Sponsor

Novartis

Generic Drug Name

Pasireotide

Therapeutic Area of Trial

Hepatic impairment

Approved Indication

Treatment of patients with Cushing's disease for whom medical therapy is appropriate

Protocol Number

CSOM230B2114

Title

A phase I, open-label, multi-center, single dose study to evaluate the pharmacokinetics and safety of subcutaneous pasireotide (SOM230) in subjects with varying degrees of hepatic function

Study Phase

Phase I.

Study Start/End Dates

07-Jul-2008 to 27-May-2009

Study Design/Methodology

This was a phase-I, open-label, multicenter, single dose study to evaluate the pharmacokinetics and safety of pasireotide s.c. injection in adult subjects with varying degrees of hepatic function according to the Child-Pugh classification. All subjects received one single s.c. injection of 600 µg pasireotide. Subjects were stratified by hepatic function (normal function and mild, moderate, and severe dysfunction) according to the Child-Pugh classification as determined at the screening visit between study day -1 and study day 1 (before study drug injection). The assignment of a subject to a particular hepatic function group was performed by the institution.

On study day -1, fasting blood glucose, insulin, and glucagon were assessed over a period of 4 hours. Blood pressure and pulse rate were also measured. On study day 1, the subject received a single dose of 600 µg pasireotide. During the observation period on study days 2, 3, 4, and 5, subjects underwent pharmacokinetic (PK) sampling and laboratory evaluations, including urinalysis, body temperature, blood pressure, and pulse rate assessments. ECG was performed 24 hours after the pasireotide dose on study day 2. On study day 5, fasting blood glucose, insulin, and glucagon were assessed over a period of 4 hours. Blood pressure and pulse rate were also measured. No food was permitted before the 4- hour sample at which time a standardized lunch was given. A study completion evaluation was performed on study day 6 or at time of

discontinuation if the subject discontinued the study prior to study day 6. On the morning of study day 6, blood samples were taken for PK analysis.

In addition, safety assessments were performed for vital signs, physical examination, ECG, gallbladder ultrasound, laboratory evaluation (hematology, blood chemistry, coagulation, urinalysis, thyroid tests, and fasting blood glucose, insulin and glucagon). All subjects were followed up with a telephone call 28 days after the dosing was completed in order to record and assess the occurrence of Serious Adverse Events (SAEs) since discharge from the unit. The investigator had to instruct the subject to notify the study site in case of SAEs during this follow-up period.

Centers

4 centers in 4 countries: Belgium (1), Germany (1), South Africa (1), USA (1)

Publication

None

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

Pasireotide was supplied in as 1-mL ampoule contained 0.6 mg of pasireotide in 1 mL of solution. One single dose of the study drug pasireotide solution 600 µg was used for s.c. injection.

Statistical Methods

For analysis of AUC_{inf}, AUC_{last}, C_{max}, and CL/F, an ANOVA model was run with and without baseline covariates, of which age and BMI were finally retained. For all PK parameters except T_{max}, summary statistics including n, arithmetic mean, SD, CV%, geometric mean, geometric CV%, median, minimum and maximum are presented by cohort. For T_{max}, a non-parametric analysis (Hodges-Lehmann) was performed to estimate the median differences (between the control group and the 3 respective hepatic impairment cohorts), and the median and confidence intervals are presented. Listings of individual PK parameters were based on the FAS. No missing pharmacokinetic parameter data were imputed.

For fasting glucose, insulin and glucagon, the percent change of the peak level from Visit 1 was calculated for each subject. The peak level and change from Visit 1 were summarized by cohort and visit using the safety set and listed using the FAS. The AUC of fasting blood glucose, insulin and glucagon were calculated for each subject based on the assessments of the 6 scheduled time points (-1 min pre-dose, 0.5 hour, 1 hour, 2 hours, 3 hours, 4 hours post-dose) using Linear trapezoidal rule, and were summarized by cohort and visit (Visit 1, Visit 2, and Visit 6) using the safety dataset. Frequency and shift tables were also provided for fasting blood glucose peak level over 4 hours at Visit 1, Visit 2 and Visit 6 based on the ADA classification: <100 mg/dL normal, 100-126< mg/dL impaired fasting glucose, ≥126 mg/dL fasting glucose. Frequency and shift tables for fasting blood insulin and glucagon over 4 hours at Visits 1, 2, and 6 were based on laboratory normal ranges. Detection of gallstones, sludge, or dilatation of the intra-or extra-hepatic ductal system is summarized. Free T4 and TSH, all vital sign and ECG parameters were also summarized. A frequency table is provided to show the number of subjects with newly occurring notable ECG abnormalities.

In addition, the final ANOVA model (included selected demographic covariates) was rerun to take into account baseline albumin level as a covariate.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion Criteria

Subjects were included if they met the following inclusion criteria:

Common inclusion criteria for all subjects:

- Male or female subjects between 18 and 75 years of age.
- Vital signs at screening and baseline (after 3 minutes resting, measured in the supine position) were within the following ranges:
  - body temperature measured with an oral thermometer between 35.0-37.5°C;
  - systolic blood pressure, 90-160 mm Hg (for HVs younger than 65 years old, 90-150 mm Hg, i.e. HVs younger than 65 years old with systolic blood pressure between 150-160 mm Hg are excluded);
  - diastolic blood pressure, cohort 1: 50-90 mm Hg; cohorts 2-4: 50-95 mm Hg;
  - pulse rate, 40-100 bpm.
- Subjects must have a BMI between 20 kg/m^2 and 30 kg/m^2 and weigh at least 50 kg and no more than 120 kg.
- Subjects must be willing to comply with dietary, fluid, and lifestyle restrictions (from day -1 to study completion).
- Subjects with a known history of impaired fasting blood glucose or diabetes mellitus may be included, however blood glucose and antidiabetic treatment must be monitored closely throughout the study and adjusted as necessary.
- Subjects for whom written informed consent to participate in the study has been obtained prior to starting any screening examinations.
- Subjects must be able to communicate well with the investigator and comply with the requirements of the study.

Inclusion criteria for cohort 2-4:

- Subjects with confirmed cirrhosis by at least one of the following criteria:
  - Histologically by prior liver biopsy showing cirrhosis;
  - Clinically by physical examination (e.g., liver firmness to palpation, splenic enlargement, spider angioma, palmar erythema, parotid hypertrophy, testicular atrophy, ascites, presence of asterixis or gynecomastia), and/or laboratory data, and/or liver imaging (CT, and/or ultrasound and/or MRI scans), and/or endoscopic findings.
- Child-Pugh Clinical Assessment Score consistent with degree of hepatic impairment.

Inclusion criteria for cohort 1:

- Generally healthy subjects as determined by past medical history, physical examination, vital signs, electrocardiogram, and standard laboratory tests at screening.

Exclusion Criteria

Subjects were excluded if they met the following exclusion criteria:

Common exclusion criteria for all subjects:

- Donation or loss of 400 mL or more of blood within 8 weeks prior to dosing.
- Subjects with additional active malignant disease within the last five years (with the exception of non-melanoma skin cancers that were not metastatic and have been treated curatively).
- Subjects who have any current or prior medical condition that may interfere with the conduct of the study or the evaluation of its results in the opinion of the Investigator or the Sponsor's Medical Monitor.
- Subjects with abnormal clinical laboratory values (except the clinical laboratory values linked to hepatic dysfunction and calcium, magnesium, potassium and sodium; however, subjects with ascites must be excluded if sodium < 130 mmol/L and/or potassium ≥ 5.6 mmol/L) considered by the Sponsor's Medical Monitor to be clinically significant and which could affect the interpretation of the study results.
- History of autonomic dysfunction.
- History of acute or chronic bronchospastic disease (including asthma and chronic obstructive pulmonary disease, treated or not treated) disease requiring therapy within the last three months prior to dosing.
- Subjects who have undergone major surgery/surgical therapy for any cause within four weeks prior to dosing.
- Any surgical or medical condition that may interfere with the conduct of the study, may jeopardize the subject in case of participation in the study or may significantly alter the absorption, distribution, metabolism or excretion of drugs. The investigator should be guided by evidence of any of the following:
    - history of inflammatory bowel syndrome, gastritis, ulcers, gastrointestinal or rectal bleeding within three months prior to dosing;
    - history of pancreatic injury or pancreatitis; indications of impaired pancreatic function/injury as indicated by abnormal lipase or amylase;
    - history of major gastrointestinal tract surgery such as gastrectomy, gastroenterostomy, or bowel resection except appendectomy;
    - evidence of urinary obstruction or difficulty in voiding at screening.
- Subjects who are not biochemically euthyroid.
- Subjects with symptomatic cholelithiasis.
- History of myocardial infarction, atherosclerosis or other clinically significant heart disease (e.g., uncontrolled hypertension, history of labile hypertension) or history of clinically significant ECG abnormalities or congestive heart failure (NYHA Class III or IV) or angina pectoris.
- Subjects with risk factors for torsades de pointes, i.e. volunteers with a baseline QTc > 480 ms, or history/ family history of long QT syndrome and taking concomitant medications known to prolong QT interval.

- History of immunocompromise, including a positive HIV test result (ELISA and Western blot). A HIV test will not be required; however, previous medical history will be reviewed.
- Female subjects who are pregnant (positive pregnancy test at screening or at baseline) or lactating, or are of childbearing potential and not practicing a medically acceptable method of birth control. Female subjects must use barrier contraception with condoms. If oral contraception is used in addition to condoms, the subject must have been practicing this method for at least two months prior to enrollment and must agree to continue the oral contraceptive throughout the course of the study, and for one month after the study has ended. Male subjects who are sexually active are required to use condoms during the study and for four weeks afterwards as a precautionary measure.
- History of clinically significant drug allergy; history of atopic allergy (asthma, urticaria, eczematous dermatitis) and or a known hypersensitivity to somatostatin analogues or any component of the pasireotide s.c. formulation.
- Participation in any clinical investigation with an investigational drug within four weeks prior to dosing; prior treatment with pasireotide.
- Consumption of grapefruit, Seville orange, grapefruit juice, star fruit, star fruit juice, or caffeinated beverages within 72 hours of dosing.
- Subjects with a history of non-compliance to medical regimens or who are considered potentially unreliable or will be unable to complete the entire study.
- Subjects with known ongoing alcohol and/or drug abuse within four weeks prior to dosing.
- Vulnerable subjects (e.g. kept in detention, handicapped persons etc.).

Exclusion criteria for cohort 2-4:

- Symptoms or history of encephalopathy (Stage III or worse) within 3 months prior to dosing.
- Hgb <9 g/dL, polymorphonuclear leukocytes <1000/µL, WBC <2,500/µL and platelets <25,000/µL at inclusion (these assessments have to be stable within the last 3 months).
- History or presence of impaired renal function; or in the absence of intrinsic renal disease, creatinine clearance <50 mL/min and/or BUN values and/or abnormal urinary constituents (e.g., albuminuria) and/or serum creatinine >1.5 mg/dL.
- Clinical evidence of severe ascites.
- International normalized ratio (INR) >3.
- Any evidence of progressive liver disease (within the last four weeks prior to dosing).
- Total bilirubin >6 mg/dL.

Exclusion criteria for cohort 1:

- Clinical evidence of liver disease or liver injury as indicated by abnormal liver function tests: AST and ALT will have to be within the normal range before inclusion, GGT <2 x ULN; alkaline phosphatase <2 x ULN, and serum bilirubin <27 µmol/L (1.6 mg/dL).
- Significant illness within four weeks prior to dosing.
- Use of any prescription drug or over-the-counter (OTC) medication within 14 days prior to dosing with the exception of paracetamol (acetaminophen) up to 2g per day.
- Hgb <10 g/dL, polymorphonuclear leukocytes <1500/µL, WBC <3,000/µL and/or platelets

<100,000/µL at inclusion.

- History or presence of impaired renal function as indicated by abnormal creatinine (creatinine clearance <80 mL/min), and/or BUN values, and/or abnormal urinary constituents (e.g., albuminuria), and/or serum creatinine ≥ 1.8 mg/dL.
- A positive Hepatitis B surface antigen (HBsAg) or Hepatitis C test result (antibody positive subjects will be allowed if non-viremic).

Participant Flow

Number of Subjects

	Normal (N = 15) n (%)	Mild (N = 6) n (%)	Moderate (N = 7) n (%)	Severe (N = 6) n (%)	All subjects (N = 34) n (%)
Enrolled	15 (100.0%)	6 (100.0%)	7 (100.0%)	6 (100.0%)	34 (100.0%)
Completed	15 (100.0%)	6 (100.0%)	7 (100.0%)	6 (100.0%)	34 (100.0%)
Discontinued	0	0	0	0	0

Baseline Characteristics

Demographic summary by varying degrees of hepatic function (FAS)

Demographic Variable	Normal (N = 15)	Mild (N = 6)	Moderate (N = 7)	Severe (N = 6)	All Subjects (N = 34)
Age (years)					
n	15	6	7	6	34
Mean	51.8	56.0	63.0	53.3	55.1
SD	8.44	10.49	6.06	5.54	8.78
Median	52.0	55.5	64.0	53.5	55.5
Min	38	44	54	45	38
Max	64	68	69	61	69
Sex					
Male	12 (80.0%)	6 (100.0%)	6 (85.7%)	4 (66.7%)	28 (82.4%)
Female	3 (20.0%)	0	1 (14.3%)	2 (33.3%)	6 (17.6%)
Race					
Black	0	0	2 (28.6%)	0	2 (5.9%)
Caucasian	13 (86.7%)	6 (100.0%)	5 (71.4%)	4 (66.7%)	28 (82.4%)
Other	2 (13.3%)	0	0	2 (33.3%)	4 (11.8%)
Weight (kg)					
n	15	6	7	6	34
Mean	76.7	84.8	79.4	82.7	79.8
SD	8.14	9.53	11.16	17.28	10.96

Median	79.6	86.3	84.6	82.1	81.0
Min	55	71	61	52	52
Max	85	98	91	100	100
Height (cm)					
n	15	6	7	6	34
Mean	172.9	179.2	173.3	174.3	174.3
SD	8.64	8.16	8.42	9.79	8.64
Median	175.0	180.0	172.0	175.5	175.0
Min	151	166	165	159	151
Max	186	191	191	185	191
BMI (kg/m^2)					
n	15	6	7	6	34
Mean	25.7	26.5	26.4	26.9	26.2
SD	1.98	2.77	3.08	3.32	2.54
Median	25.4	27.2	26.5	27.9	26.2
Min	21	21	22	21	21
Max	31	29	30	30	31

BMI (kg/m^2) = weight (kg) / height (m)^2

Outcome measures

Primary Outcome Result(s)

Summary of pasireotide PK parameters by cohort (PK set)

PK Parameter (unit)	Normal (N = 12)	Mild (N = 6)	Moderate (N = 7)	Severe (N = 6)
AUC_{inf} (ng.hr/mL)	88.9 (33.8)	100.0 (24.8)	138.9 (31.3)	125.9 (41.5)
AUC_{last} (ng.hr/mL)	83.2 (33.4)	91.9 (28.9)	120.2 (32.1)	116.3 (40.0)
C_{max} (ng/mL)	11.4 (48.4)	11.8 (29.2)	16.6 (42.4)	15.2 (46.1)
T_{max} (hr)	0.76 (0.25 - 2.00)	1.00 (0.50 - 2.00)	0.67 (0.47 - 2.00)	1.00 (0.50 - 1.00)
$T_{1/2}$ (hr)	15.4 (71.7)	22.1 (42.8)	36.4 (73.4)	29.1 (74.3)
CL/F (L/hr)	6.7 (33.7)	6.0 (24.8)	4.3 (31.4)	4.8 (41.4)
V_z/F (L)	149.6 (54.8)	191.3 (24.7)	226.3 (49.0)	199.8 (42.5)
λ_Z (1/hr)	0.045 (71.7)	0.031 (42.6)	0.019 (73.6)	0.024 (74.4)

Values are median (range) for T_{max}, and geometric mean (CV%) for all other PK parameters.

Summary of statistical analysis of key PK parameters for pasireotide (PK set)

PK Parameter	Cohort	n *	Non age-	Comparison (s)	Comparison

(unit)			and BMI-adjusted Geo-mean		Geo-mean Ratio	Lower	Upper
	Control	12	88.9				
	Mild	6	100.0	Mild : Control	1.12	0.85	1.48
	Moderate	6	138.9	Moderate : Control	1.56	1.18	2.06
AUC_{inf} (ng.hr/mL)	Severe	6	125.9	Severe : Control	1.42	1.07	1.87
	Control	12	83.2				
	Mild	6	91.9	Mild : Control	1.10	0.84	1.46
	Moderate	7	120.2	Moderate : Control	1.44	1.11	1.88
AUC_{last} (ng.hr/mL)	Severe	6	116.3	Severe : Control	1.40	1.06	1.85
	Control	12	11.4				
	Mild	6	11.8	Mild : Control	1.03	0.72	1.47
	Moderate	7	16.6	Moderate : Control	1.46	1.04	2.04
C_{max} (ng/mL)	Severe	6	15.2	Severe : Control	1.33	0.94	1.90
	Control	12	6.7				
	Mild	6	6.0	Mild : Control	0.89	0.67	1.17
	Moderate	6	4.3	Moderate : Control	0.64	0.49	0.85
CL/F (L/hr)	Severe	6	4.8	Severe : Control	0.71	0.54	0.93
	Control	12	0.76				
	Mild	6	1.00	Mild : Control	0.26	0.00	1.00
	Moderate	7	0.67	Moderate : Control	0.00	-0.33	0.48
T_{max} (hr)	Severe	6	1.00	Severe : Control	0.00	-0.02	0.50

n* = number of subjects with non-missing values

Control is the hepatic function normal cohort

PK parameters were analyzed separately on the log scale by means of an ANOVA model including cohort as a fixed effect

For T_{max}, median is presented under 'Adjusted Geo-mean', Hodges Lehmann estimate for the difference between the hepatic impairment cohort and the control cohort under "Geo-mean ratio", and the corresponding 90% distribution free CI under "Lower" and "Upper".

Summary of statistical analysis of key PK parameters for pasireotide with age and BMI as covariates (PK set)

PK Parameter (unit)	Cohort	n *	Age- and BMI-adjusted Geo-mean	Comparison (s)	Comparison		
						90 % CI	
					Geo-mean Ratio	Lower	Upper
AUC_{inf}	Control	12	95.6				
(ng.hr/mL)	Mild	6	97.6	Mild : Control	1.02	0.79	1.32

	Moderate	6	117.6	Moderate : Control	1.23	0.92	1.65
	Severe	6	131.9	Severe : Control	1.38	1.07	1.78
	Control	12	88.3				
	Mild	6	90.3	Mild : Control	1.02	0.78	1.34
	Moderate	7	105.8	Moderate : Control	1.20	0.89	1.61
AUC_{last} (ng.hr/mL)	Severe	6	121.7	Severe : Control	1.38	1.06	1.79
	Control	12	11.5				
	Mild	6	11.7	Mild : Control	1.02	0.72	1.46
	Moderate	7	15.9	Moderate : Control	1.39	0.94	2.05
C_{max} (ng/mL)	Severe	6	15.8	Severe : Control	1.38	0.98	1.94
	Control	12	6.3				
	Mild	6	6.2	Mild : Control	0.98	0.76	1.27
	Moderate	6	5.1	Moderate : Control	0.81	0.61	1.09
CL/F (L/hr)	Severe	6	4.5	Severe : Control	0.73	0.56	0.93
	Control	12	0.76				
	Mild	6	1.00	Mild : Control	0.26	0.00	1.00
	Moderate	7	0.67	Moderate : Control	0.00	-0.33	0.48
T_{max} (hr)	Severe	6	1.00	Severe : Control	0.00	-0.02	0.50

n* = number of subjects with non-missing values

Control is the hepatic function normal cohort

PK parameters were analyzed separately on the log scale by means of an ANOVA model including cohort as a fixed effect, and age and BMI as covariates

For T_{max}, median is presented under 'Adjusted Geo-mean', Hodges Lehmann estimate for the difference between the hepatic impairment cohort and the control cohort under "Geo-mean ratio", and the corresponding 90% distribution free CI under "Lower" and "Upper".

Mean fold changes in PK parameters in subjects with mild, moderate, and severe hepatic impairment vs. subjects with normal hepatic function as per Child-Pugh classification*

Hepatic impairment	PK Parameter			
	AUC_{inf}	**AUC_{last}**	**C_{max}**	**CL/F**
Mild	1.08	1.07	1.07	0.93
Moderate	1.60	1.43	1.67	0.63
Severe	1.79	1.67	1.69	0.56

*Analysis based on ANOVA model with age, BMI and baseline albumin as covariates.

Secondary Outcome Result(s)

Frequent adverse events, regardless of study drug relationship, by primary system organ class, preferred term, maximum grade and cohort (preferred term in at least 5% in all subjects) (Safety set)

Primary system organ class Preferred term Maximum grade	Normal (N = 15) n (%)	Mild (N = 6) n (%)	Moderate (N = 7) n (%)	Severe (N = 6) n (%)	All subjects (N = 34) n (%)
Any primary system organ class	12 (80.0%)	4 (66.7%)	4 (57.1%)	4 (66.7%)	24 (70.6%)
Grade 1	9 (60.0%)	2 (33.3%)	4 (57.1%)	2 (33.3%)	17 (50.0%)
Grade 2	3 (20.0%)	2 (33.3%)	0	0	5 (14.7%)
Grade 3	0	0	0	1 (16.7%)	1 (2.9%)
Grade 4	0	0	0	1 (16.7%)	1 (2.9%)
Metabolism and nutrition disorders	5 (33.3%)	2 (33.3%)	3 (42.9%)	3 (50.0%)	13 (38.2%)
Grade 1	3 (20.0%)	1 (16.7%)	3 (42.9%)	3 (50.0%)	10 (29.4%)
Grade 2	2 (13.3%)	1 (16.7%)	0	0	3 (8.8%)
Hyperglycemia	5 (33.3%)	2 (33.3%)	3 (42.9%)	3 (50.0%)	13 (38.2%)
Grade 1	3 (20.0%)	1 (16.7%)	3 (42.9%)	3 (50.0%)	10 (29.4%)
Grade 2	2 (13.3%)	1 (16.7%)	0	0	3 (8.8%)
Gastrointestinal disorders	7 (46.7%)	4 (66.7%)	1 (14.3%)	0	12 (35.3%)
Grade 1	6 (40.0%)	2 (33.3%)	1 (14.3%)	0	9 (26.5%)
Grade 2	1 (6.7%)	2 (33.3%)	0	0	3 (8.8%)
Nausea	4 (26.7%)	2 (33.3%)	0	0	6 (17.6%)
Grade 1	3 (20.0%)	1 (16.7%)	0	0	4 (11.8%)
Grade 2	1 (6.7%)	1 (16.7%)	0	0	2 (5.9%)
Diarrhea	1 (6.7%)	2 (33.3%)	0	0	3 (8.8%)
Grade 1	1 (6.7%)	2 (33.3%)	0	0	3 (8.8%)
Abdominal pain	1 (6.7%)	1 (16.7%)	0	0	2 (5.9%)

Grade 1	1 (6.7%)	1 (16.7%)	0	0	2 (5.9%)
General disorders and administration site conditions	4 (26.7%)	2 (33.3%)	2 (28.6%)	1 (16.7%)	9 (26.5%)
Grade 1	4 (26.7%)	2 (33.3%)	2 (28.6%)	1 (16.7%)	9 (26.5%)
Injection site erythema	2 (13.3%)	0	1 (14.3%)	1 (16.7%)	4 (11.8%)
Grade 1	2 (13.3%)	0	1 (14.3%)	1 (16.7%)	4 (11.8%)
Fatigue	1 (6.7%)	2 (33.3%)	0	0	3 (8.8%)
Grade 1	1 (6.7%)	2 (33.3%)	0	0	3 (8.8%)
Injection site pruritus	0	1 (16.7%)	1 (14.3%)	0	2 (5.9%)
Grade 1	0	1 (16.7%)	1 (14.3%)	0	2 (5.9%)
Vascular disorders	4 (26.7%)	1 (16.7%)	0	1 (16.7%)	6 (17.6%)
Grade 1	3 (20.0%)	1 (16.7%)	0	1 (16.7%)	5 (14.7%)
Grade 2	1 (6.7%)	0	0	0	1 (2.9%)
Hypotension	2 (13.3%)	1 (16.7%)	0	0	3 (8.8%)
Grade 1	1 (6.7%)	1 (16.7%)	0	0	2 (5.9%)
Grade 2	1 (6.7%)	0	0	0	1 (2.9%)
Flushing	1 (6.7%)	0	0	1 (16.7%)	2 (5.9%)
Grade 1	1 (6.7%)	0	0	1 (16.7%)	2 (5.9%)
Nervous system disorders	3 (20.0%)	0	1 (14.3%)	1 (16.7%)	5 (14.7%)
Grade 1	3 (20.0%)	0	1 (14.3%)	0	4 (11.8%)
Grade 4	0	0	0	1 (16.7%)	1 (2.9%)
Headache	3 (20.0%)	0	0	0	3 (8.8%)
Grade 1	3 (20.0%)	0	0	0	3 (8.8%)
Ear and labyrinth disorders	2 (13.3%)	1 (16.7%)	0	0	3 (8.8%)
Grade 1	2 (13.3%)	1 (16.7%)	0	0	3 (8.8%)
Vertigo	2 (13.3%)	1 (16.7%)	0	0	3 (8.8%)

Grade 1	2 (13.3%)	1 (16.7%)	0	0	3 (8.8%)

Primary system organ classes are presented by descending order of frequency; preferred terms are sorted within primary system organ class alphabetically.

A subject with multiple occurrences of an AE under one cohort is counted only once in the AE category for that cohort.

A subject with multiple severity ratings for an AE while on a cohort, is only counted under the maximum rating.

A subject with multiple adverse events within a primary system organ class is counted only once in the total row.

Adverse events, suspected to be study drug related, by primary system organ class, preferred term, maximum severity and cohort (preferred term occurring in at least 5% of all subjects) (Safety set)

Primary system organ class Preferred term Maximum severity	Normal (N = 15) n (%)	Mild (N = 6) n (%)	Moderate (N = 7) n (%)	Severe (N = 6) n (%)	All subjects (N = 34) n (%)
Any primary system organ class	12 (80.0%)	4 (66.7%)	4 (57.1%)	3 (50.0%)	23 (67.6%)
Grade 1	9 (60.0%)	2 (33.3%)	4 (57.1%)	3 (50.0%)	18 (52.9%)
Grade 2	3 (20.0%)	2 (33.3%)	0	0	5 (14.7%)
Metabolism and nutrition disorders	5 (33.3%)	2 (33.3%)	3 (42.9%)	3 (50.0%)	13 (38.2%)
Grade 1	3 (20.0%)	1 (16.7%)	3 (42.9%)	3 (50.0%)	10 (29.4%)
Grade 2	2 (13.3%)	1 (16.7%)	0	0	3 (8.8%)
Hyperglycemia	5 (33.3%)	2 (33.3%)	3 (42.9%)	3 (50.0%)	13 (38.2%)
Grade 1	3 (20.0%)	1 (16.7%)	3 (42.9%)	3 (50.0%)	10 (29.4%)
Grade 2	2 (13.3%)	1 (16.7%)	0	0	3 (8.8%)
Gastrointestinal disorders	5 (33.3%)	4 (66.7%)	1 (14.3%)	0	10 (29.4%)
Grade 1	4 (26.7%)	2 (33.3%)	1 (14.3%)	0	7 (20.6%)
Grade 2	1 (6.7%)	2 (33.3%)	0	0	3 (8.8%)
Nausea	4 (26.7%)	2 (33.3%)	0	0	6 (17.6%)
Grade 1	3 (20.0%)	1 (16.7%)	0	0	4 (11.8%)
Grade 2	1 (6.7%)	1 (16.7%)	0	0	2 (5.9%)
Diarrhea	1 (6.7%)	2 (33.3%)	0	0	3 (8.8%)
Grade 1	1 (6.7%)	2 (33.3%)	0	0	3 (8.8%)
Abdominal pain	1 (6.7%)	1 (16.7%)	0	0	2 (5.9%)
Grade 1	1 (6.7%)	1 (16.7%)	0	0	2 (5.9%)
General disorders and administration site conditions	3 (20.0%)	1 (16.7%)	2 (28.6%)	1 (16.7%)	7 (20.6%)

Grade 1	3 (20.0%)	1 (16.7%)	2 (28.6%)	1 (16.7%)	7 (20.6%)
Injection site erythema	2 (13.3%)	0	1 (14.3%)	0	3 (8.8%)
Grade 1	2 (13.3%)	0	1 (14.3%)	0	3 (8.8%)
Injection site pruritus	0	1 (16.7%)	1 (14.3%)	0	2 (5.9%)
Grade 1	0	1 (16.7%)	1 (14.3%)	0	2 (5.9%)
Vascular disorders	3 (20.0%)	1 (16.7%)	0	1 (16.7%)	5 (14.7%)
Grade 1	2 (13.3%)	1 (16.7%)	0	1 (16.7%)	4 (11.8%)
Grade 2	1 (6.7%)	0	0	0	1 (2.9%)
Flushing	1 (6.7%)	0	0	1 (16.7%)	2 (5.9%)
Grade 1	1 (6.7%)	0	0	1 (16.7%)	2 (5.9%)
Ear and labyrinth disorders	2 (13.3%)	1 (16.7%)	0	0	3 (8.8%)
Grade 1	2 (13.3%)	1 (16.7%)	0	0	3 (8.8%)
Vertigo	2 (13.3%)	1 (16.7%)	0	0	3 (8.8%)
Grade 1	2 (13.3%)	1 (16.7%)	0	0	3 (8.8%)
Nervous system disorders	2 (13.3%)	0	1 (14.3%)	0	3 (8.8%)
Grade 1	2 (13.3%)	0	1 (14.3%)	0	3 (8.8%)
Headache	2 (13.3%)	0	0	0	2 (5.9%)
Grade 1	2 (13.3%)	0	0	0	2 (5.9%)

Primary system organ classes are presented by descending order of frequency; preferred terms are sorted within primary system organ class alphabetically.

A subject with multiple occurrences of an AE under one cohort is counted only once in the AE category for that cohort.

A subject with multiple severity ratings for an AE while on a cohort, is only counted under the maximum rating.

A subject with multiple adverse events within a primary system organ class is counted only once in the total row.

Safety Results

AE results discussed under safety objectives results

Serious Adverse Events and Deaths

Serious or clinically significant events	Normal (N = 15) n (%)	Mild (N = 6) n (%)	Moderate (N = 7) n (%)	Severe (N = 6) n (%)	All subjects (N = 34) n (%)

All Deaths*	0	0	0	0	0
All SAEs [1]	0	0	0	2 (33.3%)	2 (5.9%)
AEs causing study drug discontinuation	0	0	0	0	0

* On treatment deaths include deaths up to 28 days after last dose of study drug

[1] The SAE counts in this table do not include an SAE of confusional state reported for one subject which occurred after the subject signed the informed consent form but before the injection of study drug. This subject belonged to the severe hepatic impairment cohort. Taking into account this additional SAE, the total number of SAEs is 3 (50.0%) in the 'Severe' column and 3 (8.8%) in the 'All subjects' column.

Other Relevant Findings

Transient increases in fasting blood glucose were seen in all subjects, with the largest elevations occurring in the normal and mild cohorts. Mean fasting blood glucose levels returned to baseline levels by Visit 6 (study day 5) after the pasireotide dose. Exceptions were 2 subjects (1 in the mild cohort and 1 in the moderate cohort) who had shifts to higher glucose categories at Visit 2 and remained in the higher categories at Visit 6. There were no clinically relevant changes in other laboratory parameters, vital signs, or gallbladder ultrasound findings. The incidence of notable QTcF intervals was low overall. Five subjects (3 in the mild cohort and 2 in the moderate cohort) had a newly occurring QTcF interval >450 msec. Two subjects in the moderate cohort had a new QTcF interval >480 msec or >500 msec, although both also had baseline QTcF intervals >450 msec and their QTcF values returned to baseline 24 hours after the dose.

Date of Clinical Trial Report

03-Nov-2009 (Report date of CSR)

20-Dec-2011 (Report date of addendum)

Date Inclusion on Novartis Clinical Trial Results Database

18-Mar-2010

Date of Latest Update

11-Apr-2013