Clinical trial results:
A phase III, multicenter, randomized, parallel-group study to assess the efficacy and safety of double-blind pasireotide LAR 40 mg and pasireotide LAR 60 mg versus open-label octreotide LAR or lanreotide ATG in patients with inadequately controlled acromegaly

Summary

EudraCT number	2009-016722-13
Trial protocol	FR ES IT NO BE DE PL GB
Global end of trial date	28 February 2017

Results information

Result version number	v1 (current)
This version publication date	16 March 2018
First version publication date	16 March 2018

Trial information

Trial identification

Sponsor protocol code	CSOM230C2402

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01137682
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novaratis Pharma AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@novartis.com
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@novartis.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	
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 February 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 February 2017
Global end of trial reached?	Yes
Global end of trial date	28 February 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to compare the proportion of patients achieving biochemical control defined as mean GH levels < 2.5 µg/L and normalization of sex- and age-adjusted IGF-1 at 24 weeks with pasireotide LAR 40 mg and pasireotide LAR 60 mg separately versus continuing the same treatment with octreotide LAR 30 mg or lanreotide ATG 120 mg

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 July 2010
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	Argentina: 6
Country: Number of subjects enrolled	Belgium: 2
Country: Number of subjects enrolled	Brazil: 62
Country: Number of subjects enrolled	Canada: 2
Country: Number of subjects enrolled	Colombia: 5
Country: Number of subjects enrolled	France: 19
Country: Number of subjects enrolled	Germany: 6
Country: Number of subjects enrolled	United Kingdom: 1
Country: Number of subjects enrolled	Israel: 3
Country: Number of subjects enrolled	Italy: 44
Country: Number of subjects enrolled	Norway: 2
Country: Number of subjects enrolled	Poland: 10
Country: Number of subjects enrolled	Romania: 6
Country: Number of subjects enrolled	Russian Federation: 12
Country: Number of subjects enrolled	Saudi Arabia: 4
Country: Number of subjects enrolled	Spain: 3
Country: Number of subjects enrolled	Turkey: 4

Country: Number of subjects enrolled	United States: 7
Worldwide total number of subjects	198
EEA total number of subjects	93

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)	182
From 65 to 84 years	16
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

One hundred ninety-eight patients were randomized and 5 patients in CORE and 1 patient in extension did not receive any study treatment

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Data analyst, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Pasireotide LAR 40 mg

Arm description:

Supplied in blinded fashion as 20 and 40 mg powder in vials and 2 mL vehicle in ampoule (for reconstitution) for intramuscular administration every 28 days

Arm type	Experimental
Investigational medicinal product name	pasireotide LAR
Investigational medicinal product code	SOM230
Other name	
Pharmaceutical forms	Powder and solution for solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

20 mg and/or 40 mg powder in vials and 2 mL vehicle ampoules for reconstitution. Administered every 28 ± 2 days

Arm title	Pasireotide LAR 60 mg

Arm description:

Supplied in blinded fashion as 20 and 40 mg powder in vials and 2 mL vehicle in ampoule (for reconstitution) for intramuscular administration every 28 days

Arm type	Experimental
Investigational medicinal product name	pasireotide LAR
Investigational medicinal product code	SOM230
Other name	
Pharmaceutical forms	Powder and solution for solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

20 mg and/or 40 mg powder in vials and 2 mL vehicle ampoules for reconstitution.

Arm title	Control arm (octreotide or lanreotide)

Arm description:

Open label octreotide LAR 30 mg or lanreotide ATG 120 mg supplied either locally or from designated depot. Administered intramuscular every 28 days

Arm type	Active comparator

Investigational medicinal product name	lanreotide ATG
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solution for solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:
lanreotide ATG 120 mg every 28 ± 2 days

Investigational medicinal product name	octreotide LAR
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solution for solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:
30 mg every 28 ± 2 days

Number of subjects in period 1	Pasireotide LAR 40 mg	Pasireotide LAR 60 mg	Control arm (octreotide or lanreotide)
Started	65	65	68
Not Treated	2 [1]	2 [2]	1 [3]
Treated	63	63	67
Completed 24-Week Core Phase	59	57	65
Not Continuing into Extension	2 [4]	3 [5]	2 [6]
Continuing into Extension	57	54	63
Safety Set - CORE	63	62	66
Safety Set - Extension	57	54	62
Completed	28	25	34
Not completed	37	40	34
Adverse Event-CORE	2	4	-
Did not enter extension	2	3	2
Protocol Violation-CORE	-	1	1
Lack of Efficacy-Extension	15	9	13
Withdrawal by Subject-Extension	6	8	8
Death-Extension	2	-	-
Administrative problems-Extension	-	2	-
Administrative problems-CORE	2	1	-
Did not receive treatment in extension	-	-	1
Adverse Event-Extension	4	8	7
Lost to Follow Up-Extension	-	1	-
Withdrawal by Subject-CORE	2	2	2
Protocol Violation-Extension	2	1	-

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: The core and extension phase were combined into Overall Study. The milestone categories were used to present more detail on the status of patients throughout the trial.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: The core and extension phase were combined into Overall Study. The milestone categories were used to present more detail on the status of patients throughout the trial.

[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: The core and extension phase were combined into Overall Study. The milestone categories were used to present more detail on the status of patients throughout the trial.

[4] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: The core and extension phase were combined into Overall Study. The milestone categories were used to present more detail on the status of patients throughout the trial.

[5] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: The core and extension phase were combined into Overall Study. The milestone categories were used to present more detail on the status of patients throughout the trial.

[6] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: The core and extension phase were combined into Overall Study. The milestone categories were used to present more detail on the status of patients throughout the trial.

Baseline characteristics

Reporting groups	
Reporting group title	Pasireotide LAR 40 mg
Reporting group description:	
Supplied in blinded fashion as 20 and 40 mg powder in vials and 2 mL vehicle in ampoule (for reconstitution) for intramuscular administration every 28 days	
Reporting group title	Pasireotide LAR 60 mg
Reporting group description:	
Supplied in blinded fashion as 20 and 40 mg powder in vials and 2 mL vehicle in ampoule (for reconstitution) for intramuscular administration every 28 days	
Reporting group title	Control arm (octreotide or lanreotide)
Reporting group description:	
Open label octreotide LAR 30 mg or lanreotide ATG 120 mg supplied either locally or from designated depot. Administered intramuscular every 28 days	

Reporting group values	Pasireotide LAR 40 mg	Pasireotide LAR 60 mg	Control arm (octreotide or lanreotide)
Number of subjects	65	65	68
Age, Customized			
CORE Period			
Units: Subjects			
<65 Years|	62	57	63
≥ 65 Years|	3	8	5
Age continuous			
Units: years			
arithmetic mean	42.9	45.8	46.2
standard deviation	± 14.05	± 14.07	± 13.11
Sex: Female, Male			
CORE Period			
Units: Subjects			
Female	38	35	38
Male	27	30	30
Race/Ethnicity, Customized			
CORE Period			
Units: Subjects			
Caucasian|	53	52	56
Black|	3	8	4
Other|	4	3	7
Native American|	2	1	1
Asian|	3	1	0

Reporting group values	Total		
Number of subjects	198		
Age, Customized			
CORE Period			
Units: Subjects			
<65 Years|	182		
≥ 65 Years|	16		

Age continuous Units: years arithmetic mean standard deviation	- 		
Sex: Female, Male			
CORE Period			
Units: Subjects			
Female	111		
Male	87		
Race/Ethnicity, Customized			
CORE Period			
Units: Subjects			
Caucasian|	161		
Black|	15		
Other|	14		
Native American|	4		
Asian|	4		

Subject analysis sets

Subject analysis set title	Pasireotide LAR 40 mg Extension
Subject analysis set type	Intention-to-treat

Subject analysis set description:

If controlled on 40 mg in CORE, remain on blinded 40 mg in extension. If patient became uncontrolled, switch to open label 60 mg

Subject analysis set title	Pasireotide LAR 60 mg Extension
Subject analysis set type	Intention-to-treat

Subject analysis set description:

If controlled on 60 mg in CORE, remain on blinded 60 mg in extension. If patient became uncontrolled, switch to open label 60 mg

Subject analysis set title	Cross over to pasireotide Extension
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Open - label 60 mg pasireotide. Control group from CORE discontinued study if controlled in CORE. If uncontrolled in CORE, switched to open label 60 mg pasireotide. Extension blinded 40 and 60 mg switched to open label if became uncontrolled.

Subject analysis set title	PK trough
Subject analysis set type	Sub-group analysis

Subject analysis set description:

PK trough concentrations for patients on 40 and 60 mg pasireotide LAR in extension phase

Reporting group values	Pasireotide LAR 40 mg Extension	Pasireotide LAR 60 mg Extension	Cross over to pasireotide Extension
Number of subjects	57	54	62
Age, Customized			
CORE Period			
Units: Subjects			
<65 Years|			
≥ 65 Years|			
Age continuous Units: years arithmetic mean	 42.5	 45.1	 46.8

standard deviation	± 13.11	± 14.22	± 13.31

Sex: Female, Male			
CORE Period			
Units: Subjects			
Female Male			
Race/Ethnicity, Customized			
CORE Period			
Units: Subjects			
Caucasian| Black| Other| Native American| Asian|			

Reporting group values	PK trough		
Number of subjects	98		
Age, Customized			
CORE Period			
Units: Subjects			
<65 Years| ≥ 65 Years|			
Age continuous Units: years arithmetic mean standard deviation	 ±		
Sex: Female, Male			
CORE Period			
Units: Subjects			
Female Male			
Race/Ethnicity, Customized			
CORE Period			
Units: Subjects			
Caucasian| Black| Other| Native American| Asian|			

End points

End points reporting groups

Reporting group title	Pasireotide LAR 40 mg
Reporting group description:	
Supplied in blinded fashion as 20 and 40 mg powder in vials and 2 mL vehicle in ampoule (for reconstitution) for intramuscular administration every 28 days	
Reporting group title	Pasireotide LAR 60 mg
Reporting group description:	
Supplied in blinded fashion as 20 and 40 mg powder in vials and 2 mL vehicle in ampoule (for reconstitution) for intramuscular administration every 28 days	
Reporting group title	Control arm (octreotide or lanreotide)
Reporting group description:	
Open label octreotide LAR 30 mg or lanreotide ATG 120 mg supplied either locally or from designated depot. Administered intramuscular every 28 days	
Subject analysis set title	Pasireotide LAR 40 mg Extension
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
If controlled on 40 mg in CORE, remain on blinded 40 mg in extension. If patient became uncontrolled, switch to open label 60 mg	
Subject analysis set title	Pasireotide LAR 60 mg Extension
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
If controlled on 60 mg in CORE, remain on blinded 60 mg in extension. If patient became uncontrolled, switch to open label 60 mg	
Subject analysis set title	Cross over to pasireotide Extension
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Open - label 60 mg pasireotide. Control group from CORE discontinued study if controlled in CORE. If uncontrolled in CORE, switched to open label 60 mg pasireotide. Extension blinded 40 and 60 mg switched to open label if became uncontrolled.	
Subject analysis set title	PK trough
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
PK trough concentrations for patients on 40 and 60 mg pasireotide LAR in extension phase	

Primary: Percentage of participants with a reduction of mean GH levels to < 2.5 µg/L and normalization of sex- and age-adjusted IGF-1.

End point title	Percentage of participants with a reduction of mean GH levels to < 2.5 µg/L and normalization of sex- and age-adjusted IGF-1.
End point description:	
The primary objective of this study was to compare the percentage of patients achieving biochemical control (defined as mean GH levels <2.5 µg/L and normalization of sex- and age- adjusted IGF-1) at 24 weeks with pasireotide LAR 40 mg and pasireotide LAR 60 mg separately versus continuing the same treatment with octreotide LAR 30 mg or lanreotide ATG 120 mg.	
End point type	Primary
End point timeframe:	
At 24 weeks	

End point values	Pasireotide LAR 40 mg	Pasireotide LAR 60 mg	Control arm (octreotide or lanreotide)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	65	65	68	
Units: percentage of participants				
number (confidence interval 95%)	15.4 (7.63 to 26.48)	20.0 (11.10 to 31.77)	0 (0 to 5.28)	

Statistical analyses

Statistical analysis title	40 LAR vs. Control
Comparison groups	Pasireotide LAR 40 mg v Control arm (octreotide or lanreotide)
Number of subjects included in analysis	133
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0006
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Variability estimate	Standard error of the mean
Dispersion value	16.63

Statistical analysis title	60 LAR vs. Control
Comparison groups	Pasireotide LAR 60 mg v Control arm (octreotide or lanreotide)
Number of subjects included in analysis	133
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Variability estimate	Standard error of the mean
Dispersion value	23.03

Secondary: Percentage of patients with mean GH < 2.5 µg/L and normalization of IGF-1, treated with pasireotide LAR alone or with concomitant medications used to treat acromegaly (Extension Full analysis set)

End point title	Percentage of patients with mean GH < 2.5 µg/L and normalization of IGF-1, treated with pasireotide LAR alone or with concomitant medications used to treat acromegaly (Extension Full analysis set)

End point description:

The percentage of patients achieving mean growth hormone (GH) levels < 2.5 µg/L and normalization of sex and age-adjusted IGF-1 was calculated with two sided 95% confidence interval. All GH assessments were based on a 5-point mean growth hormone (GH) assessed from a 2-hour profile. Scheduled time points for blood sampling were pre-dose at 0, 30, 60, 90 and 120 minutes. Total insulin-like growth factor (IGF-1) levels were assessed with one pre-dose sample at the same visits as GH. Concomitant medication known to affect GH or IGF-1 levels were allowed in patients who were not biochemically controlled after at least one year treatment with pasireotide LAR monotherapy: dopamine agonists and

growth hormone receptor antagonists (extension full analysis set)

End point type	Secondary

End point timeframe:

Extension baseline up to approximately week 268

End point values	Pasireotide LAR 40 mg Extension	Pasireotide LAR 60 mg Extension	Cross over to pasireotide Extension	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	57	54	62	
Units: percentage of participants				
number (confidence interval 95%)				
Week 16|	19.3 (10.05 to 31.91)	25.9 (14.96 to 39.65)	19.4 (10.42 to 31.37)	
Week 28|	17.5 (8.75 to 29.91)	25.9 (14.96 to 39.65)	19.4 (10.42 to 31.37)	
Week 40|	21.1 (11.38 to 33.89)	27.8 (16.46 to 41.64)	17.7 (9.20 to 29.53)	
Week 52|	21.1 (11.38 to 33.89)	29.6 (17.98 to 43.61)	21.0 (11.66 to 33.18)	
Week 64|	22.8 (12.74 to 35.84)	20.4 (10.63 to 33.53)	25.8 (15.53 to 38.50)	
Week 76|	21.1 (11.38 to 33.89)	29.6 (17.98 to 43.61)	27.4 (16.85 to 40.23)	
Week 88|	24.6 (14.13 to 37.76)	31.5 (19.52 to 45.55)	25.8 (15.53 to 38.50)	
Week 100|	24.6 (14.13 to 37.76)	24.1 (13.49 to 37.64)	32.3 (20.94 to 45.34)	
Week 112|	24.6 (14.13 to 37.76)	25.9 (14.96 to 39.65)	25.8 (15.53 to 38.50)	
Week 124|	21.1 (11.38 to 33.89)	24.1 (13.49 to 37.64)	25.8 (15.53 to 38.50)	
Week 136|	15.8 (7.48 to 27.87)	24.1 (13.49 to 37.64)	29.0 (18.20 to 41.95)	
Week 148|	21.1 (11.38 to 33.89)	20.4 (10.63 to 33.53)	29.0 (18.20 to 41.95)	
Week 160|	19.3 (10.05 to 31.91)	20.4 (10.63 to 33.53)	30.6 (19.56 to 43.65)	
Week 172|	22.8 (12.74 to 35.84)	20.4 (10.63 to 33.53)	21.0 (11.66 to 33.18)	
Week 184|	17.5 (8.75 to 29.91)	20.4 (10.63 to 33.53)	17.7 (9.20 to 29.53)	
Week 196|	15.8 (7.48 to 27.87)	20.4 (10.63 to 33.53)	24.2 (14.22 to 36.74)	
Week 208|	17.5 (8.75 to 29.91)	18.5 (9.25 to 31.43)	19.4 (10.42 to 31.37)	
Week 220|	21.1 (11.38 to 33.89)	11.1 (4.19 to 22.63)	14.5 (6.86 to 25.78)	
Week 232|	14.0 (6.26 to 25.79)	14.8 (6.62 to 27.12)	14.5 (6.86 to 25.78)	
Week 244|	14.0 (6.26 to 25.79)	7.4 (2.06 to 17.89)	11.3 (4.66 to 21.89)	
Week 256|	10.5 (3.96 to 21.52)	7.4 (2.06 to 17.89)	3.2 (0.39 to 11.17)	
Week 268|	5.3 (1.10 to 14.62)	5.6 (1.16 to 15.39)	1.6 (0.04 to 8.66)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with normalization of sex- and age-adjusted IGF-1treated with pasireotide LAR alone or with concomitant medications used to treat acromegaly (Extension Full analysis set).

End point title	Percentage of participants with normalization of sex- and age-adjusted IGF-1treated with pasireotide LAR alone or with concomitant medications used to treat acromegaly (Extension Full analysis set).

End point description:

The percentage of patients achieving normalization of sex and age-adjusted IGF-1 was calculated with two sided 95% confidence interval. Total insulin-like growth factor (IGF-1) levels were assessed with one pre-dose sample at the same visits as GH. Concomitant medication known to affect IGF-1 levels were allowed in patients who were not biochemically controlled after at least one year treatment with pasireotide LAR monotherapy: dopamine agonists and growth hormone receptor antagonists (Extension full analysis set)

End point type	Secondary

End point timeframe:

Extension baseline up to approximately week 268

End point values	Pasireotide LAR 40 mg Extension	Pasireotide LAR 60 mg Extension	Cross over to pasireotide Extension	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	57	54	62	
Units: percentage of participants				
number (confidence interval 95%)				
Week 16|	33.3 (21.40 to 47.06)	29.0 (17.98 to 43.61)	25.8 (15.53 to 38.50)	
Week 28|	29.8 (18.43 to 43.40)	33.3 (21.09 to 47.47)	22.6 (12.93 to 34.97)	
Week 40|	36.8 (24.45 to 50.66)	37.0 (24.29 to 51.26)	24.2 (14.22 to 36.74)	
Week 52|	28.1 (16.97 to 41.54)	33.3 (21.09 to 47.47)	25.8 (15.53 to 38.50)	
Week 64|	33.3 (21.40 to 47.06)	27.8 (16.46 to 41.64)	29.0 (18.20 to 41.95)	
Week 76|	26.3 (15.54 to 39.66)	35.2 (22.68 to 49.38)	29.0 (18.20 to 41.95)	
Week 88|	28.1 (16.97 to 41.54)	35.2 (22.68 to 49.38)	25.8 (15.53 to 38.50)	
Week 100|	31.6 (19.91 to 45.24)	29.6 (17.98 to 43.61)	32.3 (20.94 to 45.34)	
Week 112|	31.6 (19.91 to 45.24)	27.8 (16.46 to 41.64)	30.6 (19.56 to 43.65)	
Week 124|	24.6 (14.13 to 37.76)	31.5 (19.52 to 45.55)	29.0 (18.20 to 41.95)	

Week 136|	21.1 (11.38 to 33.89)	25.9 (14.96 to 39.65)	37.1 (25.16 to 50.31)	
Week 148|	26.3 (15.54 to 39.66)	22.2 (12.04 to 35.60)	33.9 (22.33 to 47.01)	
Week 160|	24.6 (14.13 to 37.76)	25.9 (14.96 to 39.65)	33.9 (22.33 to 47.01)	
Week 172|	26.3 (15.54 to 39.66)	22.2 (12.04 to 35.60)	22.6 (12.93 to 34.97)	
Week 184|	19.3 (10.05 to 31.91)	22.2 (12.04 to 35.60)	22.6 (12.93 to 34.97)	
Week 196|	24.6 (14.13 to 37.76)	22.2 (12.04 to 35.60)	27.4 (16.85 to 40.23)	
Week 208|	22.8 (12.74 to 35.84)	22.2 (12.04 to 35.60)	21.0 (11.66 to 33.18)	
Week 220|	22.8 (12.74 to 35.84)	11.1 (4.19 to 22.63)	19.4 (10.42 to 31.37)	
Week 232|	14.0 (6.26 to 25.79)	14.8 (6.62 to 27.12)	17.7 (9.20 to 29.53)	
Week 244|	14.0 (6.26 to 25.79)	9.3 (3.08 to 20.30)	14.5 (6.86 to 25.78)	
Week 256|	12.3 (5.08 to 23.68)	7.4 (2.06 to 17.89)	6.5 (1.79 to 15.70)	
Week 268|	5.3 (1.10 to 14.62)	5.6 (1.16 to 15.39)	1.6 (0.04 to 8.66)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of patients with mean GH < 2.5 µg/L treated with pasireotide LAR alone or with concomitant medications used to treat acromegaly (extension full analysis set)

End point title	Percentage of patients with mean GH < 2.5 µg/L treated with pasireotide LAR alone or with concomitant medications used to treat acromegaly (extension full analysis set)

End point description:

The percentage of patients achieving mean growth hormone (GH) levels < 2.5 µg/L was calculated with two sided 95% confidence interval. All GH assessments were based on a 5-point mean growth hormone (GH) assessed from a 2-hour profile. Scheduled time points for blood sampling were pre-dose at 0, 30, 60, 90 and 120 minutes. Concomitant medication known to affect GH levels were allowed in patients who were not biochemically controlled after at least one year treatment with pasireotide LAR monotherapy: dopamine agonists and growth hormone receptor antagonists (Extension full analysis set)

End point type	Secondary

End point timeframe:

Extension baseline up to approximately week 268

End point values	Pasireotide LAR 40 mg Extension	Pasireotide LAR 60 mg Extension		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	57	54		
Units: percentage of participants				
number (confidence interval 95%)				

Week 16|	38.6 (26.00 to 52.43)	55.6 (41.40 to 69.08)		
Week 28|	40.4 (27.56 to 54.18)	44.4 (30.92 to 58.60)		
Week 40|	38.6 (26.00 to 52.43)	42.6 (29.23 to 56.79)		
Week 52|	38.6 (26.00 to 52.43)	46.3 (32.62 to 60.39)		
Week 64|	40.4 (27.56 to 54.18)	37.0 (24.29 to 51.26)		
Week 76|	33.3 (21.40 to 47.06)	44.4 (30.92 to 58.60)		
Week 88|	40.4 (27.56 to 54.18)	42.6 (29.23 to 56.79)		
Week 100|	40.4 (27.56 to 54.18)	40.7 (27.57 to 54.97)		
Week 112|	36.8 (24.45 to 50.66)	44.4 (30.92 to 58.60)		
Week 124|	40.4 (27.56 to 54.18)	31.5 (19.52 to 45.55)		
Week 136|	36.8 (24.45 to 50.66)	35.2 (22.68 to 49.38)		
Week 148|	40.4 (27.56 to 54.18)	33.3 (21.09 to 47.47)		
Week 160|	38.6 (26.00 to 52.43)	33.3 (21.09 to 47.47)		
Week 172|	40.4 (27.56 to 54.18)	37.0 (24.29 to 51.26)		
Week 184|	33.3 (21.40 to 47.06)	31.5 (19.52 to 45.55)		
Week 196|	29.8 (18.43 to 43.40)	29.6 (17.98 to 43.61)		
Week 208|	31.6 (19.91 to 45.24)	24.1 (13.49 to 37.64)		
Week 220|	29.8 (18.43 to 43.40)	18.5 (9.25 to 31.43)		
Week 232|	24.6 (14.3 to 37.76)	18.5 (9.25 to 31.43)		
Week 244|	19.3 (10.05 to 31.91)	11.1 (4.19 to 22.63)		
Week 256|	15.8 (7.48 to 27.87)	9.3 (3.08 to 20.30)		
Week 268|	7.0 (1.95 to 17.00)	5.6 (1.16 to 15.39)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of patients with mean GH < 1.0 µg/L and normalization of IGF-1, treated with pasireotide LAR alone or with concomitant medications used to treat acromegaly (Extension Full analysis set)

End point title	Percentage of patients with mean GH < 1.0 µg/L and normalization of IGF-1, treated with pasireotide LAR alone or with concomitant medications used to treat acromegaly (Extension Full analysis set)

End point description:

The percentage of patients achieving mean growth hormone (GH) levels < 1.0 µg/L and normalization of

sex and age-adjusted IGF-1 was calculated with two sided 95% confidence interval. All GH assessments were based on a 5-point mean growth hormone (GH) assessed from a 2-hour profile. Scheduled time points for blood sampling were pre-dose at 0, 30, 60, 90 and 120 minutes. Total insulin-like growth factor (IGF-1) levels were assessed with one pre-dose sample at the same visits as GH. Concomitant medication known to affect GH or IGF-1 levels were allowed in patients who were not biochemically controlled after at least one year treatment with pasireotide LAR monotherapy: dopamine agonists and growth hormone receptor antagonists (Extension full analysis set

End point type	Secondary

End point timeframe:

Extension baseline up to approximately week 268

End point values	Pasireotide LAR 40 mg Extension	Pasireotide LAR 60 mg Extension	Cross over to pasireotide Extension	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	57	54	62	
Units: Participants				
number (confidence interval 95%)				
Week 16|	10.5 (3.96 to 21.52)	16.7 (7.92 to 29.29)	6.5 (1.79 to 15.70)	
Week 28|	8.8 (2.91 to 19.30)	14.8 (6.62 to 27.12)	8.1 (2.67 to 17.83)	
Week 40|	10.5 (3.96 to 21.52)	9.3 (3.08 to 20.30)	4.8 (1.01 to 13.50)	
Week 52|	8.8 (2.91 to 19.30)	13.0 (5.37 to 24.90)	4.8 (1.01 to 13.50)	
Week 64|	8.8 (2.91 to 19.30)	13.0 (5.37 to 24.90)	9.7 (3.63 to 19.88)	
Week 76|	10.5 (3.96 to 21.52)	13.0 (5.37 to 24.90)	6.5 (1.79 to 15.70)	
Week 88|	7.0 (1.95 to 17.00)	20.4 (10.63 to 33.53)	4.8 (1.01 to 13.50)	
Week 100|	12.3 (5.08 to 23.68)	14.8 (6.62 to 27.12)	8.1 (2.67 to 17.83)	
Week 112|	14.0 (6.26 to 25.79)	20.4 (10.63 to 33.53)	9.7 (3.63 to 19.88)	
Week 124|	7.0 (1.95 to 17.00)	14.8 (6.62 to 27.12)	8.1 (2.67 to 17.83)	
Week 136|	3.5 (0.43 to 12.11)	18.5 (9.25 to 31.43)	11.3 (4.66 to 21.89)	
Week 148|	10.5 (3.96 to 21.52)	14.8 (6.62 to 27.12)	8.1 (2.67 to 17.83)	
Week 160|	8.8 (2.91 to 19.30)	14.8 (6.62 to 27.12)	9.7 (3.63 to 19.88)	
Week 172|	14.0 (6.26 to 25.79)	13.0 (5.37 to 24.90)	8.1 (2.67 to 17.83)	
Week 184|	7.0 (1.95 to 17.00)	13.0 (5.37 to 24.90)	3.2 (0.39 to 11.17)	
Week 196|	8.8 (2.91 to 19.30)	13.0 (5.37 to 24.90)	8.1 (2.67 to 17.83)	
Week 208|	8.8 (2.91 to 19.30)	9.3 (3.08 to 20.30)	6.5 (1.79 to 15.70)	
Week 220|	10.5 (3.96 to 21.52)	7.4 (2.06 to 17.89)	6.5 (1.79 to 15.70)	
Week 232|	10.5 (3.96 to 21.52)	3.7 (0.45 to 12.75)	4.8 (1.01 to 13.50)	
Week 244|	8.8 (2.91 to 19.30)	3.7 (0.45 to 12.75)	6.5 (1.79 to 15.70)	

Week 256|	8.8 (2.91 to 19.30)	3.7 (0.45 to 12.75)	3.2 (0.39 to 11.17)	
Week 268|	1.8 (0.04 to 9.39)	3.7 (0.45 to 12.75)	1.6 (0.04 to 8.66)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of patients with mean GH <1.0 µg/L treated with pasireotide LAR alone or with concomitant medications used to treat acromegaly (Extension Full analysis set)

End point title	Percentage of patients with mean GH <1.0 µg/L treated with pasireotide LAR alone or with concomitant medications used to treat acromegaly (Extension Full analysis set)

End point description:

The percentage of patients achieving mean growth hormone (GH) levels < 1.0 µg/L was calculated with two sided 95% confidence interval. All GH assessments were based on a 5-point mean growth hormone (GH) assessed from a 2-hour profile. Scheduled time points for blood sampling were pre-dose at 0, 30, 60, 90 and 120 minutes. Concomitant medication known to affect GH levels were allowed in patients who were not biochemically controlled after at least one year treatment with pasireotide LAR monotherapy: dopamine agonists and growth hormone receptor antagonists (Extension full analysis set)

End point type	Secondary

End point timeframe:

Extension baseline up to approximately week 268

End point values	Pasireotide LAR 40 mg Extension	Pasireotide LAR 60 mg Extension	Cross over to pasireotide Extension	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	57	54	62	
Units: percentage of participants				
number (confidence interval 95%)				
Week 16|	14.0 (6.26 to 25.79)	27.8 (16.46 to 41.64)	8.1 (2.67 to 17.83)	
Week 28|	14.0 (6.26 to 25.79)	22.2 (12.04 to 35.60)	9.7 (3.63 to 19.88)	
Week 40|	14.0 (6.26 to 25.79)	13.0 (5.37 to 24.90)	4.8 (1.01 to 13.50)	
Week 52|	12.3 (5.08 to 23.68)	22.2 (12.04 to 35.60)	9.7 (3.63 to 19.88)	
Week 64|	15.8 (7.48 to 27.87)	18.5 (9.25 to 31.43)	11.3 (4.66 to 21.89)	
Week 76|	12.3 (5.08 to 23.68)	22.2 (12.04 to 35.60)	11.3 (4.66 to 21.89)	
Week 88|	15.8 (7.48 to 27.87)	22.2 (12.04 to 35.60)	11.3 (4.66 to 21.89)	
Week 100|	17.5 (8.75 to 29.91)	20.4 (10.63 to 33.53)	17.7 (9.20 to 29.53)	
Week 112|	17.5 (8.75 to 29.91)	25.9 (14.96 to 39.65)	16.1 (8.02 to 27.67)	
Week 124|	12.3 (5.08 to 23.68)	16.7 (7.92 to 29.29)	14.5 (6.86 to 25.78)	

Week 136|	8.8 (2.91 to 19.30)	25.9 (14.96 to 39.65)	14.5 (6.86 to 25.78)	
Week 148|	14.0 (6.26 to 25.79)	16.7 (7.92 to 29.29)	14.5 (6.86 to 25.78)	
Week 160|	17.5 (8.75 to 29.91)	18.5 (9.25 to 31.43)	14.5 (6.86 to 25.78)	
Week 172|	17.5 (8.75 to 29.91)	14.8 (6.62 to 27.12)	14.5 (6.86 to 25.78)	
Week 184|	17.5 (8.75 to 29.91)	18.5 (9.25 to 31.43)	6.5 (1.79 to 15.70)	
Week 196|	15.8 (7.48 to 27.87)	13.0 (5.37 to 24.90)	12.9 (5.74 to 23.85)	
Week 208|	17.5 (8.75 to 29.91)	13.0 (5.37 to 24.90)	9.7 (3.63 to 19.88)	
Week 220|	15.8 (7.48 to 27.87)	11.1 (4.19 to 22.63)	9.7 (3.63 to 19.88)	
Week 232|	15.8 (7.48 to 27.87)	3.7 (0.45 to 12.75)	8.1 (2.67 to 17.83)	
Week 244|	12.3 (5.08 to 23.68)	5.6 (1.16 to 15.39)	8.1 (2.67 to 17.83)	
Week 256|	12.3 (5.08 to 23.68)	3.7 (0.45 to 12.75)	4.8 (1.01 to 13.50)	
Week 268|	3.5 (0.43 to 12.11)	3.7 (0.45 to 12.75)	1.6 (0.04 to 8.66)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in mean GH values for patients treated with pasireotide LAR alone or with concomitant medications used to treat acromegaly for CORE visits (extension full analysis set)

End point title	Change from baseline in mean GH values for patients treated with pasireotide LAR alone or with concomitant medications used to treat acromegaly for CORE visits (extension full analysis set)[1]

End point description:

End point type	Secondary

End point timeframe:

CORE baseline up to approximately 24 weeks

Notes:

[1] - 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 endpoint means presented was for the two active arms (40 and 60 mg) compared to the control arm.

End point values	Pasireotide LAR 40 mg	Pasireotide LAR 60 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57	54		
Units: mcg/L				
arithmetic mean (standard deviation)				
Week 12 - CORE (n=57,52)|	-0.8 (± 29.77)	-6.4 (± 14.35)		
Week 24 - CORE (n=54,48)|	-0.6 (± 32.38)	-7.2 (± 15.19)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in mean GH values for patients treated with pasireotide LAR alone or with concomitant medications used to treat acromegaly for extension visits (extension full analysis set)

End point title	Change from baseline in mean GH values for patients treated with pasireotide LAR alone or with concomitant medications used to treat acromegaly for extension visits (extension full analysis set)

End point description:

Change from CORE baseline at each scheduled assessment was performed for patients randomized to pasireotide arms. Change from extension baseline at each scheduled assessment was performed for patients randomized to active control arm.

End point type	Secondary

End point timeframe:

CORE and extension baseline up to approximately 268 weeks

End point values	Pasireotide LAR 40 mg Extension	Pasireotide LAR 60 mg Extension	Cross over to pasireotide Extension	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	57	54	62	
Units: mcg/L				
arithmetic mean (standard deviation)				
Week 16 - extension (n=44,46,57)|	-7.9 (± 24.90)	-6.9 (± 14.88)	-8.4 (± 49.64)	
Week 28 - extension (n=44,39,56)|	-9.0 (± 24.21)	-4.5 (± 4.12)	-3.0 (± 3.86)	
Week 40 - extension (n=38,36,50)|	-9.7 (± 25.40)	-5.8 (± 13.93)	-11.2 (± 58.28)	
Week 52 - extension (n=36,35,46)|	-10.7 (± 26.60)	-7.1 (± 17.08)	-2.5 (± 3.02)	
Week 64 - extension (n=37,33,39)|	-11.3 (± 28.37)	-7.9 (± 17.30)	-15.7 (± 76.06)	
Week 76 - extension (n=32,36,42)|	-5.5 (± 5.96)	-7.2 (± 16.16)	-3.5 (± 4.27)	
Week 88 - extension (n=32,32,40)|	-5.7 (± 6.21)	-6.2 (± 8.55)	-3.6 (± 3.22)	
Week 100 - extension (n=34,31,39)|	-5.6 (± 5.71)	-5.3 (± 5.06)	-3.8 (± 4.28)	
Week 112 - extension (n=30,32,35)|	-5.8 (± 6.03)	-4.4 (± 6.57)	-3.9 (± 5.13)	
Week 124 - extension (n=30,26,35)|	-5.5 (± 5.85)	-6.0 (± 6.26)	-4.0 (± 4.36)	
Week 136 - extension (n=28,26,36)|	-6.0 (± 6.59)	-5.3 (± 4.99)	-4.0 (± 4.44)	
Week 148 - extension (n=29,25,35)|	-6.3 (± 6.21)	6.1 (± 6.28)	-3.8 (± 3.11)	
Week 160 - extension (n=29,26,33)|	-5.5 (± 4.70)	-4.9 (± 5.33)	-3.2 (± 2.25)	
Week 172 - extension (n=27,26,31)|	-6.3 (± 6.34)	-5.9 (± 5.97)	-3.0 (± 2.47)	
Week 184 - extension (n=23,25,29)|	-6.3 (± 5.44)	-5.8 (± 5.79)	-3.3 (± 2.31)	
Week 196 - extension (n=22,21,29)|	-7.1 (± 6.81)	-6.5 (± 7.17)	-3.4 (± 2.71)	
Week 208 - extension (n=22,20,23)|	-7.0 (± 6.82)	-6.2 (± 6.22)	-3.5 (± 2.50)	

Week 220 - extension (n=20,14,20)|	-7.1 (± 6.91)	-7.1 (± 8.12)	-3.8 (± 2.48)	
Week 232 - extension (n=16,15,14)|	-5.7 (± 5.46)	-6.8 (± 8.10)	-4.2 (± 2.46)	
Week 244 - extension (n=12,7,11)|	-6.0 (± 6.03)	-2.4 (± 0.90)	-4.2 (± 2.58)	
Week 256 - extension (n=10,6,6)|	-6.4 (± 5.91)	-4.9 (± 3.49)	-5.0 (± 3.26)	
Week 268 - extension (n=4,3,3)|	-3.6 (± 1.58)	-2.5 (± 0.57)	-3.7 (± 2.23)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in standardized IGF-1 values for patients treated with pasireotide LAR alone or with concomitant medications used to treat acromegaly for CORE visits (extension full analysis set)

End point title	Change from baseline in standardized IGF-1 values for patients treated with pasireotide LAR alone or with concomitant medications used to treat acromegaly for CORE visits (extension full analysis set)[2]

End point description:

Standardized IGF-1 = IGF-1 value / ULN, where ULN is the upper limit of the normal range

End point type	Secondary

End point timeframe:

CORE baseline up to approximately 24 weeks

Notes:

[2] - 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 endpoint means presented was for the two active arms (40 and 60 mg) compared to the control arm.

End point values	Pasireotide LAR 40 mg	Pasireotide LAR 60 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57	54		
Units: mcg/L				
arithmetic mean (standard deviation)				
CORE Week 12 (n=57,53)|	0.7 (± 0.97)	-1.1 (± 1.03)		
CORE Week 24 (n=56,49)|	-0.7 (± 0.97)	-1.1 (± 1.12)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in standardized IGF-1 values for patients treated with pasireotide LAR alone or with concomitant medications used to treat acromegaly for extension visits (extension full analysis set)

End point title	Change from baseline in standardized IGF-1 values for patients treated with pasireotide LAR alone or with concomitant medications used to treat acromegaly for extension visits (extension full analysis set)

End point description:

Change from CORE baseline at each scheduled assessment was performed for patients randomized to pasireotide arms. Change from extension baseline at each scheduled assessment was performed for

patients randomized to active control arm. Standardized IGF-1 = IGF-1 value / ULN, where ULN is the upper limit of the normal range

End point type	Secondary

End point timeframe:

CORE and extension baseline up to approximately 268 weeks

End point values	Pasireotide LAR 40 mg Extension	Pasireotide LAR 60 mg Extension	Cross over to pasireotide Extension	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	57	54	62	
Units: mcg/L				
arithmetic mean (standard deviation)				
Week 16 extension (n=49,47,61)|	-0.8 (± 0.99)	-1.4 (± 0.97)	-0.9 (± 0.81)	
Week 28 extension (n=45,39,58)|	-0.9 (± 1.00)	-1.3 (± 1.13)	-0.9 (± 0.88)	
Week 40 extension (n=42,37,51)|	-1.1 (± 0.95)	-1.4 (± 0.94)	-1.1 (± 0.91)	
Week 52 extension (n=39,37,46)|	-1.1 (± 0.90)	-1.3 (± 0.95)	-1.1 (± 0.95)	
Week 64 extension (n=37,35,42)|	-1.3 (± 0.99)	-1.4 (± 0.98)	-1.3 (± 0.81)	
Week 76 extension (n=33,36,43)|	-1.3 (± 0.87)	-1.5 (± 0.94)	-1.3 (± 0.84)	
Week 88 extension (n=33,32,41)|	-1.3 (± 0.80)	-1.6 (± 1.01)	-1.3 (± 0.90)	
Week 100 extension (n=32,32,40)|	-1.4 (± 0.93)	-1.5 (± 0.95)	-1.3 (± 0.92)	
Week 112 extension (n=31,32,38)|	-1.5 (± 0.87)	-1.5 (± 1.00)	-1.4 (± 0.89)	
Week 124 extension (n=31,28,38)|	-1.4 (± 0.86)	-1.5 (± 0.95)	-1.3 (± 0.97)	
Week 136 extension (n=29,27,38)|	-1.4 (± 0.91)	-1.7 (± 0.92)	-1.4 (± 0.86)	
Week 148 extension (n=28,26,36)|	-1.4 (± 0.86)	-1.5 (± 0.99)	-1.3 (± 0.84)	
Week 160 extension (n=29,28,34)|	-1.4 (± 0.90)	-1.6 (± 0.87)	-1.4 (± 0.94)	
Week 172 extension (n=26,27,31)|	-1.5 (± 0.81)	-1.6 (± 0.97)	-1.3 (± 0.98)	
Week 184 extension (n=23,25,31)|	-1.3 (± 0.70)	-1.5 (± 1.03)	-1.4 (± 0.93)	
Week 196 extension (n=23,22,29)|	-1.4 (± 0.81)	-1.5 (± 1.11)	-1.3 (± 1.11)	
Week 208 extension (n=23,22,22)|	-1.4 (± 0.79)	-1.6 (± 1.00)	-1.2 (± 0.98)	
Week 220 extension (n=20,14,20)|	-1.4 (± 0.94)	-1.6 (± 1.06)	-1.4 (± 0.91)	
Week 232 extension (n=15,15,15)|	-1.4 (± 0.92)	-1.5 (± 1.13)	-1.7 (± 0.82)	
Week 244 extension (n=12,8,11)|	-1.3 (± 0.75)	-1.9 (± 1.12)	-1.5 (± 0.79)	
Week 256 extension (n=10,6,6)|	-1.3 (± 0.58)	-1.4 (± 1.39)	-1.8 (± 0.90)	
Week 268 extension (n=4,3,3)|	-1.4 (± 0.43)	-1.7 (± 0.39)	-1.7 (± 0.81)	

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of the first response for patients achieving a reduction of mean GH level to < 2.5 µg/L and normalization of IGF-1 and treated with Pasireotide LAR alone or with concomitant medications used to treat acromegaly (extension full analysis set)

End point title	Duration of the first response for patients achieving a reduction of mean GH level to < 2.5 µg/L and normalization of IGF-1 and treated with Pasireotide LAR alone or with concomitant medications used to treat acromegaly (extension full analysis set)

End point description:

n is the number of patients achieving response criteria. The weeks correspond to duration of first response (in weeks) for patients achieving biomedical control. Median and 95% CI are derived from Kaplan-Meier curves. Kaplan-Meier estimates [95% CI] at each time point are estimates of probability of response.

End point type	Secondary

End point timeframe:

CORE baseline up to approximately 268 weeks

End point values	Pasireotide LAR 40 mg Extension	Pasireotide LAR 60 mg Extension	Cross over to pasireotide Extension	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	57	54	62	
Units: weeks				
median (confidence interval 95%)	29.1 (15.6 to 48.1)	26.9 (12.7 to 48.0)	24.9 (12.4 to 47.4)	

Statistical analyses

No statistical analyses for this end point

Secondary: Time to first response (weeks) by treatment for patients achieving a reduction of mean GH level to < 2.5 µg/L and normalization of IGF-1 and treated with Pasireotide LAR alone or with concomitant medications used to treat acromegaly

End point title	Time to first response (weeks) by treatment for patients achieving a reduction of mean GH level to < 2.5 µg/L and normalization of IGF-1 and treated with Pasireotide LAR alone or with concomitant medications used to treat acromegaly

End point description:

Time to first response is defined as the time from the date of first dose to the date of first occurrence of a reduction of mean GH < 2.5 µg/L and the normalization of IGF-1. The weeks correspond to time taken to achieve first mean GH < 2.5 µg/L and the normalization of IGF-1.

End point type	Secondary

End point timeframe:

CORE baseline up to approximately 268 weeks

End point values	Pasireotide LAR 40 mg Extension	Pasireotide LAR 60 mg Extension	Cross over to pasireotide Extension	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	57	54	62	
Units: weeks				
median (confidence interval 95%)	112.3 (76.1 to 254.1)	65.3 (40.4 to 94.9)	95.1 (65.3 to 156.0)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in AcroQoL total scores for patients treated with pasireotide LAR alone or with concomitant medications used to treat acromegaly for CORE visits(extension full analysis set)

End point title	Change from baseline in AcroQoL total scores for patients treated with pasireotide LAR alone or with concomitant medications used to treat acromegaly for CORE visits(extension full analysis set)[3]

End point description:

Acromegaly Quality of Life questionnaire (AcroQoL). AcroQoL is a validated disease specific questionnaire to measure quality of life in patients with acromegaly. The questionnaire is uni-dimensional and contains 22 items divided in two scales: one that evaluates physical aspects (8 items) and another one that evaluates psychological aspects (14 items). The latter is also divided in two sub-scales: physical appearance and personal relationships of the patient (seven items each). The total score and sub-scores will be calculated using the following formula established by the tool developer (Badia, et al 2004): ((X - Y) / 4Y) x 100, X=sum of the scores for individual items (between 1 and 5 for each item),Y=number of individual items included in above sum (i.e. 22 for the total score, 8 for the physical sub-score, 14 for the psychological sub-score, 7 for the sub-score 'appearance' and 'personal relations'). If more than 25% of items are not completed, results will be considered invalid.

End point type	Secondary

End point timeframe:

CORE baseline up to approximately 24 weeks

Notes:

[3] - 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 endpoint means presented was for the two active arms (40 and 60 mg) compared to the control arm.

End point values	Pasireotide LAR 40 mg	Pasireotide LAR 60 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57	54		
Units: scores				
arithmetic mean (standard deviation)				
Week 4 CORE (n=55,52)|	3.5 (± 11.28)	2.3 (± 11.08)		
Week 8 CORE (n=54,52)|	2.4 (± 12.97)	2.5 (± 12.11)		
Week 12 CORE (n=53,50)|	3.0 (± 12.41)	1.9 (± 11.50)		
Week 16 CORE (n=55,52)|	3.3 (± 12.99)	6.6 (± 15.33)		
Week 20 CORE (n=56,50)|	3.5 (± 12.89)	4.0 (± 16.02)		
Week24 CORE (n=55,53)|	3.0 (± 16.61)	5.4 (± 17.77)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in AcroQoL total scores for patients treated with pasireotide LAR alone or with concomitant medications used to treat acromegaly for extension visits (extension full analysis set)

End point title	Change from baseline in AcroQoL total scores for patients treated with pasireotide LAR alone or with concomitant medications used to treat acromegaly for extension visits (extension full analysis set)

End point description:

Acromegaly Quality of Life questionnaire (AcroQoL). AcroQoL is a validated disease specific questionnaire to measure quality of life in patients with acromegaly. The questionnaire is uni-dimensional and contains 22 items divided in two scales: one that evaluates physical aspects (8 items) and another one that evaluates psychological aspects (14 items). The latter is also divided in two sub-scales: physical appearance and personal relationships of the patient (seven items each). The total score and sub-scores will be calculated using the following formula established by the tool developer (Badia, et al 2004): ((X - Y) / 4Y) x 100, X=sum of the scores for individual items (between 1 and 5 for each item),Y=number of individual items included in above sum (i.e. 22 for the total score, 8 for the physical sub-score, 14 for the psychological sub-score, 7 for the sub-score 'appearance' and 'personal relations'). If more than 25% of items are not completed, results will be considered invalid.

End point type	Secondary

End point timeframe:

CORE Baseline and extension baseline up to approximately 268 weeks

End point values	Pasireotide LAR 40 mg Extension	Pasireotide LAR 60 mg Extension	Cross over to pasireotide Extension	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	57	54	62	
Units: scores				
arithmetic mean (standard deviation)				
Week 16 extension (n=50,46,61)|	4.2 (± 16.34)	2.9 (± 19.09)	0.8 (± 10.22)	
Week 28 extension (n=46,40,54)|	5.6 (± 13.21)	4.8 (± 16.83)	3.3 (± 10.70)	
Week 40 extension (n=44,41,51)|	3.2 (± 15.78)	2.5 (± 18.21)	3.2 (± 10.31)	
Week 52 extension (n=41,36,46)|	6.1 (± 14.28)	5.7 (± 18.69)	4.2 (± 11.01)	
Week 64 extension (n=37,35,43)|	5.8 (± 13.65)	4.2 (± 18.89)	5.4 (± 12.12)	
Week 76 extension (n=31,36,42)|	7.7 (± 14.93)	2.5 (± 19.30)	7.7 (± 15.17)	
Week 88 extension (n=35,32,42)|	4.6 (± 15.11)	5.6 (± 18.08)	6.4 (± 10.29)	
Week 100 extension (n=34,32,40)|	4.3 (± 14.80)	3.9 (± 16.91)	5.9 (± 11.13)	
Week 112 extension (n=32,31,39)|	4.6 (± 15.83)	6.5 (± 18.36)	4.1 (± 10.35)	
Week 124 extension (n=28,30,37)|	5.8 (± 16.46)	2.0 (± 17.95)	2.0 (± 10.97)	
Week 136 extension (n=28,28,39)|	7.5 (± 18.72)	5.4 (± 16.73)	6.5 (± 11.82)	
Week 148 extension (n=29,26,37)|	7.6 (± 18.56)	6.8 (± 16.65)	5.5 (± 12.95)	
Week 160 extension (n=30,26,31)|	7.0 (± 19.10)	5.1 (± 15.70)	1.5 (± 13.36)	
Week 172 extension (n=28,26,31)|	4.8 (± 17.97)	5.7 (± 17.52)	2.1 (± 12.13)	
Week 184 extension (n=23,25,29)|	5.8 (± 15.31)	5.8 (± 16.83)	1.6 (± 12.45)	
Week 196 extension (n=21,22,27)|	6.1 (± 16.94)	6.0 (± 18.58)	3.8 (± 13.11)	
Week 208 extension (n=22,23,21)|	1.2 (± 13.27)	6.2 (± 17.31)	4.5 (± 12.62)	
Week 220 extension (n=19,16,21)|	4.8 (± 21.99)	5.8 (± 17.12)	7.3 (± 16.28)	
Week 232 extension (n=19,12,16)|	2.1 (± 17.51)	-0.2 (± 16.73)	7.0 (± 15.15)	
Week 244 extension (n=13,7,10)|	4.5 (± 20.06)	6.3 (± 11.05)	3.0 (± 18.65)	
Week 256 extension (n=10,6,7)|	6.1 (± 25.91)	-3.0 (± 7.07)	0.3 (± 14.08)	
Week 268 extension (n=4,3,3)|	0.6 (± 16.74)	-4.9 (± 4.30)	-10.6 (± 7.57)	

Statistical analyses

No statistical analyses for this end point

Secondary: Summary of pasireotide trough concentrations in acromegaly patients following monthly i.m. injections of pasireotide LAR by incident dose from start of extension phase up to Week 196 of the extension phase (PK set)

End point title	Summary of pasireotide trough concentrations in acromegaly patients following monthly i.m. injections of pasireotide LAR by incident dose from start of extension phase up to Week 196 of the extension phase (PK set)

End point description:

PK samples were collected for those patients treated with pasireotide LAR in the core study and who continued on pasireotide LAR in the extension phase. PK samples were collected before the injection of pasireotide LAR only at weeks 112 and 196. PK samples were also collected at weeks 48 and 132 only for all patients treated with octreotide LAR 30 mg or lanreotide ATG 120 mg in the core study who started treatment with pasireotide LAR in the extension study. Blood samples (2.5 mL each sample) were collected to yield 1-mL plasma for analysis of pasireotide LAR oncentration.

End point type	Secondary

End point timeframe:

Extension baseline up to approximately 196 weeks

End point values	PK trough			
Subject group type	Subject analysis set			
Number of subjects analysed	98			
Units: mL				
arithmetic mean (standard deviation)				
40 mg Week 48 (n=51)	5.70 (± 3.159)			
40 mg Week 112 (n=25)	8.66 (± 4.154)			
40 mg Week 132 (n=35)	9.28 (± 5.067)			
40 mg Week 196 (n=21)	10.32 (± 5.473)			
60 mg Week 112 (n=72)	14.06 (± 9.807)			
60 mg Week 196 (n=65)	14.96 (± 10.210)			

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:	
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	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups	
Reporting group title	Pasireotide LAR 40 mg
Reporting group description:	
Pasireotide LAR 40 mg	
Reporting group title	Pasireotide LAR 60 mg
Reporting group description:	
Pasireotide LAR 60 mg	
Reporting group title	Cross-over to pasireotide
Reporting group description:	
Cross-over to pasireotide	

Serious adverse events	Pasireotide LAR 40 mg	Pasireotide LAR 60 mg	Cross-over to pasireotide
Total subjects affected by serious adverse events			
subjects affected / exposed	18 / 63 (28.57%)	14 / 62 (22.58%)	20 / 62 (32.26%)
number of deaths (all causes)	2	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Colon cancer			
subjects affected / exposed	1 / 63 (1.59%)	0 / 62 (0.00%)	0 / 62 (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
Lung neoplasm malignant			
subjects affected / exposed	0 / 63 (0.00%)	0 / 62 (0.00%)	1 / 62 (1.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to spine			

subjects affected / exposed	1 / 63 (1.59%)	0 / 62 (0.00%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pituitary tumour			
subjects affected / exposed	1 / 63 (1.59%)	0 / 62 (0.00%)	0 / 62 (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
Pituitary tumour benign			
subjects affected / exposed	0 / 63 (0.00%)	1 / 62 (1.61%)	1 / 62 (1.61%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine leiomyoma			
subjects affected / exposed	0 / 63 (0.00%)	0 / 62 (0.00%)	1 / 62 (1.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 63 (1.59%)	0 / 62 (0.00%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematoma			
subjects affected / exposed	0 / 63 (0.00%)	0 / 62 (0.00%)	1 / 62 (1.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypovolaemic shock			
subjects affected / exposed	1 / 63 (1.59%)	0 / 62 (0.00%)	0 / 62 (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
Surgical and medical procedures			
Joint arthroplasty			
subjects affected / exposed	0 / 63 (0.00%)	1 / 62 (1.61%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Maxillofacial operation			

subjects affected / exposed	0 / 63 (0.00%)	0 / 62 (0.00%)	1 / 62 (1.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oral surgery			
subjects affected / exposed	0 / 63 (0.00%)	0 / 62 (0.00%)	1 / 62 (1.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			
subjects affected / exposed	0 / 63 (0.00%)	1 / 62 (1.61%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pregnancy			
subjects affected / exposed	0 / 63 (0.00%)	1 / 62 (1.61%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Death			
subjects affected / exposed	1 / 63 (1.59%)	0 / 62 (0.00%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Drug ineffective			
subjects affected / exposed	0 / 63 (0.00%)	0 / 62 (0.00%)	1 / 62 (1.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	1 / 63 (1.59%)	0 / 62 (0.00%)	0 / 62 (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
Reproductive system and breast disorders			
Dysfunctional uterine bleeding			

subjects affected / exposed	1 / 63 (1.59%)	0 / 62 (0.00%)	0 / 62 (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
Ovarian cyst			
subjects affected / exposed	1 / 63 (1.59%)	0 / 62 (0.00%)	0 / 62 (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
Ovarian cyst ruptured			
subjects affected / exposed	1 / 63 (1.59%)	0 / 62 (0.00%)	0 / 62 (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
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	0 / 63 (0.00%)	1 / 62 (1.61%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epistaxis			
subjects affected / exposed	0 / 63 (0.00%)	0 / 62 (0.00%)	1 / 62 (1.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 63 (0.00%)	1 / 62 (1.61%)	1 / 62 (1.61%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Suicide attempt			
subjects affected / exposed	0 / 63 (0.00%)	1 / 62 (1.61%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Blood glucose increased			
subjects affected / exposed	1 / 63 (1.59%)	0 / 62 (0.00%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

C-reactive protein increased			
subjects affected / exposed	0 / 63 (0.00%)	1 / 62 (1.61%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Electrocardiogram ST segment elevation			
subjects affected / exposed	0 / 63 (0.00%)	1 / 62 (1.61%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Drug administration error			
subjects affected / exposed	1 / 63 (1.59%)	0 / 62 (0.00%)	0 / 62 (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
Joint dislocation			
subjects affected / exposed	0 / 63 (0.00%)	0 / 62 (0.00%)	1 / 62 (1.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumocephalus			
subjects affected / exposed	0 / 63 (0.00%)	0 / 62 (0.00%)	1 / 62 (1.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital, familial and genetic disorders			
Cowden's disease			
subjects affected / exposed	0 / 63 (0.00%)	0 / 62 (0.00%)	1 / 62 (1.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial flutter			
subjects affected / exposed	0 / 63 (0.00%)	1 / 62 (1.61%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tachycardia			

subjects affected / exposed	0 / 63 (0.00%)	1 / 62 (1.61%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular extrasystoles			
subjects affected / exposed	0 / 63 (0.00%)	1 / 62 (1.61%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Brain oedema			
subjects affected / exposed	1 / 63 (1.59%)	0 / 62 (0.00%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Cerebrospinal fluid leakage			
subjects affected / exposed	0 / 63 (0.00%)	0 / 62 (0.00%)	1 / 62 (1.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dizziness			
subjects affected / exposed	0 / 63 (0.00%)	0 / 62 (0.00%)	1 / 62 (1.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intracranial aneurysm			
subjects affected / exposed	0 / 63 (0.00%)	0 / 62 (0.00%)	1 / 62 (1.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolic encephalopathy			
subjects affected / exposed	0 / 63 (0.00%)	1 / 62 (1.61%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nerve compression			
subjects affected / exposed	1 / 63 (1.59%)	0 / 62 (0.00%)	0 / 62 (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
Transient ischaemic attack			

subjects affected / exposed	1 / 63 (1.59%)	0 / 62 (0.00%)	0 / 62 (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
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 63 (1.59%)	0 / 62 (0.00%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Inner ear disorder			
subjects affected / exposed	0 / 63 (0.00%)	1 / 62 (1.61%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vertigo			
subjects affected / exposed	0 / 63 (0.00%)	0 / 62 (0.00%)	1 / 62 (1.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 63 (1.59%)	0 / 62 (0.00%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 63 (0.00%)	1 / 62 (1.61%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhoids			
subjects affected / exposed	1 / 63 (1.59%)	0 / 62 (0.00%)	1 / 62 (1.61%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal hernia			
subjects affected / exposed	0 / 63 (0.00%)	1 / 62 (1.61%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Nausea			
subjects affected / exposed	0 / 63 (0.00%)	0 / 62 (0.00%)	1 / 62 (1.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Bile duct stone			
subjects affected / exposed	0 / 63 (0.00%)	1 / 62 (1.61%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis			
subjects affected / exposed	1 / 63 (1.59%)	1 / 62 (1.61%)	1 / 62 (1.61%)
occurrences causally related to treatment / all	1 / 1	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis acute			
subjects affected / exposed	0 / 63 (0.00%)	0 / 62 (0.00%)	1 / 62 (1.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis chronic			
subjects affected / exposed	0 / 63 (0.00%)	0 / 62 (0.00%)	1 / 62 (1.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	3 / 63 (4.76%)	1 / 62 (1.61%)	3 / 62 (4.84%)
occurrences causally related to treatment / all	2 / 3	1 / 1	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gallbladder polyp			
subjects affected / exposed	0 / 63 (0.00%)	1 / 62 (1.61%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 63 (1.59%)	1 / 62 (1.61%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Glomerulonephritis			
subjects affected / exposed	0 / 63 (0.00%)	1 / 62 (1.61%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal colic			
subjects affected / exposed	1 / 63 (1.59%)	0 / 62 (0.00%)	0 / 62 (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
Renal cyst			
subjects affected / exposed	0 / 63 (0.00%)	1 / 62 (1.61%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Thyroid mass			
subjects affected / exposed	0 / 63 (0.00%)	0 / 62 (0.00%)	2 / 62 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 63 (1.59%)	1 / 62 (1.61%)	1 / 62 (1.61%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal pain			
subjects affected / exposed	0 / 63 (0.00%)	1 / 62 (1.61%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteitis			
subjects affected / exposed	1 / 63 (1.59%)	0 / 62 (0.00%)	0 / 62 (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
Infections and infestations			
Abdominal abscess			

subjects affected / exposed	0 / 63 (0.00%)	1 / 62 (1.61%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthritis bacterial			
subjects affected / exposed	1 / 63 (1.59%)	0 / 62 (0.00%)	0 / 62 (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
Erysipelas			
subjects affected / exposed	0 / 63 (0.00%)	1 / 62 (1.61%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Flavivirus infection			
subjects affected / exposed	0 / 63 (0.00%)	0 / 62 (0.00%)	1 / 62 (1.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	1 / 63 (1.59%)	0 / 62 (0.00%)	0 / 62 (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
Herpes zoster			
subjects affected / exposed	0 / 63 (0.00%)	1 / 62 (1.61%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Liver abscess			
subjects affected / exposed	0 / 63 (0.00%)	0 / 62 (0.00%)	1 / 62 (1.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 63 (0.00%)	1 / 62 (1.61%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcal infection			

subjects affected / exposed	0 / 63 (0.00%)	1 / 62 (1.61%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subcutaneous abscess			
subjects affected / exposed	0 / 63 (0.00%)	0 / 62 (0.00%)	1 / 62 (1.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 63 (0.00%)	1 / 62 (1.61%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	0 / 63 (0.00%)	0 / 62 (0.00%)	2 / 62 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic metabolic decompensation			
subjects affected / exposed	1 / 63 (1.59%)	0 / 62 (0.00%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			
subjects affected / exposed	1 / 63 (1.59%)	1 / 62 (1.61%)	1 / 62 (1.61%)
occurrences causally related to treatment / all	1 / 1	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemia unawareness			
subjects affected / exposed	0 / 63 (0.00%)	1 / 62 (1.61%)	0 / 62 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	0 / 63 (0.00%)	0 / 62 (0.00%)	1 / 62 (1.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Pasireotide LAR 40 mg	Pasireotide LAR 60 mg	Cross-over to pasireotide
Total subjects affected by non-serious adverse events			
subjects affected / exposed	59 / 63 (93.65%)	58 / 62 (93.55%)	61 / 62 (98.39%)
Vascular disorders			
Hypertension			
subjects affected / exposed	7 / 63 (11.11%)	4 / 62 (6.45%)	5 / 62 (8.06%)
occurrences (all)	7	4	7
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 63 (1.59%)	5 / 62 (8.06%)	5 / 62 (8.06%)
occurrences (all)	1	5	5
Fatigue			
subjects affected / exposed	4 / 63 (6.35%)	4 / 62 (6.45%)	2 / 62 (3.23%)
occurrences (all)	4	4	2
Pyrexia			
subjects affected / exposed	7 / 63 (11.11%)	1 / 62 (1.61%)	2 / 62 (3.23%)
occurrences (all)	9	3	2
Psychiatric disorders			
Anxiety			
subjects affected / exposed	5 / 63 (7.94%)	3 / 62 (4.84%)	2 / 62 (3.23%)
occurrences (all)	5	3	2
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	2 / 63 (3.17%)	1 / 62 (1.61%)	6 / 62 (9.68%)
occurrences (all)	2	0	8
Blood glucose increased			
subjects affected / exposed	3 / 63 (4.76%)	6 / 62 (9.68%)	0 / 62 (0.00%)
occurrences (all)	3	6	0
Insulin-like growth factor decreased			
subjects affected / exposed	2 / 63 (3.17%)	4 / 62 (6.45%)	2 / 62 (3.23%)
occurrences (all)	2	6	2
Lipase increased			

subjects affected / exposed	4 / 63 (6.35%)	1 / 62 (1.61%)	4 / 62 (6.45%)
occurrences (all)	6	1	6
Weight increased			
subjects affected / exposed	1 / 63 (1.59%)	0 / 62 (0.00%)	5 / 62 (8.06%)
occurrences (all)	1	0	5
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 63 (0.00%)	4 / 62 (6.45%)	1 / 62 (1.61%)
occurrences (all)	0	6	1
Cardiac disorders			
Atrioventricular block first degree			
subjects affected / exposed	6 / 63 (9.52%)	2 / 62 (3.23%)	2 / 62 (3.23%)
occurrences (all)	15	2	5
Nervous system disorders			
Dizziness			
subjects affected / exposed	8 / 63 (12.70%)	3 / 62 (4.84%)	3 / 62 (4.84%)
occurrences (all)	12	7	4
Headache			
subjects affected / exposed	18 / 63 (28.57%)	6 / 62 (9.68%)	8 / 62 (12.90%)
occurrences (all)	36	17	11
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	9 / 63 (14.29%)	10 / 62 (16.13%)	16 / 62 (25.81%)
occurrences (all)	17	13	17
Leukopenia			
subjects affected / exposed	0 / 63 (0.00%)	2 / 62 (3.23%)	4 / 62 (6.45%)
occurrences (all)	0	3	6
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	10 / 63 (15.87%)	10 / 62 (16.13%)	6 / 62 (9.68%)
occurrences (all)	19	13	9
Abdominal pain upper			
subjects affected / exposed	6 / 63 (9.52%)	3 / 62 (4.84%)	1 / 62 (1.61%)
occurrences (all)	6	8	1
Constipation			

subjects affected / exposed	5 / 63 (7.94%)	3 / 62 (4.84%)	3 / 62 (4.84%)
occurrences (all)	5	4	3
Diarrhoea			
subjects affected / exposed	14 / 63 (22.22%)	17 / 62 (27.42%)	11 / 62 (17.74%)
occurrences (all)	26	47	19
Large intestine polyp			
subjects affected / exposed	2 / 63 (3.17%)	1 / 62 (1.61%)	4 / 62 (6.45%)
occurrences (all)	2	1	4
Nausea			
subjects affected / exposed	7 / 63 (11.11%)	7 / 62 (11.29%)	3 / 62 (4.84%)
occurrences (all)	13	12	5
Vomiting			
subjects affected / exposed	8 / 63 (12.70%)	1 / 62 (1.61%)	0 / 62 (0.00%)
occurrences (all)	11	1	0
Hepatobiliary disorders			
Biliary dilatation			
subjects affected / exposed	3 / 63 (4.76%)	3 / 62 (4.84%)	4 / 62 (6.45%)
occurrences (all)	3	4	4
Cholelithiasis			
subjects affected / exposed	21 / 63 (33.33%)	20 / 62 (32.26%)	17 / 62 (27.42%)
occurrences (all)	25	24	16
Gallbladder polyp			
subjects affected / exposed	4 / 63 (6.35%)	3 / 62 (4.84%)	1 / 62 (1.61%)
occurrences (all)	4	3	1
Hepatic steatosis			
subjects affected / exposed	4 / 63 (6.35%)	4 / 62 (6.45%)	2 / 62 (3.23%)
occurrences (all)	3	4	2
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	3 / 63 (4.76%)	8 / 62 (12.90%)	2 / 62 (3.23%)
occurrences (all)	3	8	2
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	7 / 63 (11.11%)	2 / 62 (3.23%)	0 / 62 (0.00%)
occurrences (all)	7	3	0
Renal cyst			

subjects affected / exposed	3 / 63 (4.76%)	5 / 62 (8.06%)	2 / 62 (3.23%)
occurrences (all)	3	6	2
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	7 / 63 (11.11%)	9 / 62 (14.52%)	3 / 62 (4.84%)
occurrences (all)	7	11	3
Back pain			
subjects affected / exposed	13 / 63 (20.63%)	7 / 62 (11.29%)	3 / 62 (4.84%)
occurrences (all)	16	9	2
Musculoskeletal pain			
subjects affected / exposed	0 / 63 (0.00%)	4 / 62 (6.45%)	1 / 62 (1.61%)
occurrences (all)	0	5	0
Pain in extremity			
subjects affected / exposed	4 / 63 (6.35%)	2 / 62 (3.23%)	4 / 62 (6.45%)
occurrences (all)	5	3	4
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	2 / 63 (3.17%)	6 / 62 (9.68%)	0 / 62 (0.00%)
occurrences (all)	3	7	0
Influenza			
subjects affected / exposed	9 / 63 (14.29%)	9 / 62 (14.52%)	5 / 62 (8.06%)
occurrences (all)	11	11	5
Upper respiratory tract infection			
subjects affected / exposed	4 / 63 (6.35%)	3 / 62 (4.84%)	1 / 62 (1.61%)
occurrences (all)	5	5	1
Urinary tract infection			
subjects affected / exposed	6 / 63 (9.52%)	5 / 62 (8.06%)	9 / 62 (14.52%)
occurrences (all)	9	7	12
Viral upper respiratory tract infection			
subjects affected / exposed	7 / 63 (11.11%)	9 / 62 (14.52%)	5 / 62 (8.06%)
occurrences (all)	16	15	7
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	20 / 63 (31.75%)	25 / 62 (40.32%)	16 / 62 (25.81%)
occurrences (all)	20	27	20
Dyslipidaemia			

subjects affected / exposed	4 / 63 (6.35%)	1 / 62 (1.61%)	3 / 62 (4.84%)
occurrences (all)	4	1	3
Hypercholesterolaemia			
subjects affected / exposed	5 / 63 (7.94%)	6 / 62 (9.68%)	8 / 62 (12.90%)
occurrences (all)	7	9	11
Hyperglycaemia			
subjects affected / exposed	25 / 63 (39.68%)	24 / 62 (38.71%)	15 / 62 (24.19%)
occurrences (all)	45	31	19
Hypertriglyceridaemia			
subjects affected / exposed	1 / 63 (1.59%)	4 / 62 (6.45%)	1 / 62 (1.61%)
occurrences (all)	1	7	1
Hypoglycaemia			
subjects affected / exposed	7 / 63 (11.11%)	7 / 62 (11.29%)	4 / 62 (6.45%)
occurrences (all)	11	11	5
Hypomagnesaemia			
subjects affected / exposed	4 / 63 (6.35%)	2 / 62 (3.23%)	0 / 62 (0.00%)
occurrences (all)	5	2	0
Type 2 diabetes mellitus			
subjects affected / exposed	1 / 63 (1.59%)	3 / 62 (4.84%)	4 / 62 (6.45%)
occurrences (all)	1	4	4

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 February 2011	To clarify that patients treated with octreotide LAR 30 mg or lanreotide ATG 120 mg and concomitant GHR-antagonist or dopamine agonists could only be included in the study if the GHR-antagonist or dopamine agonists were discontinued 8 weeks before Visit 1 (Screening) as stated in the current version of the protocol and if they fulfilled the following, additional requirement: such patients must have been treated with octreotide LAR 30 mg or lanreotide ATG 120 mg as monotherapy for at least 6 months prior to the start of concomitant GHR-antagonist or dopamine agonists. During the 6-month monotherapy patients should not have been biochemically controlled. To ensure consistency of the secondary objectives and variables concerning tumor volume with the visit evaluation schedule. According to the visit evaluation schedule in the current protocol, MRI was to be performed at Visit 1 (Screening) and not at Visit 2. corresponding analysis concerning time to response. GH and IGF-1 was only scheduled to be assessed at 12 weeks (Visit 6) and study completion which did not give suitable time intervals to calculate meaningful Kaplan-Meier estimates. To include an extension phase to the core study
01 May 2011	To specify an end-date of the extension phase (Appendix 16.1.1- Appendix 3) for Norway and the UK as Health Authorities in both countries do not accept commercial availability of the study drug (pasireotide LAR) as a valid scientific treatment endpoint
01 December 2011	To define a key secondary objective and related endpoint. IGF-1 was currently considered the most reliable measure of disease activity in patients with acromegaly and frequently used as the main driver for treatment decision (Giustina et al 2010). Therefore, the effect of pasireotide LAR 40 mg or 60 mg versus continuing the same treatment on the proportion of patients achieving normal sex- and age-adjusted IGF-1 levels at 24 weeks would become the key secondary objective
16 December 2011	To extend the end-date of the extension phase (Appendix 3) as required by the Health Authorities in Norway and the UK to 31-Dec-2015.
22 March 2013	To extend the end-date of the extension phase (Appendix 3) as required by the Health Authorities in Norway and the UK to 31-Dec-2015
22 March 2013	To allow for use of concomitant medications used to treat acromegaly with pasireotide LAR 40 mg and 60 mg in the extension phase of this study in patients who have not achieved biochemical control of acromegaly on pasireotide LAR monotherapy after a minimum of one year. To allow for use of medications with conditional risk for Torsade des Pointes and congenital long QT interval in the extension phase of this study
13 February 2015	To include a detailed description of the transition phase; Patients must be transitioned to commercial pasireotide LAR within 3 months after approval

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported