Sponsor

Novartis

Generic Drug Name

Pasireotide

Trial Indication(s)

Renal Impairment

Protocol Number

CSOM230B2126

Protocol Title

A phase I, open-label, multicenter, single-dose study to evaluate the pharmacokinetics (PK) and safety of subcutaneous (sc) pasireotide in subjects with varying degrees of renal impairment compared to a matched control group of healthy volunteers.

Clinical Trial Phase

Phase I

Phase of Drug Development

Phase III

Study Start/End Dates

First patient enrolled: 18-May-2012

Last patient completed: 24-May-2014

Reason for Termination (If applicable)

The renal function was defined at screening per eGFR (for the primary analysis) and CLcr measurements according to FDA draft guidance 2012. A total of 50 subjects were enrolled in the study, of which 22 subjects presented with normal renal function and 8 subjects each with mild, moderate and severe renal impairment and 4 subjects presented with ESRD.

The initial plan was to enroll 32 subjects in the normal group, and eight subjects each in mild, moderate, severe and End Stage Renal Disease (ESRD) groups. Per protocol, an interim analysis (IA) was planned to occur once a minimum of eight subjects in each of the mild and moderate

groups and their matching controls had been enrolled. Subjects from the severe and ESRD groups would only be included in the IA if a minimum of four subjects had been enrolled in each group. The PK IA took place when 18 subjects in the normal group, eight subjects each in mild and moderate groups, six subjects in severe and one subject in ESRD groups had been enrolled. It was shown that renal impairment has minimal impact on PK of pasireotide.

Due to very difficult and slow enrollment of subjects in the (ESRD) group (four subjects were enrolled in this group with 15months), pharmacokinetic (PK) and statistical simulation analyses were conducted to assess the potential impact of not enrolling the additional four ESRD subjects required per protocol. Based on this assessment, it was concluded that the enrollment of the additional last four ESRD subjects would not change the conclusion from the IA of PK mentioned above.

Study Design/Methodology

This was a phase I, open-label, multicenter, single dose study to evaluate the PK and safety of pasireotide sc injection in subjects with varying degrees of renal impairment compared to matched healthy subjects with normal renal function.

Subjects were classified by their respective degree of renal function (normal, mild, moderate, severe, and ESRD) according to estimated glomerular filtration rate (eGFR) as determined at the screening visit as shown below.

Degrees of renal impairment based on eGFR from MDRD equation

Stage	Description	eGFR (mL/min/1.73m^2)
1	Control (normal) GFR	≥90
2	Mild decrease in GFR	60-89
3	Moderate decrease in GFR	30-59
4	Severe decrease in GFR	15-29
5	ESRD	<15 not on dialysis

According to FDA Guidance for Industry on renal impairment (Draft, March 2010)

- Matched control group

Group 1 (normal group): Eight healthy subjects with normal renal function. Subjects from this group were matched with subjects in group 2 to group 5 by gender, age (±10 years), body weight (±20%), BMI (±5%) and race.

- Renal impairment group

Group 2 (mild group): Eight evaluable subjects with mild renal impairment stage
Group 3 (moderate group): Eight evaluable subjects with moderate renal impairment stage
Group 4 (severe group): Eight evaluable subjects with severe renal impairment stage

Group 5 (ESRD group): Eight evaluable subjects with ESRD stage

All the screening examinations occurred within 28 days prior to Baseline visit, with the exception of pregnancy test. A pregnancy test should have been performed within 5 days of baseline visit. Eligible subjects entered the study center at least 12 hours pre-dose (Day −1) for verification of inclusion/exclusion criteria. A study completion evaluation was performed on study Day 7 or earlier if the subject discontinued prior to study Day 7. Follow-up telephone calls were made to all subjects 30 days after the last dose of study treatment for safety evaluation.

Centers

Two sites enrolled subjects: Germany (1 site) and South Africa (1 site).

Publication

None

Objectives:

The primary objective was to assess the effect of varying degrees of renal impairment on the PK of pasireotide compared to a matched control group of healthy volunteers with normal renal function.

Secondary objectives were:

- To assess the effect of varying degrees of renal impairment on secondary PK parameters
- To assess the effect of varying degrees of renal impairment on the safety of pasireotide compared to a matched control group of healthy volunteers with normal renal function

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

The investigational drug was pasireotide at the dose of 900 µg administered subcutaneously.

Statistical Methods

No formal statistical hypothesis was tested as the main purpose of the statistical analysis was to estimate the effects of renal impairment on the PK of pasireotide

- Analysis of primary PK parameters:

All primary PK parameters were summarized by renal function group in descriptive statistics presenting geometric and arithmetic means, SD, CV% and CV% geo-mean, median, minimum, and maximum. Each renal function group (respectively based on the eGFR as primary analysis and based on the CLcr criteria as sensitivity analysis; FDA Guidance for Industry on renal impairment was compared to the control group for PK parameters.

A sensitivity analysis was also conducted on the primary PK parameters using descriptive statistics and the model-based approach described below when renal impairment groups were derived based on the eGFR at the baseline visit.

Primary Plasma PK parameters (Cmax, AUCinf, AUClast, CL/F, and urine PK parameter CLR) were also analyzed separately on the log scale by means of an ANOVA model including renal function group (control, mild, moderate, severe, and ESRD; as appropriate) as a fixed effect. The model included baseline covariates (such as gender, age, body weight, BMI, and race) if appropriate. The geometric mean of each PK parameter was derived from the model for each renal function group; the ratio of the PK parameter geometric means between the control group and each one of the other renal function groups and their 90% confidence interval (CI) was also derived from the model.

No adjustment of multiplicity was considered since no hypothesis testing was planned.

An additional sensitivity analysis using descriptive statistics and the model-based approach described above was run to compare the PK parameters between the control group and each one of the other renal function groups based on the eGFR-classification of renal function groups provided in European Medicines Agency (EMA), Committee for Medicinal Products for Human Use (CHMP), Note for Guidance on the evaluation of the pharmacokinetics of medicinal products in patients with impaired renal function (CHMP/EWP/225/02).

- Analysis of secondary PK parameters

All secondary PK parameters were summarized by renal function group in descriptive statistics presenting geometric and arithmetic means, SD, CV% and CV% geo-mean, median, minimum, and maximum (for Tmax only median, minimum, and maximum). Median differences between the control group and each one of the other renal function group for Tmax and the respective two-sided asymptotic 90% CI was estimated using the Hodges-Lehmann estimate.

In addition to the descriptive statistics, secondary PK parameters including Ae0-t, Vz/F, T1/2, Fu, Cmax,u, AUCinf,u, AUClast,u, CLu/F, and Vu/F were also analyzed separately on the log scale by means of an ANOVA model including renal function group (control, mild, moderate, severe, and ESRD; as appropriate) as a fixed effect. The model included baseline covariates (such as gender, age, body weight, BMI and race), if appropriate. The geometric mean of each PK parameter was derived from the model for each renal function group; the ratio of the PK parameter geometric means between the control group and each one of the other renal function groups and their 90% CI was also derived from the model.

Study Population: Key Inclusion/Exclusion Criteria

Key inclusion criteria:

- Written informed consent obtained prior to any screening procedures

- Subjects were able to communicate well with the Investigator and comply with the requirements of the study procedures
- Male or female subjects between 18 and 75 years of age
- Vital Signs at screening and baseline were within the following ranges:
- Oral body temperature: 35.0˚C to 37.5˚C and pulse rate: 40 to 90 bpm
- Subjects with 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 were willing to comply with dietary, fluid, and lifestyle restrictions (from Day −1 to study completion)
- Other than renal impairment, subjects were stable and appropriately managed relative to chronic diseases (such as diabetes and hypertension) as determined by past medical history, physical examination, electrocardiogram, and laboratory tests for chemistry and hematology

For renal impairment subjects only

- Subjects with stable renal disease without evidence of renal progressive disease (stable renal disease is defined as no significant change, such as, stable eGFR, for 12 weeks prior to study entry)
- Systolic blood pressure between 90 to 165 mmHg and diastolic blood pressure between 60 to 110 mmHg (3 minutes resting before measurement) in the supine position

For control subjects only

- Subjects were matched to at least one renal impaired subject by gender, age (±10 years), body weight (±20%), BMI (±5%) and race
- Systolic blood pressure between 90 to 140 mmHg and diastolic blood pressure between 50 to 90 mmHg (3 minutes resting before measurement) in the supine position

Key exclusion criteria:

- Clinically significant abnormal laboratory values at the screening evaluation or at the baseline re-evaluation, excluding those normally associated with mild to severe degree of renal impairment or the primary cause of renal insufficiency
- Used any over-the-counter medications or vitamins or herbal/natural supplements during 2 weeks prior to dosing (acetaminophen was acceptable, and was documented in the Concomitant Medications / Non-Drug Therapies page of the CRF)
- Current medical history of Sustained or clinically significant cardiac arrhythmias, history of syncope or family history of idiopathic sudden death, risk factors for torsades de pointes, screening QTcF >450 ms, concomitant disease(s) that could prolong QT such as autonomic neuropathy (caused by diabetes, or Parkinson's disease), HIV, cirrhosis, uncontrolled

hypothyroidism or cardiac failure and Concomitant medications known to increase the QT interval

- Participated in any clinical investigation within 4 weeks prior to dosing or longer if required by local regulation
- Donation or loss of 400 mL or more of blood within 8 weeks prior to dosing or other amount considered to compromise the health of the subject if previous history of anemia exists and significant acute illness within the 2 weeks prior to dosing
- History of immunocompromise, including a positive HIV (ELISA and Western blot) test result and history of allergies to the investigational compound/compound class being used in the study
- A positive Hepatitis B surface antigen (HBsAg) or positive HCV antibody
- History of drug or alcohol abuse within the 12 months prior to dosing or evidence of such abuse as indicated by the laboratory assays conducted during the screening or baseline evaluations
- History of liver disease (such as cirrhosis or chronic active hepatitis B and C), known gallbladder or bile duct disease, acute or chronic pancreatitis
- Baseline ALT or AST > ULN; baseline total bilirubin >1.5 x ULN
- Subjects on dialysis or potentially unreliable or vulnerable subjects (e.g. person kept in detention) and those judged by the Investigator to be unsuitable for the study

Participant Flow Table

Subject disposition by renal function group (Full Analysis Set)

	Normal (N=22)	Mild (N=8)	Moderate (N=8)	Severe (N=8)	ESRD (N=4)	All Subjects (N=50)
Disposition	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Completed	22 (100.0)	8 (100.0)	8 (100.0)	8 (100.0)	4 (100.0)	50 (100.0)
Discontinued	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Baseline Characteristics

Demographics and other baseline characteristics by renal function group (Full Analysis Set)

Demographic variable	Normal (N=22) n (%)	Mild (N=8) n (%)	Moderate (N=8) n (%)	Severe (N=8) n (%)	ESRD (N=4) n (%)	All Subjects (N=50) n (%)
Age (years)						
N	22	8	8	8	4	50

Demographic variable	Normal (N=22) n (%)	Mild (N=8) n (%)	Moderate (N=8) n (%)	Severe (N=8) n (%)	ESRD (N=4) n (%)	All Subjects (N=50) n (%)
Mean (SD)	56.3 (15.21)	59.9 (20.46)	67.1 (8.31)	53.5 (20.96)	39.5 (1.73)	56.8 (16.65)
Median (Min-Max)	61.5 (26-73)	70.5 (23-72)	70.0 (51-75)	65.5 (23-75)	40.0 (37-41)	65.5 (23-75)
Sex						
Male	11 (50.0)	4 (50.0)	3 (37.5)	4 (50.0)	1 (25.0)	23 (46.0)
Female	11 (50.0)	4 (50.0)	5 (62.5)	4 (50.0)	3 (75.0)	27 (54.0)
Race						
Caucasian	16 (72.7)	6 (75.0)	7 (87.5)	5 (62.5)	1 (25.0)	35 (70.0)
Black	6 (27.3)	2 (25.0)	1 (12.5)	3 (37.5)	3 (75.0)	15 (30.0)
Ethnicity						
Other	22 (100.0)	8 (100.0)	8 (100.0)	8 (100.0)	4 (100.0)	50 (100.0)
BMI (kg/m^2)						
N	22	8	8	8	4	50
Mean (SD)	26.00 (2.745)	26.12 (2.394)	27.79 (2.174)	25.41 (3.809)	24.15 (3.515)	26.06 (2.900)
Median (Min-Max)	25.73 (21.0-29.7)	26.18 (22.4-29.4)	28.95 (23.9-29.6)	23.95 (20.6-29.9)	23.74 (20.5-28.6)	25.73 (20.5-29.9)

- The baseline weight (kg) and baseline height (cm) were defined as the last non-missing assessment of weight and height before the first study drug administration.
- BMI (kg/m^2) = weight (kg) / height (m)^2. BMI is calculated using the baseline weight and baseline height.
- Impairment groups are derived using screening eGFR based on FDA guidance.

Summary of Efficacy

Primary Outcome Results

Summary of primary PK parameters for plasma pasireotide by renal function group. Classification based on eGFR (FDA guidance) (PAS)

Impairment group	Statistics	AUClast (hr*ng/mL)	AUCinf (hr*ng/mL)	Cmax (ng/mL)	CL/F (mL/hr)	CLR (L/hr)
Normal	n	19	16	19	16	19
	Mean (SD)	186.612 (57.4802)	192.776 (36.7917)	31.742 (9.9285)	4862.399 (1106.8777)	0.245 (0.1285)
	CV% mean	30.802	19.085	31.279	22.764	52.484
	Geo-mean	179.294	189.123	30.286	4758.813	0.213

Impairment group	Statistics	AUClast (hr*ng/mL)	AUCinf (hr*ng/mL)	Cmax (ng/mL)	CL/F (mL/hr)	CLR (L/hr)
	CV% geo-mean	29.137	21.060	32.794	21.060	60.038
	Median	189.625	199.034	30.500	4522.195	0.209
	[Min; Max]	[115.67; 363.12]	[120.53; 247.97]	[14.80; 57.50]	[3629.41; 7467.12]	[0.08; 0.50]
Mild	n	8	8	8	8	8
	Mean (SD)	146.751 (55.9731)	155.480 (64.4068)	22.125 (8.1626)	6567.768 (2229.0870)	0.373 (0.1700)
	CV% mean	38.142	41.425	36.893	33.940	45.532
	Geo-mean	138.492	145.343	20.787	6192.261	0.336
	CV% geo-mean	36.680	39.647	39.533	39.647	54.715
	Median	130.341	137.027	21.350	6570.728	0.393
	[Min; Max]	[94.76; 237.32]	[97.06; 265.17]	[13.00; 32.80]	[3394.05; 9273.00]	[0.16; 0.59]
Moderate	n	8	8	8	8	8
	Mean (SD)	158.822 (48.5129)	167.167 (51.4228)	21.987 (6.0709)	5872.257 (1847.8017)	0.190 (0.0995)
	CV% mean	30.546	30.761	27.611	31.467	52.317
	Geo-mean	152.197	160.119	21.307	5620.830	0.168
	CV% geo-mean	32.336	32.494	26.909	32.494	57.250
	Median	160.678	169.324	20.450	5395.028	0.149
	[Min; Max]	[103.30; 230.22]	[109.20; 242.94]	[15.30; 33.30]	[3704.69; 8242.12]	[0.09; 0.32]
Severe	n	8	7	8	7	8
	Mean (SD)	212.747 (106.5280)	189.402 (65.7193)	26.913 (12.1147)	5218.977 (1621.8154)	0.100 (0.0656)
	CV% mean	50.073	34.698	45.015	31.075	65.522
	Geo-mean	193.358	180.413	24.478	4988.546	0.083
	CV% geo-mean	47.785	34.168	50.950	34.168	74.620
	Median	178.443	178.277	25.000	5048.315	0.092
	[Min; Max]	[113.75; 429.49]	[122.53; 303.00]	[10.40; 47.70]	[2970.28; 7344.97]	[0.03; 0.23]
ESRD	n	4	4	4	4	4
	Mean (SD)	219.713 (42.4035)	229.066 (41.2381)	32.825 (9.2712)	4013.760 (629.4208)	0.059 (0.0138)

Impairment group	Statistics	AUClast (hr*ng/mL)	AUCinf (hr*ng/mL)	Cmax (ng/mL)	CL/F (mL/hr)	CLR (L/hr)
	CV% mean	19.300	18.003	28.244	15.682	23.302
	Geo-mean	216.913	226.523	31.788	3973.110	0.058
	CV% geo-mean	18.243	17.003	30.432	17.003	27.401
	Median	203.725	213.429	33.500	4222.250	0.065
	[Min; Max]	[190.04; 281.37]	[199.94; 289.46]	[22.00; 42.30]	[3109.20; 4501.34]	[0.04; 0.07]

- n: number of subjects with non-missing values.
- CV% = coefficient of variation (%) = sd/mean*100, CV% geo-mean = sqrt (exp (variance for log transformed data)-1)*100

Statistical analysis of primary PK parameters for pasireotide with age, gender and weight as covariates - Classification based on eGFR (FDA guidance) (PAS)

					Impairment Group Comparison		
PK Parameter (Unit)	Group	n*	Adjusted geo-mean	Comparison	Geometric mean ratio	90%CI Lower	Upper
Cmax (ng/mL)	Normal	19	29.6				
	Mild	8	21.27	Mild/Normal	0.72	0.58	0.90
	Moderate	8	22.65	Moderate/Normal	0.77	0.60	0.97
	Severe	8	24.12	Severe/Normal	0.81	0.65	1.02
	ESRD	4	26.67	ESRD/Normal	0.90	0.67	1.21
AUCinf (hr*ng/mL)	Normal	16	184.09				
	Mild	8	143.26	Mild/Normal	0.78	0.64	0.95
	Moderate	8	159.18	Moderate/Normal	0.86	0.70	1.08
	Severe	7	182.14	Severe/Normal	0.99	0.81	1.21
	ESRD	4	230.54	ESRD/Normal	1.25	0.97	1.62
AUClast (hr*ng/mL)	Normal	19	178.03				
	Mild	8	135.26	Mild/Normal	0.76	0.61	0.95
	Moderate	8	146.75	Moderate/Normal	0.82	0.64	1.05
	Severe	8	197.64	Severe/Normal	1.11	0.89	1.39
	ESRD	4	231.48	ESRD/Normal	1.30	0.96	1.76
CL/F (L/hr)	Normal	16	4888.8				
	Mild	8	6282.49	Mild/Normal	1.29	1.05	1.57

PK Parameter (Unit)	Group	n*	Adjusted geo-mean	Comparison	Impairment Group Comparison: Geometric mean ratio	90%CI Lower	90%CI Upper
	Moderate	8	5653.86	Moderate/ Normal	1.16	0.93	1.44
	Severe	7	4941.27	Severe/Normal	1.01	0.82	1.24
	ESRD	4	3903.91	ESRD/Normal	0.80	0.62	1.03
CLR (L/hr)	Normal	19	0.22				
	Mild	8	0.34	Mild/Normal	1.56	1.06	2.30
	Moderate	8	0.17	Moderate/Normal	0.80	0.53	1.22
	Severe	8	0.08	Severe/Normal	0.38	0.26	0.56
	ESRD	4	0.06	ESRD/Normal	0.29	0.17	0.48

Classification based on eGFR (FDA guidance)

- Model is a linear model of the log-transformed PK parameters, including impairment group as fixed effect, and age, gender, weight as covariates. Ratio of geometric means and their CI are back-transformed from the group differences and their CIs of the log-transformed data.
- n* = number of subjects with non-missing values

Secondary Outcome Result(s)

Summary of secondary PK parameters of plasma pasireotide based on total drug concentration by renal function group-Classification based on screening eGFR (FDA guidance) (PAS)

Impairment group	Statistics	Tmax (hr)	T1/2 (hr)	Vz/F mL)	Ae0-t (ng)
Normal	n	19	16	16	19
	Mean (SD)	N/A	39.654 (34.4992)	275155.233 (250382.320)	41063.898 (14249.5653)
	CV% mean	N/A	87.001	90.997	34.701
	Geo-mean	N/A	31	213962.106	38500.247
	CV% geo-mean	N/A	77.155	74.431	39.676
	Median	0.967	27.57	176498.338	44050.58
	[Min; Max]	[0.25; 1.98]	[10.32; 144.60]	[96921.99; 1031609.02]	[18162.36; 66377.45]
Mild	n	8	8	8	8
	Mean (SD)	N/A	28.811 (39.7051)	200819.329 (175540.8853)	48160.033 (9588.2064)

	CV% mean	N/A	137.811	87.412	19.909
	Geo-mean	N/A	18.112	162193.39	47310.256
	CV% geo-mean	N/A	108.38	68.821	20.529
	Median	0.5	14.827	122653.779	47310.561
	[Min; Max]	[0.25; 1.02]	[8.86; 125.74]	[103008.47; 615255.55]	[35360.01; 61685.97]
Moderate	n	8	8	8	8
	Mean (SD)	N/A	26.261 (13.0355)	205185.371 (73108.7463)	27511.503 (10102.7600)
	CV% mean	N/A	49.638	35.631	36.722
	Geo-mean	N/A	23.592	192960.514	26027.76
	CV% geo-mean	N/A	53.052	40.182	36.254
	Median	0.5	24.836	203452.998	24949.888
	[Min; Max]	[0.50; 1.05]	[11.79; 51.09]	[96396.87; 310723.19]	[16849.74; 45772.15]
Severe	n	8	7		8
	Mean (SD)	N/A	23.38 (9.6712)	177391.559 (94658.1851)	17575.432 (7261.2884)
	CV% mean	N/A	41.365	53.361	41.315
	Geo-mean	N/A	21.519	155806.559	16267.826
	CV% geo-mean	N/A	48.059	60.748	44.648
	Median	0.509	21.776	151724.1	17106.184
	[Min; Max]	[0.50; 3.00]	[10.74; 38.02]	[70736.17; 320187.20]	[8484.70; 28668.24]
ESRD	n	4	4	4	4
	Mean (SD)	N/A	35.462 (13.7873)	213130.959 (102283.5259)	13064.781 (4249.8862)
	CV% mean	N/A	38.879	47.991	32.529
	Geo-mean	N/A	33.792	196513.318	12545.407
	CV% geo-mean	N/A	35.383	48.464	34.118
	Median	0.375	29.918	188641.028	12688.013
	[Min; Max]	[0.25;0.50]	[26.11; 55.91]	[118614.67; 356627.10]	[8269.10; 18614.00]

Note: - Classification based on eGFR (FDA guidance)

n: number of subjects with non-missing values
- CV% = coefficient of variation (%) = sd/mean*100, CV% geo-mean = sqrt (exp (variance for log transformed data)-1)*100

Summary of Safety

Safety Results

Adverse events, regardless of study drug relationship, by primary system organ class, maximum CTCAE grade and renal function group (Safety Set)

Any primary system organ class	Normal (N=22) n(%)	Mild (N=8) n(%)	Moderate (N=8) n(%)	Severe (N=8) n(%)	ESRD (N=4) n(%)	All Subjects (N=50) n(%)
Total	18 (81.8)	8 (100.0)	8 (100.0)	6 (75.0)	3 (75.0)	43 (86.0)
Grade 1	12 (54.5)	3 (37.5)	4 (50.0)	5 (62.5)	1 (25.0)	25 (50.0)
Grade 2	5 (22.7)	5 (62.5)	4 (50.0)	1 (12.5)	1 (25.0)	16 (32.0)
Grade 3	1 (4.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (25.0)	2 (4.0)
Grade 4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Grade 3/4	1 (4.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (25.0)	2 (4.0)
Missing 0	0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Blood and lymphatic system disorders						
Total	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (25.0)	1 (2.0)
Grade 1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Grade 2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (25.0)	1 (2.0)
Grade 3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Grade 4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Grade 3/4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Eye disorders						
Total	1 (4.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)
Grade 1	1 (4.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)
Grade 2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Grade 3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Grade 4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Grade 3/4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Gastrointestinal disorders						
Total	11 (50.0)	6 (75.0)	6 (75.0)	4 (50.0)	1 (25.0)	28 (56.0)
Grade 1	8 (36.4)	4 (50.0)	5 (62.5)	4 (50.0)	1 (25.0)	22 (44.0)
Grade 2	3 (13.6)	2 (25.0)	1 (12.5)	0 (0.0)	0 (0.0)	6 (12.0)
Grade 3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Grade 4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Grade 3/4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
General disorders and administration conditions						
Total	5 (22.7)	1 (12.5)	4 (50.0)	4 (50.0)	0 (0.0)	14 (28.0)
Grade 1	5 (22.7)	1 (12.5)	4 (50.0)	4 (50.0)	0 (0.0)	14 (28.0)
Grade 2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Grade 3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Grade 4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Grade 3/4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hepatobiliary disorders						
Total	1 (4.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)
Grade 1	1 (4.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)
Grade 2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Grade 3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Grade 4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Grade 3/4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Investigations						
Total	2 (9.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (25.0)	3 (6.0)
Grade 1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Grade 2	2 (9.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (4.0)
Grade 3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (25.0)	1 (2.0)
Grade 4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Grade 3/4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (25.0)	1 (2.0)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Metabolism and nutrition disorders						
Total	5 (22.7)	2 (25.0)	5 (62.5)	3 (37.5)	1 (25.0)	16 (32.0)
Grade 1	4 (18.2)	0 (0.0)	4 (50.0)	2 (25.0)	0 (0.0)	10 (20.0)
Grade 2	1 (4.5)	2 (25.0)	1 (12.5)	1 (12.5)	1 (25.0)	6 (12.0)
Grade 3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Grade 4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Grade 3/4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Musculoskeletal and connective tissue disorders						
Total	2 (9.1)	0 (0.0)	1 (12.5)	0 (0.0)	0 (0.0)	3 (6.0)
Grade 1	1 (4.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)
Grade 2	1 (4.5)	0 (0.0)	1 (12.5)	0 (0.0)	0 (0.0)	2 (4.0)
Grade 3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Grade 4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Grade 3/4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nervous system disorders						
Total	4 (18.2)	3 (37.5)	2 (25.0)	0 (0.0)	1 (25.0)	10 (20.0)
Grade 1	3 (13.6)	2 (25.0)	1 (12.5)	0 (0.0)	1 (25.0)	7 (14.0)
Grade 2	0 (0.0)	1 (12.5)	1 (12.5)	0 (0.0)	0 (0.0)	2 (4.0)
Grade 3	1 (4.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)
Grade 4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Grade 3/4	1 (4.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Respiratory thoracic and mediastinal disorders						
Total	1 (4.5)	0 (0.0)	1 (12.5)	0 (0.0)	1 (25.0)	3 (6.0)
Grade 1	1 (4.5)	0 (0.0)	1 (12.5)	0 (0.0)	1 (25.0)	3 (6.0)

Grade 2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Grade 3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Grade 4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Grade 3/4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Skin and subcutaneous disorders						
Total	3 (13.6)	1 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)	4 (8.0)
Grade 1	3 (13.6)	1 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)	4 (8.0)
Grade 2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Grade 3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Grade 4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Grade 3/4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Vascular disorders						
Total	1 (4.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (25.0)	2 (4.0)
Grade 1	1 (4.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (25.0)	2 (4.0)
Grade 2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Grade 3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Grade 4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Grade 3/4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Adverse events, regardless of study drug relationship, by preferred term, maximum CTCAE grade and renal function group (Safety Set)

	Normal (N=22)		**Mild (N=8)**		**Moderate (N=8)**		**Severe (N=8)**		**ESRD (N=4)**		**All Subjects (N=50)**	
Preferred term	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)
-Total	18 (81.8)	1 (4.5)	8 (100.0)	0 (0.0)	8 (100.0)	0 (0.0)	6 (75.0)	0 (0.0)	3 (75.0)	1 (25.0)	43 (86.0)	2 (4.0)
Abdominal pain	7 (31.8)	0 (0.0)	2 (25.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)	0 (0.0)	1 (25.0)	0 (0.0)	11 (22.0)	0 (0.0)

	Normal (N=22)		Mild (N=8)		Moderate (N=8)		Severe (N=8)		ESRD (N=4)		All Subjects (N=50)	
Preferred term	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)
Nausea	7 (31.8)	0 (0.0)	5 (62.5)	0 (0.0)	4 (50.0)	0 (0.0)	3 (37.5)	0 (0.0)	1 (25.0)	0 (0.0)	20 (40.0)	0 (0.0)
Diarrhoea	6 (27.3)	0 (0.0)	3 (37.5)	0 (0.0)	3 (37.5)	0 (0.0)	1 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)	13 (26.0)	0 (0.0)
Hyperglycaemia	5 (22.7)	0 (0.0)	0 (0.0)	0 (0.0)	5 (62.5)	0 (0.0)	3 (37.5)	0 (0.0)	1 (25.0)	0 (0.0)	14 (28.0)	0 (0.0)
Injection site reaction	5 (22.7)	0 (0.0)	0 (0.0)	0 (0.0)	3 (37.5)	0 (0.0)	3 (37.5)	0 (0.0)	0 (0.0)	0 (0.0)	11 (22.0)	0 (0.0)
Headache	3 (13.6)	0 (0.0)	3 (37.5)	0 (0.0)	2 (25.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	8 (16.0)	0 (0.0)
Dermatitis contact	2 (9.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (4.0)	0 (0.0)
Faeces discoloured	2 (9.1)	0 (0.0)	2 (25.0)	0 (0.0)	2 (25.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	6 (12.0)	0 (0.0)
Hypoglycaemia	2 (9.1)	0 (0.0)	2 (25.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (8.0)	0 (0.0)
Muscle spasms	2 (9.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (6.0)	0 (0.0)
Amylase increased	1 (4.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (25.0)	1 (25.0)	2 (4.0)	1 (2.0)
Cholelithiasis	1 (4.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)
Epilepsy	1 (4.5)	1 (4.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	1 (2.0)
Hot flush	1 (4.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	2 (4.0)	0 (0.0)
Hyperhidrosis	1 (4.5)	0 (0.0)	1 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (4.0)	0 (0.0)
Nasal congestion	1 (4.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)
Neutrophil count decreased	1 (4.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)
Oropharyngeal pain	1 (4.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	2 (4.0)	0 (0.0)
Vision blurred	1 (4.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)

	Normal (N=22)		Mild (N=8)		Moderate (N=8)		Severe (N=8)		ESRD (N=4)		All Subjects (N=50)	
Preferred term	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)
Vomiting	1 (4.5)	0 (0.0)	1 (12.5)	0 (0.0)	3 (37.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	6 (12.0)	0 (0.0)
White blood cell count decreased	1 (4.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)
Abdominal distension	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)
Abdominal pain upper	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)
Anaemia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	1 (2.0)	0 (0.0)
Dizziness	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	2 (4.0)	0 (0.0)
Dysgeusia	0 (0.0)	0 (0.0)	1 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)
Dyspepsia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)
Gout	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	1 (2.0)	0 (0.0)
Hiccups	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)
Injection site haematoma	0 (0.0)	0 (0.0)	1 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)	2 (4.0)	0 (0.0)
Injection site pain	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)
Lipase increased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (25.0)	1 (25.0)	1 (2.0)	1 (2.0)
Rhinorrhoea	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	2 (4.0)	0 (0.0)
Somnolence	0 (0.0)	0 (0.0)	1 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)

- Preferred terms are sorted in descending frequency of all grades column, as reported in the Normal renal function group.
- A subject with multiple occurrences of an AE is counted only once in the AE category.
- A subject with multiple adverse events is counted only once in the total row.

Serious Adverse Events and Deaths

	Normal (N=22) n(%)	Mild (N=8) n(%)	Moderate (N=8) n(%)	Severe (N=8) n(%)	ESRD (N=4) n(%)	All Subjects (N=50) n(%)
Death	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
SAE (epilepsy)	1 (4.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)
Discontinued due to SAE(s)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
AEs of special interests (AESI)	14 (63.6)	8 (100)	8 (100)	6 (75.0)	2 (50.0)	38 (76.0)

AESIs are nausea, diarrhea, heperglycemia, injection reaction site, hypoglycemia, amylase increased, cholelithiasis, neutrophil count decrease, vomiting, white blood cell count decrease, abdominal distention, anemia, injection site hematoma, injection site pain, lipase increase

Conclusion:

- PK profiles and exposures of pasireotide were similar between renal impairment groups (mild, moderate, severe and ESRD) and normal group.
- Renal clearance has minimal contribution to the total clearance of pasireotide.
- Renal impairment has minimal impact on PK of pasireotide.
- The results with and without covariates (e.g. age, gender, weight) were similar, suggesting subjects in normal group well matched subjects in renal impairment groups.
- The results based on eGFR classification were similar to those based on CLcr classification.
- No new safety signals were identified in this study. The safety and tolerability observed in subjects with different degrees of renal impairment were consistent with the already known safety profile of pasireotide.
- No dose adjustment is required for pasireotide use in subjects with renal impairment.

Date of Clinical Trial Report

24-Apr-2015

Date of Initial Inclusion on Novartis Clinical Trial Results website

14-May-2015

Date of Latest Update

N/A

Reason for Update

N/A