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Effects of Subcutaneous Pasireotide on Cardiac Repolarization in Healthy Volunteers: A Single-Center, Phase I, Randomized, Four-Way Crossover Study

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Abstract

The aim of this study was to evaluate the effects of subcutaneous pasireotide on cardiac repolarization in healthy volunteers. Healthy volunteers were randomized to one of four treatment sequences (n = 112) involving four successive treatments in different order: pasireotide 600 μg (therapeutic dose) or 1,950 μg (maximum tolerated dose) bid by subcutaneous injection (sc), placebo injection and oral moxifloxacin. Maximum ΔΔQTcI occurred 2 hours post-dose for both doses of pasireotide. Mean ΔΔQTcI was 13.2 milliseconds (90% CI: 11.4, 15.0) and 16.1 milliseconds (90% CI: 14.3, 17.9) for the 600 and 1,950 μg bid doses, respectively. Maximal placebo-subtracted change in QTcI from baseline for moxifloxacin was 11.1 (90% CI: 9.3, 12.9) milliseconds. Both pasireotide doses caused a reduction in heart rate: maximal heart rate change compared with placebo occurred at 1 hour for pasireotide 600 μg bid and at 0.5 hours for pasireotide 1,950 μg bid, with heart rate reductions of 10.4 and 14.9 bpm, respectively. At the therapeutic dose of 600 μg, pasireotide has a modest QT-prolonging effect. The relatively small increase of ~3 milliseconds in ΔΔQTcI in the presence of a 3.25-fold increase in dose suggests a relatively flat dose–effect relationship of pasireotide on ΔΔQTcI in healthy volunteers. No safety concerns for pasireotide were identified during the study.

Keywords

pasireotide, QT intervals, heart rate, pharmacokinetics, healthy volunteers

Pasireotide, a somatostatin analogue, has been approved for the treatment of Cushing's disease and is being developed for acromegaly. Patients with acromegaly frequently have a prolonged QT interval,[1–4] and a recent study of patients with Cushing's disease found QT interval prolongation in males.[5] As somatostatin receptors $sst_{1,2,4,5}$ are expressed in the human heart[6] and endogenous somatostatin has been shown to prolong QT intervals,[7] the use of somatostatin analogues to treat Cushing's disease or acromegaly may potentially confer an additional risk of cardiac arrhythmias in these patients. Indeed, changes in ventricular repolarization (QT interval) have been reported following the use of octreotide.[8,9] However, the conclusion that octreotide prolongs the QT interval has been challenged by a retrospective study in 30 patients with acromegaly and 24 healthy volunteers. This study showed that although baseline-corrected QT (QTc) was significantly longer in patients versus controls, octreotide and lanreotide administration improved, and in some cases normalized, the QTc interval.[2]

A subcutaneous (sc) formulation of pasireotide (Signifor®) was recently approved by the European Medicines Agency and the US Food and Drug Administration for the treatment of Cushing's disease. A Phase III study of twice-daily (bid) pasireotide sc in patients with Cushing's disease showed a rapid reduction in urinary free cortisol levels and improved clinical signs and symptoms.[10] Whilst electrocardiograms (ECGs) were collected at trough pasireotide concentrations during steady state, rather than at C_{max} (t_{max} for pasireotide sc = 0.5 hours for C_{max} or 2 hours for peak QT effect), the Phase III study

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demonstrated a low incidence of QT prolongation for pasireotide, with treatment-emergent corrected QT interval using Fridericia's formula (QTcF) >480 milliseconds occurring in 2% of patients, which was deemed sporadic in the context of baseline values of 450 milliseconds for males and 470 milliseconds for females.[10,11]

The current thorough QT study evaluates the effect of pasireotide sc on the placebo- and baseline-corrected QT interval corrected for heart rate using an individualized correction (ΔΔQTcI) in healthy volunteers. Two pasireotide sc doses were used in the study: a therapeutic dose of 600 μg bid and a maximum tolerated dose (MTD) of 1,950 μg bid.

Methods

Study Objectives

The primary objective of the study was to evaluate the effect of pasireotide sc (600 and 1,950 μg bid) on the baseline- and placebo-corrected QTcI. The secondary objectives were to assess: (1) the effect of pasireotide sc on changes from baseline in cardiac conduction intervals (QT, QTcF, QT interval corrected for heart rate according to Bazett's formula [QTcB], and heart rate) compared with placebo; (2) the exposure–response relationship for pasireotide and the time-matched baseline- and placebo-corrected QTcI interval (ΔΔQTcI); and (3) the safety and tolerability of pasireotide sc.

Study Design

This was a single-center, Phase I, randomized, placebo- and active-controlled, blinded study with a William's square four-way crossover in healthy volunteers. Assuming a 35% dropout rate, it was expected that approximately 112 subjects should be randomized (28 per treatment arm) to ensure 72 completers. The study consisted of a 3-week screening period followed by one of four randomized treatment sequences, each with four successive treatment periods (Figure 1). Subjects were randomized equally to a treatment sequence.

Two doses of pasireotide sc were studied: a therapeutic dose of 600 μg bid and the MTD of 1,950 μg bid. The therapeutic dose was chosen as this is the recommended starting dose for pasireotide sc in patients with Cushing's disease.[10,12] Moxifloxacin hydrochloride (Avelox®, Bayer) 400 mg administered orally was used as an active comparator to establish assay sensitivity. Each treatment period lasted 5 days; therefore, the total study duration from randomization (including the 10-day washout between each period) was 51 days.

During the study, each subject received all four possible treatment regimens as follows:

A = Pasireotide 600 μg sc bid for 4 days, then a single pasireotide injection (600 μg) and a single moxifloxacin placebo oral dose on day 5;
B = Pasireotide 1,950 μg sc bid for 4 days, then a single pasireotide injection (1,950 μg) and a single moxifloxacin placebo oral dose on day 5;
C = Pasireotide placebo sc bid for 4 days, then a single pasireotide placebo injection and moxifloxacin placebo orally on day 5;
D = Pasireotide placebo sc bid for 4 days, then a single pasireotide placebo injection and moxifloxacin 400-mg oral dose on day 5.

Subjects were domiciled during the treatment periods to ensure a controlled setting. Meals and fluid intake were standardized. Meals were scheduled as follows: breakfast

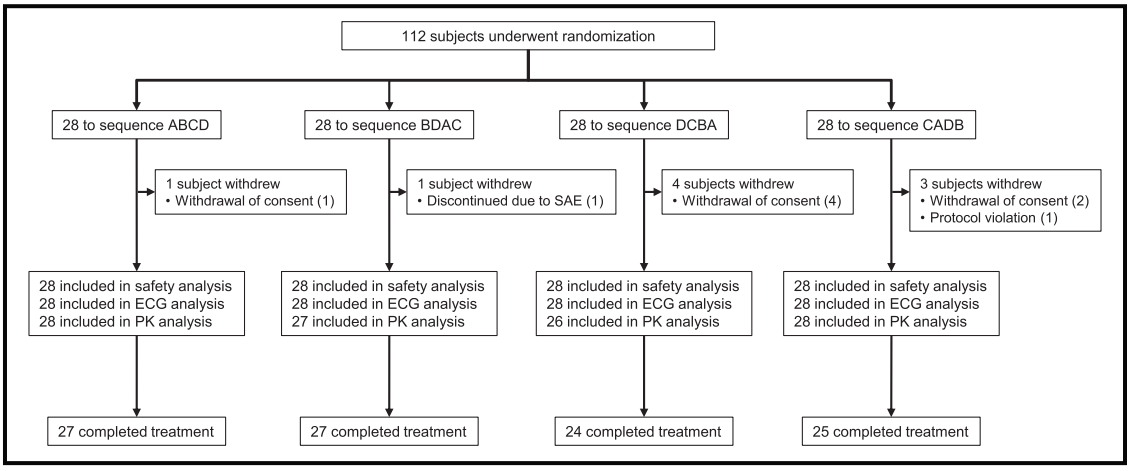

Figure 1. Study design. A = pasireotide sc 600 μg bid for 4 days, a single pasireotide 600 μg injection on day 5 and a single moxifloxacin placebo po dose on day 5; B = pasireotide sc 1,950 μg bid for 4 days, a single pasireotide 1,950 μg injection on day 5 and a single moxifloxacin placebo po dose on day 5; C = pasireotide placebo sc bid for 4 days, a single pasireotide placebo injection on day 5 and moxifloxacin placebo po on day 5; D = pasireotide placebo sc bid for 4 days, a single pasireotide placebo injection on day 5 and moxifloxacin po 400 mg on day 5. The subject who discontinued because of SAE had hypotension, syncope and supraventricular arrhythmia. bid, twice daily; po, oral; qd, once daily; SAE, serious adverse event; sc, subcutaneous.

7:00 am (2 hours prior to first sc dose), lunch 1:00 pm (4 hours after first sc dose), dinner 6:00 pm (3 hours prior to second sc dose). Subjects were not allowed to consume alcohol or caffeine; all meals were controlled and given at the same time during all four treatment phases.

Sample size. The sample size was selected to adequately power the "thorough QT/QTc study" as recommended in the ICH guidelines,[13] that is, to determine that the upper one-sided 95% confidence bounds for all the mean differences between pasireotide sc 600 μg bid and placebo (pasireotide minus placebo) on the QTcI interval change from baseline exclude 10 milliseconds.

The null hypothesis was a union of 11 individual hypotheses (one non-inferiority hypothesis at each time point), commonly referred to as an intersection–union test. The null hypothesis was rejected if the upper one-sided 95% confidence bounds for all 11 tests were less than 10 milliseconds. Therefore, the α level (type I error) did not need to be adjusted in order to maintain the overall α level. However, the need for simultaneous rejection required β (type II error) to be adjusted using the multiplicity adjustment. Since observations within the same subject were possibly correlated (assumed to be compound symmetry [cs] structure), it was expected that the hypotheses were also correlated. Given that no statistical methodology was readily available then to obtain sample size after accounting for the correlation, a simulation was conducted to obtain a sample size estimate. It was estimated that 72 subjects (18 subjects in each of the four sequences) would provide at least 90% power to claim no QT effect. The assumptions were:

- The true difference (active/placebo) was equal to 2 milliseconds at two time points and was equal to 4 milliseconds at one time point (out of 11 time points) and 0 millisecond at the other time points
- The variance–covariance matrix of $\sigma^2_{cs} = 13.4$, $\lambda = 179.8$, $\rho = 0.2$, $\sigma^2 = 97.4$, based on prior internal thorough-QT (TQT) studies[14]

For establishing assay sensitivity, based on the above variance–covariance matrix, a sample size of 72 subjects would provide at least 90% power to detect a difference of 5 milliseconds or more between moxifloxacin 400 mg and placebo groups at one of the five pre-specified time points. The above calculation was based on the Simes test[15] and an overall type I error of 5% (one sided), with the assumption that the mean differences were 5 milliseconds or more between the moxifloxacin 400 mg and placebo groups at 0.25, 0.5, 1, 1.5, 2 hours post-dose and 0 millisecond at the other time points (pre-dose, 3, 4, 8, 12, 24 hours post-dose).

Subjects

The study population comprised male and female subjects aged 18–55 years who were in good health based on past medical history, medical examination, vital signs (including blood pressure, heart rate, weight, and body mass index), ECG, and laboratory screening.

The study was approved by the Bundesinstitut für Arzneimittel und Medizinprodukte (German authority) and Ethics Committee Berlin and was conducted according to the ethical principles of the Declaration of Helsinki. All subjects provided written informed consent.

Subjects were excluded if they had type 1 or type 2 diabetes mellitus, autonomic dysfunction, acute or chronic bronchospastic disease, or clinically significant drug allergy; were positive for HIV or hepatitis B or C infection; had a history of drug or alcohol abuse or use of tobacco; or had any clinically significant laboratory abnormality or clinically significant illness within 4 weeks before dosing. Female subjects were excluded if they were pregnant or lactating. Cardiac-specific exclusion criteria included previous or current clinically significant ECG abnormalities (defined as PR >220 milliseconds, QRS >110 milliseconds, corrected QT interval [QTcF] >470 milliseconds for females and >450 milliseconds for males; any cardiac conduction abnormality; use of concomitant medications that could prolong QT interval and/or induce torsades de pointes and ventricular arrhythmia); significant heart disease (e.g., atherosclerosis, heart failure); or risk factors for torsades de pointes.

Assessments

ECG data. ECG recordings were collected using Holter monitoring over 24 hours at baseline (study days −1, 15, 30, and 45) and at steady state on day 5 of each treatment period (study days 5, 20, 35, and 50). During these specific recordings, the subjects lay quietly supine for 10 minutes, ensuring that the heart rate (HR) had been stable for 2 minutes prior to the defined ECG time point recording. Triplicate ECGs were then extracted at the pre-specified time points of 0, 0.25, 0.5, 1, 1.5, 2, 3, 4, 8, 12, and 24 hours (on day 5, 0 hour was pre-dose and all subsequent time points were post-dose). In addition, Holter monitoring was performed for 12 hours on day 1 of treatment period 1, and ECGs were extracted at 0, 0.25, 0.5, 1, 1.5, 2, 3, 4, 8, and 12 hours to accurately capture the time course of the ECG (QT and HR) effect of pasireotide and the detection of any early asymptomatic arrhythmias.

Pharmacokinetics. Pharmacokinetic (PK) blood sampling for full PK profiles and analysis was performed after the morning dose on day 1 of treatment period 1, and on day 5 of each treatment period (study days 5, 20, 35, and 50) at 0 hour (pre-dose) and 0.25, 0.5, 1, 1.5, 2, 3, 4, 8, 12, and 24 hours (treatment day 5 only) post-dose. A single PK blood sample was collected pre-dose for each treatment period to assess potential drug residue (carryover) from the

previous crossover treatment period. Blood samples for PK evaluation were collected in K2EDTA tubes after vital sign and ECG measurements at each time point; samples were stored frozen at $<-18°C$ until analysis. Duplicate PK samples were shipped to two locations: for pasireotide analysis, one full set was sent to Atlanbio, France, and for moxifloxacin analysis, the second set was sent to WuXi App Tex Co Ltd, China.

Pasireotide plasma concentrations were measured using a validated radioimmunoassay with a lower limit of quantification (LLOQ) of 0.15 ng/mL and upper limit of quantification (ULOQ) of 2.5 ng/mL. The radioimmunoassay is based on the competition between ^{125}I-pasireotide and pasireotide for a fixed number of antibody binding sites. Samples or standards were incubated with ^{125}I-pasireotide tracer and anti-serum and the complexes captured using coated magnetic beads. After elimination of the unbound fraction by washing, the bound radioactivity was determined in a gamma counter. All samples were analyzed in duplicate along with daily prepared calibration standards and quality control samples (QCs). Duplicate QCs at four concentrations spanning the quantifiable range were included in each batch and results were accepted when at least six of the eight QCs, including at least one at each QC concentration, were within 30% of the nominal concentration. In addition, results for individual samples were accepted when the coefficient of variation between duplicates was less than 30%. Moxifloxacin plasma samples underwent solid-phase extraction followed by dilution and analysis by electrospray ionization tandem mass spectrometry performed using an API4000 instrument (Applied Biosystems/Sciex, Massachusetts, USA) with a LLOQ of 50 ng/mL and ULOQ of 10,000 ng/mL. PK parameters of pasireotide and moxifloxacin were estimated by Phoenix WinNonlin (v5.2).

Safety. Safety assessments consisted of physical examinations, monitoring of vital signs and recording of all adverse events (AEs) and serious AEs (SAEs), ECG effects (rhythm, ectopy, conduction defects, ST segment changes and morphological changes in U waves and T waves) and laboratory evaluations (hematology, coagulation, and standard biochemistry parameters, including liver, renal, and thyroid function tests).

Categorical analyses. Categorical analyses were performed to summarize the frequency and percentage of subjects in each treatment arm who had a maximum increase from baseline exceeding the following thresholds using the average of the replicate ECGs at each post-dose time point:

- *QT*: QT/QTc time-matched change from baseline >30, >60 milliseconds, newly occurring QT/QTc >450, >480, >500 milliseconds.
- *PR*: 25% increase from time-matched baseline and the resultant PR duration >200 milliseconds.
- *QRS*: 25% increase from time-matched baseline and the resultant QRS duration >100 milliseconds.
- *HR*: 25% decrease from time-matched baseline (corresponding to HR <50 bpm) or a 25% increase from time-matched baseline (corresponding to HR >100 bpm).

Statistical Analyses

The primary statistical analysis of ECG data evaluated the time-matched baseline- and placebo-controlled change from baseline in QTcI ($\Delta\Delta$QTcI) on active treatments (pasireotide sc 600/1,950 μg bid, moxifloxacin). QTcI was derived using the estimated slope b from the model $\log(QT) = a + b \times \log(RR)$ for each individual ($QTcI = QT/RR^b$), using their study day -1 QT-RR data. QTcB was calculated as ($[QT(ms)]/[RR(s)]/[1{,}000^{1/2}]$); QTcF was calculated as ($[QT(ms)]/[RR(s)]/[1{,}000^{1/3}]$), considering that RR was measured in seconds.

$\Delta\Delta$QTcI was analyzed using a linear mixed-effects model that included the terms of sequence, treatment, period, time, and treatment-by-time interaction as fixed effects and the term of subject as the random effect, where time was a categorical variable. The baseline QTcI was also included as a covariate. Baseline was period specific and time point specific and defined as the average of triplicates at each of the pre-specified time points. Day -1 data and day 5 data from each of the four periods were used for analysis. Point estimates and 90% confidence intervals (CIs; two sided) were generated at each time point on each day for $\Delta\Delta$QTcI. A lack of QT effect for pasireotide was established if the upper limit of the two-sided 90% CI for the estimated $\Delta\Delta$QTcI on day 5 was <10 milliseconds for all 11 pre-defined time points.[13] Similar statistical analyses were conducted for QTcF, QTcB, and HR. A post hoc gender subgroup analysis was conducted to evaluate the placebo-corrected changes from baseline in QTcF, QTcI, PR, and HR by gender (males, $n = 70$ and females, $n = 35$) in subjects treated with pasireotide 600 and 1,950 μg bid up to 8 hours post-dose.

Analyses were performed to characterize the relationship between plasma concentrations of pasireotide and moxifloxacin with changes in cardiac intervals to assist the interpretation of the study results. To examine the relationship between pasireotide plasma concentration and QT/QTc intervals, the following three models were used.

Linear model. This analysis was performed for both pasireotide and moxifloxacin. A linear model ($\Delta\Delta QTcI = \alpha + \beta \times$ concentration) was fitted to the $\Delta\Delta$QTcI, where

the concentration was measured at the same time as the QTcI was observed. Period 1 day 1 data and day 5 data for each of the four periods were used for analysis. Assuming a linear relationship between drug exposure and ΔΔQTcI, the mean maximum effect and upper one-sided 95% confidence limit for each dose level (600 and 1,950 μg bid) were computed from the mean maximum plasma concentration using the following equation: mean maximum effect $= \alpha\hat{} + \beta\hat{} \times C_{max}$, where C_{max} is the observed maximum concentration for each pasireotide dose level (600 and 900 μg bid) or moxifloxacin 400 mg, and $\alpha\hat{}$ and $\beta\hat{}$ are the estimates of the population intercept and slope for the relationship between ΔΔQTcI and plasma concentration.

Time-lag model. This analysis was performed only for pasireotide and assumed a constant time lag between the PK and QTc (QTcI, QTcF, and QTcB) time profiles. A simple open one-compartment PK model with first-order absorption was used to predict individual PK profiles. The use of the one-compartment model is an approximation, given the fact that the time lag is evident after the peak concentration. The assumption of a constant time lag between peak PK exposure and maximum placebo-corrected change from baseline QTc is based on approximation. This approach required calculation of a time-lagged PK profile $C_{lag}(t)$ for a given lag time t_{lag}. For time $t > t_{lag}$, it was calculated as $C_{lag}(t) = C(t - t_{lag})$, while for $t < t_{lag}$, it was predicted by the concentration on the same day, assuming that steady state had been reached. $C_{lag}(t)$s were calculated separately for $t_{lag} = 0.5$, 0.8, 1, 1.2, and 1.5 hours, as in the linear mixed PK/PD model.

Simultaneous model. This analysis was based on the assumption that the concentration of pasireotide sc affects QT intervals and RR simultaneously. This analysis offers an approach for describing and analyzing a situation whereby a drug changes the QT correction factor for RR, QTc, or both.[16–18] The hypothesis of the simultaneous model is that QT has two components: $QT = P1 \times P2$. One component describes the effect of concentration on QTc intervals independent of RR that can be expressed as $P1 = \acute{a}1 + \hat{a}1 \times$ concentration. The other component describes the effect of concentration on QT through RR intervals that can be expressed as $P2 = RR^{\beta 2 + \delta \times \text{concentration}}$. Generally, QTc can be expressed as $QTc = QT/RR^{a}$, where "a" is either a constant (QTcF, QTcB) or subject specific (QTcI). This leads to the simultaneous model for the concentration effects on QT: $QT = (\alpha 1 + \beta 1 \times \text{conc}) \times RR^{\beta 2 + \delta \times \text{concentration}}$, where the parameters may contain a fixed and a random component. The model was fitted for both pasireotide and moxifloxacin. Given that the effect of moxifloxacin concentration on QT and its lack of an effect on the RR correction are known, this model was fitted for moxifloxacin as a way to validate the model.

Results

Subject Demographics

Of the 112 randomized subjects, 103 (92.0%) completed all four treatment periods (Figure 1). There were no relevant differences in demographic characteristics across treatment sequences (Table 1).

Effect of Pasireotide on QTcI on Day 5

For both pasireotide sc doses, QTcI was higher at time 0 on day 5 than the period-specific baseline, whereas the period-specific baseline QTcI for placebo at the same time was lower. The ΔΔQTcI at time 0 was 6.4 and 7.7 milliseconds for pasireotide 600 and 1,950 μg bid, respectively (Supplementary Table S1).

An hour after pasireotide injection on day 5, QTcI increased compared with baseline up to 4 hours post-dose. The maximum increase relative to the day-5 pre-dose baseline ranged from 4.3 to 8.5 milliseconds for the 600 μg bid group and from 5.5 to 11.4 milliseconds for the 1,950 μg bid group (Figure 2, Supplementary Table S1).

The placebo QTcI values were lower than the period-specific baseline at time 0 and at all time points up to 24 hours, ranging from −7.6 milliseconds (0.3 hours post-dose) to −1.6 milliseconds (4 hours post-dose).

Table 1. Demographic Characteristics for All Healthy Subjects by Treatment Sequence

	ABCD (n = 28)	BDAC (n = 28)	DCBA (n = 28)	CADB (n = 28)	All subjects (n = 112)
Mean age ± SD, years	40 ± 10	40 ± 11	42 ± 9	38 ± 8	40 ± 10
Male:female, n (%)	17:11 (61:39)	19:9 (68:32)	20:8 (71:29)	18:10 (64:36)	74:38 (66:34)
Ethnicity, n (%)					
Caucasian	27 (96)	25 (89)	28 (100)	28 (100)	108 (96)
Other	1 (4)	3 (11)	0	0	4 (4)
Mean weight ± SD, kg	72.6 ± 11.5	77.4 ± 11.2	74.3 ± 13.5	74.2 ± 12.7	74.6 ± 12.2
Mean BMI ± SD, kg/m^2	24.0 ± 2.8	25.1 ± 2.8	23.9 ± 2.7	23.9 ± 2.8	24.2 ± 2.8

A = pasireotide sc 600 μg bid for 4 days, then a single pasireotide 600 μg injection and a single moxifloxacin placebo po dose on day 5; B = pasireotide sc 1,950 μg bid for 4 days, then a single pasireotide 1,950 μg injection and a single moxifloxacin placebo po dose on day 5; C = pasireotide placebo sc bid for 4 days, then a single pasireotide placebo injection and moxifloxacin placebo po on day 5; D = pasireotide placebo sc bid for 4 days, then a single pasireotide placebo injection and moxifloxacin po 400 mg on day 5. bid, twice daily; BMI, body mass index; po, oral; qd, once daily; sc, subcutaneous; SD, standard deviation.

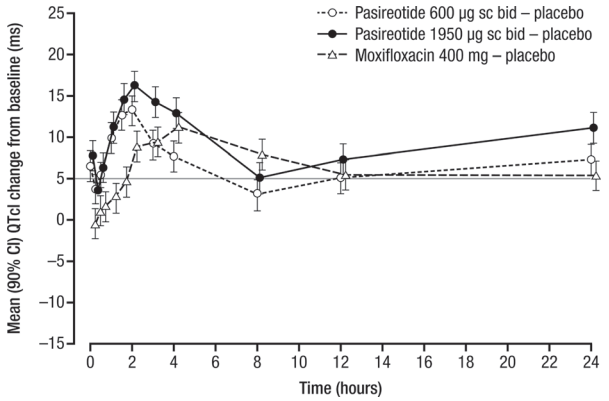

Figure 2. Placebo-subtracted change from baseline versus placebo for QTcI (ΔΔQTcI) with 90% CI for pasireotide sc and moxifloxacin on day 5. The solid line at 5 milliseconds represents the threshold level of regulatory concern.[13]

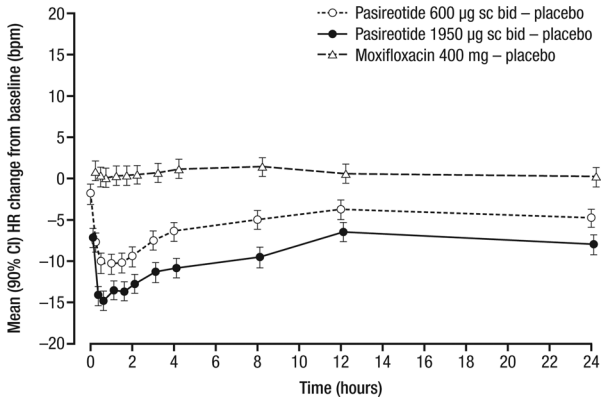

Figure 3. Placebo- and baseline-corrected mean change in heart rate with 90% CI on day 5.

The maximal mean ΔΔQTcI for both pasireotide sc doses was observed 2 hours post-dose, with 13.2 milliseconds (90% CI: 11.4, 15.0) for pasireotide 600 µg bid and 16.1 milliseconds (90% CI: 14.3, 17.9) for pasireotide 1,950 µg bid. The upper bound of the two-sided 90% CI exceeded 10 milliseconds between 1 and 3 hours post-dose for pasireotide 600 µg bid, and between 1 and 4 hours and at 24 hours for pasireotide 1,950 µg bid. For the active comparator moxifloxacin, QTcI was below the period-specific baseline at time 0 (ΔΔQTcI, −0.5 milliseconds), similar to placebo, and increased at all subsequent time points after the first hour post-dose. The peak increase of 9.6 milliseconds relative to baseline was observed 4 hours post-dose, corresponding to a maximal placebo-subtracted change from baseline of 11.1 milliseconds (90% CI: 9.3, 12.9). When analyzed by gender, increases in ΔΔQTcI were greater for male (n = 70) subjects than female (n = 35) subjects at both pasireotide doses (Supplementary Table S2).

Effect of Pasireotide on Heart Rate on Day 5

There was a marked decrease from baseline in HR during treatment with pasireotide sc 600 and 1,950 µg bid (Figure 3), which was more pronounced with the higher dose. The maximum baseline- and placebo-adjusted change in HR was observed 1 hour post-dose for pasireotide 600 µg bid (−10.4 bpm; 90% CI: −11.5, −9.2) and at 0.5 hours for pasireotide 1,950 µg bid (−14.9 bpm; 90% CI: −16.1, −13.8). Overall, the decreases in HR were of a similar magnitude between males and females, with a more pronounced effect in the pasireotide 1,950 µg bid group compared with the 600 µg bid group (Supplementary Table S2).

Minor changes in mean HR from the period-specific baseline between −1.4 and +3.9 bpm were observed after administration of placebo. For moxifloxacin, no significant differences were observed in HR compared with placebo.

Effect of Pasireotide on QTcF and QTcB on Day 5

The overall trend and magnitude of the treatment effect on QTcF were similar to those of QTcI (Figure 2). The largest difference in ΔΔQTcF was observed 2 hours post-dose for both pasireotide 600 µg bid (11.8 milliseconds; 90% CI: 10.0, 13.5) and pasireotide 1,950 µg bid (14.0 milliseconds; 90% CI: 12.3, 15.8). For moxifloxacin 400 mg, the maximal ΔΔQTcF observed at 4 hours was 10.8 milliseconds (90% CI: 9.0, 12.5).

When analyzed by gender, the mean increases in ΔΔQTcF did not differ appreciably between males and females, with smaller increases in females compared with males at both pasireotide doses (Supplementary Table S2).

For QTcB, the results were similar to those observed for QTcI and QTcF on moxifloxacin and placebo; however, no placebo-corrected treatment effect for either pasireotide dose was shown in QTcB.

Categorical Analyses of ECG Data

Overall, the proportion of subjects with notable, uncorrected QT values was higher with the pasireotide 1,950 µg bid dose than with the pasireotide 600 µg bid dose. There were no subjects with corrected QT values (QTcI, QTcF, or QTcB) that increased more than 60 milliseconds from baseline or longer than 500 milliseconds in any of the treatments (Table 2). One subject experienced QTcI >480 milliseconds at 1.5 and 2 hours following the pasireotide 1,950 µg dose. At the next time point (3 hours), QTcI was <480 milliseconds (but >450 milliseconds) and normalized at the 12-hour time point. One subject had a QTcF value >480 milliseconds at 4 hours following treatment with the pasireotide 1,950 µg bid dose. At the next time point (8 hours), QTcF was <480 milliseconds (but >450 milliseconds) and normal at the 12-hour time point. No other subjects had QTcI, QTcF, or QTcB values that were longer than 480 milliseconds (Table 2).

Following treatment with pasireotide, one subject (1/105) on pasireotide 600 µg and two subjects (2/104) on pasireotide 1,950 µg had PR values that were increased by

Table 2. Subjects With Notable Values in QT/QTc Intervals for Day 5

Parameter	Treatment	Increase >30 milliseconds, n/N (%)	Increase >60 milliseconds, n/N (%)	New >450 milliseconds, n/N (%)	New >480 milliseconds, n/N (%)	New >500 milliseconds, n/N (%)
QT	Pasireotide 600 μg sc bid	80/105 (76)	21/105 (20)	41/95 (43)	9/104 (9)	2/105 (2)
	Pasireotide 1,950 μg sc bid	96/105 (91)	42/105 (40)	59/95 (62)	19/105 (18)	8/105 (8)
	Moxifloxacin 400 mg	37/107 (35)	2/107 (2)	11/98 (11)	1/106 (1)	0/107 (0)
	Placebo	20/108 (19)	0/108 (0)	5/93 (5)	0/108 (0)	0/108 (0)
QTcF	Pasireotide 600 μg sc bid	6/105 (6)	0/105 (0)	4/101 (4)	0/105 (0)	0/105 (0)
	Pasireotide 1,950 μg sc bid	15/105 (14)	0/105 (0)	8/101 (8)	1/105 (1)	0/105 (0)
	Moxifloxacin 400 mg	4/107 (4)	0/107 (0)	5/106 (5)	0/107 (0)	0/107 (0)
	Placebo	1/108 (1)	0/108 (0)	0/107 (0)	0/108 (0)	0/108 (0)
QTcB	Pasireotide 600 μg sc bid	6/105 (6)	0/105 (0)	10/91 (11)	0/105 (0)	0/105 (0)
	Pasireotide 1,950 μg sc bid	6/105 (6)	0/105 (0)	6/89 (7)	0/104 (0)	0/105 (0)
	Moxifloxacin 400 mg	14/107 (13)	0/107 (0)	16/99 (16)	0/107 (0)	0/107 (0)
	Placebo	10/108 (9)	0/108 (0)	3/99 (3)	0/108 (0)	0/108 (0)
QTcI	Pasireotide 600 μg sc bid	7/105 (7)	0/105 (0)	4/98 (4)	0/105 (0)	0/105 (0)
	Pasireotide 1,950 μg sc bid	25/105 (24)	0/105 (0)	10/101 (10)	1/105 (1)	0/105 (0)
	Moxifloxacin 400 mg	5/107 (5)	0/107 (0)	6/106 (6)	0/107 (0)	0/107 (0)
	Placebo	2/108 (2)	0/108 (0)	0/105 (0)	0/108 (0)	0/108 (0)

at least 25% from baseline and were >200 milliseconds. No other subjects had values considered abnormal for PR, QRS, or RR intervals.

Some other treatment-emergent ECG effects and morphological changes were also recorded. The incidence of ECG abnormalities was higher with pasireotide sc (51/105 for 600 μg bid and 70/105 for 1,950 μg bid) than with moxifloxacin (16/107) or placebo (22/108) (Table 3). The most frequently reported ECG abnormality with pasireotide sc 600 and 1,950 μg was sinus bradycardia (35% and 60% of subjects, respectively). Other abnormalities were fairly comparable among all the four treatment arms.

Pharmacokinetics

Pasireotide was rapidly absorbed following subcutaneous administration of both the 600 and 1,950 μg bid doses. On period 1 day 1, mean C_{max} was 20.3 ng/mL following pasireotide sc 600 μg and 55.1 ng/mL following

Table 3. Newly Occurring ECG Abnormalities[a]

Abnormality type	Finding, n (%)	Pasireotide, 600 μg bid (N = 105)	Pasireotide, 1,950 μg bid (N = 105)	Moxifloxacin, 400 mg (N = 107)	Placebo (N = 108)
Conduction	Total subjects	11 (11)	13 (13)	2 (2)	5 (5)
	First degree AV block	7 (7)	10 (10)	1 (1)	2 (2)
	IRBBB	0 (0)	1 (1)	0 (0)	0 (0)
	IVCD	3 (3)	0 (0)	1 (1)	3 (3)
	LAH	1 (1)	2 (2)	0 (0)	1 (1)
Ectopy	Total subjects	11 (11)	5 (5)	4 (4)	4 (4)
	APC	11 (11)	5 (5)	4 (4)	2 (2)
	VPC	0 (0)	0 (0)	0 (0)	2 (2)
Rhythm	Total subjects	41 (39)	64 (62)	6 (6)	10 (9.3)
	Ectopic supraventricular rhythm	3 (3)	1 (1)	0 (0)	3 (3)
	Junctional rhythm	1 (1)	2 (2)	1 (1)	0 (0)
	Sinus bradycardia	37 (35)	62 (60)	5 (5)	7 (7)
	Sinus tachycardia	1 (1)	1 (1)	0 (0)	0 (0)
ST segment	Total subjects	0 (0)	1 (1)	2 (2)	0 (0)
	Depressed ST segment	0 (0)	1 (1)	2 (2)	0 (0)
T waves	Total subjects	1 (1)	3 (3)	3 (3)	3 (3)
	Flat T waves	1 (1)	3 (3)	3 (3)	3 (3)

APC, atrial premature complexes; AV, atrioventricular; IRBBB, incomplete right bundle branch block; ECG, electrocardiogram; IVCD, intraventricular conduction delay; LAH, left anterior hemiblock; VPC, ventricular premature complexes.

[a]A subject may have experienced multiple abnormalities, that is, a patient who experienced abnormal junctional rhythm may have also experienced sinus bradycardia. Only newly occurring ECG abnormalities are included, that is, an abnormal ECG finding at post-baseline but not present at baseline.

pasireotide sc 1,950 μg. Mean $AUC_{0–12\,hours}$ (i.e., AUC_{tau}) was 77.6 h ng/mL for pasireotide sc 600 μg and 226 h ng/mL for pasireotide sc 1,950 μg. On day 5, the mean pasireotide C_{max} and $AUC_{0–12\,hours}$ values were approximately dose proportional: 24.3 ng/mL and 116 h ng/mL for the 600 μg group, 80.6 ng/mL and 425 h ng/mL for the 1,950 μg group (Supplementary Table S3).

The apparent clearance (CL/F_{ss}; 5.6 vs. 5.1 L/h), volume of distribution (V_z/F_{ss}; 101 vs. 77 L/h), and half-life ($t_{1/2ss}$; 12.8 vs. 10.7 hours) on day 5 at steady state were comparable between 600 and 1,950 μg bid of pasireotide sc (Supplementary Table S3), suggesting linear pharmacokinetics for pasireotide sc. Median $t_{max,ss}$ was observed between 0.5 and 0.6 hours, which was 1.5 hours earlier than the peak ΔΔQTcI effect (2 hours). Following administration of a single oral dose of 400 mg moxifloxacin on day 5, the mean values of C_{max} and AUC_{inf} were 2,413 ng/mL and 28,073 h ng/mL, respectively (Supplementary Table S3).

Linear Model

The regression line observed in the linear model indicated that the concentration–response relationship was relatively flat. At the median C_{max} for pasireotide sc 600 (23.4 ng/mL) and 1,950 μg bid (77.8 ng/mL), the estimated mean QTcI change from baseline versus placebo was 8.5 and 11.9 milliseconds for the respective doses (Figure 4a). For moxifloxacin, the corresponding change at median C_{max} (2330 ng/mL) was 12.2 milliseconds. In agreement with the primary analysis, these values were above 5 milliseconds; furthermore, the upper one-sided 95% confidence bound exceeded 10 milliseconds (Figure 4b).

Time-Lag Model

Peak effect of pasireotide on QTcI was observed at 2 hours post-dose, whilst the median peak pasireotide concentration was observed at about 0.5 hours post-dose. The time-lag model provides an estimate of 0.8 hours for the time lag between peak exposure pasireotide sc concentration and peak effect on ΔΔQTcI. The estimated mean (upper bound of 95% CI) effect at the median C_{max} of 23.4 ng/mL for pasireotide 600 μg bid was 9.02 milliseconds (10.7). At the median C_{max} of 77.8 ng/mL for the 1,950 μg bid dose, the mean (upper bound of 95% CI) effect on ΔΔQTcI change was 17.0 milliseconds (19.3), which was comparable to the observed ΔΔQTcI of 16.2 milliseconds. Applying the time-lag model to QTcF data provided similar results to those for QTcI; for QTcB, the results were consistent with a lack of overall effect at the 600 μg bid dose.

Simultaneous Model

The *P*-value generated in the simultaneous model does not indicate statistical significance for either of the two pasireotide doses, suggesting that the pasireotide concentration may not affect the QT–RR relationship. For the pasireotide 600 μg bid dose, the estimated mean QT change from placebo baseline (upper bound of the 95% CI) effect at the median C_{max} of 23.4 ng/mL was 4.6 milliseconds (7.0), whereas for the pasireotide 1,950 μg bid dose, the effect at the median C_{max} of 77.8 ng/mL was 4.3 milliseconds (7.5). The QT correction factor for RR prior to dosing, β2, was estimated to be 0.4 and 0.4 for pasireotide sc 600 and 1,950 μg bid, respectively; these values are in the same order as the Fridericia correction factor for QTcF (1/3, or ∼0.3). Similarly, moxifloxacin concentration does not appear to affect the QT–RR relationship and β2 was estimated to be 0.3. The estimated mean placebo-subtracted change from baseline in QT at median C_{max} (2,330 ng/mL) for moxifloxacin was 14.0 milliseconds (upper bound of 95% CI: 16.2).

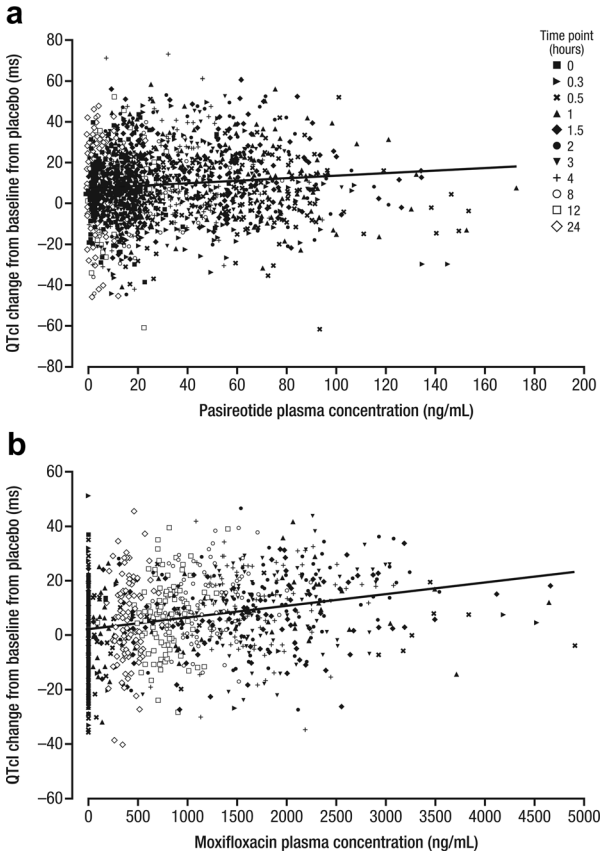

Figure 4. Time-matched baseline- and placebo-corrected QTcI (ΔΔQTcI) for (a) pasireotide sc and (b) moxifloxacin plasma concentration ECG set.

Safety/Tolerability

Most subjects (97%) experienced at least one AE during the study. The incidence of AEs was higher with pasireotide sc than with moxifloxacin or placebo (Supplementary Table S4).

The most frequently reported AEs with pasireotide sc 600 and 1,950 μg bid were injection-site erythema (73% and 90%, respectively) and gastrointestinal disorders; these AEs were less common with moxifloxacin and placebo.

Gastrointestinal-related AEs tended to occur more frequently and be of greater severity with the higher pasireotide dose than with the lower dose. Nausea and diarrhea were reported most frequently (>50% and >80% in the pasireotide 600 and 1,950 μg bid groups, respectively, vs. <10% in the moxifloxacin/placebo groups). Headache, dizziness, and fatigue were also more common with pasireotide than with moxifloxacin or placebo.

All AEs reported by subjects were grade 1 or 2, with the exception of one subject who developed syncope (grade 3) and supraventricular arrhythmia (grade 4) associated with hypotension following the first injection of pasireotide 1,950 μg on day 1 of period 1. These events were considered SAEs and led to study discontinuation of this subject from the study. The subject recovered within 24 hours of the events. The events were suspected to be related to study drug, but were considered to be vasovagal in nature and not related to QT prolongation. No other grade 3 or 4 AEs were reported in the study and no other events leading to discontinuation were reported. No deaths occurred during the study.

Laboratory evaluations revealed no clinically significant abnormalities in hematology parameters. For biochemistry parameters, the most frequent grade 3 abnormality was recorded for elevated lipase, which occurred in seven subjects receiving the higher dose of pasireotide. Six of these subjects had normal lipase at baseline, and the grade 3 abnormality was recorded following pasireotide 1,950 μg bid. The seventh subject had grade 3 lipase abnormality at screening and intermittently increased lipase values both during and after the study. Grade 3 increases in alanine transaminase (ALT) following administration of pasireotide 1,950 μg bid were observed in one subject. The subject had normal ALT (20.8 U/L), aspartate transaminase (AST; 20.9 U/L), and bilirubin (4.7 μmol/L) values at baseline, and no abnormally elevated ALT, AST, or bilirubin values were recorded prior to study end. However, at the end of the study period, ALT was 175.2 U/L (grade 3), AST was 98.0 U/L (grade 2), and bilirubin was 26.2 μmol/L (grade 2). One subject also met the biochemical criteria for Hy's law. At baseline, the subject had normal bilirubin (7.5 μmol/L), ALT (17.2 U/L), and AST (17.9 U/L). At study end, bilirubin and ALT were elevated to 68.9 μmol/L (four times the upper limit of normal) and 157.6 U/L (three times the upper limit of normal), respectively. Elevated AST (147.1 U/L) was also confirmed. Five days after the last dose of study drug, total bilirubin and AST levels had returned to normal. ALT was still elevated (165.9 U/L) but returned to normal 18 days after the last dose of study drug (39.2 U/L). There were no clinical sequelae. A grade 3 increased creatine kinase value was recorded for one subject following administration of moxifloxacin, which decreased before the end of the study (day 31). Thyroxine (FT4) and thyroid-stimulating hormone (TSH) levels were within normal limits for most subjects at screening and the end of the study. Seven of eight subjects with normal screening TSH and elevated TSH at the end of the study had pasireotide in their last treatment period (five with 1,950 μg bid, two with 600 μg bid), and one had moxifloxacin in the last period. With the exception of a slight decrease in pulse rate for subjects who received pasireotide in their last treatment period before the end of the study, no relevant changes in vital signs were observed.

Discussion

This Phase I study was conducted to provide information on the cardiac safety profile of pasireotide at steady state (day 5) in healthy volunteers; specifically, to determine the effect of pasireotide on QT/QTc interval. The study demonstrates a modest effect of subcutaneous pasireotide on QTcI at both the 600 and 1,950 μg bid doses. The maximal placebo-subtracted change from baseline in QTcI (ΔΔQTcI) was observed at 2 hours post-dose and was 13.2 and 16.1 milliseconds for the 600 and 1,950 μg doses, respectively. The small QTc difference between the two doses (2.9 milliseconds) in the presence of a 3.25-fold increase in dose and exposure suggests that the effect of pasireotide on QTcI could reach a plateau at this dose and exposure range (corresponding to a mean C_{max} range of 24.3–80.6 ng/mL).

The cardiovascular safety of pasireotide has previously been examined using in vitro and in vivo models. An in vitro electrophysiological study did not reveal inhibition of the hERG tail currents at concentrations up to 10 μM (10,472 ng/mL). In a 39-week toxicity study in monkeys receiving 3.2 mg/kg pasireotide (n = 4), no ECG or histopathological changes were seen. The C_{max} for the pasireotide concentration of 10 μM (9549 ng/mL) used in the hERG assay was well above the $C_{max,ss}$ (80.6 ± 25.2 ng/mL) for pasireotide 1,950 μg sc bid (n = 103) observed in healthy volunteers in the present study (Supplementary Table S3).

Our study is fully compliant with the ICHE14 guidance for evaluating the potential QT/QTc prolongation of drugs,[13] and the use of 24-hour Holter monitoring allowed continuous ECG collection. The crossover design reduced inter-subject variability, allowing smaller sample sizes. We conducted this thorough QT study in healthy volunteers because patients with Cushing's disease and acromegaly display an abnormally prolonged QT interval, making interpretation of a drug-induced QT effect more difficult.[5,19]

Prolongation of the corrected absolute QT interval beyond 500 milliseconds is considered to represent a threshold for increased risk of proarrhythmia. In our study, there were no individuals with QTc (QTcI, QTcF, or QTcB) intervals >500 milliseconds or a change from baseline >60 milliseconds following treatment with either dose of pasireotide.

Both pasireotide doses caused a reduction in HR, with the maximum reduction compared with placebo observed at 1 hour for pasireotide 600 μg bid (10.4 bpm) and at 0.5 hours for pasireotide 1,950 μg bid (14.9 bpm). Neither placebo nor moxifloxacin had a significant effect on HR. Findings for QTcF were consistent with those for QTcI for both pasireotide and moxifloxacin. For QTcB, no pasireotide treatment effect was observed, whereas the results on moxifloxacin were consistent with those for QTcI and QTcF, illustrating that QTcB overcorrects the QT interval in the presence of bradycardia, which is well known.

The results of the PK analysis showed that pasireotide sc was rapidly absorbed, with a t_{max} between 0.5 and 0.6 hours. PK analysis of moxifloxacin demonstrated similar C_{max} and AUC values compared to other TQT studies.[20,21] In accordance with ICH guidelines, moxifloxacin was used as the positive control to verify assay sensitivity as it has been shown to induce QTc prolongation. Based on the assessment of assay sensitivity, the null hypothesis of no effect of moxifloxacin on QTcI could not be rejected ($P = .065$) and assay sensitivity was not formally confirmed. However, the test may have failed because of the inclusion of early time points in the analysis. The assay sensitivity was actually met (null hypothesis rejected with $P < .05$) after excluding the early time points (0.5 and 1 hours) from the assessment.

The predictions based on the linear regression for the estimated mean ΔΔQTcI moxifloxacin and the maximal placebo-subtracted change in QTcI (11.1 milliseconds [90% CI: 9.3, 12.9]) were consistent with previously reported values and confirms the sensitivity of the study for testing the existence of QT effects of pasireotide.[14,21–25] The linear regression of the pasireotide sc concentration versus ΔΔQTcI resulted in predicted effects on ΔΔQTcI at the median C_{max} for pasireotide 600 μg bid (23.4 ng/mL) and 1,950 μg bid (77.8 ng/mL) that were consistent with the primary analysis (upper bound of the one-sided 95% CI exceeded 10 milliseconds).

Two additional models were used to further understand the pasireotide concentration–time relationship and the time course of the pasireotide effect on ΔΔQTcI. One of those two models was used to estimate and take into account the time lag between the peak pasireotide exposure and the peak effect of pasireotide on QT. The modeling results of the time-lag analysis suggested a lag of 0.8 hours between the peak exposure of pasireotide and the peak effect on ΔΔQTcI. This underestimation (observed time lag was 1.5 hours) could be accounted for by modeling the PK concentration data in a one-compartment model. Whilst the effects with the time-lag and linear models were similar at the therapeutic dose of 600 μg bid, the effect was somewhat larger at the MTD in the time-lag analysis compared with the linear model. Another model was used to estimate and take into account the effect of pasireotide concentration on HR. This model underpredicted the pasireotide effect on QT intervals at both doses, perhaps because it did not take into account the time lag between peak concentration and peak effect on QT.

No new safety concerns for pasireotide sc were observed in the study.[10,26–28] Most AEs were mild and transient. One subject discontinued because of a SAE that was considered vasovagal in nature, with no QT prolongation present and which resolved without treatment. Although most AEs were related to injection-site reactions and the majority were grade 1, they occurred more frequently with pasireotide than with placebo. Furthermore, an increased incidence of AEs at the higher dose indicates dose dependence; a similar trend was observed for gastrointestinal AEs. The primary objective of the study was to evaluate the effect of pasireotide on the baseline- and placebo-corrected QTcI and was not specifically designed to evaluate the safety of pasireotide treatment. Nevertheless, these findings are consistent with results from other Phase I studies conducted in healthy volunteers, in which pasireotide demonstrated good tolerability at single doses up to 1,500 μg or with daily infusion up to 2,050 μg for 7 days, with the most common treatment-related AEs being gastrointestinal.[29–33]

Although early studies have indicated that somatostatin analogues may prolong QT interval, a direct comparison between the effects of pasireotide and other somatostatin analogues is not possible as there are no ICH E14-compliant TQT studies published on these other agents.[13] A recent Phase III pasireotide study in patients with Cushing's disease reported treatment-emergent QTcF prolongation of >480 milliseconds in only 3/162 (2%) patients.[10] These QT prolongations were sporadic and did not require intervention or interruption of pasireotide treatment, and none were associated with arrhythmic events.[10] Two patients had syncope which was not associated with notable ECG changes.[10] No cases of torsades de pointes have been reported in the pasireotide clinical experience. Pasireotide has been approved by the US Food and Drug Administration and the European Medicines Agency for the treatment of adult patients with Cushing's disease for whom surgery is not an option or for whom surgery has failed. Before starting pasireotide therapy, monitoring for an effect on QTc interval is advised and an ECG should be performed prior to and 1 week after beginning treatment.[34]

In conclusion, the results of this study confirm an effect of pasireotide on QTcI in healthy volunteers at 600 and

1,950 μg bid doses, with a maximal placebo-subtracted change from baseline at 2 hours post-dose. Both pasireotide doses also decreased heart rate. Although the clinical relevance of the effect of pasireotide on cardiac repolarization observed in this study is not clear, we note that there were no QTc outlier values (>500 milliseconds, or QTc changes >60 milliseconds) or QT-prolongation-associated AEs in this study.

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Declaration of Conflicting Interests

C.D., M.L.S., P.J., D.S., K.H., and M.H. are employees of Novartis. A.B. is a Clinical Pharmacologist employed at Parexel International GmbH. As a Senior Clinical Research Physician in the Early Phase, she is involved in the preparation and conduct of mainly Phase I/II clinical studies for a number of pharmaceutical companies, including Novartis. R.S. was formerly a Senior Clinical Assessor at the Medicines and Healthcare Products Regulatory Agency (MHRA), London, UK. He is now the Director of Rashmi Shah Consultancy Ltd, which provides expert consultancy services on the development of new drugs to a number of pharmaceutical companies. He has provided consultancy services specifically to Novartis on a number of new drugs under development and was a member of their two Data Safety Monitoring Boards. He has not been paid for this manuscript.

References

1. Colao A, Baldelli R, Marzullo P, et al. Systemic hypertension and impaired glucose tolerance are independently correlated to the severity of the acromegalic cardiomyopathy. *J Clin Endocrinol Metab.* 2000;85:193–199.
2. Fatti LM, Scacchi M, Lavezzi E, et al. Effects of treatment with somatostatin analogues on QT interval duration in acromegalic patients. *Clin Endocrinol (Oxf).* 2006;65:626–630.
3. Lombardi G, Colao A, Ferone D, et al. Cardiovascular aspects in acromegaly: effects of treatment. *Metabolism.* 1996;45:57–60.
4. Lombardi G, Colao A, Marzullo P, Biondi B, Palmieri E, Fazio S. Improvement of left ventricular hypertrophy and arrhythmias after lanreotide-induced GH and IGF-I decrease in acromegaly. A prospective multi-center study. *J Endocrinol Invest.* 2002;25:971–976.
5. Pecori Giraldi F, Toja PM, Michailidis G, et al. High prevalence of prolonged QT interval duration in male patients with Cushing's disease. *Exp Clin Endocrinol Diabetes.* 2011;119:221–224.
6. Smith WH, Nair RU, Adamson D, Kearney MT, Ball SG, Balmforth AJ. Somatostatin receptor subtype expression in the human heart: differential expression by myocytes and fibroblasts. *J Endocrinol.* 2005;187:379–386.
7. Bubinski R, Kus W, Goch J. Effect of somatostatin on the conduction system of the heart. *Kardiol Pol.* 1993;38:258–262.
8. Arizona CERT. Drugs that prolong the QT interval and/or induce torsades de pointes ventricular arrhythmia. 2011. Available at: http://www.qtdrugs.org/ (last accessed September 2013).
9. Marfella R, Nappo F, De Angelis L, Siniscalchi M, Rossi F, Giugliano D. The effect of acute hyperglycaemia on QTc duration in healthy man. *Diabetologia.* 2000;43:571–575.
10. Colao A, Petersenn S, Newell-Price J, et al. A 12-month Phase 3 study of pasireotide in Cushing's disease. *N Engl J Med.* 2012;366: 914–924.
11. Boscaro M, Ludlam WH, Atkinson B, 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.* 2009;94:115–122.
12. Novartis Pharma AG. Signifor Summary of Product Characteristics. 2012. Available at: http://www.signifor.com/european-product-characteristics.jsp (last accessed February 2013).
13. FDA. Guidance for Industry: E14 Clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarryhthmic drugs. 2005. Available at: http://www.fda.gov/downloads/Regulatory/Guidances/ucm129357.pdf (last accessed October 2013).
14. Hosmane B, Locke C. A simulation study of power in thorough QT/QTc studies and a normal approximation for planning purposes. *Drug Inf J.* 2005;39:447–455.
15. Simes RJ. An improved Bonferroni procedure for multiple tests of significance. *Biometrika.* 1986;73:751–754.
16. Li J, Birmingham B, Mosqueda-Garcia R, Sander N, Newbold P, Sager P. Evaluation of a drug-induced QT/QTc prolongation in the presence of the drug induced changes in heart rate by using population PK/PD modeling approach: sibenadet experience. *Clin Pharmacol Ther.* 2008;83(S41–S42):abst OII-E-2.
17. Dmitrienko A, Smith B. Analysis of QT interval in clinical trials. *Drug Inf J.* 2002;36:269–279.
18. Dmitrienko A, Smith B. Repeated-measures models in the analysis of QT interval. *Pharmaceut Statist.* 2003;2:175–190.
19. Alexandraki KI, Kaltsas GA, Vouliotis AI, et al. Specific electrocardiographic features associated with Cushing's disease. *Clin Endocrinol (Oxf).* 2011;74:558–564.
20. Sullivan JT, Woodruff M, Lettieri J, et al. Pharmacokinetics of a once-daily oral dose of moxifloxacin (Bay 12-8039), a new enantiomerically pure 8-methoxy quinolone. *Antimicrob Agents Chemother.* 1999;43:2793–2797.
21. Bloomfield DM, Kost JT, Ghosh K, et al. The effect of moxifloxacin on QTc and implications for the design of thorough QT studies. *Clin Pharmacol Ther.* 2008;84:475–480.
22. Stass H, Kubitza D. Pharmacokinetics and elimination of moxifloxacin after oral and intravenous administration in man. *J Antimicrob Chemother.* 1999;43(Suppl. B):83–90.
23. Zhang J. Testing for positive control activity in a thorough QTc study. *J Biopharm Stat.* 2008;18:517–528.
24. Florian JA, Tornoe CW, Brundage R, Parekh A, Garnett CE. Population pharmacokinetic and concentration—QTc models for moxifloxacin: pooled analysis of 20 thorough QT studies. *J Clin Pharmacol.* 2011;51:1152–1162.
25. Dixon R, Job S, Oliver R, et al. Lamotrigine does not prolong QTc in a thorough QT/QTc study in healthy subjects. *Br J Clin Pharmacol.* 2008;66:396–404.
26. Petersenn S, Schopohl J, Barkan A, et al. Pasireotide (SOM230) demonstrates efficacy and safety in patients with acromegaly: a randomized, multicenter, Phase II trial. *J Clin Endocrinol Metab.* 2010;95:2781–2789.
27. Petersenn S, Farrall AJ, Block C, et al. Long-term efficacy and safety of subcutaneous pasireotide in acromegaly: results from an open-ended, multicenter, Phase II extension study. *Pituitary.* 2013; Mar 26:[Epub ahead of print]
28. Cozzi R, Attanasio R. Octreotide for acromegaly. *Expert Rev Endocrinol Metab.* 2007;2:129–145.

29. Ma P, Wang Y, Van Der Hoek J, et al. Pharmacokinetic-pharmacodynamic comparison of a novel multiligand somatostatin analog, SOM230, with octreotide in patients with acromegaly. *Clin Pharmacol Ther.* 2005;78:69–80.
30. Petersenn S, Unger N, Hu K, 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.* 2012;52:1017–1027.
31. Beglinger C, Hu K, Wang Y, et al. 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. *Endocrine.* 2012;42:366–374.
32. Golor G, Hu K, Ruffin M, et al. A first-in-man study to evaluate the safety, tolerability and pharmacokinetics of pasireotide (SOM230), a multireceptor-targeted somatostatin analog, in healthy volunteers. *Drug Des Dev Ther.* 2012;6:71–79.
33. Petersenn S, Hu K, Maldonado M, 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.* 2012;34:677–688.
34. Novartis Pharmaceuticals. Signifor Prescribing Information. 2012. Available at: http://www.pharma.us.novartis.com/cs/www.pharma.us.novartis.com/product/pi/pdf/signifor.pdf (last accessed February 2013).

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