Clinical trial results:
Open-label, multicenter, single arm, phase II study assessing treatment patient preference for new deferasirox formulation (film-coated tablet) compared to the reference deferasirox dispersible tablet formulation

Summary

EudraCT number	2016-002282-61
Trial protocol	Outside EU/EEA
Global end of trial date	11 March 2021

Results information

Result version number	v1 (current)
This version publication date	22 September 2021
First version publication date	22 September 2021

Trial information

Trial identification

Sponsor protocol code	CICL670FIC05

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02993224
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, novartis.email@novartis.com
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, novartis.email@novartis.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	11 March 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	11 March 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective was to evaluate patient preference between deferasirox film-coated tablets (FCTs) and deferasirox dispersible tablets (DTs)

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 July 2017
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	Turkey: 10
Country: Number of subjects enrolled	Egypt: 45
Country: Number of subjects enrolled	Lebanon: 5
Country: Number of subjects enrolled	Saudi Arabia: 17
Country: Number of subjects enrolled	Morocco: 8
Country: Number of subjects enrolled	Thailand: 51
Country: Number of subjects enrolled	Vietnam: 12
Worldwide total number of subjects	148
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)	73
Adolescents (12-17 years)	20
Adults (18-64 years)	54
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Participants took part in 17 investigative sites in 7 countries

Period 1

Period 1 title	Core Phase - Period 1
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Deferasirox DT followed by deferasirox FCT

Arm description:

Participants were treated with deferasirox DT followed by deferasirox FCT (core phase). Those who entered the extension phase were treated with deferasirox FCT

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

Dosage and administration details:

Deferasirox DT was provided as 125 mg, 250 mg, 500 mg dispersible tablets for oral use. The strengths provided in an individual country could differ and reflected the strengths available commercially in each country.
For iron chelation naive participants, the starting dose on Baseline Day 1 was 20 mg/kg/day in TDT and 10 mg/kg/day in NTDT.
For iron chelation (deferoxamine and/or deferiprone) participants, the starting dose was equivalent to the dose of deferoxamine received (for participants pre-treated with deferoxamine) and based on their serum ferritin levels (for participants pre-treated with deferiprone).
Participants took deferasirox DT once daily for 24 weeks (core phase). The required number of deferasirox DT tablets were to be dispersed with gentle stirring in a glass of water.

Number of subjects in period 1	Deferasirox DT followed by deferasirox FCT
Started	148
Completed	140
Not completed	8
Consent withdrawn by subject	1
Adverse event, non-fatal	4
Lost to follow-up	3

Period 2

Period 2 title	Core Phase- Period 2
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Deferasirox DT followed by deferasirox FCT

Arm description:

Participants were treated with deferasirox DT followed by deferasirox FCT (core phase). Those who entered the extension phase were treated with deferasirox FCT

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

Dosage and administration details:

Deferasirox FCT was provided as 90 mg, 180 mg, 360 mg film coated tablets for oral use. The FCT starting dose on Week 25 was 14 mg/kg/day in TDT and 7 mg/kg/day in NTDT.
Participants took deferasirox FCT once daily for 24 weeks during the core phase. For patients with difficulties in swallowing deferasirox FCT, it was allowed to crush the film-coated tablets and administer the study drug by sprinkling the full dose on soft food (like yogurt or apple puree).

Number of subjects in period 2	Deferasirox DT followed by deferasirox FCT
Started	140
Completed	136
Not completed	4
Adverse event, non-fatal	1
Unwillingness To Comply With Protocol Procedures	2
Allogenic stem cell transplantation	1

Period 3

Period 3 title	Extension Phase
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Deferasirox DT followed by deferasirox FCT

Arm description:

Participants were treated with deferasirox DT followed by deferasirox FCT (core phase). Those who entered the extension phase were treated with deferasirox FCT

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

Dosage and administration details:

Deferasirox FCT was provided as 90 mg, 180 mg, 360 mg film coated tablets for oral use. Participants took deferasirox FCT once daily up to 48 weeks during the extension phase. For patients with difficulties in swallowing deferasirox FCT, it was allowed to crush the film-coated tablets and administer the study drug by sprinkling the full dose on soft food (like yogurt or apple puree).

