Sponsor

Novartis

Generic Drug Name

Pasireotide

Trial Indication(s)

Acromegaly and carcinoid disease

Protocol Number

CSOM230C2110

Protocol Title

A Phase I, multicenter, open-label, randomized study assessing the pharmacokinetics, safety, and tolerability of monthly doses of SOM230 i.m LAR injection in patients with acromegaly and patients with carcinoid disease.

Clinical Trial Phase

Phase I

Phase of Drug Development

Phase III

Study Start/End Dates

21-Jun-2006 to 07-Nov-2013.

Reason for Termination (If applicable)

Not applicable.

Study Design/Methodology

Study CSOM230C2110 was a Phase I, multicenter, open-label, randomized study. Patients with acromegaly and patients with carcinoid disease were independently enrolled into the core phase of the study and randomized 1:1:1 to receive pasireotide LAR 20 mg, 40 mg, or 60 mg injected every 28 days for three months (i.e. 3 injections). Enrollment and assessment of pharmacokinetic (PK) and safety were done independently for each of the two patient populations. Pharmacodynamic (PD) assessments were exploratory in nature.

Patients who have not previously received SOM230 s.c. received a single 300 µg dose to ensure they could tolerate SOM230, as determined by the physician, before administering the SOM230 LAR dose. The s.c. dose was followed by a washout period of at least 5 days.

Patients who completed the three month core phase of the study had the option to continue in extension 1 (E1) for an additional three months. At the discretion of the treating physician, patients who completed E1 were able to enter the open-ended extension 2 (E2) which was ongoing for 93 months.
At any time during the extension stages (after the initial three months of pasireotide LAR treatment), the pasireotide LAR dose could be adjusted (increased or decreased) by 20 mg up to a maximum and minimum dose of 60 mg and 20 mg per injection, respectively at the discretion of Investigator or designee.

Centers

Belgium (3), Canada (3), Germany (5), Norway (1), Netherlands (1), United States of America (4)

Publication

None

Objectives:

Primary objectives (core phase only)

- Determine the pharmacokinetic profile of single and monthly doses of pasireotide LAR i.m. (20, 40 and 60 mg) injection in patients with acromegaly and in patients with carcinoid disease.
- Investigate the safety/tolerability profile of single and monthly doses of pasireotide LAR i.m. (20, 40 and 60 mg) injection in patients with acromegaly and in patients with carcinoid disease.

Secondary objective (core phase only)

- To explore the pharmacodynamic profile of single and monthly doses of pasireotide LAR i.m. (20, 40 and 60 mg) injection in patients with acromegaly and in patients with carcinoid disease.

The purpose of the extension phase was to obtain long-term safety and tolerability data as well as to allow patients continued access to pasireotide LAR therapy after the completion of the core phase of the study.

Test Product (s), Dose(s), and Mode(s) of Administration

The study medication was prepared by Novartis and supplied to the investigational sites as open-label bulk medication. Pasireotide s.c. was provided as 0.3 mg/l mL ampoules, pasireotide LAR i.m. was provided as a powder in vials.

Statistical Methods

The PK profile parameters were summarized for each pasireotide LAR dose group separately. The pasireotide concentration was also summarized by dose group and time-point by means of descriptive statistics.

The adverse events (AEs) were coded using the MedDRA (version 16.0) dictionary and were summarized by clinical indication, and incident dose level by presenting the number and percentage of patients having any AE, having an AE in each primary system organ class (SOC) and having each preferred term. The AEs were reported cumulatively up to the end of the study. Laboratory and other safety parameters were summarized using shift tables and summary statistics.

No formal analysis of efficacy was performed. Clinical response was measured by quantitative assessment of PD markers in patients with acromegaly and assessment of disease symptoms in patients with carcinoid disease.

For patients with acromegaly, the PD variables included growth hormone (GH), prolactin (PRL), insulin-like growth factor (IGF-1), and acromegaly symptoms (headache, perspiration, paresthesia, fatigue and osteoarthralgia scored on a 5-point scale).

The actual levels, actual level change and percentage change at each visit from the core baseline for GH, PRL, total IGF-1 and free IGF-1 were summarized by means of descriptive statistics by incident dose level. Symptoms of acromegaly were summarized using shift tables.

For patients with carcinoid disease, the PD variable was average daily number of bowel movements, and change from core baseline were summarized by means of descriptive statistics for each LAR treatment period (Month 1 to Month 6) by incident dose level. Daily bowel movement data was not collected in E2.

Study Population: Key Inclusion/Exclusion Criteria

Key inclusion criteria: Core phase

Patients with acromegaly:

- Aged between 18 and 80 years
- Active acromegaly due to a pituitary adenoma

Patients with carcinoid disease:

- Aged ≥ 18 years
- Biopsy-proven metastatic carcinoid tumors of the digestive system with disease determined by computerized tomography scan or magnetic resonance imaging
- Histopathologically confirmed primary and/or metastatic lesion and elevation of chromogranin-A (CgA) and/or serotonin
- Karnofsky Performance Status ≥ 60 and disease not adequately controlled by somatostatin analogues

In addition, for both indications enrollment was allowed for:

- Diabetic patients provided their blood glucose and anti-diabetic treatment were closely monitored throughout the trial
- Patients previously treated with pasireotide s.c. who complied with the enrollment criteria and
- Patients on medical treatment who completed the washouts specified in the protocol.

Key exclusion criteria: Core phase

Patients with acromegaly were excluded if they had:

- Compression of the optic chiasm causing any visual field defect
- Liver disease such as cirrhosis, chronic active hepatitis or chronic persistent hepatitis
- Alanine aminotransferase (ALT) / aspartate aminotransferase (AST) more than 2 X upper limit of normal (ULN), serum creatinine >2.0 X ULN, serum bilirubin >2.0 X ULN, serum albumin <0.67 X lower limit of normal (LLN)

Patients with carcinoid disease were excluded if they had:

- Hepatic artery embolization within the last 6 months (1 month if there are other sites of measurable disease), or patients who have undergone cryoablation of hepatic metastasis within the last 2 months
- Malabsorption syndrome
- Short bowel or chologenic diarrhea not controlled by specific therapeutic means
- Patients with liver disease such as cirrhosis, chronic active hepatitis or chronic persistent hepatitis with serum creatinine > 2.0 X ULN, serum bilirubin > 2 X ULN, serum albumin < 0.67 X LLN, and/ or ALT/AST more than 2 X ULN for patients without liver metastases or ALT/AST more than 5X ULN for patients with documented liver metastases

In addition for both indications the patients were excluded if they had:

- Uncontrolled diabetes mellitus as indicated by the presence of ketoacidosis or HbA1C >10%, symptomatic cholelithiasis
- Abnormal coagulation (PT and PTT elevated by 30% above normal limits)
- Congestive heart failure (NYHA Class III or IV)
- Unstable angina
- Sustained ventricular tachycardia
- Ventricular fibrillation
- Bradycardia
- Advanced heart block or a history of acute myocardial infarction within the three months preceding enrollment
- Female patients who were pregnant or lactating, or are of childbearing potential and not practicing a medically acceptable method of birth control

Patients with acromegaly and patients with carcinoid disease who completed the core phase were eligible to enroll in the extension. No additional inclusion or exclusion criteria applied to the extension.

Participant Flow Table

Patient disposition by treatment (All patients)

Clinical Indication	Disposition Reason	Pasireotide s.c. only (N = 5) n (%)	Pasireotide LAR 20 mg (N = 10) n (%)	Pasireotide LAR 40 mg (N = 12) n (%)	Pasireotide LAR 60 mg (N = 13) n (%)
Acromegaly (N = 40)	Completed	0	10 (100.0)	12 (100.0)	13 (100.0)
	Discontinued	5 (100.0)	0	0	0
	Adverse event(s)	0	0	0	0
	Abnormal laboratory value(s)	5 (100.0)	0	0	0
	Abnormal test procedure result(s)	0	0	0	0
	Unsatisfactory therapeutic effect	0	0	0	0
	Subject's condition no longer requires study drug	0	0	0	0
	Protocol deviation	0	0	0	0
	Subject withdrew consent	0	0	0	0
	Lost to follow-up	0	0	0	0
	Administrative problems	0	0	0	0
	Death	0	0	0	0

Clinical Indication	Disposition Reason	Pasireotide s.c. only (N = 3) n (%)	Pasireotide LAR 20 mg (N = 12) n (%)	Pasireotide LAR 40 mg (N = 14) n (%)	Pasireotide LAR 60 mg (N = 16) n (%)
Carcinoid (N = 45)	Completed	0	11 (91.7)	11 (78.6)	14 (87.5)
	Discontinued	3 (100.0)	1 (8.3)	3 (21.4)	2 (12.5)
	Adverse event(s)	1 (33.3)	0	2 (14.3)	1 (6.3)
	Abnormal laboratory value(s)	0	0	0	0
	Abnormal test procedure result(s)	1 (33.3)	0	0	0
	Unsatisfactory therapeutic effect	0	0	0	0
	Subject' s condition no longer requires study drug	0	0	0	0
	Protocol deviation	1 (33.3)	0	0	0
	Subject withdrew consent	0	0	0	1 (6.3)
	Lost to follow-up	0	0	0	0
	Administrative problems	0	0	0	0
	Death	0	1 (8.3)	1 (7.1)	0

Extension phase

Summary of patient disposition by last dose received during extension phase – Acromegaly (Safety population)

	Pasireotide LAR 20mg	Pasireotide LAR 40mg	Pasireotide LAR 60mg	Pasireotide LAR any dose
	N=9	N=10	N=10	N=29
	n (%)	n (%)	n (%)	n (%)
Completed extension 1 but not entered extension 2	**0**	**1 (10.0)**	**0**	**1 (3.4)**
Discontinued during extension phase	**9 (100.0)**	**9 (90.0)**	**10 (100.0)**	**28 (96.6)**
Abnormal laboratory value(s)	1 (11.1)	0	4 (40.0)	5 (17.2)
Adverse Event(s)*	1 (11.1)	0	1 (10.0)	2 (6.9)
Disease progression	1 (11.1)	1 (10.0)	2 (20.0)	4 (13.8)
Subject withdrew consent	1 (11.1)	1 (10.0)	1 (10.0)	3 (10.3)
Treatment duration completed as per protocol	5 (55.6)	7 (70.0)	2 (20.0)	14 (48.3)

N=the number of patients whose last received dose during extension phase was in the corresponding dose level. This number was the denominator for the percentages presented.

*The number of patients who discontinued study treatment due to AEs does not match with number of patients who discontinued study drug due to AEs. The main reason of this difference (disposition vs AE) is that this information is collected on different case report form (CRF) panel, disposition information is collected on end of treatment CRF panel and AE information is collected on AE panel, even though on the CRF AE panel a patient may have permanently discontinued study drug due to AE, the primary reason for the end of treatment on the end of treatment CRF panel may not have been AE.

Summary of patient disposition by last dose received during extension phase – Carcinoid (Safety population)

	Pasireotide LAR 20 mg	Pasireotide LAR 40 mg	Pasireotide LAR 60 mg	Pasireotide LAR any dose
	N=3	N=9	N=19	N=31
	(N = %)	(N = %)	(N = %)	(N=%)
Completed extension 1 but not entered extension 2	**0**	**2 (22.2)**	**0**	**2 (6.5)**
Discontinued during extension phase	**3 (100.0)**	**7 (77.8)**	**19 (100.0)**	**29 (93.5)**
Adverse Event(s)*	0	2 (22.2)	1 (5.3)	3 (9.7)
Death	0	0	3 (15.8)	3 (9.7)
Disease progression	1 (33.3)	1 (11.1)	11 (57.9)	13 (41.9)
Subject withdrew consent	1 (33.3)	3 (33.3)	2 (10.5)	6(19.4)
Treatment duration completed as per protocol	1 (33.3)	1 (11.1)	2 (10.5)	4 (12.9)

N=the number of patients whose last received dose during extension phase was in the corresponding dose level. This number was the denominator for the percentages presented.

*The number of patients who discontinued study treatment due to AEs does not match with number of patients who discontinued study drug due to AEs. The main reason of this difference (disposition vs AE) is that this information is collected on different case report form (CRF) panel, disposition information is collected on end of treatment CRF panel and AE information is collected on AE panel, even though on the CRF AE panel a patient may have permanently discontinued study drug due to AE, the primary reason for the end of treatment on the end of treatment CRF panel may not have been AE.

Baseline Characteristics

Summary of demographics – acromegaly (Safety population): Core phase

	Pasireotide LAR 20 mg (N = 10)	Pasireotide LAR 40 mg (N = 12)	Pasireotide LAR 60 mg (N = 13)	Total (N = 35)
Age (years)				
Mean (SD)	45.8 (10.48)	45.0 (11.09)	46.5 (12.12)	45.8 (11.00)
Sex - n (%)				
Male	7 (70.0)	9 (75.0)	7 (53.8)	23 (65.7)
Female	3 (30.0)	3 (25.0)	6 (46.2)	12 (34.3)
Race - n (%)				
Caucasian	10 (100.0)	12 (100.0)	13 (100.0)	35 (100.0)
Black	0	0	0	0
Asian	0	0	0	0
Native American	0	0	0	0
Pacific Islander	0	0	0	0
Other	0	0	0	0
Height (cm)				
Mean (SD)	175.7 (9.91)	182.7 (15.17)	173.0 (7.28)	177.1 (11.71)
Weight (Kg)				
Mean (SD)	89.4 (16.57)	95.3 (20.33)	89.3 (21.13)	91.38 (19.29)
BMI (kg/m^2)				
Mean (SD)	28.9 (4.26)	28.4 (4.45)	29.6 (5.56)	28.99 (4.73)

N=the number of patients whose last received dose during extension phase was in the corresponding dose level. This number was the denominator for the percentages presented.

Summary of demographics – carcinoid (Safety population): Core phase

	Pasireotide LAR 20 mg (N = 12)	Pasireotide LAR 40 mg (N = 14)	Pasireotide LAR 60 mg (N = 16)	Total (N = 42)
Age (years)				
Mean (SD)	56.3 (12.61)	58.9 (12.68)	62.5 (9.64)	59.5 (11.58)
Sex – n (%)				
Male	9 (75.0)	6 (42.9)	7 (43.8)	22 (52.4)
Female	3 (25.0)	8 (57.1)	9 (56.3)	20 (47.6)
Race - n (%)				
Caucasian	10 (83.3)	13 (92.9)	16 (100.0)	39 (92.9)
Black	1 (8.3)	0	0	1 (2.4)
Asian	1 (8.3)	0	0	1 (2.4)
Native American	0	1 (7.1)	0	1 (2.4)
Pacific Islander	0	0	0	0
Other	0	0	0	0
Height (cm)				
Mean (SD)	176.4 (11.50)	169.5 (13.10)	168.9 (7.57)	171.2 (11.03)

	Pasireotide LAR 20 mg (N = 12)	Pasireotide LAR 40 mg (N = 14)	Pasireotide LAR 60 mg (N = 16)	Total (N = 42)
Weight (Kg)				
Mean (SD)	82.4 (15.87)	75.7 (18.66)	72.1 (12.31)	76.22 (15.85)
BMI (kg/m^2)				
Mean (SD)	26.6 (5.33)	26.5 (6.66)	25.3 (3.97)	26.05 (5.28)

Summary of Efficacy

Primary Outcome Result(s)

Refer to Safety result and other relevant finding section for primary outcome result.

Secondary Outcome Result(s)

Core phase

Summary of PD parameters – Acromegaly (PD population)

Parameter	Pasireotide LAR 20 mg N = 10				Pasireotide LAR 40 mg N = 12				Pasireotide LAR 60 mg N = 13			
Growth hormone (µg/L)[1*]	**≤ 1 n (%)**	**≤ 2.5 n (%)**	**≤ 5 n (%)**	**> 5 n (%)**	**≤ 1 n (%)**	**≤ 2.5 n (%)**	**≤ 5 n (%)**	**> 5 n (%)**	**≤ 1 n (%)**	**≤ 2.5 n (%)**	**≤ 5 n (%)**	**> 5 n (%)**
Screening	0	1 (10.0)	2 (20.0)	5 (50.0)	0	2 (16.7)	1 (8.3)	8 (66.7)	0	1 (7.7)	2 (15.4)	5 (38.5)
Day 1 Injection 1	0	1 (10.0)	4 (40.0)	4 (40.0)	0	2 (16.7)	1 (8.3)	9 (75.0)	0	0	4 (30.8)	9 (69.2)
Day 2 Injection 1	3 (30.0)	2 (20.0)	2 (20.0)	3 (30.0)	3 (25.0)	2 (16.7)	5 (41.7)	2 (16.7)	2 (15.4)	6 (46.2)	3 (23.1)	2 (15.4)
Day 15 Injection 1	2 (20.0)	5 (50.0)	0	3 (30.0)	3 (25.0)	1 (8.3)	5 (41.7)	3 (25.0)	2 (15.4)	4 (30.8)	4 (30.8)	2 (15.4)
Day 1 Injection 2	2 (20.0)	2 (20.0)	3 (30.0)	3 (30.0)	1 (8.3)	4 (33.3)	6 (50.0)	1 (8.3)	4 (30.8)	2 (15.4)	4 (30.8)	3 (23.1)
Day 15 Injection 2	2 (20.0)	1 (10.0)	4 (40.0)	1 (10.0)	2 (16.7)	2 (16.7)	4 (33.3)	2 (16.7)	5 (38.5)	4 (30.8)	1 (7.7)	1 (7.7)
Day 1 Injection 3	2 (20.0)	3 (30.0)	1 (10.0)	4 (40.0)	2 (16.7)	2 (16.7)	7 (58.3)	1 (8.3)	3 (23.1)	3 (23.1)	2 (15.4)	4 (30.8)
Day 15 Injection 3	2 (20.0)	3 (30.0)	2 (20.0)	3 (30.0)	3 (25.0)	3 (25.0)	5 (41.7)	1 (8.3)	4 (30.8)	4 (30.8)	2 (15.4)	2 (15.4)
Core study completion	1 (10.0)	4 (40.0)	1 (10.0)	4 (40.0)	3 (25.0)	3 (25.0)	5 (41.7)	1 (8.3)	6 (46.2)	1 (7.7)	3 (23.1)	3 (23.1)
Insulin-like growth factor-1 (serum)[2]	**Low n (%)**	**Normal n (%)**	**High n (%)**	**Low n (%)**	**Normal n (%)**	**High n (%)**	**Low n (%)**	**Normal n (%)**	**High n (%)**			
Screening	0	2 (20.0)	8 (80.0)	0	2 (16.7)	9 (75.0)	0	1 (7.7)	12 (92.3)			
Baseline visit	0	0	10 (100.0)	0	0	12 (100.0)	0	1 (7.7)	12 (92.3)			

Parameter	Pasireotide LAR 20 mg N = 10			Pasireotide LAR 40 mg N = 12			Pasireotide LAR 60 mg N = 13		
Day 1 Injection 1	0	0	9 (90.0)	0	1 (8.3)	11 (91.7)	0	0	13 (100.0)
Day 2 Injection 1	0	0	10 (100.0)	0	2 (16.7)	9 (75.0)	0	1 (7.7)	12 (92.3)
Day 15 Injection 1	0	3 (30.0)	7 (70.0)	0	2 (16.7)	10 (83.3)	0	4 (30.8)	9 (69.2)
Day 22 Injection 1	1 (10.0)	4 (40.0)	5 (50.0)	1 (8.3)	5 (41.7)	6 (50.0)	3 (23.1)	5 (38.5)	5 (38.5)
Day 1 Injection 2	0	5 (50.0)	5 (50.0)	1 (8.3)	7 (58.3)	4 (33.3)	3 (23.1)	5 (38.5)	5 (38.5)
Day 15 Injection 2	0	5 (50.0)	4 (40.0)	1 (8.3)	2 (16.7)	7 (58.3)	3 (23.1)	3 (23.1)	6 (46.2)
Day 1 Injection 3	0	5 (50.0)	5 (50.0)	0	8 (66.7)	4 (33.3)	4 (30.8)	4 (30.8)	5 (38.5)
Day 15 Injection 3	1 (10.0)	4 (40.0)	5 (50.0)	0	6 (50.0)	6 (50.0)	2 (15.4)	6 (46.2)	5 (38.5)
Core study completion	1 (10.0)	4 (40.0)	5 (50.0)	0	7 (58.3)	4 (33.3)	3 (23.1)	5 (38.5)	5 (38.5)
Free insulin-like growth factor [2]	**Low n (%)**	**Normal n (%)**	**High n (%)**	**Low n (%)**	**Normal n (%)**	**High n (%)**	**Low n (%)**	**Normal n (%)**	**High n (%)**
Screening	0	0	0	0	0	0	0	0	0
Baseline visit	0	0	10 (100.0)	0	1 (8.3)	11 (91.7)	0	2 (15.4)	11 (84.6)
Day 1 Injection 1	0	1 (10.0)	8 (80.0)	0	1 (8.3)	11 (91.7)	0	2 (15.4)	11 (84.6)
Day 2 Injection 1	0	0	10 (100.0)	0	1 (8.3)	10 (83.3)	0	2 (15.4)	10 (76.9)
Day 15 Injection 1	0	3 (30.0)	7 (70.0)	0	4 (33.3)	8 (66.7)	0	5 (38.5)	7 (53.8)
Day 22 Injection 1	0	5 (50.0)	5 (50.0)	0	7 (58.3)	5 (41.7)	0	10 (76.9)	2 (15.4)
Day 1 Injection 2	0	4 (40.0)	6 (60.0)	0	7 (58.3)	4 (33.3)	0	8 (61.5)	5 (38.5)
Day 15 Injection 2	0	4 (40.0)	5 (50.0)	0	6 (50.0)	4 (33.3)	0	7 (53.8)	5 (38.5)
Day 1 Injection 3	0	4 (40.0)	6 (60.0)	0	7 (58.3)	5 (41.7)	0	6 (46.2)	5 (38.5)
Day 15 Injection 3	0	5 (50.0)	5 (50.0)	0	5 (41.7)	7 (58.3)	0	7 (53.8)	4 (30.8)
Core study completion	0	4 (40.0)	6 (60.0)	0	6 (50.0)	5 (41.7)	0	8 (61.5)	4 (30.8)

[1] For growth hormone patients were classified according to the mean of 5-point (t0, 30, 60, 90, 120 minutes) when 2-hour profile was available.
[*] Columns are mutually exclusive
[2] For insulin-like growth factor-1 (serum) and free insulin-like growth factor results were reported as high, if the result was greater than the upper normal limit and as low, if the respective result was smaller than the lower normal limit.

Summary of average number of daily bowel movements per week (PD population)

Clinical indication = Carcinoid	Pasireotide LAR 20 mg N = 12		Pasireotide LAR 40 mg N = 14		Pasireotide LAR 60 mg N = 16	
Time point	**Actual**	**% change from baseline**	**Actual**	**% change from baseline**	**Actual**	**% change from baseline**
Baseline [a] - n	11		11		15	
Mean (SD)	3.3 (1.86)		2.8 (1.68)		4.2 (2.80)	
Median	2.7		3.0		2.9	
Min	1		1		1	

Clinical indication = Carcinoid	Pasireotide LAR 20 mg N = 12		Pasireotide LAR 40 mg N = 14		Pasireotide LAR 60 mg N = 16	
Time point	**Actual**	**% change from baseline**	**Actual**	**% change from baseline**	**Actual**	**% change from baseline**
Max	6		6		12	
Patients with > 12 daily bowel movements*	0		1 (7.1%)		0	
LAR Inj 1 Week 1 - n	11	11	13	11	16	15
Mean (SD)	3.7 (2.19)	11.5 (28.65)	2.5 (1.71)	-4.7 (29.74)	4.4 (2.77)	9.3 (23.91)
Median	3.1	15.1	2.3	0.0	3.6	3.4
Min	1	-50	0	-75	1	-34
Max	7	52	6	25	12	67
Patients with > 12 daily bowel movements*	0		1 (7.1%)		0	
LAR Inj 1 Week 2 - n	11	11	13	11	16	15
Mean (SD)	3.9 (2.49)	12.4 (36.20)	2.5 (1.76)	-5.8 (20.53)	3.9 (2.29)	0.0 (19.14)
Median	3.7	19.0	2.0	0.0	3.0	0.0
Min	0	-75	1	-50	1	-39
Max	8	71	6	22	10	29
Patients with > 12 daily bowel movements*	0		1 (7.1%)		0	
LAR Inj 1 Week 3 – n	11	11	13	11	16	15
Mean (SD)	3.9 (1.88)	25.0 (46.92)	2.3 (1.63)	-8.3 (26.20)	3.6 (1.96)	-7.1 (26.29)
Median	3.9	12.5	1.3	-4.8	2.9	-12.2
Min	1	-31	1	-46	2	-35
Max	7	141	5	35	8	71
Patients with > 12 daily bowel movements*	0		1 (7.1%)		0	
LAR Inj 1 Week 4 - n	11	11	13	11	16	15
Mean (SD)	4.1 (2.13)	34.1 (58.44)	2.3 (1.63)	-5.5 (33.88)	3.2 (1.75)	-14.6 (23.46)
Median	4.4	12.5	1.6	2.9	2.8	-16.7
Min	1	-23	1	-57	1	-62
Max	8	177	6	53	7	33
Patients with > 12 daily bowel movements*	0		0		0	
LAR Inj 2 Week 1 - n	10	10	13	11	16	15
Mean (SD)	3.6 (1.82)	23.9 (25.95)	2.4 (1.45)	-9.1 (26.49)	3.5 (1.73)	-2.3 (31.76)
Median	3.4	30.3	2.1	0.0	3.1	0.0
Min	1	-24	1	-53	1	-60
Max	7	65	6	19	7	71
Patients with > 12 daily bowel movements*	1 (8.3%)		0		0	
LAR Inj 2 Week 2 - n	11	11	13	11	16	15
Mean (SD)	3.9 (2.10)	21.8 (34.92)	2.7 (1.52)	-2.7 (25.88)	3.5 (1.97)	-6.4 (27.07)
Median	3.3	8.9	2.7	-11.1	3.1	-10.7

Clinical indication = Carcinoid	Pasireotide LAR 20 mg N = 12		Pasireotide LAR 40 mg N = 14		Pasireotide LAR 60 mg N = 16	
Time point	**Actual**	**% change from baseline**	**Actual**	**% change from baseline**	**Actual**	**% change from baseline**
Min	1	-20	1	-39	1	-47
Max	7	98	6	48	9	57
Patients with > 12 daily bowel movements*	0		0		0	
LAR Inj 2 Week 3 - n	11	11	12	10	15	14
Mean (SD)	4.1 (2.24)	25.3 (35.05)	2.7 (1.45)	6.5 (30.48)	3.2 (1.65)	-9.0 (26.88)
Median	4.4	17.9	2.3	9.5	2.7	-10.6
Min	1	-29	1	-33	1	-44
Max	7	104	5	75	7	43
Patients with > 12 daily bowel movements*	0		0		0	
LAR Inj 2 Week 4 - n	11	11	12	10	15	14
Mean (SD)	3.8 (2.08)	19.4 (27.60)	2.4 (1.56)	-7.0 (23.70)	3.1 (1.56)	-12.1 (35.26)
Median	3.7	27.3	2.0	-10.0	2.6	-27.1
Min	1	-36	1	-38	1	-48
Max	8	71	6	22	7	86
Patients with > 12 daily bowel movements*	0		0		0	
LAR Inj 3 Week 1 - n	11	11	11	9	14	13
Mean (SD)	3.6 (2.48)	11.9 (43.39)	2.9 (1.91)	8.6 (32.52)	3.1 (1.70)	-11.3 (25.92)
Median	3.0	14.7	2.1	0.0	2.5	-20.0
Min	1	-61	1	-22	1	-59
Max	9	92	6	86	6	25
Patients with > 12 daily bowel movements*	0		0		0	
LAR Inj 3 Week 2 -n	11	11	11	9	13	12
Mean (SD)	3.7 (2.09)	22.5 (53.01)	2.8 (1.60)	9.3 (27.60)	3.1 (1.60)	-8.1 (33.83)
Median	3.9	17.6	2.0	7.1	2.7	-13.2
Min	1	-47	1	-28	1	-59
Max	8	141	6	52	7	57
Patients with > 12 daily bowel movements*	0		0		0	
LAR Inj 3 Week 3 - n	11	11	10	8	13	12
Mean (SD)	3.9 (2.65)	18.1 (47.22)	3.2 (1.35)	9.7 (24.37)	3.0 (1.84)	-12.0 (35.59)
Median	4.3	12.5	3.0	13.9	2.3	-17.7
Min	1	-33	1	-32	1	-59
Max	10	118	6	43	8	47
Patients with > 12 daily bowel movements*	0		0		0	
LAR Inj 3 Week 4 - n	10	10	9	7	13	12
Mean (SD)	3.8 (2.49)	12.4 (47.21)	2.8 (1.62)	-7.2 (32.04)	2.9 (1.31)	-11.3 (36.46)

Clinical indication = Carcinoid	Pasireotide LAR 20 mg N = 12		Pasireotide LAR 40 mg N = 14		Pasireotide LAR 60 mg N = 16	
Time point	**Actual**	**% change from baseline**	**Actual**	**% change from baseline**	**Actual**	**% change from baseline**
Median	4.2	1.9	2.8	-13.8	2.4	-15.0
Min	1	-40	1	-43	1	-58
Max	7	112	6	44	5	67
Patients with > 12 daily bowel movements*	0		0		0	

[a] Baseline = mean of the 7 days prior to the first LAR injection.
*Patients reporting more than 12 daily bowel movements on any day at baseline or afterwards were excluded from the summary statistics for that period.

Extension phase

Summary of actual level and change from baseline in GH in patients with acromegaly – any dose (PD population)

		GH (µg/L)			
Timepoint	**Statistics**	**Core baseline**	**Level**	**Level change**	**% change**
Month 3	N	29	29	29	29
	Mean	16.96	6.13	-10.82	-55.56
	SD	32.289	9.908	26.985	55.609
	Median	7.40	2.65	-4.20	-71.28
	Min	1.8	0.3	-140.7	-97.4
	Max	175.5	38.1	25.6	204.8
Month 6	N	27	27	27	27
	Mean	17.02	4.08	-12.94	-69.30
	SD	33.493	7.254	26.667	24.084
	Median	6.85	2.40	-6.30	-76.15
	Min	1.8	0.2	-138.6	-96.9
	Max	175.5	36.9	-0.7	-13.7
Month 12	n	25	25	25	25
	Mean	17.73	4.24	-13.49	-73.96
	SD	34.752	10.803	24.598	20.538
	Median	6.85	1.80	-5.90	-80.00
	Min	1.8	0.1	-120.2	-96.6
	Max	175.5	55.3	-1.4	-28.4
Month 24	n	20	20	20	20
	Mean	18.87	3.17	-15.70	-79.59
	SD	38.507	6.889	31.939	13.879
	Median	7.13	1.30	-6.50	-82.87
	Min	1.8	0.1	-143.6	-96.9
	Max	175.5	31.9	-1.6	-51.1
Month 36	n	20	20	20	20

		GH (µg/L)			
Timepoint	**Statistics**	**Core baseline**	**Level**	**Level change**	**% change**
	Mean	10.72	1.85	-8.87	-79.39
	SD	11.129	2.887	10.901	24.130
	Median	7.13	0.90	-5.78	-85.48
	Min	1.8	0.2	-46.3	-97.0
	Max	48.9	13.3	1.6	13.2
Month 48	n	17	17	17	17
	Mean	7.75	1.35	-6.40	-82.00
	SD	5.539	1.256	5.026	11.199
	Median	6.50	1.00	-4.85	-83.94
	Min	1.8	0.1	-21.9	-94.7
	Max	23.6	5.3	-1.7	-54.9
Month 60	n	16	16	16	16
	Mean	8.12	1.18	-6.94	-84.00
	SD	5.497	0.997	5.163	10.336
	Median	6.68	0.95	-5.53	-87.01
	Min	2.3	0.2	-22.2	-94.7
	Max	23.6	4.2	-2.1	-64.3
Month 72	n	14	14	14	14
	Mean	8.12	1.25	-6.87	-79.65
	SD	5.656	1.118	5.660	25.747
	Median	6.68	0.80	-5.38	-90.07
	Min	2.3	0.2	-22.4	-95.8
	Max	23.6	3.9	0.1	2.6
Month 84	n	11	11	11	11
	Mean	8.21	1.13	-7.09	-83.26
	SD	6.239	1.271	5.955	19.018
	Median	6.50	0.50	-6.00	-92.31
	Min	2.3	0.1	-21.7	-97.9
	Max	23.6	4.1	-1.9	-42.5
Month 93	n	1	1	1	1
	Mean	4.35	3.50	-0.85	-19.54
	SD				
	Median	4.35	3.50	-0.85	-19.54
	Min	4.4	3.5	-0.8	-19.5
	Max	4.4	3.5	-0.8	-19.5

For month x, the incident dose is the x^{th} dose. For month 3, the actual GH level is the mean of the pre-dose GH levels at -30 min and 0 min.

Summary of GH level distribution in patients with acromegaly by incident dose level (PD population)

			GH level (µg/L)			
			≤ 1	>1 to ≤ 2.5	>2.5 to ≤ 5	>5
Timepoint	**Incident dose**	**Total**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Screening		23	0	3 (13.0)	4 (17.4)	16 (69.6)
Day 1 Inj. 1		28	0	2 (7.1)	9 (32.1)	17 (60.7)
Month 3	20 mg	9	1 (11.1)	5 (55.6)	0	3 (33.3)
	40 mg	9	2 (22.2)	2 (22.2)	5 (55.6)	0
	60 mg	11	4 (36.4)	2 (18.2)	2 (18.2)	3 (27.3)
	Any dose	29	7 (24.1)	9 (31.0)	7 (24.1)	6 (20.7)
Month 6	20 mg	6	3 (50.0)	0	2 (33.3)	1 (16.7)
	40 mg	12	2 (16.7)	5 (41.7)	4 (33.3)	1 (8.3)
	60 mg	9	3 (33.3)	1 (11.1)	3 (33.3)	2 (22.2)
	Any dose	27	8 (29.6)	6 (22.2)	9 (33.3)	4 (14.8)
Month 12	20 mg	9	4 (44.4)	4 (44.4)	1 (11.1)	0
	40 mg	7	3 (42.9)	3 (42.9)	1 (14.3)	0
	60 mg	9	2 (22.2)	1 (11.1)	4 (44.4)	2 (22.2)
	Any dose	25	9 (36.0)	8 (32.0)	6 (24.0)	2 (8.0)
Month 24	20 mg	12	5 (41.7)	3 (25.0)	4 (33.3)	0
	40 mg	5	2 (40.0)	3 (60.0)	0	0
	60 mg	3	1 (33.3)	1 (33.3)	0	1 (33.3)
	Any dose	20	8 (40.0)	7 (35.0)	4 (20.0)	1 (5.0)
Month 36	20 mg	12	8 (66.7)	2 (16.7)	1 (8.3)	1 (8.3)
	40 mg	5	3 (60.0)	1 (20.0)	1 (20.0)	0
	60 mg	3	2 (66.7)	1 (33.3)	0	0
	Any dose	20	13 (65.0)	4 (20.0)	2 (10.0)	1 (5.0)
Month 48	20 mg	9	6 (66.7)	2 (22.2)	1 (11.1)	0
	40 mg	4	2 (50.0)	1 (25.0)	0	1 (25.0)
	60 mg	4	1 (25.0)	3 (75.0)	0	0
	Any dose	17	9 (52.9)	6 (35.3)	1 (5.9)	1 (5.9)
Month 60	20 mg	7	5 (71.4)	2 (28.6)	0	0
	40 mg	5	2 (40.0)	2 (40.0)	1 (20.0)	0
	60 mg	4	2 (50.0)	2 (50.0)	0	0
	Any dose	16	9 (56.3)	6 (37.5)	1 (6.3)	0
Month 72	20 mg	6	4 (66.7)	2 (33.3)	0	0
	40 mg	6	3 (50.0)	1 (16.7)	2 (33.3)	0
	60 mg	2	1 (50.0)	1 (50.0)	0	0
	Any dose	14	8 (57.1)	4 (28.6)	2 (14.3)	0
Month 84	20 mg	4	3 (75.0)	1 (25.0)	0	0
	40 mg	6	3 (50.0)	2 (33.3)	1 (16.7)	0
	60 mg	1	1 (100.0)	0	0	0
	Any dose	11	7 (63.6)	3 (27.3)	1 (9.1)	0
Month 93	40 mg	1	0	0	1(100.0)	0

			GH level (µg/L)			
			≤ 1	>1 to ≤ 2.5	>2.5 to ≤ 5	>5
Timepoint	**Incident dose**	**Total**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
	Any dose	1	0	0	1(100.0)	0

The Total column shows the number of patients with non-missing GH level at each timepoint, and is the denominator for calculation of percentages within the row. For month x, the incident dose is the x^{th} dose.

Note: For Month 3, the GH level is determined by the mean of assessments at 0 min, 30 min, 1 h, 1.5 h and 2 h at Visit 12.

Summary of actual level and change from baseline in total IGF-1 in patients with acromegaly – any dose (PD population)

		Total IGF-1 (µg/L)			
Timepoint	**Statistics**	**Core baseline**	**Level**	**Level change**	**% change**
Month 3	N	29	29	29	29
	Mean	495.88	269.99	-225.88	-44.89
	SD	125.523	181.065	180.641	32.741
	Median	519.00	219.30	-193.50	-48.51
	Min	274.9	81.4	-546.8	-84.5
	Max	747.3	859.4	291.8	51.4
Month 6	N	28	28	28	28
	Mean	500.12	260.56	-239.55	-48.24
	SD	125.691	205.854	185.742	29.377
	Median	540.85	207.90	-240.65	-53.21
	Min	274.9	77.4	-532.9	-83.6
	Max	747.3	1144.2	396.9	53.1
Month 12	N	25	25	25	25
	Mean	495.99	274.74	-221.24	-44.23
	SD	130.344	191.486	173.402	33.068
	Median	519.00	212.00	-234.50	-49.31
	Min	274.9	83.2	-471.4	-80.9
	Max	747.3	937.1	189.8	42.7
Month 24	N	19	19	19	19
	Mean	476.82	265.85	-210.97	-42.66
	SD	126.922	195.831	190.494	34.571
	Median	460.50	209.20	-213.90	-48.36
	Min	274.9	57.5	-491.5	-86.4
	Max	747.3	968.6	221.3	32.1
Month 36	N	20	20	20	20
	Mean	474.46	169.41	-305.05	-62.03
	SD	112.785	65.837	132.189	18.557
	Median	470.90	161.45	-336.85	-68.26
	Min	274.9	60.3	-489.3	-87.0
	Max	647.0	297.9	-57.4	-16.2
Month 48	N	17	17	17	17

		Total IGF-1 (µg/L)			
Timepoint	**Statistics**	**Core baseline**	**Level**	**Level change**	**% change**
	Mean	460.29	182.01	-278.28	-57.95
	SD	116.413	78.440	140.883	21.495
	Median	459.50	176.70	-239.40	-62.89
	Min	274.9	54.6	-517.0	-87.2
	Max	647.0	356.3	-30.5	-11.1
Month 60	N	16	16	16	16
	Mean	464.31	140.56	-323.75	-67.87
	SD	119.007	58.516	132.242	15.717
	Median	460.00	142.40	-300.35	-72.19
	Min	274.9	58.4	-581.9	-89.9
	Max	647.0	262.0	-97.2	-35.4
Month 72	N	14	14	14	14
	Mean	446.71	161.57	-285.14	-62.03
	SD	116.909	66.697	125.194	16.572
	Median	440.65	160.55	-255.05	-68.54
	Min	274.9	70.8	-505.8	-87.7
	Max	647.0	288.8	-104.8	-37.2
Month 84	N	11	11	11	11
	Mean	457.67	150.15	-307.52	-63.92
	SD	112.524	66.663	147.414	22.310
	Median	459.50	141.50	-279.40	-70.04
	Min	274.9	56.5	-509.6	-88.4
	Max	647.0	246.1	-32.4	-11.8
Month 93	N	1	1	1	1
	Mean	460.50	343.70	-116.80	-25.36
	SD				
	Median	460.50	343.70	-116.80	-25.36
	Min	460.5	343.7	-116.8	-25.4
	Max	460.5	343.7	-116.8	-25.4

For month x, the incident dose is the x^{th} dose. For month 3, the actual IGF-1 level is the mean of the pre-dose IGF-1 levels at -30 min and 0 min.

Summary of total IGF-1 level distribution in patients with acromegaly by incident dose level (PD population)

			IGF-1 level		
			Low	**Normal**	**High**
Timepoint	**Incident dose**	**Total**	**n (%)**	**n (%)**	**n (%)**
Baseline		**29**	**0**	**1 (3.4)**	**28 (96.6)**
Month 3	20 mg	9	1 (11.1)	4 (44.4)	4 (44.4)
	40 mg	9	0	6 (66.7)	3 (33.3)
	60 mg	11	2 (18.2)	4 (36.4)	5 (45.5)
	Any dose	29	3 (10.3)	14 (48.3)	12 (41.4)

			IGF-1 level		
			Low	Normal	High
Timepoint	Incident dose	Total	n (%)	n (%)	n (%)
Month 6	20 mg	6	0	6 (100.0)	0
	40 mg	12	1 (8.3)	7 (58.3)	4 (33.3)
	60 mg	10	0	4 (40.0)	6 (60.0)
	Any dose	28	1 (3.6)	17 (60.7)	10 (35.7)
Month 12	20 mg	9	2 (22.2)	5 (55.6)	2 (22.2)
	40 mg	7	0	4 (57.1)	3 (42.9)
	60 mg	9	0	2 (22.2)	7 (77.8)
	Any dose	25	2 (8.0)	11 (44.0)	12 (48.0)
Month 24	20 mg	11	2 (18.2)	6 (54.5)	3 (27.3)
	40 mg	5	0	4 (80.0)	1 (20.0)
	60 mg	3	0	1 (33.3)	2 (66.7)
	Any dose	19	2 (10.5)	11 (57.9)	6 (31.6)
Month 36	20 mg	12	3 (25.0)	7 (58.3)	2 (16.7)
	40 mg	5	0	5 (100.0)	0
	60 mg	3	0	2 (66.7)	1 (33.3)
	Any dose	20	3 (15.0)	14 (70.0)	3 (15.0)
Month 48	20 mg	9	3 (33.3)	5 (55.6)	1 (11.1)
	40 mg	4	0	2 (50.0)	2 (50.0)
	60 mg	4	0	2 (50.0)	2 (50.0)
	Any dose	17	3 (17.6)	9 (52.9)	5 (29.4)
Month 60	20 mg	7	4 (57.1)	3(42.9)	0
	40 mg	5	0	5(100.0)	0
	60 mg	4	0	3 (75.0)	1 (25.0)
	Any dose	16	4 (25.0)	11 (68.8)	1 (6.3)
Month 72	20 mg	6	2 (33.3)	4 (66.7)	0
	40 mg	6	0	5 (83.3)	1 (16.7)
	60 mg	2	0	1 (50.0)	1 (50.0)
	Any dose	14	2 (14.3)	10 (71.4)	2 (14.3)
Month 84	20 mg	4	2 (50.0)	2 (50.0)	0
	40 mg	6	0	5 (83.3)	1 (16.7)
	60 mg	1	0	0	1 (100.0)
	Any dose	11	2 (18.2)	7(63.6)	2 (18.2)
Month 93	40 mg	1	0	0	1 (100.0)
	Any dose	1	0	0	1 (100.0)

The Total column shows the number of patients with non-missing total IGF-1 assessment at each timepoint, and is the denominator for calculation of percentages within the row. For month x, the incident dose is the x^{th} dose.

Summary of observed response rates based on GH and IGF-1 criteria in patients with acromegaly by incident dose level (PD population)

Timepoint	Responders	Pasireotide LAR 20 mg n (%)	Pasireotide LAR 40 mg n (%)	Pasireotide LAR 60 mg n (%)	Pasireotide LAR any dose n (%)
Month 3	Total	9	9	11	29
	Yes	4 (44.4)	3 (33.3)	4 (36.4)	11 (37.9)
	No	5 (55.6)	6 (66.7)	7 (63.6)	18 (62.1)
Month 6	Total	6	12	10	28
	Yes	3 (50.0)	5 (41.7)	2 (20.0)	10 (35.7)
	No	3 (50.0)	7 (58.3)	8 (80.0)	18 (64.3)
Month 12	Total	9	7	9	25
	Yes	4 (44.4)	4 (57.1)	1 (11.1)	9 (36.0)
	No	5 (55.6)	3 (42.9)	8 (88.9)	16 (64.0)
Month 24	Total	12	5	3	20
	Yes	4 (33.3)	4 (80.0)	1 (33.3)	9 (45.0)
	No	8 (66.7)	1 (20.0)	2 (66.7)	11 (55.0)
Month 36	Total	12	5	3	20
	Yes	6 (50.0)	4 (80.0)	2 (66.7)	12 (60.0)
	No	6 (50.0)	1 (20.0)	1 (33.3)	8 (40.0)
Month 48	Total	9	4	4	17
	Yes	4 (44.4)	2 (50.0)	2 (50.0)	8 (47.1)
	No	5 (55.6)	2 (50.0)	2 (50.0)	9 (52.9)
Month 60	Total	7	5	4	16
	Yes	3 (42.9)	4 (80.0)	3 (75.0)	10 (62.5)
	No	4 (57.1)	1 (20.0)	1 (25.0)	6 (37.5)
Month 72	Total	6	6	2	14
	Yes	4 (66.7)	3 (50.0)	1 (50.0)	8 (57.1)
	No	2 (33.3)	3 (50.0)	1 (50.0)	6 (42.9)
Month 84	Total	4	6	1	11
	Yes	2 (50.0)	4 (66.7)	0	6 (54.5)
	No	2 (50.0)	2 (33.3)	1 (100.0)	5 (45.5)
Month 93	Total	0	1	0	1
	No	0	1 (100.0)	0	1(100.0)

Patients are summarized according to incident dose and once in the “Pasireotide LAR any dose” column.

Note: For Month 3, the GH level is determined by the mean of assessments at 0 min, 30 min, 1 h, 1.5 h and 2 h on Day 1 Inj 4, and the incident dose level is the 3rd dose level.

Average daily number of bowel movements below 4 in patients with carcinoid disease by incident dose level (PD population)

	Pasireotide LAR 20 mg		Pasireotide LAR 40 mg		Pasireotide LAR 60 mg		Pasireotide LAR any dose	
Timepoint	**Total**	**n (%)**	**Total**	**n (%)**	**Total**	**n (%)**	**Total**	**n (%)**
Month 3	5	2 (40.0)	7	5 (71.4)	2	2 (100.0)	14	9 (64.3)
Month 6	1	1 (100.0)	3	2 (66.7)	3	2 (66.7)	7	5 (71.4)

If a dose is not the final received dose, the average daily number of bowel movements is determined as the mean of the last 28 days prior to the next dose or the mean of all days in the treatment period (including the incident dosing day) if the treatment period is less than 28 days. If a dose is the final received dose, the average daily number of bowel movements is determined as the mean of the 28 days following the dose (including the dosing day).

Note: The denominator of each percentage for a dose level is the number of patients dosed with that level of pasireotide LAR incident to the observation period (month).

Summary of Safety

Safety Results

Adverse Events by System Organ Class

Core phase

Number (%) of patients with adverse events overall and by system organ class – Acromegaly indication (Safety population)

System organ class	Pasireotide LAR 20 mg N = 10 n (%)	Pasireotide LAR 40 mg N = 12 n (%)	Pasireotide LAR 60 mg N = 13 n (%)	Any pasiretide LAR dose N = 35 n (%)
Any primary system organ class	7 (70.0)	7 (58.3)	10 (76.9)	24 (68.6)
Gastrointestinal disorders	3 (30.0)	4 (33.3)	6 (46.2)	13 (37.1)
Infections & infestations	4 (40)	3 (25.0)	5 (38.5)	12 (34.3)
Metabolism & nutrition disorders	1 (10.0)	3 (25.0)	5 (38.5)	9 (25.7)
Investigations	2 (20.0)	2 (16.7)	2 (15.4)	6 (17.1)
General disorders & administration site conditions	0	0	3 (23.1)	3 (8.6)
Hepatobiliary disorders	0	1 (8.3)	2 (15.4)	3 (8.6)
Musculoskeletal & connective tissue disorders	1 (10.0)	2 (16.7)	0	3 (8.6)
Blood & lymphatic system disorders	1 (10.0)	0	1 (7.7)	2 (5.7)
Cardiac disorders	0	0	2 (15.4)	2 (5.7)
Renal & urinary disorders	0	1 (8.3)	1 (7.7)	2 (5.7)
Eye disorders	1 (10.0)	0	0	1 (2.9)
Nervous system disorders	0	1 (8.3)	0	1 (2.9)
Respiratory, thoracic & mediastinal disorders	0	1 (8.3)	0	1 (2.9)

Number (%) of patients with AEs overall and by system organ class – Carcinoid indication (Safety population)

System organ class	Pasireotide LAR 20 mg N = 12 n (%)	Pasireotide LAR 40 mg N = 14 n (%)	Pasireotide LAR 60 mg N = 16 n (%)	Any pasiretide LAR dose N = 42 n (%)
Any primary system organ class	10 (83.3)	11 (78.6)	13 (81.3)	34 (81.0)
Gastrointestinal disorders	8 (66.7)	10 (71.4)	6 (37.5)	24 (57.1)
General disorders & administration site conditions	6 (50.0)	5 (35.7)	6 (37.5)	17 (40.5)
Metabolism & nutrition disorders	3 (25.0)	6 (42.9)	8 (50.0)	17 (40.5)
Musculoskeletal & connective tissue disorders	5 (41.7)	6 (42.9)	4 (25.0)	15 (35.7)
Nervous system disorders	3 (25.0)	2 (14.3)	5 (31.3)	10 (23.8)
Respiratory, thoracic & mediastinal disorders	4 (33.3)	5 (35.7)	1 (6.3)	10 (23.8)
Skin & subcutaneous tissue disorders	1 (8.3)	3 (21.4)	3 (18.8)	7 (16.7)

System organ class	Pasireotide LAR 20 mg N = 12 n (%)	Pasireotide LAR 40 mg N = 14 n (%)	Pasireotide LAR 60 mg N = 16 n (%)	Any pasiretide LAR dose N = 42 n (%)
Vascular disorders	3 (25.0)	1 (7.1)	2 (12.5)	6 (14.3)
Cardiac disorders	1 (8.3)	4 (28.6)	0	5 (11.9)
Investigations	1 (8.3)	1 (7.1)	2 (12.5)	4 (9.5)
Psychiatric disorders	1 (8.3)	1 (7.1)	2 (12.5)	4 (9.5)
Renal & urinary disorders	2 (16.7)	0	2 (12.5)	4 (9.5)
Hepatobiliary disorders	1 (8.3)	2 (14.3)	0	3 (7.1)
Infections & infestations	1 (8.3)	1 (7.1)	0	2 (4.8)
Injury, poisoning & procedural complications	0	0	2 (12.5)	2 (4.8)
Neoplasms benign, malignant & unspecified (incl systs and polyps)	0	1 (7.1)	1 (6.3)	2 (4.8)
Blood & lymphatic system disorders	0	0	1 (6.3)	1 (2.4)
Endocrine disorders	0	0	1 (6.3)	1 (2.4)
Immune system disorders	0	1 (7.1)	0	1 (2.4)
Reproductive system & breast disorders	1 (8.3)	0	0	1 (2.4)

Most Frequently Reported AEs Overall by Preferred Term n (%)

Most frequently reported adverse events (at least 10% in any dose group) by preferred term - Acromegaly indication (Safety population)

Preferred term	Pasireotide LAR 20 mg N = 10 n (%)	Pasireotide LAR 40 mg N = 12 n (%)	Pasireotide LAR 60 mg N = 13 n (%)	Any pasireotide LAR dose N = 35 n (%)
Abdominal distension	0	1 (8.3)	1 (7.7)	2 (5.7)
Abdominal pain	2 (20.0)	0	1 (7.7)	3 (8.6)
Diarrhea	3 (30.0)	3 (25.0)	6 (46.2)	12 (34.3)
Nausea	1 (10.0)	1 (8.3)	0	2 (5.7)
Cholelithiasis	0	1 (8.3)	1 (7.7)	2 (5.7)
Nasopharyngitis	2 (20.0)	1 (8.3)	2 (15.4)	5 (14.3)
Blood glucose increased	0	2 (16.7)	1 (7.7)	3 (8.6)
Blood insulin decreased	1 (10.0)	2 (16.7)	0	3 (8.6)
Diabetes mellitus	1 (10.0)	1 (8.3)	1 (7.7)	3 (8.6)
Hyperglycemia	0	1 (8.3)	3 (23.1)	4 (11.4)

Most frequently reported adverse events (at least 10% in any dose group) by preferred term - Carcinoid indication (Safety population)

Preferred term	Pasireotide LAR 20 mg N = 12 n (%)	Pasireotide LAR 40 mg N = 14 n (%)	Pasireotide LAR 60 mg N = 16 n (%)	Any pasireotide LAR dose N = 42 n (%)
Diarrhea	4 (33.3)	4 (28.6)	4 (25.0)	12 (28.6)
Fatigue	3 (25.0)	3 (21.4)	3 (18.8)	9 (21.4)
Abdominal pain	3 (25.0)	4 (28.6)	1 (6.3)	8 (19.0)

Preferred term	Pasireotide LAR 20 mg N = 12 n (%)	Pasireotide LAR 40 mg N = 14 n (%)	Pasireotide LAR 60 mg N = 16 n (%)	Any pasireotide LAR dose N = 42 n (%)
Nausea	2 (16.7)	3 (21.4)	2 (12.5)	7 (16.7)
Diabetes mellitus	1 (8.3)	3 (21.4)	2 (12.5)	6 (14.3)
Dyspnea	2 (16.7)	3 (21.4)	1 (6.3)	6 (14.3)
Flushing	3 (25.0)	1 (7.1)	2 (12.5)	6 (14.3)
Headache	1 (8.3)	2 (14.3)	3 (18.8)	6 (14.3)
Anorexia	1 (8.3)	3 (21.4)	1 (6.3)	5 (11.9)
Asthenia	2 (16.7)	2 (14.3)	1 (6.3)	5 (11.9)

Serious Adverse Events and Deaths

Number (%) of patients who died, had other serious AEs (SAEs) or discontinued because of AEs under pasireotide s.c. (second safety population)

	Pasireotide s.c. n (%)
Acromegaly (N = 32)	
Deaths	0
Any SAEs and AEs leading to study drug discontinuation	0
SAEs	0
Discontinued study drug due to AEs	0
Carcinoid (N = 45)	
Deaths	0
Any SAEs and AEs leading to study drug discontinuation	2 (4.4)
SAEs	2 (4.4)
Discontinued study drug due to AEs	1 (2.2)

Extension phase

Adverse Events by System Organ Class

Adverse events regardless of study drug relationship by primary system organ class, and incident dose – Acromegaly (Safety population)

System organ class	Pasireotide LAR 20 mg N=18 n (%)	Pasireotide LAR 40 mg N=24 n (%)	Pasireotide LAR 60 mg N=17 n (%)	Pasireotide LAR any dose N=29 n (%)
Any system organ class	**16 (88.9)**	**22 (91.7)**	**17 (100)**	**29 (100.0)**
Gastrointestinal disorders	7 (38.9)	6 (25.0)	11 (64.7)	20 (69.0)
Infections and infestations	9 (50.0)	8 (33.3)	10 (58.8)	18 (62.1)
Metabolism and nutrition disorders	9 (50.0)	6 (25.0)	10 (58.8)	18 (62.1)
Hepatobiliary disorders	4 (22.2)	5 (20.8)	5 (29.4)	14 (48.3)
Musculoskeletal and connective tissue disorders	5 (27.8)	5 (20.8)	5 (29.4)	13 (44.8)

System organ class	Pasireotide LAR 20 mg N=18 n (%)	Pasireotide LAR 40 mg N=24 n (%)	Pasireotide LAR 60 mg N=17 n (%)	Pasireotide LAR any dose N=29 n (%)
Investigations	5 (27.8)	5 (20.8)	4 (23.5)	12 (41.4)
General disorders and administration site conditions	2 (11.1)	5 (20.8)	6 (35.3)	11 (37.9)
Respiratory, thoracic and mediastinal disorders	4 (22.2)	3 (12.5)	1 (5.9)	8 (27.6)
Nervous system disorders	3 (16.7)	2 (8.3)	3 (17.6)	8 (27.6)
Cardiac disorders	3 (16.7)	2 (8.3)	2 (11.8)	6 (20.7)
Injury, poisoning and procedural complications	3 (16.7)	2 (8.3)	1 (5.9)	6 (20.7)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (11.1)	3 (12.5)	1 (5.9)	6 (20.7)
Skin and subcutaneous tissue disorders	1 (5.6)	2 (8.3)	3 (17.6)	6 (20.7)
Endocrine disorders	2 (11.1)	1 (4.2)	2 (11.8)	5 (17.2)
Reproductive system and breast disorders	3 (16.7)	1 (4.2)	1 (5.9)	5 (17.2)
Psychiatric disorders	2 (11.1)	0	3 (17.6)	5 (17.2)
Renal and urinary disorders	1 (5.6)	0	3 (17.6)	4 (13.8)
Vascular disorders	2 (11.1)	0	2 (11.8)	4 (13.8)
Blood and lymphatic system disorders	2 (11.1)	0	1 (5.9)	3 (10.3)
Ear and labyrinth disorders	0	2 (8.3)	1 (5.9)	3 (10.3)
Eye disorders	1 (5.6)	0	2 (11.8)	3 (10.3)
Immune system disorders	2 (11.1)	0	0	2 (6.9)
Social circumstances	1 (5.6)	0	0	1 (3.4)

N = Total number of patients having ever received the specific dose level.

Adverse events regardless of study drug relationship by primary system organ class, and incident dose – carcinoid (Safety population)

System organ class	Pasireotide LAR 20 mg N=8 n (%)	Pasireotide LAR 40 mg N=18 n (%)	Pasireotide LAR 60 mg N=20 n (%)	Pasireotide LAR any dose N=31 n (%)
Any primary system organ class	**8 (100)**	**15 (83.3)**	**19 (95.0)**	**29 (93.5)**
Gastrointestinal disorders	8 (100)	13 (72.2)	17 (85.0)	29 (93.5)
Metabolism and nutrition disorders	4 (50.0)	10 (55.6)	14 (70.0)	24 (77.4)
General disorders and administration site conditions	5 (62.5)	8 (44.4)	13 (65.0)	21 (67.7)
Infections and infestations	3 (37.5)	5 (27.8)	12 (60.0)	19 (61.3)
Musculoskeletal and connective tissue disorders	5 (62.5)	7 (38.9)	11 (55.0)	18 (58.1)
Respiratory, thoracic and mediastinal disorders	5 (62.5)	7 (38.9)	9 (45.0)	16 (51.6)
Vascular disorders	3 (37.5)	5 (27.8)	11 (55.0)	15 (48.4)
Psychiatric disorders	2 (25.0)	4 (22.2)	7 (35.0)	12 (38.7)

System organ class	Pasireotide LAR 20 mg N=8 n (%)	Pasireotide LAR 40 mg N=18 n (%)	Pasireotide LAR 60 mg N=20 n (%)	Pasireotide LAR any dose N=31 n (%)
Nervous system disorders	3 (37.5)	3 (16.7)	8 (40.0)	11 (35.5)
Skin and subcutaneous tissue disorders	2 (25.0)	5 (27.8)	7 (35.0)	11 (35.5)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (12.5)	3 (16.7)	6 (30.0)	10 (32.3)
Cardiac disorders	1 (12.5)	4 (22.2)	4 (20.0)	8 (25.8)
Injury, poisoning and procedural complications	1 (12.5)	1 (5.6)	6 (30.0)	8 (25.8)
Investigations	2 (25.0)	2 (11.1)	4 (20.0)	8 (25.8)
Renal and urinary disorders	2 (25.0)	2 (11.1)	4 (20.0)	8 (25.8)
Blood and lymphatic system disorders	0	2 (11.1)	5 (25.0)	7 (22.6)
Hepatobiliary disorders	1 (12.5)	3 (16.7)	3 (15.0)	7 (22.6)
Eye disorders	1 (12.5)	2 (11.1)	3 (15.0)	6 (19.4)
Endocrine disorders	0	1 (5.6)	3 (15.0)	4 (12.9)
Immune system disorders	0	1 (5.6)	1 (5.0)	2 (6.5)
Reproductive system and breast disorders	1 (12.5)	0	1 (5.0)	2 (6.5)
Ear and labyrinth disorders	0	1 (5.6)	0	1 (3.2)

N = Total number of patients having ever received the specific dose level.

Most Frequently Reported AEs Overall by Preferred Term n (%)

Frequently reported adverse events (at least 10% patients in any dose group) by preferred term and incident dose– acromegaly (Safety population)

Preferred term	Pasireotide LAR 20 mg N=18 n (%)	Pasireotide LAR 40 mg N=24 n (%)	Pasireotide LAR 60 mg N=17 n (%)	Pasireotide LAR any dose N=29 n (%)
Total	**16 (88.9)**	**22 (91.7)**	**17 (100)**	**29 (100)**
Diarrhoea	3 (16.7)	6 (25.0)	9 (52.9)	15 (51.7)
Nasopharyngitis	5 (27.8)	5 (20.8)	7 (41.2)	14 (48.3)
Cholelithiasis	4 (22.2)	4 (16.7)	2 (11.8)	10 (34.5)
Abdominal pain	5 (27.8)	1 (4.2)	2 (11.8)	8 (27.6)
Back pain	3 (16.7)	0	3 (17.6)	6 (20.7)
Blood glucose increased	1 (5.6)	4 (16.7)	1 (5.9)	6 (20.7)
Diabetes mellitus	3 (16.7)	1 (4.2)	2 (11.8)	6 (20.7)
Dizziness	2 (11.1)	1 (4.2)	2 (11.8)	5 (17.2)
Hyperglycaemia	1 (5.6)	2 (8.3)	3 (17.6)	5 (17.2)
Nausea	0	3 (12.5)	3 (17.6)	5 (17.2)
Arthralgia	1 (5.6)	2 (8.3)	1 (5.9)	4 (13.8)
Bronchitis	2 (11.1)	2 (8.3)	0	4 (13.8)
Flatulence	1 (5.6)	1 (4.2)	2 (11.8)	4 (13.8)

Preferred term	Pasireotide LAR 20 mg N=18 n (%)	Pasireotide LAR 40 mg N=24 n (%)	Pasireotide LAR 60 mg N=17 n (%)	Pasireotide LAR any dose N=29 n (%)
Sinusitis	4 (22.2)	1 (4.2)	0	4 (13.8)
Asthenia	1 (5.6)	1 (4.2)	1 (5.9)	3 (10.3)
Biliary dilatation	2 (11.1)	0	1 (5.9)	3 (10.3)
Constipation	0	1 (4.2)	2 (11.8)	3 (10.3)
Diabetes mellitus inadequate control	2 (11.1)	0	2 (11.8)	3 (10.3)
Fatigue	0	1 (4.2)	2 (11.8)	3 (10.3)
Gastroenteritis	1 (5.6)	1 (4.2)	1 (5.9)	3 (10.3)
Headache	0	1 (4.2)	2 (11.8)	3 (10.3)
Hypercholesterolaemia	1 (5.6)	1 (4.2)	1 (5.9)	3 (10.3)
Hypoglycaemia	1 (5.6)	0	3 (17.6)	3 (10.3)
Insulin-like growth factor increased	1 (5.6)	0	2 (11.8)	3 (10.3)
Osteoarthritis	1 (5.6)	1 (4.2)	1 (5.9)	3 (10.3)
Sinus bradycardia	1 (5.6)	1 (4.2)	1 (5.9)	3 (10.3)
Vertigo	0	2 (8.3)	1 (5.9)	3 (10.3)

Frequently reported adverse events (at least 10% of patients in any dose group) by preferred term and incident dose– carcinoid (Safety population)

Preferred term	Pasireotide LAR 20 mg N=8 n (%)	Pasireotide LAR 40 mg N=18 n (%)	Pasireotide LAR 60 mg N=20 n (%)	Pasireotide LAR any dose N=31 n (%)
Total	**8 (100)**	**15 (83.3)**	**19 (95.0)**	**29 (93.5)**
Abdominal pain	4 (50.0)	6 (33.3)	8 (40.0)	15 (48.4)
Diarrhoea	2 (25.0)	7 (38.9)	8 (40.0)	13 (41.9)
Fatigue	2 (25.0)	4 (22.2)	8 (40.0)	12 (38.7)
Flushing	3 (37.5)	4 (22.2)	9 (45.0)	12 (38.7)
Nausea	1 (12.5)	3 (16.7)	9 (45.0)	12 (38.7)
Back pain	0	4 (22.2)	7 (35.0)	10 (32.3)
Asthenia	1 (12.5)	3 (16.7)	5 (25.0)	9 (29.0)
Dyspnoea	2 (25.0)	4 (22.2)	6 (30.0)	9 (29.0)
Insomnia	2 (25.0)	1 (5.6)	6 (30.0)	9 (29.0)
Type 2 diabetes mellitus	0	5 (27.8)	4 (20.0)	9 (29.0)
Decreased appetite	1 (12.5)	3 (16.7)	6 (30.0)	8 (25.8)
Headache	1 (12.5)	2 (11.1)	6 (30.0)	7 (22.6)
Nasopharyngitis	0	2 (11.1)	5 (25.0)	7 (22.6)
Cough	2 (25.0)	2 (11.1)	2 (10.0)	6 (19.4)
Hyperglycaemia	1 (12.5)	3 (16.7)	3 (15.0)	6 (19.4)
Hypokalaemia	1 (12.5)	0	5 (25.0)	6 (19.4)
Oedema peripheral	1 (12.5)	3 (16.7)	3 (15.0)	6 (19.4)

Preferred term	Pasireotide LAR 20 mg N=8 n (%)	Pasireotide LAR 40 mg N=18 n (%)	Pasireotide LAR 60 mg N=20 n (%)	Pasireotide LAR any dose N=31 n (%)
Vomiting	0	2 (11.1)	6 (30.0)	6 (19.4)
Anaemia	0	2 (11.1)	3 (15.0)	5 (16.1)
Arthralgia	1 (12.5)	2 (11.1)	2 (10.0)	5 (16.1)
Cholelithiasis	0	3 (16.7)	2 (10.0)	5 (16.1)
Dehydration	2 (25.0)	0	3 (15.0)	5 (16.1)
Flatulence	1 (12.5)	2 (11.1)	2 (10.0)	5 (16.1)
Musculoskeletal pain	0	1 (5.6)	4 (20.0)	5 (16.1)
Palpitations	0	2 (11.1)	4 (20.0)	5 (16.1)
Constipation	0	1 (5.6)	3 (15.0)	4 (12.9)
Hypertension	0	1 (5.6)	3 (15.0)	4 (12.9)
Hypoglycaemia	1 (12.5)	0	3 (15.0)	4 (12.9)
Hypotension	0	0	4 (20.0)	4 (12.9)
Muscle spasms	1 (12.5)	2 (11.1)	1 (5.0)	4 (12.9)
Stomatitis	2 (25.0)	1 (5.6)	1 (5.0)	4 (12.9)
Upper respiratory tract infection	1 (12.5)	1 (5.6)	2 (10.0)	4 (12.9)
Urinary tract infection	1 (12.5)	1 (5.6)	3 (15.0)	4 (12.9)
Weight decreased	0	1 (5.6)	3 (15.0)	4 (12.9)

Serious Adverse Events and Deaths

Deaths, other serious AEs, AEs leading to discontinuation, and SAEs (Safety population)

	Pasireotide LAR 20 mg n (%)	Pasireotide LAR 40 mg n (%)	Pasireotide LAR 60 mg n (%)	Pasireotide LAR Any dose n (%)
Acromegaly	**18**	**24**	**17**	**29**
Deaths	0	0	0	0
Any SAEs and AEs leading to discontinuation	8 (44.4)	4 (16.7)	8 (47.1)	18 (62.1)
SAEs	5 (27.8)	4 (16.7)	7 (41.2)	15 (51.7)
Discontinued due to AEs	3 (16.7)	1 (4.2)	3 (17.6)	6 (20.7)
Carcinoid	**8**	**18**	**20**	**31**
Deaths	0	0	3 (15.0)	3 (9.7)
Any SAEs and AEs leading to discontinuation	2 (25.0)	5 (27.8)	13 (65.0)	20 (64.5)
SAEs	2 (25.0)	5 (27.8)	11 (55.0)	18 (58.1)
Discontinued due to AEs	0	2 (11.1)	5 (25.0)	7 (22.6)

Other Relevant Findings

Core phase: Pharmacokinetics

Pharmacokinetic parameters of pasireotide in patients with acromegaly following three monthly i.m. injections of 20, 40, or 60 mg pasireotide LAR

PK parameters	Pasireotide LAR 20 mg (N = 10)	Pasireotide LAR 40 mg (N = 12)	Pasireotide LAR 60 mg (N = 13)
Cmax, day 0-1,1st inj (ng/mL)	2.28 (3.48 ± 2.31)	3.90 (4.61 ± 4.04)	5.90 (6.28 ± 5.82)
Ctrough day28, 1st inj (ng/mL)	2.48 (2.99 ± 2.81)	6.42 (6.51 ± 2.78)	9.51 (9.46 ± 8.69)
Ctrough day28, 2nd inj (ng/mL)	4.16 (3.66 ± 1.77)	6.62 (7.66 ± 3.79)	11.7 (14.3 ± 12.0)
Ctrough day28, 3rd inj (ng/mL)	3.10 (3.77 ± 1.94)	7.12 (7.16 ± 3.13)	13.0 (13.3 ± 8.9)
Cmax,3rd inj (ng/mL)	4.67 (5.04 ± 2.00)	7.15 (8.03 ± 3.17)	14.6 (17.8 ± 8.9)
Cmin,3rd inj (ng/mL)	2.55 (2.74 ± 1.33)	5.11 (5.92 ± 2.85)	8.82 (8.87 ± 4.53)
Cavg, day 0-28,3rd inj (ng/mL)	4.07 (4.04 ± 1.62)	6.27 (6.94 ± 2.88)	11.0 (13.0 ± 5.82)
AUC day 0-28,3rd inj (hr.ng/mL)	2741 (2749 ± 1099)	4164 (4788 ± 1974)	7639 (8700 ± 3822)
FR3rd inj	1.71 (2.22 ± 1.56)	1.29 (1.41 ± 0.28)	1.80 (2.77 ± 2.14)
AR	1.04 (1.37 ± 1.23)	1.01 (1.06 ± 0.35)	0.977 (1.11 ± 0.74)

Pharmacokinetic parameters of pasireotide in patients with carcinoid disease following three monthly i.m. injections of 20, 40, or 60 mg pasireotide LAR: Core phase

PK parameters [a]	Pasireotide LAR 20 mg (N = 12)	Pasireotide LAR 40 mg (N = 14)	Pasireotide LAR 60 mg (N = 16)
Cmax, day 0-1,1st inj (ng/mL)	3.55 (4.50 ± 2.88)	5.39 (6.17 ± 4.08)	6.09 (6.99 ± 4.09)
Ctroughday28, 1st inj (ng/mL)	6.43 (6.31 ± 2.98)	8.56 (9.65 ± 5.89)	16.5 (18.7 ± 9.3)
Ctroughday28, 2nd inj (ng/mL)	5.74 (6.14 ± 2.47)	9.68 (11.7 ± 7.7)	24.4 (27.6 ± 14.6)
Ctroughday28, 3rd inj (ng/mL)	4.82 (5.55 ± 2.01)	12.0 (16.5 ± 10.2)	19.7 (25.0 ± 20.5)
Cmax,3rd inj (ng/mL)	8.18 (8.83 ± 4.06)	13.9 (18.4 ± 10.2)	31.9 (34.4 ± 20.2)
Cmin,3rd inj (ng/mL)	4.01 (4.37 ± 1.78)	7.90 (9.29 ± 5.52)	15.1 (19.6 ± 12.0)
Cavg, day 0-28,3rd inj (ng/mL)	6.11 (6.62 ± 2.78)	10.3 (12.5 ± 6.4)	20.7 (25.6 ± 15.4)
AUCday 0-28,3rd inj (hr.ng/mL)	4174 (4494 ± 1893)	7712 (11349 ± 9460)	16543 (17476 ± 10554)
FR3rd inj	1.98 (2.07 ± 0.61)	1.85 (2.21 ± 1.07)	1.57 (1.86 ± 0.74)
AR	0.998 (1.05 ± 0.57)	1.08 (1.68 ± 1.14)	0.801 (0.896 ± 0.423)

Extension phase: Safety

Newly occurring or worsening CTC grade 3 or 4 biochemistry abnormalities by incident dose– acromegaly (Safety population)

	Worsening from baseline to grade	Pasireotide LAR 20 mg N=18		Pasireotide LAR 40 mg N=24		Pasireotide LAR 60 mg N=17		Pasireotide LAR any dose N=29	
		Total	n (%)	Total	n (%)	Total	n (%)	Total	n (%)
Albumin (hypo)	Grade 3	17	0	24	0	17	0	29	0

	Worsening from baseline to grade	Pasireotide LAR 20 mg N=18		Pasireotide LAR 40 mg N=24		Pasireotide LAR 60 mg N=17		Pasireotide LAR any dose N=29	
		Total	n (%)	Total	n (%)	Total	n (%)	Total	n (%)
	Grade 4	17	0	24	0	17	0	29	0
Alkaline phosphatase	Grade 3	17	0	24	0	17	0	29	0
	Grade 4	17	0	24	0	17	0	29	0
Amylase	Grade 3	17	1 (5.9)	24	0	17	0	29	1 (3.4)
	Grade 4	17	0	24	0	17	0	29	0
CPK	Grade 3	17	0	24	0	17	0	29	0
	Grade 4	17	0	24	0	17	0	29	0
Calcium (hyper)	Grade 3	17	0	24	0	17	0	29	0
	Grade 4	17	0	24	0	17	0	29	0
Calcium (hypo)	Grade 3	17	0	24	0	17	0	29	0
	Grade 4	17	0	24	0	17	0	29	0
Cholesterol	Grade 3	17	0	24	0	17	0	29	0
	Grade 4	17	0	24	0	17	0	29	0
Creatinine	Grade 3	17	0	24	0	17	0	29	0
	Grade 4	17	0	24	0	17	0	29	0
GGT	Grade 3	17	1 (5.9)	24	0	17	0	29	1 (3.4)
	Grade 4	17	0	24	0	17	0	29	0
Glucose (hyper)	Grade 3	18	3 (16.7)	24	3 (12.5)	17	2 (11.8)	29	5 (17.2)
	Grade 4	18	0	24	0	17	1 (5.9)	29	1 (3.4)
Glucose (hypo)	Grade 3	18	0	24	1 (4.2)	17	0	29	1 (3.4)
	Grade 4	18	0	24	0	17	0	29	0
Inorganic phosphorus	Grade 3	17	0	24	0	17	0	29	0
	Grade 4	17	0	24	0	17	0	29	0
Lipase	Grade 3	17	1 (5.9)	24	0	17	2 (11.8)	29	3 (10.3)
	Grade 4	17	0	24	0	17	0	29	0
Potassium (hyper)	Grade 3	17	0	24	0	17	0	29	0
	Grade 4	17	0	24	0	17	0	29	0
Potassium (hypo)	Grade 3	17	0	24	0	17	0	29	0
	Grade 4	17	0	24	0	17	0	29	0
AST	Grade 3	17	0	24	0	17	0	29	0
	Grade 4	17	0	24	0	17	0	29	0
ALT	Grade 3	17	0	24	0	17	0	29	0
	Grade 4	17	0	24	0	17	0	29	0
Sodium (hyper)	Grade 3	17	0	24	0	17	0	29	0
	Grade 4	17	0	24	0	17	0	29	0
Sodium (hypo)	Grade 3	17	0	24	0	17	0	29	0
	Grade 4	17	0	24	0	17	0	29	0

	Worsening from baseline to grade	Pasireotide LAR 20 mg N=18		Pasireotide LAR 40 mg N=24		Pasireotide LAR 60 mg N=17		Pasireotide LAR any dose N=29	
		Total	n (%)	Total	n (%)	Total	n (%)	Total	n (%)
Total bilirubin	Grade 3	17	0	24	0	17	0	29	0
	Grade 4	17	0	24	0	17	0	29	0
Triglycerides	Grade 3	17	0	24	0	17	0	29	0
	Grade 4	17	0	24	0	17	0	29	0

GGT = gamma-glutamyltransferase, ALT = alanine aminotransferase, AST = aspartate aminotransferase, CPK = Creatine phosphokinase

Patients with a new or worsened abnormality are summarized according to the dose taken prior to the visit at which the new or worsened abnormality was recorded.

N = Total number of patients having ever received the specific dose level.

Total = Number of patients having evaluable pot-baseline for that dose level who had less than grade x at baseline. It is the denominator for the percentages.

n = the number of patients who had less than grade x at core baseline, and worsened to grade x post-baseline.

Patients are counted only for the worst grade observed at that dose.

Patients with missing core baseline values are excluded.

Newly occurring or worsening CTC grade 3 or 4 biochemistry abnormalities by incident dose – carcinoid (Safety population)

	Worsening from baseline to grade	Pasireotide LAR 20 mg N=8		Pasireotide LAR 40 mg N=18		Pasireotide LAR 60 mg N=20		Pasireotide LAR any dose N=31	
		Total	n (%)	Total	n (%)	Total	n (%)	Total	n (%)
Albumin (hypo)	Grade 3	8	0	18	0	20	0	31	0
	Grade 4	8	0	18	0	20	0	31	0
Alkaline phosphatase	Grade 3	8	0	18	0	19	0	30	0
	Grade 4	8	0	18	0	20	0	31	0
Amylase	Grade 3	8	0	17	0	19	0	30	0
	Grade 4	8	0	17	0	19	0	30	0
CPK	Grade 3	8	1 (12.5)	18	0	20	0	31	1 (3.2)
	Grade 4	8	0	18	0	20	0	31	0
Calcium (hyper)	Grade 3	8	0	18	0	20	0	31	0
	Grade 4	8	0	18	0	20	0	31	0
Calcium (hypo)	Grade 3	8	0	18	0	20	0	31	0
	Grade 4	8	0	18	0	20	1 (5.0)	31	1 (3.2)
Cholesterol	Grade 3	7	0	16	0	20	0	30	0
	Grade 4	7	0	16	0	20	0	30	0
Creatinine	Grade 3	8	0	18	0	20	0	31	0
	Grade 4	8	0	18	0	20	0	31	0
GGT	Grade 3	8	1 (12.5)	18	3 (16.7)	18	1 (5.6)	29	4 (13.8)
	Grade 4	8	0	18	0	20	1 (5.0)	31	1 (3.2)
Glucose (hyper)	Grade 3	8	2	18	4	20	7	31	11

	Worsening from baseline to grade	Pasireotide LAR 20 mg N=8		Pasireotide LAR 40 mg N=18		Pasireotide LAR 60 mg N=20		Pasireotide LAR any dose N=31	
		Total	n (%)	Total	n (%)	Total	n (%)	Total	n (%)
			(25.0)		(22.2)		(35.0)		(35.5)
	Grade 4	8	0	18	1 (5.6)	20	0	31	1 (3.2)
Glucose (hypo)	Grade 3	8	0	18	0	20	0	31	0
	Grade 4	8	0	18	0	20	0	31	0
Inorganic phosphorus	Grade 3	8	0	18	0	20	2 (10.0)	31	2 (6.5)
	Grade 4	8	0	18	0	20	0	31	0
Lipase	Grade 3	8	1 (12.5)	17	1 (5.9)	20	0	31	2 (6.5)
	Grade 4	8	0	17	0	20	0	31	0
Potassium (hyper)	Grade 3	8	0	18	0	20	0	31	0
	Grade 4	8	0	18	0	20	0	31	0
Potassium (hypo)	Grade 3	8	1 (12.5)	18	0	19	1 (5.3)	30	2 (6.7)
	Grade 4	8	0	18	1 (5.6)	20	0	31	1 (3.2)
AST	Grade 3	8	0	18	0	20	0	31	0
	Grade 4	8	0	18	0	20	0	31	0
ALT	Grade 3	8	0	18	0	20	0	31	0
	Grade 4	8	0	18	0	20	0	31	0
Sodium (hyper)	Grade 3	8	0	18	0	20	0	31	0
	Grade 4	8	0	18	0	20	0	31	0
Sodium (hypo)	Grade 3	8	0	18	1 (5.6)	19	0	30	1 (3.3)
	Grade 4	8	0	18	0	20	0	31	0
Total bilirubin	Grade 3	8	0	18	0	20	2 (10.0)	31	2 (6.5)
	Grade 4	8	0	18	0	20	0	31	0
Triglycerides	Grade 3	8	0	17	1 (5.9)	20	0	31	1 (3.2)
	Grade 4	8	0	17	0	20	0	31	0

GGT = gamma-glutamyltransferase, ALT = alanine aminotransferase, AST = aspartate aminotransferase, CPK = Creatine phosphokinase

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n = the number of patients who had less than grade x at core baseline, and worsened to grade x post-baseline.

Patients are counted only for the worst grade observed at that dose.

Patients with missing core baseline values are excluded.

Conclusion:

- A steady state of pasireotide concentration appeared to be achieved following three monthly i.m. injections of pasireotide LAR in patients with acromegaly or carcinoid

disease. PK exposures were approximately dose proportional in patients with acromegaly and appeared to be over dose proportional in patients with carcinoid disease. The drug accumulation after repeated dosing was minimal.

- Patients with acromegaly had similar exposures as healthy volunteers [CSOM230C2101], while patients with carcinoid had approximately 2-fold PK exposures of those in healthy volunteers.
- Reduction effect of pasireotide LAR on levels of GH, IGF-1 and free IGF-1 were well maintained over three-month treatment period for all three dose groups.
- Pasireotide LAR was safe and tolerable in both indications studied. Although increases in blood glucose were seen during the first months of treatment, improvements were noted with longer follow-up, indicating that the hyperglycemia was manageable. An increase in the incidence of biliary-related AEs and gallbladder findings was evident with long term treatment, but was generally manageable; no patient discontinued due to such an event.
- In patients with acromegaly, pasireotide LAR induced rapid reduction in GH and IGF-1 levels and improvement in disease symptoms that was sustained with long term treatment. For patients with carcinoid disease, no relevant conclusions can be drawn based on the results of this study regarding efficacy due to limited amount of PD data.

Date of Clinical Trial Report

27-Aug-2014

Date of Initial Inclusion on Novartis Clinical Trial Results website

5-Nov-2014

Date of Latest Update

18-Dec-2014

Reason for Update

Added clarification to the Study Design/Methodology section (last paragraph) for better understanding of the results.