Clinical trial results:
A randomized, open-label, multicenter, two arm, phase II study to investigate the benefits of an improved deferasirox formulation (film-coated tablet)

Summary

EudraCT number	2013-004167-32
Trial protocol	AT ES IT GB FR GR
Global end of trial date	24 February 2016

Results information

Result version number	v2 (current)
This version publication date	07 August 2017
First version publication date	09 September 2016
Version creation reason	• Correction of full data set The time frame for the primary end point was updated to 28 weeks.

Trial information

Trial identification

Sponsor protocol code	CICL670F2201

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02125877
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)	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?	Yes

Notes:

Results analysis stage

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

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

Notes:

General information about the trial

Main objective of the trial:

To evaluate the overall safety of deferasirox FCT and deferasirox DT formulations in patients with transfusion-dependent thalassemia or myelodysplastic syndrome at very low, low or intermediate (int) risk.

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	08 July 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	Argentina: 2
Country: Number of subjects enrolled	Austria: 6
Country: Number of subjects enrolled	France: 2
Country: Number of subjects enrolled	Germany: 14
Country: Number of subjects enrolled	Greece: 17
Country: Number of subjects enrolled	United Kingdom: 10
Country: Number of subjects enrolled	Italy: 52
Country: Number of subjects enrolled	Lebanon: 20
Country: Number of subjects enrolled	Malaysia: 10
Country: Number of subjects enrolled	Mexico: 3
Country: Number of subjects enrolled	Russian Federation: 1
Country: Number of subjects enrolled	Saudi Arabia: 9
Country: Number of subjects enrolled	Spain: 1
Country: Number of subjects enrolled	Thailand: 6
Country: Number of subjects enrolled	United States: 7
Country: Number of subjects enrolled	United Arab Emirates: 13
Worldwide total number of subjects	173
EEA total number of subjects	102

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)	2
Adolescents (12-17 years)	19
Adults (18-64 years)	126
From 65 to 84 years	26
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Participants were randomized in a 1:1 ratio.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Deferasirox dispersible tablet (DFX-DT)

Arm description:

Iron chelation naïve participants received DFX-DT 20 mg/kg/day once daily orally from weeks 1 - 4. After week 4, the dose could be adjusted by +/- 5 to 10 mg/kg/day, with a maximum dose of 40 mg/kg/day. Iron chelation pre-treated participants were supposed to start on a dose that was equivalent to their pre-washout dose.

Arm type	Active comparator
Investigational medicinal product name	Deferasirox (DFX-DT)
Investigational medicinal product code	ICL670
Other name	
Pharmaceutical forms	Dispersible tablet
Routes of administration	Oral use

Dosage and administration details:

Iron chelation naïve participants received DFX-DT 20 mg/kg/day once daily orally from weeks 1 - 4. After week 4, the dose could be adjusted by +/- 5 to 10 mg/kg/day, with a maximum dose of 40 mg/kg/day. Iron chelation pre-treated
participants were supposed to start on a dose that was equivalent to their pre-washout dose.

Arm title	Deferasirox film-coated tablet (DFX-FCT)

Arm description:

Participants received DFX-FCT 14 mg/kg/day once daily orally from weeks 1 - 4. After week 4, the dose could be adjusted by +/- 3.5 to 7 mg/kg/day, with a maximum dose of 28 mg/kg/day. Iron chelation pre-treated participants were supposed to start on a dose that was equivalent to their pre-washout dose

Arm type	Experimental
Investigational medicinal product name	Deferasirox (DFX-FCT)
Investigational medicinal product code	ICL670
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received DFX-FCT 14 mg/kg/day once daily orally from weeks 1 - 4. After week 4, the dose could be adjusted by +/- 3.5 to 7 mg/kg/day, with a maximum dose of 28 mg/kg/day. Iron chelation pre-treated
participants were supposed to start on a dose that was equivalent to their pre-washout dose

Number of subjects in period 1	Deferasirox dispersible tablet (DFX-DT)	Deferasirox film-coated tablet (DFX-FCT)
Started	86	87
Pharmacokinetic analysis set	83	83
Pharmacokinetic subset A	16 [1]	15 [2]
Safety set	86	87
Completed	73	77
Not completed	13	10
Adverse event, serious fatal	-	1
Consent withdrawn by subject	2	1
Physician decision	1	-
Adverse event, non-fatal	6	4
Protocol deviation	4	1
Administrative problems	-	1
Participant/guardian decision	-	2

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: The number is correct.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: The number is correct.

Baseline characteristics

Reporting groups	
Reporting group title	Deferasirox dispersible tablet (DFX-DT)
Reporting group description:	
Iron chelation naïve participants received DFX-DT 20 mg/kg/day once daily orally from weeks 1 - 4. After week 4, the dose could be adjusted by +/- 5 to 10 mg/kg/day, with a maximum dose of 40 mg/kg/day. Iron chelation pre-treated participants were supposed to start on a dose that was equivalent to their pre-washout dose.	
Reporting group title	Deferasirox film-coated tablet (DFX-FCT)
Reporting group description:	
Participants received DFX-FCT 14 mg/kg/day once daily orally from weeks 1 - 4. After week 4, the dose could be adjusted by +/- 3.5 to 7 mg/kg/day, with a maximum dose of 28 mg/kg/day. Iron chelation pre-treated participants were supposed to start on a dose that was equivalent to their pre-washout dose	

Reporting group values	Deferasirox dispersible tablet (DFX-DT)	Deferasirox film-coated tablet (DFX-FCT)	Total
Number of subjects	86	87	173
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)	2	0	2
Adolescents (12-17 years)	8	11	19
Adults (18-64 years)	64	62	126
From 65-84 years	12	14	26
85 years and over	0	0	0
Age Continuous Units: Years			
arithmetic mean	35.1	34.6	
standard deviation	± 18.6	± 19.97	-
Gender, Male/Female Units: Subjects			
Female	47	41	88
Male	39	46	85

End points

End points reporting groups

Reporting group title	Deferasirox dispersible tablet (DFX-DT)

Reporting group description:

Iron chelation naïve participants received DFX-DT 20 mg/kg/day once daily orally from weeks 1 - 4. After week 4, the dose could be adjusted by +/- 5 to 10 mg/kg/day, with a maximum dose of 40 mg/kg/day. Iron chelation pre-treated participants were supposed to start on a dose that was equivalent to their pre-washout dose.

Reporting group title	Deferasirox film-coated tablet (DFX-FCT)

Reporting group description:

Participants received DFX-FCT 14 mg/kg/day once daily orally from weeks 1 - 4. After week 4, the dose could be adjusted by +/- 3.5 to 7 mg/kg/day, with a maximum dose of 28 mg/kg/day. Iron chelation pre-treated participants were supposed to start on a dose that was equivalent to their pre-washout dose

Primary: Overall safety as measured by adverse events

End point title	Overall safety as measured by adverse events[1]

End point description:

The percentage of participants with adverse events, serious adverse events and deaths was assessed.

End point type	Primary

End point timeframe:

28 weeks

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 does not apply to this end point.

End point values	Deferasirox dispersible tablet (DFX-DT)	Deferasirox film-coated tablet (DFX-FCT)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	86	87		
Units: Percentage of participants				
number (not applicable)				
Adverse events	89.5	89.7		
SAEs	15.1	18.4		
Deaths	0	1.1		

Statistical analyses

No statistical analyses for this end point

Primary: Overall safety as measured by changes in laboratory values from baseline

End point title	Overall safety as measured by changes in laboratory values from baseline[2]

End point description:

The percentage of participants with post-baseline laboratory values meeting specified criteria for notable/extended range was assessed. The following laboratory parameters were measured: platelet

count, absolute neutrophils, serum creatinine , creatinine clearance, urinary protein/urinary creatinine ratio, alanine aminotransferase (ALT) and aspartate aminotransferase (AST). Note that within data categories, creat = creatinine, cons = consecutive, ULN = upper limit of normal and urin = urinary.

End point type	Primary

End point timeframe:

30 weeks

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 does not apply to this end point.

End point values	Deferasirox dispersible tablet (DFX-DT)	Deferasirox film-coated tablet (DFX-FCT)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	86	87		
Units: Percentage of participants				
number (not applicable)				
platelet count, notable range: <100 x 10^9/L	9.3	8		
platelet count, extended range: <50 x 10^9/L	3.5	5.7		
absolute neutrophils, notable range: <1.5 x 10^9/L	8.1	13.8		
absolute neutrophils, extended range: <0.5 x10^9/L	4.7	0		
serum creat, 2 cons >33% inc from BL and >ULN	4.7	3.4		
creat clearance, notable range: 2 cons <60 mL/min	7	2.3		
creat clearance, extended range: 2 cons <40 mL/min	2.3	2.3		
urin protein/urin creat ratio, 2 cons >1.0 mg/mg	2.3	0		
ALT, notable range: >5 x ULN and >2 x BL	1.2	1.1		
ALT, extended range: >10 x ULN and >2 x BL	1.2	0		
AST, notable range: >5 x ULN and >2 x BL	0	1.1		
AST, extended range: >10 x ULN and >2 x BL	1.2	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Frequency of selected gastro-intestinal (GI) adverse events

End point title	Frequency of selected gastro-intestinal (GI) adverse events

End point description:

The percentage of participants with any GI adverse event, diarrhea, constipation, nausea, vomiting, abdominal pain was assessed.

End point type	Secondary

End point timeframe:

28 weeks

End point values	Deferasirox dispersible tablet (DFX-DT)	Deferasirox film-coated tablet (DFX-FCT)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	86	87		
Units: Percentage of participants				
number (not applicable)				
Any GI adverse event	61.6	58.6		
Abdominal pain	26.7	26.4		
Constipation	15.1	8		
Diarrhea	34.9	33.3		
Nausea	26.7	27.6		
Vomiting	22.1	17.2		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean domain scores of the modified Satisfaction with Iron Chelation Therapy (modified SICT)

End point title	Mean domain scores of the modified Satisfaction with Iron Chelation Therapy (modified SICT)

End point description:

The modified SICT consisted of 13 items that represent 3 domains: adherence, satisfaction and concerns. The adherence domain consisted of 7 items, 6 which were measured using a 5-point response scale and was calculated by summing the 6 items. The score range from 6 to 30 and higher scores indicated worse adherence. The satisfaction domain consisted of 3 items, 2 which were measured using a 5-point response scale and was calculated by summing the 2 items. The score range from 2 to 10 and higher scores indicated worse satisfaction. The concerns domain consisted of 3 items to address any concerns or worries with his/her medication. All 3 items were measured on a 5-point response scale and were calculated by summing the 3 items. The score range from 3 to 15 and higher scores indicated fewer concerns. For all three domains, the meaningful difference between two treatment arms was determined to be 1 point.

End point type	Secondary

End point timeframe:

weeks 2, 3, 13 and 24 (end of treatment or within 7 days of last dose)

End point values	Deferasirox dispersible tablet (DFX-DT)	Deferasirox film-coated tablet (DFX-FCT)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	86	87		
Units: score on a scale				

arithmetic mean (standard deviation)				
week 2, adherence (n=70,70)	10.3 (± 3.8)	7.6 (± 2.14)		
week 2, satisfaction/preference (n=70,70)	5.2 (± 2.24)	2.8 (± 1.37)		
week 2, concerns (n=70,70)	12.9 (± 2.94)	13.8 (± 2.02)		
week 3, adherence (n=58,51)	10.9 (± 4.09)	7.7 (± 2.06)		
week 3, satisfaction/preference (n=58,51)	5.4 (± 2.22)	2.6 (± 1.05)		
week 3, concerns (n=58,51)	12.4 (± 2.73)	14 (± 1.49)		
week 13, adherence (n=59,64)	11.2 (± 3.56)	7.8 (± 2.05)		
week 13, satisfaction/preference (n=59,64)	5.4 (± 2.14)	2.9 (± 1.54)		
week 13, concerns (n=59,64)	12.7 (± 2.5)	13.6 (± 1.87)		
week 24, adherence (n=63,60)	12.5 (± 5.32)	7.5 (± 2.41)		
week 24, satisfaction/preference (n=63,60)	5.8 (± 2.28)	2.9 (± 1.58)		
week 24, concerns (n=63,60)	11.8 (± 3.07)	13.7 (± 1.84)		

Statistical analyses

No statistical analyses for this end point

Secondary: Palatability questionnaire score

End point title	Palatability questionnaire score

End point description:

The palatability questionnaire consisted of 4 items. The first item measured the taste and aftertaste of the medication and were scored a on a 5-point response scale. The second item offered an additional response option of "no aftertaste". The last 2 items referred to whether the medication was taken, i.e. swallowed or vomited, and how the participant perceived the amount of medication to be taken. The palatability summary score was calculated using a scoring matrix from items 1, 3 and 4 scores and the score ranges from 0 - 11. Higher scores indicated the best palatability. A meaningful difference between two treatment arms was determined to be 1 point.

End point type	Secondary

End point timeframe:

weeks 2, 3, 13 and 24 (end of treatment or within 7 days of last dose)

End point values	Deferasirox dispersible tablet (DFX-DT)	Deferasirox film-coated tablet (DFX-FCT)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	86	87		
Units: score on a scale				
arithmetic mean (standard deviation)				
week 2 (n=69,70)	9 (± 3.01)	10.8 (± 0.5)		
week 3 (n=57,51)	8.8 (± 3.01)	10.8 (± 0.45)		
week 13 (n=59,62)	9.3 (± 2.84)	10.8 (± 1.16)		
week 24 (n=63,60)	8.8 (± 3.1)	10.9 (± 0.34)		

Statistical analyses

No statistical analyses for this end point

Secondary: Weekly average of daily scores of the gastrointestinal (GI) symptom diary

End point title	Weekly average of daily scores of the gastrointestinal (GI) symptom diary

End point description:

The GI symptom diary consisted of 6 items, five which were scored using a 0 - 10 rating scale with item appropriate anchors to rate the symptom, for example, Pain in your belly: 0 = no pain and 10 = worst pain. The GI diary summary score was created using the 10 point response scale for the 5 items. The GI symptom daily diary had a minimum score of 0 and a maximum score of 50. The weekly average score for the 7 days was calculated for each individual item and the GI summary score was created from these weekly averages. Higher scores indicated worse symptoms. A meaningful difference between two treatment arms was determined to be 0.3 point.

End point type	Secondary

End point timeframe:

weeks -1, 4, 8, 12, 16, 20, 24

End point values	Deferasirox dispersible tablet (DFX-DT)	Deferasirox film-coated tablet (DFX-FCT)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	86	87		
Units: score on a scale				
arithmetic mean (standard deviation)				
week -1 (n=69,65)	1.4 (± 2.1)	1.9 (± 3.69)		
week 4 (n=60,64)	1.8 (± 3.49)	1.1 (± 2.15)		
week 8 (n=59,51)	1.4 (± 2.45)	1.1 (± 2.16)		
week 12 (n=51,45)	1.7 (± 3.16)	1 (± 1.78)		
week 16 (n=48,41)	1.9 (± 3.75)	0.9 (± 1.92)		
week 20 (n40,39)	1.5 (± 3.27)	0.9 (± 1.44)		
week 24 (n32,26)	1.5 (± 3.29)	1.2 (± 1.89)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with weekly average compliance of medication consumption

End point title	Number of participants with weekly average compliance of

	medication consumption

End point description:

A compliance questionnaire assessed whether the medication was taken. Weekly average compliance was calculated when there were at least four non-missing daily responses.

End point type	Secondary

End point timeframe:

Weeks 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24

End point values	Deferasirox dispersible tablet (DFX-DT)	Deferasirox film-coated tablet (DFX-FCT)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	86	87		
Units: Participants				
week 1	56	53		
week 2	64	64		
week 3	62	56		
week 4	58	58		
week 5	56	58		
week 6	62	51		
week 7	55	48		
week 8	56	46		
week 9	53	45		
week 10	52	46		
week 11	50	42		
week 12	50	41		
week 13	49	47		
week 14	51	42		
week 15	48	42		
week 16	48	40		
week 17	43	39		
week 18	43	38		
week 19	40	37		
week 20	40	36		
week 21	39	36		
week 22	38	34		
week 23	36	33		
week 24	30	24		

Statistical analyses

No statistical analyses for this end point

Secondary: Weekly dose violation rate

End point title	Weekly dose violation rate

End point description:

The dose violation is defined as a dose either missed completely or not taken in accordance with the timing instruction (no later than 12:00 pm. The rate was calculated as [number of dose violations/drug exposure (days)] x 100.

End point type	Secondary

End point timeframe:

weeks 1, 4, 8, 12, 16, 20, 24

End point values	Deferasirox dispersible tablet (DFX-DT)	Deferasirox film-coated tablet (DFX-FCT)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	86	87		
Units: (number of dose violations/days)*100				
arithmetic mean (standard deviation)				
week 1 (n=56,53)	17.7 (± 31.04)	15.8 (± 29.42)		
week 4 (n=58,58)	15.8 (± 32.51)	6.7 (± 15.45)		
week 8 (n=56,46)	18 (± 35.38)	8.4 (± 22.17)		
week 12 (n=50,41)	15.7 (± 34.22)	10.7 (± 22.63)		
week 16 (n=48,40)	13.5 (± 31.08)	10 (± 24.5)		
week 20 (n=40,36)	22.6 (± 38.38)	11.3 (± 26.67)		
week 24 (n=30,24)	17.1 (± 34.26)	10.1 (± 25.47)		

Statistical analyses

No statistical analyses for this end point

Secondary: Area under the plasma concentration-time curve from time zero to the last quantifiable concentration (AUClast)

End point title	Area under the plasma concentration-time curve from time zero to the last quantifiable concentration (AUClast)

End point description:

Blood samples were collected to assess AUClast.

End point type	Secondary

End point timeframe:

week 1, day 1: pre-dose (0 hour) and 1, 2, 3, 4, 8 and 24 hours post dose; week 3, day 1: pre-dose (0 hour) and 1, 2, 3, 4, 8 and 24 hours post dose

End point values	Deferasirox dispersible tablet (DFX-DT)	Deferasirox film-coated tablet (DFX-FCT)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	15		
Units: umol/L*h				
arithmetic mean (standard deviation)				
week1 (n=14,15)	1110 (± 495)	1040 (± 405)		
week 3 (n=13,15)	1590 (± 540)	2110 (± 987)		

Statistical analyses

No statistical analyses for this end point

Secondary: Observed maximum plasma concentration following drug administration (Cmax)

End point title	Observed maximum plasma concentration following drug administration (Cmax)

End point description:

Blood samples were collected to assess Cmax.

End point type	Secondary

End point timeframe:

week 1, day 1: pre-dose (0 hour) and 1, 2, 3, 4, 8 and 24 hours post dose; week 3, day 1: pre-dose (0 hour) and 1, 2, 3, 4, 8 and 24 hours post dose

End point values	Deferasirox dispersible tablet (DFX-DT)	Deferasirox film-coated tablet (DFX-FCT)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	15		
Units: umol/L				
arithmetic mean (standard deviation)				
week 1 (n=14,15)	74.6 (± 30.7)	79.3 (± 23.5)		
week 3 (n=14,15)	118 (± 82.3)	139 (± 57.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to reach the maximum plasma concentration after drug administration (Tmax)

End point title	Time to reach the maximum plasma concentration after drug administration (Tmax)

End point description:

Blood samples were collected to assess Tmax.

End point type	Secondary

End point timeframe:

week 1, day 1: pre-dose (0 hour) and 1, 2, 3, 4, 8 and 24 hours post dose; week 3, day 1: pre-dose (0 hour) and 1, 2, 3, 4, 8 and 24 hours post dose

End point values	Deferasirox dispersible tablet (DFX-DT)	Deferasirox film-coated tablet (DFX-FCT)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	15		
Units: hour				
median (full range (min-max))				
week 1 (n=14,15)	3.57 (1.15 to 7.89)	2 (1.15 to 15.6)		
week 3 (n=14,15)	2.85 (1.4 to 8.39)	2.02 (1.07 to 5.06)		

Statistical analyses

No statistical analyses for this end point

Secondary: Dererasirox plasma concentration

End point title	Dererasirox plasma concentration

End point description:

Blood samples were collected to assess deferasirox concentration. Dose-adjusted calculations are presented: (concentration/actual dose)*20 for participants on DFX-DT and (concentration/actual dose)*14 for participants on DFX-FCT.

End point type	Secondary

End point timeframe:

Week 3, day 1, pre-dose (0 hour (h)) and 2 h post-dose; week 13, day 1, pre-dose (0 hour (h)) and 2 h post-dose; and week 21, day 1, pre-dose (0 hour (h)) and 2 h post-dose

End point values	Deferasirox dispersible tablet (DFX-DT)	Deferasirox film-coated tablet (DFX-FCT)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	83	83		
Units: umol/L				
arithmetic mean (standard deviation)				
week 3, pre-dose (n=63,70)	39.6 (± 48.4)	27.3 (± 20.4)		
week 3, 2 hours post-dose (n=67,76)	80.8 (± 52.2)	95.5 (± 53)		
week 13, pre-dose (n=69.56)	37.1 (± 37.8)	31.3 (± 22.9)		
week 13, 2 hours post-dose (n=74,59)	78.7 (± 39.5)	92.5 (± 39.1)		
week 21, pre-dose (n=54,59)	46.6 (± 46.4)	43.1 (± 36.8)		
week 21, 2 hours post-dose (n=59,64)	89.8 (± 59.3)	105 (± 51.2)		

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.

Adverse event reporting additional description:

Consistent with EudraCT disclosure specifications, Novartis has reported under the Serious adverse events field "number of deaths resulting from adverse events" all those deaths, resulting from serious adverse events that are deemed to be causally related to treatment by the investigator.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	DFX DT
Reporting group description:	
DFX DT	
Reporting group title	DFX FCT
Reporting group description:	
DFX FCT	

Serious adverse events	DFX DT	DFX FCT	
Total subjects affected by serious adverse events			
subjects affected / exposed	13 / 86 (15.12%)	16 / 87 (18.39%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma pancreas			
subjects affected / exposed	0 / 86 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukaemia			
subjects affected / exposed	0 / 86 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Face oedema			

subjects affected / exposed	1 / 86 (1.16%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema			
subjects affected / exposed	1 / 86 (1.16%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	0 / 86 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Suicide attempt			
subjects affected / exposed	1 / 86 (1.16%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Ejection fraction decreased			
subjects affected / exposed	1 / 86 (1.16%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urine protein/creatinine ratio increased			
subjects affected / exposed	0 / 86 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	0 / 86 (0.00%)	2 / 87 (2.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Delayed haemolytic transfusion reaction			

subjects affected / exposed	1 / 86 (1.16%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower limb fracture			
subjects affected / exposed	1 / 86 (1.16%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Patella fracture			
subjects affected / exposed	0 / 86 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 86 (1.16%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure acute			
subjects affected / exposed	1 / 86 (1.16%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 86 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 86 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Autoimmune haemolytic anaemia			
subjects affected / exposed	1 / 86 (1.16%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Febrile neutropenia			
subjects affected / exposed	0 / 86 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Haemolysis			
subjects affected / exposed	1 / 86 (1.16%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	1 / 86 (1.16%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal fissure			
subjects affected / exposed	1 / 86 (1.16%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	1 / 86 (1.16%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 86 (0.00%)	2 / 87 (2.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	1 / 86 (1.16%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic colitis			
subjects affected / exposed	0 / 86 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			

subjects affected / exposed	1 / 86 (1.16%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 86 (1.16%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Biliary colic			
subjects affected / exposed	0 / 86 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	1 / 86 (1.16%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis			
subjects affected / exposed	0 / 86 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 86 (1.16%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	1 / 86 (1.16%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal impairment			
subjects affected / exposed	1 / 86 (1.16%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 86 (1.16%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint effusion			
subjects affected / exposed	0 / 86 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neck pain			
subjects affected / exposed	1 / 86 (1.16%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 86 (1.16%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brucellosis			
subjects affected / exposed	0 / 86 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 86 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 86 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural pneumonia			
subjects affected / exposed	1 / 86 (1.16%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Respiratory tract infection			
subjects affected / exposed	1 / 86 (1.16%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 86 (0.00%)	2 / 87 (2.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	0 / 86 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcutaneous abscess			
subjects affected / exposed	1 / 86 (1.16%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	1 / 86 (1.16%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 86 (1.16%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	1 / 86 (1.16%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	0 / 86 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	DFX DT	DFX FCT	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	69 / 86 (80.23%)	72 / 87 (82.76%)	
Investigations			
Blood creatinine increased			
subjects affected / exposed	7 / 86 (8.14%)	8 / 87 (9.20%)	
occurrences (all)	7	11	
Urine protein/creatinine ratio increased			
subjects affected / exposed	11 / 86 (12.79%)	17 / 87 (19.54%)	
occurrences (all)	15	23	
Nervous system disorders			
Headache			
subjects affected / exposed	12 / 86 (13.95%)	5 / 87 (5.75%)	
occurrences (all)	30	5	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	8 / 86 (9.30%)	4 / 87 (4.60%)	
occurrences (all)	8	4	
Fatigue			
subjects affected / exposed	7 / 86 (8.14%)	5 / 87 (5.75%)	
occurrences (all)	7	5	
Pyrexia			
subjects affected / exposed	7 / 86 (8.14%)	7 / 87 (8.05%)	
occurrences (all)	8	9	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	23 / 86 (26.74%)	23 / 87 (26.44%)	
occurrences (all)	33	33	
Constipation			
subjects affected / exposed	13 / 86 (15.12%)	7 / 87 (8.05%)	
occurrences (all)	19	10	
Abdominal pain upper			
subjects affected / exposed	6 / 86 (6.98%)	10 / 87 (11.49%)	
occurrences (all)	7	11	

Diarrhoea			
subjects affected / exposed	30 / 86 (34.88%)	27 / 87 (31.03%)	
occurrences (all)	62	55	
Dyspepsia			
subjects affected / exposed	2 / 86 (2.33%)	6 / 87 (6.90%)	
occurrences (all)	2	7	
Nausea			
subjects affected / exposed	23 / 86 (26.74%)	24 / 87 (27.59%)	
occurrences (all)	43	43	
Vomiting			
subjects affected / exposed	18 / 86 (20.93%)	15 / 87 (17.24%)	
occurrences (all)	29	19	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	4 / 86 (4.65%)	7 / 87 (8.05%)	
occurrences (all)	4	7	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	2 / 86 (2.33%)	8 / 87 (9.20%)	
occurrences (all)	2	11	
Proteinuria			
subjects affected / exposed	4 / 86 (4.65%)	8 / 87 (9.20%)	
occurrences (all)	4	10	
Pyuria			
subjects affected / exposed	2 / 86 (2.33%)	6 / 87 (6.90%)	
occurrences (all)	2	9	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	5 / 86 (5.81%)	4 / 87 (4.60%)	
occurrences (all)	5	4	
Infections and infestations			
Bacteriuria			
subjects affected / exposed	5 / 86 (5.81%)	5 / 87 (5.75%)	
occurrences (all)	6	7	
Gastroenteritis			

subjects affected / exposed	3 / 86 (3.49%)	5 / 87 (5.75%)	
occurrences (all)	3	5	
Influenza			
subjects affected / exposed	5 / 86 (5.81%)	0 / 87 (0.00%)	
occurrences (all)	6	0	
Upper respiratory tract infection			
subjects affected / exposed	6 / 86 (6.98%)	6 / 87 (6.90%)	
occurrences (all)	6	6	
Urinary tract infection			
subjects affected / exposed	6 / 86 (6.98%)	3 / 87 (3.45%)	
occurrences (all)	8	3	
Metabolism and nutrition disorders			
Hyperphosphataemia			
subjects affected / exposed	5 / 86 (5.81%)	4 / 87 (4.60%)	
occurrences (all)	7	5	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 September 2014	The purpose of the amendment was to clarify exclusion criteria and provide guidance regarding dose modifications, concomitant medications, and contraception. The exclusion criteria and dose modification guidelines were updated to exclude patients with moderate and severe hepatic impairment (Child-Pugh Class B and C). In addition, guidance on treating patients who develop moderate hepatic impairment (Child-Pugh Class B) during the trial and immediate discontinuation if Stevens-Johnson syndrome occurs is provided, in alignment with the prescribing Exjade® information. Guidance was updated on the use of contraception. Effective contraception is required in alignment with the prescribing Exjade® information. Additional guidance was added regarding treatment discontinuation of patients with creatinine clearance <40 mL/min or serum creatinine >2 times the age appropriate ULN and caution should be used in patients with creatinine clearance between 40 and less than 60 mL/min, particularly in cases where there are additional risk factors that may impair renal function such as concomitant medications, dehydration, or severe infections in alignment with the prescribing Exjade® information. Guidance was added regarding the concomitant administration of deferasirox with CYP1A2 substrates that have a narrow therapeutic index and the concomitant use of bile acid sequestrants in alignment with the prescribing Exjade® information. An interim analysis was added to provide additional safety data to the Health Authorities during their review of the first FCT submission. Serum iron and total iron binding capacity (TIBC) were added to the visit evaluation schedule (VES) to further characterize Fe homeostasis status. Guidance for starting dose for patients pre-treated with deferiprone is being provided. In addition, clarifications were added regarding visit schedules, PK assessments and to correct typographical errors and inconsistencies.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported