



Clinical trial results:

An open-label, multi-center, efficacy and safety study of deferasirox in iron overloaded patients with nontransfusion dependent thalassemia (THETIS)

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use <https://www.novctrd.com/CtrdWeb/home.novfor> complete trial results.

Summary

EudraCT number	2012-000650-64
Trial protocol	GB IT GR
Global end of trial date	17 January 2019

Results information

Result version number	v1 (current)
This version publication date	02 August 2019
First version publication date	02 August 2019

Trial information

Trial identification

Sponsor protocol code	CICL670E2419
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01709838
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 CICL670E2419, novartis.email@novartis.com
Scientific contact	Study Director, Novartis Pharma, AG, +41 CICL670E2419, 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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	17 January 2019
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	17 January 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Assess the efficacy of deferasirox in liver iron removal after Week 52

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	06 December 2012
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	China: 68
Country: Number of subjects enrolled	Greece: 5
Country: Number of subjects enrolled	Italy: 3
Country: Number of subjects enrolled	Lebanon: 20
Country: Number of subjects enrolled	Thailand: 16
Country: Number of subjects enrolled	Tunisia: 3
Country: Number of subjects enrolled	Turkey: 17
Country: Number of subjects enrolled	United Kingdom: 2
Worldwide total number of subjects	134
EEA total number of subjects	10

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)	7
Adolescents (12-17 years)	18
Adults (18-64 years)	109
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

At least 117 patients were planned to be enrolled; 134 patients were enrolled (68 Chinese and 66 non-Chinese).

Pre-assignment

Screening details:

The target population of this study was iron overloaded NTDT patients, at least ten years old. Pediatric patients were required to weigh ≥ 20 kg, to allow dosing of 5 mg/kg with one 125 mg tablet.

Period 1

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

Arms

Arm title	Deferasirox
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Arm description:

All patients were treated with 10mg/kg/day deferasirox with dose adjustments after 4 weeks of treatment according to baseline Liver Iron Concentration (LIC).

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:

All patients were treated with 10 mg/kg/day deferasirox (4 weeks). Dose adjustments after 4 weeks of treatment according to baseline LIC to 10 mg/kg/day, 15 mg/kg/day, 20 mg/kg/day. Dose adjustments at Week 24 and approximately every 6 months thereafter according to LIC.

Number of subjects in period 1	Deferasirox
Started	134
Completed	67
Not completed	67
Adverse event, serious fatal	3
Consent withdrawn by subject	21
Physician decision	4
Adverse event, non-fatal	4
Pregnancy	10
Lost to follow-up	16
Subject/guardian decision	8
Protocol deviation	1

Baseline characteristics

Reporting groups

Reporting group title	Deferasirox
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Reporting group description:

All patients were treated with 10mg/kg/day deferasirox with dose adjustments after 4 weeks of treatment according to baseline Liver Iron Concentration (LIC).

Reporting group values	Deferasirox	Total	
Number of subjects	134	134	
Age, Customized Units: Subjects			
<2y - <12 years	7	7	
12y - <18 years	18	18	
18y - < 65 years	109	109	
Age Continuous Units: years			
arithmetic mean	28.0		
standard deviation	± 11.10	-	
Sex: Female, Male Units: Subjects			
Female	58	58	
Male	76	76	
Race/Ethnicity, Customized Units: Subjects			
Asian	85	85	
Caucasian	48	48	
Other	1	1	

End points

End points reporting groups

Reporting group title	Deferasirox
Reporting group description: All patients were treated with 10mg/kg/day deferasirox with dose adjustments after 4 weeks of treatment according to baseline Liver Iron Concentration (LIC).	

Primary: Absolute Change in Liver Iron Content (LIC) at 52 weeks from baseline

End point title	Absolute Change in Liver Iron Content (LIC) at 52 weeks from baseline ^[1]
End point description: Absolute change in liver iron concentration measured by MRI from baseline after 52 weeks of treatment	
End point type	Primary
End point timeframe: Baseline, 52 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: No statistical analysis was done, only an exploratory statistical inference was done.

End point values	Deferasirox			
Subject group type	Reporting group			
Number of subjects analysed	134			
Units: mg Fe/g dw				
arithmetic mean (standard deviation)	-6.68 (± 7.018)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with baseline LIC>15 achieving LIC<5 mg Fe/g dw

End point title	Percentage of participants with baseline LIC>15 achieving LIC<5 mg Fe/g dw
End point description: The percentage of participants with baseline LIC>15 mg Fe/g dw achieving an LIC <5 mg Fe/g dw during the study	
End point type	Secondary
End point timeframe: 5 years	

End point values	Deferasirox			
Subject group type	Reporting group			
Number of subjects analysed	134			
Units: percentage of participants				
number (not applicable)	51.0			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to achieving LIC <5 mg Fe/g dw

End point title	Time to achieving LIC <5 mg Fe/g dw
End point description: Time to achieving LIC <5 mg Fe/g dw for participants with baseline LIC>15 mg Fe/g dw during the study	
End point type	Secondary
End point timeframe: 5 years	

End point values	Deferasirox			
Subject group type	Reporting group			
Number of subjects analysed	134			
Units: months				
median (confidence interval 95%)	36.3 (28.55 to 48.30)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time from target LIC of 3 mg Fe/g dw to the first LIC ≥5 mg Fe/g dw in the follow up period

End point title	Time from target LIC of 3 mg Fe/g dw to the first LIC ≥5 mg Fe/g dw in the follow up period
End point description: Time from the target LIC <3 mg Fe/g dw to the first LIC ≥5 mg Fe/g dw in the follow-up period	
End point type	Secondary
End point timeframe: post-baseline, up to 260 weeks	

End point values	Deferasirox			
Subject group type	Reporting group			
Number of subjects analysed	134			
Units: days				
median (confidence interval 95%)	27.4 (17.68 to 999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Change in health-related outcomes using Medical Outcomes Study Form 36 (SF-36v2)

End point title	Absolute Change in health-related outcomes using Medical Outcomes Study Form 36 (SF-36v2)
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End point description:

The SF-36 is a self-administered questionnaire for adults (from 18 years of age) and contains 36 items which measure: Physical functioning, Role limitation due to physical health problems, Bodily pain, General health perceptions, Vitality, Social functioning, Role limitations due to emotional problems and General mental health . The higher values indicate a better evaluation of health. Range: 0 to 100 [0 (worst possible health state measured by the questionnaire) to 100 (best possible health state)].

End point type	Secondary
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End point timeframe:

Baseline, 52, 104 & 156 Weeks

End point values	Deferasirox			
Subject group type	Reporting group			
Number of subjects analysed	134			
Units: scores on a scale				
arithmetic mean (standard deviation)				
Physical Functioning Week 52 (n= 89)	-0.5 (± 5.5)			
Physical Functioning Week 104 (n = 74)	-0.7 (± 4.9)			
Physical Functioning Week 156 (n = 64)	0.6 (± 6.1)			
Role Physical Week 52 (n= 89)	0.9 (± 9.1)			
Role Physical Week 104 (n = 74)	-1.0 (± 10.2)			
Role Physical Week 156 (n = 64)	1.0 (± 10.9)			
Bodily Pain Week 52 (n= 89)	-0.0 (± 11.6)			
Bodily Pain Week 104 (n = 74)	-1.3 (± 10.8)			
Bodily Pain Week 156 (n = 64)	0.9 (± 12.2)			
General Health Week 52 (n= 89)	-2.3 (± 9.1)			
General Health Pain Week 104 (n = 74)	-1.9 (± 9.2)			
General Health Week 156 (n = 64)	-1.1 (± 8.6)			
Vitality Week 52 (n= 89)	1.1 (± 9.7)			
Vitality Week 104 (n = 74)	-0.2 (± 8.7)			
Vitality Week 156 (n = 64)	2.1 (± 9.6)			
Social Functioning Week 52 (n = 89)	0.9 (± 9.8)			
Social Functioning Week 104 (n = 74)	-1.2 (± 9.6)			
Social Functioning Week 156 (n = 64)	1.6 (± 10.6)			

Role Emotional Week 52 (n = 89)	-0.1 (± 11.3)			
Role Emotional Week 104 (n = 74)	-2.5 (± 12.2)			
Role Emotional Week 156 (n = 64)	0.7 (± 11.2)			
Mental Health Week 52 (n = 88)	1.5 (± 11.7)			
Mental Health Week 104 (n = 73)	-0.6 (± 11.4)			
Mental Health Week 156 (n = 63)	2.8 (± 10.9)			
Physical Component Week 52 (n = 89)	-0.8 (± 7.2)			
Physical Component Week 104 (n = 74)	-1.0 (± 7.4)			
Physical Component Week 156 (n = 64)	-0.1 (± 7.9)			
Mental Component Week 52 (n = 88)	1.1 (± 10.9)			
Mental Component Week 104 (n = 73)	-1.3 (± 11.1)			
Mental Component Week 156 (n = 63)	2.2 (± 10.8)			
SF6D Health Utility Index Week 52 (n = 88)	0.0 (± 0.1)			
SF6D Health Utility Index Week 104 (n = 73)	-0.0 (± 0.1)			
SF6D Health Utility Index Week 156 (n = 63)	0.0 (± 0.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Change in health-related outcomes using the Pediatric Quality of Life questionnaire (PedsQL™)

End point title	Absolute Change in health-related outcomes using the Pediatric Quality of Life questionnaire (PedsQL™)
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End point description:

The PedsQL™ is a modular approach to measuring health-related quality of life (HRQOL) in children and adolescents. The 23-item PedsQL™ Generic Core Scales encompass the essential core domains for pediatric HRQOL measurement: 1) Physical Functioning (8 items), 2) Emotional Functioning (5 items), 3) Social Functioning (5 items), and 4) School Functioning (5 items). The Generic Core Scales are designed to enable comparisons across patient and healthy populations. The higher values indicate a better evaluation of health. Range: 0 to 100 [0 (worst possible health state measured by the questionnaire) to 100 (best possible health state)].

End point type	Secondary
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End point timeframe:

Baseline, 52, 104 & 156 Weeks

End point values	Deferasirox			
Subject group type	Reporting group			
Number of subjects analysed	134			
Units: scores on a scale				
arithmetic mean (standard deviation)				
Physical Functioning - Teenager Wk 52 (n=15)	2.3 (± 13.7)			
Physical Functioning - Teenager Wk 104 (n=13)	1.0 (± 19.3)			
Physical Functioning - Teenager Wk 156 (n=11)	-0.9 (± 15.4)			

Emotional Functioning - Teenager Wk 52 (n=15)	0.7 (± 17.8)			
Emotional Functioning - Teenager Wk 104 (n=13)	3.1 (± 27.6)			
Emotional Functioning - Teenager Wk 156 (n=11)	10.9 (± 25.9)			
Social Functioning - Teenager Wk 52 (n= 15)	-9.3 (± 17.5)			
Social Functioning - Teenager Wk 104 (n= 13)	-10.0 (± 17.8)			
Social Functioning - Teenager Wk 156 (n= 11)	-5.0 (± 20.1)			
School Functioning - Teenager Wk 52 (n= 14)	0.7 (± 12.4)			
School Functioning - Teenager Wk 104 (n= 12)	-3.8 (± 16.4)			
School Functioning - Teenager Wk 156 (n= 10)	1.0 (± 21.4)			
Physical Health - Teenager Wk 52 (n= 15)	2.3 (± 13.7)			
Physical Health - Teenager Wk 104 (n= 13)	1.0 (± 19.3)			
Physical Health - Teenager Wk 156 (n= 11)	-0.9 (± 15.4)			
Psychosocial Health - Teenager Wk 52 (n= 15)	-3.3 (± 13.0)			
Psychosocial Health - Teenager Wk 104 (n= 13)	-4.0 (± 16.9)			
Psychosocial Health - Teenager Wk 156 (n= 11)	2.0 (± 19.1)			
Total Score - Teenager Wk 52 (n= 15)	-1.0 (± 10.6)			
Total Score - Teenager Wk 104 (n= 13)	-1.9 (± 14.4)			
Total Score - Teenager Wk 156 (n= 11)	1.2 (± 15.8)			
Physical Functioning - Parent Wk 52 (n=15)	-2.9 (± 19.0)			
Physical Functioning - Parent Wk 104 (n=13)	0.0 (± 18.6)			
Physical Functioning - Parent Wk 156 (n=10)	-0.3 (± 15.6)			
Emotional Functioning - Parent Wk 52 (n= 15)	-8.7 (± 19.1)			
Emotional Functioning - Parent Wk 104 (n= 13)	-3.8 (± 20.8)			
Emotional Functioning - Parent Wk 156 (n= 10)	2.0 (± 20.6)			
Social Functioning - Parent Wk 52 (n= 15)	-3.7 (± 15.5)			
Social Functioning - Parent Wk 104 (n= 13)	-4.6 (± 18.0)			
Social Functioning - Parent Wk 156 (n= 10)	-6.0 (± 20.9)			
School Functioning - Parent Wk 52 (n= 14)	-3.6 (± 20.6)			
School Functioning - Parent Wk 104 (n= 12)	0.0 (± 11.7)			
School Functioning - Parent Wk 156 (n= 9)	-0.6 (± 21.1)			
Physical Health - Parent Wk 52 (n= 15)	-2.9 (± 19.0)			
Physical Health - Parent Wk 104 (n= 13)	0.0 (± 18.6)			
Physical Health - Parent Wk 156 (n= 10)	-0.3 (± 15.6)			

Psychosocial Health - Parent Wk 52 (n= 15)	-5.5 (± 15.0)			
Psychosocial Health - Parent Wk 104 (n= 13)	-3.2 (± 12.3)			
Psychosocial Health - Parent Wk 156 (n= 10)	-1.8 (± 14.1)			
Total Score - Parent Wk 52 (n= 15)	-4.6 (± 14.8)			
Total Score - Parent Wk 104 (n= 13)	-1.9 (± 12.0)			
Total Score - Parent Wk 156 (n= 10)	-1.1 (± 12.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change in LIC from baseline over time

End point title	Absolute change in LIC from baseline over time
End point description:	
Absolute change in serum ferritin from baseline over time up to 260 weeks	
End point type	Secondary
End point timeframe:	
24, 52, 76, 104, 128, 156, 180, 208, 232, 260 Weeks	

End point values	Deferasirox			
Subject group type	Reporting group			
Number of subjects analysed	134			
Units: mg Fe/g dw				
arithmetic mean (standard deviation)				
Week 24 (n= 126)	-3.67 (± 3.778)			
Week 52 (n= 118)	-7.02 (± 7.132)			
Week 76 (n= 107)	-8.93 (± 8.922)			
Week 104 (n= 100)	-9.63 (± 9.474)			
Week 128 (n= 95)	-10.03 (± 9.445)			
Week 156 (n= 92)	-10.20 (± 9.746)			
Week 180 (n= 86)	-9.94 (± 9.838)			
Week 208 (n= 81)	-10.04 (± 10.010)			
Week 232 (n= 66)	-10.58 (± 10.045)			
Week 260 (n= 66)	-10.57 (± 10.366)			

Statistical analyses

No statistical analyses for this end point

Secondary: Serum Ferritin (SF) vs LIC at baseline and EOS (Week 260 + 30 days follow-up)

End point title	Serum Ferritin (SF) vs LIC at baseline and EOS (Week 260 + 30 days follow-up)
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End point description:

Correlation between serum ferritin and LIC is assessed using scatter plots with pearson correlation coefficient and simple linear model Absolute change in liver iron concentration measured by MRI from baseline after 52 weeks of treatment by underlying NTDT syndrome

End point type	Secondary
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End point timeframe:

Baseline, End of Study (EOS): Week 260 + 30 days follow up

End point values	Deferasirox			
Subject group type	Reporting group			
Number of subjects analysed	134			
Units: correlation (r)				
number (not applicable)				
At Baseline	0.730			
Change from Baseline at EOS	0.740			

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Change in LIC from baseline after 52 weeks of treatment by underlying Non-transfusion dependent thalassemia (NTDT) syndrome

End point title	Absolute Change in LIC from baseline after 52 weeks of treatment by underlying Non-transfusion dependent thalassemia (NTDT) syndrome
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End point description:

Absolute change in liver iron concentration measured by MRI from baseline after 52 weeks of treatment by underlying NTDT syndrome. The 4 underlying disease types: Beta-thalassemia intermedia (N =69), HbE beta-thalassemia (N = 24), Alpha-thalassemia intermedia (HbH disease) (N = 40), Other, specify (N = 1)

End point type	Secondary
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End point timeframe:

Baseline, 52 Weeks

End point values	Deferasirox			
Subject group type	Reporting group			
Number of subjects analysed	134			
Units: mg Fe/g dw				
arithmetic mean (standard deviation)				
Beta-thalassemia intermedia (n = 65)	-6.11 (± 6.481)			
HbE beta-thalassemia (n = 23)	-6.18 (± 7.572)			
Alpha-thalassemia intermedia (HbH disease) (n= 38)	-7.97 (± 7.652)			
Other, specify (n = 1)	-6.00 (± 999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Change in Serum Ferritin from baseline after 52 weeks

End point title	Absolute Change in Serum Ferritin from baseline after 52 weeks
End point description:	Absolute change in serum ferritin from baseline after 52 weeks of treatment
End point type	Secondary
End point timeframe:	Baseline, 52 weeks

End point values	Deferasirox			
Subject group type	Reporting group			
Number of subjects analysed	134			
Units: ng/mL				
arithmetic mean (standard deviation)	-494.64 (± 760.782)			

Statistical analyses

No statistical analyses for this end point

Secondary: PK parameters: AUCtau

End point title	PK parameters: AUCtau
End point description:	The pharmacokinetic parameter, AUCtau was determined using non-compartmental method(s) for deferasirox and its iron complex. AUC=area under the concentration-time curve during a dosing interval at steady state (amount × time × volume).
End point type	Secondary

End point timeframe:

4 Weeks

End point values	Deferasirox			
Subject group type	Reporting group			
Number of subjects analysed	22			
Units: hr*umol/L				
geometric mean (geometric coefficient of variation)	678.2 (± 61.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: PK parameters: Cmax

End point title	PK parameters: Cmax
End point description: The pharmacokinetic parameter, Cmax, was determined using non-compartmental method(s) for deferiasirox and its iron complex. Cmax (maximum/peak plasma drug concentration after drug administration)=amount × volume	
End point type	Secondary
End point timeframe: 4 Weeks	

End point values	Deferasirox			
Subject group type	Reporting group			
Number of subjects analysed	22			
Units: umol/L				
geometric mean (geometric coefficient of variation)	53.367 (± 60.960)			

Statistical analyses

No statistical analyses for this end point

Secondary: PK parameters: Tmax

End point title	PK parameters: Tmax
End point description: The pharmacokinetic parameter, Tmax, may be determined using non-compartmental method(s) for deferiasirox and its iron complex. Tmax=time to reach maximum/peak concentration following drug administration.	
End point type	Secondary

End point timeframe:

4 Weeks

End point values	Deferasirox			
Subject group type	Reporting group			
Number of subjects analysed	22			
Units: hr				
geometric mean (geometric coefficient of variation)	2.5131 ($\pm$ 33.9321)			

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma pharmacokinetics (PK) deferasirox concentrations

End point title	Plasma pharmacokinetics (PK) deferasirox concentrations
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End point description:

Blood samples for PK evaluation were collected for a sub-group of patients. The patient had to have been on treatment without dose adjustment or treatment interruption (for any reason) for at least 4 consecutive days prior to scheduled PK sampling visit. If there was a dosage change or interruption within 4 days of the visit, no PK blood samples was collected, and an appropriate comment had to be made on the PK CRF page.

End point type	Secondary
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End point timeframe:

4 Weeks: pre-dose (0hr), 2hr & 4hr post-dose

End point values	Deferasirox			
Subject group type	Reporting group			
Number of subjects analysed	22			
Units: hr*umol/L				
geometric mean (geometric coefficient of variation)				
4 weeks: 0hr pre-dose	6.513 ($\pm$ 75.891)			
4 weeks: 2hr post-dose	48.556 ($\pm$ 58.006)			
4 weeks: 4hr post-dose	44.652 ($\pm$ 69.392)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events and serious adverse events were collected for the maximum actual duration of treatment exposure and follow up for a participant per the protocol for approximately 63.2 months.

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
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	21.1
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Reporting groups

Reporting group title	Chinese
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Reporting group description:

This group was comprised of Chinese participants only

Reporting group title	All Patients
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Reporting group description:

This group was comprised of all patients: Chinese and non-Chinese participants

Reporting group title	Non-Chinese
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Reporting group description:

This group was comprised of non-Chinese participants only

Serious adverse events	Chinese	All Patients	Non-Chinese
Total subjects affected by serious adverse events			
subjects affected / exposed	15 / 68 (22.06%)	45 / 134 (33.58%)	30 / 66 (45.45%)
number of deaths (all causes)	2	2	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Hepatocellular carcinoma			
subjects affected / exposed	0 / 68 (0.00%)	1 / 134 (0.75%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 68 (0.00%)	2 / 134 (1.49%)	2 / 66 (3.03%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Generalised oedema			

subjects affected / exposed	0 / 68 (0.00%)	1 / 134 (0.75%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malaise			
subjects affected / exposed	0 / 68 (0.00%)	1 / 134 (0.75%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	0 / 68 (0.00%)	3 / 134 (2.24%)	3 / 66 (4.55%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Bronchospasm			
subjects affected / exposed	0 / 68 (0.00%)	1 / 134 (0.75%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 68 (0.00%)	1 / 134 (0.75%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary hypertension			
subjects affected / exposed	0 / 68 (0.00%)	1 / 134 (0.75%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Compression fracture			
subjects affected / exposed	0 / 68 (0.00%)	1 / 134 (0.75%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fracture			
subjects affected / exposed	0 / 68 (0.00%)	1 / 134 (0.75%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Limb injury			
subjects affected / exposed	0 / 68 (0.00%)	1 / 134 (0.75%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin laceration			
subjects affected / exposed	0 / 68 (0.00%)	1 / 134 (0.75%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal compression fracture			
subjects affected / exposed	0 / 68 (0.00%)	1 / 134 (0.75%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal fracture			
subjects affected / exposed	0 / 68 (0.00%)	1 / 134 (0.75%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper limb fracture			
subjects affected / exposed	0 / 68 (0.00%)	1 / 134 (0.75%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 68 (0.00%)	1 / 134 (0.75%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	2 / 68 (2.94%)	2 / 134 (1.49%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Sinus tachycardia			
subjects affected / exposed	1 / 68 (1.47%)	1 / 134 (0.75%)	0 / 66 (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
Nervous system disorders			

Cerebrovascular accident			
subjects affected / exposed	0 / 68 (0.00%)	1 / 134 (0.75%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dizziness			
subjects affected / exposed	0 / 68 (0.00%)	1 / 134 (0.75%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 68 (2.94%)	6 / 134 (4.48%)	4 / 66 (6.06%)
occurrences causally related to treatment / all	0 / 2	0 / 6	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Extramedullary haemopoiesis			
subjects affected / exposed	0 / 68 (0.00%)	2 / 134 (1.49%)	2 / 66 (3.03%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemolysis			
subjects affected / exposed	0 / 68 (0.00%)	1 / 134 (0.75%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemolytic anaemia			
subjects affected / exposed	1 / 68 (1.47%)	1 / 134 (0.75%)	0 / 66 (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
Hypersplenism			
subjects affected / exposed	2 / 68 (2.94%)	2 / 134 (1.49%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Splenomegaly			
subjects affected / exposed	2 / 68 (2.94%)	2 / 134 (1.49%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytosis			

subjects affected / exposed	0 / 68 (0.00%)	1 / 134 (0.75%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Cataract			
subjects affected / exposed	0 / 68 (0.00%)	1 / 134 (0.75%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 68 (0.00%)	2 / 134 (1.49%)	2 / 66 (3.03%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain upper			
subjects affected / exposed	0 / 68 (0.00%)	1 / 134 (0.75%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 68 (0.00%)	1 / 134 (0.75%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enteritis			
subjects affected / exposed	0 / 68 (0.00%)	1 / 134 (0.75%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal hernia			
subjects affected / exposed	1 / 68 (1.47%)	2 / 134 (1.49%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	0 / 68 (0.00%)	1 / 134 (0.75%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peptic ulcer			

subjects affected / exposed	0 / 68 (0.00%)	1 / 134 (0.75%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Superior mesenteric artery syndrome			
subjects affected / exposed	0 / 68 (0.00%)	1 / 134 (0.75%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Biliary colic			
subjects affected / exposed	0 / 68 (0.00%)	1 / 134 (0.75%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis			
subjects affected / exposed	1 / 68 (1.47%)	1 / 134 (0.75%)	0 / 66 (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
Cholecystitis acute			
subjects affected / exposed	0 / 68 (0.00%)	1 / 134 (0.75%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	1 / 68 (1.47%)	4 / 134 (2.99%)	3 / 66 (4.55%)
occurrences causally related to treatment / all	0 / 1	0 / 4	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic fibrosis			
subjects affected / exposed	0 / 68 (0.00%)	1 / 134 (0.75%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Jaundice			
subjects affected / exposed	1 / 68 (1.47%)	1 / 134 (0.75%)	0 / 66 (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
Musculoskeletal and connective tissue disorders			

Osteoporosis			
subjects affected / exposed	1 / 68 (1.47%)	1 / 134 (0.75%)	0 / 66 (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
Spinal osteoarthritis			
subjects affected / exposed	1 / 68 (1.47%)	1 / 134 (0.75%)	0 / 66 (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
Tendonitis			
subjects affected / exposed	0 / 68 (0.00%)	1 / 134 (0.75%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 68 (1.47%)	2 / 134 (1.49%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epididymitis			
subjects affected / exposed	1 / 68 (1.47%)	1 / 134 (0.75%)	0 / 66 (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
Gastroenteritis			
subjects affected / exposed	0 / 68 (0.00%)	4 / 134 (2.99%)	4 / 66 (6.06%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung infection			
subjects affected / exposed	1 / 68 (1.47%)	1 / 134 (0.75%)	0 / 66 (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
Pharyngitis			
subjects affected / exposed	0 / 68 (0.00%)	2 / 134 (1.49%)	2 / 66 (3.03%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pharyngotonsillitis			

subjects affected / exposed	0 / 68 (0.00%)	1 / 134 (0.75%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	3 / 68 (4.41%)	7 / 134 (5.22%)	4 / 66 (6.06%)
occurrences causally related to treatment / all	0 / 4	0 / 9	0 / 5
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Pyelonephritis acute			
subjects affected / exposed	0 / 68 (0.00%)	1 / 134 (0.75%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	1 / 68 (1.47%)	1 / 134 (0.75%)	0 / 66 (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
Tonsillitis			
subjects affected / exposed	0 / 68 (0.00%)	1 / 134 (0.75%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	0 / 68 (0.00%)	1 / 134 (0.75%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 68 (0.00%)	3 / 134 (2.24%)	3 / 66 (4.55%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Varicella			
subjects affected / exposed	0 / 68 (0.00%)	1 / 134 (0.75%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hyperglycaemic hyperosmolar nonketotic syndrome			

subjects affected / exposed	0 / 68 (0.00%)	1 / 134 (0.75%)	1 / 66 (1.52%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Type 2 diabetes mellitus			
subjects affected / exposed	1 / 68 (1.47%)	1 / 134 (0.75%)	0 / 66 (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

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

Non-serious adverse events	Chinese	All Patients	Non-Chinese
Total subjects affected by non-serious adverse events			
subjects affected / exposed	26 / 68 (38.24%)	84 / 134 (62.69%)	58 / 66 (87.88%)
Investigations			
Blood creatinine increased			
subjects affected / exposed	1 / 68 (1.47%)	5 / 134 (3.73%)	4 / 66 (6.06%)
occurrences (all)	1	5	4
Platelet count increased			
subjects affected / exposed	13 / 68 (19.12%)	14 / 134 (10.45%)	1 / 66 (1.52%)
occurrences (all)	15	16	1
Urine protein/creatinine ratio increased			
subjects affected / exposed	0 / 68 (0.00%)	6 / 134 (4.48%)	6 / 66 (9.09%)
occurrences (all)	0	7	7
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 68 (0.00%)	8 / 134 (5.97%)	8 / 66 (12.12%)
occurrences (all)	0	10	10
Headache			
subjects affected / exposed	0 / 68 (0.00%)	27 / 134 (20.15%)	27 / 66 (40.91%)
occurrences (all)	0	84	84
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 68 (0.00%)	5 / 134 (3.73%)	5 / 66 (7.58%)
occurrences (all)	0	5	5
General disorders and administration site conditions			

Fatigue			
subjects affected / exposed	1 / 68 (1.47%)	13 / 134 (9.70%)	12 / 66 (18.18%)
occurrences (all)	1	24	23
Influenza like illness			
subjects affected / exposed	0 / 68 (0.00%)	7 / 134 (5.22%)	7 / 66 (10.61%)
occurrences (all)	0	7	7
Pyrexia			
subjects affected / exposed	3 / 68 (4.41%)	17 / 134 (12.69%)	14 / 66 (21.21%)
occurrences (all)	3	33	30
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	2 / 68 (2.94%)	7 / 134 (5.22%)	5 / 66 (7.58%)
occurrences (all)	2	7	5
Abdominal pain			
subjects affected / exposed	0 / 68 (0.00%)	15 / 134 (11.19%)	15 / 66 (22.73%)
occurrences (all)	0	40	40
Abdominal pain upper			
subjects affected / exposed	0 / 68 (0.00%)	9 / 134 (6.72%)	9 / 66 (13.64%)
occurrences (all)	0	12	12
Constipation			
subjects affected / exposed	0 / 68 (0.00%)	4 / 134 (2.99%)	4 / 66 (6.06%)
occurrences (all)	0	5	5
Dental caries			
subjects affected / exposed	0 / 68 (0.00%)	5 / 134 (3.73%)	5 / 66 (7.58%)
occurrences (all)	0	7	7
Diarrhoea			
subjects affected / exposed	1 / 68 (1.47%)	20 / 134 (14.93%)	19 / 66 (28.79%)
occurrences (all)	1	58	57
Dyspepsia			
subjects affected / exposed	0 / 68 (0.00%)	4 / 134 (2.99%)	4 / 66 (6.06%)
occurrences (all)	0	7	7
Gastritis			
subjects affected / exposed	0 / 68 (0.00%)	5 / 134 (3.73%)	5 / 66 (7.58%)
occurrences (all)	0	6	6
Nausea			

subjects affected / exposed occurrences (all)	2 / 68 (2.94%) 2	12 / 134 (8.96%) 20	10 / 66 (15.15%) 18
Toothache subjects affected / exposed occurrences (all)	0 / 68 (0.00%) 0	7 / 134 (5.22%) 10	7 / 66 (10.61%) 10
Vomiting subjects affected / exposed occurrences (all)	1 / 68 (1.47%) 1	12 / 134 (8.96%) 18	11 / 66 (16.67%) 17
Hepatobiliary disorders Cholelithiasis subjects affected / exposed occurrences (all)	1 / 68 (1.47%) 1	7 / 134 (5.22%) 7	6 / 66 (9.09%) 6
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	0 / 68 (0.00%) 0	8 / 134 (5.97%) 8	8 / 66 (12.12%) 8
Dyspnoea subjects affected / exposed occurrences (all)	0 / 68 (0.00%) 0	6 / 134 (4.48%) 6	6 / 66 (9.09%) 6
Nasal congestion subjects affected / exposed occurrences (all)	0 / 68 (0.00%) 0	11 / 134 (8.21%) 16	11 / 66 (16.67%) 16
Oropharyngeal pain subjects affected / exposed occurrences (all)	0 / 68 (0.00%) 0	16 / 134 (11.94%) 31	16 / 66 (24.24%) 31
Productive cough subjects affected / exposed occurrences (all)	0 / 68 (0.00%) 0	8 / 134 (5.97%) 11	8 / 66 (12.12%) 11
Pulmonary hypertension subjects affected / exposed occurrences (all)	0 / 68 (0.00%) 0	5 / 134 (3.73%) 5	5 / 66 (7.58%) 5
Rhinorrhoea subjects affected / exposed occurrences (all)	0 / 68 (0.00%) 0	5 / 134 (3.73%) 6	5 / 66 (7.58%) 6
Psychiatric disorders			

Anxiety subjects affected / exposed occurrences (all)	0 / 68 (0.00%) 0	4 / 134 (2.99%) 4	4 / 66 (6.06%) 4
Insomnia subjects affected / exposed occurrences (all)	0 / 68 (0.00%) 0	5 / 134 (3.73%) 9	5 / 66 (7.58%) 9
Renal and urinary disorders Dysuria subjects affected / exposed occurrences (all)	0 / 68 (0.00%) 0	4 / 134 (2.99%) 4	4 / 66 (6.06%) 4
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	0 / 68 (0.00%) 0	8 / 134 (5.97%) 11	8 / 66 (12.12%) 11
Back pain subjects affected / exposed occurrences (all)	0 / 68 (0.00%) 0	16 / 134 (11.94%) 16	16 / 66 (24.24%) 16
Flank pain subjects affected / exposed occurrences (all)	0 / 68 (0.00%) 0	4 / 134 (2.99%) 4	4 / 66 (6.06%) 4
Myalgia subjects affected / exposed occurrences (all)	0 / 68 (0.00%) 0	10 / 134 (7.46%) 13	10 / 66 (15.15%) 13
Osteoporosis subjects affected / exposed occurrences (all)	1 / 68 (1.47%) 1	5 / 134 (3.73%) 5	4 / 66 (6.06%) 4
Pain in extremity subjects affected / exposed occurrences (all)	0 / 68 (0.00%) 0	6 / 134 (4.48%) 7	6 / 66 (9.09%) 7
Infections and infestations Conjunctivitis subjects affected / exposed occurrences (all)	0 / 68 (0.00%) 0	5 / 134 (3.73%) 6	5 / 66 (7.58%) 6
Gastroenteritis subjects affected / exposed occurrences (all)	1 / 68 (1.47%) 1	10 / 134 (7.46%) 19	9 / 66 (13.64%) 18

Influenza			
subjects affected / exposed	0 / 68 (0.00%)	11 / 134 (8.21%)	11 / 66 (16.67%)
occurrences (all)	0	14	14
Pharyngitis			
subjects affected / exposed	0 / 68 (0.00%)	11 / 134 (8.21%)	11 / 66 (16.67%)
occurrences (all)	0	17	17
Tonsillitis			
subjects affected / exposed	0 / 68 (0.00%)	12 / 134 (8.96%)	12 / 66 (18.18%)
occurrences (all)	0	21	21
Upper respiratory tract infection			
subjects affected / exposed	7 / 68 (10.29%)	34 / 134 (25.37%)	27 / 66 (40.91%)
occurrences (all)	8	68	60
Urinary tract infection			
subjects affected / exposed	2 / 68 (2.94%)	10 / 134 (7.46%)	8 / 66 (12.12%)
occurrences (all)	2	11	9
Metabolism and nutrition disorders			
Hyperphosphataemia			
subjects affected / exposed	0 / 68 (0.00%)	8 / 134 (5.97%)	8 / 66 (12.12%)
occurrences (all)	0	10	10
Hyperuricaemia			
subjects affected / exposed	1 / 68 (1.47%)	6 / 134 (4.48%)	5 / 66 (7.58%)
occurrences (all)	1	7	6
Vitamin D deficiency			
subjects affected / exposed	0 / 68 (0.00%)	4 / 134 (2.99%)	4 / 66 (6.06%)
occurrences (all)	0	4	4

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 June 2013	Amendment 1, issued after the inclusion of 35 patients, introduced the following changes: Extended study duration up to five years, as the previous study generated limited long-term data; Secondary objectives were added to assess the efficacy of treatment in patients with very high LIC, and in those who need re-treatment after reaching the target LIC during the study, to reflect the extended study duration; Added interruption of treatment when SF < 300 ng/mL based on safety data from another study, and in accordance with the label recommendation of deferasirox treatment interruption in NTDT patients with iron overload; Dose adjustments based on LIC were modified for clarification and the extended study duration; The analysis of serum transaminases, bilirubin, and alkaline phosphatase were added to the schedule of assessments, per recommended safety monitoring. The schedule of assessments was modified for the extended study duration; Clarifications regarding sample handling, ocular and auditory examination details, and new pregnancy language were included.
04 September 2014	Amendment 2, issued after closure of study recruitment and 134 patients enrolled. Following changes were made in alignment with the approved deferasirox prescribing information: Provided guidance on treating patients with moderate hepatic impairment and immediate discontinuation if Stevens-Johnson syndrome or severe hepatic impairment occurs; Changed the "highly effective" contraception methods to "effective". The former was inadvertently introduced into protocol Amendment 1; Added additional guidance regarding treatment discontinuation of patients with creatinine clearance < 40 mL/min or serum creatinine > 2×ULN, and caution should be used in patients with creatinine clearance between 40 to < 60 mL/min; Added additional guidance regarding the concomitant administration of deferasirox with CYP1A2 substrates. Vitamin C was moved from the prohibited concomitant medication category to drugs that should be administered with caution; Criteria for patient withdrawal, definition of the end of study, the maximum recommended restart dose and visit schedules were clarified; this amendment also clarified the timing of the two analyses of this study. A CSR was written based on the 1-year analysis (report date 12-Jun-2015); this final CSR is based on the final analysis at the end of the study, after 5 years of follow up

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use <https://www.novctrd.com/CtrdWeb/home.novfor> complete trial results.

Notes: