



Clinical trial results:

Phase II, open-label, single-arm, multicenter study to evaluate the efficacy and safety of deferasirox in combination with deferoxamine followed by deferasirox monotherapy in patients with severe cardiac iron overload due to chronic blood transfusion (HYPERION)

Summary

EudraCT number	2010-021062-29
Trial protocol	GB IT GR
Global end of trial date	18 November 2013

Results information

Result version number	v1 (current)
This version publication date	13 July 2016
First version publication date	07 August 2015

Trial information

Trial identification

Sponsor protocol code	CICL670A2214
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01254227
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002 , Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111 ,
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111 ,

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes
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	18 November 2013
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	18 November 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the effect of DFX-DFO combination therapy followed by DFX monotherapy on myocardial iron content as depicted by change in cardiac T2* at Month 12

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	19 January 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects**Subjects enrolled per country**

Country: Number of subjects enrolled	United Kingdom: 3
Country: Number of subjects enrolled	Greece: 2
Country: Number of subjects enrolled	Italy: 14
Country: Number of subjects enrolled	Egypt: 15
Country: Number of subjects enrolled	Thailand: 7
Country: Number of subjects enrolled	Turkey: 18
Country: Number of subjects enrolled	Taiwan: 1
Worldwide total number of subjects	60
EEA total number of subjects	19

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)	4
Adolescents (12-17 years)	10
Adults (18-64 years)	46
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A screening period (up to 50 days) was used to assess eligibility of patients. Patients with confirmed eligibility discontinued any current chelation therapy and underwent a 5-day washout period prior to commencing the treatment with DFX-DFO combination.

Period 1

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

Arms

Arm title	All Patients
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Arm description:

The investigational study drugs were the following:

- Deferasirox + Deferoxamine = DFX-DFO combination treatment
- Deferasirox = DFX monotherapy

All patients started on the combination therapy. After 6 months of treatment, patients could be switched to DFX monotherapy depending on cardiac T2* assessment

Arm type	Experimental
Investigational medicinal product name	Deferasirox
Investigational medicinal product code	
Other name	ICL670, Exjade®
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Clinical supplies of Deferasirox consisted of dispersible tablets in strengths of 125 mg, 250 mg and 500 mg. All patients started with a daily dose of 20 mg/kg of DFX. At the end of the 1st month, DFX dose was increased to 30 mg/kg/day, unless the patient met any of the criteria for dose reduction or drug interruption. Further dose increases of DFX to 40 mg/kg/day was done after the 6-month assessment of cardiac T2, evaluation of cardiac function and safety.

Investigational medicinal product name	Deferoxamine
Investigational medicinal product code	
Other name	DFO, Desferal®
Pharmaceutical forms	Powder for dispersion for infusion
Routes of administration	Parenteral use

Dosage and administration details:

Clinical supplies of Deferoxamine vials consisted of a powder formulation in vials of 500 mg and 2000 mg. Concomitantly, 40 mg/kg/day DFO for 5 days/week for at least 8 hours/day was administered. Dose escalation of DFO was not permitted in the study.

Number of subjects in period 1	All Patients
Started	60
Completion of 12 months	39
Completion of 24 months	34
Completed	34
Not completed	26
Adverse event, serious fatal	1
Consent withdrawn by subject	6
Adverse event, non-fatal	5
Lost to follow-up	6
Abnormal test procedure result(s)	5
'Administrative problems '	2
Protocol deviation	1

Baseline characteristics

Reporting groups

Reporting group title	All Patients
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Reporting group description:

The investigational study drugs were the following:

- Deferasirox + Deferoxamine = DFX-DFO combination treatment
- Deferasirox = DFX monotherapy

All patients started on the combination therapy. After 6 months of treatment, patients could be switched to DFX monotherapy depending on cardiac T2* assessment

Reporting group values	All Patients	Total	
Number of subjects	60	60	
Age categorical			
Units: Subjects			
2 y - <12 y	4	4	
12 y - <18 y	10	10	
18 y - <65 y	46	46	
Age continuous			
Units: years			
arithmetic mean	22.8		
standard deviation	± 7.33	-	
Gender categorical			
Units: Subjects			
Female	32	32	
Male	28	28	

End points

End points reporting groups

Reporting group title	All Patients
Reporting group description: The investigational study drugs were the following: <ul style="list-style-type: none">• Deferasirox + Deferoxamine = DFX-DFO combination treatment• Deferasirox = DFX monotherapy All patients started on the combination therapy. After 6 months of treatment, patients could be switched to DFX monotherapy depending on cardiac T2* assessment	
Subject analysis set title	Full Analysis Set (FAS)
Subject analysis set type	Full analysis
Subject analysis set description: The FAS includes all patients to whom study treatment had been assigned. Patients were considered evaluable for the efficacy endpoint if they had received at least one dose of study treatment and had baseline and a post baseline assessment prior to or on the time of the assessment of the corresponding efficacy endpoint. Patients who did not have a baseline value or did not have any post-baseline value of an efficacy endpoint were excluded from the analysis of this endpoint.	
Subject analysis set title	Per-Protocol Set (PPS)
Subject analysis set type	Per protocol
Subject analysis set description: All enrolled patients who received at least 6 months of study treatment, had baseline and a postbaseline T2* value before or at Month 12, and without major protocol deviations (including myocardial T2* value < 5 or ≥ 10 ms.	

Primary: The change in cardiac iron content as measured by cardiac T2* at Month 12 divided by the cardiac T2* value at Baseline

End point title	The change in cardiac iron content as measured by cardiac T2* at Month 12 divided by the cardiac T2* value at Baseline ^[1]
End point description: Cardiac T2* is the most sensitive and reproducible test in detecting myocardial iron load. A cardiac T2* value of <10 ms is defined as severe cardiac iron overload. Patients who do not have baseline T2* or do not have any post-baseline T2* are excluded from the analysis.	
End point type	Primary
End point timeframe: Baseline and Month 12	

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 analyses have not been performed for this primary end point.

End point values	Full Analysis Set (FAS)	Per-Protocol Set (PPS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	52 ^[2]	51 ^[3]		
Units: ms				
geometric mean (confidence interval 95%)				
Baseline	7.19 (6.83 to 7.58)	7.05 (6.65 to 7.46)		
Month 12	7.68 (7.1 to 8.3)	7.73 (7.14 to 8.36)		
Change from Baseline	1.09 (1.04 to 1.15)	1.1 (1.04 to 1.16)		

Notes:

[2] - Fifty-two patients (86.7%) were evaluable for this endpoint in the FAS.

[3] - 51 patients (85.0%) in the PPS and were included in the calculation of the primary endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of patients achieving MRI-measured cardiac T2* ≥ 10 ms (but at least 10% relative increase in cardiac T2* from baseline)

End point title	Percentage of patients achieving MRI-measured cardiac T2* ≥ 10 ms (but at least 10% relative increase in cardiac T2* from baseline)
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End point description:

Only evaluable patients at each visit were used as the denominator for the calculation of proportion.

End point type	Secondary
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End point timeframe:

Months 6, 12, 18 and 24

End point values	Full Analysis Set (FAS)			
Subject group type	Subject analysis set			
Number of subjects analysed	60			
Units: percentage of patients				
number (confidence interval 95%)				
Month 6 (n=6)	12.5 (31.99 to 62.99)			
Month 12 (n=10)	19.23 (5.86 to 24.7)			
Month 18 (n=11)	33.33 (10.8 to 31.9)			
Month 24 (n=17)	47.22 (19.75 to 50.39)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in cardiac iron content as measured by T2* divided by baseline T2*

End point title	Change in cardiac iron content as measured by T2* divided by baseline T2*
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End point description:

End point type	Secondary
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End point timeframe:

Months 6, 18 and 24

End point values	Full Analysis Set (FAS)			
Subject group type	Subject analysis set			
Number of subjects analysed	60			
Units: GM ratio				
geometric mean (confidence interval 95%)				
Month 6 Change from Baseline (n=48)	1.02 (0.98 to 1.07)			
Month 18 Change from Baseline (n=33)	1.17 (1.08 to 1.28)			
Month 24 Change from Baseline (n=36)	1.3 (1.17 to 1.44)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in MRI-measured parameters of the left and right ventricle: ejection fraction (LVEF, RVEF), ventricular volumes, and masses

End point title	Change in MRI-measured parameters of the left and right ventricle: ejection fraction (LVEF, RVEF), ventricular volumes, and masses
End point description:	
End point type	Secondary
End point timeframe:	
Months 6, 12, 18 and 24	

End point values	Full Analysis Set (FAS)			
Subject group type	Subject analysis set			
Number of subjects analysed	60			
Units: percent				
arithmetic mean (standard deviation)				
LVEF Month 6 absolute change from Baseline (n=48)	0.1 (± 4.62)			
LVEF Month 12 absolute change from Baseline (n=45)	-0.2 (± 4.84)			
LVEF Month 18 absolute change from Baseline (n=33)	0.6 (± 7.04)			
LVEF Month 24 absolute change from Baseline (n=36)	0.9 (± 5.98)			
RVEF Month 6 absolute change from Baseline (n=47)	-1.2 (± 5.35)			
RVEF Month 12 absolute change from Baseline (n=45)	-1.6 (± 4.4)			

RVEF Month 18 absolute change from Baseline (n=33)	-2.1 (± 6.1)			
RVEF Month 24 absolute change from Baseline (n=36)	-1.4 (± 4.25)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to achieve T2* ≥ 10 ms (but at least 10% relative increase from baseline)

End point title	Time to achieve T2* ≥ 10 ms (but at least 10% relative increase from baseline)
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End point description:

End point type	Secondary
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End point timeframe:

Month 24

End point values	Full Analysis Set (FAS)			
Subject group type	Subject analysis set			
Number of subjects analysed	60 ^[4]			
Units: ms				
median (confidence interval 95%)	722 (520 to 999)			

Notes:

[4] - 999.0 = the upper value was not estimable

Statistical analyses

No statistical analyses for this end point

Secondary: Cardiac Iron Concentration Levels During the Study

End point title	Cardiac Iron Concentration Levels During the Study
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End point description:

End point type	Secondary
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End point timeframe:

Baseline, Month 6, 12, 18 and Month 24

End point values	Full Analysis Set (FAS)			
Subject group type	Subject analysis set			
Number of subjects analysed	60			
Units: mg Fe/g dw				
arithmetic mean (standard deviation)				
Baseline (n=60)	4.18 (± 1.045)			
Month 6 (n=48)	4.31 (± 1.442)			
Month 12 (n=46)	3.93 (± 1.429)			
Month 18 (n=33)	3.51 (± 1.348)			
Month 24 (n=36)	3.14 (± 1.381)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

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

Adverse event reporting additional description:

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

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	All patients
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Reporting group description:

All patients

Serious adverse events	All patients		
Total subjects affected by serious adverse events			
subjects affected / exposed	17 / 60 (28.33%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	1		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Ovarian germ cell teratoma benign			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Reproductive system and breast disorders			
Fallopian tube cyst			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ovarian cyst			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Chest injury			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Spinal column injury			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Congenital, familial and genetic disorders			
Dermoid cyst			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Altered state of consciousness			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Ischaemic stroke			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
VIIth nerve paralysis			

subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 60 (3.33%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Irritable bowel syndrome			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pancreatitis acute			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Reflux gastritis			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Biliary colic			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Cholecystitis			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Drug reaction with eosinophilia and systemic symptoms			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Costochondritis			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Myalgia			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Abscess neck			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bronchitis			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Febrile infection			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infection			

subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pharyngitis			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Calcium deficiency			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hyperglycaemia			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypocalcaemia			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypoglycaemia			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypophosphataemia			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Type 1 diabetes mellitus			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	All patients		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	46 / 60 (76.67%)		
Investigations			
Blood creatinine increased			
subjects affected / exposed	5 / 60 (8.33%)		
occurrences (all)	6		
Electrocardiogram T wave amplitude decreased			
subjects affected / exposed	3 / 60 (5.00%)		
occurrences (all)	4		
Electrocardiogram T wave inversion			
subjects affected / exposed	4 / 60 (6.67%)		
occurrences (all)	4		
Urine protein/creatinine ratio increased			
subjects affected / exposed	6 / 60 (10.00%)		
occurrences (all)	8		
Cardiac disorders			
Atrioventricular block first degree			
subjects affected / exposed	3 / 60 (5.00%)		
occurrences (all)	4		
Nervous system disorders			
Headache			
subjects affected / exposed	9 / 60 (15.00%)		
occurrences (all)	23		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	4 / 60 (6.67%)		
occurrences (all)	6		
Pyrexia			
subjects affected / exposed	14 / 60 (23.33%)		
occurrences (all)	20		
Ear and labyrinth disorders			

Deafness neurosensory subjects affected / exposed occurrences (all)	3 / 60 (5.00%) 3		
Gastrointestinal disorders			
Abdominal pain subjects affected / exposed occurrences (all)	8 / 60 (13.33%) 24		
Abdominal pain upper subjects affected / exposed occurrences (all)	4 / 60 (6.67%) 8		
Diarrhoea subjects affected / exposed occurrences (all)	8 / 60 (13.33%) 14		
Enteritis subjects affected / exposed occurrences (all)	3 / 60 (5.00%) 3		
Nausea subjects affected / exposed occurrences (all)	8 / 60 (13.33%) 19		
Toothache subjects affected / exposed occurrences (all)	7 / 60 (11.67%) 11		
Vomiting subjects affected / exposed occurrences (all)	3 / 60 (5.00%) 4		
Respiratory, thoracic and mediastinal disorders			
Cough subjects affected / exposed occurrences (all)	5 / 60 (8.33%) 9		
Oropharyngeal pain subjects affected / exposed occurrences (all)	6 / 60 (10.00%) 6		
Renal and urinary disorders			
Proteinuria subjects affected / exposed occurrences (all)	6 / 60 (10.00%) 10		

Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Back pain subjects affected / exposed occurrences (all) Pain in extremity subjects affected / exposed occurrences (all)	8 / 60 (13.33%) 11 12 / 60 (20.00%) 20 4 / 60 (6.67%) 4		
Infections and infestations Gastroenteritis subjects affected / exposed occurrences (all) Influenza subjects affected / exposed occurrences (all) Nasopharyngitis subjects affected / exposed occurrences (all) Sinusitis subjects affected / exposed occurrences (all) Tonsillitis subjects affected / exposed occurrences (all) Tooth abscess subjects affected / exposed occurrences (all) Upper respiratory tract infection subjects affected / exposed occurrences (all)	4 / 60 (6.67%) 4 8 / 60 (13.33%) 18 9 / 60 (15.00%) 11 3 / 60 (5.00%) 3 4 / 60 (6.67%) 5 5 / 60 (8.33%) 7 10 / 60 (16.67%) 10		
Metabolism and nutrition disorders Hypocalcaemia subjects affected / exposed occurrences (all)	3 / 60 (5.00%) 3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported