EU Clinical Trials Register

Clinical trial results:
A randomized, open label, single center, phase I, two way, cross-over study to evaluate the pharmacokinetic comparability of deferasirox new granule formulation with the reference dispersible formulation in healthy subjects.

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	2016-000307-93
Trial protocol	Outside EU/EEA
Global end of trial date	02 December 2013
Results information	
Result version number	v1 (current)
This version publication date	02 September 2018
First version publication date	02 September 2018

Trial information

Trial identification

Sponsor protocol code	CICL670F2105

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 613241111,
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, +41 613241111,

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-001103-PIP01-10
Does article 45 of REGULATION (EC) No	No

1901/2006 apply to this trial?	
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	02 December 2013
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	02 December 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Evaluate the PK comparability of a reduced dose of the deferasirox granule formulation given with a small amount of a soft food matrix (apple sauce) versus the reference dispersible tablet formulation of deferasirox under fasted conditions in healthy subjects.

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	29 July 2013
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	United States: 53
Worldwide total number of subjects	53
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)	53
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Informed consent was obtained from each subject in writing before screening. The study was described by the Investigator or designee, who answered any questions, and written information was also provided.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	No sequence

Arm description:

Those subjects that were non-compliant with the iron supplement pre-treatment, or did not meet all inclusion and exclusion criteria at the Baseline Visit or when target recruitment had been completed, were discontinued prior to randomization and were assigned to the 'no sequence' group.

Arm type	Supportive treatment
Investigational medicinal product name	ferrous sulfate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

The supportive treatment was an iron supplement, ferrous sulfate 325 mg strength oral tablet, which was equivalent to 65 mg Fe^{++} (elemental iron).

Arm title	A/B sequence

Arm description:

Treatment A: Single dose of 1200 mg of deferasirox granule formulation (3 stick packs of 400 mg) with apple sauce under fasted conditions.
Treatment B: Single dose of 1500 mg reference DT formulation of deferasirox dispersed in 200 ml water under fasted conditions.

Arm type	Experimental
Investigational medicinal product name	deferasirox granule formulation
Investigational medicinal product code	
Other name	Treatment A
Pharmaceutical forms	Granules
Routes of administration	Oral use

Dosage and administration details:

Single dose of 1200 mg of deferasirox granule formulation (3 stick packs of 400 mg) with apple sauce under fasted conditions.

Investigational medicinal product name	reference DT formulation
Investigational medicinal product code	
Other name	deferasirox
Pharmaceutical forms	Dispersible tablet
Routes of administration	Oral use

Dosage and administration details:

Single dose of 1500 mg reference DT formulation (3 tablets of 500 mg) of deferasirox under fasted conditions dispersed in 200 ml water.

Arm title	B/A sequence

Arm description:

Treatment B: Single dose of 1500 mg reference DT formulation (3 tablets of 500 mg) of deferasirox under fasted conditions dispersed in 200 ml water.
Treatment A: Single dose of 1200 mg of deferasirox granule formulation (3 stick packs of 400 mg) with apple sauce under fasted conditions.

Arm type	Experimental
Investigational medicinal product name	deferasirox granule formulation
Investigational medicinal product code	
Other name	Treatment A
Pharmaceutical forms	Granules
Routes of administration	Oral use

Dosage and administration details:

Single dose of 1200 mg of deferasirox granule formulation (3 stick packs of 400 mg) with apple sauce under fasted conditions.

Investigational medicinal product name	reference DT formulation
Investigational medicinal product code	
Other name	Treatment B
Pharmaceutical forms	Dispersible tablet
Routes of administration	Oral use

Dosage and administration details:

Single dose of 1500 mg reference DT formulation (3 tablets of 500 mg) of deferasirox under fasted conditions dispersed in 200 ml water.

Number of subjects in period 1	No sequence	A/B sequence	B/A sequence
Started	12	21	20
Completed treatment	0	18	20
Completed	0	18	20
Not completed	12	3	0
Consent withdrawn by subject	4	1	-
Administrative problems	8	-	-
Protocol deviation	-	2	-

Baseline characteristics

Reporting groups

Reporting group title	No sequence

Reporting group description:

Those subjects that were non-compliant with the iron supplement pre-treatment, or did not meet all inclusion and exclusion criteria at the Baseline Visit or when target recruitment had been completed, were discontinued prior to randomization and were assigned to the 'no sequence' group.

Reporting group title	A/B sequence

Reporting group description:

Treatment A: Single dose of 1200 mg of deferasirox granule formulation (3 stick packs of 400 mg) with apple sauce under fasted conditions.
Treatment B: Single dose of 1500 mg reference DT formulation of deferasirox dispersed in 200 ml water under fasted conditions.

Reporting group title	B/A sequence

Reporting group description:

Treatment B: Single dose of 1500 mg reference DT formulation (3 tablets of 500 mg) of deferasirox under fasted conditions dispersed in 200 ml water.
Treatment A: Single dose of 1200 mg of deferasirox granule formulation (3 stick packs of 400 mg) with apple sauce under fasted conditions.

Reporting group values	No sequence	A/B sequence	B/A sequence
Number of subjects	12	21	20
Age categorical			
Units: Subjects			
Adults (18-64 years)	12	21	20
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	28	31.2	31.5
standard deviation	± 5.61	± 8.98	± 10.29
Gender categorical			
Units: Subjects			
Female	6	12	7
Male	6	9	13

Reporting group values	Total		
Number of subjects	53		
Age categorical			
Units: Subjects			
Adults (18-64 years)	53		
From 65-84 years	0		
85 years and over	0		
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	25		

Male	28		

End points

End points reporting groups

Reporting group title	No sequence

Reporting group description:

Those subjects that were non-compliant with the iron supplement pre-treatment, or did not meet all inclusion and exclusion criteria at the Baseline Visit or when target recruitment had been completed, were discontinued prior to randomization and were assigned to the 'no sequence' group.

Reporting group title	A/B sequence

Reporting group description:

Treatment A: Single dose of 1200 mg of deferasirox granule formulation (3 stick packs of 400 mg) with apple sauce under fasted conditions.
Treatment B: Single dose of 1500 mg reference DT formulation of deferasirox dispersed in 200 ml water under fasted conditions.

Reporting group title	B/A sequence

Reporting group description:

Treatment B: Single dose of 1500 mg reference DT formulation (3 tablets of 500 mg) of deferasirox under fasted conditions dispersed in 200 ml water.
Treatment A: Single dose of 1200 mg of deferasirox granule formulation (3 stick packs of 400 mg) with apple sauce under fasted conditions.

Subject analysis set title	Pharmacokinetic analysis set (PAS)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Consisted of all safety subjects who had completed the two Treatment Periods with evaluable deferasirox PK data allowing a comparison between the test formulation and the reference formulation.

Subject analysis set title	Deferasirox granule formulation
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Treatment A: Single dose of 1200 mg of deferasirox granule formulation (3 stick packs of 400 mg) with apple sauce under fasted conditions

Subject analysis set title	Deferasirox DTs
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Treatment B: Single dose of 1500 mg reference DT formulation of deferasirox under fasted conditions dispersed in 200 ml water.

Subject analysis set title	Safety Set
Subject analysis set type	Safety analysis

Subject analysis set description:

All randomized subjects who received at least one dose of study drug (defined as either deferasirox or iron supplement). If an enrolled subject was randomized but received iron supplement only, he/she was included in the Safety Set.

Primary: Analysis of AUCinf for plasma deferasirox by treatment

End point title	Analysis of AUCinf for plasma deferasirox by treatment[1]

End point description:

The area under the curve (AUC) from time zero to infinity.

End point type	Primary

End point timeframe:

Days 1 through 4 and 10 to 13 of Treatment Periods 1 and 2 at the following time points: 0 (pre-dose) and at 0.5 h, 1 h, 1.5 h, 2 h, 3 h, 4 h, 6 h, 8 h, 12 h, 24 h, 36 h, 48 h, and 72 hours

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: Analysis was done within a single arm. A comparison groups was not use for statistical analysis.

End point values	Deferasirox granule formulation	Deferasirox DTs		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	38[2]	36[3]		
Units: µmol/L*hr				
arithmetic mean (standard deviation)	1720 (± 476)	1440 (± 481)		

Notes:

[2] - Pharmacokinetic Analysis Set (PAS): safety subjects with evaluable deferasirox PK data

[3] - number of subjects with non-missing values

Statistical analyses

No statistical analyses for this end point

Primary: Analysis of AUClast for plasma deferasirox by treatment

End point title	Analysis of AUClast for plasma deferasirox by treatment[4]
End point description:	
The AUC from time zero to the last measurable concentration sampling time (Tlast)	
End point type	Primary
End point timeframe:	
Days 1 through 4 and 10 to 13 of Treatment Periods 1 and 2 at the following time points: 0 (pre-dose) and at 0.5 h, 1 h, 1.5 h, 2 h, 3 h, 4 h, 6 h, 8 h, 12 h, 24 h, 36 h, 48 h, and 72 hours	

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: Analysis was done within a single arm. A comparison groups was not use for statistical analysis.

End point values	Deferasirox granule formulation	Deferasirox DTs		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	38	38		
Units: µmol/L*hr				
arithmetic mean (standard deviation)	1680 (± 456)	1380 (± 420)		

Statistical analyses

No statistical analyses for this end point

Primary: Analysis of Cmax for plasma deferasirox by treatment

End point title	Analysis of Cmax for plasma deferasirox by treatment[5]
End point description:	
The maximum (peak) observed plasma concentration after single dose administration	
End point type	Primary
End point timeframe:	
Days 1 through 4 and 10 to 13 of Treatment Periods 1 and 2 at the following time points: 0 (pre-dose) and at 0.5 h, 1 h, 1.5 h, 2 h, 3 h, 4 h, 6 h, 8 h, 12 h, 24 h, 36 h, 48 h, and 72 hours	

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: Analysis was done within a single arm. A comparison groups was not use for statistical analysis.

End point values	Deferasirox granule formulation	Deferasirox DTs		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	38	38		
Units: µmol/L				
arithmetic mean (standard deviation)	124 (± 33.1)	86.8 (± 19.6)		

Statistical analyses

No statistical analyses for this end point

Primary: Analysis of Tmax for plasma deferasirox by treatment

End point title	Analysis of Tmax for plasma deferasirox by treatment[6]

End point description:

The time to reach maximum (peak) plasma concentration after single dose administration

End point type	Primary

End point timeframe:

Days 1 through 4 and 10 to 13 of Treatment Periods 1 and 2 at the following time points: 0 (pre-dose) and at 0.5 h, 1 h, 1.5 h, 2 h, 3 h, 4 h, 6 h, 8 h, 12 h, 24 h, 36 h, 48 h, and 72 hours

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: Analysis was done within a single arm. A comparison groups was not use for statistical analysis.

End point values	Deferasirox granule formulation	Deferasirox DTs		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	38	38		
Units: hr				
median (full range (min-max))	3 (1.5 to 6)	3 (1.5 to 4)		

Statistical analyses

No statistical analyses for this end point

Primary: Analysis of T1/2 for plasma deferasirox by treatment

End point title	Analysis of T1/2 for plasma deferasirox by treatment[7]

End point description:

The elimination half-life associated with the terminal slope (lambda_z) of a semi-logarithmic concentration-time curve.

End point type	Primary

End point timeframe:

Days 1 through 4 and 10 to 13 of Treatment Periods 1 and 2 at the following time points: 0 (pre-dose) and at 0.5 h, 1 h, 1.5 h, 2 h, 3 h, 4 h, 6 h, 8 h, 12 h, 24 h, 36 h, 48 h, and 72 hours

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: Analysis was done within a single arm. A comparison groups was not use for statistical analysis.

End point values	Deferasirox granule formulation	Deferasirox DTs		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	38	36[8]		
Units: hr				
arithmetic mean (standard deviation)	12.5 (± 4.08)	14.5 (± 5.83)		

Notes:

[8] - number of subjects with non-missing values

Statistical analyses

No statistical analyses for this end point

Primary: Analysis of Lambda_z for plasma deferasirox by treatment

End point title	Analysis of Lambda_z for plasma deferasirox by treatment[9]

End point description:

The terminal slope of elimination phase.

End point type	Primary

End point timeframe:

Days 1 through 4 and 10 to 13 of Treatment Periods 1 and 2 at the following time points: 0 (pre-dose) and at 0.5 h, 1 h, 1.5 h, 2 h, 3 h, 4 h, 6 h, 8 h, 12 h, 24 h, 36 h, 48 h, and 72 hours

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: Analysis was done within a single arm. A comparison groups was not use for statistical analysis.

End point values	Deferasirox granule formulation	Deferasirox DTs		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	38	36[10]		
Units: 1/hr				
arithmetic mean (standard deviation)	0.0604 (± 0.0171)	0.0557 (± 0.0218)		

Notes:

[10] - number of subjects with non-missing values

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants that experienced an adverse event (AE)

End point title	Percentage of participants that experienced an adverse event (AE)

End point description:

End point type	Secondary

End point timeframe:

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.

End point values	Safety Set			
Subject group type	Subject analysis set			
Number of subjects analysed	41			
Units: percent				
number (not applicable)	14.6			

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

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups

Reporting group title	All subjects
Reporting group description:	
All subjects	

Serious adverse events	All subjects		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 41 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	All subjects		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 41 (14.63%)		
Vascular disorders			
Flushing			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Nervous system disorders			
Presyncope			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		

Anal haemorrhage			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Diarrhoea			
subjects affected / exposed	2 / 41 (4.88%)		
occurrences (all)	2		
Reproductive system and breast disorders			
Menstruation irregular			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Muscle tightness			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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: