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Pharmacokinetic (PK) and Pharmacodynamic (PD) Analyses of Pasireotide LAR From a Randomised, Phase III Study in Patients With Inadequately Controlled Acromegaly

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INTRODUCTION

- Pasireotide, a next-generation somatostatin analogue (SSA) has been recently approved for use in patients with acromegaly in US and Europe.[1,2]
- Results from the 24-week, phase III, PAOLA study demonstrated superior efficacy of both doses of pasireotide LAR (40 mg and 60 mg) over active control (continued treatment with octreotide LAR 30 mg or lanreotide Autogel 120 mg) in providing biochemical control (15.4%, 20.0% vs 0%) in patients with inadequately controlled acromegaly by the first-generation SSAs.[3]
- A pharmacokinetic (PK) and pharmacodynamic (PD) analysis report which examined the relationship between concentrations of pasireotide LAR and efficacy/safety endpoints from the phase III PAOLA study will be presented in this poster.

METHODS

Patients

- Patients aged ≥ 18 years with inadequately controlled acromegaly despite receiving octreotide LAR 30 mg or lanreotide Autogel 120 mg monotherapy for ≥ 6 months were enrolled.
  - Inadequate biochemical control was defined as mean growth hormone (GH) levels ≥ 2.5 µg/L and insulin-like growth factor 1 (IGF-1) >1.3 times the sex- and age-adjusted upper normal limit (ULN).
- In both the pasireotide LAR treatment arms (40 mg or 60 mg dose), a dose decrease by 20 mg was allowed in case of tolerability issues and once the issue resolves the dose is returned to pasireotide LAR 40 mg or 60 mg.

PK Assessments

PK Sample Collections and Analysis Set

- Blood samples (2.5 mL each) for PK assessment were taken prior to each injection of pasireotide LAR every 4 weeks, at visits 2, 4, 5, 6, 8, 9, and 10 (end of study); and at visits 3 (week 3) and 7 (week 15).
- Analyses were performed on the PK analysis set, which comprised all patients who received at least one injection of pasireotide LAR and had at least one evaluable post-dose PK measurement.

Dose Proportionality

- Dose proportionality for pasireotide LAR doses (40 mg and 60 mg) was explored using a power model,[4] fitted with a linear mixed effects model on log-transformed steady-state trough concentration (C_{trough}) vs log-transformed dose.
- The estimate and 90% confidence interval (CI) of the slope were reported and compared to the target dose proportionality range (0.80, 1.25).[4]

PK Covariate Analysis

- A linear mixed-effect model was used to test whether demographic, baseline renal function, or baseline liver function parameters had potential covariate effects on steady-state C_{trough} of pasireotide LAR.

PK/PD Assessments – Data Cut-Off at Week 24

Relationship Between Pasireotide Concentration and Efficacy

- Relationship between pasireotide LAR exposure and efficacy endpoints (mean GH or standardised IGF-1 levels) was explored by nonlinear inhibitory E_{max} model.
- Repeated measures logistic regression models (generalised linear model fitted by generalised estimating equations [GEE] methods) were used to explore the correlation between pasireotide C_{trough} and binomial response (in terms of the probabilities of normalisation of GH, IGF-1, and respectively both GH + IGF-1). Effect of covariates such as baseline GH and IGF-1 levels were also investigated.

Relationship Between Pasireotide Concentration and Safety

- The relationship between pasireotide exposure and the probability of hyperglycaemia was explored using a repeated measures generalised linear model (generalised linear model fitted by GEE methods).
- The relationship between pasireotide LAR concentration with change in QTcF and QTcB from baseline and pasireotide exposure association with liver function tests was explored using a linear mixed model.

RESULTS

Patient Population

- The PK analysis set included 63/65 and 62/65 patients from the pasireotide LAR 40 mg and 60 mg treatment arms, respectively.

Steady-State Trough Concentrations

- Pasireotide concentrations reached steady state after 3 consecutive monthly injections. The inter-patient PK variability was moderate to high (**Figure 1**).
- The mean steady-state C_{trough} values of pasireotide LAR 40 mg and 60 mg (ie, from day 113-169) ranged from 8.84 to 9.24 ng/mL at 40 mg (n=63), and from 12.73 to 13.50 ng/mL at 60 mg (n=62), respectively.

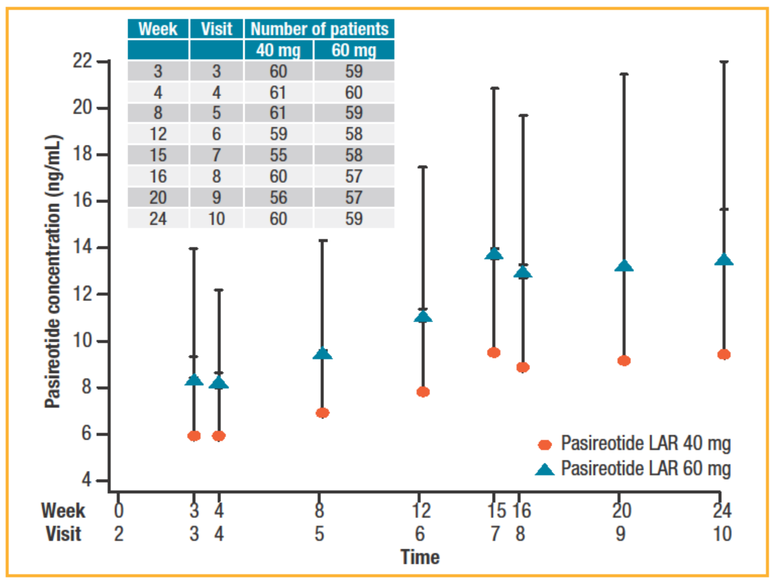
Dose Proportionality

- The model slope estimate was 0.935, close to 1, with a 90% CI (0.819, 1.066), which was within the predefined dose proportional target range (0.80, 1.25).
- The dose-exposure relationship for pasireotide LAR was approximately dose proportional within the 40 to 60 mg dose range.

PK Covariates

- Age, baseline total bilirubin levels, and gender were statistically significant PK covariates for C_{trough} values of pasireotide although none had a clinically meaningful impact on PK exposure.
- The covariate effect of gender suggested that with the same age and equal baseline total bilirubin, female patients would have approximately 51% higher steady-state C_{trough} than male patients for pasireotide. However, this PK difference in gender was considered not clinically meaningful because efficacy and safety profiles were similar between female and male patients.

Figure 1. Pasireotide Concentration-Time Profile (Mean ± SD) by Incident Dose Over Time



Note: Includes scheduled visits only
LAR, long-acting release.

Relationships Between Pasireotide Concentration and Efficacy

- There was a clear exposure-response relationship between pasireotide concentration and GH and IGF-1 levels.
- The estimated maximum IGF-1 suppression (67.1%) was relatively lower than the estimated maximum GH suppression (83.0%); the estimated effective concentration to suppress IGF-1 to 1 × ULN was much higher than the estimated effective concentration of pasireotide to suppress GH to 2.5 µg/L (**Table 1**).
- These results were in line with the observed higher response rate for GH vs IGF-1 with both 40 mg (35.4% vs 24.6%) and 60 mg (43.1% vs 26.2%).

Table 1. Key Model Parameters Estimated Using the Nonlinear E_{max} Model on the Suppression Effect of Pasireotide LAR on GH and IGF-1

GH (mean ± SE)			Standardised IGF-1 (mean ± SE)		
EC_{50} (ng/mL)	$C_{effective}$ (ng/mL)	Maximum suppression (%)	EC_{50} (ng/mL)	$C_{effective}$ (ng/mL)	Maximum suppression (%)
2.83 ± 1.06	12.28 ± 3.3	83.0 ± 6.5	8.13 ± 1.8	42.3 ± 16.6	67.1 ± 5.8

$C_{effective}$, estimated effective concentration for suppressing GH levels to <2.5 µg/L and IGF-1 to within the upper limit of age- and sex-related normal values; EC_{50}, drug concentration inducing half-maximal possible relative suppression; GH, growth hormone; IGF-1, insulin-like growth factor 1; LAR, long-acting release; SE, standard error.

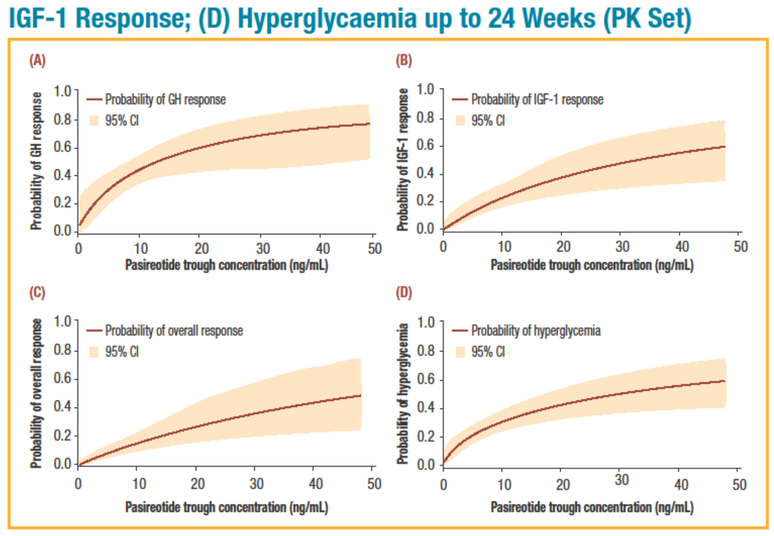
- Repeated measures logistic regression analysis, adjusting for baseline GH, baseline IGF-1, and both, respectively, suggested that a 1.5-fold increase in pasireotide C_{trough} (corresponding to dose increase from 40 to 60 mg) was associated with a 44%, 51%, and 54% increase in the odds of GH, and IGF-1, and GH + IGF-1 responses, respectively (**Figure 2A, 2B, and 2C**).

Relationships Between Pasireotide Concentration and Safety

Associations with hyperglycaemia risk

- A 1.5-fold increase in pasireotide C_{trough} (corresponding to dose increase from 40 to 60 mg) was associated with a 36% increase in the odds of having hyperglycaemia, in the repeated measures logistic regression analysis. (**Figure 2D**).

Figure 2. Relationship Between Pasireotide Trough Concentration and Probability of (A) GH Response; (B) IGF-1 Response; (C) GH + IGF-1 Response; (D) Hyperglycaemia up to 24 Weeks (PK Set)



CI, confidence interval; GH, growth hormone; IGF-1, insulin-like growth factor 1; PK, pharmacokinetic.

Associations with change in QTc and liver function tests

- A relatively flat relationship with no clinically significant effect was found between pasireotide exposure and change from baseline for both QTcF and QTcB.
- No clinically significant effect was found between pasireotide exposure and liver function tests.

CONCLUSIONS

- **The dose-exposure relationship of pasireotide LAR was considered to be approximately dose proportional in acromegaly patients within the dose range evaluated (40 to 60 mg).**
- **The PK/PD analyses demonstrated a positive relationship between pasireotide exposure and efficacy endpoints (GH and IGF-1), and also support the clinical finding of higher GH and IGF-1 response rates at 60 mg than 40 mg.**
- **The PK/efficacy and PK/safety analyses results support the clinical observation of a positive benefit/risk profile for pasireotide LAR treatment in patients with acromegaly inadequately controlled by first-generation SSAs.**

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