**Effect of Pasireotide on GH, IGF-1, IGFBP-2, IGFBP-3, HbA1c, and Glucose in Patients with Inadequately Controlled Acrômegaly: Exploratory Results from a Multicentre, Randomized, 24-Week Study (PAOLA)**

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**INTRODUCTION**

- Pasireotide is a multi-receptor-targeted somatostatin analogue with higher affinity for sst5, sst6, sst2b, and sst3 in vitro and in vivo compared to octreotide and lanreotide.
- Pasireotide LAR has demonstrated superior efficacy over octreotide LAR in medically naïve patients with acromegaly and was recently versus continued treatment with octreotide LAR or lanreotide Autogel in patients with inadequately controlled acromegaly, as shown by results from the PAOLA (SOM2032C2402) study (see poster PS03).
- In both of these studies, pasireotide treatment was associated with elevations in blood glucose levels in a majority of patients.
- An exploratory analysis of the PAOLA study was to measure changes in various associated biomarkers, including insulin-like growth factor 1 (IGF-1), IGFBP-2 (IGFBP-2), IGFBP-3, fasting plasma glucose (FPG) and glycaemic haemoglobin (HbA1c) levels, during the 24-week treatment period.
- The aim of this analysis was to gain more insight into the mechanism of action of pasireotide in patients not adequately controlled with octreotide or lanreotide.

**METHODS**

**Patients**

- Male and female patients aged ≥18 years with inadequately controlled acromegaly – Defined as mean growth hormone (GH) levels ≥2.5 μg/L, and IGF-1 >1.3 times the sex- and age-adjusted upper normal limit (ULN).
- All patients received octreotide LAR 30 mg or lanreotide Autogel 125 mg monotherapy for ≥6 months before screening.

**Study Design**

- Prospective, 24-week, multicentre, randomized, parallel-group study.
- Patients randomized to double-blind pasireotide LAR 40 mg/day or 60 mg/28 days; or continued treatment with open-label octreotide LAR or lanreotide Autogel (active control) (Figure 1).

**Analysis**

- The primary endpoint was the proportion of patients achieving biochemical control as mean GH levels <1.0 μg/L and normalized IGF-1 levels at 24 weeks.
- A detailed analysis of biomarkers was conducted to gain additional insights into the mode of action of somatostatin analogues in patients with acromegaly.
- Time profiles of GH, IGF-1, IGFBP-2, IGFBP-3, FPG and HbA1c levels were generated from patients who completed the study and analyzed together and separately in relevant subgroups of patients:
  - Patients who were responders (GH <1.0 μg/L, and normalized IGF-1) and non-responders (GH ≥2.5 μg/L, and IGF-1 >1.3 ULN) at week 24.
  - Patients who did not receive antidiabetic medication (ADM) at any time during the study.
  - Patients who were receiving ADM at baseline.
  - Patients who initiated ADM post-baseline.
  - Patients who received pasireotide LAR 40 mg/day or 60 mg/28 days (non-responders to active control).

**RESULTS**

**Patient Population**

- 198 patients were randomized to pasireotide LAR 40 mg (n=65), pasireotide LAR 60 mg (n=60) and active control (n=73).
- In total, 59 (29.6%), 57 (28.9%) and 65 (33.4%) patients in the pasireotide LAR 40 mg, pasireotide LAR 60 mg and active control groups, respectively, completed the 24-week study.

**GH, IGF-1 and IGFBP-3**

- Biochemical control at 24 weeks was achieved by:
  - 15.4% of pasireotide LAR 40 mg patients (P=0.006 vs active control)
  - 20.0% of pasireotide LAR 60 mg patients (P=0.001 vs active control)
  - No patients in the active control group.
- GH, IGF-1 and IGFBP-3 levels decreased dose dependently and remained consistently suppressed during pasireotide LAR treatment (Figure 2).

**FPG and HbA1c**

- Among patients not receiving ADM at baseline, 30% (n=19) and 49% (n=10) of patients with baseline FPG >100 mg/dL developed hyperglycaemia (defined as post-baseline FPG >126 mg/dL) or receiving ADM during treatment with pasireotide LAR 40 mg and 60 mg, respectively, compared with 52% (n=11) and 71% (n=15) of patients with baseline FPG >100 mg/dL (Figure 6).

**CONCLUSIONS**

- Pasireotide LAR provided superior efficacy in patients with inadequately controlled acromegaly on continued treatment with octreotide LAR or lanreotide Autogel.
- Responders to pasireotide LAR had lower GH and IGF-1 levels at baseline than non-responders.
- 47% of patients treated with pasireotide LAR did not receive ADM at any time during the study, these patients had lower baseline FPG levels than those who did receive ADM.
- A key predictive factor for the development of hyperglycaemia during pasireotide treatment was baseline glucose level; patients with higher FPG and/or HbA1c at baseline experienced a higher degree of hyperglycaemia during pasireotide treatment.
- Hyperglycaemia after pasireotide was similar in responders versus non-responders and depended more on the baseline FPG level.
- The development of hyperglycaemia was rapid and plateaued during continuous treatment.
- The long-term effects of pasireotide LAR on glucose homeostasis may be lessened by increased insulin sensitivity due to the compensatory increase in IGFBP-2.

**REFERENCES**


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**Table 1. FPG and HbA1c Levels during 24 Weeks of Treatment in All Patients, and in Patients Receiving ADM, Patients Not Receiving ADM Post-baseline (Geometric Mean ± Standard Error)**

**Table 2. Response Rates in Patients Treated with Pasireotide LAR Receiving and Not Receiving ADM**

**Figure 1. Study Design**

**Figure 2. Effect of Pasireotide LAR and Active Control on (A) GH, (B) IGF-1 and (C) IGFBP-3 Levels during 24 Weeks of Treatment in All Patients, and in Responders and Non-responders (Geometric Mean ± Standard Error)**

**Figure 3. Effect of Pasireotide LAR and Active Control on (A) FPG and (B) HbA1c, in All Patients, Patients Receiving ADM, Patients Not Receiving ADM Post-baseline (Geometric Mean ± Standard Error)**

**Figure 4. Effect of Pasireotide LAR and Active Control on IGFBP-2 Levels in All Patients and in Responders and Non-responders (Geometric Mean ± Standard Error)**

**Figure 5. Effect of Pasireotide LAR and Active Control on (A) FPG and (B) HbA1c, in Baseline Patients with FPG >100 or ≤100 mg/dL (Geometric Mean ± Standard Error)**

**Figure 6. Percentage of Patients Developing Hyperglycaemia (Post-baseline FPG >126 mg/dL or Receiving ADM Post-baseline) during Treatment with Pasireotide LAR or Active Control, Stratified by Baseline FPG levels >100 or ≤100 mg/dL, in Patients without Baseline ADM**

**Figure 7. Effect of Pasireotide LAR and Active Control on (A) FPG and (B) HbA1c, in All Patients, and in Responders and Non-responders (Geometric Mean ± Standard Error)**

**Figure 8. Percentage of Patients Developing Hyperglycaemia (Post-baseline FPG >126 mg/dL or Receiving ADM Post-baseline) during Treatment with Pasireotide LAR or Active Control, Stratified by Baseline FPG levels >100 or ≤100 mg/dL, in Patients without Baseline ADM**