Clinical trial results:
Phase III, multicentre, open study to assess the efficacy and safety profiles of the co-administration of lanreotide Autogel 120 mg (administered via deep subcutaneous injections every 28 days) and pegvisomant 40 to 120 mg per week (administered via subcutaneous route once or twice a week) in acromegalic patients failing to respond to lanreotide Autogel 120 mg alone

Summary

EudraCT number	2006-000297-72
Trial protocol	SE GR DE CZ DK IT GB
Global end of trial date	27 October 2008

Results information

Result version number	v1 (current)
This version publication date	03 May 2016
First version publication date	03 May 2016

Trial information

Trial identification

Sponsor protocol code	2-55-52030-727

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00383708
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Ipsen Pharma
Sponsor organisation address	65, Quai Georges Gorse, Boulogne-Billancourt, France, 92100
Public contact	Medical Director, Endocrinology., Ipsen Pharma, clinical.trials@ipsen.com
Scientific contact	Medical Director, Endocrinology., Ipsen Pharma, clinical.trials@ipsen.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	22 January 2010
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 October 2008
Global end of trial reached?	Yes
Global end of trial date	27 October 2008
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the efficacy of the co-administration of lanreotide Autogel 120 mg (administered via deep sub-cutaneous injections every 28 days) and pegvisomant (administered at 40 to 120 mg per week via sub-cutaneous injection given once or twice a week) on IGF-1 levels over 28 weeks in acromegalic patients. The primary endpoint was the percentage of acromegalic patients with normalised (age and sex adjusted) IGF-1 level at the end of the co-treatment period.

Protection of trial subjects:

This clinical study was designed and implemented and reported in accordance with the International Conference on Harmonization (ICH) Harmonized Tripartite Guidelines for Good Clinical Practice (GCP), with applicable local regulations (including European Directive 2001/20/EC, US Code of Federal Regulations Title 21 and with the ethical principles laid down in the Declaration of Helsinki.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 October 2006
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	Netherlands: 7
Country: Number of subjects enrolled	Sweden: 5
Country: Number of subjects enrolled	United Kingdom: 10
Country: Number of subjects enrolled	Czech Republic: 14
Country: Number of subjects enrolled	Denmark: 4
Country: Number of subjects enrolled	France: 23
Country: Number of subjects enrolled	Germany: 13
Country: Number of subjects enrolled	Greece: 18
Country: Number of subjects enrolled	Italy: 19
Country: Number of subjects enrolled	Spain: 12
Worldwide total number of subjects	125
EEA total number of subjects	125

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)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	103
From 65 to 84 years	22
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

All subjects enrolled over 25 study centers located in 10 European countries.

Pre-assignment

Screening details:

A total of 125 subjects screened.

Pre-assignment period milestones

Number of subjects started	125
Number of subjects completed	92

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Did not meet entry criteria: 32
Reason: Number of subjects	Consent withdrawn: 1

Period 1

Period 1 title	Run-in period
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	All Subjects

Arm description:

Lanreotide Autogel 120 mg which was administered every 28 days via deep Subcutaneous route in the upper external quadrant of the buttock.

Arm type	Experimental
Investigational medicinal product name	Lanreotide Autogel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Lanreotide Autogel 120 mg which was administered every 28 days via deep Subcutaneous route in the upper external quadrant of the buttock.

Number of subjects in period 1	All Subjects
Started	92
Completed	85
Not completed	7
Protocol violation	4
Other	1
Adverse event	2

Period 2

Period 2 title	Treated Co-administration
Is this the baseline period?	Yes[1]
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Titration Basis

Arm description:

Lanreotide Autogel 120 mg was co-administered with Pegvisomant at various doses as Co-administration dose 1 in visit 4 and 5, Co-administration dose 2 in visit 6 and 7, Co-administration dose 3 in visit 7 and 8 and Co-administration dose 4 in visit 9 and 10.

Arm type	Experimental
Investigational medicinal product name	Lanreotide Autogel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Lanreotide Autogel 120 mg which was administered every 28 days via deep Subcutaneous route in the upper external quadrant of the buttock.

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: Period 1 is the initial phase of study 'Run-in period' and period 2 is the second phase 'Co-administration phase' which is of the main interest of this study and hence Period 2 is considered as the baseline period.

Number of subjects in period 2[2][3]	Titration Basis
Started	57
Completed	52
Not completed	5
Adverse event	5

Notes:

[2] - 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: The worldwide data is reported for all subjects who got enrolled in the study. However, baseline data is reported only for the subjects who entered Period 2: 'Co-administration phase'
[3] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same

as the number completing the preceding period.

Justification: 85 patients completed period 1 (run-in), however, of these for 28 patients IGF-1 values assessed at Visit 4 made them ineligible for period 2 (co-administration) and were withdrawn at Visit 4.

Baseline characteristics

Reporting groups	
Reporting group title	Titration Basis

Reporting group description:

Lanreotide Autogel 120 mg was co-administered with Pegvisomant at various doses as Co-administration dose 1 in visit 4 and 5, Co-administration dose 2 in visit 6 and 7, Co-administration dose 3 in visit 7 and 8 and Co-administration dose 4 in visit 9 and 10.

Reporting group values	Titration Basis	Total	
Number of subjects	57	57	
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	 51.6 ± 12.7	 -	
Gender categorical Units: Subjects			
Female	28	28	
Male	29	29	
Race Units: Subjects			
Asian	2	2	
Caucasian	55	55	
Diabetic Status at Study Entry			
Diabetic status at study entry was derived from medical history at Visit 1.			
Units: Subjects			
Diabetic	15	15	
Non diabetic	42	42	
Height Units: cm arithmetic mean standard deviation	 172.4 ± 10.5	 -	
IGF-1 at Baseline			
Baseline is defined as Visit 3.			
Units: z-score arithmetic mean standard deviation	 6.485 ± 4.113	 -	

End points

End points reporting groups

Reporting group title	All Subjects

Reporting group description:

Lanreotide Autogel 120 mg which was administered every 28 days via deep Subcutaneous route in the upper external quadrant of the buttock.

Reporting group title	Titration Basis

Reporting group description:

Lanreotide Autogel 120 mg was co-administered with Pegvisomant at various doses as Co-administration dose 1 in visit 4 and 5, Co-administration dose 2 in visit 6 and 7, Co-administration dose 3 in visit 7 and 8 and Co-administration dose 4 in visit 9 and 10.

Primary: The percentage of subjects with acromegaly with a normalised IGF-1 level

End point title	The percentage of subjects with acromegaly with a normalised IGF-1 level[1]

End point description:

The intention to treat (ITT) population is co-administered subjects having at least one baseline and at least one post baseline assessment of the primary efficacy endpoint.

Method of estimation is Clopper-Pearson and p-value is < 0.0001.

End point type	Primary

End point timeframe:

At visit 9 and 10

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: End point data is reported for single arm, hence statistical details is mentioned in description.

End point values	Titration Basis			
Subject group type	Reporting group			
Number of subjects analysed	57			
Units: Percentage of subjects				
number (not applicable)				
Serum IGF-1 normalised at end of co-administration	57.9			

Statistical analyses

No statistical analyses for this end point

Primary: The percentage of subjects with Serum IGF-1 Normalisation by Previous Treatment and Final DosePegvisomant at End of Co-administration

End point title	The percentage of subjects with Serum IGF-1 Normalisation by Previous Treatment and Final DosePegvisomant at End of Co-administration[2]

End point description:

ITT population

Previously treated with pegvisomant: Method of estimation is Clopper-Pearson and p-value is 0.1654.
Previously treated with lanreotide Autogel: Method of estimation is Clopper-Pearson and p-value is 0.0115.
Previously treated with octreotide LAR: Method of estimation is Clopper-Pearson and p-value is 0.0003.

End point type	Primary

End point timeframe:

At visit 9 and 10

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: End point data is reported for single arm, hence statistical details is mentioned in description.

End point values	Titration Basis			
Subject group type	Reporting group			
Number of subjects analysed	57			
Units: Percentage of subjects				
number (not applicable)				
Previous Treatment: Pegvisomant (N=13)	46.2			
Previous Treatment: Lanreotide Autogel (N=24)	54.2			
Previous Treatment: Octreotide LAR (N=20)	70			
Final Dose Pegvisomant: 40 mg/week (N=13)	76.9			
Final Dose Pegvisomant: 60 mg/week (N= 13)	61.5			
Final Dose Pegvisomant: 80 mg/week (N=16)	75			
Final Dose Pegvisomant: 40 mg 2x/week (N=5)	60			
Final Dose Pegvisomant: 60 mg 2x/week (N=10)	0			

Statistical analyses

No statistical analyses for this end point

Primary: The percentage of subjects with Serum IGF-1 Normalisation at End of Co-administration by Diabetic Status

End point title	The percentage of subjects with Serum IGF-1 Normalisation at End of Co-administration by Diabetic Status[3]

End point description:

ITT population

Diabetic subjects: Method of estimation is Clopper-Pearson and p-value is 0.084.
Non-Diabetic subjects: Method of estimation is Clopper-Pearson and p-value is < 0.0001.

End point type	Primary

End point timeframe:

At visit 9 and 10

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: End point data is reported for single arm, hence statistical details is mentioned in description.

End point values	Titration Basis			
Subject group type	Reporting group			
Number of subjects analysed	57			
Units: Percentage of subjects				
number (not applicable)				
Diabetic Subjects (N=19)	47.4			
Non Diabetic Subjects (N=38)	63.2			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects normalised at least once in serum IGF-1 levels

End point title	Percentage of subjects normalised at least once in serum IGF-1 levels

End point description:

The intention to treat (ITT) population is co-administered subjects having at least one baseline and at least one post baseline assessment of the primary efficacy endpoint.

Estimation method is Clopper-Pearson and for both categories p-value is < 0.0001.

End point type	Secondary

End point timeframe:

At visit 11

End point values	Titration Basis			
Subject group type	Reporting group			
Number of subjects analysed	57			
Units: Percentage of subjects				
number (not applicable)				
During co-administration, while taking final dose	66.7			
During co-administration, at any time	78.9			

Statistical analyses

No statistical analyses for this end point

Secondary: Serum growth hormone level

End point title	Serum growth hormone level

End point description:

The intention to treat (ITT) population is co-administered subjects having at least one baseline and at least one post baseline assessment of the primary efficacy endpoint.

End point type	Secondary

End point timeframe:

At visit 3 (Baseline) and visit 11 (7 months)

End point values	Titration Basis			
Subject group type	Reporting group			
Number of subjects analysed	57			
Units: ng/ml				
arithmetic mean (standard deviation)				
Visit 3 (n= 57)	6.1 (± 7.2)			
Change at visit 11 (n= 52)	6.6 (± 9.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Growth Hormone Binding Protein

End point title	Growth Hormone Binding Protein

End point description:

The intention to treat (ITT) population is co-administered subjects having at least one baseline and at least one post baseline assessment of the primary efficacy endpoint.

End point type	Secondary

End point timeframe:

At visit 3 (Baseline) and visit 11 (7 months).

End point values	Titration Basis			
Subject group type	Reporting group			
Number of subjects analysed	57			
Units: pmol/L				
arithmetic mean (standard deviation)				
Visit 3 (n= 57)	274 (± 184)			
Change at visit 11 (n= 52)	841 (± 302)			

Statistical analyses

No statistical analyses for this end point

Secondary: Acid Labile Subunit (ALS)

End point title	Acid Labile Subunit (ALS)

End point description:

The intention to treat (ITT) population is co-administered subjects having at least one baseline and at least one post baseline assessment of the primary efficacy endpoint.

End point type	Secondary

End point timeframe:

At visit 3 (Baseline) and visit 11 (7 months).

End point values	Titration Basis			
Subject group type	Reporting group			
Number of subjects analysed	57			
Units: mIU/ml				
arithmetic mean (standard deviation)				
Visit 3 (n= 57)	1842 (± 497)			
Change at visit 11 (n= 52)	-561 (± 528)			

Statistical analyses

No statistical analyses for this end point

Secondary: Prolactin level

End point title	Prolactin level

End point description:

The intention to treat (ITT) population is co-administered subjects having at least one baseline and at least one post baseline assessment of the primary efficacy endpoint.

End point type	Secondary

End point timeframe:

At visit 3 (Baseline) and visit 11 (7 months).

End point values	Titration Basis			
Subject group type	Reporting group			
Number of subjects analysed	57			
Units: µg/l				
arithmetic mean (standard deviation)				
Visit 3 (n= 57)	25.8 (± 49.2)			
Change at visit 11 (n= 52)	-0.1 (± 8.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects with serum growth hormone lesser or equal 2.5 ng/ml

End point title	Percentage of subjects with serum growth hormone lesser or equal 2.5 ng/ml

End point description:

The intention to treat (ITT) population is co-administered subjects having at least one baseline and at least one post baseline assessment of the primary efficacy endpoint.

End point type	Secondary

End point timeframe:

At visit 3 (Baseline) and visit 11 (7 months)

End point values	Titration Basis			
Subject group type	Reporting group			
Number of subjects analysed	57			
Units: Percentage of subjects				
number (not applicable)				
Visit 3 (n= 57) At visit 11 (n=52)	38.6 25			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in acromegaly symptoms during the study

End point title	Change in acromegaly symptoms during the study

End point description:

The intention to treat (ITT) population is co-administered subjects having at least one baseline and at least one post baseline assessment of the primary efficacy endpoint.

Headache, excessive perspiration, fatigue, soft tissue swelling and arthralgia were to be assessed with scores ranging from 0 (no symptoms) to 8 (severe, incapacitating symptoms). Symptoms were assessed by the subject in paper format before any other procedure planned during the visit.

End point type	Secondary

End point timeframe:

At visit 3 (Baseline) and visit 11 (7 months)

End point values	Titration Basis			
Subject group type	Reporting group			
Number of subjects analysed	57			
Units: Units on scale				
arithmetic mean (standard deviation)				
Arthralgia, visit 3 (n=56)	3.7 (± 2.3)			
Arthralgia, change at visit 11 (n=50)	-0.7 (± 1.5)			
Excessive Perspiration, visit 3 (n=56)	2.1 (± 2)			
Excessive Perspiration, change at visit 11 (n=50)	-0.4 (± 1.9)			
Fatigue, visit 3 (n=56)	3.2 (± 2.2)			
Fatigue, change at visit 11 (n=50)	-0.2 (± 1.6)			
Headache, visit 3 (n=55)	2.2 (± 2.3)			
Headache, change at visit 11 (n=49)	-0.4 (± 1.6)			
Soft Tissue Swelling, visit 3 (n=56)	2.1 (± 1.9)			
Soft Tissue Swelling, change at visit 11 (n=50)	-0.6 (± 1.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in acromegaly quality of life (ACROQOL) assessments during the study

End point title	Change in acromegaly quality of life (ACROQOL) assessments during the study

End point description:

ITT population; Relationship (Relnship); Dimension(Dim)
ACROQOL is a new health-related quality of life questionnaire for patients with acromegaly: development & psychometric properties. Questionnaire will be filled by each patient in paper forms, before any other procedure planned during visit,at same time as acromegaly symptoms assessment. Questionnaire is simple & time required to complete is approximately 7 minutes. It is self-administered,so filling out ACROQoL requires quiet place,privacy & prior explanation by investigator. Investigator should emphasise that responses are confidential, explain all questions, & ensure patient understands them. Investigator will specify that only 1 response is allowed for each question, & there is no incorrect response (patient chooses option that best describes his/her situation). Investigator should remind that all questions should be carefully read before answering, patient should check there is no missing answer in completed questionnaire

End point type	Secondary

End point timeframe:

At visit 3 (Baseline) and visit 11 (7 months)

End point values	Titration Basis			
Subject group type	Reporting group			
Number of subjects analysed	57			
Units: Units on scale				
arithmetic mean (standard deviation)				
Global Score-V3 n=57	55.2 (± 19.8)			
Global Score-change at V11 n=52	2.4 (± 9.1)			
Physical Dimensions Score-V3 n=57	50.5 (± 24.1)			

Physical Dimensions Score-change at V11 n=52	4.2 (± 12)			
Psychological Dimensions Score-V3 n=57	57.9 (± 19.3)			
Psychological Dimensions Score-change at V11 n=52	1.3 (± 10.4)			
Appearance Sub-Dimension Score-V3 n=57	46.9 (± 23.1)			
Appearance Sub-Dimension Score-change at V11 n=52	3.8 (± 13)			
Personal Relnship Sub-Dim Score-V3 n=57	68.9 (± 20.3)			
Personal Relnship Sub-Dim Score-change at V11 n=52	-0.1 (± 12.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Serum IGF-1 level (expressed as z-scores)

End point title	Serum IGF-1 level (expressed as z-scores)
End point description: ITT population	
End point type	Secondary
End point timeframe: At visit 3 (Baseline) and visit 11 (7 months)	

End point values	Titration Basis			
Subject group type	Reporting group			
Number of subjects analysed	57			
Units: z-scores				
arithmetic mean (standard deviation)				
Visit 3 (n=57) Change at visit 11 (n=52)	6.49 (± 4.11) -4.5 (± 4.01)			

Statistical analyses

No statistical analyses for this end point

Secondary: Correlation between the change in quality of life and the change in z-score of IGF-1 level

End point title	Correlation between the change in quality of life and the change in z-score of IGF-1 level
End point description: ITT population A decrease in IGF-1 z-score represents an improvement and an increase in ACROQoL score represents	

an improvement.

Appearance and personal Relationships are Psychological Sub-Dimension.

The values reported are Spearman's rank correlation (r) values

End point type	Secondary
End point timeframe: At visit 2, visit 3 and visit 11.	

End point values	Titration Basis			
Subject group type	Reporting group			
Number of subjects analysed	57			
Units: nanogram(s)				
number (not applicable)				
Change From V2 To V3 - Global Score	-0.16			
Change From V2 To V3 - Physical Dimension	-0.17			
Change From V2 To V3 - Psychological Dimension	-0.1			
Change From V2 To V3 - Appearance	-0.12			
Change From V2 To V3 - Personal Relationships	-0.01			
Change From V3 To V11 - Global Score	0.09			
Change From V3 To V11 - Physical Dimension	0.14			
Change From V3 To V11 - Psychological Dimension	0.08			
Change From V3 To V11 - Appearance	0.04			
Change From V3 To V11 - Personal Relationships	0.02			

Statistical analyses

No statistical analyses for this end point

Secondary: The percentage of subjects with Serum IGF-1 Normalisation at Each Visit

End point title	The percentage of subjects with Serum IGF-1 Normalisation at Each Visit
End point description: ITT population	
End point type	Secondary
End point timeframe: At visit 1, 2, 3, 5, 7, 9 and 11	

End point values	Titration Basis			
Subject group type	Reporting group			
Number of subjects analysed	57			
Units: Percentage of subjects				
number (not applicable)				
Visit 1 (n= 10)	17.5			
Visit 2 (n= 13)	24.5			
Visit 3 (n= 0)	0			
Visit 5 (n= 31)	56.4			
Visit 7 (n= 26)	48.1			
Visit 9 (n= 30)	57.7			
Visit 11 (n= 32)	61.5			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Changes in Mean Weight from Baseline

End point title	Changes in Mean Weight from Baseline

End point description:

The safety population is defined as all subjects who received at least one dose of each Investigational medicinal product (i.e. one dose of Lanreotide autogel 120 mg and one dose of Pegvisomant during the co-administration period).

End point type	Other pre-specified

End point timeframe:

At visit 3 (Baseline) and visit 11 (7 months)

End point values	Titration Basis			
Subject group type	Reporting group			
Number of subjects analysed	57			
Units: Kg				
arithmetic mean (standard deviation)				
Visit 3 (n= 55)	87.3 (± 19.6)			
Change at visit 11 (n= 49)	-0.3 (± 2.9)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Changes in Mean Supine Systolic BP from Baseline

End point title	Changes in Mean Supine Systolic BP from Baseline

End point description:

The safety population is defined as all subjects who received at least one dose of each Investigational medicinal product (i.e. one dose of Lanreotide autogel 120 mg and one dose of Pegvisomant during the

co-administration period).

End point type	Other pre-specified

End point timeframe:

At visit 3 (Baseline) and visit 11 (7 months)

End point values	Titration Basis			
Subject group type	Reporting group			
Number of subjects analysed	57			
Units: mmHg				
arithmetic mean (standard deviation)				
Visit 3 (n= 57)	130.1 (± 13.6)			
Change at visit 11 (n= 52)	-0.4 (± 17.1)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Changes in Mean Supine Diastolic BP from Baseline.

End point title	Changes in Mean Supine Diastolic BP from Baseline.

End point description:

The safety population is defined as all subjects who received at least one dose of each Investigational medicinal product (i.e. one dose of Lanreotide autogel 120 mg and one dose of Pegvisomant during the co-administration period).

End point type	Other pre-specified

End point timeframe:

At visit 3 (Baseline) and visit 11 (7 months)

End point values	Titration Basis			
Subject group type	Reporting group			
Number of subjects analysed	57			
Units: mmHg				
arithmetic mean (standard deviation)				
Visit 3 (n= 57)	81.3 (± 9.5)			
Change at visit 11 (n= 52)	-0.1 (± 11.4)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Changes in Mean Supine Heart Rate from Baseline

End point title	Changes in Mean Supine Heart Rate from Baseline

End point description:

The safety population is defined as all subjects who received at least one dose of each Investigational medicinal product (i.e. one dose of Lanreotide autogel 120 mg and one dose of Pegvisomant during the co-administration period).

End point type	Other pre-specified

End point timeframe:

At visit 3 (Baseline) and visit 11 (7 months)

End point values	Titration Basis			
Subject group type	Reporting group			
Number of subjects analysed	57			
Units: bpm				
arithmetic mean (standard deviation)				
Visit 3 (n= 57) Change at visit 11 (n= 50)	69.8 (± 10.3) -3.1 (± 12.6)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Changes in electrocardiogram (ECG) Mean Heart Rate from Baseline

End point title	Changes in electrocardiogram (ECG) Mean Heart Rate from Baseline

End point description:

The safety population is defined as all subjects who received at least one dose of each Investigational medicinal product (i.e. one dose of Lanreotide autogel 120 mg and one dose of Pegvisomant during the co-administration period).

End point type	Other pre-specified

End point timeframe:

At visit 3 (Baseline) and visit 11 (7 months)

End point values	Titration Basis			
Subject group type	Reporting group			
Number of subjects analysed	57			
Units: bpm				
arithmetic mean (standard deviation)				
Visit 3 (n= 56) Change at visit 11 (n= 50)	64.6 (± 11.2) -2.8 (± 11)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Changes in Mean PR Interval, QRS Interval, QT Interval, RR Interval and QTc Interval Fridericia from Baseline.

End point title	Changes in Mean PR Interval, QRS Interval, QT Interval, RR Interval and QTc Interval Fridericia from Baseline.

End point description:

The safety population is defined as all subjects who received at least one dose of each Investigational medicinal product (i.e. one dose of Lanreotide autogel 120 mg and one dose of Pegvisomant during the co-administration period).

End point type	Other pre-specified

End point timeframe:

At visit 3 (Baseline) and visit 11 (7 months).

End point values	Titration Basis			
Subject group type	Reporting group			
Number of subjects analysed	57			
Units: ms				
arithmetic mean (standard deviation)				
PR Interval, Visit 3 (n=55)	165.9 (± 21.1)			
PR Interval, Change at visit 11 (n=48)	1.1 (± 15.8)			
QRS Interval, Visit 3 (n=56)	101.7 (± 16.5)			
QRS Interval, Change at visit 11 (n=50)	0.1 (± 10.1)			
QT Interval, Visit 3 (n=52)	402 (± 33.4)			
QT Interval, Change at visit 11 (n=45)	4 (± 29.7)			
RR Interval, Visit 3 (n=56)	959 (± 175.7)			
RR Interval, Change at visit 11 (n=50)	34.7 (± 175.4)			
QTc Interval Fridericia, Visit 3 (n=52)	410.8 (± 25.7)			
QTc Interval Fridericia, Change at visit 11 (n=45)	-1.8 (± 16.9)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of subjects with shift in presence/absence of Lithiasis and/or Sludge during co-administration

End point title	Number of subjects with shift in presence/absence of Lithiasis and/or Sludge during co-administration

End point description:

Safety population.

End point type	Other pre-specified

End point timeframe:

At visit 3 (Baseline) and visit 11 (7 months)

End point values	Titration Basis			
Subject group type	Reporting group			
Number of subjects analysed	57			
Units: Number of subjects				
Subjects developed Sludge	3			
Subjects resolved Sludge	5			
Subjects developed Lithiasis	2			
Subjects resolved Lithiasis	1			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change in Mean Pituitary tumour Size

End point title	Change in Mean Pituitary tumour Size
End point description: Safety population	
End point type	Other pre-specified
End point timeframe: At visit 2, visit 3 and visit 11.	

End point values	Titration Basis			
Subject group type	Reporting group			
Number of subjects analysed	57			
Units: mm^3				
arithmetic mean (standard deviation)				
Visit 3 (n=56)	2966.7 (± 4519)			
Change at visit 11 (n=49)	2.4 (± 729.7)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change in mean Blood Glucose Cmax from Oral Glucose Tolerance Test (OGTT) for Non Diabetic subjects

End point title	Change in mean Blood Glucose Cmax from Oral Glucose Tolerance Test (OGTT) for Non Diabetic subjects
End point description: Safety population	

End point type	Other pre-specified
End point timeframe: At visit 3 and visit 11	

End point values	Titration Basis			
Subject group type	Reporting group			
Number of subjects analysed	38			
Units: mmol/L				
arithmetic mean (standard deviation)				
Visit 3 (n=38) Change at visit 11 (N=34)	10.3 (± 2.28) 0.53 (± 1.72)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change in Mean Fasting insulin During Co-administration in Non Diabetic Subjects

End point title	Change in Mean Fasting insulin During Co-administration in Non Diabetic Subjects
End point description: Safety population	
End point type	Other pre-specified
End point timeframe: At visit 3 and visit 11	

End point values	Titration Basis			
Subject group type	Reporting group			
Number of subjects analysed	37			
Units: pmol/L				
arithmetic mean (standard deviation)				
At visit 3 (n=37) Change at visit 11 (n=32)	56.1 (± 28.4) -12.7 (± 41.5)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change in Mean Blood Glucose Fasting for Non Diabetic Subjects

End point title	Change in Mean Blood Glucose Fasting for Non Diabetic

	Subjects
End point description: Safety population	
End point type	Other pre-specified
End point timeframe: At visit 3 and visit 11	

End point values	Titration Basis			
Subject group type	Reporting group			
Number of subjects analysed	37			
Units: mmol/L				
arithmetic mean (standard deviation)				
At visit 3 (n=37) Change at visit 11 (n=32)	5.42 (± 0.59) -0.05 (± 0.71)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change in Mean Fasting Insulin / Glucose Ratio for Non Diabetic Subjects

End point title	Change in Mean Fasting Insulin / Glucose Ratio for Non Diabetic Subjects
End point description: Safety population	
End point type	Other pre-specified
End point timeframe: At visit 3 and visit 11	

End point values	Titration Basis			
Subject group type	Reporting group			
Number of subjects analysed	36			
Units: N/A				
arithmetic mean (standard deviation)				
At visit 3 (n=36) Change at visit 11 (n=30)	10.66 (± 5.97) -2.61 (± 8.12)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change in Mean HbA1C	
End point title	Change in Mean HbA1C
End point description: Safety population HbA1C - Glycosylated Haemoglobin	
End point type	Other pre-specified
End point timeframe: At visit 3 and visit 11	

End point values	Titration Basis			
Subject group type	Reporting group			
Number of subjects analysed	57			
Units: Percentage				
arithmetic mean (standard deviation)				
Diabetic Subjects at visit 3 (n=19)	7 (± 1.26)			
Diabetic Subjects Change at visit 11 (n=18)	-0.05 (± 0.71)			
Non Diabetic Subjects at visit 3 (n=38)	5.88 (± 0.32)			
Non Diabetic Subjects Change at visit 11 (n=33)	0.05 (± 0.2)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Laboratory tests - Changes in Liver Function Test Parameters	
End point title	Laboratory tests - Changes in Liver Function Test Parameters
End point description: Safety population	
End point type	Other pre-specified
End point timeframe: At visit 3 and visit 11	

End point values	Titration Basis			
Subject group type	Reporting group			
Number of subjects analysed	57			
Units: IU/L				
arithmetic mean (standard deviation)				
Aspartate Amino Transferase at visit 3 (n=57)	17.8 (± 6.4)			
Aspartate Amino Transferase change at V11 (n=52)	3.3 (± 10.7)			
Alanine Amino Transferase at visit 3 (n=57)	15.1 (± 5.4)			

Alanine Amino Transferase change at visit 11(n=52)	4.1 (± 11.7)			
Gamma Glutamyl Transferase at visit 3 (n=57)	24.5 (± 31.7)			
Gamma Glutamyl Transferase change at V11(n=52)	-1 (± 17.8)			
Alkaline Phosphatase at visit 3 (n=57)	73.2 (± 33.9)			
Alkaline Phosphatase change at visit 11 (n=52)	-1.7 (± 14.5)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Changes in Liver Function Test - Total Bilirubin

End point title	Changes in Liver Function Test - Total Bilirubin
End point description: Safety population	
End point type	Other pre-specified
End point timeframe: At visit 3 and visit 11	

End point values	Titration Basis			
Subject group type	Reporting group			
Number of subjects analysed	57			
Units: µmol/L				
arithmetic mean (standard deviation)				
At visit 3 (n=57)	8.3 (± 4.2)			
Change at visit 11 (n=52)	-1.3 (± 2.9)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Changes in Liver Function Test - Prothrombin Level

End point title	Changes in Liver Function Test - Prothrombin Level
End point description: Safety population	
End point type	Other pre-specified
End point timeframe: At visit 3 and visit 11	

End point values	Titration Basis			
Subject group type	Reporting group			
Number of subjects analysed	57			
Units: percent				
arithmetic mean (standard deviation)				
At visit 3 (n=57)	92.4 (± 12.8)			
Change at visit 11 (n=51)	-3.7 (± 16)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Analyses for putative antibodies during the co-administration period

End point title	Analyses for putative antibodies during the co-administration period
End point description:	
Safety population	
End point type	Other pre-specified
End point timeframe:	
At visit 11	

End point values	Titration Basis			
Subject group type	Reporting group			
Number of subjects analysed	57			
Units: Number of subjects				
Antibodies for Lanreotide	4			
Antibodies for Pegvisomant	6			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Subjects with Adverse Events

End point title	Number of Subjects with Adverse Events
End point description:	
ITT population AE (Adverse Event) TEAE (Treatment Emergent Adverse Event) SAE (Serious Adverse Event)	
End point type	Other pre-specified
End point timeframe:	
Up to visit 11	

End point values	Titration Basis			
Subject group type	Reporting group			
Number of subjects analysed	57			
Units: Number of subjects				
Run-in: Any AE	33			
Run-in: Any TEAE	30			
Run-in: Any severe TEAE	2			
Run-in: Any severe treatment related TEAE	0			
Run-in: Any SAE	2			
Run-in: Any AE leading to withdrawal	0			
Run-in: Any AE leading to death	0			
Co-administration: Any AE	44			
Co-administration: Any TEAE	41			
Co-administration: Any severe TEAE	7			
Coadministration:Any severe treatment related TEAE	2			
Co-administration: Any SAE	8			
Co-administration: Any AE leading to withdrawal	5			
Co-administration: Any AE leading to death	0			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Up to visit 11.	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	10.0
Reporting groups	
Reporting group title	Run-in period
Reporting group description: -	
Reporting group title	Co-administration period
Reporting group description: -	

Serious adverse events	Run-in period	Co-administration period	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 57 (3.51%)	8 / 57 (14.04%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Skin cancer			
subjects affected / exposed	0 / 57 (0.00%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 57 (0.00%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Amnesia			
subjects affected / exposed	0 / 57 (0.00%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial palsy			

subjects affected / exposed	0 / 57 (0.00%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Petit mal epilepsy			
subjects affected / exposed	0 / 57 (0.00%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	0 / 57 (0.00%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	0 / 57 (0.00%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Impaired healing			
subjects affected / exposed	0 / 57 (0.00%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 57 (0.00%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 57 (0.00%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Urticaria			

subjects affected / exposed	0 / 57 (0.00%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal colic			
subjects affected / exposed	0 / 57 (0.00%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	0 / 57 (0.00%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Adrenocortical insufficiency acute			
subjects affected / exposed	1 / 57 (1.75%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Wound infection			
subjects affected / exposed	1 / 57 (1.75%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Run-in period	Co-administration period	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	29 / 57 (50.88%)	33 / 57 (57.89%)	
Vascular disorders			
Aortic aneurysm			
subjects affected / exposed	1 / 57 (1.75%)	0 / 57 (0.00%)	
occurrences (all)	1	0	
Hypertension			
subjects affected / exposed	1 / 57 (1.75%)	1 / 57 (1.75%)	
occurrences (all)	1	1	

Hypotension			
subjects affected / exposed	0 / 57 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Orthostatic hypotension			
subjects affected / exposed	0 / 57 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Venous insufficiency			
subjects affected / exposed	0 / 57 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Application site induration			
subjects affected / exposed	1 / 57 (1.75%)	0 / 57 (0.00%)	
occurrences (all)	1	0	
Application site pain			
subjects affected / exposed	1 / 57 (1.75%)	0 / 57 (0.00%)	
occurrences (all)	1	0	
Injection site nodule			
subjects affected / exposed	1 / 57 (1.75%)	2 / 57 (3.51%)	
occurrences (all)	1	2	
Injection site pain			
subjects affected / exposed	2 / 57 (3.51%)	0 / 57 (0.00%)	
occurrences (all)	2	0	
Fatigue			
subjects affected / exposed	0 / 57 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Injection site bruising			
subjects affected / exposed	0 / 57 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	10	
Injection site erythema			
subjects affected / exposed	0 / 57 (0.00%)	2 / 57 (3.51%)	
occurrences (all)	0	4	
Injection site haemorrhage			
subjects affected / exposed	0 / 57 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Injection site rash			

subjects affected / exposed	0 / 57 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Injection site swelling			
subjects affected / exposed	0 / 57 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Oedema peripheral			
subjects affected / exposed	0 / 57 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Pyrexia			
subjects affected / exposed	0 / 57 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	0 / 57 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Upper respiratory tract infection			
subjects affected / exposed	0 / 57 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Reproductive system and breast disorders			
Oligomenorrhoea			
subjects affected / exposed	1 / 57 (1.75%)	1 / 57 (1.75%)	
occurrences (all)	1	1	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 57 (1.75%)	1 / 57 (1.75%)	
occurrences (all)	1	1	
Nasal congestion			
subjects affected / exposed	0 / 57 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Pharyngolaryngeal pain			
subjects affected / exposed	0 / 57 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Psychiatric disorders			
Depression			
subjects affected / exposed	2 / 57 (3.51%)	1 / 57 (1.75%)	
occurrences (all)	2	1	

Anxiety			
subjects affected / exposed	0 / 57 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Insomnia			
subjects affected / exposed	0 / 57 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Investigations			
Blood prolactin increased			
subjects affected / exposed	1 / 57 (1.75%)	0 / 57 (0.00%)	
occurrences (all)	1	0	
Smear cervix abnormal			
subjects affected / exposed	1 / 57 (1.75%)	0 / 57 (0.00%)	
occurrences (all)	1	0	
Alanine aminotransferase increased			
subjects affected / exposed	0 / 57 (0.00%)	2 / 57 (3.51%)	
occurrences (all)	0	2	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 57 (0.00%)	2 / 57 (3.51%)	
occurrences (all)	0	2	
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 57 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Hepatic enzyme increased			
subjects affected / exposed	0 / 57 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	1 / 57 (1.75%)	0 / 57 (0.00%)	
occurrences (all)	1	0	
Fall			
subjects affected / exposed	1 / 57 (1.75%)	0 / 57 (0.00%)	
occurrences (all)	1	0	
Foot fracture			
subjects affected / exposed	0 / 57 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	

Intervertebral disc injury subjects affected / exposed occurrences (all)	0 / 57 (0.00%) 0	1 / 57 (1.75%) 1	
Cardiac disorders bradycardia subjects affected / exposed occurrences (all)	1 / 57 (1.75%) 1	0 / 57 (0.00%) 0	
Nervous system disorders Headache subjects affected / exposed occurrences (all)	2 / 57 (3.51%) 2	1 / 57 (1.75%) 1	
Paraesthesia subjects affected / exposed occurrences (all)	0 / 57 (0.00%) 0	2 / 57 (3.51%) 2	
Radiculopathy subjects affected / exposed occurrences (all)	0 / 57 (0.00%) 0	1 / 57 (1.75%) 1	
Syncope subjects affected / exposed occurrences (all)	0 / 57 (0.00%) 0	1 / 57 (1.75%) 1	
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	1 / 57 (1.75%) 1	0 / 57 (0.00%) 0	
Macrocytosis subjects affected / exposed occurrences (all)	1 / 57 (1.75%) 1	0 / 57 (0.00%) 0	
Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all)	0 / 57 (0.00%) 0	2 / 57 (3.51%) 2	
Gastrointestinal disorders Abdominal rigidity subjects affected / exposed occurrences (all)	1 / 57 (1.75%) 3	0 / 57 (0.00%) 0	
Constipation			

subjects affected / exposed	1 / 57 (1.75%)	0 / 57 (0.00%)	
occurrences (all)	1	0	
Diarrhoea			
subjects affected / exposed	5 / 57 (8.77%)	4 / 57 (7.02%)	
occurrences (all)	12	7	
Dyspepsia			
subjects affected / exposed	1 / 57 (1.75%)	0 / 57 (0.00%)	
occurrences (all)	1	0	
Nausea			
subjects affected / exposed	1 / 57 (1.75%)	1 / 57 (1.75%)	
occurrences (all)	2	1	
Rectal haemorrhage			
subjects affected / exposed	1 / 57 (1.75%)	0 / 57 (0.00%)	
occurrences (all)	1	0	
Abdominal distension			
subjects affected / exposed	0 / 57 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Abdominal pain			
subjects affected / exposed	0 / 57 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Abdominal pain upper			
subjects affected / exposed	0 / 57 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Flatulence			
subjects affected / exposed	0 / 57 (0.00%)	2 / 57 (3.51%)	
occurrences (all)	0	2	
Hepatobiliary disorders			
Gallbladder polyp			
subjects affected / exposed	1 / 57 (1.75%)	0 / 57 (0.00%)	
occurrences (all)	1	0	
Cytolytic hepatitis			
subjects affected / exposed	0 / 57 (0.00%)	4 / 57 (7.02%)	
occurrences (all)	0	4	
Hepatotoxicity			
subjects affected / exposed	0 / 57 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	

Cholelithiasis			
subjects affected / exposed	6 / 57 (10.53%)	2 / 57 (3.51%)	
occurrences (all)	7	3	
Skin and subcutaneous tissue disorders			
Night sweats			
subjects affected / exposed	1 / 57 (1.75%)	0 / 57 (0.00%)	
occurrences (all)	1	0	
Blood blister			
subjects affected / exposed	0 / 57 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Hyperhidrosis			
subjects affected / exposed	0 / 57 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Lipodystrophy acquired			
subjects affected / exposed	0 / 57 (0.00%)	2 / 57 (3.51%)	
occurrences (all)	0	2	
Lipohypertrophy			
subjects affected / exposed	0 / 57 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Pruritus			
subjects affected / exposed	0 / 57 (0.00%)	2 / 57 (3.51%)	
occurrences (all)	0	2	
RASH			
subjects affected / exposed	0 / 57 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	2	
Renal and urinary disorders			
Hydronephrosis			
subjects affected / exposed	0 / 57 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	0 / 57 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Hypothyroidism			
subjects affected / exposed	0 / 57 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue			

disorders				
Arthralgia				
subjects affected / exposed	1 / 57 (1.75%)	2 / 57 (3.51%)		
occurrences (all)	1	2		
Bone pain				
subjects affected / exposed	1 / 57 (1.75%)	0 / 57 (0.00%)		
occurrences (all)	1	0		
Muscular weakness				
subjects affected / exposed	1 / 57 (1.75%)	0 / 57 (0.00%)		
occurrences (all)	1	0		
Musculoskeletal chest pain				
subjects affected / exposed	1 / 57 (1.75%)	0 / 57 (0.00%)		
occurrences (all)	1	0		
Musculoskeletal pain				
subjects affected / exposed	2 / 57 (3.51%)	0 / 57 (0.00%)		
occurrences (all)	2	0		
Myalgia				
subjects affected / exposed	1 / 57 (1.75%)	1 / 57 (1.75%)		
occurrences (all)	2	1		
Pain in extremity				
subjects affected / exposed	1 / 57 (1.75%)	1 / 57 (1.75%)		
occurrences (all)	1	1		
Rotator cuff syndrome				
subjects affected / exposed	1 / 57 (1.75%)	1 / 57 (1.75%)		
occurrences (all)	1	1		
Bone cyst				
subjects affected / exposed	0 / 57 (0.00%)	1 / 57 (1.75%)		
occurrences (all)	0	1		
Intervertebral disc protrusion				
subjects affected / exposed	0 / 57 (0.00%)	1 / 57 (1.75%)		
occurrences (all)	0	1		
Lumbar spinal stenosis				
subjects affected / exposed	0 / 57 (0.00%)	1 / 57 (1.75%)		
occurrences (all)	0	1		
Osteoarthritis				

subjects affected / exposed	0 / 57 (0.00%)	2 / 57 (3.51%)	
occurrences (all)	0	2	
Infections and infestations			
Influenza			
subjects affected / exposed	3 / 57 (5.26%)	4 / 57 (7.02%)	
occurrences (all)	3	4	
Nasopharyngitis			
subjects affected / exposed	2 / 57 (3.51%)	5 / 57 (8.77%)	
occurrences (all)	2	6	
Gastroenteritis			
subjects affected / exposed	0 / 57 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	2	
Urinary tract infection			
subjects affected / exposed	0 / 57 (0.00%)	2 / 57 (3.51%)	
occurrences (all)	0	3	
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	4 / 57 (7.02%)	2 / 57 (3.51%)	
occurrences (all)	4	2	
Diabetes mellitus non insulin dependent			
subjects affected / exposed	1 / 57 (1.75%)	0 / 57 (0.00%)	
occurrences (all)	1	0	
Glucose tolerance impaired			
subjects affected / exposed	1 / 57 (1.75%)	0 / 57 (0.00%)	
occurrences (all)	1	0	
Fluid retention			
subjects affected / exposed	0 / 57 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Hyperkalaemia			
subjects affected / exposed	0 / 57 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	
Iron deficiency			
subjects affected / exposed	0 / 57 (0.00%)	1 / 57 (1.75%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 February 2007	Protocol amendment 1 was issued primarily to change the proportion of subjects treated by pegvisomant and somatostatin analogues at study entry. The restriction that 50% of subjects should be previously treated with daily pegvisomant, and 50% should previously be treated with a somatostatin analogue (25% with lanreotide Autogel, 25% with octreotide LAR) was removed in order to improve recruitment into the study. Currently about 4% of patients with acromegaly receive daily treatment with pegvisomant across Europe. Aiming to have a fixed percentage of subjects previously treated by pegvisomant (that is 30 evaluable subjects) is not realistic considering the current therapeutic regimen of patients with acromegaly. In addition the criteria for hepatic toxicity was modified from Aspartate Amino Transferase (AST), Alanine Amino Transferase (ALT), Gamma Glutamyl Transferase (GGT), Alkaline Phosphatase (ALP), prothrombin time or total bilirubin > 2 x Upper Limit of Normal (ULN) to AST or ALT, > 2 x ULN; the number of participating sites was increased from 25 to 30; and the protocol was modified for the use of paper CRFs instead of electronic data capture (EDC).
24 June 2008	Protocol amendment 2 was issued to include a sensitivity analysis of the primary efficacy endpoint as an additional secondary endpoint. This additional endpoint assessed the correlation between changes in QoL with corresponding changes in z-score for IGF-1 levels. In addition protocol amendment 2 detailed the change in the location of analysis for lanreotide Autogel serum concentrations from Ipsen Pharma S.A. to SGS Cephac Europe.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported