Routes of administration	Oral use

Dosage and administration details:

On day 10, participants received a single dose of 990 mg of deferasirox granule formulation orally.

Investigational medicinal product name	Treatment B
Investigational medicinal product code	
Other name	Deferasirox
Pharmaceutical forms	Granules
Routes of administration	Oral use

Dosage and administration details:

On day 19, participants received a single dose of 1080 mg of deferasirox granule formulation orally.

Arm title	Part 1 - Arm B/A/C
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Arm description:

On day 1, participants received a single dose of 1080 mg of deferasirox granule formulation orally. On day 10, participants received a single dose of 1500 mg dispersible tablet formulation of deferasirox orally. On day 19, participants received a single dose of 990 mg of deferasirox granule formulation orally.

Arm type	Experimental
Investigational medicinal product name	Treatment B
Investigational medicinal product code	
Other name	Deferasirox
Pharmaceutical forms	Granules
Routes of administration	Oral use

Dosage and administration details:

On day 1, participants received a single dose of 1080 mg of deferasirox granule formulation orally.

Investigational medicinal product name	Treatment A
Investigational medicinal product code	ICL670
Other name	Deferasirox
Pharmaceutical forms	Dispersible tablet
Routes of administration	Oral use

Dosage and administration details:

On day 10, participants received a single dose of 1500 mg dispersible tablet formulation of deferasirox orally.

Investigational medicinal product name	Treatment C
Investigational medicinal product code	
Other name	Deferasirox
Pharmaceutical forms	Granules
Routes of administration	Oral use

Dosage and administration details:

On day 19, participants received a single dose of 990 mg of deferasirox granule formulation orally.

Arm title	Part 1 - Arm B/C/A
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Arm description:

On day 1, participants received a single dose of 1080 mg of deferasirox granule formulation orally. On day 10, participants received a single dose of 990 mg of deferasirox granule formulation orally. On day 19, participants received a single dose of 1500 mg dispersible tablet formulation of deferasirox orally

Arm type	Experimental
Investigational medicinal product name	Treatment B
Investigational medicinal product code	
Other name	Deferasirox
Pharmaceutical forms	Granules
Routes of administration	Oral use

Dosage and administration details:

On day 1, participants received a single dose of 1080 mg of deferasirox granule formulation orally.

Investigational medicinal product name	Treatment C
Investigational medicinal product code	
Other name	Deferasirox
Pharmaceutical forms	Granules
Routes of administration	Oral use

Dosage and administration details:

On day 10, participants received a single dose of 990 mg of deferasirox granule formulation orally

Investigational medicinal product name	Treatment A
Investigational medicinal product code	ICL670
Other name	Deferasirox
Pharmaceutical forms	Dispersible tablet
Routes of administration	Oral use

Dosage and administration details:

On day 19, participants received a single dose of 1500 mg dispersible tablet formulation of deferasirox orally.

Arm title	Part 1 - ARM C/A/B
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Arm description:

On day 1, participants received a single dose of 990 mg of deferasirox granule formulation orally. On day 10, participants received a single dose of 1500 mg dispersible tablet formulation of deferasirox orally. On day 19, participants received a single dose of 1080 mg of deferasirox granule formulation orally.

Arm type	Experimental
Investigational medicinal product name	Treatment C
Investigational medicinal product code	
Other name	Deferasirox
Pharmaceutical forms	Granules
Routes of administration	Oral use

Dosage and administration details:

On day 1, participants received a single dose of 990 mg of deferasirox granule formulation orally.

Investigational medicinal product name	Treatment A
Investigational medicinal product code	ICL670
Other name	Deferasirox
Pharmaceutical forms	Dispersible tablet
Routes of administration	Oral use

Dosage and administration details:

On day 10, participants received a single dose of 1500 mg dispersible tablet formulation of deferasirox orally.

Investigational medicinal product name	Treatment B
Investigational medicinal product code	
Other name	Deferasirox
Pharmaceutical forms	Granules

Routes of administration	Oral use
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Dosage and administration details:

On day 19, participants received a single dose of 1080 mg of deferasirox granule formulation orally.

Arm title	Part 1 - Arm C/B/A
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Arm description:

On day 1, participants received a single dose of 990 mg of deferasirox granule formulation orally. On day 10, participants received a single dose of 1080 mg of deferasirox granule formulation orally. On day 19, participants received a single dose of 1500 mg dispersible tablet formulation of deferasirox orally.

Arm type	Experimental
Investigational medicinal product name	Treatment C
Investigational medicinal product code	
Other name	Deferasirox
Pharmaceutical forms	Granules
Routes of administration	Oral use

Dosage and administration details:

On day 1, participants received a single dose of 990 mg of deferasirox granule formulation orally.

Investigational medicinal product name	Treatment B
Investigational medicinal product code	
Other name	Deferasirox
Pharmaceutical forms	Granules
Routes of administration	Oral use

Dosage and administration details:

On day 10, participants received a single dose of 1080 mg of deferasirox granule formulation orally.

Investigational medicinal product name	Treatment A
Investigational medicinal product code	ICL670
Other name	Deferasirox
Pharmaceutical forms	Dispersible tablet
Routes of administration	Oral use

Dosage and administration details:

On day 19, participants received a single dose of 1500 mg dispersible tablet formulation of deferasirox orally.

Arm title	Part 2 - Arm D/E
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Arm description:

On day 1, participants received a single dose of 1500 mg dispersible tablet formulation of deferasirox orally. On day 10, participants received a single dose of 900 mg of deferasirox granule formulation orally.

Arm type	Experimental
Investigational medicinal product name	Treatment D
Investigational medicinal product code	ICL670
Other name	Deferasirox
Pharmaceutical forms	Dispersible tablet
Routes of administration	Oral use

Dosage and administration details:

On day 1, participants received a single dose of 1500 mg dispersible tablet formulation of deferasirox orally.

Investigational medicinal product name	Treatment E
Investigational medicinal product code	
Other name	Deferasirox
Pharmaceutical forms	Granules
Routes of administration	Oral use

Dosage and administration details:

On day 10, participants received a single dose of 900 mg of deferasirox granule formulation orally.

Arm title	Part 2 - Arm E/D
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Arm description:

On day 1, participants received a single dose of 900 mg of deferasirox granule formulation orally. On day 10, participants received a single dose of 1500 mg dispersible tablet formulation of deferasirox orally.

Arm type	Experimental
Investigational medicinal product name	Treatment E
Investigational medicinal product code	
Other name	Deferasirox
Pharmaceutical forms	Granules
Routes of administration	Oral use

Dosage and administration details:

On day 1, participants received a single dose of 900 mg of deferasirox granule formulation orally.

Investigational medicinal product name	Treatment D
Investigational medicinal product code	ICL670
Other name	Deferasirox
Pharmaceutical forms	Dispersible tablet
Routes of administration	Oral use

Dosage and administration details:

On day 10, participants received a single dose of 1500 mg dispersible tablet formulation of deferasirox orally.

Number of subjects in period 1	Part 1 - Arm A/B/C	Part 1 - Arm A/C/B	Part 1 - Arm B/A/C
Started	17	16	16
PK analysis set	17	16	16
Completed	16	16	16
Not completed	1	0	0
Physician decision	1	-	-
Consent withdrawn by subject	-	-	-
Adverse event, non-fatal	-	-	-

Number of subjects in period 1	Part 1 - Arm B/C/A	Part 1 - ARM C/A/B	Part 1 - Arm C/B/A
Started	16	16	16
PK analysis set	16	16	16
Completed	14	16	15
Not completed	2	0	1
Physician decision	1	-	-
Consent withdrawn by subject	-	-	-
Adverse event, non-fatal	1	-	1

Number of subjects in period 1	Part 2 - Arm D/E	Part 2 - Arm E/D
Started	48	48
PK analysis set	48	48
Completed	47	48
Not completed	1	0
Physician decision	-	-
Consent withdrawn by subject	1	-
Adverse event, non-fatal	-	-

Baseline characteristics

Reporting groups

Reporting group title	Part 1 - Arm A/B/C
Reporting group description: On day 1, participants received a single dose of 1500 mg dispersible tablet formulation of deferasirox orally. On day 10, participants received a single dose of 1080 mg of deferasirox granule formulation orally. On day 19, participants received a single dose of 990 mg of deferasirox granule formulation orally.	
Reporting group title	Part 1 - Arm A/C/B
Reporting group description: On day 1, participants received a single dose of 1500 mg dispersible tablet formulation of deferasirox orally. On day 10, participants received a single dose of 990 mg of deferasirox granule formulation orally. On day 19, participants received a single dose of 1080 mg of deferasirox granule formulation orally.	
Reporting group title	Part 1 - Arm B/A/C
Reporting group description: On day 1, participants received a single dose of 1080 mg of deferasirox granule formulation orally. On day 10, participants received a single dose of 1500 mg dispersible tablet formulation of deferasirox orally. On day 19, participants received a single dose of 990 mg of deferasirox granule formulation orally.	
Reporting group title	Part 1 - Arm B/C/A
Reporting group description: On day 1, participants received a single dose of 1080 mg of deferasirox granule formulation orally. On day 10, participants received a single dose of 990 mg of deferasirox granule formulation orally. On day 19, participants received a single dose of 1500 mg dispersible tablet formulation of deferasirox orally.	
Reporting group title	Part 1 - ARM C/A/B
Reporting group description: On day 1, participants received a single dose of 990 mg of deferasirox granule formulation orally. On day 10, participants received a single dose of 1500 mg dispersible tablet formulation of deferasirox orally. On day 19, participants received a single dose of 1080 mg of deferasirox granule formulation orally.	
Reporting group title	Part 1 - Arm C/B/A
Reporting group description: On day 1, participants received a single dose of 990 mg of deferasirox granule formulation orally. On day 10, participants received a single dose of 1080 mg of deferasirox granule formulation orally. On day 19, participants received a single dose of 1500 mg dispersible tablet formulation of deferasirox orally.	
Reporting group title	Part 2 - Arm D/E
Reporting group description: On day 1, participants received a single dose of 1500 mg dispersible tablet formulation of deferasirox orally. On day 10, participants received a single dose of 900 mg of deferasirox granule formulation orally.	
Reporting group title	Part 2 - Arm E/D
Reporting group description: On day 1, participants received a single dose of 900 mg of deferasirox granule formulation orally. On day 10, participants received a single dose of 1500 mg dispersible tablet formulation of deferasirox orally.	

Reporting group values	Part 1 - Arm A/B/C	Part 1 - Arm A/C/B	Part 1 - Arm B/A/C
Number of subjects	17	16	16
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0

Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	17	16	16
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous			
Units: Years			
arithmetic mean	27.6	30	28.1
standard deviation	± 6.95	± 7.41	± 6.01
Gender, Male/Female			
Units: Participants			
Female	1	1	1
Male	16	15	15

Reporting group values	Part 1 - Arm B/C/A	Part 1 - ARM C/A/B	Part 1 - Arm C/B/A
Number of subjects	16	16	16
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	16	16	16
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous			
Units: Years			
arithmetic mean	29	32.2	30.6
standard deviation	± 8.09	± 9.01	± 8.14
Gender, Male/Female			
Units: Participants			
Female	1	1	1
Male	15	15	15

Reporting group values	Part 2 - Arm D/E	Part 2 - Arm E/D	Total
Number of subjects	48	48	193
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0

Adults (18-64 years)	48	48	193
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous			
Units: Years			
arithmetic mean	32.2	30.9	
standard deviation	± 7.74	± 8.4	-
Gender, Male/Female			
Units: Participants			
Female	0	0	6
Male	48	48	187

End points

End points reporting groups

Reporting group title	Part 1 - Arm A/B/C
Reporting group description: On day 1, participants received a single dose of 1500 mg dispersible tablet formulation of deferasirox orally. On day 10, participants received a single dose of 1080 mg of deferasirox granule formulation orally. On day 19, participants received a single dose of 990 mg of deferasirox granule formulation orally.	
Reporting group title	Part 1 - Arm A/C/B
Reporting group description: On day 1, participants received a single dose of 1500 mg dispersible tablet formulation of deferasirox orally. On day 10, participants received a single dose of 990 mg of deferasirox granule formulation orally. On day 19, participants received a single dose of 1080 mg of deferasirox granule formulation orally.	
Reporting group title	Part 1 - Arm B/A/C
Reporting group description: On day 1, participants received a single dose of 1080 mg of deferasirox granule formulation orally. On day 10, participants received a single dose of 1500 mg dispersible tablet formulation of deferasirox orally. On day 19, participants received a single dose of 990 mg of deferasirox granule formulation orally.	
Reporting group title	Part 1 - Arm B/C/A
Reporting group description: On day 1, participants received a single dose of 1080 mg of deferasirox granule formulation orally. On day 10, participants received a single dose of 990 mg of deferasirox granule formulation orally. On day 19, participants received a single dose of 1500 mg dispersible tablet formulation of deferasirox orally.	
Reporting group title	Part 1 - ARM C/A/B
Reporting group description: On day 1, participants received a single dose of 990 mg of deferasirox granule formulation orally. On day 10, participants received a single dose of 1500 mg dispersible tablet formulation of deferasirox orally. On day 19, participants received a single dose of 1080 mg of deferasirox granule formulation orally.	
Reporting group title	Part 1 - Arm C/B/A
Reporting group description: On day 1, participants received a single dose of 990 mg of deferasirox granule formulation orally. On day 10, participants received a single dose of 1080 mg of deferasirox granule formulation orally. On day 19, participants received a single dose of 1500 mg dispersible tablet formulation of deferasirox orally.	
Reporting group title	Part 2 - Arm D/E
Reporting group description: On day 1, participants received a single dose of 1500 mg dispersible tablet formulation of deferasirox orally. On day 10, participants received a single dose of 900 mg of deferasirox granule formulation orally.	
Reporting group title	Part 2 - Arm E/D
Reporting group description: On day 1, participants received a single dose of 900 mg of deferasirox granule formulation orally. On day 10, participants received a single dose of 1500 mg dispersible tablet formulation of deferasirox orally.	
Subject analysis set title	Part 1 - Treatment A
Subject analysis set type	Full analysis
Subject analysis set description: Participants received a single dose of 1500 mg dispersible tablet formulation of deferasirox orally.	
Subject analysis set title	Part 1 - Treatment B
Subject analysis set type	Full analysis
Subject analysis set description: Participants received a single dose of 1080 mg of deferasirox granule formulation orally.	
Subject analysis set title	Part 1 - Treatment C

Subject analysis set type	Full analysis
Subject analysis set description:	
Participants received a single dose of 990 mg of deferasirox granule formulation orally.	
Subject analysis set title	Part 1 - Treatment A
Subject analysis set type	Full analysis
Subject analysis set description:	
Participants received a single dose of 1500 mg dispersible tablet formulation of deferasirox orally.	
Subject analysis set title	Part 1 - Treatment B
Subject analysis set type	Full analysis
Subject analysis set description:	
Participants received a single dose of 1080 mg of deferasirox granule formulation orally.	
Subject analysis set title	Part 1 - Treatment C
Subject analysis set type	Full analysis
Subject analysis set description:	
Participants received a single dose of 990 mg of deferasirox granule formulation orally.	
Subject analysis set title	Part 2 -Treatment D
Subject analysis set type	Full analysis
Subject analysis set description:	
Participants received a single dose of 1500 mg dispersible tablet formulation of deferasirox orally.	
Subject analysis set title	Part 2 - Treatment E
Subject analysis set type	Full analysis
Subject analysis set description:	
Participants received a single dose of 900 mg of deferasirox granule formulation orally.	
Subject analysis set title	Part 2 -Treatment D
Subject analysis set type	Full analysis
Subject analysis set description:	
Participants received a single dose of 1500 mg dispersible tablet formulation of deferasirox orally.	
Subject analysis set title	Part 2 - Treatment E
Subject analysis set type	Full analysis
Subject analysis set description:	
Participants received a single dose of 900 mg of deferasirox granule formulation orally.	
Subject analysis set title	Part 2 - Treatment D
Subject analysis set type	Full analysis
Subject analysis set description:	
Participants received a single dose of 1500 mg dispersible tablet formulation of deferasirox orally.	
Subject analysis set title	Part 2 - Treatment D
Subject analysis set type	Full analysis
Subject analysis set description:	
Participants received a single dose of 1500 mg dispersible tablet formulation of deferasirox orally.	
Primary: Part 1 - Summary of PK parameter: area under the curve from time zero to infinity (AUCinf)	
End point title	Part 1 - Summary of PK parameter: area under the curve from time zero to infinity (AUCinf)
End point description:	
Serial blood samples for plasma deferasirox concentration were collected to analyze PK parameters.	
End point type	Primary
End point timeframe:	
Days 1, 10, 19 at 0 hour (pre-dose) and 0.5, 1, 1.5, 2, 3, 46, 8, 12, 24,36, 48 and 72 hours post-dose.	

End point values	Part 1 - Treatment A	Part 1 - Treatment B	Part 1 - Treatment C	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	88	93	93	
Units: umol/L*hr				
arithmetic mean (standard deviation)	1790 (± 596)	1940 (± 552)	1780 (± 505)	

Statistical analyses

Statistical analysis title	AUCinf treatment comparison between A and B
Comparison groups	Part 1 - Treatment A v Part 1 - Treatment B
Number of subjects included in analysis	181
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Geometric mean ratio
Point estimate	1.0954
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.0479
upper limit	1.1451

Statistical analysis title	AUCinf treatment comparison between A and C
Comparison groups	Part 1 - Treatment A v Part 1 - Treatment C
Number of subjects included in analysis	181
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Geometric mean ratio
Point estimate	1.0048
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.9612
upper limit	1.0503

Primary: Part 1 - Summary of PK parameter: area under the curve from time zero to last measurable concentration sampling time (AUClast)

End point title	Part 1 - Summary of PK parameter: area under the curve from time zero to last measurable concentration sampling time (AUClast)
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End point description:

Serial blood samples for plasma deferasirox concentration were collected to analyze PK parameters.

End point type	Primary
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End point timeframe:

Days 1, 10, 19 at 0 hour (pre-dose) and 0.5, 1, 1.5, 2, 3, 46, 8, 12, 24, 36, 48 and 72 hours post-dose.

End point values	Part 1 - Treatment A	Part 1 - Treatment B	Part 1 - Treatment C	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	94	94	94	
Units: umol/L*hr				
arithmetic mean (standard deviation)	1710 (± 524)	1870 (± 518)	1690 (± 484)	

Statistical analyses

Statistical analysis title	AUClast treatment comparison between A and B
Comparison groups	Part 1 - Treatment A v Part 1 - Treatment B
Number of subjects included in analysis	188
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Geometric mean ratio
Point estimate	1.0994
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.0546
upper limit	1.1461

Statistical analysis title	AUClast treatment comparison between A and C
Comparison groups	Part 1 - Treatment A v Part 1 - Treatment C
Number of subjects included in analysis	188
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Geometric mean ratio
Point estimate	0.9984
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.9577
upper limit	1.0408

Primary: Part 1 - Summary of PK parameter: maximum (peak) observed plasma concentration after single dose administration (Cmax)

End point title	Part 1 - Summary of PK parameter: maximum (peak) observed plasma concentration after single dose administration (Cmax)
End point description: Serial blood samples for plasma deferasirox concentration were collected to analyze PK parameters.	
End point type	Primary
End point timeframe: Days 1, 10, 19 at 0 hour (pre-dose) and 0.5, 1, 1.5, 2, 3, 46, 8, 12, 24,36, 48 and 72 hours post-dose.	

End point values	Part 1 - Treatment A	Part 1 - Treatment B	Part 1 - Treatment C	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	94	94	94	
Units: umol/L				
arithmetic mean (standard deviation)	96.6 (± 26.7)	130 (± 37.7)	120 (± 33.5)	

Statistical analyses

Statistical analysis title	Cmax treatment comparison between A and B
Comparison groups	Part 1 - Treatment A v Part 1 - Treatment B
Number of subjects included in analysis	188
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Geometric mean ratio
Point estimate	1.3398
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.2794
upper limit	1.403

Statistical analysis title	Cmax treatment comparison between A and C
Comparison groups	Part 1 - Treatment A v Part 1 - Treatment C
Number of subjects included in analysis	188
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Geometric mean ratio
Point estimate	1.2432
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.1872
upper limit	1.3019

Primary: Part 2 - Summary of PK parameter: area under the curve from time zero to infinity (AUCinf)

End point title	Part 2 - Summary of PK parameter: area under the curve from time zero to infinity (AUCinf)
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End point description:

Serial blood samples for plasma deferasirox concentration were collected to analyze PK parameters.

End point type	Primary
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End point timeframe:

Days 1 and 10 at 0 hour (pre-dose) and 0.5, 1, 1.5, 2, 3, 46, 8, 12, 24,36, 48 and 72 hours post-dose.

End point values	Part 2 - Treatment D	Part 2 - Treatment E		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	79	87		
Units: umol/L*hr				
arithmetic mean (standard deviation)	1830 (± 611)	1800 (± 511)		

Statistical analyses

Statistical analysis title	AUCinf treatment comparison between D and E
Comparison groups	Part 2 -Treatment D v Part 2 - Treatment E
Number of subjects included in analysis	166
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Geometric mean ratio
Point estimate	0.9708
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.929
upper limit	1.0144

Primary: Part 2 - Summary of PK parameter: area under the curve from time zero to last measurable concentration sampling time (AUClast)

End point title	Part 2 - Summary of PK parameter: area under the curve from time zero to last measurable concentration sampling time (AUClast)
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End point description:

Serial blood samples for plasma deferasirox concentration were collected to analyze PK parameters.

End point type	Primary
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End point timeframe:

Days 1 and 10 at 0 hour (pre-dose) and 0.5, 1, 1.5, 2, 3, 46, 8, 12, 24,36, 48 and 72 hours post-dose.

End point values	Part 2 - Treatment D	Part 2 - Treatment E		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	96	95		
Units: umol/L*hr				
arithmetic mean (standard deviation)	1810 (± 561)	1720 (± 452)		

Statistical analyses

Statistical analysis title	AUClast treatment comparison between D and E
Comparison groups	Part 2 -Treatment D v Part 2 - Treatment E
Number of subjects included in analysis	191
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Geometric mean ratio
Point estimate	0.9546
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.9196
upper limit	0.9909

Primary: Part 2 - Summary of PK parameter: maximum (peak) observed plasma concentration after single dose administration (Cmax)

End point title	Part 2 - Summary of PK parameter: maximum (peak) observed plasma concentration after single dose administration (Cmax)
End point description:	Serial blood samples for plasma deferasirox concentration were collected to analyze PK parameters.
End point type	Primary
End point timeframe:	Days 1 and 10 at 0 hour (pre-dose) and 0.5, 1, 1.5, 2, 3, 46, 8, 12, 24,36, 48 and 72 hours post-dose.

End point values	Part 2 - Treatment D	Part 2 - Treatment E		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	96	95		
Units: umol/L				
arithmetic mean (standard deviation)	97.1 (± 24.8)	116 (± 31.4)		

Statistical analyses

Statistical analysis title	Cmax treatment comparison between D and E
Comparison groups	Part 2 -Treatment D v Part 2 - Treatment E
Number of subjects included in analysis	191
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Geometric mean ratio
Point estimate	1.1895
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.1382
upper limit	1.2431

Secondary: Part 1 - Summary of PK parameter: time to reach maximum (peak) plasma concentration after single dose administration (Tmax)

End point title	Part 1 - Summary of PK parameter: time to reach maximum (peak) plasma concentration after single dose administration (Tmax)
End point description:	Serial blood samples for plasma deferasirox concentration were collected to analyze PK parameters.
End point type	Secondary
End point timeframe:	Days 1, 10, 19 at 0 hour (pre-dose) and 0.5, 1, 1.5, 2, 3, 46, 8, 12, 24,36, 48 and 72 hours post-dose.

End point values	Part 1 - Treatment A	Part 1 - Treatment B	Part 1 - Treatment C	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	94	94	94	
Units: hour				
median (full range (min-max))	4 (1.5 to 6)	4 (1.5 to 8)	3 (1.5 to 8)	

Statistical analyses

No statistical analyses for this end point

Secondary: Part 1 - Summary of PK parameter: elimination half-life associated with the terminal slope (Lambda_z) of a semi logarithmic concentration-time curve (T1/2)

End point title	Part 1 - Summary of PK parameter: elimination half-life associated with the terminal slope (Lambda_z) of a semi logarithmic concentration-time curve (T1/2)
End point description:	Serial blood samples for plasma deferasirox concentration were collected to analyze PK parameters.
End point type	Secondary

End point timeframe:

Days 1, 10, 19 at 0 hour (pre-dose) and 0.5, 1, 1.5, 2, 3, 46, 8, 12, 24,36, 48 and 72 hours post-dose.

End point values	Part 1 - Treatment B	Part 1 - Treatment C	Part 1 - Treatment A	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	93	93	94	
Units: hour				
arithmetic mean (standard deviation)	14.8 (± 5.35)	15.5 (± 6.13)	16.9 (± 9.54)	

Statistical analyses

No statistical analyses for this end point

Secondary: Part 1 - Summary of PK parameter: the mean residence time from time of dosing to the last measurable concentration sampling time (MRTlast)

End point title	Part 1 - Summary of PK parameter: the mean residence time from time of dosing to the last measurable concentration sampling time (MRTlast)
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End point description:

Serial blood samples for plasma deferasirox concentration were collected to analyze PK parameters.

End point type	Secondary
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End point timeframe:

Days 1, 10, 19 at 0 hour (pre-dose) and 0.5, 1, 1.5, 2, 3, 46, 8, 12, 24,36, 48 and 72 hours post-dose.

End point values	Part 1 - Treatment A	Part 1 - Treatment B	Part 1 - Treatment C	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	94	94	94	
Units: hour				
arithmetic mean (standard deviation)	19 (± 3.9)	16.9 (± 3.11)	16.8 (± 3.1)	

Statistical analyses

No statistical analyses for this end point

Secondary: Part - 1 Summary of PK parameter: terminal slope of elimination phase (Lambda_z)

End point title	Part - 1 Summary of PK parameter: terminal slope of elimination phase (Lambda_z)
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End point description:

Serial blood samples for plasma deferasirox concentration were collected to analyze PK parameters.

End point type	Secondary
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End point timeframe:

Days 1, 10, 19 at 0 hour (pre-dose) and 0.5, 1, 1.5, 2, 3, 46, 8, 12, 24,36, 48 and 72 hours post-dose.

End point values	Part 1 - Treatment B	Part 1 - Treatment C	Part 1 - Treatment A	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	93	93	94	
Units: 1/hr				
arithmetic mean (standard deviation)	0.0513 (± 0.0139)	0.0508 (± 0.0168)	0.0489 (± 0.017)	

Statistical analyses

No statistical analyses for this end point

Secondary: Part 2 - Summary of PK parameter: time to reach maximum (peak) plasma concentration after single dose administration (Tmax)

End point title	Part 2 - Summary of PK parameter: time to reach maximum (peak) plasma concentration after single dose administration (Tmax)
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End point description:

Serial blood samples for plasma deferasirox concentration were collected to analyze PK parameters.

End point type	Secondary
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End point timeframe:

Days 1 and 10 at 0 hour (pre-dose) and 0.5, 1, 1.5, 2, 3, 46, 8, 12, 24,36, 48 and 72 hours post-dose.

End point values	Part 2 - Treatment E	Part 2 - Treatment D		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	95	96		
Units: hour				
median (full range (min-max))	3 (1.5 to 8)	4 (1 to 8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Part 2 - Summary of PK parameter: elimination half-life associated with the terminal slope (Lambda_z) of a semi logarithmic concentration-time curve (T1/2)

End point title	Part 2 - Summary of PK parameter: elimination half-life associated with the terminal slope (Lambda_z) of a semi logarithmic concentration-time curve (T1/2)
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End point description:

Serial blood samples for plasma deferasirox concentration were collected to analyze PK parameters.

End point type	Secondary
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End point timeframe:

Days 1 and 10 at 0 hour (pre-dose) and 0.5, 1, 1.5, 2, 3, 46, 8, 12, 24,36, 48 and 72 hours post-dose.

End point values	Part 2 - Treatment E	Part 2 - Treatment D		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	95	89		
Units: hour				
arithmetic mean (standard deviation)	18.1 (± 9.69)	23.4 (± 34.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Part 2 - Summary of PK parameter: mean residence time from time of dosing to the last measurable concentration sampling time (MRTlast)

End point title	Part 2 - Summary of PK parameter: mean residence time from time of dosing to the last measurable concentration sampling time (MRTlast)
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End point description:

Serial blood samples for plasma deferasirox concentration were collected to analyze PK parameters.

End point type	Secondary
----------------	-----------

End point timeframe:

Days 1 and 10 at 0 hour (pre-dose) and 0.5, 1, 1.5, 2, 3, 46, 8, 12, 24,36, 48 and 72 hours post-dose.

End point values	Part 2 - Treatment E	Part 2 - Treatment D		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	95	96		
Units: hour				
arithmetic mean (standard deviation)	18.3 (± 3.37)	20.3 (± 4.27)		

Statistical analyses

No statistical analyses for this end point

Secondary: Part - 2 Summary of PK parameter: terminal slope of elimination phase (Lambda_z)

End point title	Part - 2 Summary of PK parameter: terminal slope of elimination phase (Lambda_z)
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End point description:

Serial blood samples for plasma deferasirox concentration were collected to analyze PK parameters.

End point type	Secondary
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End point timeframe:

Days 1 and 10 at 0 hour (pre-dose) and 0.5, 1, 1.5, 2, 3, 46, 8, 12, 24,36, 48 and 72 hours post-dose.

End point values	Part 2 - Treatment E	Part 2 - Treatment D		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	95	89		
Units: 1/hour				
arithmetic mean (standard deviation)	0.0452 (± 0.0152)	0.0433 (± 0.0162)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All adverse events reported in this record are from date of First Patient First Treatment until Last Patient Last Visit.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	Arm A/B/C
Reporting group description:	A/B/C
Reporting group title	Arm A/C/B
Reporting group description:	A/C/B
Reporting group title	Arm B/A/C
Reporting group description:	B/A/C
Reporting group title	Arm B/C/A
Reporting group description:	B/C/A
Reporting group title	Arm C/A/B
Reporting group description:	C/A/B
Reporting group title	Arm C/B/A
Reporting group description:	C/B/A
Reporting group title	Arm D/E
Reporting group description:	D/E
Reporting group title	Arm E/D
Reporting group description:	E/D

Serious adverse events	Arm A/B/C	Arm A/C/B	Arm B/A/C
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 17 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Serious adverse events	Arm B/C/A	Arm C/A/B	Arm C/B/A
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Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Serious adverse events	Arm D/E	Arm E/D	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 48 (0.00%)	0 / 48 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Arm A/B/C	Arm A/C/B	Arm B/A/C
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 17 (23.53%)	1 / 16 (6.25%)	5 / 16 (31.25%)
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 17 (0.00%)	0 / 16 (0.00%)	2 / 16 (12.50%)
occurrences (all)	0	0	2
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 17 (0.00%)	0 / 16 (0.00%)	2 / 16 (12.50%)
occurrences (all)	0	0	2
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 17 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 17 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Eosinophil count increased			
subjects affected / exposed	0 / 17 (0.00%)	0 / 16 (0.00%)	2 / 16 (12.50%)
occurrences (all)	0	0	2
Gamma-glutamyltransferase increased			

subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0	0 / 16 (0.00%) 0	1 / 16 (6.25%) 1
Protein urine present subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0	0 / 16 (0.00%) 0	1 / 16 (6.25%) 1
Urine bilirubin increased subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0	0 / 16 (0.00%) 0	1 / 16 (6.25%) 1
Nervous system disorders Dizziness subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0	0 / 16 (0.00%) 0	0 / 16 (0.00%) 0
Headache subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0	0 / 16 (0.00%) 0	0 / 16 (0.00%) 0
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0	1 / 16 (6.25%) 2	0 / 16 (0.00%) 0
Diarrhoea subjects affected / exposed occurrences (all)	3 / 17 (17.65%) 4	0 / 16 (0.00%) 0	3 / 16 (18.75%) 6
Enterocolitis subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0	0 / 16 (0.00%) 0	1 / 16 (6.25%) 1
Nausea subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 2	0 / 16 (0.00%) 0	0 / 16 (0.00%) 0
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0	0 / 16 (0.00%) 0	0 / 16 (0.00%) 0

Non-serious adverse events	Arm B/C/A	Arm C/A/B	Arm C/B/A
Total subjects affected by non-serious adverse events subjects affected / exposed	4 / 16 (25.00%)	4 / 16 (25.00%)	3 / 16 (18.75%)

Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 16 (6.25%)	1 / 16 (6.25%)	1 / 16 (6.25%)
occurrences (all)	1	1	1
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 16 (6.25%)	1 / 16 (6.25%)	1 / 16 (6.25%)
occurrences (all)	1	1	1
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Eosinophil count increased			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	1	0	1
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Protein urine present			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Urine bilirubin increased			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Headache			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Abdominal pain			

subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Diarrhoea			
subjects affected / exposed	1 / 16 (6.25%)	3 / 16 (18.75%)	2 / 16 (12.50%)
occurrences (all)	2	4	3
Enterocolitis			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Nausea			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0

Non-serious adverse events	Arm D/E	Arm E/D	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 48 (14.58%)	4 / 48 (8.33%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 48 (0.00%)	0 / 48 (0.00%)	
occurrences (all)	0	0	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 48 (0.00%)	0 / 48 (0.00%)	
occurrences (all)	0	0	
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 48 (0.00%)	0 / 48 (0.00%)	
occurrences (all)	0	0	
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 48 (0.00%)	0 / 48 (0.00%)	
occurrences (all)	0	0	
Eosinophil count increased			
subjects affected / exposed	0 / 48 (0.00%)	0 / 48 (0.00%)	
occurrences (all)	0	0	
Gamma-glutamyltransferase			

increased subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	0 / 48 (0.00%) 0	
Protein urine present subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	0 / 48 (0.00%) 0	
Urine bilirubin increased subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	0 / 48 (0.00%) 0	
Nervous system disorders Dizziness subjects affected / exposed occurrences (all)	1 / 48 (2.08%) 1	0 / 48 (0.00%) 0	
Headache subjects affected / exposed occurrences (all)	2 / 48 (4.17%) 2	1 / 48 (2.08%) 1	
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	1 / 48 (2.08%) 1	
Diarrhoea subjects affected / exposed occurrences (all)	5 / 48 (10.42%) 8	1 / 48 (2.08%) 1	
Enterocolitis subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	0 / 48 (0.00%) 0	
Nausea subjects affected / exposed occurrences (all)	1 / 48 (2.08%) 1	0 / 48 (0.00%) 0	
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0	1 / 48 (2.08%) 2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 May 2014	Amendment 1, issued before the start of the study, was written because some of the measurement methods need to be adjusted to the actual operation in the Investigator site in Japan. In addition, the editorial changes and corrections in the protocol text and the table were made for consistency and/or clarifications. The most important changes to the protocol were: Added the description regarding water intake during drug administration under the fasted condition; changed 3 mL to 4 mL of PK blood samples; added detailed tube description because an available tube without plasma separation gel is only for 4mL blood collection in Japan; and added description of samples collection window at 12 hours post-dose.
11 December 2014) issued after the release of part 1 clinical study report (27-Nov-2014), because although Part 1 study demonstrated comparable bioavailability (AUC) between the reference DT at a dose of 1500 mg and the granule formulation at doses of 1080 mg and 990 mg, Cmax did not satisfy the predefined criteria i.e., Cmax of 990 mg or 1080 mg DFX granule was 24% and 34% higher compared to the 1500 mg DT treatment. Amendment 2 proposed a further reduced dose of granule formulation at 900 mg to be investigated as Part 2 of this study. The selection of 900 mg was based on simulation using data obtained in Part 1 of the current study. The most important changes to the protocol were: added the description of protocol amendment rationale; added the objective and related end-points of Part 2 study; added the description of study design of Part 2 study; added the description of study design of Part 2 study; added the description of study treatment of Part 2 study; added the description of dietary, fluid, and other restrictions of Part 2 study; added the description of treatment assignment or randomization of Part 2 study; added the description of study drug packaging and labeling of Part 2 study; added the visit schedule, assessment, and PK log table of Part 2 study; added the description of analysis sets of Part 2 study; added the description of statistical hypothesis, model, and method of analysis of Part 2 study; added the secondary objectives of Part 2 study; and added the description of sample size calculation of Part 2 study.

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.

Due to EudraCT system limitations, which EMA is aware of, results of crossover studies are not accurately represented in this record. Please go to <https://www.novctrd.com/CtrdWeb/home.nov> for complete trial results.

Notes: