
Xia Chen, MD1; Guoxiang Shen, PhD2; Ji Jiang, PhD1; Hongzhong Liu, MD1; Ke Hu, PhD2; Christelle Darstein, MS3; Janet Lasher, HT2; and Pei Hu, MD1

1Clinical Pharmacology Research Centre, Peking Union Medical College Hospital, Beijing, China; 2Novartis Pharmaceutical Corporation, Oncology Business Unit, East Hanover, New Jersey; and 3Novartis Pharma AG, Basel, Switzerland

ABSTRACT

Purpose: The purpose of this study was to assess the pharmacokinetic (PK) properties and safety of single and multiple doses of subcutaneous (SC) pasireotide and a single-dose intramuscular (IM) long-acting release (LAR) formulation of pasireotide in Chinese healthy volunteers (HVs) versus the PK properties in Western HVs (pooled from previous PK studies).

Methods: In this phase I, single-center, open-label study, 45 Chinese male HVs were evenly randomized to 1 to 9 treatment sequences: each volunteer received a single dose of 300, 600, or 900 μg of pasireotide SC on day 1, followed by administration of the same dose BID from day 15 to the morning of day 19, and then a single IM dose of 20, 40, or 60 mg of pasireotide LAR on day 33. The PK parameters were assessed with noncompartmental analysis. Statistical comparison of PK parameters, including AUC, Cmax, and CL/F from both formulations, was made for Chinese versus Western male HVs (pooled from previous PK studies).

Findings: Of the 45 randomized HVs, 42 completed the study per protocol, 1 withdrew his informed consent for personal reasons, and 2 prematurely discontinued the study because of adverse events (AEs). Concentration-time and safety profiles of both formulations were similar to those reported in Western HVs. Mean geometric mean ratios (GMRs) of Chinese versus Western HVs ranged from 0.79 to 1.42. For most primary PK parameters, 90% CIs for GMRs were within a predefined ethnic insensitivity interval (90% CI, 0.70–1.43). After considering age and weight as covariates in the statistical model, the GMRs and 90% CIs for other PK parameters were within the predefined interval (Cmax in single-dose SC administration) or significantly decreased (Cmin,ss in multiple BID SC doses and first peak Cmax in the single-dose LAR formulation). No serious AEs were reported. Both formulations were well tolerated; pasireotide SC caused transient changes in glucose metabolism. Owing to the differential binding affinity to the somatostatin receptor subtypes, pasireotide LAR elicited a concentration-dependent increase of fasting blood glucose, substantial reduction in triglyceride, and a mild decrease in cholesterol. The most frequently reported AEs after single-dose and multiple-dose pasireotide SC were injection site reaction, nausea, dizziness, and diarrhea; most HVs developed diarrhea with single-dose pasireotide LAR.

Implications: The pasireotide formulations had similar PK and safety profiles between Chinese and Western male HVs. Thus, no ethnic sensitivity was found for pasireotide SC or LAR. (Clin Ther. 2014;36:1196–1210) © 2014 The Authors. Published by Elsevier HS Journals, Inc.

Key words: Chinese, healthy volunteers, long-acting release, pasireotide, pharmacokinetics, subcutaneous.

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INTRODUCTION

Somatostatins are endogenous peptides that exert broad, mostly inhibitory effects on exocrine and endocrine secretions. Somatostatin receptor subtypes (ssts) are expressed in different tissues under normal physiologic conditions and in many solid tumors, such as neuroendocrine tumors. Somatostatin analogues (SSAs) activate these receptors with different potencies, thereby decreasing cellular activity and subsequently inhibiting hormone secretion.

Pasireotide (SOM230) is a cyclohexapeptide SSA. Like natural somatostatin and other SSAs, pasireotide exerts its pharmacologic activity through binding to ssts. Owing to its high-binding affinity to 4 (sst1, sst2, sst3, and sst5) of the 5 known human ssts, it exhibits a unique binding profile that is the closest, known thus far, to natural somatostatin. Compared with the clinically available SSA octreotide, pasireotide exhibits a 30- to 40-fold greater binding affinity for sst1 and sst5, a 5-fold greater binding affinity for sst3, and a slightly lower (2 times) binding affinity for sst2.

Compared with another SSA, lanreotide, the binding affinity of pasireotide for sst1, sst3, and sst5 is 19-, 9-, and 106-fold higher, respectively, whereas the affinity for sst2 is slightly lower (2 times). Such a pharmacologic profile may indicate an improved efficacy profile for clinical indications currently treated with octreotide and lanreotide (such as acromegaly and gastroenteropancreatic neuroendocrine tumors). Pasireotide may also be beneficial in conditions where octreotide and lanreotide have not been effective. Indeed, in 2012, pasireotide was approved by the European Medicines Agency and the US Food and Drug Administration for the treatment of adult patients with Cushing’s disease when surgery has failed or is not an option.

Two types of injectable formulations of pasireotide have been developed: one for subcutaneous (SC) administration and the other as a long-acting release (LAR) formulation for intramuscular (IM) injection. Previous studies in the healthy Western population, mainly in white populations, have provided comprehensive pharmacokinetic (PK) and safety profile data for pasireotide SC up to 1500 μg administered as a single dose or BID doses and for pasireotide LAR 40 and 60 mg administered as a single dose. Moreover, studies on the clinical efficacy and safety profile of pasireotide have been performed in patients with acromegaly, Cushing’s disease, and neuroendocrine tumors. However, there has been little comprehensive PK investigation of an injectable formulation of pasireotide in Chinese male healthy volunteers (HVs) or patients. Such a study was expected to assess the PK and safety profiles in Chinese HVs and allow comparison with Western populations.

The present study evaluated the PK and safety profiles of pasireotide SC and pasireotide LAR in Chinese HVs and addressed potential ethnic differences by comparing the PK and safety profiles of Chinese male HVs in this study with those reported in Western male HVs and unpublished data in Western HVs from a bioequivalence study with pasireotide LAR 60 mg (unpublished data on file, Novartis Oncology, Clinical Pharmacology, East Hanover, New Jersey). In addition to the previously investigated glucose metabolism parameters, including blood glucose, insulin, and glucagon, this study also tested measures that reflect the effects of pasireotide (pasireotide LAR at 3 different dose levels) on relatively long-term glucose control, lipid metabolism and systemic concentrations of pancreatic enzymes, thyrotropin, and thyroid function measurements.

METHODS

Study Design

This was a Phase I, single-center, open-label, randomized, 3-period study. All HVs were recruited into the trial for medical screening. After medical screening, 45 eligible individuals were randomized on day 1 to 1 of 9 treatment sequences (Figure 1). The total study duration was a maximum of 124 days for each participant, which included a 21-day screening period, 3 treatment periods (SC single dose → multiple SC BID → IM LAR single dose) separated by two 14-day washout periods and a 70-day follow-up period after single-dose pasireotide LAR administration. Participants were allocated (1:1:1) to 1 of the 3 SC dose groups (300, 600, or 900 μg).

This study was sponsored by Novartis Pharmaceutical Corporation. The study was conducted in accordance with the Declaration of Helsinki and complied with the International Conference of Harmonisation Tripartite Guidelines for Good Clinical Practice and local laws. The Independent Ethics Committee of Peking Union Medical College Hospital (Beijing, China) approved the study protocol. All participants provided written informed consent to participate in the trial.
Study Population

Chinese male HVs age 18 to 45 years who weighed between 50 and 120 kg, had a body mass index (BMI) of 18.5 to 30 kg/m², and had no history of medical disorders were enrolled. They were assessed as healthy based on medical history, physical evaluation (including vital sign measurements), clinical laboratory test results, abdominal ultrasonography report, and triple 12-lead ECG. Participants were excluded if they had a QTcF interval $\geq 450$ milliseconds at screening or a history or clinical evidence of type 1 or type 2 diabetes mellitus or impaired fasting glucose, psychiatric disorders (including depression and anxiety disorders), gallbladder diseases, pancreatic disease, thyroid disease, or other clinically significant disorders. Use of any prescription or over-the-counter medication (except for paracetamol [acetaminophen] $\leq 2$ g/d) within 14 days of the first dosing day or a history within 12 months or evidence of drug or alcohol abuse also resulted in exclusion.

Study Drug and Administration

The pasireotide SC* and LAR formulations were prepared and supplied to the study center by Novartis. The pasireotide SC formulation was supplied in 1-mL vials that contained 300, 600, and 900 $\mu$g of pasireotide, whereas the pasireotide LAR formulation was supplied as a powder in vials that contained 20 and 40 mg of pasireotide with a 2-mL vehicle in separate vials (for reconstitution). Both formulations were administered immediately after preparation. Participants were required to stay at the research center on each dosing day and were confined to the site for 48 hours after the last dose of each study period. On day 1, a single dose of 300, 600, or 900 $\mu$g of pasireotide SC was injected at approximately 08:00 hours by 2 study nurses after an overnight fast. No food was permitted until at least 4 hours after dosing. In the next treatment period, multiple BID SC injections of the same pasireotide dose were administered at the same clock time under an overnight fasting condition on the mornings of days 15, 16, 17, 18, and 19 and 12 hours later in the evenings of days 15, 16, 17, and 18. Standard lunch and dinner were provided at 4 hours and 10 hours after the morning dose, respectively. In the last treatment period, on day 33, a single IM injection of 20, 40, or 60 mg of pasireotide LAR was administered into study participants’ left or right gluteal muscle at approximately 08:00 hours in a fasted condition. During this period, standard meals were provided between 12:00 and 13:00 hours and between 18:00 and 19:00 hours on the days HVs stayed at the research center.

PK Assessments

Blood samples for PK bioanalysis were collected in the SC single-dose period before dosing and at 0.25,
0.5, 1, 2, 4, 6, 8, 10, and 12 hours on day 1 and 24, 48, 72, 96, 120, and 144 hours after dosing, during the SC multiple-dose period on days 17 and 18 at predosing and on day 19 at predosing and a series of postdose time points identical to those defined for the SC single-dose period, and after the LAR single-dose injection on day 33 at predosing and at 0.5, 1, and 2 hours and then 2 hourly up to 12 hours after dosing, as well as on the first and second days, then every 2 days up to 4 weeks, and then weekly up to day 70.

A total of 2.5 mL of blood was collected into a Monovette EDTA tube for each sample and placed upright in an ice bath. Within 20 minutes, the samples were centrifuged (approximately 4°C, 15 minutes, approximately 1000g). Immediately after centrifugation, the plasma was transferred into polypropylene freezing vials and stored at −20°C. Pasireotide plasma concentrations were measured at Atlantbio SA (Saint-Nazaire, France) using a validated radioimmunoassay with a lower limit of quantitation (LLOQ) of 0.15 ng/mL.

For LAR administration, the dosing vial and injection syringe from each participant were collected to determine the residual dose using a validated HPLC method (WuXi AppTech Co, Shanghai, China) with a LLOQ of 0.15 ng/mL.

The PK parameters were estimated by Phoenix software, version 6.1 (Pharsight, Mountain View, California), using noncompartmental analysis (NCA). The reported NCA PK parameters include \( \text{AUC}_{\infty} \), \( C_{\text{max}} \), \( CL/F \), apparent volume of distribution \( (V_{z/F}) \), and \( t_{1/2} \) for single-dose pasireotide SC. For SC BID multiple dose, steady-state PK parameters, including \( \text{AUC}_{0-12,\text{ss}} \), \( C_{\text{max,ss}} \) and \( CL_{\text{ss}}/F \) were presented. The accumulation ratio (AR) of SC BID multiple dose was calculated as \( \text{AUC}_{0-12,\text{ss}} \) on day 19 divided by \( \text{AUC}_{0-12} \) on day 1. The NCA PK parameters for LAR single-dose administration include \( C_{\text{max}} \) (of the first peak \( [C_{\text{max,p1}}] \) and second peak \( [C_{\text{max,p2}}] \), \( \text{AUC}_{\infty} \), \( CL/F \), \( V_{z/F} \), and \( t_{1/2} \). In addition, the relative bioavailability of LAR using the SC single dose in the same HVs as reference was determined. For the PK data from LAR single-dose administration, the exact dose (corrected for residual dose) was used in the NCA.

**Safety Assessments**

Adverse events (AEs) were identified throughout the study. During each treatment period, vital signs, 12-lead ECG, and clinical laboratory evaluations (clinical chemical analysis, hematologic testing, and urinalysis) were recorded.

Blood samples to assess fasting insulin, fasting glucagon, fasting blood glucose, and \( \alpha \)-amylase assays were collected before dosing and at 0.5, 1, 2, 4, 6, and 8 hours after dosing on day 1. For the multiple-dose SC period, these measurements were taken before dosing in the morning on day 19 (the last dosing day) and at the same postdosing time points as that for the SC single-dose period, after the last morning dose on day 19. For single-dose IM LAR formulation administration, these measurements were taken before dosing and at the same time points after dosing as for the single-dose SC period. As follow-up, these evaluations were also performed 2 days after administration of the LAR dose, followed by every alternate day for 4 weeks and then weekly up to 70 days after dosing. Lipase assay was performed at screening, at the predosing time points on the first and fourth days of the multiple-dose SC period, and before dosing and on 6, 20, 28, and 70 days after the single-dose pasireotide LAR dose.

Both 1,5-anhydroglucitol (1,5-AG) and glycosylated hemoglobin (HbA1c) were measured to evaluate blood glucose homeostasis during the study. Blood samples for 1,5-AG assays were taken before dosing in each period and on days 6, 14, and 22 after the single-dose pasireotide LAR dose. HbA1c was measured at screening, before dosing of the multiple-dose SC period and the LAR period, and on day 70 of the LAR dose. In addition, thyrotropin, thyroid function (free and total thyroxine), cholesterol, and triglyceride were assessed at screening, before the first dose in the multiple-dose SC period and before dosing, and on days 6, 20, 28, and 70 after a single dose of the LAR formulation.

Laboratory samples of glucose, insulin, glucagon, 1,5-AG, and HbA1c were assessed by Quintiles Central Laboratory (Beijing, China), and the assays of hematologic tests and blood chemical tests other than glucose, \( \alpha \)-amylase, thyrotropin, and thyroid function were performed by the central laboratory of Peking Union Medical College Hospital.

**Statistical Analysis**

The PK set (by treatment) consisted of all HVs who received at least a single dose of pasireotide and provided evaluable PK profiles for at least one treatment period. The safety set included all HVs who

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received at least one dose of pasireotide (even those who took only part of the scheduled dose for a treatment day were considered).

Descriptive statistics of PK parameters from NCA in Chinese HVs were summarized by single-dose pasireotide SC and multiple-dose BID treatments and by single-dose LAR treatment. The primary PK parameters, including C\text{max}, AUC\text{ss}, and CL/F for single-dose pasireotide SC; AR, C\text{max,ss}, AUC\text{0–12,ss}, and CL\text{ss}/F for multiple-dose pasireotide SC BID; and C\text{max,p1}, C\text{max,p2}, AUC\text{ss}, and CL/F for single-dose pasireotide LAR from both Chinese HVs and those pooled Western HVs were compared using a statistical model:

$$Y_{ijk} = \mu + \alpha_i + \beta * x_j + \epsilon_{ijk}$$

in which, $Y_{ijk}$ denotes log-transformed (natural base) primary PK parameters mentioned above for individual $k$ from region $i$ ($i = 1, 2$; Chinese or Western) treated with $j$ dose level (single-dose pasireotide SC, multiple-dose SC BID, or single-dose LAR), $x_j$ denotes log of dose $j$, and $\epsilon_{ijk}$ is the error assumed to be independent and identically normal distributed with mean 0 and variance $\sigma^2$. The parameter $\mu$ refers to overall mean, $\alpha_i$ is the effect of region $i$, and $\beta$ is the slope parameter. In addition, weight and age were also explored as covariates. To assess the dose-exposure relationship between Chinese and Western study participants, the point estimates and 90% CIs for mean difference between these 2 regions for these primary PK parameters (in log scale) of the pasireotide SC single dose, SC multiple BID doses, and LAR single dose were calculated between Chinese and Western HVs based on the above model. This point estimate and its corresponding 90% CI were antilogged to obtain the point estimate and the 90% CI for geometric mean ratio (GMR) in the original scale. If the 90% CI for the GMR of the primary PK parameters in the original scale between these 2 regions (Chinese and Western) were contained in the range of 0.70 to 1.43, it would be claimed that Chinese and Western HVs are similar in a dose-exposure relationship (ie, there is no ethnic difference on PK parameters between Chinese and Western HVs for pasireotide). The ethnic insensitivity interval (90% CI, 0.70–1.43) was determined based on high intersubject PK variability of pasireotide SC observed in HVs and patients.

The dose proportionality of pasireotide was evaluated for single SC, multiple SC, and single LAR doses with a power model, in which simple linear regression was applied to log-transformed PK parameters and log-transformed dose as follows: $\ln(\text{PK parameter}) = \ln(a) + b*\ln(\text{dose}) + \epsilon$. The point estimate and associated 90% CI for the slope parameter $b$ were provided and compared with the target region (90% CI, 0.80–1.25) for a maximum dose ratio of 3 (300–900 µg and 20–60 mg).

For safety profile assessments, baseline was period specific with day 1 baseline defined for the SC single dose, day 15 baseline for the multiple doses, and day 33 baseline for the LAR single dose. Profiles of insulin, glucagon, and glucose were graphically presented as the percentage of changes from baseline against time. The log-transformed overall percentage responses were also compared using a mixed-effect linear model, with fixed factors of treatment and time point and random factors of study participant and study participant by time. The estimates of fixed effects were calculated within the statistical model for different study periods. Contrasts between any 2 dose groups were reported along with their 95% CIs for the LAR period. All statistical analyses were performed with SAS statistical software, version 9.2 (SAS Institute, Cary, North Carolina).

**RESULTS**

**Participant Demographic Characteristics and Disposition**

A total of 45 male HVs were randomized to 1 of the 9 treatment sequences; 42 completed the study per protocol. Two HVs prematurely discontinued study treatment because of AEs, 1 during the single-dose pasireotide SC period and the other during the multiple-dose SC BID period. One HV withdrew his informed consent shortly after receiving single-dose pasireotide SC 900 µg for personal reasons. These 3 dropout cases were still included in safety assessments. For PK analysis, HVs whose full PK profiles were available were included.

All HVs randomized in this study were Chinese men, with a mean (SD) age of 28.8 (6.55) years, weight of 62.8 (7.76) kg, and BMI of 22.5 (2.14) kg/m\(^2\). Demographic parameters were similar among the 3 dose groups of each pasireotide formulation and across the 9 treatment sequences (Table I).
**PK Results**

**Single-Dose Pasireotide SC PK Profile**

Pasireotide arithmetic mean (SD) concentration-time profiles after single doses of pasireotide SC of 300, 600, or 900 μg are given on semilog scales in Figure 2A. Pasireotide was rapidly absorbed after SC injection, with the maximum concentration being reached in a median $T_{\text{max}}$ of 0.5 hour after dosing at all dose levels. Plasma pasireotide concentrations subsequently declined triexponentially during the 144-hour observation period for all test dose levels. The summary of descriptive statistics of PK parameters for single-dose pasireotide SC is presented in Table II. The $t_{1/2}$ ranged from 9.6 to 12.6 hours. The CL/F was relatively constant (range, 7.3–8.4 L/h) across the 3 dose levels. The AUC and $C_{\text{max}}$ increased with dose level. In the dose-exposure proportionality analysis, the estimated slope for AUC was 0.90, with a 90% CI of 0.73 to 1.07. For the $C_{\text{max}}$, the estimated slope was 1.13, with a 90% CI of 1.00 to 1.25.

**Multiple-Dose BID Pasireotide SC PK Profile**

For the SC multiple BID dosing, pasireotide plasma concentration-time profiles after the last morning dose in the multiple-dose SC period were similar to the SC single-dose profiles (Figure 2B). The summary of descriptive statistics of PK parameters from pasireotide SC multiple BID dosing is given in Table II. The AR ranged from 1.39 to 1.53 and was relatively constant for the 3 dose levels. The AUC and $C_{\text{max}}$ increased in a dose-dependent manner. The estimated slope in the dose proportionality analyses for AUC was 1.03, and the 90% CI for the slope was 0.80 to 1.20. The estimated slope for $C_{\text{max}}$ was 1.15, and the 90% CI for the slope estimate was 1.03 to 1.27.

**Single-Dose Pasireotide LAR PK Profile**

After a single IM injection of pasireotide LAR at 20, 40, or 60 mg, an initial burst release of pasireotide was seen within 24 hours followed by a decrease from days 1 to 4. Thereafter, the plasma concentration increased gradually from day 6, reached a plateau at approximately day 20 (median second $T_{\text{max}}$ peaks in the 20-, 40-, and 60-mg LAR formulations were 16, 18, and 20 days, respectively), and ended with a slow elimination phase (Figure 2C). The first peak plasma level of pasireotide was generally lower than the second peak for all tested doses (Figure 2C and Table II). The relative bioavailability (using the single-dose pasireotide SC PK profile as the reference) was slightly >1. The CL/F was constant for the LAR dose range of 20 to 60 mg. In the dose proportionality analysis, the estimated slopes for AUC and $C_{\text{max}}$ were 0.99 and 1.04, respectively, suggested a dose-proportional relationship. The estimated slope for $C_{\text{max}}$ was low at 0.53, with a 90% CI of 0.35 to 0.71. This parameter mainly represents the initial release and peak concentration on day 1 immediately after IM injection. Because $C_{\text{max}}$ has a lower or comparable level compared with $C_{\text{max}}$, it would have much less significant effect.

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Table I. Demographic and baseline characteristics of the study participants.*

<table>
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<tr>
<th>Variable</th>
<th>300 μg† (n = 15)</th>
<th>600 μg† (n = 15)</th>
<th>900 μg† (n = 15)</th>
<th>20 mg (n = 15)</th>
<th>40 mg (n = 14)</th>
<th>60 mg (n = 13)</th>
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<tr>
<td>Age, y</td>
<td>30.2 (8.20)</td>
<td>28.6 (6.66)</td>
<td>27.7 (4.48)</td>
<td>27.3 (5.92)</td>
<td>28.7 (6.35)</td>
<td>29.6 (7.34)</td>
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<tr>
<td>Weight, kg</td>
<td>61.7 (6.42)</td>
<td>64.1 (7.33)</td>
<td>62.5 (9.53)</td>
<td>61.8 (5.68)</td>
<td>64.5 (10.23)</td>
<td>63.2 (7.46)</td>
</tr>
<tr>
<td>Height, cm</td>
<td>165.6 (6.82)</td>
<td>168.2 (6.21)</td>
<td>166.5 (7.59)</td>
<td>167.2 (6.88)</td>
<td>169.1 (6.06)</td>
<td>164.9 (7.41)</td>
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<tr>
<td>BMI, kg/m²†</td>
<td>22.5 (1.33)</td>
<td>22.7 (2.31)</td>
<td>22.5 (2.69)</td>
<td>22.2 (2.29)</td>
<td>22.4 (2.31)</td>
<td>23.2 (1.98)</td>
</tr>
<tr>
<td>BSA, m²</td>
<td>1.695 (0.116)</td>
<td>1.739 (0.117)</td>
<td>1.708 (0.151)</td>
<td>1.702 (0.095)</td>
<td>1.746 (0.162)</td>
<td>1.712 (0.127)</td>
</tr>
</tbody>
</table>

BMI = body mass index; BSA = body surface area; LAR = long-acting release; SC = subcutaneous; y = year.

*Data are presented as mean (SD).

†Demographic and baseline characteristics for the pasireotide SC BID doses in Chinese male healthy volunteers are not presented here; they were similar to those for the corresponding pasireotide SC single-dose groups.
than C_{max,p2} on steady-state plasma exposure in multiple dosing regimen, especially at therapeutic doses of 40 mg or above.

The Vz/F was large (>3500 L) for 20, 40, and 60 mg. However, this Vz/F value was most likely over-estimated owing to the flip-flop PK characteristics of pasireotide LAR. The actual volume of distribution should be better estimated by using the SC formulation data, with Vz/F ranging from 90.7 to 154.6 L. The t_{1/2} ranges from 375.7 to 443.2 hours, much longer than that in the SC single dose; again, this is due to the flip-flop phenomenon associated with slow release of pasireotide from the LAR formulation.

**Statistical Comparison of Primary PK Parameters Between Chinese and Western Male HVs**

The results of statistical comparison of primary PK parameters between Chinese and Western male HVs are summarized in Table III. After single pasireotide SC doses, the 90% CI for the GMRs of the primary
PK parameters (AUC∞ and CL/F) were completely within the predefined target interval of 0.70 to 1.43, whereas the 90% CI for the GMRs of the primary PK parameter Cmax extended above the upper bound of the target interval.

After pasireotide SC BID doses at steady state, the PK parameters (AUC0–12,ss, Cmax,ss, and CLss/F) in Chinese HVs were similar to those of Western HVs. All 90% CIs of the GMRs for these 3 PK parameters were within the predefined target interval. For AR too, the 90% CI of the GMR of Chinese compared with Western HVs was within the interval of 0.70 to 1.43. The combined statistical analysis of primary PK parameters from single and multiple SC dosing suggests that there was no clinically relevant PK exposure difference between Chinese and Western male HVs after SC administration of pasireotide.

Similarly, after pasireotide LAR doses, the PK parameters (AUC∞, Cmax,p1, and Cmax,p2) in Chinese male HVs were similar to those of Western male HVs. All 90% CIs of the GMRs for these 3 PK parameters were within the predefined target interval. Although Cmax,p1 was 75% higher in Chinese male HVs and the 90% CI of its ratio (1.39–2.21) was out of the predefined target interval, the effect of Cmax,p1 related to the initial burst release may be less significant (because of the addition of high-level predose concentrations that are more relevant to Cmax,p2 on day 28 in a monthly dosing regimen) at steady state after multiple dosing, especially at doses of ≥40 mg. Thus, there was no clinically relevant PK

<table>
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<th>Drug</th>
<th>Low Dose</th>
<th>Medium Dose</th>
<th>High Dose</th>
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<tbody>
<tr>
<td>Pasireotide SC single dose</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUC∞, ng·h/mL</td>
<td>46.5 (17.67)</td>
<td>78.3 (23.61)</td>
<td>123.2 (34.36)</td>
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<tr>
<td>Cmax, ng/mL</td>
<td>9.8 (2.07)</td>
<td>20.4 (7.08)</td>
<td>33.9 (5.77)</td>
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<tr>
<td>CL/F, L/h</td>
<td>7.3 (2.55)</td>
<td>8.4 (2.58)</td>
<td>7.8 (2.09)</td>
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<tr>
<td>Vz/F, L</td>
<td>90.7 (30.84)</td>
<td>142.7 (85.73)</td>
<td>154.6 (103.45)</td>
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<td>t½, h</td>
<td>9.6 (4.88)</td>
<td>12.6 (8.56)</td>
<td>11.6 (4.3)</td>
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<tr>
<td>Tmax, median (range), h</td>
<td>0.5 (0.25-1.00)</td>
<td>0.5 (0.25-1.00)</td>
<td>0.5 (0.25-1.00)</td>
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<td>Pasireotide SC BID</td>
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<td></td>
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</tr>
<tr>
<td>Cmax,ss, ng/mL</td>
<td>11.6 (2.72)</td>
<td>25.6 (4.46)</td>
<td>40.4 (5.76)</td>
</tr>
<tr>
<td>AUC0–12,ss, ng·h/mL</td>
<td>45 (13.52)</td>
<td>84.4 (15.06)</td>
<td>136.2 (18.97)</td>
</tr>
<tr>
<td>AR†</td>
<td>1.4 (0.22)</td>
<td>1.5 (0.27)</td>
<td>1.5 (0.42)</td>
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<td>Pasireotide LAR single dose</td>
<td></td>
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</tr>
<tr>
<td>AUC∞, ng·h/mL†</td>
<td>3260 (720)</td>
<td>6274 (1777)</td>
<td>9915 (2596)</td>
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<tr>
<td>CL/F, L/h</td>
<td>6.4 (1.27)</td>
<td>6.8 (1.76)</td>
<td>6.4 (1.62)</td>
</tr>
<tr>
<td>Vz/F, L</td>
<td>3895 (1542)</td>
<td>3674 (1602)</td>
<td>3583 (1181)</td>
</tr>
<tr>
<td>t½, h</td>
<td>443.2 (202.28)</td>
<td>375.7 (140.63)</td>
<td>399 (137.4)</td>
</tr>
<tr>
<td>Cmax,p1, ng/mL‡</td>
<td>6.7 (2.54)</td>
<td>9.4 (3.25)</td>
<td>11.9 (2.94)</td>
</tr>
<tr>
<td>Cmax,p2, ng/mL‡</td>
<td>6.1 (1.51)</td>
<td>12 (4.82)</td>
<td>19.6 (5.27)</td>
</tr>
<tr>
<td>BALR/SC</td>
<td>1.18 (0.23)</td>
<td>1.20 (0.22)</td>
<td>1.32 (0.35)</td>
</tr>
</tbody>
</table>

AR = accumulation ratio; BA = bioavailability; Cmax,p1 = Cmax of the first peak; Cmax,p2 = Cmax of the second peak; LAR = long-acting release; SC = subcutaneous; Vz/F = apparent volume of distribution.

*Data are presented as mean (SD) unless otherwise indicated.
†The AR after multiple SC BID dosing was assessed based on AUC0–12,ss divided by AUC0–12 on day 1 of SC single dose.
‡The pharmacokinetic parameters AUC∞, Cmax,p1, and Cmax,p2 for the pasireotide LAR treatments are corrected based on the exact doses of LAR ([parameter/exact dose] × planned dose).
exposure difference after single-dose pasireotide LAR between Chinese and Western male HVs.

Safety Profile Results

Adverse Events

No serious AEs were reported during the study. AEs are summarized as preferred terms by treatment in Table IV. One participant discontinued study treatment from the multiple-dose SC period onward because of the development of frequent supraventricular extrasystoles on day 1 after receiving a single dose of 300 \( \mu \)g of pasireotide SC. Another participant withdrew his consent because of moderate diarrhea and abdominal pain during treatment with 600 \( \mu \)g SC BID.

Overall, 44 of 45 HVs (97.8%) reported at least 1 AE during the study. The 1 HV who did not report any AEs withdrew his consent for personal reasons after a single SC dose of 900 \( \mu \)g. The most frequently reported AEs were injection site reaction, nausea, dizziness, and diarrhea after single-dose pasireotide SC and multiple-dose pasireotide SC, with relatively higher incidence observed after the latter. In addition, abdominal pain and discomfort were reported by approximately one-third of the HVs in each dose group during the multiple-dose SC period. The incidences of these AEs did not reveal a dose-dependent trend of increase.

After a single dose of pasireotide LAR, most HVs developed diarrhea. Elevated levels of blood glucose and lipase were reported more frequently with 40 and 60 mg of pasireotide LAR. Injection site reaction, dizziness, and nausea were less frequent during the LAR period compared with the single- and multiple-dose SC periods.

In the follow-up visit scheduled on day 70 of the LAR period, gallbladder polyp was reported for 3 HVs based on their results of abdominal ultrasonography examination. All these gallbladder polyps had a diameter smaller than 0.5 cm, were judged as mild in severity, and required no medical intervention.

**Glucose, Insulin, and Glucagon**

The 8-hour postdose profiles of glucose, insulin, and glucagon are presented in Figure 3. The change-from-baseline profiles of fasting glucose were similar to those of plasma pasireotide concentration during the 70-day LAR treatment period, when a rapid 20% to 30% increase was seen shortly after LAR injection, followed by a relatively shunt peak that appeared between 10 and 20 days after dosing (Figure 4A). The overall increases in blood glucose were larger with pasireotide LAR 60 mg (mean overall change, 23.2%; 95% CI, 18.9%–27.6%) than with LAR 20 mg (mean overall change, 16.1%; 95% CI, 12.5%–19.9%; 60 vs 20 mg; \( P = 0.016 \)) and marginally larger than with LAR 40 mg (mean overall change, 18.0%; 95% CI, 14.0%–22.2%; 60 vs 40 mg; \( P = 0.080 \)).

In all treatment periods, the level of insulin stayed low for the first 4 hours after dosing and could not be fully evaluated because of a relatively high LLOQ (14 mU/L) of insulin assay. Insulin quickly increased after meal and returned to baseline level between 4 and 8 hours after dosing. The mean concentration of glucagon initially subsided and then gradually increased to its baseline level during the 8 hours after SC pasireotide. A much slower decrease in glucagon was seen after IM pasireotide LAR, where a trough concentration occurred approximately 8 hours after dosing. As such, a slight increase in mean blood glucose was observed during the fasting section and was followed...
by a much larger surge of glucose in the postprandial section of each dosing period.

**1,5-AG and HbA1c**

The level of 1,5-AG decreased during the 22 days after dosing in a dose-related manner ($P = 0.047$). The largest estimated overall geometric mean changes (negative values represent reduction from baseline) were found in HVs treated with pasireotide 60 mg (vs 60 mg: $-4.4\%$ [95% CI, $-7.4\%$ to $-1.4\%$] vs $-10.0\%$ [95% CI, $-13.0\%$ to $-6.9\%$], $P = 0.014$; 40 vs 60 mg: $-7.1\%$ [95% CI, $-10.1\%$ to $-4.1\%$] vs $-10.0\%$ [95% CI, $-13.0\%$ to $-6.9\%$], $P = 0.192$) (Figure 4B). The levels of HbA1c were generally comparable between baseline and day 70 among the 3 LAR dose groups.

**Triglyceride and Cholesterol**

Serum cholesterol levels were slightly and non-significantly decreased at approximately 20 to 30 days.

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**Table IV. Number (percentage) of adverse events with an incidence of at least 20% in at least 1 treatment by preferred term and treatment (safety set).**

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Low Dose</th>
<th>Medium Dose</th>
<th>High Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pasireotide SC single dose</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injection site reaction</td>
<td>12 (80)</td>
<td>10 (67)</td>
<td>9 (60)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2 (13)</td>
<td>2 (13)</td>
<td>3 (20)</td>
</tr>
<tr>
<td>Nausea</td>
<td>5 (33)</td>
<td>7 (47)</td>
<td>6 (40)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>2 (13)</td>
<td>2 (13)</td>
<td>6 (40)</td>
</tr>
<tr>
<td>Pasireotide SC BID</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injection site reaction</td>
<td>14 (100)</td>
<td>14 (93)</td>
<td>12 (86)</td>
</tr>
<tr>
<td>Abdominal discomfort</td>
<td>4 (29)</td>
<td>5 (33)</td>
<td>5 (36)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>5 (36)</td>
<td>2 (13)</td>
<td>4 (29)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>8 (57)</td>
<td>8 (53)</td>
<td>9 (64)</td>
</tr>
<tr>
<td>Nausea</td>
<td>6 (43)</td>
<td>7 (47)</td>
<td>8 (57)</td>
</tr>
<tr>
<td>Mouth ulceration</td>
<td>2 (14)</td>
<td>3 (20)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>6 (43)</td>
<td>4 (27)</td>
<td>5 (36)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>3 (21)</td>
<td>1 (7)</td>
<td>1 (7)</td>
</tr>
<tr>
<td>Back pain</td>
<td>3 (21)</td>
<td>1 (7)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Pasireotide LAR single dose</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal discomfort</td>
<td>2 (13)</td>
<td>3 (21)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>2 (13)</td>
<td>3 (21)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>11 (73)</td>
<td>12 (86)</td>
<td>9 (69)</td>
</tr>
<tr>
<td>Blood glucose increased</td>
<td>4 (27)</td>
<td>4 (29)</td>
<td>6 (46)</td>
</tr>
<tr>
<td>Blood thyrotropin increased</td>
<td>1 (7)</td>
<td>3 (21)</td>
<td>2 (15)</td>
</tr>
<tr>
<td>Lipase increased</td>
<td>3 (20)</td>
<td>5 (36)</td>
<td>6 (46)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>6 (40)</td>
<td>4 (29)</td>
<td>1 (8)</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>3 (20)</td>
<td>1 (7)</td>
<td>2 (15)</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>1 (7)</td>
<td>1 (7)</td>
<td>3 (23)</td>
</tr>
<tr>
<td>Injection site reaction</td>
<td>3 (20)</td>
<td>3 (21)</td>
<td>1 (8)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>2 (13)</td>
<td>3 (21)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Headache</td>
<td>2 (13)</td>
<td>3 (21)</td>
<td>1 (8)</td>
</tr>
<tr>
<td>Gallbladder polyp</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>3 (23)</td>
</tr>
</tbody>
</table>

LAR = long-acting release; SC = subcutaneous.
Figure 3. Mean (SD) plasma concentration-time profiles of glucose, insulin, and glucagon up to 8 hours after dosing. (A) Single subcutaneous (SC) doses (300, 600, and 900 µg). (B) Multiple BID SC doses (300, 600, and 900 µg). (C) Single long-acting release (LAR) doses (20, 40, and 60 mg). Because a standard lunch was provided shortly after 4 hours after dosing, the 8-hour postdose profiles consist of a fasting section from before dosing to 4 hours after dosing and a postprandial section between 4 and 8 hours after dosing for each treatment period.
after dosing during the LAR period (Figure 4C). The mean triglyceride levels were below baseline levels from 6 to 28 days after the LAR doses and restored to their predose levels on day 70 (Figure 4D). The reduction in triglyceride levels was similar among the 3 doses of pasireotide LAR (Figure 4D).

**Amylase and Lipase**

None of the pasireotide doses administered in the single and multiple SC periods caused a statistically significant change from baseline in amylase or lipase levels during the first 8 hours after dosing. Likewise, the postdose values of amylase or lipase did not significantly differ from the baseline levels in any of the dose groups in the LAR period.

**Thyrotropin and Thyroid Function**

The levels of thyrotropin and thyroid function had small fluctuations during the LAR period, which did not suggest any dose-related or time-dependent changes.

**ECG and Vital Signs (Heart Rate and Blood Pressure)**

Only minor deviations from normal were found in ECG tracings. No QTcF >480 milliseconds was reported. An increase of >30 milliseconds in QTcF was reported for 1 HV after the 900 μg SC BID dose and no increase of >60 milliseconds was recorded. No trends over time or between dose levels and pasireotide formulations were observed in the mean and median measurements of heart rate or blood pressure.

**DISCUSSION**

The concentration-time profiles of pasireotide SC (300, 600, and 900 μg) single and multiple BID doses in Chinese HVs exhibited triexponential disposition characteristics as observed previously in Western HVs.4,9,10 The contribution of the partial AUC in the terminal γ phase (in triexponential disposition profiles) to AUC∞ was minimal in pasireotide SC PK profiles. Pasireotide was rapidly absorbed, with Cmax observed at approximately 0.5 hour after dosing.
(T_max) in both Chinese and Western HVs. The absorption and disposition phases of pasireotide were similar between Chinese and Western HVs. After SC multiple BID dosing, the PK profiles were similar to those after SC single dosing with low accumulation (AR of approximately 1.5). After a single pasireotide LAR dose, the plasma concentration versus time profiles in Chinese HVs were also similar to those of Western HVs, revealing an initial burst release profile, a slow release for 2 to 5 days, a plateau concentration at approximately day 20, and a slow elimination thereafter. In contrast to PK profiles of the SC formulation, the absorption phase is very slow from the LAR formulation as evidenced by the flip-flop kinetics of the LAR PK profiles in both Chinese and Western HVs.

After the SC single dose, although the geometric mean AUC∞ and C_max levels in Chinese HVs were slightly higher than Western HVs, the magnitudes of differences were moderate (18% and 42%, respectively). Because the overall mean weights of Chinese HVs were approximately 10 to 20 kg lower than those of the Western study HVs,4,10 statistical adjustment with the weight was warranted to evaluate the ethnic differences of PK parameters between Chinese and Western HVs. Indeed, weight and age, were both identified as statistically significant factors correlated with the PK properties of pasireotide. This result is consistent with the findings in population nonlinear mixed-effects modeling of pasireotide SC PK assessment in Westerner HVs and linear mixed-effects modeling of pasireotide LAR PK assessment in patients with acromegaly disease (data not given). After adjustment for the covariates of age and weight, the magnitudes of differences (Chinese vs Western HVs) were only 14% and 13% for AUC∞ and C_max parameters (data not given), respectively. The 90% CI for the GMRs of the PK exposure parameters (AUC∞, C_max and CL/F) were completely within the predefined target interval (90% CI, 0.70–1.43). In addition, after multiple SC BID doses of pasireotide until steady state, GMRs of AR, AUC0−12,ss, C_max,ss and CLss/F were all within the predefined target interval of 0.70 to 1.43. The combined results from both SC single and multiple BID doses suggest the PK parameters of Chinese and Western male HVs are comparable.

The PK parameters in Chinese male HVs were also comparable to those of Western male HVs after single LAR dosing. There are only 3% difference in AUC∞, 8% for C_max,p2, and 3% for CL/F. The relatively large difference observed for C_max,p1 (GMR, 1.75; 90% CI, 1.39–2.21) may not be that clinically significant because C_max,p1 mainly represents an initial drug release (ie, from drug residue on the surface of microparticle) after IM injection on day 1, and its level is generally lower than or comparable to C_max,p2. Because the partial AUC (from 0 to 24 hours after LAR due to initial burst release)–associated C_max,p1 is much smaller than that related to C_max,p2 because of sustained high concentrations around C_max,p2 from the slow release profile, the contribution of C_max,p1 to the overall plasma exposure of pasireotide is considered not clinically relevant. In addition, the GMR of C_max,p1 was decreased from 1.75 to 1.31 on adjustment with covariates of weight and age, but the upper bound of its 90% CI of 1.01 to 1.72 is still outside the target boundary of 0.70 to 1.43.

An approximate dose-proportional relationship was observed for AUC and C_max after single and multiple SC BID doses of 300 to 900 μg, as well as after single IM LAR doses of 20, 40, and 60 mg. These results add to our knowledge regarding the PK properties of SC and LAR formulations of pasireotide in Chinese male HVs and are consistent with the linearity of pasireotide PK properties concluded from studies with pasireotide SC and LAR in Western male HVs.4,9 The values of CL/F were similar between the 2 formulations of pasireotide, suggesting the systemic elimination of pasireotide is independent of the formulation administered.

This study also investigated the effects of pasireotide, particularly pasireotide LAR, on glucose metabolism, lipid profile, and other endocrinial and pancreatic agents. The blood glucose level changed, almost immediately, with plasma pasireotide. Hence, a pulse like increase in fasting glucose was seen during the LAR dosing day, followed by a much slower surge in approximately 2 to 5 days. Interestingly, this profile was similar to the double-peak concentration-time profile of plasma pasireotide LAR, which, in conjunction with the dose-related overall glucose increments, indicated a concentration-dependent effect of pasireotide on fasting blood glucose. The effect of pasireotide LAR on glucose metabolism is complex. On one hand, pasireotide suppressed insulin secretion through modification of sst1 and sst5 on the islet β-cells, and on the other hand, it reduced the production of glucagon by acting on sst2 that expresses on the islet α-cells.15 The balance of these 2 effects determines whether pasireotide LAR impairs glucose metabolism or not.
Because the suppressed levels of insulin and glucagon were frequently below the LLOQ of these bioassays, the expected changes in either insulin or glucagon were not observed during the LAR period. Increases in the fasting glucose levels indicate that pasireotide LAR has a stronger affinity for sst5 than for sst2. Although the level of HbA1c was stable during the LAR period, the dose-related decreases in 1,5-AG provided further evidence about glucose excursions and were attributed to the effect of pasireotide.

Pasireotide LAR considerably decreased triglyceride levels. Similar findings were reported in previous studies with other SSAs, such as octreotide LAR\textsuperscript{16} and the slow-released formulation of lanreotide,\textsuperscript{17} in patients with acromegaly. Other studies found that animals with metabolic syndrome had relatively lower somatostatin levels and that administration of exogenous SSAs improved hypertriglyceridemia.\textsuperscript{18} Therefore, the effect of pasireotide on triglyceride may be related to the physiologic functions of natural somatostatin.

Overall, single and multiple doses of pasireotide SC and the single IM dose of pasireotide LAR were safe and well tolerated in Chinese HVs. The observed AE profile was as expected based on previous studies of pasireotide LAR,\textsuperscript{9} pasireotide SC,\textsuperscript{4} or other SSAs.\textsuperscript{19}

This study was not designed as a blind and placebo-controlled trial. Interpretations of treatment-related AEs should keep these limitations in mind. Moreover, the selection of male HVs as study participants may weaken the clinical relevance of those endocrinial outcomes.

**CONCLUSION**

The 2 formulations (SC and LAR) of pasireotide had similar PK and safety profiles between Chinese and Western male HVs at the same dose levels. No clinically relevant ethnic PK exposure differences were found between Chinese and Western male HVs after SC pasireotide or pasireotide LAR doses when age and weight were included in the analysis model as covariates. As in the Western population, pasireotide SC induced transient changes in glucose metabolism; pasireotide LAR increased fasting glucose levels and reduced triglyceride levels in a dose-dependent manner.

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**CONFLICTS OF INTEREST**

Drs. Chen, Jang and Liu had no support from any organization for the submitted work. Drs. Chen, Jiang, Liu and P. Hu had no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years. Dr. Shen, Dr. Hu and Ms. Lasher are full-time employees of Novartis Pharmaceutical Corporation. Ms. Darstein is full-time employee of Novartis Pharma AG; no other relationships or activities that could appear to have influenced the submitted work.

**REFERENCES**


Address correspondence to: Pei Hu, MD, Clinical Pharmacology Research Center Peking Union Medical College Hospital, 41 Damucang Alley, Xicheng District, Beijing 100032, China. E-mail: pei.hu.pumc@gmail.com