Clinical trial results:
A multicenter, randomized, blinded study to assess safety and efficacy of Pasireotide LAR vs octreotide LAR in patients with active acromegaly

Due to EudraCT system limitations, which EMA is aware of, results of crossover studies and data using 999 as data points are not accurately represented in this record. Please go to https://www.novctrd.com/CtrdWeb/home.nov for complete trial results

Summary

EudraCT number	2007-001972-36
Trial protocol	CZ FR BE GB GR IT ES NL DK SE HU PL PT DE
Global end of trial date	11 March 2016

Results information

Result version number	v1 (current)
This version publication date	19 July 2018
First version publication date	19 July 2018

Trial information

Trial identification

Sponsor protocol code	SOM230C2305

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00600886
WHO universal trial number (UTN)	-

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	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	11 March 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	11 March 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Compare proportion of patients with reduction of GH to <2.5 µg/L and normalization of IGF-1 (age and sex related) between the two treatment groups at 12 months.

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	11 February 2008
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 9
Country: Number of subjects enrolled	Spain: 5
Country: Number of subjects enrolled	United States: 41
Country: Number of subjects enrolled	Colombia: 8
Country: Number of subjects enrolled	Russian Federation: 28
Country: Number of subjects enrolled	Belgium: 8
Country: Number of subjects enrolled	Hungary: 2
Country: Number of subjects enrolled	Poland: 7
Country: Number of subjects enrolled	Korea, Republic of: 18
Country: Number of subjects enrolled	Argentina: 9
Country: Number of subjects enrolled	Greece: 2
Country: Number of subjects enrolled	Sweden: 2
Country: Number of subjects enrolled	Denmark: 5
Country: Number of subjects enrolled	Norway: 1
Country: Number of subjects enrolled	France: 20
Country: Number of subjects enrolled	Canada: 18
Country: Number of subjects enrolled	Taiwan: 25

Country: Number of subjects enrolled	Italy: 26
Country: Number of subjects enrolled	Mexico: 22
Country: Number of subjects enrolled	Israel: 3
Country: Number of subjects enrolled	China: 35
Country: Number of subjects enrolled	Netherlands: 11
Country: Number of subjects enrolled	United Kingdom: 2
Country: Number of subjects enrolled	Turkey: 8
Country: Number of subjects enrolled	Brazil: 40
Country: Number of subjects enrolled	Czech Republic: 1
Country: Number of subjects enrolled	Switzerland: 2
Worldwide total number of subjects	358
EEA total number of subjects	101

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)	335
From 65 to 84 years	22
85 years and over	1

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

151 patients (pts) planned per treatment group; study enrolled 358 pts. 176 & 182 were randomized to receive pasireotide & octreotide, respectively. From pasireotide group, 74 pts continued same treatment in extension & 38 crossed over to octreotide; from octreotide group 46 pts continued same treatment in extension & 81 crossed over to pasireotide

Period 1

Period 1 title	Core Phase - Full Analysis Set (FAS)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer

Arms

Are arms mutually exclusive?	Yes
Arm title	Pasireotide LAR

Arm description:

Patients in this arm received Pasireotide LAR 40 mg im depot injection, blinded, once every 28 days (± 2 days) for 12 months. Dose could be down- or up-titrated to 20 or 60 mg, respectively. Patients who responded to Pasireotide LAR (i.e. the randomized treatment) at the end of the core (Month 12), continued Pasireotide LAR treatment in the extension. Patients who did not respond to Pasireotide LAR at the end of the core (Month 12) were allowed to switch to receive Octreotide LAR in the extension.

Arm type	Experimental
Investigational medicinal product name	Pasireotide
Investigational medicinal product code	SOM230
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

Pasireotide LAR - intramuscular (i.m.) depot injection given once every 28 days.

Arm title	Octreotide LAR

Arm description:

Patients in this arm received Octreotide LAR 20 mg im depot injection, blinded, once every 28 days (± 2 days) for 12 months. Dose could be down- or up-titrated to 10 or 30 mg, respectively. Patients who responded to Octreotide LAR (i.e. the randomized treatment) at the end of the core (Month 12) continued Octreotide LAR treatment in the extension (up to 2 years of treatment). Patients who did not respond to Octreotide LAR at the end of the core (Month 12) were allowed to switch to receive Pasireotide LAR in the extension.

Arm type	Experimental
Investigational medicinal product name	Octreotide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

Octreotide LAR - i.m. depot injection given once every 28 days.

Number of subjects in period 1	Pasireotide LAR	Octreotide LAR
Started	176	182
Completed	141	156
Not completed	35	26
Abnormal laboratory value(s)	1	-
Adverse event, serious fatal	-	1
Consent withdrawn by subject	5	3
Adverse event, non-fatal	14	6
Administrative Problems	2	-
Lost to follow-up	1	-
Protocol deviation	7	8
Lack of efficacy	5	8

Period 2

Period 2 title	Extension - Same Treatment (FAS)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Pasireotide LAR

Arm description:

Patients in this arm received Pasireotide LAR 40 mg im depot injection, blinded, once every 28 days (± 2 days) for 12 months. Dose could be down- or up-titrated to 20 or 60 mg, respectively. Patients who responded to Pasireotide LAR (i.e. the randomized treatment) at the end of the core (Month 12), continued Pasireotide LAR treatment in the extension. Patients who did not respond to Pasireotide LAR at the end of the core (Month 12) were allowed to switch to receive Octreotide LAR in the extension.

Arm type	Experimental
Investigational medicinal product name	Pasireotide
Investigational medicinal product code	SOM230
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

Pasireotide LAR - intramuscular (i.m.) depot injection given once every 28 days.

Arm title	Octreotide LAR

Arm description:

Patients in this arm received Octreotide LAR 20 mg im depot injection, blinded, once every 28 days (± 2 days) for 12 months. Dose could be down- or up-titrated to 10 or 30 mg, respectively. Patients who responded to Octreotide LAR (i.e. the randomized treatment) at the end of the core (Month 12) continued Octreotide LAR treatment in the extension (up to 2 years of treatment). Patients who did not respond to Octreotide LAR at the end of the core (Month 12) were allowed to switch to receive Pasireotide LAR in the extension.

Arm type	Experimental

Investigational medicinal product name	Octreotide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

Octreotide LAR - i.m. depot injection given once every 28 days.

Number of subjects in period 2[1]	Pasireotide LAR	Octreotide LAR
Started	74	46
Completed	28	35
Not completed	46	11
Adverse event, serious fatal	1	1
Consent withdrawn by subject	16	2
Adverse event, non-fatal	4	1
Abnormal Lab Value (s)	4	-
Condition no longer requires study drug	6	-
Administrative Problems	9	3
Lost to follow-up	3	1
Lack of efficacy	3	3

Notes:

[1] - 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: Completed = anyone who did not discontinue prior to month 12.. I t di not mean completed the study.

Period 3

Period 3 title	Extension - after crossover (CAS)
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	No
Arm title	Pasireotide LAR

Arm description:

Patients in this arm received Pasireotide LAR 40 mg im depot injection, blinded, once every 28 days (± 2 days) for 12 months. Dose could be down- or up-titrated to 20 or 60 mg, respectively. Patients who responded to Pasireotide LAR (i.e. the randomized treatment) at the end of the core (Month 12), continued Pasireotide LAR treatment in the extension. Patients who did not respond to Pasireotide LAR at the end of the core (Month 12) were allowed to switch to receive Octreotide LAR in the extension.

Arm type	Experimental

Investigational medicinal product name	Pasireotide
Investigational medicinal product code	SOM230
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

Pasireotide LAR - intramuscular (i.m.) depot injection given once every 28 days.

Arm title	Octreotide LAR

Arm description:

Patients in this arm received Octreotide LAR 20 mg im depot injection, blinded, once every 28 days (± 2 days) for 12 months. Dose could be down- or up-titrated to 10 or 30 mg, respectively. Patients who responded to Octreotide LAR (i.e. the randomized treatment) at the end of the core (Month 12) continued Octreotide LAR treatment in the extension (up to 2 years of treatment). Patients who did not respond to Octreotide LAR at the end of the core (Month 12) were allowed to switch to receive Pasireotide LAR in the extension.

Arm type	Experimental
Investigational medicinal product name	Octreotide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

Octreotide LAR - i.m. depot injection given once every 28 days.

Number of subjects in period 3	Pasireotide LAR	Octreotide LAR
Started	81	38
Completed	19	25
Not completed	62	13
Adverse event, serious fatal	1	-
Consent withdrawn by subject	19	4
Adverse event, non-fatal	19	1
Subject no longer requires study drug	3	-
Abnormal Lab Value (s)	3	-
Administrative Problems	4	4
Lack of efficacy	13	4

Baseline characteristics

Reporting groups	
Reporting group title	Pasireotide LAR
Reporting group description:	
Patients in this arm received Pasireotide LAR 40 mg im depot injection, blinded, once every 28 days (± 2 days) for 12 months. Dose could be down- or up-titrated to 20 or 60 mg, respectively. Patients who responded to Pasireotide LAR (i.e. the randomized treatment) at the end of the core (Month 12), continued Pasireotide LAR treatment in the extension. Patients who did not respond to Pasireotide LAR at the end of the core (Month 12) were allowed to switch to receive Octreotide LAR in the extension.	
Reporting group title	Octreotide LAR
Reporting group description:	
Patients in this arm received Octreotide LAR 20 mg im depot injection, blinded, once every 28 days (± 2 days) for 12 months. Dose could be down- or up-titrated to 10 or 30 mg, respectively. Patients who responded to Octreotide LAR (i.e. the randomized treatment) at the end of the core (Month 12) continued Octreotide LAR treatment in the extension (up to 2 years of treatment). Patients who did not respond to Octreotide LAR at the end of the core (Month 12) were allowed to switch to receive Pasireotide LAR in the extension.	

Reporting group values	Pasireotide LAR	Octreotide LAR	Total
Number of subjects	176	182	358
Age Categorical Units: Subjects			
<65 Years	168	167	335
>=65 years	8	15	23
Age Continuous Units: Years			
arithmetic mean	45.1	45.6	
standard deviation	± 12.37	± 12.97	-
Gender, Male/Female Units: Subjects			
Female	91	95	186
Male	85	87	172

End points reporting groups

Reporting group title	Pasireotide LAR

Reporting group description:

Patients in this arm received Pasireotide LAR 40 mg im depot injection, blinded, once every 28 days (± 2 days) for 12 months. Dose could be down- or up-titrated to 20 or 60 mg, respectively. Patients who responded to Pasireotide LAR (i.e. the randomized treatment) at the end of the core (Month 12), continued Pasireotide LAR treatment in the extension. Patients who did not respond to Pasireotide LAR at the end of the core (Month 12) were allowed to switch to receive Octreotide LAR in the extension.

Reporting group title	Octreotide LAR

Reporting group description:

Patients in this arm received Octreotide LAR 20 mg im depot injection, blinded, once every 28 days (± 2 days) for 12 months. Dose could be down- or up-titrated to 10 or 30 mg, respectively. Patients who responded to Octreotide LAR (i.e. the randomized treatment) at the end of the core (Month 12) continued Octreotide LAR treatment in the extension (up to 2 years of treatment). Patients who did not respond to Octreotide LAR at the end of the core (Month 12) were allowed to switch to receive Pasireotide LAR in the extension.

Reporting group title	Pasireotide LAR

Reporting group description:

Patients in this arm received Pasireotide LAR 40 mg im depot injection, blinded, once every 28 days (± 2 days) for 12 months. Dose could be down- or up-titrated to 20 or 60 mg, respectively. Patients who responded to Pasireotide LAR (i.e. the randomized treatment) at the end of the core (Month 12), continued Pasireotide LAR treatment in the extension. Patients who did not respond to Pasireotide LAR at the end of the core (Month 12) were allowed to switch to receive Octreotide LAR in the extension.

Reporting group title	Octreotide LAR

Reporting group description:

Patients in this arm received Octreotide LAR 20 mg im depot injection, blinded, once every 28 days (± 2 days) for 12 months. Dose could be down- or up-titrated to 10 or 30 mg, respectively. Patients who responded to Octreotide LAR (i.e. the randomized treatment) at the end of the core (Month 12) continued Octreotide LAR treatment in the extension (up to 2 years of treatment). Patients who did not respond to Octreotide LAR at the end of the core (Month 12) were allowed to switch to receive Pasireotide LAR in the extension.

Reporting group title	Pasireotide LAR

Reporting group description:

Patients in this arm received Pasireotide LAR 40 mg im depot injection, blinded, once every 28 days (± 2 days) for 12 months. Dose could be down- or up-titrated to 20 or 60 mg, respectively. Patients who responded to Pasireotide LAR (i.e. the randomized treatment) at the end of the core (Month 12), continued Pasireotide LAR treatment in the extension. Patients who did not respond to Pasireotide LAR at the end of the core (Month 12) were allowed to switch to receive Octreotide LAR in the extension.

Reporting group title	Octreotide LAR

Reporting group description:

Patients in this arm received Octreotide LAR 20 mg im depot injection, blinded, once every 28 days (± 2 days) for 12 months. Dose could be down- or up-titrated to 10 or 30 mg, respectively. Patients who responded to Octreotide LAR (i.e. the randomized treatment) at the end of the core (Month 12) continued Octreotide LAR treatment in the extension (up to 2 years of treatment). Patients who did not respond to Octreotide LAR at the end of the core (Month 12) were allowed to switch to receive Pasireotide LAR in the extension.

Subject analysis set title	Pasireotide LAR (Core)
Subject analysis set type	Full analysis

Subject analysis set description:

Includes data from the 12-month blinded core phase for patients randomized to receive Pasireotide LAR.

Subject analysis set title	Octreotide LAR (Core)
Subject analysis set type	Full analysis

Subject analysis set description:

Includes data from the 12-month blinded core phase for patients randomized to receive Octreotide LAR.

Subject analysis set title	Pasireotide LAR (Core & Extension)
Subject analysis set type	Full analysis

Subject analysis set description:

Includes data from both blinded core and extension phase (up to Month 26) for patients who continued the same treatment (Pasireotide LAR) as in the core. For patients who switched from blinded Pasireotide LAR to Octreotide LAR treatment in the extension, only data collected before crossover is included.

Subject analysis set title	Octreotide LAR (Core & Extension)
Subject analysis set type	Full analysis

Subject analysis set description:

Includes data from both blinded core and extension phase (up to Month 26) for patients who continued the same treatment (Octreotide LAR) as in the core. For patients who switched from blinded Octreotide LAR to Pasireotide LAR treatment in the extension, only data collected before crossover is included.

Subject analysis set title	Pasireotide LAR 20 mg
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Patients in this arm received Pasireotide LAR 20 mg injection prior to PK sample collection.

Subject analysis set title	Pasireotide LAR 40 mg
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Patients in this arm received Pasireotide LAR 40 mg injection prior to PK sample collection.

Subject analysis set title	Pasireotide LAR 60mg
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Patients in this arm received Pasireotide LAR 60 mg injection prior to PK sample collection.

Subject analysis set title	Octreotide LAR 10mg
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Patients in this arm received Octreotide LAR 10 mg injection prior to PK sample collection.

Subject analysis set title	Octreotide LAR 20 mg
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Patients in this arm received Octreotide LAR 20 mg injection prior to PK sample collection.

Subject analysis set title	Octreotide LAR 30 mg
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Patients in this arm received Octreotide LAR 30 mg injection prior to PK sample collection.

Subject analysis set title	Crossed over to Pasireotide LAR (Extension)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Includes data from the blinded extension phase (up to Month 26) collected after the crossover time point for patients who crossed over from Octreotide LAR treatment in the core to Pasireotide LAR treatment in the extension phase.

Subject analysis set title	Crossed over to Octreotide LAR (Extension)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Includes data from the blinded extension phase (up to Month 26) collected after the crossover time point for patients who crossed over from Pasireotide LAR treatment in the core to Octreotide LAR treatment in the extension phase.

Primary: Percentage of participants with a reduction of Mean GH Level to <2.5 µg/L and the Normalization of IGF-1

End point title	Percentage of participants with a reduction of Mean GH Level to <2.5 µg/L and the Normalization of IGF-1

End point description:

Percentage of participants with a reduction of mean GH levels to <2.5µg/L (based on a 5-point 2-hour profile). Missing mean GH levels at M12 were imputed using data obtained at or after M6 by the last observation carried forward method; otherwise, patients were considered as non-responders. Post

surgery = patients with prior surgery but no previous medical treatment for acromegaly De novo = patients with de novo disease who refused pituitary surgery or for whom pituitary surgery was contraindicated.

End point type	Primary
End point timeframe:	
12 months	

End point values	Pasireotide LAR (Core)	Octreotide LAR (Core)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	176	182		
Units: Percentage of Participants				
number (confidence interval 95%)				
Overall (N=176, 182)	31.3 (24.5 to 38.7)	19.2 (13.8 to 25.7)		
Post Surgery (N=71, 78)	39.4 (28 to 51.7)	21.8 (13.2 to 32.6)		
De novo (N=105, 104)	25.7 (17.7 to 35.2)	17.3 (10.6 to 26)		

Statistical analyses

Statistical analysis title	Stats Analysis between treatment groups -Overall
Comparison groups	Pasireotide LAR (Core) v Octreotide LAR (Core)
Number of subjects included in analysis	358
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.007
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	1.942
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.19
upper limit	3.168

Statistical analysis title	Analysis between treatment groups: Post Surgery
Comparison groups	Pasireotide LAR (Core) v Octreotide LAR (Core)
Number of subjects included in analysis	358
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	2.337

Confidence interval	
level	95 %
sides	2-sided
lower limit	1.14
upper limit	4.79

Statistical analysis title	Analysis between treatment groups: De Novo
Comparison groups	Pasireotide LAR (Core) v Octreotide LAR (Core)
Number of subjects included in analysis	358
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	1.654
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.846
upper limit	3.234

Secondary: Percentage of participants with a reduction of mean GH Level to < 2.5µg/L

End point title	Percentage of participants with a reduction of mean GH Level to < 2.5µg/L

End point description:

Percentage of participants with a reduction of mean GH levels to < 2.5µg/L (based on a 5-point 2-hour profile). Missing mean GH levels at M12 were imputed using data obtained at or after M6 by the last observation carried forward method; otherwise, patients were considered as non-responders. Post surgery = patients with prior surgery but no previous medical treatment for acromegaly De novo = patients with de novo disease who refused pituitary surgery or for whom pituitary surgery was contraindicated.

End point type	Secondary

End point timeframe:

12 Months

End point values	Pasireotide LAR (Core)	Octreotide LAR (Core)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	176	182		
Units: Percentage of participants				
number (confidence interval 95%)				
Overall (n = 176, n = 182)	48.3 (40.7 to 55.9)	51.6 (44.1 to 59.1)		
Post surgery (n = 71, n = 78)	52.1 (39.9 to 64.1)	51.3 (39.7 to 62.8)		
De novo (n = 105, n = 104)	45.7 (36 to 55.7)	51.9 (41.9 to 61.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in tumor volume at 12 months

End point title	Change from baseline in tumor volume at 12 months

End point description:

Absolute and percentage change from baseline in tumor volume (assessed by pituitary MRI) Post surgery = patients with prior surgery but no previous medical treatment for acromegaly De novo = patients with de novo disease who refused pituitary surgery or for whom pituitary surgery was contraindicated.

End point type	Secondary

End point timeframe:

Baseline, 12 Months

End point values	Pasireotide LAR (Core)	Octreotide LAR (Core)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	176	182		
Units: mm^3				
arithmetic mean (standard deviation)				
Overall (n = 166, 169) at baseline	2420.7 (± 4159.21)	2259.2 (± 3390.2)		
Overall (n = 120, 124) % change at month 12	-39.7 (± 21.83)	-38 (± 24.47)		
Post surgery (n = 70, 74) at baseline	2185.2 (± 2861.09)	2196.5 (± 3922.08)		
Post surgery (n = 44, 52) % change at month 12	-39.5 (± 20.6)	-39 (± 23.81)		
De novo (n = 96, 95) at baseline	2592.4 (± 4901.99)	2308.1 (± 2930.84)		
De novo (n = 76, 72) % change at month 12	-39.9 (± 22.65)	-37.2 (± 25.07)		
Overall (n = 121, 128) absolute change at month 12	-987.1 (± 2448.14)	-801.2 (± 1676.62)		
Post surgery (n = 44, 55) abs. change at month 12	-873.7 (± 1282.06)	-713.8 (± 1708.2)		
De novo (n = 77, 73) absolute change at month 12	-1051.9 (± 2919.18)	-867.1 (± 1661.24)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with normalization of IGF-1

End point title	Percentage of participants with normalization of IGF-1

End point description:

Percentage of participants with normalization of sex- and age-adjusted IGF-1. Missing IGF-1 levels at M12 were imputed using data obtained at or after M6 by the last observation carried forward method; otherwise, patients were considered as non-responders.
Post surgery = patients with prior. Post surgery = patients with prior surgery but no previous medical treatment for acromegaly De novo = patients with de novo disease who refused pituitary surgery or for whom pituitary surgery was contraindicated.

End point type	Secondary

End point timeframe:

12 Months

End point values	Pasireotide LAR (Core)	Octreotide LAR (Core)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	176	182		
Units: Percentage of participants				
number (confidence interval 95%)				
Overall (n = 176, 182)	38.6 (31.4 to 46.3)	23.6 (17.7 to 30.5)		
Post surgery (n = 71, 78)	50.7 (38.6 to 62.8)	26.9 (17.5 to 38.2)		
De novo (n = 105, 104)	30.5 (21.9 to 40.2)	21.2 (13.8 to 30.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with a reduction of mean GH Level to < 2.5µg/L and normalization of IGF-1

End point title	Percentage of participants with a reduction of mean GH Level to < 2.5µg/L and normalization of IGF-1

End point description:

Percentage of participants with a reduction of mean GH levels to < 2.5µg/L (based on a 5-point 2-hour profile) and normalization of sex- and age-adjusted IGF-1. Denominator for time points up to Month 12 is the Full Analysis Set (FAS). Denominator for time points after Month 12 excludes patients who completed the core and did not enter the extension. Patients who discontinued were considered non-responders for the time points after discontinuation, patients who crossed over were considered non-responders for all time points after crossover. Analysis was based on data up to crossover (i.e., included data from both blinded core & ext. phase up to 26 Months for patients who continued the same treatment in the extension. For patients who switched to the other treatment, only data collected before crossover was included.)

End point type	Secondary

End point timeframe:

Months 3, 6, 9, 12, 16, 19, 22, 25

End point values	Pasireotide LAR (Core & Extension)	Octreotide LAR (Core & Extension)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	176	182		
Units: Percentage of participants				
number (confidence interval 95%)				
Month 3 (n = 176, 182)	30.1 (23.4 to 37.5)	21.4 (15.7 to 28.1)		
Month 6 (n = 176, 182)	30.1 (23.4 to 37.5)	19.8 (14.3 to 26.3)		
Month 9 (n = 176, 182)	27.8 (21.4 to 35.1)	23.1 (17.2 to 29.9)		
Month 12 (n = 176, 182)	29 (22.4 to 36.3)	17.6 (12.3 to 23.9)		
Month 16 (n = 147, 153)	25.2 (18.4 to 33)	12.4 (7.6 to 18.7)		
Month 19 (n = 147, 153)	23.1 (16.6 to 30.8)	13.7 (8.7 to 20.2)		
Month 22 (n = 147, 153)	25.2 (18.4 to 33)	16.3 (10.9 to 23.2)		
Month 25 (n = 147, 153)	24.5 (17.8 to 32.3)	13.7 (8.7 to 20.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Summary of mean GH values

End point title	Summary of mean GH values

End point description:

Mean GH levels (based on a 5-point profile over 2 hours). Analysis was based on data up to crossover (i.e., included data from both blinded core and extension phase up to 26 Months for patients who continued the same treatment in the extension. For patients who switched to the other treatment, only data collected before crossover was included).

End point type	Secondary

End point timeframe:

Baseline, Months 3, 6, 9, 12, 16, 19, 22, 25

End point values	Pasireotide LAR (Core & Extension)	Octreotide LAR (Core & Extension)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	176	182		
Units: µg/L				
arithmetic mean (standard deviation)				
Baseline (n = 167, 178)	21.9 (± 32.14)	18.8 (± 25.95)		
Month 3 (n = 164, 173)	6.3 (± 12.54)	5.8 (± 12.87)		
Month 6 (n = 151, 165)	5.6 (± 11.47)	5.2 (± 10.99)		
Month 9 (n = 136, 157)	4.9 (± 9.62)	4.3 (± 9.7)		
Month 12 (n = 136, 151)	4.6 (± 9.51)	4.5 (± 11.34)		

Month 16 (n = 64, 38)	2.3 (± 5.64)	1.4 (± 1.49)		
Month 19 (n = 62, 38)	2.1 (± 5.68)	1.5 (± 1.68)		
Month 22 (n = 60, 39)	2.1 (± 6.15)	1.4 (± 1.43)		
Month 25 (n = 62, 40)	2 (± 5.02)	1.2 (± 1.11)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to first response for patients achieving a reduction of mean GH level to < 2.5 µg/L and normalization of IGF-1 (No. of Responders: Pasireotite LAR = 81, Octreotide LAR = 63))

End point title	Time to first response for patients achieving a reduction of mean GH level to < 2.5 µg/L and normalization of IGF-1 (No. of Responders: Pasireotite LAR = 81, Octreotide LAR = 63))

End point description:

Time to first response for patients achieving a reduction of mean GH level to < 2.5 µg/L and normalization of IGF-1. Analysis was based on data up to crossover (i.e., included data from both blinded core and extension phase up to 26 Months for patients who continued the same treatment in the extension. For patients who switched to the other treatment, only data collected before crossover was included).

End point type	Secondary

End point timeframe:

Up to 26 months

End point values	Pasireotide LAR (Core & Extension)	Octreotide LAR (Core & Extension)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	176	182		
Units: Weeks				
median (confidence interval 95%)	12.6 (12.3 to 13)	12.4 (12.3 to 13.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Severity scores of acromegaly symptoms

End point title	Severity scores of acromegaly symptoms

End point description:

Severity scores of acromegaly symptoms (Headache, Fatigue, Perspiration, Paresthesias, Osteoarthralgia). Symptoms were scored from 0 (no symptom) to 4 (very severe). Analysis was based on data up to crossover (i.e., included data from both blinded core and extension phase up to 26 Months for patients who continued the same treatment in the extension. For patients who switched to the other treatment, only data collected before crossover was included).

End point type	Secondary

End point timeframe:

Baseline, Months 12, 25

End point values	Pasireotide LAR (Core & Extension)	Octreotide LAR (Core & Extension)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	176	182		
Units: scores on a scale				
arithmetic mean (standard deviation)				
Headache - Baseline (n = 175, 181)	0.9 (± 1.05)	1 (± 1.14)		
Fatigue - Baseline (n = 175, 181)	1.2 (± 1.13)	1.4 (± 1.23)		
Perspiration - Baseline (n = 175, 181)	1.1 (± 1.21)	1.3 (± 1.31)		
Paresthesia - Baseline (n = 175, 180)	0.7 (± 1)	0.8 (± 1.15)		
Osteoarthraliga - Baseline (n = 174, 178)	1 (± 1.05)	1.3 (± 1.26)		
Headache - M12 (n = 138, 149)	0.5 (± 0.77)	0.6 (± 0.79)		
Fatigue - M12 (n = 138, 149)	0.8 (± 0.95)	0.7 (± 0.99)		
Perspiration - M12 (n = 138, 149)	0.4 (± 0.81)	0.5 (± 0.91)		
Paresthesia - M12 (n = 138, 149)	0.3 (± 0.63)	0.4 (± 0.72)		
Osteoarthraliga - M12 (n = 137, 149)	0.5 (± 0.8)	0.7 (± 1)		
Headache - M25 (n = 64, 40)	0.4 (± 0.61)	0.6 (± 0.77)		
Fatigue - M25 (n = 64, 40)	0.5 (± 0.71)	0.7 (± 0.89)		
Perspiration - M25 (n = 64, 40)	0.4 (± 0.72)	0.4 (± 0.67)		
Paresthesia - M25 (n = 64, 40)	0.2 (± 0.49)	0.4 (± 0.67)		
Osteoarthraliga - M25 (n = 64, 40)	0.4 (± 0.79)	0.8 (± 1.07)		

Statistical analyses

No statistical analyses for this end point

Secondary: Ring size

End point title	Ring size

End point description:

Ring size (based on jeweler’s finger gauge). Analysis was based on data up to crossover (i.e., included data from both blinded core and extension phase up to 26 Months for patients who continued the same treatment in the extension. For patients who switched to the other treatment, only data collected before crossover was included).

End point type	Secondary

End point timeframe:

Baseline, Months 12, 25

End point values	Pasireotide LAR (Core & Extension)	Octreotide LAR (Core & Extension)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	176	182		
Units: ring zize				
arithmetic mean (standard deviation)				
Baseline left hand (LH) 4th digit (n = 112, 115)	11.6 (± 2)	11.8 (± 1.97)		
Baseline left hand 5th digit (n = 21, 18)	11.7 (± 2.82)	12.4 (± 2.88)		
Baseline right hand (RH) 4th digit (n = 23, 29)	12.5 (± 2.01)	11.4 (± 2.54)		
Baseline right hand 5th digit (n = 5, 8)	11.2 (± 3.35)	11.3 (± 2.95)		
M12 LH 4th digit (n = 97, 102)	10.6 (± 2.05)	11.1 (± 1.95)		
M12 LH 5th digit (n = 12, 10)	11.8 (± 1.81)	12.4 (± 1.78)		
M12 RH 4th digit (21, 25)	12.2 (± 2.12)	11.3 (± 2.18)		
M12 RH 5th digit (n = 5, 6)	10.7 (± 3.96)	10.5 (± 2.14)		
M25 LH 4th digit (n = 49, 33)	10.1 (± 2.12)	11.1 (± 1.95)		
M25 LH 5th digit (n = 5, 2)	10 (± 2.45)	14.3 (± 0.35)		
M25 RH 4th digit (n = 8, 4)	11.8 (± 1.98)	10.9 (± 1.65)		
M25 RH 5th digit (n = 2, 1)	7.8 (± 4.6)	7.5 (± 9.99)		

Statistical analyses

No statistical analyses for this end point

Secondary: Health-related Quality-of-life as measured by the AcroQoL questionnaire

End point title	Health-related Quality-of-life as measured by the AcroQoL questionnaire

End point description:

Acromegalyy quality of life (AcroQoL) total scores. The AcroQoL questionnaire is unidimensional and contains 22 items divided in two scales: one that evaluates physical aspects (eight items) and another one that evaluates psychological aspects (14 items). The scoring of the questionnaire was performed as specified by the instrument developers. Higher scores represent better quality of life. Analysis was based on data up to crossover (i.e., included data from both blinded core and extension phase up to 26 Months for patients who continued the same treatment in the extension. For patients who switched to the other treatment, only data collected before crossover was included).

End point type	Secondary

End point timeframe:

Baseline, Months 12, 25

End point values	Pasireotide LAR (Core & Extension)	Octreotide LAR (Core & Extension)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	176	182		
Units: Score on a scale				
arithmetic mean (standard deviation)				
Baseline (n =173, 178)	58.4 (± 19.97)	55.6 (± 19.79)		
M12 (n = 136, 148)	65.7 (± 21.64)	61.6 (± 21.01)		

M25 (n = 58, 38)	69.3 (± 18.76)	62.9 (± 18.86)		

Statistical analyses

No statistical analyses for this end point

Secondary: Summary of prolactin levels

End point title	Summary of prolactin levels

End point description:

Prolactin Levels. Analysis was based on data up to crossover (i.e., included data from both blinded core and extension phase up to 26 Months for patients who continued the same treatment in the extension. For patients who switched to the other treatment, only data collected before crossover was included).

End point type	Secondary

End point timeframe:

Baseline, Months 12, 25

End point values	Pasireotide LAR (Core & Extension)	Octreotide LAR (Core & Extension)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	176	182		
Units: µg/L				
arithmetic mean (standard deviation)				
Baseline (n = 176, 182)	20.6 (± 53)	15.8 (± 22.05)		
M12 (n = 135, 146)	8.9 (± 19.24)	11.7 (± 19.09)		
M25 (n = 63, 40)	5.4 (± 4.37)	6.7 (± 4.63)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of response for patients achieving a reduction of mean GH level to <2.5 µg/L and the normalization of IGF-1 at Month 12 (No. of Responders: Pasireotide LAR = 51, Octreotide LAR = 32)

End point title	Duration of response for patients achieving a reduction of mean GH level to <2.5 µg/L and the normalization of IGF-1 at Month 12 (No. of Responders: Pasireotide LAR = 51, Octreotide LAR = 32)

End point description:

The duration of response is defined as the time from the date that patient first met and maintained the response criteria based on primary efficacy variable to the date that patient lost response status. Median and corresponding 95% CI are derived based on Kaplan-Meier method. Analysis was based on data up to crossover (i.e., included data from both blinded core and extension phase up to 26 Months for patients who continued the same treatment in the extension. For patients who switched to the other treatment, only data collected before crossover was included).

End point type	Secondary
End point timeframe: Up to 26 months	

End point values	Pasireotide LAR (Core & Extension)	Octreotide LAR (Core & Extension)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	176	182		
Units: Weeks				
median (confidence interval 95%)	64.4 (52.1 to 100.4)	64.6 (40 to 92)		

Statistical analyses

No statistical analyses for this end point

Secondary: Pasireotide trough concentrations by incident dose

End point title	Pasireotide trough concentrations by incident dose
End point description: Pasireotide LAR trough concentrations by incident dose (last dose administered prior to PK sample collection). PK observations with missing concentrations, missing dose, missing elapsed time or an elapsed time from previous injection outside of 28±2 days window were excluded. 5 patients with evaluable PK data in the pasireotide arm received erroneously 20 mg pasireotide LAR at baseline.	
End point type	Secondary
End point timeframe: Months 1 - 12	

End point values	Pasireotide LAR 20 mg	Pasireotide LAR 40 mg	Pasireotide LAR 60mg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	172	172	172	
Units: ng/mL				
arithmetic mean (standard deviation)				
M1 (n = 5, 146, 0)	4.65 (± 0.645)	6.65 (± 3.641)	99.99 (± 9.999)	
M2 (n = 6, 135, 0)	2.88 (± 1.371)	7.81 (± 3.505)	99.99 (± 9.999)	
M3 (n = 2,135, 0)	3.39 (± 2.659)	8.7 (± 5.402)	99.99 (± 9.999)	
M4 (n = 3, 88, 49)	3.93 (± 1.858)	9.51 (± 5.487)	13.48 (± 7.75)	
M5 (n = 4, 77, 56)	5.22 (± 4.077)	10.92 (± 6.017)	13.42 (± 6.902)	
M6 (n = 3, 71, 57)	2.87 (± 1.101)	10.59 (± 6.216)	13.08 (± 6.967)	
M7 (n =3, 69, 60)	2.29 (± 0.857)	11.85 (± 7.781)	14.76 (± 6.868)	

M8 (n =3, 63, 70)	3.65 (± 1.865)	12.33 (± 7.619)	15.88 (± 9.073)	
M9 (n =4, 59, 65)	4.8 (± 1.957)	12.75 (± 8.604)	16.03 (± 10.852)	
M10 (n =5, 61, 59)	5.66 (± 3.606)	12.42 (± 7.252)	16.01 (± 11.497)	
M11 (n =5, 53, 65)	5.1 (± 2.375)	12.62 (± 6.92)	16.31 (± 10.596)	
M12 (n =4, 45, 58)	4.54 (± 1.634)	11.11 (± 6.489)	16.16 (± 9.323)	

Statistical analyses

No statistical analyses for this end point

Secondary: Octreotide trough concentrations by incident dose

End point title	Octreotide trough concentrations by incident dose

End point description:

Octreotide LAR trough concentrations by incident dose (last dose administered prior to PK sample collection). PK observations with missing concentrations, missing dose, missing elapsed time or an elapsed time from previous injection outside of 28±2 days window were excluded.

End point type	Secondary

End point timeframe:

Months 1 - 12

End point values	Octreotide LAR 10mg	Octreotide LAR 20 mg	Octreotide LAR 30 mg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	178	178	178	
Units: ng/mL				
arithmetic mean (standard deviation)				
M1 (n = 0, 153, 0)	9.99 (± 9.999)	0.86 (± 0.493)	9.99 (± 9.999)	
M2 (n = 2, 139, 0)	0.61 (± 0.28)	1.21 (± 0.663)	9.99 (± 9.999)	
M3 (n = 2, 134, 0)	0.62 (± 0.107)	1.29 (± 0.654)	9.99 (± 9.999)	
M4 (n = 1, 79, 64)	0.19 (± 9.999)	1.45 (± 0.653)	1.55 (± 0.658)	
M5 (n = 0, 63, 82)	9.99 (± 9.999)	1.65 (± 0.876)	2.14 (± 1.156)	
M6 (n = 2, 62, 88)	1.33 (± 0.754)	1.58 (± 0.811)	2.12 (± 0.99)	
M7 (n = 1, 61, 82)	0.7 (± 9.999)	1.46 (± 0.704)	2.14 (± 1.009)	
M8 (n = 0, 50, 88)	9.99 (± 9.999)	1.55 (± 0.727)	2.16 (± 1.127)	
M9 (n = 0, 47, 93)	9.99 (± 9.999)	1.74 (± 1.013)	2.2 (± 0.992)	
M10 (n = 0, 49, 82)	9.99 (± 9.999)	1.66 (± 0.995)	2.5 (± 1.194)	
M11 (n = 0, 43, 87)	9.99 (± 9.999)	1.74 (± 0.89)	2.39 (± 1.103)	
M12 (n = 1, 37, 76)	0.3 (± 9.999)	1.58 (± 0.695)	2.55 (± 1.252)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with a reduction of mean GH Level to < 2.5µg/L and normalization of IGF-1 after crossover

End point title	Percentage of participants with a reduction of mean GH Level to < 2.5µg/L and normalization of IGF-1 after crossover

End point description:

Percentage of participants with a reduction of mean GH levels to < 2.5µg/L (based on a 5-point 2-hour profile) and normalization of sex- and age-adjusted IGF-1. Analysis was based on data after crossover (i.e., included data from blinded extension phase collected after the crossover time point for patients who crossed over). Denominator for all time points is the Crossover Analysis Set (CAS).

End point type	Secondary

End point timeframe:

Months 3, 6, 9, 12 after crossover

End point values	Crossed over to Pasireotide LAR (Extension)			
Subject group type	Subject analysis set			
Number of subjects analysed	81			
Units: Percentage of participants				
number (confidence interval 95%)				
M3 after crossover	17.3 (9.8 to 27.3)			
M6 after crossover	21 (12.7 to 31.5)			
M9 after crossover	22.2 (13.7 to 32.8)			
M12 after crossover	17.3 (9.8 to 27.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with a reduction of mean GH Level to < 2.5µg/L

End point title	Percentage of participants with a reduction of mean GH Level to < 2.5µg/L

End point description:

Percentage of participants with a reduction of mean GH levels to < 2.5µg/L (based on a 5-point 2-hour profile). Analysis was based on data up to crossover (i.e., included data from both blinded core and extension phase up to 26 Months for patients who continued the same treatment in the extension. For patients who switched to the other treatment, only data collected before crossover was included). Denominator for time points up to Month 12 is the Full Analysis Set. Denominator for time points after Month 12 excludes patients who completed the core and did not enter the extension. Patients who discontinued were considered non-responders for the time points after discontinuation, patients who crossed over were considered non-responders for all time points after crossover.

End point type	Secondary

End point timeframe:

Months 3, 6, 9, 12, 16, 19, 22, 25

End point values	Pasireotide LAR (Core & Extension)	Octreotide LAR (Core & Extension)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	176	182		
Units: Percentage of participants				
number (confidence interval 95%)				
M3 (n= 176, 182)	49.4 (41.8 to 57.1)	43.4 (36.1 to 50.9)		
M6 (n= 176, 182)	45.5 (37.9 to 53.1)	47.8 (40.4 to 55.3)		
M9 (n= 176, 182)	42.6 (35.2 to 50.3)	46.2 (38.8 to 53.7)		
M12 (n= 176, 182)	43.2 (35.8 to 50.8)	47.3 (39.8 to 54.8)		
M16 (n = 147, 153)	33.3 (25.8 to 41.6)	22.2 (15.9 to 29.6)		
M19 (n = 147, 153)	36.7 (28.9 to 45.1)	21.6 (15.3 to 28.9)		
M22 (n = 147, 153)	35.4 (27.7 to 43.7)	22.2 (15.9 to 29.6)		
M25 (n = 147, 153)	35.4 (27.7 to 43.7)	24.2 (17.6 to 31.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with normalization of IGF-1

End point title	Percentage of participants with normalization of IGF-1

End point description:

Percentage of participants with normalization of sex- and age-adjusted IGF-1. Analysis was based on data up to crossover (i.e., included data from both blinded core and extension phase up to 26 Months for patients who continued the same treatment in the extension. For patients who switched to the other treatment, only data collected before crossover was included). Denominator for time points up to Month 12 is the FAS. Denominator for time points after Month 12 excludes patients who completed the core and did not enter the extension. Patients who discontinued were considered non-responders for the time points after discontinuation, patients who crossed over were considered non-responders for all time points after crossover.

End point type	Secondary

End point timeframe:

Months 3, 6, 9, 12, 16, 19, 22, 25

End point values	Pasireotide LAR (Core & Extension)	Octreotide LAR (Core & Extension)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	176	182		
Units: Percentage of participants				
number (confidence interval 95%)				
M3 (n = 176, 182)	35.2 (28.2 to 42.8)	25.3 (19.1 to 32.2)		
M6 (n = 176, 182)	35.8 (28.7 to 43.4)	24.2 (18.1 to 31.1)		
M9 (n = 176, 182)	34.1 (27.1 to 41.6)	28 (21.6 to 35.1)		
M12 (n = 176, 182)	35.8 (28.7 to 43.4)	22 (16.2 to 28.7)		
M16 (n = 147, 153)	29.9 (22.7 to 38)	13.7 (8.7 to 20.2)		
M19 (n = 147, 153)	25.2 (18.4 to 33)	15.7 (10.3 to 22.4)		
M22 (n = 147, 153)	25.9 (19 to 33.7)	17 (11.4 to 23.9)		
M25 (n = 147, 153)	25.9 (19 to 33.7)	14.4 (9.2 to 21)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in tumor volume

End point title	Change from baseline in tumor volume

End point description:

Percentage change from baseline in tumor volume (assessed by pituitary MRI). Analysis was based on data up to crossover (i.e., included data from both blinded core and extension phase up to 26 Months for patients who continued the same treatment in the extension. For patients who switched to the other treatment, only data collected before crossover was included).

End point type	Secondary

End point timeframe:

Baseline, months 6, 12, 19, 25

End point values	Pasireotide LAR (Core)	Octreotide LAR (Core)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	176	182		
Units: mm^3				
arithmetic mean (standard deviation)				
Baseline (n = 166, 169)	2420.7 (± 4159.21)	2259.2 (± 3390.2)		
M6 (n = 148, 160)	1614.1 (± 2536.46)	1565.4 (± 2245.99)		
M12 (n = 125, 138)	1482.4 (± 2387.88)	1390.4 (± 2179.93)		

M19 (n = 59, 37)	956.6 (± 1806.72)	1009.9 (± 1578.75)		
M25 (n = 59, 36)	840.4 (± 1706.07)	814.1 (± 1306.58)		
% change at M6 (n = 142, 145)	-29.9 (± 21.73)	-28.8 (± 20.22)		
% change at M12 (n = 120, 124)	-39.7 (± 21.83)	-38 (± 24.47)		
% change at M19 (n = 56, 35)	-48.9 (± 22.81)	-47.2 (± 24.08)		
% change at M25 (n = 54, 34)	-51.8 (± 20.81)	-55 (± 21.27)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with a reduction of mean GH Level to < 2.5µg/L after crossover

End point title	Percentage of participants with a reduction of mean GH Level to < 2.5µg/L after crossover

End point description:

Percentage of participants with a reduction of mean GH levels to < 2.5µg/L (based on a 5-point 2-hour profile). Analysis was based on data after crossover (i.e., included data from blinded extension phase collected after the crossover time point for patients who crossed over). Denominator for all time points is the Crossover Analysis Set (CAS).

End point type	Secondary

End point timeframe:

Months 3, 6, 9, 12 after crossover

End point values	Crossed over to Pasireotide LAR (Extension)	Crossed over to Octreotide LAR (Extension)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	81	38		
Units: Percentage of participants				
number (confidence interval 95%)				
M3 after crossover	49.4 (38.1 to 60.7)	28.9 (15.4 to 45.9)		
M6 after crossover	43.2 (32.2 to 54.7)	31.6 (17.5 to 48.7)		
M9 after crossover	54.3 (42.9 to 65.4)	31.6 (17.5 to 48.7)		
M12 after crossover	44.4 (33.4 to 55.9)	23.7 (11.4 to 40.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with normalization of IGF-1 after crossover

End point title	Percentage of participants with normalization of IGF-1 after crossover

End point description:

Percentage of participants with normalization of sex- and age-adjusted IGF-1. Analysis was based on data after crossover (i.e., included data from blinded extension phase collected after the crossover time point for patients who crossed over). Denominator for all time points is the Crossover Analysis Set (CAS).

End point type	Secondary

End point timeframe:

Months 3, 6, 9, 12 after crossover

End point values	Crossed over to Pasireotide LAR (Extension)	Crossed over to Octreotide LAR (Extension)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	81	38		
Units: Percentage of participants				
number (confidence interval 95%)				
M3 after crossover	19.8 (11.7 to 30.1)	7.9 (1.7 to 21.4)		
M6 after crossover	30.9 (21.1 to 42.1)	7.9 (1.7 to 21.4)		
M9 after crossover	29.6 (20 to 40.8)	10.5 (2.9 to 24.8)		
M12 after crossover	27.2 (17.9 to 38.2)	5.3 (0.6 to 17.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Summary of mean GH values after crossover

End point title	Summary of mean GH values after crossover

End point description:

Mean GH levels (based on a 5-point profile over 2 hours). Extension baseline was defined as last measurement prior to the start of crossover treatment. Analysis was based on data after crossover (i.e., included data from blinded extension phase collected after the crossover time point for patients who crossed over).

End point type	Secondary

End point timeframe:

Extension baseline, months 3, 6, 9, 12 after crossover

End point values	Crossed over to Pasireotide LAR (Extension)	Crossed over to Octreotide LAR (Extension)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	81	38		
Units: µg/L				
arithmetic mean (standard deviation)				
Ext. Baseline (n = 78, 33)	5.9 (± 15.02)	7.1 (± 9.8)		
M3 after crossover (n = 72, 36)	5.9 (± 19.7)	9.8 (± 17.09)		
M6 after crossover (n= 68, 32)	4.8 (± 14.51)	9.8 (± 20.49)		
M9 after crossover (n = 61, 32)	2.6 (± 3.03)	8.7 (± 19.26)		
M12 after crossover (n = 57, 29)	2.5 (± 2.47)	10.4 (± 26)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from extension baseline in tumor volume after crossover

End point title	Change from extension baseline in tumor volume after crossover

End point description:

Percentage change from extension baseline in tumor volume (assessed by pituitary MRI). Extension baseline was defined as last assessment prior to the administration of the new treatment after crossover. Analysis was based on data after crossover (i.e., included data from blinded extension phase collected after the crossover time point for patients who crossed over).

End point type	Secondary

End point timeframe:

Extension baseline, months 6, 12 after crossover

End point values	Crossed over to Pasireotide LAR (Extension)	Crossed over to Octreotide LAR (Extension)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	81	38		
Units: mm^3				
arithmetic mean (standard deviation)				
Ext. Baseline (n = 73, 32)	1420.9 (± 1914.58)	1809.6 (± 2579.25)		
Value at M6 after crossover (n = 65, 31)	1027.5 (± 1282.42)	1794.9 (± 2823.08)		
% change - M6 after crossover (n = 59, 27)	-18.1 (± 17.68)	-12.3 (± 24.11)		
Value at M12 after crossover (n = 51, 30)	949 (± 1169.49)	1610.4 (± 2666.66)		
% change - M12 after crossover (n = 46, 26)	-24.7 (± 25.2)	-17.9 (± 27.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Severity scores of acromegaly symptoms after crossover

End point title	Severity scores of acromegaly symptoms after crossover

End point description:

Severity scores of acromegaly symptoms (Headache, Fatigue, Perspiration, Paresthesias, Osteoarthralgia). Symptoms were scored from 0 (no symptom) to 4 (very severe). Extension baseline was defined as last measurement prior to the start of crossover treatment. Analysis was based on data after crossover (i.e., included data from blinded extension phase collected after the crossover time point for patients who crossed over).

End point type	Secondary

End point timeframe:

Extension baseline, month 12 after crossover

End point values	Crossed over to Pasireotide LAR (Extension)	Crossed over to Octreotide LAR (Extension)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	81	38		
Units: scores on a scale				
arithmetic mean (standard deviation)				
Headache: Ext. BL (n = 81, 38)	0.6 (± 0.89)	0.4 (± 0.6)		
Headache: M12 after crossover (n = 60, 32)	0.5 (± 0.83)	0.7 (± 0.79)		
Fatigue: Ext. BL (n = 81, 38)	0.8 (± 1.07)	0.7 (± 0.76)		
Fatigue: M12 after crossover (n = 60, 32)	0.8 (± 0.91)	0.7 (± 0.68)		
Perspiration: Ext. BL (n = 81, 38)	0.5 (± 0.85)	0.6 (± 0.86)		
Perspiration: M12 after crossover (n = 60, 32)	0.6 (± 0.98)	0.5 (± 0.8)		
Paresthesia: Ext. BL (n = 81, 38)	0.4 (± 0.75)	0.4 (± 0.054)		
Paresthesia: M12 after crossover (n = 60, 32)	0.3 (± 0.56)	0.4 (± 0.76)		
Osteoarthralgia: Ext. BL (n=81,38)	0.6 (± 0.91)	0.6 (± 0.79)		
Osteoarthralgia: M12 after crossover (n =60, 32)	0.5 (± 0.89)	0.7 (± 0.86)		

Statistical analyses

No statistical analyses for this end point

Secondary: Ring size after crossover

End point title	Ring size after crossover

End point description:

Ring size (based on jeweler's finger gauge). Extension baseline was defined as last measurement prior to the start of crossover treatment. Analysis was based on data after crossover (i.e., included data from blinded extension phase collected after the crossover time point for patients who crossed over). BL = baseline, LH = left hand, RH = right hand, CO = crossover

End point type	Secondary

End point timeframe:

Extension baseline, month 12 after crossover

End point values	Crossed over to Octreotide LAR (Extension)			
Subject group type	Subject analysis set			
Number of subjects analysed	38			
Units: ring size				
arithmetic mean (standard deviation)				
Ext. BL LH 4th digit (n = 55, 26)	11 (± 1.87)			
Ext. BL LH 5th digit (n = 6, 5)	12.3 (± 2.46)			
Ext. BL RH 4th digit (n = 15, 7)	12.4 (± 2.11)			
Ext. BL RH 5th digit (n = 3, 0)	99.9 (± 9.99)			
M12 after CO LH 4th digit (n = 42, 24)	11.2 (± 2.01)			
M12 after CO LH 5th digit CO (n = 4, 4)	12.5 (± 1.35)			
M12 after CO RH 4th digit (n = 11, 4)	11.4 (± 2.56)			
M12 after CO RH 5th digit (n =2, 0)	99.9 (± 9.99)			

Statistical analyses

No statistical analyses for this end point

Secondary: Health-related Quality-of-life as measured by the AcroQoL questionnaire after crossover

End point title	Health-related Quality-of-life as measured by the AcroQoL questionnaire after crossover

End point description:

AcroQoL total scores. The AcroQoL questionnaire is unidimensional and contains 22 items divided in two scales: one that evaluates physical aspects (eight items) and another one that evaluates psychological aspects (14 items). The scoring of the questionnaire was performed as specified by the instrument developers. Extension baseline was defined as last measurement prior to the start of crossover treatment. Analysis was based on data after crossover (i.e., included data from blinded extension phase collected after the crossover time point for patients who crossed over). Higher scores represent better quality of life.

End point type	Secondary

End point timeframe:

Extension baseline, months 12 after crossover

End point values	Crossed over to Pasireotide LAR (Extension)	Crossed over to Octreotide LAR (Extension)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	81	38		
Units: scores on a scale				
arithmetic mean (standard deviation)				
Ext. Baseline (n = 79, 34)	58.9 (± 23.11)	59.8 (± 22.4)		
M12 after crossover (n = 57, 30)	60.3 (± 24.34)	61.2 (± 21.62)		

Statistical analyses

No statistical analyses for this end point

Secondary: Summary of prolactin levels after crossover

End point title	Summary of prolactin levels after crossover

End point description:

Prolactin (PRL) levels. Analysis was based on data after crossover (i.e., included data from blinded extension phase collected after the crossover time point for patients who crossed over). Extension baseline was defined as last measurement prior to the start of crossover treatment.

End point type	Secondary

End point timeframe:

Extension baseline, month 12 after crossover

End point values	Crossed over to Pasireotide LAR (Extension)	Crossed over to Octreotide LAR (Extension)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	81	38		
Units: µg/L				
arithmetic mean (standard deviation)				
Ext. Baseline (n = 78, 34)	11.9 (± 18.42)	15.7 (± 36.76)		
M12 after crossover (n = 60, 31)	7.5 (± 8.95)	16.1 (± 25.37)		

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 reported in this record are from date of First Patient First Treatment until Last Patient Last Visit

Adverse event reporting additional description:

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

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	Pasireotide LAR - up to 26 Months

Reporting group description:

Includes data from both blinded core and extension phase (up to Month 26 cutoff date of 29-Dec-2011) for patients who continued the same treatment (Pasireotide LAR) as in the core. For patients who switched from blinded Pasireotide LAR to Octreotide LAR treatment, only data collected before crossover is included.

Reporting group title	Octreotide LAR - up to 26 Months

Reporting group description:

Includes data from both blinded core and extension phase (up to Month 26 cutoff date of 29-Dec-2011) for patients who continued the same treatment (Octreotide LAR) as in the core. For patients who switched from blinded Octreotide LAR to Pasireotide LAR treatment, only data collected before crossover is included.

Reporting group title	Crossed over to Pasireotide LAR - up to 26 Months

Reporting group description:

Includes all data in the extension phase (up to 26-Month cutoff date of 29-Dec-2011) collected after the crossover time point for patients who crossed over from Octreotide LAR in the core to Pasireotide LAR treatment in the extension phase.

Reporting group title	Crossed over to Octreotide LAR - up to 26 Months

Reporting group description:

Includes all data in the extension phase (up to 26-Month cutoff date of 29-Dec-2011) collected after the crossover time point for patients who crossed over from Pasireotide LAR in the core to Octreotide LAR treatment in the extension phase.

Reporting group title	Pasireotide LAR - up to EOS

Reporting group description:

Includes data from both core and extension phase (up to End-of-study date of 11-Mar-2016) for patients who continued the same treatment (Pasireotide LAR) as in the core. For patients who switched from blinded Pasireotide LAR to Octreotide LAR treatment, only data collected before crossover is included. Per protocol, patients on Pasireotide LAR could continue to receive open-label Pasireotide LAR after treatment unblinding at Month 26, whereas those on Octreotide LAR were not followed after Month 26.

Reporting group title	Crossed over to Pasireotide LAR - up to EOS

Reporting group description:

Includes all data in the extension phase (up to End-of-study date of 11-Mar-2016) collected after the crossover time point for patients who crossed over from Octreotide LAR in the core to Pasireotide LAR treatment in the extension phase.
Per protocol, patients on Pasireotide LAR could continue to receive open-label Pasireotide LAR after treatment unblinding at Month 26, whereas those on Octreotide LAR were not followed after Month 26.

Serious adverse events	Pasireotide LAR - up to 26 Months	Octreotide LAR - up to 26 Months	Crossed over to Pasireotide LAR - up to 26 Months
Total subjects affected by serious adverse events			
subjects affected / exposed	35 / 178 (19.66%)	28 / 180 (15.56%)	8 / 81 (9.88%)
number of deaths (all causes)	1	2	1
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute myeloid leukaemia			
subjects affected / exposed	1 / 178 (0.56%)	0 / 180 (0.00%)	0 / 81 (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
Benign breast neoplasm			
subjects affected / exposed	0 / 178 (0.00%)	1 / 180 (0.56%)	0 / 81 (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
Cervix carcinoma			
subjects affected / exposed	0 / 178 (0.00%)	0 / 180 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypopharyngeal neoplasm			
subjects affected / exposed	0 / 178 (0.00%)	0 / 180 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Invasive ductal breast carcinoma			
subjects affected / exposed	1 / 178 (0.56%)	0 / 180 (0.00%)	0 / 81 (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
Lipoma			
subjects affected / exposed	0 / 178 (0.00%)	1 / 180 (0.56%)	0 / 81 (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
Mixed hepatocellular cholangiocarcinoma			

subjects affected / exposed	1 / 178 (0.56%)	0 / 180 (0.00%)	0 / 81 (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
Papillary thyroid cancer			
subjects affected / exposed	1 / 178 (0.56%)	0 / 180 (0.00%)	0 / 81 (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 / 178 (0.00%)	1 / 180 (0.56%)	0 / 81 (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
Plasma cell myeloma			
subjects affected / exposed	0 / 178 (0.00%)	0 / 180 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal oncocytoma			
subjects affected / exposed	0 / 178 (0.00%)	1 / 180 (0.56%)	0 / 81 (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
Respiratory papilloma			
subjects affected / exposed	0 / 178 (0.00%)	0 / 180 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Aortic aneurysm rupture			
subjects affected / exposed	0 / 178 (0.00%)	0 / 180 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Arteriovenous fistula			
subjects affected / exposed	0 / 178 (0.00%)	1 / 180 (0.56%)	0 / 81 (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
Hypertension			

subjects affected / exposed	0 / 178 (0.00%)	1 / 180 (0.56%)	0 / 81 (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
Peripheral venous disease			
subjects affected / exposed	0 / 178 (0.00%)	0 / 180 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			
subjects affected / exposed	0 / 178 (0.00%)	0 / 180 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Chills			
subjects affected / exposed	0 / 178 (0.00%)	1 / 180 (0.56%)	0 / 81 (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
Concomitant disease progression			
subjects affected / exposed	2 / 178 (1.12%)	0 / 180 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	1 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fatigue			
subjects affected / exposed	1 / 178 (0.56%)	0 / 180 (0.00%)	0 / 81 (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
Hernia			
subjects affected / exposed	0 / 178 (0.00%)	1 / 180 (0.56%)	0 / 81 (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
Multi-organ failure			
subjects affected / exposed	0 / 178 (0.00%)	1 / 180 (0.56%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0

Oedema peripheral			
subjects affected / exposed	1 / 178 (0.56%)	0 / 180 (0.00%)	0 / 81 (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
Pyrexia			
subjects affected / exposed	0 / 178 (0.00%)	1 / 180 (0.56%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Breast mass			
subjects affected / exposed	1 / 178 (0.56%)	0 / 180 (0.00%)	0 / 81 (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
Uterine prolapse			
subjects affected / exposed	1 / 178 (0.56%)	0 / 180 (0.00%)	0 / 81 (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			
Lung infiltration			
subjects affected / exposed	0 / 178 (0.00%)	1 / 180 (0.56%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Nasal polyps			
subjects affected / exposed	0 / 178 (0.00%)	0 / 180 (0.00%)	1 / 81 (1.23%)
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 mass			
subjects affected / exposed	0 / 178 (0.00%)	1 / 180 (0.56%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Catatonia			

subjects affected / exposed	1 / 178 (0.56%)	0 / 180 (0.00%)	0 / 81 (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
Completed suicide			
subjects affected / exposed	1 / 178 (0.56%)	0 / 180 (0.00%)	0 / 81 (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
Major depression			
subjects affected / exposed	1 / 178 (0.56%)	0 / 180 (0.00%)	0 / 81 (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
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 178 (0.56%)	2 / 180 (1.11%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood creatinine increased			
subjects affected / exposed	0 / 178 (0.00%)	0 / 180 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood sodium decreased			
subjects affected / exposed	0 / 178 (0.00%)	0 / 180 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Weight decreased			
subjects affected / exposed	0 / 178 (0.00%)	0 / 180 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Back injury			
subjects affected / exposed	1 / 178 (0.56%)	0 / 180 (0.00%)	0 / 81 (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

Brain contusion			
subjects affected / exposed	0 / 178 (0.00%)	0 / 180 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Contusion			
subjects affected / exposed	0 / 178 (0.00%)	0 / 180 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Facial bones fracture			
subjects affected / exposed	0 / 178 (0.00%)	0 / 180 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fibula fracture			
subjects affected / exposed	1 / 178 (0.56%)	0 / 180 (0.00%)	0 / 81 (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
Head injury			
subjects affected / exposed	0 / 178 (0.00%)	0 / 180 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Jaw fracture			
subjects affected / exposed	0 / 178 (0.00%)	0 / 180 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Kidney rupture			
subjects affected / exposed	0 / 178 (0.00%)	1 / 180 (0.56%)	0 / 81 (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
Ligament sprain			
subjects affected / exposed	0 / 178 (0.00%)	0 / 180 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post-traumatic neck syndrome			

subjects affected / exposed	1 / 178 (0.56%)	0 / 180 (0.00%)	0 / 81 (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
Rib fracture			
subjects affected / exposed	0 / 178 (0.00%)	0 / 180 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Road traffic accident			
subjects affected / exposed	1 / 178 (0.56%)	1 / 180 (0.56%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal column injury			
subjects affected / exposed	0 / 178 (0.00%)	0 / 180 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subdural haematoma			
subjects affected / exposed	1 / 178 (0.56%)	0 / 180 (0.00%)	0 / 81 (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
Thoracic vertebral fracture			
subjects affected / exposed	0 / 178 (0.00%)	0 / 180 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tibia fracture			
subjects affected / exposed	0 / 178 (0.00%)	1 / 180 (0.56%)	0 / 81 (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
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 178 (0.00%)	0 / 180 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina unstable			

subjects affected / exposed	0 / 178 (0.00%)	0 / 180 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	1 / 178 (0.56%)	0 / 180 (0.00%)	0 / 81 (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
Cardiac arrest			
subjects affected / exposed	0 / 178 (0.00%)	1 / 180 (0.56%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Cardiovascular disorder			
subjects affected / exposed	1 / 178 (0.56%)	0 / 180 (0.00%)	0 / 81 (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
Myocardial infarction			
subjects affected / exposed	0 / 178 (0.00%)	1 / 180 (0.56%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Myocardial ischaemia			
subjects affected / exposed	0 / 178 (0.00%)	0 / 180 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Diabetic hyperglycaemic coma			
subjects affected / exposed	1 / 178 (0.56%)	0 / 180 (0.00%)	0 / 81 (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
Dizziness			
subjects affected / exposed	1 / 178 (0.56%)	0 / 180 (0.00%)	0 / 81 (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
Migraine			

subjects affected / exposed	0 / 178 (0.00%)	1 / 180 (0.56%)	0 / 81 (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
Multiple sclerosis			
subjects affected / exposed	1 / 178 (0.56%)	0 / 180 (0.00%)	0 / 81 (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
Seizure			
subjects affected / exposed	0 / 178 (0.00%)	1 / 180 (0.56%)	0 / 81 (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
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	1 / 178 (0.56%)	0 / 180 (0.00%)	0 / 81 (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
Ear and labyrinth disorders			
Hypoacusis			
subjects affected / exposed	1 / 178 (0.56%)	0 / 180 (0.00%)	0 / 81 (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 disorders			
Abdominal pain			
subjects affected / exposed	0 / 178 (0.00%)	1 / 180 (0.56%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain upper			
subjects affected / exposed	0 / 178 (0.00%)	2 / 180 (1.11%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal fissure			
subjects affected / exposed	1 / 178 (0.56%)	0 / 180 (0.00%)	0 / 81 (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

Colitis			
subjects affected / exposed	0 / 178 (0.00%)	1 / 180 (0.56%)	0 / 81 (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
Constipation			
subjects affected / exposed	0 / 178 (0.00%)	0 / 180 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 178 (0.00%)	1 / 180 (0.56%)	0 / 81 (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
Gastritis			
subjects affected / exposed	0 / 178 (0.00%)	1 / 180 (0.56%)	0 / 81 (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 / 178 (0.56%)	0 / 180 (0.00%)	0 / 81 (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
Intestinal obstruction			
subjects affected / exposed	0 / 178 (0.00%)	1 / 180 (0.56%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Irritable bowel syndrome			
subjects affected / exposed	0 / 178 (0.00%)	1 / 180 (0.56%)	0 / 81 (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
Large intestine polyp			
subjects affected / exposed	0 / 178 (0.00%)	1 / 180 (0.56%)	0 / 81 (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 / 178 (0.00%)	0 / 180 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal obstruction			
subjects affected / exposed	0 / 178 (0.00%)	0 / 180 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatic cyst			
subjects affected / exposed	0 / 178 (0.00%)	1 / 180 (0.56%)	0 / 81 (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
Pancreatitis acute			
subjects affected / exposed	1 / 178 (0.56%)	0 / 180 (0.00%)	0 / 81 (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
Vomiting			
subjects affected / exposed	0 / 178 (0.00%)	0 / 180 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	2 / 178 (1.12%)	1 / 180 (0.56%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	2 / 2	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis acute			
subjects affected / exposed	2 / 178 (1.12%)	1 / 180 (0.56%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	2 / 2	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	5 / 178 (2.81%)	4 / 180 (2.22%)	2 / 81 (2.47%)
occurrences causally related to treatment / all	5 / 5	5 / 5	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hydrocholecystis			

subjects affected / exposed	0 / 178 (0.00%)	1 / 180 (0.56%)	0 / 81 (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
Skin and subcutaneous tissue disorders			
Chronic pigmented purpura			
subjects affected / exposed	0 / 178 (0.00%)	1 / 180 (0.56%)	0 / 81 (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
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 178 (0.00%)	1 / 180 (0.56%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Hydronephrosis			
subjects affected / exposed	0 / 178 (0.00%)	1 / 180 (0.56%)	0 / 81 (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
Nephrolithiasis			
subjects affected / exposed	2 / 178 (1.12%)	0 / 180 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary incontinence			
subjects affected / exposed	1 / 178 (0.56%)	0 / 180 (0.00%)	0 / 81 (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
Endocrine disorders			
Acromegaly			
subjects affected / exposed	2 / 178 (1.12%)	0 / 180 (0.00%)	0 / 81 (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
Adrenal insufficiency			
subjects affected / exposed	0 / 178 (0.00%)	1 / 180 (0.56%)	0 / 81 (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

Toxic nodular goitre			
subjects affected / exposed	0 / 178 (0.00%)	1 / 180 (0.56%)	0 / 81 (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
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 178 (0.56%)	0 / 180 (0.00%)	0 / 81 (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
Back pain			
subjects affected / exposed	0 / 178 (0.00%)	1 / 180 (0.56%)	0 / 81 (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
Chondritis			
subjects affected / exposed	0 / 178 (0.00%)	0 / 180 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc protrusion			
subjects affected / exposed	1 / 178 (0.56%)	0 / 180 (0.00%)	0 / 81 (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
Musculoskeletal pain			
subjects affected / exposed	1 / 178 (0.56%)	0 / 180 (0.00%)	0 / 81 (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
Osteoarthritis			
subjects affected / exposed	1 / 178 (0.56%)	1 / 180 (0.56%)	0 / 81 (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
Pain in extremity			
subjects affected / exposed	1 / 178 (0.56%)	0 / 180 (0.00%)	0 / 81 (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

Pathological fracture			
subjects affected / exposed	0 / 178 (0.00%)	0 / 180 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tendonitis			
subjects affected / exposed	1 / 178 (0.56%)	0 / 180 (0.00%)	0 / 81 (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			
Appendicitis			
subjects affected / exposed	0 / 178 (0.00%)	1 / 180 (0.56%)	0 / 81 (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
Febrile infection			
subjects affected / exposed	1 / 178 (0.56%)	0 / 180 (0.00%)	0 / 81 (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
Gastroenteritis			
subjects affected / exposed	0 / 178 (0.00%)	1 / 180 (0.56%)	0 / 81 (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
Influenza			
subjects affected / exposed	0 / 178 (0.00%)	0 / 180 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia bacterial			
subjects affected / exposed	0 / 178 (0.00%)	0 / 180 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			
subjects affected / exposed	0 / 178 (0.00%)	1 / 180 (0.56%)	0 / 81 (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
Rectal abscess			

subjects affected / exposed	0 / 178 (0.00%)	1 / 180 (0.56%)	0 / 81 (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 abscess			
subjects affected / exposed	0 / 178 (0.00%)	1 / 180 (0.56%)	0 / 81 (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
Septic shock			
subjects affected / exposed	0 / 178 (0.00%)	1 / 180 (0.56%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Tonsillitis			
subjects affected / exposed	0 / 178 (0.00%)	0 / 180 (0.00%)	1 / 81 (1.23%)
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	1 / 178 (0.56%)	1 / 180 (0.56%)	0 / 81 (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
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 178 (0.00%)	1 / 180 (0.56%)	0 / 81 (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
Diabetes mellitus			
subjects affected / exposed	3 / 178 (1.69%)	0 / 180 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	3 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic ketoacidosis			
subjects affected / exposed	0 / 178 (0.00%)	0 / 180 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			

subjects affected / exposed	1 / 178 (0.56%)	0 / 180 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperlipidaemia			
subjects affected / exposed	0 / 178 (0.00%)	0 / 180 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemia			
subjects affected / exposed	0 / 178 (0.00%)	1 / 180 (0.56%)	0 / 81 (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 / 178 (0.00%)	0 / 180 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 178 (0.00%)	0 / 180 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Crossed over to Octreotide LAR - up to 26 Months	Pasireotide LAR - up to EOS	Crossed over to Pasireotide LAR - up to EOS
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 38 (15.79%)	37 / 178 (20.79%)	12 / 81 (14.81%)
number of deaths (all causes)	0	1	1
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute myeloid leukaemia			
subjects affected / exposed	0 / 38 (0.00%)	1 / 178 (0.56%)	0 / 81 (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
Benign breast neoplasm			

subjects affected / exposed	0 / 38 (0.00%)	0 / 178 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cervix carcinoma			
subjects affected / exposed	0 / 38 (0.00%)	0 / 178 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypopharyngeal neoplasm			
subjects affected / exposed	0 / 38 (0.00%)	0 / 178 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Invasive ductal breast carcinoma			
subjects affected / exposed	0 / 38 (0.00%)	1 / 178 (0.56%)	0 / 81 (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
Lipoma			
subjects affected / exposed	0 / 38 (0.00%)	0 / 178 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mixed hepatocellular cholangiocarcinoma			
subjects affected / exposed	0 / 38 (0.00%)	1 / 178 (0.56%)	0 / 81 (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
Papillary thyroid cancer			
subjects affected / exposed	0 / 38 (0.00%)	1 / 178 (0.56%)	0 / 81 (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
Pituitary tumour benign			
subjects affected / exposed	0 / 38 (0.00%)	0 / 178 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Plasma cell myeloma			

subjects affected / exposed	0 / 38 (0.00%)	0 / 178 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal oncocytoma			
subjects affected / exposed	0 / 38 (0.00%)	0 / 178 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory papilloma			
subjects affected / exposed	0 / 38 (0.00%)	0 / 178 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Aortic aneurysm rupture			
subjects affected / exposed	0 / 38 (0.00%)	0 / 178 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Arteriovenous fistula			
subjects affected / exposed	0 / 38 (0.00%)	0 / 178 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			
subjects affected / exposed	0 / 38 (0.00%)	0 / 178 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral venous disease			
subjects affected / exposed	1 / 38 (2.63%)	0 / 178 (0.00%)	0 / 81 (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
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			
subjects affected / exposed	1 / 38 (2.63%)	0 / 178 (0.00%)	0 / 81 (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

General disorders and administration site conditions			
Chills			
subjects affected / exposed	0 / 38 (0.00%)	0 / 178 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Concomitant disease progression			
subjects affected / exposed	0 / 38 (0.00%)	2 / 178 (1.12%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fatigue			
subjects affected / exposed	0 / 38 (0.00%)	1 / 178 (0.56%)	0 / 81 (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
Hernia			
subjects affected / exposed	0 / 38 (0.00%)	0 / 178 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multi-organ failure			
subjects affected / exposed	0 / 38 (0.00%)	0 / 178 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema peripheral			
subjects affected / exposed	0 / 38 (0.00%)	1 / 178 (0.56%)	0 / 81 (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
Pyrexia			
subjects affected / exposed	0 / 38 (0.00%)	0 / 178 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Breast mass			

subjects affected / exposed	0 / 38 (0.00%)	1 / 178 (0.56%)	0 / 81 (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
Uterine prolapse			
subjects affected / exposed	0 / 38 (0.00%)	1 / 178 (0.56%)	0 / 81 (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
Respiratory, thoracic and mediastinal disorders			
Lung infiltration			
subjects affected / exposed	0 / 38 (0.00%)	0 / 178 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nasal polyps			
subjects affected / exposed	0 / 38 (0.00%)	0 / 178 (0.00%)	1 / 81 (1.23%)
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 mass			
subjects affected / exposed	0 / 38 (0.00%)	0 / 178 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Catatonia			
subjects affected / exposed	0 / 38 (0.00%)	1 / 178 (0.56%)	0 / 81 (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
Completed suicide			
subjects affected / exposed	0 / 38 (0.00%)	1 / 178 (0.56%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Major depression			
subjects affected / exposed	0 / 38 (0.00%)	1 / 178 (0.56%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0

Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 38 (0.00%)	1 / 178 (0.56%)	0 / 81 (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
Blood creatinine increased			
subjects affected / exposed	0 / 38 (0.00%)	0 / 178 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood sodium decreased			
subjects affected / exposed	0 / 38 (0.00%)	0 / 178 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Weight decreased			
subjects affected / exposed	0 / 38 (0.00%)	0 / 178 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Back injury			
subjects affected / exposed	0 / 38 (0.00%)	1 / 178 (0.56%)	0 / 81 (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
Brain contusion			
subjects affected / exposed	0 / 38 (0.00%)	0 / 178 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Contusion			
subjects affected / exposed	0 / 38 (0.00%)	1 / 178 (0.56%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Facial bones fracture			

subjects affected / exposed	0 / 38 (0.00%)	1 / 178 (0.56%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fibula fracture			
subjects affected / exposed	0 / 38 (0.00%)	1 / 178 (0.56%)	0 / 81 (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
Head injury			
subjects affected / exposed	0 / 38 (0.00%)	0 / 178 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Jaw fracture			
subjects affected / exposed	0 / 38 (0.00%)	1 / 178 (0.56%)	0 / 81 (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
Kidney rupture			
subjects affected / exposed	0 / 38 (0.00%)	0 / 178 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ligament sprain			
subjects affected / exposed	1 / 38 (2.63%)	0 / 178 (0.00%)	0 / 81 (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
Post-traumatic neck syndrome			
subjects affected / exposed	0 / 38 (0.00%)	1 / 178 (0.56%)	0 / 81 (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
Rib fracture			
subjects affected / exposed	0 / 38 (0.00%)	1 / 178 (0.56%)	0 / 81 (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
Road traffic accident			

subjects affected / exposed	0 / 38 (0.00%)	1 / 178 (0.56%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal column injury			
subjects affected / exposed	0 / 38 (0.00%)	0 / 178 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subdural haematoma			
subjects affected / exposed	0 / 38 (0.00%)	1 / 178 (0.56%)	0 / 81 (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
Thoracic vertebral fracture			
subjects affected / exposed	0 / 38 (0.00%)	0 / 178 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tibia fracture			
subjects affected / exposed	0 / 38 (0.00%)	0 / 178 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 38 (2.63%)	0 / 178 (0.00%)	0 / 81 (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
Angina unstable			
subjects affected / exposed	1 / 38 (2.63%)	0 / 178 (0.00%)	0 / 81 (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
Atrial fibrillation			
subjects affected / exposed	0 / 38 (0.00%)	1 / 178 (0.56%)	0 / 81 (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
Cardiac arrest			

subjects affected / exposed	0 / 38 (0.00%)	0 / 178 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiovascular disorder			
subjects affected / exposed	0 / 38 (0.00%)	1 / 178 (0.56%)	0 / 81 (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
Myocardial infarction			
subjects affected / exposed	0 / 38 (0.00%)	0 / 178 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial ischaemia			
subjects affected / exposed	1 / 38 (2.63%)	0 / 178 (0.00%)	0 / 81 (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
Nervous system disorders			
Diabetic hyperglycaemic coma			
subjects affected / exposed	0 / 38 (0.00%)	1 / 178 (0.56%)	0 / 81 (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
Dizziness			
subjects affected / exposed	0 / 38 (0.00%)	1 / 178 (0.56%)	0 / 81 (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
Migraine			
subjects affected / exposed	0 / 38 (0.00%)	0 / 178 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple sclerosis			
subjects affected / exposed	0 / 38 (0.00%)	1 / 178 (0.56%)	0 / 81 (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
Seizure			

subjects affected / exposed	0 / 38 (0.00%)	0 / 178 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	0 / 38 (0.00%)	1 / 178 (0.56%)	0 / 81 (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
Ear and labyrinth disorders			
Hypoacusis			
subjects affected / exposed	0 / 38 (0.00%)	1 / 178 (0.56%)	0 / 81 (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
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 38 (0.00%)	0 / 178 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain upper			
subjects affected / exposed	0 / 38 (0.00%)	0 / 178 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal fissure			
subjects affected / exposed	0 / 38 (0.00%)	1 / 178 (0.56%)	0 / 81 (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
Colitis			
subjects affected / exposed	0 / 38 (0.00%)	0 / 178 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	0 / 38 (0.00%)	0 / 178 (0.00%)	2 / 81 (2.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Diarrhoea			
subjects affected / exposed	0 / 38 (0.00%)	0 / 178 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			
subjects affected / exposed	0 / 38 (0.00%)	0 / 178 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhoids			
subjects affected / exposed	0 / 38 (0.00%)	1 / 178 (0.56%)	0 / 81 (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
Intestinal obstruction			
subjects affected / exposed	0 / 38 (0.00%)	0 / 178 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Irritable bowel syndrome			
subjects affected / exposed	0 / 38 (0.00%)	0 / 178 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestine polyp			
subjects affected / exposed	0 / 38 (0.00%)	0 / 178 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 38 (0.00%)	0 / 178 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal obstruction			
subjects affected / exposed	0 / 38 (0.00%)	0 / 178 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatic cyst			

subjects affected / exposed	0 / 38 (0.00%)	0 / 178 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis acute			
subjects affected / exposed	0 / 38 (0.00%)	1 / 178 (0.56%)	0 / 81 (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
Vomiting			
subjects affected / exposed	0 / 38 (0.00%)	0 / 178 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 38 (0.00%)	2 / 178 (1.12%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis acute			
subjects affected / exposed	0 / 38 (0.00%)	3 / 178 (1.69%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	3 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	1 / 38 (2.63%)	5 / 178 (2.81%)	3 / 81 (3.70%)
occurrences causally related to treatment / all	1 / 1	5 / 5	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hydrocholecystis			
subjects affected / exposed	0 / 38 (0.00%)	0 / 178 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Chronic pigmented purpura			
subjects affected / exposed	0 / 38 (0.00%)	0 / 178 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			

Acute kidney injury			
subjects affected / exposed	0 / 38 (0.00%)	0 / 178 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hydronephrosis			
subjects affected / exposed	0 / 38 (0.00%)	0 / 178 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrolithiasis			
subjects affected / exposed	0 / 38 (0.00%)	2 / 178 (1.12%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary incontinence			
subjects affected / exposed	0 / 38 (0.00%)	1 / 178 (0.56%)	0 / 81 (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			
Acromegaly			
subjects affected / exposed	0 / 38 (0.00%)	2 / 178 (1.12%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Adrenal insufficiency			
subjects affected / exposed	0 / 38 (0.00%)	0 / 178 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Toxic nodular goitre			
subjects affected / exposed	0 / 38 (0.00%)	0 / 178 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 38 (0.00%)	1 / 178 (0.56%)	0 / 81 (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

Back pain			
subjects affected / exposed	0 / 38 (0.00%)	0 / 178 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chondritis			
subjects affected / exposed	0 / 38 (0.00%)	0 / 178 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc protrusion			
subjects affected / exposed	0 / 38 (0.00%)	1 / 178 (0.56%)	0 / 81 (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
Musculoskeletal pain			
subjects affected / exposed	0 / 38 (0.00%)	1 / 178 (0.56%)	0 / 81 (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
Osteoarthritis			
subjects affected / exposed	0 / 38 (0.00%)	2 / 178 (1.12%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain in extremity			
subjects affected / exposed	0 / 38 (0.00%)	1 / 178 (0.56%)	0 / 81 (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
Pathological fracture			
subjects affected / exposed	0 / 38 (0.00%)	0 / 178 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tendonitis			
subjects affected / exposed	0 / 38 (0.00%)	1 / 178 (0.56%)	0 / 81 (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
Infections and infestations			

Appendicitis			
subjects affected / exposed	0 / 38 (0.00%)	0 / 178 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile infection			
subjects affected / exposed	0 / 38 (0.00%)	1 / 178 (0.56%)	0 / 81 (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
Gastroenteritis			
subjects affected / exposed	0 / 38 (0.00%)	0 / 178 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	0 / 38 (0.00%)	1 / 178 (0.56%)	0 / 81 (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
Pneumonia bacterial			
subjects affected / exposed	0 / 38 (0.00%)	1 / 178 (0.56%)	0 / 81 (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
Pyelonephritis			
subjects affected / exposed	0 / 38 (0.00%)	0 / 178 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal abscess			
subjects affected / exposed	0 / 38 (0.00%)	0 / 178 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal abscess			
subjects affected / exposed	0 / 38 (0.00%)	0 / 178 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			

subjects affected / exposed	0 / 38 (0.00%)	0 / 178 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tonsillitis			
subjects affected / exposed	0 / 38 (0.00%)	0 / 178 (0.00%)	1 / 81 (1.23%)
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 / 38 (0.00%)	1 / 178 (0.56%)	0 / 81 (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			
Decreased appetite			
subjects affected / exposed	0 / 38 (0.00%)	0 / 178 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetes mellitus			
subjects affected / exposed	0 / 38 (0.00%)	3 / 178 (1.69%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	3 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic ketoacidosis			
subjects affected / exposed	0 / 38 (0.00%)	0 / 178 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			
subjects affected / exposed	0 / 38 (0.00%)	1 / 178 (0.56%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperlipidaemia			
subjects affected / exposed	0 / 38 (0.00%)	0 / 178 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemia			

subjects affected / exposed	0 / 38 (0.00%)	0 / 178 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	1 / 38 (2.63%)	0 / 178 (0.00%)	0 / 81 (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
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 38 (0.00%)	0 / 178 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 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 - up to 26 Months	Octreotide LAR - up to 26 Months	Crossed over to Pasireotide LAR - up to 26 Months
Total subjects affected by non-serious adverse events			
subjects affected / exposed	169 / 178 (94.94%)	161 / 180 (89.44%)	74 / 81 (91.36%)
Vascular disorders			
Hypertension			
subjects affected / exposed	18 / 178 (10.11%)	16 / 180 (8.89%)	5 / 81 (6.17%)
occurrences (all)	24	17	5
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	20 / 178 (11.24%)	21 / 180 (11.67%)	6 / 81 (7.41%)
occurrences (all)	26	27	8
Injection site pain			
subjects affected / exposed	13 / 178 (7.30%)	9 / 180 (5.00%)	0 / 81 (0.00%)
occurrences (all)	17	13	0
Pyrexia			
subjects affected / exposed	8 / 178 (4.49%)	10 / 180 (5.56%)	1 / 81 (1.23%)
occurrences (all)	8	12	1
Respiratory, thoracic and mediastinal disorders			
Cough			

subjects affected / exposed	11 / 178 (6.18%)	17 / 180 (9.44%)	1 / 81 (1.23%)
occurrences (all)	13	19	1
Oropharyngeal pain			
subjects affected / exposed	8 / 178 (4.49%)	15 / 180 (8.33%)	3 / 81 (3.70%)
occurrences (all)	8	15	4
Psychiatric disorders			
Anxiety			
subjects affected / exposed	9 / 178 (5.06%)	7 / 180 (3.89%)	1 / 81 (1.23%)
occurrences (all)	10	8	1
Insomnia			
subjects affected / exposed	8 / 178 (4.49%)	9 / 180 (5.00%)	2 / 81 (2.47%)
occurrences (all)	11	10	3
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	15 / 178 (8.43%)	10 / 180 (5.56%)	3 / 81 (3.70%)
occurrences (all)	23	19	4
Aspartate aminotransferase increased			
subjects affected / exposed	12 / 178 (6.74%)	8 / 180 (4.44%)	3 / 81 (3.70%)
occurrences (all)	22	11	3
Blood bilirubin increased			
subjects affected / exposed	9 / 178 (5.06%)	5 / 180 (2.78%)	1 / 81 (1.23%)
occurrences (all)	15	8	1
Blood creatine phosphokinase increased			
subjects affected / exposed	25 / 178 (14.04%)	24 / 180 (13.33%)	7 / 81 (8.64%)
occurrences (all)	43	33	9
Blood glucose increased			
subjects affected / exposed	17 / 178 (9.55%)	6 / 180 (3.33%)	8 / 81 (9.88%)
occurrences (all)	26	11	11
Blood thyroid stimulating hormone decreased			
subjects affected / exposed	4 / 178 (2.25%)	2 / 180 (1.11%)	1 / 81 (1.23%)
occurrences (all)	4	2	1
Blood triglycerides increased			
subjects affected / exposed	4 / 178 (2.25%)	4 / 180 (2.22%)	2 / 81 (2.47%)
occurrences (all)	4	4	2
Blood uric acid increased			

subjects affected / exposed	6 / 178 (3.37%)	3 / 180 (1.67%)	1 / 81 (1.23%)
occurrences (all)	8	4	1
Electrocardiogram QT prolonged			
subjects affected / exposed	9 / 178 (5.06%)	10 / 180 (5.56%)	3 / 81 (3.70%)
occurrences (all)	13	13	3
Gamma-glutamyltransferase increased			
subjects affected / exposed	3 / 178 (1.69%)	11 / 180 (6.11%)	1 / 81 (1.23%)
occurrences (all)	4	19	1
Glycosylated haemoglobin increased			
subjects affected / exposed	11 / 178 (6.18%)	5 / 180 (2.78%)	7 / 81 (8.64%)
occurrences (all)	11	5	8
Insulin-like growth factor decreased			
subjects affected / exposed	1 / 178 (0.56%)	0 / 180 (0.00%)	1 / 81 (1.23%)
occurrences (all)	1	0	1
Lipase increased			
subjects affected / exposed	10 / 178 (5.62%)	13 / 180 (7.22%)	3 / 81 (3.70%)
occurrences (all)	14	21	3
Weight decreased			
subjects affected / exposed	9 / 178 (5.06%)	8 / 180 (4.44%)	2 / 81 (2.47%)
occurrences (all)	9	8	2
Cardiac disorders			
Sinus bradycardia			
subjects affected / exposed	13 / 178 (7.30%)	10 / 180 (5.56%)	2 / 81 (2.47%)
occurrences (all)	16	12	2
Nervous system disorders			
Dizziness			
subjects affected / exposed	21 / 178 (11.80%)	20 / 180 (11.11%)	7 / 81 (8.64%)
occurrences (all)	26	29	10
Headache			
subjects affected / exposed	41 / 178 (23.03%)	49 / 180 (27.22%)	17 / 81 (20.99%)
occurrences (all)	58	77	22
Paraesthesia			
subjects affected / exposed	8 / 178 (4.49%)	4 / 180 (2.22%)	0 / 81 (0.00%)
occurrences (all)	11	4	0
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	14 / 178 (7.87%)	10 / 180 (5.56%)	6 / 81 (7.41%)
occurrences (all)	17	14	6
Eye disorders			
Cataract			
subjects affected / exposed	0 / 178 (0.00%)	1 / 180 (0.56%)	1 / 81 (1.23%)
occurrences (all)	0	1	1
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	8 / 178 (4.49%)	1 / 180 (0.56%)	0 / 81 (0.00%)
occurrences (all)	9	1	0
Abdominal distension			
subjects affected / exposed	21 / 178 (11.80%)	22 / 180 (12.22%)	0 / 81 (0.00%)
occurrences (all)	27	33	0
Abdominal pain			
subjects affected / exposed	33 / 178 (18.54%)	43 / 180 (23.89%)	3 / 81 (3.70%)
occurrences (all)	52	67	4
Abdominal pain upper			
subjects affected / exposed	12 / 178 (6.74%)	17 / 180 (9.44%)	3 / 81 (3.70%)
occurrences (all)	14	18	3
Constipation			
subjects affected / exposed	10 / 178 (5.62%)	19 / 180 (10.56%)	4 / 81 (4.94%)
occurrences (all)	15	20	4
Diarrhoea			
subjects affected / exposed	70 / 178 (39.33%)	79 / 180 (43.89%)	20 / 81 (24.69%)
occurrences (all)	192	207	54
Dyspepsia			
subjects affected / exposed	8 / 178 (4.49%)	7 / 180 (3.89%)	3 / 81 (3.70%)
occurrences (all)	8	12	3
Flatulence			
subjects affected / exposed	10 / 178 (5.62%)	11 / 180 (6.11%)	0 / 81 (0.00%)
occurrences (all)	10	12	0
Gastrooesophageal reflux disease			
subjects affected / exposed	2 / 178 (1.12%)	2 / 180 (1.11%)	2 / 81 (2.47%)
occurrences (all)	2	2	2
Large intestine polyp			

subjects affected / exposed	1 / 178 (0.56%)	0 / 180 (0.00%)	2 / 81 (2.47%)
occurrences (all)	1	0	2
Nausea			
subjects affected / exposed	27 / 178 (15.17%)	41 / 180 (22.78%)	8 / 81 (9.88%)
occurrences (all)	34	57	10
Vomiting			
subjects affected / exposed	19 / 178 (10.67%)	15 / 180 (8.33%)	3 / 81 (3.70%)
occurrences (all)	26	17	5
Hepatobiliary disorders			
Biliary dilatation			
subjects affected / exposed	5 / 178 (2.81%)	8 / 180 (4.44%)	4 / 81 (4.94%)
occurrences (all)	5	8	5
Cholelithiasis			
subjects affected / exposed	56 / 178 (31.46%)	69 / 180 (38.33%)	18 / 81 (22.22%)
occurrences (all)	91	99	21
Gallbladder polyp			
subjects affected / exposed	5 / 178 (2.81%)	3 / 180 (1.67%)	4 / 81 (4.94%)
occurrences (all)	5	3	4
Hepatic steatosis			
subjects affected / exposed	10 / 178 (5.62%)	11 / 180 (6.11%)	6 / 81 (7.41%)
occurrences (all)	11	13	6
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	34 / 178 (19.10%)	36 / 180 (20.00%)	3 / 81 (3.70%)
occurrences (all)	35	37	3
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	6 / 178 (3.37%)	2 / 180 (1.11%)	1 / 81 (1.23%)
occurrences (all)	11	3	1
Pyelocaliectasis			
subjects affected / exposed	0 / 178 (0.00%)	0 / 180 (0.00%)	0 / 81 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	21 / 178 (11.80%)	25 / 180 (13.89%)	10 / 81 (12.35%)
occurrences (all)	23	33	13

Back pain			
subjects affected / exposed	22 / 178 (12.36%)	21 / 180 (11.67%)	6 / 81 (7.41%)
occurrences (all)	33	29	6
Muscle spasms			
subjects affected / exposed	8 / 178 (4.49%)	10 / 180 (5.56%)	7 / 81 (8.64%)
occurrences (all)	9	12	7
Musculoskeletal pain			
subjects affected / exposed	7 / 178 (3.93%)	3 / 180 (1.67%)	1 / 81 (1.23%)
occurrences (all)	10	3	1
Osteoarthritis			
subjects affected / exposed	4 / 178 (2.25%)	4 / 180 (2.22%)	1 / 81 (1.23%)
occurrences (all)	4	4	1
Pain in extremity			
subjects affected / exposed	14 / 178 (7.87%)	8 / 180 (4.44%)	6 / 81 (7.41%)
occurrences (all)	15	10	7
Infections and infestations			
Bronchitis			
subjects affected / exposed	10 / 178 (5.62%)	4 / 180 (2.22%)	0 / 81 (0.00%)
occurrences (all)	11	4	0
Influenza			
subjects affected / exposed	16 / 178 (8.99%)	11 / 180 (6.11%)	3 / 81 (3.70%)
occurrences (all)	19	11	4
Nasopharyngitis			
subjects affected / exposed	32 / 178 (17.98%)	29 / 180 (16.11%)	13 / 81 (16.05%)
occurrences (all)	76	54	28
Sinusitis			
subjects affected / exposed	6 / 178 (3.37%)	6 / 180 (3.33%)	2 / 81 (2.47%)
occurrences (all)	6	6	4
Upper respiratory tract infection			
subjects affected / exposed	16 / 178 (8.99%)	7 / 180 (3.89%)	3 / 81 (3.70%)
occurrences (all)	22	8	3
Urinary tract infection			
subjects affected / exposed	9 / 178 (5.06%)	12 / 180 (6.67%)	5 / 81 (6.17%)
occurrences (all)	15	22	9
Metabolism and nutrition disorders			

Diabetes mellitus			
subjects affected / exposed	38 / 178 (21.35%)	8 / 180 (4.44%)	18 / 81 (22.22%)
occurrences (all)	39	8	18
Glucose tolerance impaired			
subjects affected / exposed	3 / 178 (1.69%)	1 / 180 (0.56%)	5 / 81 (6.17%)
occurrences (all)	3	2	5
Hypercholesterolaemia			
subjects affected / exposed	7 / 178 (3.93%)	4 / 180 (2.22%)	2 / 81 (2.47%)
occurrences (all)	8	4	2
Hyperglycaemia			
subjects affected / exposed	55 / 178 (30.90%)	18 / 180 (10.00%)	25 / 81 (30.86%)
occurrences (all)	71	27	31
Hyperlipidaemia			
subjects affected / exposed	5 / 178 (2.81%)	4 / 180 (2.22%)	5 / 81 (6.17%)
occurrences (all)	7	4	5
Hyperuricaemia			
subjects affected / exposed	5 / 178 (2.81%)	2 / 180 (1.11%)	1 / 81 (1.23%)
occurrences (all)	7	2	2
Hypoglycaemia			
subjects affected / exposed	11 / 178 (6.18%)	14 / 180 (7.78%)	7 / 81 (8.64%)
occurrences (all)	13	29	23
Type 2 diabetes mellitus			
subjects affected / exposed	12 / 178 (6.74%)	0 / 180 (0.00%)	3 / 81 (3.70%)
occurrences (all)	12	0	3

Non-serious adverse events	Crossed over to Octreotide LAR - up to 26 Months	Pasireotide LAR - up to EOS	Crossed over to Pasireotide LAR - up to EOS
Total subjects affected by non-serious adverse events			
subjects affected / exposed	33 / 38 (86.84%)	170 / 178 (95.51%)	76 / 81 (93.83%)
Vascular disorders			
Hypertension			
subjects affected / exposed	3 / 38 (7.89%)	21 / 178 (11.80%)	6 / 81 (7.41%)
occurrences (all)	3	27	6
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	3 / 38 (7.89%)	21 / 178 (11.80%)	7 / 81 (8.64%)
occurrences (all)	3	29	9

Injection site pain			
subjects affected / exposed	1 / 38 (2.63%)	14 / 178 (7.87%)	0 / 81 (0.00%)
occurrences (all)	1	18	0
Pyrexia			
subjects affected / exposed	0 / 38 (0.00%)	11 / 178 (6.18%)	2 / 81 (2.47%)
occurrences (all)	0	12	2
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 38 (2.63%)	16 / 178 (8.99%)	3 / 81 (3.70%)
occurrences (all)	1	18	3
Oropharyngeal pain			
subjects affected / exposed	1 / 38 (2.63%)	9 / 178 (5.06%)	4 / 81 (4.94%)
occurrences (all)	2	9	5
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 38 (0.00%)	11 / 178 (6.18%)	2 / 81 (2.47%)
occurrences (all)	0	12	2
Insomnia			
subjects affected / exposed	1 / 38 (2.63%)	12 / 178 (6.74%)	4 / 81 (4.94%)
occurrences (all)	1	16	5
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 38 (0.00%)	16 / 178 (8.99%)	5 / 81 (6.17%)
occurrences (all)	0	31	7
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 38 (0.00%)	13 / 178 (7.30%)	5 / 81 (6.17%)
occurrences (all)	0	28	5
Blood bilirubin increased			
subjects affected / exposed	1 / 38 (2.63%)	11 / 178 (6.18%)	3 / 81 (3.70%)
occurrences (all)	1	17	5
Blood creatine phosphokinase increased			
subjects affected / exposed	6 / 38 (15.79%)	27 / 178 (15.17%)	8 / 81 (9.88%)
occurrences (all)	6	51	11
Blood glucose increased			

subjects affected / exposed	0 / 38 (0.00%)	18 / 178 (10.11%)	8 / 81 (9.88%)
occurrences (all)	0	27	14
Blood thyroid stimulating hormone decreased			
subjects affected / exposed	2 / 38 (5.26%)	5 / 178 (2.81%)	1 / 81 (1.23%)
occurrences (all)	2	6	1
Blood triglycerides increased			
subjects affected / exposed	4 / 38 (10.53%)	8 / 178 (4.49%)	2 / 81 (2.47%)
occurrences (all)	5	8	2
Blood uric acid increased			
subjects affected / exposed	0 / 38 (0.00%)	10 / 178 (5.62%)	2 / 81 (2.47%)
occurrences (all)	0	15	2
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 38 (0.00%)	10 / 178 (5.62%)	4 / 81 (4.94%)
occurrences (all)	0	15	4
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 38 (0.00%)	3 / 178 (1.69%)	2 / 81 (2.47%)
occurrences (all)	0	4	3
Glycosylated haemoglobin increased			
subjects affected / exposed	0 / 38 (0.00%)	12 / 178 (6.74%)	9 / 81 (11.11%)
occurrences (all)	0	12	10
Insulin-like growth factor decreased			
subjects affected / exposed	0 / 38 (0.00%)	2 / 178 (1.12%)	5 / 81 (6.17%)
occurrences (all)	0	2	7
Lipase increased			
subjects affected / exposed	2 / 38 (5.26%)	11 / 178 (6.18%)	3 / 81 (3.70%)
occurrences (all)	4	16	3
Weight decreased			
subjects affected / exposed	0 / 38 (0.00%)	9 / 178 (5.06%)	5 / 81 (6.17%)
occurrences (all)	0	9	5
Cardiac disorders			
Sinus bradycardia			
subjects affected / exposed	1 / 38 (2.63%)	15 / 178 (8.43%)	3 / 81 (3.70%)
occurrences (all)	1	19	4
Nervous system disorders			

Dizziness			
subjects affected / exposed	4 / 38 (10.53%)	22 / 178 (12.36%)	9 / 81 (11.11%)
occurrences (all)	5	28	12
Headache			
subjects affected / exposed	5 / 38 (13.16%)	42 / 178 (23.60%)	20 / 81 (24.69%)
occurrences (all)	5	63	28
Paraesthesia			
subjects affected / exposed	1 / 38 (2.63%)	9 / 178 (5.06%)	0 / 81 (0.00%)
occurrences (all)	1	14	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 38 (2.63%)	19 / 178 (10.67%)	8 / 81 (9.88%)
occurrences (all)	1	24	12
Eye disorders			
Cataract			
subjects affected / exposed	2 / 38 (5.26%)	0 / 178 (0.00%)	1 / 81 (1.23%)
occurrences (all)	2	0	1
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 38 (0.00%)	10 / 178 (5.62%)	0 / 81 (0.00%)
occurrences (all)	0	11	0
Abdominal distension			
subjects affected / exposed	2 / 38 (5.26%)	21 / 178 (11.80%)	0 / 81 (0.00%)
occurrences (all)	5	27	0
Abdominal pain			
subjects affected / exposed	1 / 38 (2.63%)	36 / 178 (20.22%)	4 / 81 (4.94%)
occurrences (all)	1	58	6
Abdominal pain upper			
subjects affected / exposed	0 / 38 (0.00%)	14 / 178 (7.87%)	4 / 81 (4.94%)
occurrences (all)	0	16	4
Constipation			
subjects affected / exposed	1 / 38 (2.63%)	13 / 178 (7.30%)	5 / 81 (6.17%)
occurrences (all)	2	20	5
Diarrhoea			
subjects affected / exposed	6 / 38 (15.79%)	72 / 178 (40.45%)	26 / 81 (32.10%)
occurrences (all)	9	207	68
Dyspepsia			

subjects affected / exposed	1 / 38 (2.63%)	9 / 178 (5.06%)	4 / 81 (4.94%)
occurrences (all)	1	9	4
Flatulence			
subjects affected / exposed	0 / 38 (0.00%)	11 / 178 (6.18%)	0 / 81 (0.00%)
occurrences (all)	0	11	0
Gastrooesophageal reflux disease			
subjects affected / exposed	2 / 38 (5.26%)	2 / 178 (1.12%)	2 / 81 (2.47%)
occurrences (all)	2	2	2
Large intestine polyp			
subjects affected / exposed	2 / 38 (5.26%)	1 / 178 (0.56%)	2 / 81 (2.47%)
occurrences (all)	2	1	2
Nausea			
subjects affected / exposed	2 / 38 (5.26%)	29 / 178 (16.29%)	10 / 81 (12.35%)
occurrences (all)	4	37	13
Vomiting			
subjects affected / exposed	1 / 38 (2.63%)	22 / 178 (12.36%)	4 / 81 (4.94%)
occurrences (all)	1	30	6
Hepatobiliary disorders			
Biliary dilatation			
subjects affected / exposed	1 / 38 (2.63%)	5 / 178 (2.81%)	5 / 81 (6.17%)
occurrences (all)	1	6	6
Cholelithiasis			
subjects affected / exposed	6 / 38 (15.79%)	59 / 178 (33.15%)	23 / 81 (28.40%)
occurrences (all)	9	102	31
Gallbladder polyp			
subjects affected / exposed	2 / 38 (5.26%)	8 / 178 (4.49%)	5 / 81 (6.17%)
occurrences (all)	2	8	5
Hepatic steatosis			
subjects affected / exposed	3 / 38 (7.89%)	11 / 178 (6.18%)	6 / 81 (7.41%)
occurrences (all)	3	13	6
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	1 / 38 (2.63%)	34 / 178 (19.10%)	4 / 81 (4.94%)
occurrences (all)	1	38	4
Renal and urinary disorders			

Haematuria			
subjects affected / exposed	2 / 38 (5.26%)	8 / 178 (4.49%)	2 / 81 (2.47%)
occurrences (all)	2	13	2
Pyelocaliectasis			
subjects affected / exposed	2 / 38 (5.26%)	0 / 178 (0.00%)	0 / 81 (0.00%)
occurrences (all)	2	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 38 (5.26%)	24 / 178 (13.48%)	14 / 81 (17.28%)
occurrences (all)	2	30	20
Back pain			
subjects affected / exposed	3 / 38 (7.89%)	24 / 178 (13.48%)	8 / 81 (9.88%)
occurrences (all)	4	35	8
Muscle spasms			
subjects affected / exposed	1 / 38 (2.63%)	10 / 178 (5.62%)	8 / 81 (9.88%)
occurrences (all)	1	12	8
Musculoskeletal pain			
subjects affected / exposed	1 / 38 (2.63%)	9 / 178 (5.06%)	2 / 81 (2.47%)
occurrences (all)	1	12	2
Osteoarthritis			
subjects affected / exposed	2 / 38 (5.26%)	4 / 178 (2.25%)	2 / 81 (2.47%)
occurrences (all)	2	5	2
Pain in extremity			
subjects affected / exposed	1 / 38 (2.63%)	16 / 178 (8.99%)	6 / 81 (7.41%)
occurrences (all)	1	18	7
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 38 (0.00%)	13 / 178 (7.30%)	2 / 81 (2.47%)
occurrences (all)	0	15	3
Influenza			
subjects affected / exposed	3 / 38 (7.89%)	18 / 178 (10.11%)	4 / 81 (4.94%)
occurrences (all)	4	23	5
Nasopharyngitis			
subjects affected / exposed	7 / 38 (18.42%)	34 / 178 (19.10%)	15 / 81 (18.52%)
occurrences (all)	9	120	56
Sinusitis			

subjects affected / exposed	1 / 38 (2.63%)	9 / 178 (5.06%)	3 / 81 (3.70%)
occurrences (all)	1	12	11
Upper respiratory tract infection			
subjects affected / exposed	2 / 38 (5.26%)	20 / 178 (11.24%)	5 / 81 (6.17%)
occurrences (all)	2	30	10
Urinary tract infection			
subjects affected / exposed	0 / 38 (0.00%)	11 / 178 (6.18%)	10 / 81 (12.35%)
occurrences (all)	0	18	22
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	3 / 38 (7.89%)	40 / 178 (22.47%)	19 / 81 (23.46%)
occurrences (all)	3	43	19
Glucose tolerance impaired			
subjects affected / exposed	0 / 38 (0.00%)	3 / 178 (1.69%)	5 / 81 (6.17%)
occurrences (all)	0	3	5
Hypercholesterolaemia			
subjects affected / exposed	1 / 38 (2.63%)	10 / 178 (5.62%)	2 / 81 (2.47%)
occurrences (all)	1	11	2
Hyperglycaemia			
subjects affected / exposed	5 / 38 (13.16%)	56 / 178 (31.46%)	29 / 81 (35.80%)
occurrences (all)	5	81	52
Hyperlipidaemia			
subjects affected / exposed	2 / 38 (5.26%)	5 / 178 (2.81%)	5 / 81 (6.17%)
occurrences (all)	2	7	6
Hyperuricaemia			
subjects affected / exposed	0 / 38 (0.00%)	9 / 178 (5.06%)	2 / 81 (2.47%)
occurrences (all)	0	15	3
Hypoglycaemia			
subjects affected / exposed	2 / 38 (5.26%)	14 / 178 (7.87%)	8 / 81 (9.88%)
occurrences (all)	4	21	77
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 38 (0.00%)	12 / 178 (6.74%)	4 / 81 (4.94%)
occurrences (all)	0	12	4

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 February 2008	The main reason for this protocol amendment was to change the duration of the study. Although six months is an adequate time point to establish steady state pharmacokinetics, it was not adequate to establish long-term efficacy in both treatment groups (Pasireotide LAR and Octreotide LAR). Therefore, the study was extended to twelve months to provide sufficient time to assess the clinical response of patients to the study drugs. Additional secondary efficacy objectives were added in order to further assess the efficacy of pasireotide LAR.
21 May 2008	Decreased levels of Vitamin B12 were been observed as a rare adverse event in patients treated with Octreotide . Therefore, blood levels of Vitamin B12 was be tested at baseline (visit 2) and every 3 months during the core and the extension phases of the study. The use of Gadolinium as a type of contrast material during the MRI procedure performed during the core and the extension phases of the study was explicitly mentioned in the protocol.
25 September 2008	As requested by the Chinese Health Authorities, patients enrolled into the study in China had to have a normal serum creatinine level for inclusion.
23 April 2009	Extended blinding to patient's treatment from month 12 to month 26. In order to have a benchmark for the evaluation of the long-term safety and efficacy of pasireotide, patients randomized to octreotide, who responded to treatment at month 12 were offered to enter a 14 months extension period with the same medication. Patients not responding to either pasireotide or octreotide at month 12 were offered to be switched to the other study medication in order to explore the safety and efficacy of switching from pasireotide to octreotide and from octreotide to pasireotide. Patients who crossed over to the other treatment arm at month 13 followed the same schedule of evaluations as patients continuing in the extension phase in the same arm. A new secondary objective was added, which was, duration of response for patients considered responders at month 12 in order to evaluate the duration of the efficacy of the study medications. In line with the published guidelines established by experts' associations for management of diabetes, changes were made in the criteria for monitoring hyperglycemia reflecting standard of care. Clarifications to the schedule of dose increase were made. Serum cortisol is a key safety measure and was added to the list of the tests to be performed at the Central Lab. Modifications to the inclusion and exclusion criteria were made to clarify the eligibility of patients who may have received a single dose of short-acting octreotide or short-acting dopamine agonists prior to study entry. In order to fully utilize the response data in patients who discontinued early, a Last Observation Carried Forward (LOCF) approach was introduced and was applied for the primary analysis.
03 May 2010	Recent results from the thorough QT/QTc (TQT) study provided data on the QT/QTc intervals of a supra-therapeutic dose of pasireotide in healthy volunteers. As a consequence of the ECG study results, study discontinuation criteria were modified and additional ECG and pharmacokinetic monitoring was implemented for the ongoing SOM230 clinical trials to further strengthen the safety of patients. This amendment also clarified wording across the protocol for the sake of the consistency as well as added clarification for the applicable procedures for patients who entered the extension prior and after Amendment 4 implementation. Additionally, further recommendations regarding serum cortisol samples collection were provided as well as clarification on first study drug dose administration window. Furthermore, a section including secondary objectives for the analysis of the blinded extension phase was added and clarification was made in the statistical analysis section in order to further explain analysis of the data collected in the extension phase of the study.

26 July 2011	The purpose of this amendment was to clarify the statistical analysis of the secondary objectives in the extension phase and the statistical analysis of the pharmacokinetics and pharmacodynamics assessments. The amendment did not change any study objectives. The extension phase was divided into two data subsets: data before cross-over and data after crossover. After the first analysis performed with 12 months data, an additional data cut-off for analysis for the purpose of submission was added to include the extension data collected up to the Month 19 (Visit 8E) assessment in addition to the data cut-off at month 27. A second Per Protocol (PP) analysis set was defined for that purpose. As a consequence of the additional data cut-off, Global Novartis team Clinical Trial Team (CTT) were unblinded after database lock, which occurred approximately 4 months prior to last patient last visit (LPLV) of the first year of the extension phase. The cut-off date for this database lock was performed when the last patient completed the Month 19 (Visit 8E) assessment (09-June-2011). There was no impact on study conduct since all measures were in place to ensure that investigators and Local Novartis teams (CPOs) remain blinded as planned until the last patient completed the Month 26 (Visit 15E) assessment. The unblinding process at the clinical sites in preparation of Visit 15E (Month 26) was clarified. In addition, the schedule of assessments during the extension phase after Month 26 regarding GH suppression post OGTT profiles was modified. After this timepoint, this assessment was performed every 6 months instead of every 3 months as this high frequency was not necessary anymore for follow up assessments.
12 December 2011	The protocol was amended to include additional hepatic-related safety measures as a result of an internal hepatic medical review of pasireotide trials. During this internal medical review of liver related laboratory values, 3 healthy volunteers were identified with elevations in liver function tests. An assessment of liver enzyme categorical outliers was completed across the pasireotide s.c. development program (up to October 2011). The pasireotide Compassionate Use Program was also reviewed. A review of the unblinded data from the clinical program with the pasireotide long acting release (LAR) formulation did not reveal cases meeting the Hy's law criteria. As a consequence of these observations, enhanced hepatic-related safety measures were taken to ensure patient safety.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

Due to EudraCT system limitations, which EMA is aware of, results of crossover studies and data using 999 as data points are not accurately represented in this record. Please go to https://www.novctrd.com/CtrdWeb/home.nov for complete trial results

Notes: