CLINICAL STUDY

Safety, tolerability, and pharmacokinetics of a single dose of pasireotide long-acting release in healthy volunteers: a single-center Phase I study

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Abstract

Objective: This study was conducted to evaluate the safety, tolerability, and pharmacokinetics (PKs) of different doses of a long-acting release (LAR) formulation of pasireotide in healthy subjects.

Design: Single-center, open-label, randomized Phase I study.

Methods: Twelve healthy male subjects received a single s.c. dose of pasireotide 300 µg followed by a washout period of 7 days (or at least 5 days), before receiving an i.m. injection of pasireotide LAR 40 mg ($n=5$) or 60 mg ($n=7$). Assessments included adverse events (AEs), PKs, and glucose, insulin, glucagon, and HbA1c levels.

Results: Pasireotide LAR showed an extended-release profile over 1 month with two concentration peaks observed 1 and around 20 days after injection. The area under curve exposure of pasireotide LAR was dose proportional when the dose levels were compared, and the bioavailability of the LAR relative to the s.c. formulation was complete. Administration of pasireotide LAR resulted in an increase in fasting and postprandial glucose levels; however, an attenuation of the hyperglycemic effect was observed after 15 days. The most frequently reported AEs were mild-to-moderate diarrhea, abdominal pain, and flatulence. Only gastrointestinal AEs and injection site reactions were suspected to be drug related.

Conclusions: Pasireotide LAR was generally well tolerated with mostly mild AEs at doses up to 60 mg and showed a dose-proportional, extended-release profile in healthy subjects. Based on the favorable results of this study, further clinical development of pasireotide LAR is under way, which will give insight into the PKs, efficacy, and safety of pasireotide LAR in patient populations.

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Introduction

Pasireotide (SOM230) is a cyclohexapeptide somatostatin analog with a molecular weight of 1047 kDa and contains the structural elements [(2-aminoethyl)aminocarbonyl oxy]-L-proline, phenylglycine, and tyrosine (benzyl). Pasireotide was developed in a diaspertate form for s.c. administration (Fig. 1A) and in a pamoate form for i.m. injection as part of a long-acting release (LAR) formulation (Fig. 1B).

Pasireotide is a multireceptor-targeted somatostatin analog with high affinity for four of the five somatostatin receptor subtypes (sst; the greatest for sst₅) that regulate anterior pituitary hormone secretion (1). Compared with other somatostatin analogs such as octreotide and lanreotide, pasireotide binds with higher affinity to sst₁, sst₃, and sst₅ and with slightly lower

affinity to sst₂ (2). Given this unique receptor-binding profile, pasireotide may have enhanced potential in targeting pituitary adenomas, such as those seen in patients with Cushing's disease or acromegaly. The corticotroph pituitary adenomas that underlie Cushing's disease express multiple sst, but sst₅ predominates (3). Activation of sst₅ inhibits ACTH secretion *in vitro* and is a potential therapeutic target for the treatment of Cushing's disease (4, 5, 6). The rationale for the therapeutic applicability of pasireotide in acromegaly is also based on the differences in binding affinity and functional activity of pasireotide and octreotide. It has been suggested that in tumors that express sst other than sst₂, pasireotide may have a stronger inhibitory effect on hormone secretion than octreotide.

In healthy volunteers, pasireotide is generally well tolerated when administered once or twice daily as a s.c.

Figure 1 The chemical structures of pasireotide s.c. (A) and LAR (B).

injection and after daily infusion of doses up to 2050 $\mu\text{g}/\text{day}$ for 7 days (7, 8, 9, 10, 11).

Phase II and III clinical studies have shown that twice-daily pasireotide s.c. is effective in controlling GH and insulin-like growth factor 1 (IGF1) levels and reducing pituitary tumor volume in patients with acromegaly (12, 13) and urinary free cortisol levels in patients with Cushing's disease (14, 15). These studies also showed that twice-daily pasireotide s.c. has a safety profile similar to that of other somatostatin analogs except for the degree of hyperglycemia, with no unexpected adverse events (AEs) reported.

For chronic disease treatment, twice-daily s.c. injections may not be convenient for patients, and development of a LAR formulation is warranted. The pasireotide LAR formulation was designed with biodegradable polymers to release the active drug over an extended period in order to facilitate once-monthly i.m. administration, which is similar in design to that of the octreotide LAR formulation. Furthermore, by controlling the drug release rate, pasireotide LAR is expected to produce less peak-to-trough fluctuation than pasireotide s.c., thereby potentially minimizing AEs such as nausea, vomiting, and hyperglycemia, which can be observed with immediate-release pasireotide s.c.

This paper presents the results of a single-center, open-label, Phase I study of the safety, tolerability, and pharmacokinetic (PK) profile of a single dose of pasireotide LAR in healthy subjects.

Materials and methods

Subjects

Healthy male subjects aged 18–40 years with a body mass index (BMI) of 20–30 kg/m^2 , a body weight > 50 kg, no history of relevant medical disorders, normal screening physical evaluation, and normal laboratory blood tests were enrolled in the study.

Subjects were excluded if they used any prescription drug or over-the-counter medication (except for paracetamol) 14 days before dosing, participated in any clinical investigation within 4 weeks prior, donated or lost ≥ 400 ml of blood within 8 weeks before dosing, or had been diagnosed at any time as having either type 1 or type 2 diabetes mellitus or impaired glucose tolerance. A medical history of clinically significant electrocardiogram (ECG) abnormalities or a family history of a prolonged QT interval syndrome also resulted in exclusion. The study was approved by the independent ethics committee, research ethics board, or institutional review board 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

This was a single-center, open-label, Phase I study. All subjects received a single dose of pasireotide 300 μg s.c. in the abdominal wall followed by a washout period of 5–7 days before receiving an i.m. injection of pasireotide LAR into the left or right gluteal muscle. Subjects were consecutively allocated into a cohort; those in cohort 1 received pasireotide LAR 40 mg and subjects in cohort 2 received pasireotide LAR 60 mg. All subjects were asked to report to the study site at ~ 0800 h (1 h before dosing) for each visit in a fasted state for predose evaluations. The screening period was days -21 to -1 . Pasireotide 300 μg s.c. was administered on study day 1 and pasireotide LAR (40 or 60 mg) was administered on study day 7. Day 70 was the study completion day.

Objectives

The primary objectives were to assess the safety, tolerability, and PK profile of different doses of pasireotide LAR. Secondary objectives were to estimate the bioavailability of pasireotide LAR at different dose levels relative to a single dose of an s.c. injection and to investigate the effects of pasireotide LAR on glucose, insulin, and glucagon levels.

Assessments

Clinical laboratory evaluations, ECG, vital signs, and physical examination results were recorded. ECG

readings were taken on days 1, 7, 21, and at end of study with a standard 12-lead ECG. The tracings were dated and signed by the person who made the interpretation and the same person evaluated the tracings throughout the study. Blood pressure and pulse rate were assessed before pasireotide s.c. or LAR injection on days 1 and 7 respectively, in the supine position and after standing for 3 min. Assessments were also taken during the study screening period and on days 1, 7, and 21 at 0.5, 1, 2, and 8 h after dosing. Single measures were taken on days 2 and 8, every 2 days from days 9 to 35, and on days 42, 49, 63, and 70 (end of study).

Blood samples for PK analysis were collected on days 1 and 7 at 0 (0.25 h at day 1 only), 0.5, 1, 2, 3, 4, 6, 8, 10 (12 h at day 1 only), and 24 h at day 7 only. In addition, PK blood samples were collected every 2 days from study day 9 until study day 35 and on days 2, 42, 49, and 63. Subjects returned to the study center on day 70 for study completion, evaluation, and final blood sample collection.

For measurement of fasting and postprandial glucose, insulin, and glucagon levels, subjects had 8-h assessments on 4 days during the study: screening visit (days -21 to -1), study day 1 (pasireotide 300 μ g, s.c.), 7 (pasireotide LAR injection), and 21 (15 days after pasireotide LAR injection). During the 8-h assessments, subjects remained in the fasting state for the first 4 h and blood was collected at 0, 0.5, 1, 2, 3, and 4 h. After the 4-h collection time point, a standardized lunch was provided and blood was collected at 6 and 8 h. HbA_{1c} was measured at screening and at study end.

PK parameters analyzed after pasireotide LAR administration included the following: maximum concentrations observed in the first 3 days and from day 4 postdose ($C_{\max,p1}$ and $C_{\max,p2}$ respectively), time to reach $C_{\max}$ in the first 3 days and from day 4 postdose ($t_{\max,p1}$ and $t_{\max,p2}$ respectively), area under the concentration–time curve from time zero to the last quantifiable concentration time point postdose (AUC_{last}), AUC from zero to infinity (AUC_{inf}), elimination half-life ($t_{1/2}$), mean residence time (MRT), apparent total body clearance of drug from plasma (CL/F), apparent volume of distribution (V_z/F), and bioavailability of pasireotide LAR relative to pasireotide s.c. ($BA_{\text{LAR/s.c.}}$). Pasireotide LAR PK parameters (AUC_{inf} , AUC_{last} , $C_{\max,p1}$, and $C_{\max,p2}$) are presented as adjusted or corrected based on the actual dose of LAR administered, which was calculated based on the amount of drug left in the syringe after dosing using the following formula:

Dose-adjusted parameter

$$= (\text{parameter/actual dose}) \times \text{planned dose.}$$

Plasma concentrations were determined by a validated RIA with a lower limit of quantification of 150 pg/ml (0.15 ng/ml; intra-assay and interassay

precision: coefficient of variation (CV%) $\leq 30\%$; accuracy: within 70–130% of the nominal concentration). Noncompartmental PK analysis was performed using WinNonlin software (version 5.2; Pharsight, Mountain View, CA, USA). Laboratory samples for PK bioanalysis were analyzed at Novartis Pharma AG.

AEs and serious AEs (SAEs) were recorded throughout the study period.

Statistical analysis

All subjects who received the planned doses of pasireotide LAR were included in the safety and tolerability analysis. The PK analysis population included all subjects who received the planned dose of pasireotide LAR and had adequate PK samples.

Descriptive statistics of PK parameters included mean, s.d., CV%, minimum, maximum, geometric mean, and geometric mean CV%. $t_{\max}$ was treated as a discrete time variable and, thus, median values and ranges were presented. The geometric mean and 90% confidence interval (CI) of the bioavailability of pasireotide LAR relative to that of pasireotide s.c. was evaluated as follows: $(AUC_{\text{inf,LAR}}/\text{LAR dose})/(AUC_{\text{inf,s.c.}}/\text{s.c. dose})$. RiaSmart was the statistical package used to acquire raw data and calculate concentrations.

One-way ANOVA with the Bonferroni *post hoc* test was used for statistical comparison for the AUC (both fasting and postprandial) for glucose, insulin, and glucagon at screening, study day 1, and study day 15. $P < 0.05$ was considered significant. The paired *t*-test was used for statistical comparison for the AUC for glucose, insulin, and glucagon between the fasting and postprandial period.

Results

A total of 12 healthy subjects were enrolled to receive pasireotide LAR 40 mg ($n=5$) or pasireotide LAR 60 mg ($n=7$). Subject baseline demographics were similar between the two groups (Table 1). One subject in the pasireotide LAR 60 mg cohort was excluded from the safety and PK analyses because the subject received only $\sim 15\%$ of the planned dose due to a blockage in the syringe. Another subject in the pasireotide LAR 60 mg group withdrew consent after receiving the LAR dose and discontinued. This subject did not have adequate PK samples to be included in the PK analysis. As such, five subjects per cohort were included in the PK analysis population.

Pharmacokinetics

Pasireotide LAR showed an extended-release profile following a single i.m. dose of 40 or 60 mg in healthy volunteers. After administration, an initial increase in pasireotide concentration (burst) was observed with

Table 1 Subject baseline demographics (safety population).

	Pasireotide LAR	
	40 mg (n=5)	60 mg (n=6)
Age (years), mean $\pm$ s.d.	28.6 $\pm$ 2.61	32.0 $\pm$ 7.62
Sex – male, n (%)	5 (100)	6 (100)
Race-Caucasian, n (%)	5 (100)	6 (100)
Height (cm), mean $\pm$ s.d.	181.0 $\pm$ 6.82	179.2 $\pm$ 5.71
Weight (kg), mean $\pm$ s.d.	81.1 $\pm$ 4.91	78.1 $\pm$ 7.39
BMI (kg/m ²), mean $\pm$ s.d.	24.8 $\pm$ 2.27	24.3 $\pm$ 2.03

BMI, body mass index.

a peak at 10–24 h followed by a decrease from days 1 to 7. The slow-release phase then followed, characterized by a peak at around day 20 (pasireotide LAR 40 mg: $t_{\max,p2}$ 18 days; pasireotide LAR 60 mg: $t_{\max,p2}$ 22 days) and a slow decline to the last sampling point (Fig. 2).

The exposure data of $C_{\max,p2}$, AUC_{last} , and AUC_{inf} were approximately dose proportional for pasireotide LAR 40 and 60 mg. For the pasireotide LAR 40 and 60 mg doses, $C_{\max,p1}$ values were 6.1 ± 3.9 and 5.5 ± 1.2 ng/ml respectively; $C_{\max,p2}$: 9.6 ± 5.1 and 15.8 ± 3.3 ng/ml; AUC_{last} : 4589 ± 1153 and 7516 ± 705 ng h/ml; AUC_{inf} : 4959 ± 1067 and 7970 ± 650 ng h/ml respectively (Table 2). The bioavailability of pasireotide LAR relative to that of pasireotide s.c. was 148% (90% CI: 130, 168) and 133% (90% CI: 110, 155) for the pasireotide LAR 40 and 60 mg doses respectively. Individual subject plasma pasireotide concentration profiles for the pasireotide LAR 40 and 60 mg doses are shown in Supplementary Figure 1, see section on supplementary data given at the end of this article.

Safety and tolerability

No SAEs or deaths occurred during the study. All subjects who received pasireotide LAR experienced AEs. The most frequently reported drug-related AEs were diarrhea, abdominal pain, injection site pain, and flatulence (Table 3), with the majority being mild or moderate in intensity.

No pasireotide LAR recipient showed QT prolongation during therapy, and no subject had either QT interval ≥ 480 ms or QTc interval ≥ 450 ms before or during the study. All subjects developed bradycardia during the study period with a maximum change from 60 bpm (median; range: 51–73 bpm) at baseline to 55 bpm (median; range: 46–68 bpm) at day 21 (15 days after pasireotide LAR injection). No subject developed clinically significant or symptomatic bradycardia, and all subjects had a heart rate similar to that exhibited at baseline and day 70 (end of study).

At screening, six subjects had a normal heart rate (> 60 bpm; median 67 bpm; range 61–73 bpm) and six subjects had bradycardia (< 60 bpm; median 57 bpm; range 51–58 bpm). Subjects with a normal heart rate at

baseline developed maximum bradycardia at day 21 (median 55 bpm; range 46–68 bpm) that normalized by day 70 (median 63 bpm; range 50–81 bpm). Subjects with bradycardia at baseline remained bradycardic throughout the trial (at day 21: median 55 bpm, range 46–68 bpm; at day 70: median 59 bpm, range 50–65 bpm).

No clinically significant changes in liver function tests were found. No subjects displayed any significant abnormalities in the gallbladder ultrasounds recorded prestudy or at study completion.

Glucose, insulin, and glucagon evaluations

At screening, all 11 subjects had normal fasting blood glucose levels (< 100 mg/dl (< 5.5 mmol/l)). After injection of pasireotide LAR, nine subjects had a peak fasting blood glucose level that shifted to the next category (100–125 mg/dl (5.6–6.9 mmol/l)) and the remaining two subjects (one from each cohort) had fasting blood glucose levels ≥ 126 mg/dl (≥ 7.0 mmol/l).

Pasireotide (either s.c. (on day 1) or LAR (on day 7)) resulted in increases in fasting glucose levels compared with baseline values (samples taken during the screening period). In addition, both pasireotide LAR 40 and 60 mg recipients experienced elevated postprandial glucose levels, which appeared to be dose and concentration dependent (Supplementary Figure 2, see section on supplementary data given at the end of this article). Although postprandial values at day 21 (15 days after pasireotide LAR injection) remained higher than at baseline for both doses, the elevated fasting and postprandial blood glucose levels showed an attenuation compared with day 7 (Table 4). At the end of the study (70 days), fasting blood glucose levels had decreased to similar levels observed at baseline.

Figure 2 Mean (s.d.) plasma concentration vs time profiles of pasireotide in healthy volunteers following a single i.m. injection of pasireotide LAR 40 or 60 mg. In this figure, day 1 refers to the day on which pasireotide LAR was administered (study day 7).

Table 2 Pharmacokinetic parameters of pasireotide LAR 40 and 60 mg. All parameters are presented as mean $\pm$ S.D., except $t_{\max}$ data that are expressed as median (range).

	Pasireotide LAR	
	40 mg (n=5)	60 mg (n=5 ^a)
$C_{\max,p1}$ (ng/ml)	6.08 $\pm$ 3.89	5.52 $\pm$ 1.20
$t_{\max,p1}$, h (range)	10 (8–10)	24 (10–25)
$C_{\max,p2}$ (ng/ml)	9.60 $\pm$ 5.13	15.77 $\pm$ 3.27
$t_{\max,p2}$, h (range)	432 (336–840)	528 (432–672)
AUC _{last} (ng h/ml)	4589 $\pm$ 1153	7516 $\pm$ 705
AUC _{inf} (ng h/ml)	4959 $\pm$ 1067	7970 $\pm$ 650
$t_{1/2}$ (h)	336 $\pm$ 97	316 $\pm$ 76
MRT _{last} (h)	588 $\pm$ 119	622 $\pm$ 81
MRT _{inf} (h)	699 $\pm$ 211	697 $\pm$ 91
CL/F (l/h)	8.5 $\pm$ 2.4	7.6 $\pm$ 0.6
V_z/F (l)	4196 $\pm$ 1920	3444 $\pm$ 863
BA _{LAR/s.c.}	1.48 $\pm$ 0.15	1.33 $\pm$ 0.23

$C_{\max,p1}$, maximum concentration observed in the first 3 days; $t_{\max,p1}$, time to reach maximum concentration ($C_{\max}$) in the first 3 days; $C_{\max,p2}$, maximum concentration observed from day 4 postdose; $t_{\max,p2}$, time to reach $C_{\max}$ from day 4 postdose; AUC_{last}, area under the concentration–time curve (AUC) from time zero to the last quantifiable concentration time point postdose (last); AUC_{inf}, area under the concentration–time curve from zero to infinity; $t_{1/2}$, elimination half-life; MRT, mean residence time; MRT_{last}, mean residence time determined as area under first moment curve (AUMC)_{last}/AUC_{last}; MRT_{inf}, mean residence time determined as AUMC_{inf}/AUC_{inf}; CL/F, apparent total body clearance of drug from plasma; V_z/F , apparent volume of distribution; BA_{LAR/s.c.}, bioavailability of pasireotide LAR relative to pasireotide s.c.

^aOne patient received ~15% of the planned dose of LAR (10 mg instead of 60 mg) due to clogging inside the syringe and was excluded. Another subject received the LAR dose but withdrew consent and discontinued before providing adequate PK samples.

During the fasting period, pasireotide resulted in marked decreases in insulin AUC values compared with baseline values (Table 4), and the extent of the decrease appeared to be dose and concentration dependent (Supplementary Figure 2). After pasireotide LAR 40 and 60 mg injection on day 7, postprandial mean insulin AUC was higher than at baseline in both the 40 and 60 mg cohorts. Fifteen days after pasireotide LAR injection, postprandial mean insulin AUC was lower than at baseline for both cohorts.

Decreases in glucagon AUC values during pasireotide treatment in the fasting period were smaller compared with decreases in insulin AUC values, but these were larger in the postprandial period. After pasireotide LAR 40 and 60 mg injection, the mean glucagon AUC was lower than at baseline for both doses (Table 4). Fifteen days after pasireotide LAR injection, changes in mean glucagon AUC for both doses in the fasting state were more similar to those observed on the day of dosing. No changes in HbA1c levels were detected.

Discussion

Following a single i.m. injection in healthy subjects, pasireotide LAR showed a dose-proportional, extended-release profile suitable for monthly administration. A first peak (burst) in pasireotide concentration was

observed on day 1 after administration of pasireotide LAR followed by a decrease in concentration from days 1 to 7. A second slow-release peak with maximum concentrations around day 20 was observed, after which pasireotide plasma concentrations gradually decreased.

The plasma AUC ratio of pasireotide LAR relative to that of pasireotide s.c. was 148 and 133% for the 40 and 60 mg doses respectively, suggesting that the bioavailability of the LAR formulation relative to the s.c. formulation was complete. The >100% AUC ratio was probably due to an underestimation of the plasma AUC for the pasireotide 300 μ g s.c. dose as a result of the terminal phase falling below the limit of quantification of the bioanalytical assay.

In general, pasireotide LAR was well tolerated in this study of healthy volunteers. The majority of the observed AEs were typical of those expected with somatostatin analogs (16). The most frequently reported AEs were mild-to-moderate gastrointestinal disorders, predominantly diarrhea, which was sometimes associated with abdominal pain and flatulence. Adverse gastrointestinal events are commonly seen during the first few weeks of treatment with currently available somatostatin analogs and become less frequent during ongoing treatment (17). As only one dose of pasireotide LAR was administered to each subject in this study, the rate of AEs seen in this study may not represent the frequency of potential AEs during routine clinical use.

Administration of pasireotide LAR resulted in increases in fasting glucose levels and fasting glucose AUC values; elevated levels were seen 15 days after injection compared with baseline in both the fasting and the postprandial state. The hyperglycemic effect decreased over time, and by day 43, fasting blood glucose levels had returned to those observed during the screening visit. During the fasting period, there were also marked decreases in insulin AUC levels and small decreases in glucagon AUC levels relative to screening

Table 3 Adverse events suspected to be study-drug related.

Adverse event	Pasireotide LAR (n (%))	
	40 mg (n=5)	60 mg (n=6 ^a)
Diarrhea	3 (60)	6 (100)
Abdominal pain	1 (20)	4 (67)
Flatulence	1 (20)	3 (50)
Abdominal discomfort	0	1 (17)
Abnormal bowel sounds	–	1 (17)
Pale feces	1 (20)	1 (17)
Frequent bowel movements	0	1 (17)
Injection site pain	4 (80)	1 (17)
Dizziness	1 (20)	1 (17)
Headache	0	1 (17)
Abdominal distension	1 (20)	0

^aOne patient received ~15% of the planned dose of LAR (10 mg instead of 60 mg) due to clogging inside the syringe and was excluded.

Table 4 Mean $\pm$ S.D. (percentage change $\pm$ S.D. from predose) AUC for glucose, insulin, and glucagon over 8 h at screening and days 1 and 15 after pasireotide LAR administration.

Pasireotide LAR dose and visit	Fasting AUC (0–4 h)			PP peak glucose levels*			PP AUC* (4–8 h)		
	Glucose (mg h/dl)	Insulin (mU h/l)	Glucagon (ng h/l)	Glucose (mg/dl)	Insulin (mU h/l)	Glucose (mg h/dl)	Insulin (mU h/l)	Glucose (mg h/dl)	Insulin (mU h/l)
40 mg, screening (n=5)	91.4 $\pm$ 5.9	19.9 $\pm$ 8.8	825.1 $\pm$ 211.5	86.6 $\pm$ 5.4 (NS)	73.2 $\pm$ 23.9 (0.0022)	332.6 $\pm$ 24.1 (NS)	101.9 $\pm$ 37.7 (37.9 $\pm$ 16.9%)	1374.9 $\pm$ 384.5 (0.029)	528.7 $\pm$ 226.3 (–57.8 $\pm$ 24.9%)
40 mg, study day 7 (day 1 of pasireotide LAR dose)	118.2 $\pm$ 12.4	12.4 $\pm$ 6.6 (–34.9 $\pm$ 24.4%)	641.6 $\pm$ 109.7 (–18.2 $\pm$ 23.9%)	164.0 $\pm$ 43.7 (0.041)	67.3 $\pm$ 33.3 (–8.5 $\pm$ 41.0%)	563 $\pm$ 112.7 (70.1 $\pm$ 37.2%)	101.9 $\pm$ 37.7 (37.9 $\pm$ 16.9%)	492.9 $\pm$ 139.4 (–61.9 $\pm$ 13.7%)	528.7 $\pm$ 226.3 (–57.8 $\pm$ 24.9%)
40 mg, study day 21 (day 15 of pasireotide LAR dose)	107.2 $\pm$ 9.5	8.7 $\pm$ 2.6 (–53.7 $\pm$ 8.6%)	735.8 $\pm$ 297.1 (–10.3 $\pm$ 28.4%)	99.8 $\pm$ 4.1 (NS)	67.3 $\pm$ 33.3 (–8.5 $\pm$ 41.0%)	384.6 $\pm$ 28.2 (16.0 $\pm$ 10.1%)	67.3 $\pm$ 33.3 (–8.5 $\pm$ 41.0%)	528.7 $\pm$ 226.3 (–57.8 $\pm$ 24.9%)	528.7 $\pm$ 226.3 (–57.8 $\pm$ 24.9%)
P value among screening, day 1, and day 15	0.0023	NS	NS	0.0009	NS	0.0005	NS	0.0003	NS
60 mg, screening (n=6)	88.5 $\pm$ 4.1	22.8 $\pm$ 11.6	650.9 $\pm$ 235.2	96.2 $\pm$ 8.2 (0.035)	73.2 $\pm$ 35.5 (0.0056)	354.5 $\pm$ 25.7 (NS)	64.4 $\pm$ 17.4 (–0.6 $\pm$ 34.5%)	1417.7 $\pm$ 734.9 (0.015)	1417.7 $\pm$ 734.9 (0.015)
60 mg, study day 7 (day 1 of pasireotide LAR dose)	113.0 $\pm$ 10.6	11.6 $\pm$ 4.3 (–46.0 $\pm$ 11.0%)	463.0 $\pm$ 138.0 (–26.9 $\pm$ 11.1%)	169.0 $\pm$ 45.1 (0.015)	64.4 $\pm$ 17.4 (–0.6 $\pm$ 34.5%)	579.8 $\pm$ 123.4 (64.6 $\pm$ 37.7%)	64.4 $\pm$ 17.4 (–0.6 $\pm$ 34.5%)	458.9 $\pm$ 233.1 (–63.1 $\pm$ 21.6%)	458.9 $\pm$ 233.1 (–63.1 $\pm$ 21.6%)
60 mg, study day 21 (day 15 of pasireotide LAR dose)	103.6 $\pm$ 7.9	7.1 $\pm$ 3.0 (–66.0 $\pm$ 10.3%)	549.6 $\pm$ 278.8 (–11.4 $\pm$ 15.0%)	97.8 $\pm$ 7.5 (NS)	46.6 $\pm$ 23.3 (–34.5 $\pm$ 25.5%)	379.2 $\pm$ 30.3 (7.5 $\pm$ 10.8%)	46.6 $\pm$ 23.3 (–34.5 $\pm$ 25.5%)	546.6 $\pm$ 141.0 (–50.2 $\pm$ 21.7%)	546.6 $\pm$ 141.0 (–50.2 $\pm$ 21.7%)
P value among screening, day 1, and day 15	0.0004	0.018	NS	0.0042	NS	0.0003	NS	0.0059	NS

FPG, fasting peak glucose; PP, postprandial; AUC, area under curve; NS, nonsignificant ($P > 0.05$). *P value compared with fasting is presented within parentheses.

values. Postprandially, insulin AUC levels did not decrease to the extent seen in the fasting state, although the small sample size and large s.d. make interpretation of the data difficult. Glucagon levels were lower postprandially compared with fasting levels. The higher insulin levels and lower glucagon levels may be due to an incretin effect (i.e. an increase in insulin secretion after eating because of gastrointestinal secretion of glucagon-like peptide 1 and glucose-dependent insulinotropic peptide). However, incretin hormones were not measured in the current study; therefore, limited conclusions can be drawn from this study regarding the mechanism of postprandial hyperglycemia. Further studies on larger populations are warranted to address this. Changes in HbA_{1c} were negligible, although given the short exposure time of 70 days, pasireotide was unlikely to have a discernable influence on HbA_{1c}.

Results from a recent Phase III trial showed that treatment with twice-daily pasireotide s.c. significantly reduced cortisol levels and provided clinical benefit in patients with Cushing's disease. In this Phase III study, pasireotide had a safety profile similar to that of other somatostatin analogs (mostly transient gastrointestinal discomfort), with the exception of the degree of hyperglycemia; ~70% of patients experienced a hyperglycemia-related AE (15). Although patients with Cushing's disease are predisposed to impairments in glucose homeostasis because of the effects of chronic hypercortisolism, results from that study suggest that glucose levels should be monitored during treatment with pasireotide. Hyperglycemia should be proactively managed following current guidelines. Studies on pasireotide LAR in patient populations including Cushing's disease will determine the incidence of hyperglycemia and other AEs with pasireotide LAR. In the current single-dose study on healthy volunteers, cortisol levels were not assessed.

In conclusion, the results of this study indicate that a single dose of pasireotide LAR was generally well tolerated, with mostly mild and transient AEs at doses up to 60 mg, consistent with earlier studies of pasireotide s.c. in healthy volunteers. The PK results showed a dose-proportional, extended-release profile in healthy subjects. Further clinical development of pasireotide LAR is underway with studies on patient populations. Results from these studies will give further insight into the efficacy, safety, and PK of pasireotide LAR.

Supplementary data

This is linked to the online version of the paper at <http://dx.doi.org/10.1530/EJE-11-0773>.

Declaration of interest

K Hu, M Ruffin, D Song, E Bouillaud, Y Wang, and J Hasskarl are employees of Novartis. H Dietrich has no conflict of interest to disclose.

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