Endocrine (2012) 42:366–374
DOI 10.1007/s12020-012-9668-1

ORIGINAL ARTICLE

Multiple once-daily subcutaneous doses of pasireotide were well tolerated in healthy male volunteers: a randomized, double-blind, placebo-controlled, cross-over, Phase I study

Christoph Beglinger · Ke Hu · Ying Wang · Emmanuel Bouillaud · Christelle Darstein · Yanfeng Wang · Pharis Mohideen

Received: 21 December 2011 / Accepted: 28 March 2012 / Published online: 21 April 2012

Abstract A randomized, double-blind, placebo-controlled, cross-over, dose-escalating, single-center study was conducted to evaluate the safety, tolerability, and pharmacokinetic (PK) profile of multiple once-daily (qd) subcutaneous (sc) doses of pasireotide in healthy male subjects. Subjects received pasireotide 50, 200, or 600 μg sc qd for 14 days and placebo in separate sequences. Thirty-three subjects were randomized. The most frequently reported drug-related adverse events were injection–site reactions ($n = 18$), diarrhea ($n = 14$) and nausea ($n = 10$), which were mostly mild or moderate in intensity. Pasireotide 600 μg sc was associated with pre- and post-prandial elevations in glucose levels relative to placebo; however, this effect was less pronounced on day 14 compared with day 1. PK steady state appeared to be achieved after 3 days of dosing and PK exposures had a moderate accumulation of 20–40 % across doses. Pasireotide demonstrated fast absorption ($T_{max,ss}$: 0.25–0.5 h), low clearance (CL/F_{ss}: 8.10–9.03 L/h), long effective half-life ($T_{½,eff}$: ~12 h, on average between 9.7 and 13.1 h for 50, 200, and 600 μg sc qd), and large volume of distribution (V_z/F_{ss}: 251–1,091 L) at steady state. Dose proportionality was confirmed for $C_{max,ss}$; other PK parameters (C_{max}, $AUC_{0–24\ h}$ and AUC_{tau}) were approximately dose proportional. Growth hormone inhibition was observed with pasireotide 200 and 600 μg sc qd. Gallbladder volume increased post-prandially with pasireotide 200 and 600 μg sc qd, which appeared to correlate with reduced levels of cholecystokinin at these doses. Pasireotide was generally well tolerated up to the tested dose of 600 μg qd, with a linear and time-independent PK profile after sc qd dosing in healthy subjects.

Keywords Pasireotide · Safety · Tolerability · Pharmacokinetics · Healthy volunteers

C. Beglinger
Division of Gastroenterology, University Hospital Basel, Basel, Switzerland

C. Beglinger (✉)
Department of Biomedicine, University Hospital Basel, Hebelstrasse 20, 4031 Basel, Switzerland
e-mail: beglingerc@uhbs.ch

K. Hu · Y. Wang · Y. Wang · P. Mohideen
Novartis Pharmaceuticals, East Hanover, NJ, USA

E. Bouillaud · C. Darstein
Novartis Pharma AG, Basel, Switzerland

Introduction

Somatostatin receptor subtypes are expressed at high levels in many tumor cells, which provides the rationale for the development of medical therapies that specifically target these receptors [1–3]. Pasireotide (SOM230) is a multireceptor-targeted somatostatin analog that binds with high affinity to four of the five somatostatin receptor subtypes ($sst_{1,2,3}$ and sst_5). Compared with octreotide, pasireotide has a 39-, 30- and 5-fold higher binding affinity for sst_5, sst_1 and sst_3, respectively, and a slightly lower (0.4-times lower) binding affinity for sst_2 [3]. Pasireotide also has a 2-fold higher binding affinity for sst_5 than endogenous somatostatin [4].

The unique binding profile of pasireotide offers potential therapeutic benefits in the indications associated with sst_2 for somatostatin analogs (e.g., octreotide and lanreotide), such as acromegaly [5, 6] and neuroendocrine tumors (NET) [7–9]. The multireceptor binding profile of pasireotide also provides a rationale for its potential use as a tumor-targeted management option for diseases in which

somatostatin receptor subtypes other than sst_2 are involved, e.g., other pituitary adenomas, such as corticotroph adenomas (Cushing's disease, where sst_5 is abundantly expressed) [4].

Data from pre-clinical studies have shown that the inhibitory effects of pasireotide on the secretion of growth hormone (GH) and subsequent production of insulin-like growth factor 1 (IGF-1) are more potent and are of longer duration than those of octreotide, and that pasireotide effectively inhibits the release of adrenocorticotropic hormone (ACTH) from human corticotroph adenoma cells with or without glucocorticoid pre-treatment [10, 11]. Pasireotide also significantly suppressed cell proliferation and ACTH secretion in primary cultures of human corticotroph tumors [12]. Based on these promising preclinical results, a series of clinical studies for pasireotide were initiated [13–25].

This article presents the results of a randomized, double-blind, placebo-controlled, cross-over, dose-escalating, single-center Phase I study to evaluate the safety, tolerability, and pharmacokinetic (PK) profile of multiple once-daily (qd) subcutaneous (sc) doses of pasireotide in healthy volunteers.

Methods

Subjects

Healthy male subjects aged 18–40 years with normal findings from evaluations performed at screening (e.g., physical examination, vital signs, electrocardiogram [ECG], and laboratory tests) were enrolled. Subjects' body mass index (BMI) must have been within ± 15 kg/m^2 of normal according to the Metropolitan Life Insurance Tables [26]. Subjects were excluded if they used any prescription drug or over-the-counter medication 14 days prior to dosing, participated in any clinical investigation within 4 weeks or had donated or lost $\geq$400 mL of blood within 8 weeks prior to dosing. Subjects were also excluded if they had a history of autonomic dysfunction, acute or chronic bronchospastic disease, clinically significant drug allergy, or any surgical or medical condition that significantly altered the absorption, distribution, metabolism, or excretion of drugs (e.g., history of cholecystitis or gallstones, pancreatic injury or pancreatitis, clinical evidence of liver disease or injury as indicated by abnormal liver function tests, history of impaired renal function, evidence of urinary obstruction or difficult voiding at screening, or polymorphonuclear leukocytes $<$1,500/μL or platelets $<$100,000/μL at inclusion).

The study was approved by the independent ethics committee, research ethics board or institutional review board at the center and complied with the International Conference of Harmonization (ICH), Harmonized Tripartite Guidelines for Good Clinical Practice, the Declaration of Helsinki and local laws. All subjects provided written informed consent.

Study design

Thirty male subjects were to be randomized into one of two treatment sequences (pasireotide followed by placebo or placebo followed by pasireotide) within three dose-level cohorts ($n = 10$ in each cohort). Subjects received either pasireotide 50, 200, or 600 μg sc qd. Study medication was injected in the abdominal wall by study center personnel each day between 08:00 am and 09:00 am. Subjects received a daily dose of pasireotide or placebo for 14 days (treatment period 1). Twenty-four hours after the final drug administration in treatment period 1, subjects entered a minimum 14-day washout period. Subjects then received the other treatment (placebo or, respectively, pasireotide) for an additional 14 days (treatment period 2; Fig. 1).

Outcomes and assessments

The primary objective was to assess the safety and tolerability of multiple doses of pasireotide sc in healthy subjects. Adverse events (AEs) and serious AEs (SAEs) were recorded throughout the study period. Blood chemistry, hematology and urine values, laboratory tests, ECG measurements, vital signs and physical examination results were recorded. The secondary objectives were to characterize the PK profile of multiple doses of pasireotide sc and to investigate the effects of pasireotide on a number of pharmacodynamic (PD) parameters as indicators of biologic activity.

Blood samples for the PK evaluation were collected pre-dose and then 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 h after the first injection in each treatment period. The same sampling times were used after the last administration in each treatment period, with additional samples at 36, 48, 72, and 96 h. Blood samples for trough concentrations were collected pre-dose on days 3, 4, 5, 9, 12, and 13 in each treatment period. All blood samples were collected by either direct venipuncture or indwelling cannula inserted in a forearm vein. A total of 2.5 mL of blood was collected to yield approximately 1 mL of plasma for analysis of pasireotide concentration. Laboratory samples for PK analysis were analyzed by the Department of Bioanalytics and Pharmacokinetics (Novartis Pharma AG, Basel, Switzerland). Plasma concentrations were determined by a validated radioimmunoassay (RIA) with a lower limit of quantification (LLOQ) of 0.03 ng/mL.

PK non-compartmental analysis was performed using WinNonlin software (version 5.2; Pharsight Corp.,

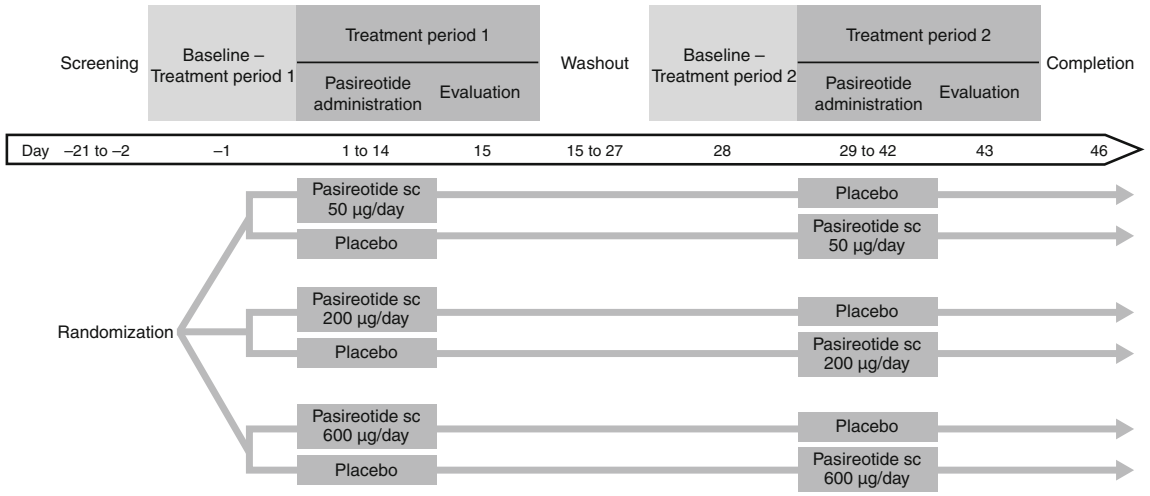

Fig. 1 Study design

Mountain View, CA, USA). PK parameters after the first administration on day 1 included: maximum (peak) observed plasma concentration (C_{max}), time to reach C_{max} (T_{max}), area under the plasma concentration–time curve from time zero to 24 h ($AUC_{0–24\ h}$), and apparent total body clearance (CL/F). PK parameters after the last administration on day 14 included: maximum steady-state drug concentration ($C_{max,ss}$), minimum concentration at steady state ($C_{min,ss}$), mean concentration at steady state ($C_{avg,ss}$), time to reach $C_{max,ss}$ ($T_{max,ss}$), area under the plasma concentration–time curve at steady state during one dosing interval ($AUC_{tau,ss} = AUC_{0–24\ h,ss}$), apparent total body clearance at steady state (CL/F_{ss}), apparent volume of distribution at steady state (V_z/F_{ss}), effective half-life ($T_{½,eff}$) at steady state, accumulation ratio at steady state (R_{acc}), and peak-to-trough fluctuation at steady state ($=C_{max,ss}/C_{min,ss} \times 100\ \%$).

The effective half-life ($T_{½,eff}$) of pasireotide was determined by the following equation [27]: $T_{½,eff} = \ln 2 \cdot \tau / \ln[R_{acc}/(R_{acc} - 1)]$, where τ (tau) is the dosing interval (24 h) and R_{acc} is the AUC accumulation ratio, $AUC_{0–24\ h,d14}/AUC_{0–24\ h,d1}$.

For the PD analyses, a GH-releasing hormone (GHRH) stimulation test was performed between 11:00 am and 12:00 pm on study days 2, 13, 30, and 41. Blood samples for evaluation of GH levels were collected at 1 and 30 min before GHRH injection and every 30 min for 2 h (30, 60, 90, and 120 min) after GHRH injection. Glucose, insulin, cholecystokinin (CCK), glucagon, gastrin, and gallbladder contraction profiles were measured on days 1, 14, 29, and 42. Measurements were performed at 1 and 30 min before a standardized meal and every 30 min for 2 h (30, 60, 90, and 120 min) after a standardized meal. For stool fat analysis, stools were collected over two 3-day periods during both treatment periods. Laboratory samples for PD analysis were processed at the Institute of Experimental Clinical Research, Medical Research Laboratories (Aarhus Kommunehospital, Aarhus University Hospital, Aarhus, Denmark).

Statistical methods

Descriptive statistics were generated for demographic variables such as age, weight, height, sex and race, as well as for PK parameters. Dose proportionality for C_{max}, $AUC_{0–24\ h}$, $C_{max,ss}$ and $AUC_{tau,ss}$ was evaluated using the power model ($PK = \alpha \cdot Dose^{\beta}$), and by comparing the estimated slope β with the critical region 0.91–1.09 [28].

Results

Thirty healthy male subjects were initially randomized in the study, with 10 subjects in each treatment group. Of the 30 initial subjects, 25 completed the study and five prematurely discontinued the study. Three additional subjects were randomized to replace the subjects who dropped out, with all three completing the study (Table 1). In total, 28 subjects completed the study.

One subject withdrew from the study because of drug-related vomiting of moderate intensity after receiving the first dose of pasireotide 600 µg. Four additional subjects discontinued the study (two withdrew consent, one had a protocol violation, and one had an AE not related to the study medication [severe lumbago]). All subjects who received at least one dose of study drug ($n = 33$) were included in the safety and tolerability, and PD evaluations. The PK analysis population included 31 subjects on day 1 and 28 subjects on day 14.

Table 1 Baseline characteristics for the study population

	Total number of subjects ($n = 33$)
Age (years), mean ± SD	28.3 ± 6.22
Race, *n* (%)	
Caucasian	32 (97)
Other	1 (3)
Height (cm), mean ± SD	180.5 ± 7.05
Weight (kg), mean ± SD	74.5 ± 9.33
BMI (kg/m^2), mean ± SD	22.9 ± 2.44

BMI body mass index, *SD* standard deviation

Safety and tolerability

All subjects except one experienced at least one AE during the study. The most frequent AEs were gastrointestinal symptoms (abdominal pain, nausea, vomiting, and diarrhea), which occurred in a similar percentage of subjects with pasireotide and placebo, and administration site reactions (bruising, erythema, irritation, and pruritus), which occurred predominantly during pasireotide treatment compared with placebo. The majority of AEs were mild to moderate in intensity. Ten subjects experienced nausea after receiving pasireotide 200 or 600 μg. Three subjects receiving 200 μg reported mild-to-moderate nausea, which started within 10 min of injection and lasted for 10 and 45 min, and 4 days. At 600 μg, seven subjects experienced mild-to-moderate nausea, starting approximately 10–15 min after injection and lasting 1–12 h. Five subjects experienced mild-to-moderate vomiting, after receiving pasireotide 600 μg. This occurred primarily on days 1 and 2, although two subjects experienced vomiting on day 14. Five subjects experienced severe AEs, including back pain, abdominal distension, erythema, injection–site irritation and headache, of which back pain and headache were considered not to be related to the study drug.

Twenty-seven subjects experienced at least one AE that was considered to be related to the study drug. The most frequently reported drug-related AEs were injection–site reactions, diarrhea, nausea, and vomiting (Table 2). No SAEs or deaths occurred during this study. There were no clinically significant abnormalities in the laboratory parameters, vital signs, or ECG results. No subjects had a notable QTcF interval after receiving pasireotide, and one had a QTcB interval increase >30 ms (but <60 ms) with pasireotide 200 μg. With placebo, two subjects had a QTcB interval increase >30 ms.

Pharmacokinetics

Pasireotide was absorbed rapidly following the first dosing, and C_{max} was observed mostly within 30 min post-injection (Fig. 2; Table 3). The systemic drug exposure of pasireotide appeared to increase proportionally with dose escalation (Fig. 2; Table 3). It appeared that pasireotide plasma concentrations reached steady state after 3 days of daily injections, as indicated by similar mean trough concentrations between day 3 and day 14 (Table 3). At steady state, the peak plasma concentration ($C_{max,ss}$) of pasireotide mostly occurred within 30 min of administration (Fig. 2; Table 3). Pasireotide had a long $T_{½,eff}$ (approximately 12 h on average) across the three doses: pasireotide 50 μg: 10.4 ± 3.4 h; pasireotide 200 μg: 9.7 ± 3.4 h; pasireotide 600 μg: 13.1 ± 3.7 h (Table 3). The CL/F_{ss} was low and similar across all three doses (range 8.10 ± 2.14 to 9.03 ± 1.37 L/hour; Table 3). Pasireotide had a large V_z/F_{ss}, which

Table 2 Adverse events with a suspected study–drug relationship

Adverse event, *n* (%)	Pasireotide 50 μg ($n = 11$)	Pasireotide 200 μg ($n = 10$)	Pasireotide 600 μg ($n = 12$)	Placebo ($n = 30$)
Injection–site reactions	6 (54.5)	8 (80.0)	4 (33.3)	5 (16.7)
Diarrhea	4 (36.4)	5 (50.0)	4 (33.3)	6 (20.0)
Nausea	0	3 (30.0)	7 (58.3)	0
Vomiting	0	0	5 (41.7)	0
Other GI symptoms (e.g., abdominal distension)	2 (18.2)	5 (50.0)	7 (58.3)	8 (26.7)
Dizziness	1 (9.1)	0	1 (8.3)	0
Headache	0	2 (20.0)	2 (16.7)	0
Halitosis	0	1 (10.0)	0	0
Dry mouth	1 (9.1)	0	1 (8.3)	2 (6.7)
Pain over kidneys	0	0	1 (8.3)	1 (3.3)
Leg cramps	0	0	1 (8.3)	0
Fainting during injection	0	1 (10.0)	0	0
Muscle fibrillation after injection	0	1 (10.0)	0	0

GI gastrointestinal

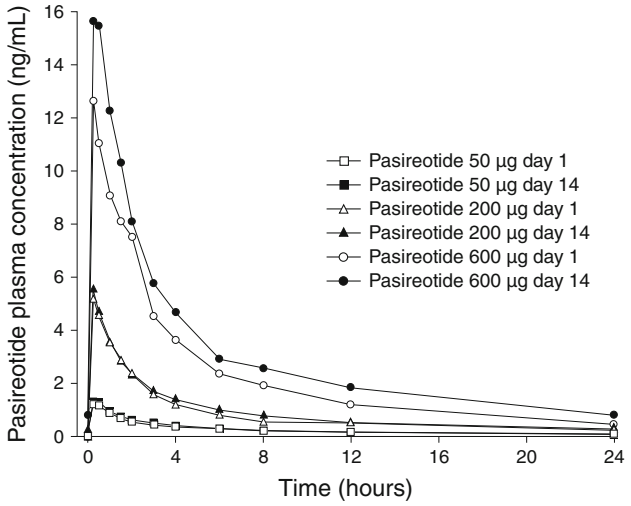

Fig. 2 Mean plasma pasireotide concentration versus time profiles over 24 h on day 1 and day 14

appeared to be increased at higher doses (range up to 1,091 ± 656 L; Table 3). The accumulation of pasireotide at steady state (R_{acc}) was moderate, approximately 20–40 % across doses. The steady-state peak-to-trough concentration fluctuation in each dose cohort was approximately 530 % on average.

In order to confirm dose proportionality, the 90 % confidence interval (CI) for the slope was compared to the critical range of 0.91, 1.09. Dose proportionality was confirmed for $C_{max,ss}$ (slope estimate; 0.99; 90 % CI: 0.91, 1.07); however, other PK parameters, C_{max} (slope: 0.92; 90 % CI: 0.82, 1.02), $AUC_{0–24\ h}$ (slope: 0.95; 90 % CI: 0.90, 1.00) and $AUC_{tau,ss}$ (slope: 0.97: 90 % CI: 0.90, 1.04), fell slightly outside these limits.

Pharmacodynamics

GH levels

The ability of pasireotide to decrease GH secretion was demonstrated during a GHRH stimulation test. Inhibition of GHRH-stimulated GH secretion was observed with pasireotide 200 and 600 µg sc (Fig. 3). An average pasireotide concentration of approximately 0.4 µg/L yielded half of the maximal GH reduction (EC_{50}), based on an inhibitory E_{max}

Table 3 PK parameters on days 1, 3, 4, 5, 9, 12, 13, and 14

Study day	PK parameter	Pasireotide dose		
		50 µg qd ($n = 11$)	200 µg qd ($n = 9$)	600 µg qd ($n = 11$)
1	T_{max} (h)	0.30 (0.25–0.83)	0.30 (0.25–1.47)	0.25 (0.23–2.00)
	C_{max} (ng/mL)	1.3 ± 0.4	5.3 ± 1.8	13.1 ± 4.5
	$AUC_{0–24\ h}$ (h ng/mL)	5.2 ± 1.0	19.8 ± 4.3	54.1 ± 7.0
	CL/*F* (L/h)	9.4 ± 1.9	9.2 ± 1.8	10.4 ± 1.4
3	$C_{min,d3}$ (ng/mL)	0.05 ± 0.05	0.23 ± 0.06	0.65 ± 0.31
4	$C_{min,d4}$ (ng/mL)	0.07 ± 0.05	0.27 ± 0.07	0.64 ± 0.25
5	$C_{min,d5}$ (ng/mL)	0.07 ± 0.05	0.28 ± 0.08	0.69 ± 0.33
9	$C_{min,d9}$ (ng/mL)	0.08 ± 0.05	0.29 ± 0.09	0.73 ± 0.26
12	$C_{min,d12}$ (ng/mL)	0.08 ± 0.06	0.29 ± 0.08	0.77 ± 0.23
13	$C_{min,d13}$ (ng/mL)	0.09 ± 0.05	0.27 ± 0.08	0.78 ± 0.25
14	$T_{max,ss}$ (h)	0.35 (0.23, 0.53)	0.25 (0.25, 0.50)	0.50 (0.25, 1.05)
	$C_{max,ss}$ (ng/mL)	1.39 ± 0.28	5.53 ± 1.22	16.76 ± 4.96
	$C_{min,ss}$ (ng/mL)	0.08 ± 0.06	0.25 ± 0.10	0.74 ± 0.33
	$AUC_{tau,ss}$ (h ng/mL)	6.6 ± 1.8	22.6 ± 3.5	72.9 ± 14.7
	$C_{avg,ss}$ (ng/mL)	0.27 ± 0.08	0.94 ± 0.15	3.04 ± 0.61
	CL/F_{ss} (L/h)	8.10 ± 2.14	9.03 ± 1.37	8.54 ± 1.76
	V_z/F_{ss} (L)	251 ± 274	1,051 ± 774	1,091 ± 656
	$T_{½,eff}$ (h)	10.4 ± 3.4	9.7 ± 3.4	13.1 ± 3.7
	R_{acc}	1.26 ± 0.17	1.20 ± 0.17	1.36 ± 0.22
	Fluctuation (%)	498 ± 129	573 ± 158	525 ± 119

Data are median (range) for $T_{max,ss}$, and arithmetic mean ± SD for all parameters

$AUC_{0–24\ h,ss}$ (=$AUC_{tau,ss}$) area under the plasma concentration–time curve at steady state during one dosing interval (tau) of 24 h, $C_{avg\ ss}$ mean steady-state drug concentration, *CL/F* apparent total body clearance, CL/F_{ss} apparent total body clearance at steady state, $T_{max,ss}$ time to reach peak or maximum concentration following drug administration at steady state, $C_{max,ss}$ maximum steady-state drug concentration, $C_{min,ss}$ minimum steady-state concentration, R_{acc} AUC accumulation ratio, $T_{½,eff}$ effective half-life, V_z/F_{ss} apparent volume of distribution at steady state associated with the terminal disposition phase

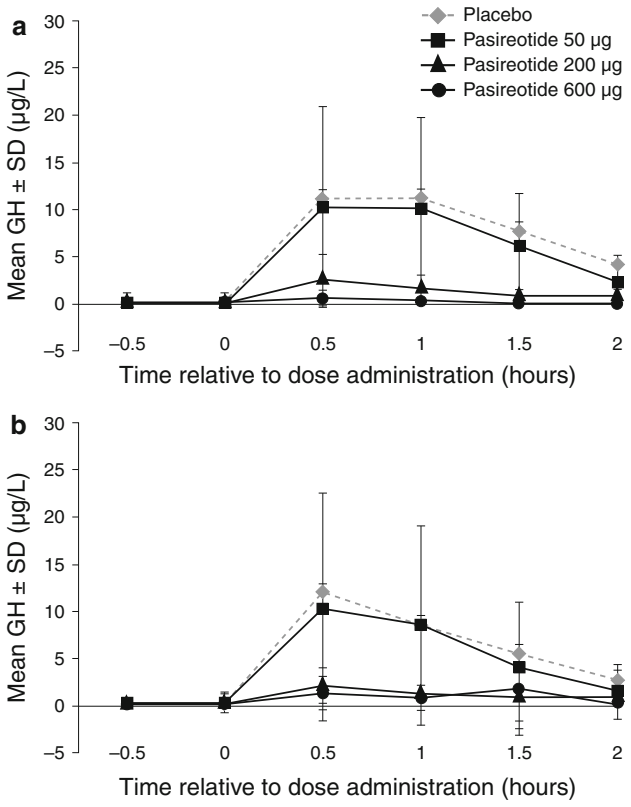

Fig. 3 Mean GH levels ± SD following GHRH stimulation on **a** day 2 and **b** day 13. Placebo treatment is shown as a summary of placebo values at all three treatment levels

model. GH inhibition was similar on days 2 and 13 (Fig. 3a, b).

Blood glucose metabolism

There were minimal changes in post-prandial glucose (0–2 h), insulin or glucagon levels on days 1 and 14 in the pasireotide 50 and 200 µg treatment groups compared with placebo (Table 4). In the pasireotide 600 µg group, post-prandial glucose and insulin levels (0–2 h) were higher on days 1 and 14 compared with placebo; however, post-prandial glucose levels (0–2 h) in the pasireotide 600 µg group were lower on day 14 than day 1. There were no clinically significant shifts in the 2-h post-prandial glucose levels as all subjects in the study had a shift of <140 mg/dL with both placebo and pasireotide (50, 200, and 600 µg) on day 1 and day 14. Subjects receiving pasireotide 600 µg sc had lower glucagon levels than subjects receiving placebo on day 1, but a higher glucagon level on day 14, although there was only one subject in each group.

Cholecystokinin levels

With pasireotide 200 µg, CCK levels were reduced on average by 38–51 % (i.e., mean decreases of −1 to −0.6 pmol/L) compared with placebo between 30 min pre- and post-lunch on day 1. By day 14, there were no noticeable differences in CCK levels between pasireotide and placebo subjects relative to day 1. Reductions in CCK levels for pasireotide 600 µg compared with placebo were similar at days 1 and 14, with differences ranging on average between 21 and 53 % (i.e., mean decreases of 0.3–1.3 pmol/L) from 30 min pre-lunch to 120 min post-lunch.

Gallbladder volume

Gallbladder volume increased for all pasireotide doses compared with placebo, with a greater volume increase observed with higher pasireotide doses (Fig. 4). The average increases were: pasireotide 50 µg: between 1.1 mL (28.6 %) and 5.3 mL (161.6 %); pasireotide 200 µg: between 15.9 mL (150.3 %) and 18.7 mL (450.1 %); pasireotide 600 µg: between 11.6 mL (1,154.8 %) and 19.4 mL (711.7 %).

Table 4 Mean $AUC_{(0–2\ h)}$ ± SD for post-prandial glucose, insulin, and glucagon levels

	Post-prandial glucose $AUC_{(0–2\ h)}$ h mg/dL		Post-prandial insulin $AUC_{(0–2\ h)}$ h mU/L		Post-prandial glucagon $AUC_{(0–2\ h)}$ h ng/L	
	Day 1	Day 14	Day 1	Day 14	Day 1	Day 14
Placebo ($n = 10$)	193.1 ± 16.0	183.0 ± 10.6	10.3 ± 10.8	8.3 ± 4.8	133.8 ± 27.3	128.8 ± 22.9
Pasireotide 50 µg ($n = 10$)	179.6 ± 14.0	186.9 ± 19.0	7.9 ± 5.6	10.4 ± 7.0	132.1 ± 18.8	128.8 ± 19.1
Placebo ($n = 8$)	194.3 ± 19.7	199.5 ± 20.5	19.3 ± 9.6	19.1 ± 13.1	127.7 ± 22.0	121.8 ± 24.3
Pasireotide 200 µg ($n = 8$)	195.4 ± 8.2	184.7 ± 16.5	18.0 ± 9.3	20.9 ± 9.8	121.6 ± 29.9	130.1 ± 31.1
Placebo ($n = 10$)	197.0 ± 15.8	195.3 ± 21.5	26.2 ± 9.0	31.8 ± 15.5	159.9 ± 36.0	139.5*
Pasireotide 600 µg ($n = 10$)	231.7 ± 46.4	212.8 ± 43.3	36.6 ± 23.8	45.6 ± 30.2	131.5 ± 36.4	150.5*

The post-lunch AUC for blood glucose, insulin, and glucagon is calculated based on the assessments from five scheduled time points (pre-lunch, 30, 60, 90, and 120 min post-lunch) using the linear trapezoidal rule

AUC area under the curve

* Only one patient had available data for assessment of day 14 post-prandial glucagon in the 600 µg cohort

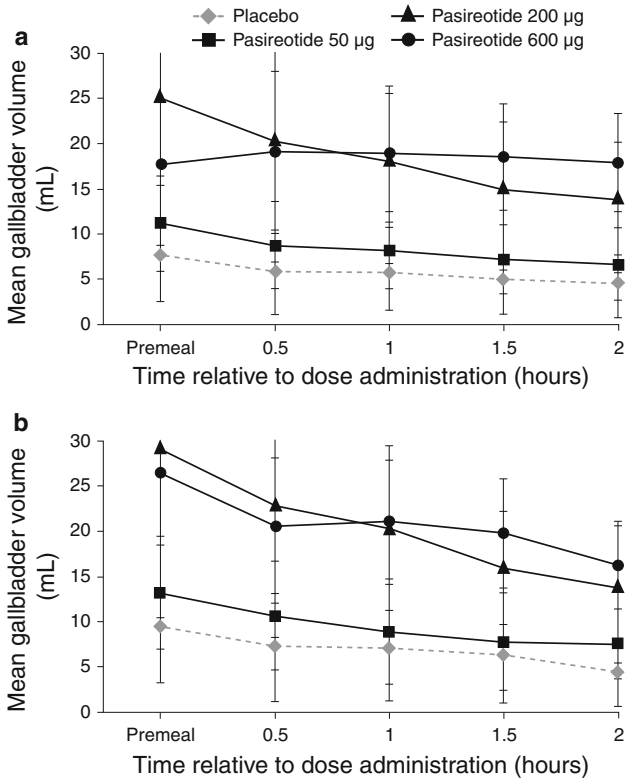

Fig. 4 Mean gallbladder volume ± SD over time at **a** day 1 and **b** day 14. Placebo treatment is shown as a summary of placebo values at all three treatment levels

Stool fat

The difference in the percentage of stool fat increased with higher pasireotide doses. The differences compared with placebo were: pasireotide 50 µg: between −0.3 and 2.9 %; pasireotide 200 µg: between 2.0 and 4.9 %; pasireotide 600 µg: between 4.7 and 7.7 %.

Gastrin and thyroid hormones

No significant differences in gastrin levels and thyroid hormone levels were observed for any pasireotide sc doses compared with placebo.

Discussion

This study evaluated the safety, tolerability, and PK of pasireotide sc in healthy male volunteers. Pasireotide 50, 200, and 600 µg sc administered qd for 14 days was generally well tolerated. AEs were mostly mild or moderate in intensity and gastrointestinal in nature. A total of 10 subjects treated with pasireotide 200 or 600 µg experienced nausea, which occurred within 15 min of injection and lasted between 10 min and 4 days. In the five subjects who reported vomiting during the study, this was transient, occurring predominantly on days 1 and 2. All AEs resolved without clinical intervention and no SAEs or deaths were recorded in this study. AEs considered to be potentially drug related were also mostly gastrointestinal and mild or moderate in intensity. No clinically significant changes in laboratory parameters, vital signs and ECG findings were reported during the study period.

PK steady state seemed to be achieved after 3 days of daily pasireotide sc injections and PK exposures were approximately dose proportional on day 1 after a single dose and on day 14 at steady state. The T_{max} and CL/F values were similar between days 1 and 14, suggesting linear and time-independent PK of pasireotide sc. In addition, the approximate 12-h (mean 9.7–13.1 h across doses) effective half-life ($T_{½,eff}$) of pasireotide is longer than that of octreotide sc (∼1.7 h [14]), which suggests that it is suitable for a twice-daily dosing regimen. Phase II and III trials investigating the clinical efficacy and safety of twice-daily (bid) pasireotide sc, as well as a long-acting repeatable formulation (pasireotide LAR), in patients with acromegaly, Cushing's disease, NET and other solid tumors that express multiple somatostatin receptor subtypes are currently ongoing [18–24, 29]. The results of the Phase I study reported here were obtained (although not published) prior to the Phase II trials discussed above [18, 19, 23, 24] and contributed toward the establishment of the pasireotide bid dosing regimen.

As expected for this class of compound, pasireotide had an effect on glucose metabolism. Single doses of pasireotide 600 µg sc were associated with pre- and post-prandial elevations in glucose levels relative to placebo on day 1. Glucose levels on day 14 were lower than on day 1 in pasireotide 600 µg sc recipients (mean post-prandial glucose $AUC_{(0–2\ h)}$ of 212.8 versus 231.7 h mg/dL), but higher than glucose levels on day 14 in placebo recipients. This suggests that increases in glucose levels are transient. Similar elevations in blood glucose levels following pasireotide administration have been reported in patients with Cushing's disease [18]. The potential clinical impact of pasireotide-associated hyperglycemia in patients with pre-existing diabetes or glucose intolerance has been discussed elsewhere in the literature [30]. Compared with day 1, post-prandial insulin levels on day 14 were generally elevated in all groups. This is in contrast to other studies, where insulin levels have been observed to be lower in the post-prandial period [15]. A study in healthy volunteers confirmed that administration of pasireotide is related to decreases in insulin secretion, with no changes in insulin sensitivity [31].

Pasireotide 200 and 600 µg inhibited GHRH-stimulated GH secretion, as expected for this somatostatin analog. This effect was similar on days 1 and 14, indicating a

sustained effect. Gallbladder volume increased for all doses of pasireotide, with a greater increase observed for higher pasireotide doses. The post-prandial increase in gallbladder volume appeared to correlate with reduced levels of CCK at these doses. The increase in gallbladder volume was similar in subjects receiving both pasireotide 200 and 600 μg, while CCK levels were reduced to a greater extent after pasireotide 600 μg than pasireotide 200 μg. This suggests that only a slight reduction in CCK levels is sufficient to significantly delay gallbladder contractions, or it could indicate that pasireotide acts through another mechanism to decrease contractions. Further studies are required to confirm this. The incidence of fatty stools was more prevalent in subjects receiving higher doses of pasireotide (200 and 600 μg); however, there was no effect on overall stool weight at any dose. Pasireotide did not have any effect on gastrin and thyroid hormone secretion.

Conclusions

Pasireotide was generally well tolerated at doses up to 600 μg sc qd and the PK results showed a dose-proportional and time-independent PK profile after qd dosing of pasireotide sc in healthy male subjects. Based on these results, further studies have been undertaken to evaluate the tolerability of pasireotide sc at doses ≥600 μg administered once or twice daily. Investigation is also under way into the clinical efficacy and safety of pasireotide in patients with acromegaly, Cushing's disease, NET, and other solid tumors that express multiple somatostatin receptor subtypes.

Acknowledgments This study was funded by Novartis Pharma AG. Financial support for medical editorial assistance was provided by Novartis Pharmaceuticals Corporation. We thank Helene Darmofal for medical editorial assistance with this manuscript.

Conflict of interest CB has no conflicts of interest regarding the content of this article. KH, YW, EB, CD, YfW, and PM are employees of Novartis.

References

1. U. Kumar, Cross-talk and modulation of signaling between somatostatin and growth factor receptors. Endocrine **40**, 168–180 (2011)
2. A. Ben-Shlomo, H. Schmid, K. Wawrowsky et al., Differential ligand-mediated pituitary somatostatin receptor subtype signaling: implications for corticotroph tumor therapy. J. Clin. Endocrinol. Metab. **94**, 4342–4350 (2009)
3. C. Bruns, I. Lewis, U. Briner, G. Meno-Tetang, G. Weckbecker, SOM230: a novel somatostatin peptidomimetic with broad somatotropin release inhibiting factor (SRIF) receptor binding and a unique antisecretory profile. Eur. J. Endocrinol. **146**, 707–716 (2002)
4. H.A. Schmid, Pasireotide (SOM230): development, mechanism of action and potential applications. Mol. Cell. Endocrinol. **286**, 69–74 (2008)
5. J. Van Der Hoek, W.W. de Herder, R.A. Feelders et al., A single-dose comparison of the acute effects between the new somatostatin analog SOM230 and octreotide in acromegalic patients. J. Clin. Endocrinol. Metab. **89**, 638–645 (2004)
6. I. Donangelo, S. Melmed, Treatment of acromegaly: future. Endocrine **28**, 123–128 (2005)
7. L. Kvols, J.E. Glusman, E.A. Hahn et al., The effects of pasireotide (SOM230) on health-related quality of life in patients with metastatic carcinoid tumors refractory or resistant to octreotide LAR. J. Clin. Oncol. **25(18S)**, abst 4558 (2007)
8. L. Kvols, B. Wiedenmann, K. Oberg et al., Safety and efficacy of pasireotide (SOM230) in patients with metastatic carcinoid tumors refractory or resistant to octreotide LAR: results of a Phase II study. ASCO Gastrointestinal Cancers Symposium, San Francisco, 26–28 January 2006, abst 171
9. K.I. Alexandraki, G. Kaltsas, Gastroenteropancreatic neuroendocrine tumors: new insights in the diagnosis and therapy. Endocrine **41**, 40–52 (2012)
10. L.J. Hofland, S.W. Lamberts, The pathophysiological consequences of somatostatin receptor internalization and resistance. Endocr. Rev. **24**, 28–47 (2003)
11. L.J. Hofland, J. Van Der Hoek, R. Feelders et al., The multiligand somatostatin analogue SOM230 inhibits ACTH secretion by cultured human corticotroph adenomas via somatostatin receptor type 5. Eur. J. Endocrinol. **152**, 645–654 (2005)
12. D.L. Batista, X. Zhang, R. Gejman et al., The effects of SOM230 on cell proliferation and adrenocorticotropin secretion in human corticotroph pituitary adenomas. J. Clin. Endocrinol. Metab. **91**, 4482–4488 (2006)
13. Y. Horsmans, K. Hu, M. Ruffin et al., Effect of hepatic impairment on the pharmacokinetics of pasireotide (SOM230): results from a multicenter Phase I study. J. Clin. Pharmacol. **52**, 552–558 (2012)
14. P. Ma, Y. Wang, J. Van Der Hoek et al., Pharmacokinetic-pharmacodynamic comparison of a novel multiligand somatostatin analog, SOM230, with octreotide in patients with acromegaly. Clin. Pharmacol. Ther. **78**, 69–80 (2005)
15. S. Petersenn, N. Unger, K. Hu et al., Pasireotide (SOM230), a novel multi-receptor-targeted somatostatin analogue, is well tolerated when administered as a continuous 7-day subcutaneous infusion in healthy male volunteers. J. Clin. Pharmacol. doi: 10.1177/0091270011408727, [Epub ahead of print] (2011)
16. S. Petersenn, K. Hu, M. Maldonado et al., Tolerability and dose-proportional pharmacokinetics of pasireotide administered as a single dose or two divided doses in healthy male volunteers: a single-center, open-label, ascending-dose study. Clin. Ther. **34**, 677–688 (2012)
17. M. Shenouda, M. Maldonado, Y. Wang et al., An open-label, dose-escalation study of once- and twice-daily pasireotide in healthy volunteers: safety, tolerability and effects on glucose, insulin and glucagon levels. Am. J. Ther. (2012 in press)
18. M. Boscaro, W.H. Ludlam, B. Atkinson et al., Treatment of pituitary dependent Cushing's disease with the multi-receptor ligand somatostatin analog pasireotide (SOM230): a multicenter, Phase II trial. J. Clin. Endocrinol. Metab. **94**, 115–122 (2009)
19. M. Boscaro, Y. Zhang, K. Sen et al., Long-term treatment of Cushing's disease with pasireotide (SOM230): results from a Phase II extension study. Endocr. Rev. **31**(3 Suppl 1), S333, abst P1-274 (2010)
20. M. Bronstein, F. Gu, C.-C. Shen et al. A randomized, blinded, multicenter, Phase III study to assess the efficacy and safety of

pasireotide LAR versus octreotide LAR in patients with active acromegaly. 14th European NeuroEndocrine Association Congress, Liege, 22–25 September 2010, abst OC-6.1
21. A. Colao, J. Fleck, S. Pain et al., Pasireotide LAR versus octreotide LAR or lanreotide autogel in patients with inadequately controlled acromegaly: a Phase III, multicenter, randomized, parallel-group study. 14th European Neuroendocrine Association Congress, Liege, 22–25 September 2010, abst OC-6.2
22. A. Colao, S. Petersenn, J. Newell-Price et al., A 12-month Phase 3 study of pasireotide in Cushing's disease. N. Engl. J. Med. **366**, 914–924 (2012)
23. L. Kvols, K. Oberg, T.M. O'Dorisio et al., Efficacy, safety and pharmacokinetic results from a Phase II study of pasireotide (SOM230) in the treatment of patients with metastatic NETs refractory or resistant to octreotide LAR. Neuroendocrinology **92**(1), abst C57 (2010)
24. S. Petersenn, J. Schopohl, A. Barkan et al., Pasireotide (SOM230) demonstrates efficacy and safety in patients with acromegaly: a randomized, multicenter, Phase II trial. J. Clin. Endocrinol. Metab. **95**, 2781–2789 (2010)
25. H. Dietrich, K. Hu, M. Ruffin et al., Safety, tolerability and pharmacokinetics of a single dose of pasireotide long-acting release (LAR) in healthy volunteers: a single-center Phase I study. Eur. J. Endocrinol. doi:10.1530/EJE-11-0773, [Epub ahead of print] (2012)
26. Metropolitan Life Insurance Company, Metropolitan height and weight tables. Stat. Bull. **64**, 2–9 (1983)
27. H. Boxenbaum, M. Battle, Effective half-life in clinical pharmacology. J. Clin. Pharmacol. **35**, 763–766 (1995)
28. B.P. Smith, F.R. Vandenhende, K.A. DeSante et al., Confidence interval criteria for assessment of dose proportionality. Pharm. Res. **17**, 1278–1283 (2000)
29. J. Hasskarl, M. Kaufmann, H.A. Schmid, Somatostatin receptors in non-neuroendocrine malignancies: the potential role of somatostatin analogs in solid tumors. Future Oncol. **7**, 895–913 (2011)
30. G. Mazziotti, C. Gazzaruso, A. Giustina, Diabetes in Cushing syndrome: basic and clinical aspects. Trends Endocrinol. Metab. **22**, 499–506 (2011)
31. R.R. Henry, S. Mudaliar, K. Wetli-Hermosillo et al., Mechanism and management of hyperglycemia associated with pasireotide: results from studies in healthy volunteers. Endocr. Rev. **32**(03), abst P3-274 (2011)