Number of subjects in period 3[1]	Deferasirox DT followed by deferasirox FCT
Started	116
Completed	80
Not completed	36
Consent withdrawn by subject	3
Adverse event, non-fatal	3
Unwillingness To Comply With Protocol Procedures	1
Deferasirox FCT locally reimbursed	27
Lost to follow-up	2

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: Not all participants who completed the core phase started the extension phase (optional)

Baseline characteristics

Reporting groups	
Reporting group title	Deferasirox DT followed by deferasirox FCT
Reporting group description:	
Participants were treated with deferasirox DT followed by deferasirox FCT (core phase). Those who entered the extension phase were treated with deferasirox FCT	

Reporting group values	Deferasirox DT followed by deferasirox FCT	Total	
Number of subjects	148	148	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	73	73	
Adolescents (12-17 years)	20	20	
Adults (18-64 years)	54	54	
From 65-84 years	1	1	
85 years and over	0	0	
Age Continuous Units: Years			
arithmetic mean	15.32		
standard deviation	± 13.824	-	
Sex: Female, Male Units: Participants			
Female	82	82	
Male	66	66	
Race/Ethnicity, Customized Units: Subjects			
Indian (Indian subcontinent)	5	5	
Other	143	143	

End points

End points reporting groups

Reporting group title	Deferasirox DT followed by deferasirox FCT

Reporting group description:

Participants were treated with deferasirox DT followed by deferasirox FCT (core phase). Those who entered the extension phase were treated with deferasirox FCT

Reporting group title	Deferasirox DT followed by deferasirox FCT

Reporting group description:

Participants were treated with deferasirox DT followed by deferasirox FCT (core phase). Those who entered the extension phase were treated with deferasirox FCT

Reporting group title	Deferasirox DT followed by deferasirox FCT

Reporting group description:

Participants were treated with deferasirox DT followed by deferasirox FCT (core phase). Those who entered the extension phase were treated with deferasirox FCT

Subject analysis set title	Deferasirox DT followed by deferasirox FCT (Full Analysis Set)
Subject analysis set type	Full analysis

Subject analysis set description:

Participants to whom study treatment was assigned and who received at least one dose of each study treatment (deferasirox DT and FCT).

Primary: Number of participants preferring deferasirox FCT or DT at Week 48 based on preference questionnaire (item 2)

End point title	Number of participants preferring deferasirox FCT or DT at Week 48 based on preference questionnaire (item 2)[1]

End point description:

Number of participants preferring deferasirox FCT or DT as measured by preference questionnaire (item 2) at Week 48. The preference questionnaire was a 3-item questionnaire. At Week 48, the second item of the preference questionnaire asked the patients (or parents of young patients from 2 to 9 years old) which medicine did the patient "like best": "Tablet to dissolve in liquid" (=deferasirox DT), "Film coated tablet" (=deferasirox FCT), "Sprinkle powder on food" (=deferasirox FCT) and "I don't know" (=none of the above). The number of participants who selected each response option for item 2 was assessed. The analysis was performed for participants who answered the item 2 of the preference questionnaire.

End point type	Primary

End point timeframe:

Week 48

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: Due to EudraCT system limitations, no statistical analyses have been specified for the endpoints, as this is a single arm study and comparisons within an arm are not supported by the system

End point values	Deferasirox DT followed by deferasirox FCT (Full Analysis Set)			
Subject group type	Subject analysis set			
Number of subjects analysed	134			
Units: Participants				
Preference for deferasirox DT	10			
Preference for deferasirox FCT	121			
Preference for none of the above	3			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants preferring deferasirox FCT, deferasirox DT or previous iron chelation therapy at Week 28 based on preference questionnaire (item 2)

End point title	Number of participants preferring deferasirox FCT, deferasirox DT or previous iron chelation therapy at Week 28 based on preference questionnaire (item 2)

End point description:

Number of participants preferring deferasirox FCT, deferasirox DT or previous iron chelation therapy as measured by preference questionnaire (item 2) at Week 28. The preference questionnaire was a 3-item questionnaire. At Week 28, the second item of this questionnaire asked the patients (or parents of young patients from 2 to 9 years old) which medicine did the patient "like best": "Tablet to dissolve in liquid" (=deferasirox DT), "Film coated tablet (taken once a day)" (=deferasirox FCT), "Sprinkle powder on food" (=deferasirox FCT), "Tablet (taken 3 times a day)" (=previous iron chelation therapy), "Injection" (=previous iron chelation therapy) and "I don't know" (=none of the above). The number of participants who selected each response option for item 2 was assessed. This analysis was performed only for patients who had received iron chelation therapy prior to enrolling in the study and who answered the item 2 of the preference questionnaire.

End point type	Secondary

End point timeframe:

Week 28

End point values	Deferasirox DT followed by deferasirox FCT (Full Analysis Set)			
Subject group type	Subject analysis set			
Number of subjects analysed	69			
Units: Participants				
Preference for deferasirox DT	6			
Preference for deferasirox FCT	60			
Preference for iron chelation therapy	3			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants preferring deferasirox DT or previous iron chelation therapy at Week 4 and Week 24 based on preference questionnaire (item 2)

End point title	Number of participants preferring deferasirox DT or previous

	iron chelation therapy at Week 4 and Week 24 based on preference questionnaire (item 2)

End point description:

Number of participants preferring deferasirox DT or previous iron chelation therapy as measured by preference questionnaire (item 2) at Week 4 and 24. The preference questionnaire was a 3-item questionnaire. At Week 4 and 24, the second item of the preference questionnaire asked the patients (or parents of young patients from 2 to 9 years old) which medicine did the patient "like best": "Tablet to dissolve in liquid" (=deferasirox DT), "Tablet (taken 3 times a day)" (=previous iron chelation therapy), "Injection" (=previous iron chelation therapy) and "I don't know" (=none of the above). The number of participants who selected each response option for item 2 was assessed. This analysis was performed only for patients who had received iron chelation therapy prior to enrolling in the study and who answered item 2 of the preference questionnaire

End point type	Secondary

End point timeframe:

Week 4 and Week 24

End point values	Deferasirox DT followed by deferasirox FCT (Full Analysis Set)			
Subject group type	Subject analysis set			
Number of subjects analysed	70			
Units: Participants				
Preference for deferasirox DT (Week 4)	57			
Preference for iron chelation therapy (Week 4)	11			
Preference for none of the above (Week 4)	2			
Preference for deferasirox DT (Week 24)	52			
Preference for iron chelation therapy (Week 24)	11			
Preference for none of the above (Week 24)	6			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants selecting each reason for treatment preference as assessed by the preference questionnaire at Week 28 and Week 48

End point title	Number of participants selecting each reason for treatment preference as assessed by the preference questionnaire at Week 28 and Week 48

End point description:

The preference questionnaire was a 3 item questionnaire. The first item asked the patients (or parents of young patients from 2 to 9 years old) which medicine they were taking. The second item asked which of the medicines did the patient "Like best". Finally, the third item asked the patient why he/she preferred the medicine they chose in the second item. The number of participants who selected each response option for item 3 was assessed. Participants could select multiple reasons for treatment preference at each timepoint.

End point type	Secondary

End point timeframe:
Week 28 and Week 48

End point values	Deferasirox DT followed by deferasirox FCT (Full Analysis Set)			
Subject group type	Subject analysis set			
Number of subjects analysed	139			
Units: Participants				
Aftertaste (Week 28)	9			
Can correctly prepare the medicine (Week 28)	35			
Convenience (Week 28)	109			
Easier to remember to take the medicine (Week 28)	57			
Gain personal time with family/friends (Week 28)	35			
No/ less pain on the injection site (Week 28)	31			
No/ less side effects (Week 28)	50			
Number of pills (Week 28)	46			
Number of times to take the medicine (Week 28)	42			
Other (Week 28)	5			
Taste (Week 28)	30			
Aftertaste (Week 48)	17			
Can correctly prepare the medicine (Week 48)	48			
Convenience (Week 48)	103			
Easier to remember to take the medicine (Week 48)	61			
Gain personal time with family/friends (Week 48)	36			
No/ less pain on the injection site (Week 48)	37			
No/ less side effects (Week 48)	48			
Number of pills (Week 48)	41			
Number of times to take the medicine (Week 48)	47			
Other (Week 48)	0			
Taste (Week 48)	51			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of consumed tablet counts during deferasirox DT and deferasirox FCT treatment periods

End point title	Percentage of consumed tablet counts during deferasirox DT

	and deferasirox FCT treatment periods

End point description:

The percentage of consumed tablet counts (compliance) was calculated for each treatment period in the core phase: deferasirox DT (period 1) and deferasirox FCT (period 2). Compliance was defined as the total tablet count consumed divided by total tablet count prescribed and multiplied by 100. Total tablet count consumed was calculated as total number of tablets dispensed minus total number of tablets lost/wasted or returned. Total tablet count prescribed was calculated as the number of tablets that the patient should have taken during this period. If a patient did not return the study drug, the compliance was not calculated.

End point type	Secondary

End point timeframe:

Deferasirox DT: Baseline Day 1 to Week 24. Deferasirox FCT: Week 25 to Week 48

End point values	Deferasirox DT followed by deferasirox FCT (Full Analysis Set)			
Subject group type	Subject analysis set			
Number of subjects analysed	139			
Units: Percentage of tablet counts				
arithmetic mean (standard deviation)				
Deferasirox DT (Baseline to Week 24) n=139 Deferasirox FCT (Week 25 to Week 48) n=138	98.68 (± 22.373) 95.07 (± 15.368)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change over time in aftertaste score of palatability questionnaire

End point title	Change over time in aftertaste score of palatability questionnaire

End point description:

The palatability questionnaire consisted of 4 items, three items measuring taste and one item measuring aftertaste. The aftertaste item scored on a 5-point response scale with the response option: Very good = 1, Good = 2, Neither good nor bad = 3, Bad = 4, Very bad = 5. This item offered an additional response option of "no aftertaste". The aftertaste score was calculated among participants who had an aftertaste. Higher aftertaste scores indicated a worse aftertaste.
For participants less than (<) 10 years old, an observer palatability questionnaire was administered. Items and scoring algorithm remained the same as for participants greater than (≥) 10 years old. Change in aftertaste score over time was assessed.
Note: 9999 indicates value is not applicable.

End point type	Secondary

End point timeframe:

Week 4, 24, 28 and 48

End point values	Deferasirox DT followed by deferasirox FCT (Full Analysis Set)			
Subject group type	Subject analysis set			
Number of subjects analysed	139			
Units: Score on a Scale				
arithmetic mean (standard deviation)				
Week 4 - 24: treated with deferasirox DT (n=102)	-0.1 (± 0.80)			
Week 4 - 24: treated with deferasirox FCT (n=6)	-0.5 (± 1.22)			
Week 24 - 28: treated with deferasirox DT (n=0)	9999 (± 9999)			
Week 24 - 28: treated with deferasirox FCT (n=106)	-0.5 (± 1.16)			
Week 24 - 48: treated with deferasirox DT (n=0)	9999 (± 9999)			
Week 24 - 48: treated with deferasirox FCT (n=98)	-0.5 (± 1.08)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change over time in palatability score of palatability questionnaire

End point title	Change over time in palatability score of palatability questionnaire

End point description:

The palatability questionnaire consisted of 4 items, three items measuring taste and one item measuring aftertaste. Among the taste items, first one measured taste on a 5-point response The palatability questionnaire consisted of 4 items, three items measuring taste and one item measuring aftertaste. Among the taste items, first one measured taste on a 5-point response scale. The other two items measured what happened after taking the medicine and how the perceived amount of liquid taken with the medicine was. Responses to these 3 items were combined and converted into a single palatability score using a scoring matrix: each combination of responses on each of 3 items corresponded to a predefined palatability score. For participants <10 years old, an observer palatability questionnaire was administered. Items and scoring algorithm were the same as for participants ≥10 years old. Change in palatability score over time was assessed.
Note: 9999 indicates value is not applicable

End point type	Secondary

End point timeframe:

Week 4, 24, 28 and 48

End point values	Deferasirox DT followed by deferasirox FCT (Full Analysis Set)			
Subject group type	Subject analysis set			
Number of subjects analysed	139			
Units: Score on a Scale				
arithmetic mean (standard deviation)				

Week 4 - 24: treated with deferasirox DT (n=131)	-0.1 (± 2.46)			
Week 4 - 24: treated with deferasirox FCT (n=7)	0.0 (± 0.00)			
Week 24 - 28: treated with deferasirox DT (n=0)	9999 (± 9999)			
Week 24 - 28: treated with deferasirox FCT (n=137)	1.1 (± 2.77)			
Week 24 - 48: treated with deferasirox DT (n=0)	9999 (± 9999)			
Week 24 - 48: treated with deferasirox FCT (n=134)	1.3 (± 2.54)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in adherence domain score of modified satisfaction with iron chelation (mSICT) questionnaire

End point title	Change from baseline in adherence domain score of modified satisfaction with iron chelation (mSICT) questionnaire

End point description:

The mSICT patient reported outcome (PRO) consisted of 15 items that represented 3 domains: Adherence, Preference, and Concerns. The adherence domain score consisted of 6 adherence items, measured using a 5-point response scale. The adherence score was calculated by summing these 6 items, with scores ranging from 6 to 30. Higher scores indicated worse adherence.
For participants <10 years old, an observer version (ObsRO) was administered. The adherence score remained the same as for participants ≥10 years old.
Note: 9999 indicates value is not applicable

End point type	Secondary

End point timeframe:

Baseline (week 2 or, if missing, week 3), week 24, 28 and 48

End point values	Deferasirox DT followed by deferasirox FCT (Full Analysis Set)			
Subject group type	Subject analysis set			
Number of subjects analysed	139			
Units: Score on a scale				
arithmetic mean (standard deviation)				
Week 24-treated with deferasirox DT (PRO) (n=72)	-0.3 (± 3.37)			
Week 24 -treated with deferasirox FCT (PRO) (n=4)	-1.0 (± 2.94)			
Week 28 -treated with deferasirox DT (PRO) (n=0)	9999 (± 9999)			
Week 28 -treated with deferasirox FCT (PRO) (n=77)	0.5 (± 3.59)			
Week 48 -treated with deferasirox DT (PRO) (n=0)	9999 (± 9999)			
Week 48 -treated with deferasirox FCT (PRO) (n=75)	0.5 (± 3.29)			

Week 24-treated with deferasirox DT(ObsRO)(n=56)	-0.2 (± 3.35)			
Week 24-treated with deferasirox FCT(ObsRO)(n=3)	-0.7 (± 4.16)			
Week 28-treated with deferasirox DT (ObsRO)(n=0)	9999 (± 9999)			
Week 28-treated with deferasirox FCT(ObsRO)(n=58)	0.8 (± 3.68)			
Week 48-treated with deferasirox DT(ObsRO)(n=0)	9999 (± 9999)			
Week 48-treated with deferasirox FCT(ObsRO)(n=55)	1.1 (± 3.79)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in preference domain score of modified satisfaction with iron chelation (mSICT) questionnaire

End point title	Change from baseline in preference domain score of modified satisfaction with iron chelation (mSICT) questionnaire

End point description:

The mSICT patient reported outcome (PRO) consisted of 15 items that represented 3 domains: Adherence, Preference, and Concerns.
The preference/satisfaction domain score consisted of 2 preference/satisfaction items, measured using a 5-point response scale. The preference score was calculated by summing these 2 items, with scores ranging from 2 to 10. Higher scores indicated worse satisfaction.
For participants < 10 years old, an observer version (ObsRO) was administered. Preference score remained the same as for participants ≥ 10 years old.
Note: 9999 indicates value is not applicable.

End point type	Secondary

End point timeframe:

Baseline (week 2 or, if missing, week 3), week 24, 28 and 48

End point values	Deferasirox DT followed by deferasirox FCT (Full Analysis Set)			
Subject group type	Subject analysis set			
Number of subjects analysed	139			
Units: Score on a scale				
arithmetic mean (standard deviation)				
Week 24-treated with deferasirox DT(PRO)(n=72)	0.5 (± 1.21)			
Week 24-treated with deferasirox FCT(PRO)(n=4)	0.5 (± 3.70)			
Week 28-treated with deferasirox DT(PRO)(n=0)	9999 (± 9999)			
Week 28-treated with deferasirox FCT(PRO)(n=77)	-1.1 (± 1.83)			
Week 48-treated with deferasirox DT(PRO)(n=0)	9999 (± 9999)			

Week 48-treated with deferasirox FCT(PRO)(n=75)	-0.9 (± 2.02)			
Week 24-treated with deferasirox DT(ObsRO)(n=55)	0.0 (± 1.49)			
Week 24-treated with deferasirox FCT(ObsRO)(n=3)	0.0 (± 1.73)			
Week 28-treated with deferasirox DT(ObsRO)(n=0)	9999 (± 9999)			
Week 28-treated with deferasirox FCT(ObsRO)(n=57)	-0.8 (± 1.74)			
Week 48-treated with deferasirox DT(ObsRO)(n=0)	9999 (± 9999)			
Week 48-treated with deferasirox FCT(ObsRO)(n=54)	-0.9 (± 1.75)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in concerns domain score of modified satisfaction with iron chelation (mSICT) questionnaire

End point title	Change from baseline in concerns domain score of modified satisfaction with iron chelation (mSICT) questionnaire

End point description:

The mSICT patient reported outcome (PRO) consisted of 15 items that represented 3 domains: Adherence, Preference, and Concerns.
The concerns domain score consisted of 3 items to address any concerns or worries with the medication. All 3 items were measured on a 5-point response scale. The concerns score was calculated by summing the 3 items, with scores ranging from 3 to 15. Higher scores indicated fewer concerns. For participants < 10 years old, an observer version (ObsRO) was administered. Concerns score remained the same as for participants ≥ 10 years old.
Note: 9999 indicates value is not applicable

End point type	Secondary

End point timeframe:

Baseline (week 2 or, if missing, week 3), week 24, 28 and 48

End point values	Deferasirox DT followed by deferasirox FCT (Full Analysis Set)			
Subject group type	Subject analysis set			
Number of subjects analysed	139			
Units: Score on a scale				
arithmetic mean (standard deviation)				
Week 24-treated with deferasirox DT(PRO)(n=72)	-0.1 (± 1.99)			
Week 24-treated with deferasirox FCT(PRO)(n=4)	-1.0 (± 1.15)			
Week 24-treated with deferasirox DT (PRO)(n=0)	9999 (± 9999)			
Week 28-treated with deferasirox FCT(PRO)(n=77)	0.3 (± 1.84)			

Week 48-treated with deferasirox DT (PRO)(n=0)	9999 (± 9999)			
Week 48-treated with deferasirox FCT(PRO)(n=75)	0.5 (± 1.80)			
Week 24-treated with deferasirox DT (ObsRO)(n=55)	-0.4 (± 1.33)			
Week 24-treated with deferasirox FCT(ObsRO)(n=3)	-0.7 (± 1.15)			
Week 28-treated with deferasirox DT (ObsRO)(n=0)	9999 (± 9999)			
Week 28-treated with deferasirox FCT(ObsRO)(n=58)	0.1 (± 2.05)			
Week 48-treated with deferasirox DT(ObsRO)(n=0)	9999 (± 9999)			
Week 48-treated with deferasirox FCT(ObsRO)(n=54)	0.1 (± 1.58)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in gastrointestinal (GI) symptom score based on GI questionnaire

End point title	Change from baseline in gastrointestinal (GI) symptom score based on GI questionnaire

End point description:

The GI symptom score was calculated from responses to 5 questions of the GI questionnaire, each with a possible score of 1 to 5, for an overall possible score range of 5 to 25, where a lower score represents a less severe GI symptom and a higher score represents a more severe GI symptom.
An observer GI symptom questionnaire was administered to those patients who were < 10 years old. The questionnaire was completed by the parents of the participants. All items and the scoring algorithm remained the same as for participants ≥ 10 years old.
Note: 9999 indicates value is not applicable

End point type	Secondary

End point timeframe:

Baseline (week -1 or, if missing, week -2), week 24, 28 and 48

End point values	Deferasirox DT followed by deferasirox FCT (Full Analysis Set)			
Subject group type	Subject analysis set			
Number of subjects analysed	139			
Units: Score on a scale				
arithmetic mean (standard deviation)				
Week 24 <10yrs treated with deferasirox DT(n=60)	0.2 (± 2.78)			
Week 24 <10yrs treated with deferasirox FCT(n=3)	-2.0 (± 2.65)			
Week 28 <10yrs treated with deferasirox DT(n=0)	9999 (± 9999)			
Week 28 <10yrs treated with deferasirox FCT(n=62)	-0.5 (± 2.49)			

Week 48 <10yrs treated with deferasirox DT(n=0)	9999 (± 9999)			
Week 48 <10yrs treated with deferasirox FCT(n=61)	-0.6 (± 2.33)			
Week 24 ≥10yrs treated with deferasirox DT(n=71)	1.4 (± 5.53)			
Week 24 ≥10yrs treated with deferasirox FCT(n=4)	5.8 (± 12.82)			
Week 28 ≥10yrs treated with deferasirox DT(n=0)	9999 (± 9999)			
Week 28 ≥10yrs treated with deferasirox FCT(n=75)	-1.9 (± 4.33)			
Week 48 ≥10yrs treated with deferasirox DT(n=0)	9999 (± 9999)			
Week 48 ≥10yrs treated with deferasirox FCT(n=75)	-2.2 (± 4.74)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in serum ferritin levels

End point title	Change from baseline in serum ferritin levels
End point description:	
Absolute change from baseline over time in serum ferritin levels	
End point type	Secondary
End point timeframe:	
Baseline (Day 1) up to 96 weeks	

End point values	Deferasirox DT followed by deferasirox FCT (Full Analysis Set)			
Subject group type	Subject analysis set			
Number of subjects analysed	139			
Units: microgram/liter (ug/L)				
arithmetic mean (standard deviation)				
Week 2 - treated with deferasirox DT(n=108)	363.654 (± 323.3828)			
Week 4 - treated with deferasirox DT (n=120)	393.126 (± 457.8032)			
Week 8 - treated with deferasirox DT (n=121)	462.560 (± 427.7138)			
Week 12 - treated with deferasirox DT (n=129)	510.455 (± 548.6222)			
Week 16 - treated with deferasirox DT (n=131)	519.038 (± 508.7432)			
Week 20 - treated with deferasirox DT (n=134)	540.618 (± 548.2318)			
Week 24 - treated with deferasirox DT (n=130)	644.849 (± 629.6687)			

Week 28 - treated with deferasirox FCT (n=114)	679.610 (± 701.6219)			
Week 32 - treated with deferasirox FCT (n=126)	623.600 (± 629.5417)			
Week 36 - treated with deferasirox FCT (n=127)	679.011 (± 674.6716)			
Week 40 - treated with deferasirox FCT (n=120)	739.016 (± 659.0840)			
Week 44 - treated with deferasirox FCT (n=120)	748.063 (± 647.3000)			
Week 48 - treated with deferasirox FCT (n=120)	833.700 (± 788.0650)			
Week 52 - treated with deferasirox FCT	760.229 (± 798.0836)			
Week 56 - treated with deferasirox FCT (n=113)	903.622 (± 832.9872)			
Week 60 - treated with deferasirox FCT (n=106)	980.644 (± 994.4445)			
Week 64 - treated with deferasirox FCT (n=102)	863.579 (± 854.8592)			
Week 68 - treated with deferasirox FCT (n=92)	921.725 (± 860.8738)			
Week 72 - treated with deferasirox FCT (n=91)	971.112 (± 872.7306)			
Week 76 - treated with deferasirox FCT (n=90)	888.917 (± 869.0805)			
Week 80 - treated with deferasirox FCT (n=77)	1005.758 (± 868.4338)			
Week 84 - treated with deferasirox FCT (n=87)	1013.683 (± 924.5828)			
Week 88 - treated with deferasirox FCT (n=80)	1117.849 (± 985.0767)			
Week 92 - treated with deferasirox FCT (n=74)	1222.429 (± 1027.2565)			
Week 96 - treated with deferasirox FCT (n=74)	1137.347 (± 972.1286)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events (AEs) were collected from day of first dose to 30 days after last dose of study medication, assessed up to approx. 30 weeks for deferasirox DT treatment, 39 weeks for deferasirox FCT treatment and 70 weeks for deferasirox FCT treatment

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	23.1

Reporting groups

Reporting group title	Deferasirox DT (Core Phase)

Reporting group description:

Participants who were treated with deferasirox DT once daily in the core phase

Reporting group title	Deferasirox FCT (Extension phase)

Reporting group description:

Participants who were treated with deferasirox FCT once daily in the extension phase

Reporting group title	Deferasirox FCT (Core Phase)

Reporting group description:

Participants who were treated with deferasirox FCT once daily in the core phase

Serious adverse events	Deferasirox DT (Core Phase)	Deferasirox FCT (Extension phase)	Deferasirox FCT (Core Phase)
Total subjects affected by serious adverse events			
subjects affected / exposed	13 / 148 (8.78%)	16 / 116 (13.79%)	6 / 140 (4.29%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cholangiocarcinoma			
subjects affected / exposed	0 / 148 (0.00%)	1 / 116 (0.86%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 148 (0.68%)	0 / 116 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration			

site conditions			
Pyrexia			
subjects affected / exposed	1 / 148 (0.68%)	2 / 116 (1.72%)	1 / 140 (0.71%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	2 / 148 (1.35%)	1 / 116 (0.86%)	1 / 140 (0.71%)
occurrences causally related to treatment / all	3 / 3	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 148 (1.35%)	0 / 116 (0.00%)	1 / 140 (0.71%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood bilirubin increased			
subjects affected / exposed	1 / 148 (0.68%)	0 / 116 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic enzyme increased			
subjects affected / exposed	1 / 148 (0.68%)	0 / 116 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Abdominal injury			
subjects affected / exposed	0 / 148 (0.00%)	1 / 116 (0.86%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur fracture			
subjects affected / exposed	0 / 148 (0.00%)	1 / 116 (0.86%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal injury			

subjects affected / exposed	0 / 148 (0.00%)	1 / 116 (0.86%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Road traffic accident			
subjects affected / exposed	0 / 148 (0.00%)	1 / 116 (0.86%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Splenic rupture			
subjects affected / exposed	0 / 148 (0.00%)	1 / 116 (0.86%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ulna fracture			
subjects affected / exposed	0 / 148 (0.00%)	1 / 116 (0.86%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Cardiac failure congestive			
subjects affected / exposed	1 / 148 (0.68%)	0 / 116 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure chronic			
subjects affected / exposed	0 / 148 (0.00%)	0 / 116 (0.00%)	1 / 140 (0.71%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Polyneuropathy			
subjects affected / exposed	1 / 148 (0.68%)	0 / 116 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Haemolysis			
subjects affected / exposed	0 / 148 (0.00%)	1 / 116 (0.86%)	1 / 140 (0.71%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Leukopenia			
subjects affected / exposed	2 / 148 (1.35%)	0 / 116 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	2 / 148 (1.35%)	0 / 116 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	0 / 148 (0.00%)	1 / 116 (0.86%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Optic nerve cupping			
subjects affected / exposed	0 / 148 (0.00%)	1 / 116 (0.86%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Pancreatitis			
subjects affected / exposed	0 / 148 (0.00%)	1 / 116 (0.86%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholangitis acute			
subjects affected / exposed	0 / 148 (0.00%)	1 / 116 (0.86%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Jaundice cholestatic			
subjects affected / exposed	0 / 148 (0.00%)	1 / 116 (0.86%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Angioedema			

subjects affected / exposed	1 / 148 (0.68%)	0 / 116 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 148 (0.68%)	1 / 116 (0.86%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Proteinuria			
subjects affected / exposed	1 / 148 (0.68%)	1 / 116 (0.86%)	1 / 140 (0.71%)
occurrences causally related to treatment / all	1 / 1	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Cellulitis			
subjects affected / exposed	0 / 148 (0.00%)	0 / 116 (0.00%)	1 / 140 (0.71%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis			
subjects affected / exposed	1 / 148 (0.68%)	0 / 116 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea infectious			
subjects affected / exposed	0 / 148 (0.00%)	1 / 116 (0.86%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ecthyma			
subjects affected / exposed	0 / 148 (0.00%)	1 / 116 (0.86%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal infection			
subjects affected / exposed	0 / 148 (0.00%)	1 / 116 (0.86%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			

subjects affected / exposed	1 / 148 (0.68%)	1 / 116 (0.86%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Otitis media			
subjects affected / exposed	0 / 148 (0.00%)	1 / 116 (0.86%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			
subjects affected / exposed	0 / 148 (0.00%)	1 / 116 (0.86%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral infection			
subjects affected / exposed	0 / 148 (0.00%)	1 / 116 (0.86%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	0 / 148 (0.00%)	1 / 116 (0.86%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolic acidosis			
subjects affected / exposed	0 / 148 (0.00%)	1 / 116 (0.86%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Deferasirox DT (Core Phase)	Deferasirox FCT (Extension phase)	Deferasirox FCT (Core Phase)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	82 / 148 (55.41%)	49 / 116 (42.24%)	59 / 140 (42.14%)
Investigations			
Hepatic enzyme increased			
subjects affected / exposed	5 / 148 (3.38%)	6 / 116 (5.17%)	4 / 140 (2.86%)
occurrences (all)	7	6	6

Serum ferritin increased			
subjects affected / exposed	8 / 148 (5.41%)	1 / 116 (0.86%)	2 / 140 (1.43%)
occurrences (all)	9	1	2
Urine protein/creatinine ratio increased			
subjects affected / exposed	13 / 148 (8.78%)	7 / 116 (6.03%)	12 / 140 (8.57%)
occurrences (all)	15	8	14
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	7 / 148 (4.73%)	5 / 116 (4.31%)	8 / 140 (5.71%)
occurrences (all)	7	10	8
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	16 / 148 (10.81%)	2 / 116 (1.72%)	5 / 140 (3.57%)
occurrences (all)	17	3	5
Hepatobiliary disorders			
Hepatomegaly			
subjects affected / exposed	8 / 148 (5.41%)	0 / 116 (0.00%)	0 / 140 (0.00%)
occurrences (all)	8	0	0
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	8 / 148 (5.41%)	12 / 116 (10.34%)	9 / 140 (6.43%)
occurrences (all)	8	18	10
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	6 / 148 (4.05%)	3 / 116 (2.59%)	7 / 140 (5.00%)
occurrences (all)	6	3	9
Pharyngitis			
subjects affected / exposed	7 / 148 (4.73%)	6 / 116 (5.17%)	6 / 140 (4.29%)
occurrences (all)	10	7	7
Upper respiratory tract infection			
subjects affected / exposed	8 / 148 (5.41%)	4 / 116 (3.45%)	8 / 140 (5.71%)
occurrences (all)	9	4	8
Urinary tract infection			
subjects affected / exposed	9 / 148 (6.08%)	3 / 116 (2.59%)	3 / 140 (2.14%)
occurrences (all)	9	3	3

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 February 2019	The purpose of this amendment was to provide additional clarity to the study Investigators in relation to dosing of deferasirox for patients with non-transfusion dependent thalassemia (NTDT), those patients changing therapy from deferiprone, and those patients with body weight lower than 20 kg; to provide additional guidance in relation to the ocular and auditory assessments; to revise the underlying assumptions used to calculate the sample size of the study; to clarify the inclusion criterion that relates to prior therapy; to correct inconsistencies and typos; and to update withdrawal of consent language.

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, no statistical analyses have been specified for the endpoints, as this is a single arm study and comparisons within an arm are not supported by the system. Please use https://www.novctrd.com/ for complete results.

Notes: