Clinical trial results:
A multicenter, Phase 2, randomized, open label, active-controlled, parallel-group study investigating the safety, tolerability, and efficacy of different dose levels of ACP-001 administered once weekly versus standard daily rhGH replacement therapy in pre-pubertal children with Growth Hormone Deficiency (GHD)

Summary

EudraCT number	2012-002787-27
Trial protocol	HU DE CZ GR BG SI FR
Global end of trial date	22 July 2015

Results information

Result version number	v1 (current)
This version publication date	04 February 2017
First version publication date	04 February 2017

Trial information

Trial identification

Sponsor protocol code	ACP-001_CT-004

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01947907
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Ascendis Pharma A/S
Sponsor organisation address	Tuborg Boulevard 5, Hellerup, Denmark, DK-2900
Public contact	Michael Beckert, VP Clinical Development , Ascendis Pharma A/S, +49 172 155 2596, mb@ascendispharma.com
Scientific contact	Michael Beckert, VP Clinical Development , Ascendis Pharma A/S, +49 172 155 2596, mb@ascendispharma.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	28 January 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	22 July 2015
Global end of trial reached?	Yes
Global end of trial date	22 July 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the safety and PK/PD profile of three different ACP-001 doses to that of a commercially available standard daily rhGH formulation in pre-pubertal children with growth failure due to GHD.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	16 July 2013
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	Belarus: 8
Country: Number of subjects enrolled	Poland: 1
Country: Number of subjects enrolled	Bulgaria: 1
Country: Number of subjects enrolled	Greece: 3
Country: Number of subjects enrolled	Hungary: 1
Country: Number of subjects enrolled	Egypt: 7
Country: Number of subjects enrolled	Russian Federation: 21
Country: Number of subjects enrolled	Turkey: 3
Country: Number of subjects enrolled	Ukraine: 7
Country: Number of subjects enrolled	Romania: 3
Worldwide total number of subjects	55
EEA total number of subjects	9

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)	55
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 170 subjects from 38 initiated centers were screened for inclusion into the study of which 115 subjects were classified as screen failures. A total of 55 subjects were randomized at 20 centers in 10 countries located in Europe and North Africa (EEA and non-EEA).

Pre-assignment

Screening details:

A total of 170 subjects from 30 recruiting centers were screened for inclusion into the study of which 115 subjects were classified as screen failures.

Pre-assignment period milestones

Number of subjects started	55
Number of subjects completed	53

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Consent withdrawn by subject: 2

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort 1

Arm description:

ACP-001 once weekly in a dose equivalent to 0.14 mg rhGH/kg/week

Arm type	Experimental
Investigational medicinal product name	ACP-001
Investigational medicinal product code	
Other name	TransCon PEG hGH
Pharmaceutical forms	Powder for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

ACP-001 was administered in a weekly dose strength equivalent to 0.14 mg rhGH/kg/week, for 26 weeks. Provided in glass vials, reconstituted with sterile water for injection, administered in the morning hours.

Arm title	Cohort 2

Arm description:

ACP-001 once weekly in a dose equivalent to 0.21 mg rhGH/kg/week

Arm type	Experimental
Investigational medicinal product name	ACP-001
Investigational medicinal product code	
Other name	TransCon PEG hGH
Pharmaceutical forms	Powder for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

ACP-001 was administered in a weekly dose strength equivalent to 0.21 mg rhGH/kg/week, for 26

weeks. Provided in glass vials, reconstituted with sterile water for injection, administered in the morning hours.

Arm title	Cohort 3
Arm description:	
ACP-001 once weekly in a dose equivalent to 0.30 mg rhGH/kg/week	
Arm type	Experimental
Investigational medicinal product name	ACP-001
Investigational medicinal product code	
Other name	TransCon PEG hGH
Pharmaceutical forms	Powder for injection
Routes of administration	Subcutaneous use
Dosage and administration details:	
ACP-001 was administered in a weekly dose strength equivalent to 0.30 mg rhGH/kg/week, for 26 weeks. Provided in glass vials, reconstituted with sterile water for injection, administered in the morning hours.	

Arm title	Cohort 4
Arm description:	
Genotropin® once daily in a dose equivalent to 0.21 mg rhGH/kg/week	
Arm type	Active comparator
Investigational medicinal product name	Genotropin®
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for solution for injection
Routes of administration	Subcutaneous use
Dosage and administration details:	
Genotropin® was administered daily in a standard daily dose of 0.03 mg rhGH/kg/day (equivalent to 0.21 mg rhGH/kg/week), for 26 weeks. Provided as sterile white lyophilized powder dispensed in a two-chamber cartridge, administered with an injection device in the evening hours.	

Number of subjects in period 1[1]	Cohort 1	Cohort 2	Cohort 3
Started	12	14	14
Completed	12	14	14

Number of subjects in period 1[1]	Cohort 4
Started	13
Completed	13

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: During the pre-assignment period 2 subjects withdrew the consent.

Baseline characteristics

Reporting groups	
Reporting group title	Cohort 1
Reporting group description:	
ACP-001 once weekly in a dose equivalent to 0.14 mg rhGH/kg/week	
Reporting group title	Cohort 2
Reporting group description:	
ACP-001 once weekly in a dose equivalent to 0.21 mg rhGH/kg/week	
Reporting group title	Cohort 3
Reporting group description:	
ACP-001 once weekly in a dose equivalent to 0.30 mg rhGH/kg/week	
Reporting group title	Cohort 4
Reporting group description:	
Genotropin® once daily in a dose equivalent to 0.21 mg rhGH/kg/week	

Reporting group values	Cohort 1	Cohort 2	Cohort 3
Number of subjects	12	14	14
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	12	14	14
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	7.98	8.24	7.32
standard deviation	± 2.889	± 2.13	± 2.784
Gender categorical Units: Subjects			
Female	3	4	5
Male	9	10	9
Race Units: Subjects			
White	12	14	14
Baseline IGF-I SDS Units: --			
arithmetic mean	-2.034	-2.017	-2.19
standard deviation	± 0.7429	± 0.7713	± 0.7169
Baseline Height SDS Units: --			
arithmetic mean	-3.05	-2.75	-3.17

standard deviation	± 1.127	± 0.383	± 1.04
Screening Peak GH Levels			
The highest GH peak serum level of the two GH stimulation tests at Screening was used for calculation.			
Units: ng/mL			
arithmetic mean	5.09	5.16	4.44
standard deviation	± 3.169	± 2.598	± 2.77

Reporting group values	Cohort 4	Total	
Number of subjects	13	53	
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)	13	53	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous			
Units: years			
arithmetic mean	7.53		
standard deviation	± 2.483	-	
Gender categorical			
Units: Subjects			
Female	3	15	
Male	10	38	
Race			
Units: Subjects			
White	13	53	
Baseline IGF-I SDS			
Units: --			
arithmetic mean	-2.502		
standard deviation	± 0.896	-	
Baseline Height SDS			
Units: --			
arithmetic mean	-3.27		
standard deviation	± 1.077	-	
Screening Peak GH Levels			
The highest GH peak serum level of the two GH stimulation tests at Screening was used for calculation.			
Units: ng/mL			
arithmetic mean	5.15		
standard deviation	± 3.068	-	

Subject analysis sets

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

Subject analysis set description:

The Safety Analysis Set (SAS) includes all patients who receive at least one dose of planned study medication.

Subject analysis set title	Full Analysis Set
Subject analysis set type	Full analysis

Subject analysis set description:

The Full Analysis Set (FAS) includes all patients who are randomized, receive at least one dose of planned study medication and provide a baseline and at least one post-baseline height measurement value.

Subject analysis set title	Per Protocol Analysis Set
Subject analysis set type	Per protocol

Subject analysis set description:

Patients with major protocol deviations or premature termination of the treatment due to reasons that were definitely not related to study medication will be excluded from the Per-Protocol (PP) analysis. Major protocol deviations will be detailed in the Protocol Deviation Plan and will include aspects of:
o availability of measurements,
o non-compliance with respect to assigned study medication, assigned dose level and / or dose regimen,
o non-compliance to visit schedule (flexibility defined by visit windows),
o failure to satisfy inclusion or exclusion criteria,
o taking any not permitted concomitant medication during the study,
o other parameters.

Reporting group values	Safety Analysis Set	Full Analysis Set	Per Protocol Analysis Set
Number of subjects	53	53	51
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	53	53	51
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	7.76	7.76	7.76
standard deviation	± 2.53	± 2.53	± 2.542
Gender categorical Units: Subjects			
Female	15	15	15
Male	38	38	36
Race Units: Subjects			
White	53	53	51
Baseline IGF-I SDS Units: --			
arithmetic mean			
standard deviation	±	±	±
Baseline Height SDS Units: --			
arithmetic mean			

standard deviation	±	±	±
Screening Peak GH Levels			
The highest GH peak serum level of the two GH stimulation tests at Screening was used for calculation.			
Units: ng/mL arithmetic mean standard deviation	±	±	±

End points

End points reporting groups

Reporting group title	Cohort 1
Reporting group description:	
ACP-001 once weekly in a dose equivalent to 0.14 mg rhGH/kg/week	
Reporting group title	Cohort 2
Reporting group description:	
ACP-001 once weekly in a dose equivalent to 0.21 mg rhGH/kg/week	
Reporting group title	Cohort 3
Reporting group description:	
ACP-001 once weekly in a dose equivalent to 0.30 mg rhGH/kg/week	
Reporting group title	Cohort 4
Reporting group description:	
Genotropin® once daily in a dose equivalent to 0.21 mg rhGH/kg/week	
Subject analysis set title	Safety Analysis Set
Subject analysis set type	Safety analysis
Subject analysis set description:	
The Safety Analysis Set (SAS) includes all patients who receive at least one dose of planned study medication.	
Subject analysis set title	Full Analysis Set
Subject analysis set type	Full analysis
Subject analysis set description:	
The Full Analysis Set (FAS) includes all patients who are randomized, receive at least one dose of planned study medication and provide a baseline and at least one post-baseline height measurement value.	
Subject analysis set title	Per Protocol Analysis Set
Subject analysis set type	Per protocol
Subject analysis set description:	
Patients with major protocol deviations or premature termination of the treatment due to reasons that were definitely not related to study medication will be excluded from the Per-Protocol (PP) analysis. Major protocol deviations will be detailed in the Protocol Deviation Plan and will include aspects of: o availability of measurements, o non-compliance with respect to assigned study medication, assigned dose level and / or dose regimen, o non-compliance to visit schedule (flexibility defined by visit windows), o failure to satisfy inclusion or exclusion criteria, o taking any not permitted concomitant medication during the study, o other parameters.	

Primary: Incidence of anti-hGH binding antibody formation

End point title	Incidence of anti-hGH binding antibody formation[1]
End point description:	
Number of subjects with positive results for Anti-hGH binding antibodies at two consecutive post-dose visits	
End point type	Primary
End point timeframe:	
Visit 2 - Visit 5	

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: As this is an exploratory study, no hypothesis tests were performed.

End point values	Cohort 1	Cohort 2	Cohort 3	Cohort 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	14	14	13
Units: Number of subjects with positive results	1	0	0	0

Statistical analyses

No statistical analyses for this end point

Primary: Incidence of anti-hGH neutralizing antibody formation

End point title	Incidence of anti-hGH neutralizing antibody formation[2]

End point description:

Number of subjects with positive results for anti-hGH neutralizing antibodies at two consecutive post-dose visits

End point type	Primary

End point timeframe:

Visit 2 - Visit 5

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: As this is an exploratory study, no hypothesis tests were performed.

End point values	Cohort 1	Cohort 2	Cohort 3	Cohort 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	14	14	13
Units: Number of subjects with positive results	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Primary: Local tolerability (assessed by the patient and the investigator)

End point title	Local tolerability (assessed by the patient and the

End point description:

Overview of subject number of local tolerability assessment results

End point type	Primary

End point timeframe:

From start of study treatment and continues until the end of the patient’s participation in the study

Notes:

[3] - 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: As this is an exploratory study, no hypothesis tests were performed.

End point values	Cohort 1	Cohort 2	Cohort 3	Cohort 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	14	14	13
Units: Number of Subjects with ISRs	7	6	6	6

Statistical analyses

No statistical analyses for this end point

Primary: Cmax of hGH

End point title	Cmax of hGH[4]

End point description:

As part of the following endpoint:
PK profile of serum hGH from ACP-001 treated patients compared between ACP-001 dose groups and to the PK profile of hGH from the daily rhGH group during V1 and V3

Uncorrected Cmax (maximum value of concentration) values at Week 13

End point type	Primary

End point timeframe:

0 hours to 168 hours at Visit 3 (Week 13)

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: As this is an exploratory study, no hypothesis tests were performed.

End point values	Cohort 1	Cohort 2	Cohort 3	Cohort 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	14	14	13
Units: ng/mL				
arithmetic mean (standard deviation)	12.558 (± 8.678)	13.418 (± 9.428)	31.8 (± 17.499)	16.612 (± 12.777)

Statistical analyses

No statistical analyses for this end point

Primary: AUC0-168h of hGH

End point title	AUC0-168h of hGH[5]

End point description:

As part of the following endpoint:
PK profile of serum hGH from ACP-001 treated patients compared between ACP-001 dose groups and to the PK profile of hGH from the daily rhGH group during V1 and V3.

Uncorrected AUC0-168h (area under the curve from 0h to 168h) values at Week 13
For Cohort 4 AUC0-24h*7 has been presented

End point type	Primary

End point timeframe:

0 hours to 168 hours at Visit 3 (Week 13)

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: As this is an exploratory study, no hypothesis tests were performed.

End point values	Cohort 1	Cohort 2	Cohort 3	Cohort 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	14	14	13
Units: h*ng/mL				
arithmetic mean (standard deviation)	696.34 (± 410.096)	787.41 (± 483.169)	2167.43 (± 1064.729)	556.88 (± 412.618)

Statistical analyses

No statistical analyses for this end point

Primary: Etrough of IGF-I

End point title	Etrough of IGF-I[6][7]

End point description:

As part of the following endpoint:
PD profile of serum IGF-I during V1 and V3 compared between the ACP-001 dose groups and to the daily rhGH group.

Uncorrected Etrough (the pre-dose efficacy response) values at Week 13

End point type	Primary

End point timeframe:

0 hours to 168 hours at Visit 3 (Week 13)

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: As this is an exploratory study, no hypothesis tests were performed.

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The difference in the dosing regimen of investigational product and comparator does not enable to consistently compare PD parameters across treatments.

End point values	Cohort 1	Cohort 2	Cohort 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	12	14	14	
Units: ng/mL				
arithmetic mean (standard deviation)	97.17 (± 50.53)	156 (± 76.235)	167.83 (± 74.01)	

Statistical analyses

No statistical analyses for this end point

Primary: Emax of IGF-I

End point title	Emax of IGF-I[8][9]

End point description:

As part of the following endpoint:
PD profile of serum IGF-I during V1 and V3 compared between the ACP-001 dose groups and to the daily rhGH group.

Uncorrected Emax (the maximum observed efficacy response) values at Week 13

End point type	Primary

End point timeframe:

0 hours to 168 hours at Visit 3 (Week 13)

Notes:

[8] - 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: As this is an exploratory study, no hypothesis tests were performed.

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The difference in the dosing regimen of investigational product and comparator does not enable to consistently compare PD parameters across treatments.

End point values	Cohort 1	Cohort 2	Cohort 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	12	14	14	
Units: ng/mL				
arithmetic mean (standard deviation)	209.5 (± 120.189)	276 (± 126.632)	289.92 (± 129.469)	

Statistical analyses

No statistical analyses for this end point

Primary: AUEC0-168h of IGF-I

End point title	AUEC0-168h of IGF-I[10][11]

End point description:

As part of the following endpoint:
PD profile of serum IGF-I during V1 and V3 compared between the ACP-001 dose groups and to the daily rhGH group.

Uncorrected AUEC0-168 (Area Under the Efficacy Curve (AUC) from 0h to 168h) values at Week 13

End point type	Primary

End point timeframe:

0 hours to 168 hours at Visit 3 (Week 13)

Notes:

[10] - 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: As this is an exploratory study, no hypothesis tests were performed.

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The difference in the dosing regimen of investigational product and comparator does not enable to consistently compare PD parameters across treatments.

End point values	Cohort 1	Cohort 2	Cohort 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	12	14	14	
Units: h*ng/mL				
arithmetic mean (standard deviation)	28526.19 (± 15756.44)	35591.94 (± 17068.59)	36066.01 (± 17379.44)	

Statistical analyses

No statistical analyses for this end point

Secondary: Annualized HV during treatment with ACP-001 or daily rhGH at the end of 6 months, for each ACP-001 dose group and for the daily rhGH dose group

End point title	Annualized HV during treatment with ACP-001 or daily rhGH at the end of 6 months, for each ACP-001 dose group and for the daily rhGH dose group

End point description:

Descriptive Statistics of Annualized Height Velocity

End point type	Secondary

End point timeframe:

Baseline to 6 Months (Visit 5)

End point values	Cohort 1	Cohort 2	Cohort 3	Cohort 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	14	14	13
Units: cm/year				
arithmetic mean (standard deviation)	11.93 (± 4.066)	12.89 (± 3.464)	13.85 (± 4.009)	11.64 (± 3.592)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From start of study treatment and continues until the end of the patient's participation in the study (until 4 weeks after stop of patient's study participation for serious adverse events).

Adverse event reporting additional description:

Treatment-emergent adverse events are summarized.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.1

Reporting groups

Reporting group title	Cohort 1

Reporting group description:

ACP-001 once weekly in a dose equivalent to 0.14 mg rhGH/kg/week

Reporting group title	Cohort 2

Reporting group description:

ACP-001 once weekly in a dose equivalent to 0.21 mg rhGH/kg/week

Reporting group title	Cohort 3

Reporting group description:

ACP-001 once weekly in a dose equivalent to 0.30 mg rhGH/kg/week

Reporting group title	Cohort 4

Reporting group description:

Genotropin® once daily in a dose equivalent to 0.21 mg rhGH/kg/week

Serious adverse events	Cohort 1	Cohort 2	Cohort 3
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 12 (8.33%)	0 / 14 (0.00%)	0 / 14 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Gastrointestinal disorders			
Inguinal hernia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 14 (0.00%)	0 / 14 (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

Serious adverse events	Cohort 4		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 13 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

Gastrointestinal disorders			
Inguinal hernia			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Cohort 1	Cohort 2	Cohort 3
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 12 (58.33%)	6 / 14 (42.86%)	8 / 14 (57.14%)
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 12 (0.00%)	0 / 14 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Hyperthermia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	2	0	0
Pyrexia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 14 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Immune system disorders			
Food allergy			
subjects affected / exposed	0 / 12 (0.00%)	0 / 14 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Oropharyngeal pain			
subjects affected / exposed	0 / 12 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Investigations			
Blood triglycerides			
subjects affected / exposed	0 / 12 (0.00%)	1 / 14 (7.14%)	0 / 14 (0.00%)
occurrences (all)	0	1	0

Injury, poisoning and procedural complications			
Heat exhaustion			
subjects affected / exposed	1 / 12 (8.33%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Open wound			
subjects affected / exposed	0 / 12 (0.00%)	1 / 14 (7.14%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Procedural dizziness			
subjects affected / exposed	1 / 12 (8.33%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Congenital, familial and genetic disorders			
Thalassaemia beta			
subjects affected / exposed	0 / 12 (0.00%)	0 / 14 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 12 (16.67%)	0 / 14 (0.00%)	1 / 14 (7.14%)
occurrences (all)	2	0	1
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 12 (0.00%)	2 / 14 (14.29%)	1 / 14 (7.14%)
occurrences (all)	0	2	1
Iron deficiency anaemia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 14 (0.00%)	2 / 14 (14.29%)
occurrences (all)	0	0	2
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	1 / 12 (8.33%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Middle ear inflammation			
subjects affected / exposed	0 / 12 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Strabismus			
subjects affected / exposed	0 / 12 (0.00%)	1 / 14 (7.14%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			

Anal pruritus			
subjects affected / exposed	0 / 12 (0.00%)	0 / 14 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Diarrhoea			
subjects affected / exposed	0 / 12 (0.00%)	0 / 14 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Inguinal hernia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Nausea			
subjects affected / exposed	1 / 12 (8.33%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Vomiting			
subjects affected / exposed	1 / 12 (8.33%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	0 / 12 (0.00%)	1 / 14 (7.14%)	1 / 14 (7.14%)
occurrences (all)	0	1	1
Secondary hyperthyroidism			
subjects affected / exposed	1 / 12 (8.33%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 12 (0.00%)	1 / 14 (7.14%)	2 / 14 (14.29%)
occurrences (all)	0	1	2
Nasopharyngitis			
subjects affected / exposed	1 / 12 (8.33%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Respiratory tract infection			
subjects affected / exposed	1 / 12 (8.33%)	0 / 14 (0.00%)	1 / 14 (7.14%)
occurrences (all)	1	0	1
Rhinitis			
subjects affected / exposed	1 / 12 (8.33%)	0 / 14 (0.00%)	1 / 14 (7.14%)
occurrences (all)	1	0	1
Tonsillitis			

subjects affected / exposed	0 / 12 (0.00%)	0 / 14 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Tooth abscess			
subjects affected / exposed	0 / 12 (0.00%)	1 / 14 (7.14%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Tracheitis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 14 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Varicella			
subjects affected / exposed	0 / 12 (0.00%)	0 / 14 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 12 (8.33%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0

Non-serious adverse events	Cohort 4		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 13 (61.54%)		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Hyperthermia			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Pyrexia			
subjects affected / exposed	3 / 13 (23.08%)		
occurrences (all)	3		
Immune system disorders			
Food allergy			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			
Epistaxis			

subjects affected / exposed occurrences (all) Oropharyngeal pain subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1 1 / 13 (7.69%) 1		
Investigations Blood triglycerides subjects affected / exposed occurrences (all)	 0 / 13 (0.00%) 0		
Injury, poisoning and procedural complications Heat exhaustion subjects affected / exposed occurrences (all) Open wound subjects affected / exposed occurrences (all) Procedural dizziness subjects affected / exposed occurrences (all)	 0 / 13 (0.00%) 0 0 / 13 (0.00%) 0 0 / 13 (0.00%) 0		
Congenital, familial and genetic disorders Thalassaemia beta subjects affected / exposed occurrences (all)	 0 / 13 (0.00%) 0		
Nervous system disorders Headache subjects affected / exposed occurrences (all)	 1 / 13 (7.69%) 1		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) Iron deficiency anaemia subjects affected / exposed occurrences (all)	 0 / 13 (0.00%) 0 1 / 13 (7.69%) 1		
Ear and labyrinth disorders			

Ear pain subjects affected / exposed occurrences (all) Middle ear inflammation subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0 1 / 13 (7.69%) 1		
Eye disorders Strabismus subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0		
Gastrointestinal disorders Anal pruritus subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Inguinal hernia subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0 0 / 13 (0.00%) 0 0 / 13 (0.00%) 0 0 / 13 (0.00%) 0 1 / 13 (7.69%) 1		
Endocrine disorders Hypothyroidism subjects affected / exposed occurrences (all) Secondary hyperthyroidism subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1 0 / 13 (0.00%) 0		
Infections and infestations Bronchitis subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1		

Nasopharyngitis subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1		
Respiratory tract infection subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0		
Rhinitis subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0		
Tonsillitis subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0		
Tooth abscess subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1		
Tracheitis subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0		
Varicella subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 April 2013	The Protocol was amended: To address changes in Exclusion criteria To clarify and specify study procedures To add new references To address a change of address To clarify abbreviations and address typographical and grammar mistakes

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported