P845

Pasireotide LAR and Octreotide LAR Maintain Inhibition of GH and IGF-1 in Patients With Acromegaly: 12-Month Extension Phase of a Randomized, Double-Blind, Multicenter, Phase III Study

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INTRODUCTION

- Acromegaly, if left untreated, is associated with a 2 to 2.5 times increased mortality risk compared with the general population. Reducing growth hormone (GH) levels <2.5 µg/L and insulin-like growth factor-1 (IGF-1) to normal levels significantly reduces mortality.[1]
- Pasireotide, a multireceptor-targeted somatostatin analogue (SSA) that has broader somatostatin receptor binding profile (high affinity binding to 4 out of 5 somatostatin receptor subtypes) than the currently available SSA, provides effective control of GH and IGF-1 levels in patients with GH-secreting pituitary adenomas.[2-4]
- Pasireotide long-acting release (LAR) demonstrated significantly superior biochemical control ($P = 0.007$) than octreotide LAR in a randomized, double-blind, 12-month trial in 358 medically naïve patients with acromegaly.[5]

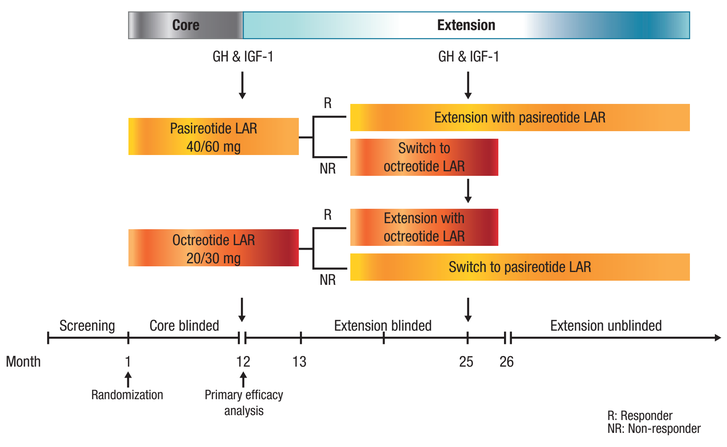
- An extension phase to this study allowed patients to continue receiving their randomized therapy or crossover at month 13, depending on their GH and IGF-1 levels as well as whether they were receiving clinical benefit from the study drug.
- This poster reports the results up to month 26 in patients with clinical benefit or GH <2.5 µg/L and IGF-1 ≤upper limit of normal (ULN) at month 13 who continued receiving their randomized therapy in extension phase.
- Poster 847 reports the results in patients who switched treatments at month 13.

METHODS

Study Design

- Medically naïve patients (either post-pituitary surgery or *de novo* with visible pituitary adenoma on magnetic resonance imaging who refused pituitary surgery or for whom pituitary surgery was contraindicated) with active acromegaly (GH >5 µg/L or GH nadir ≥1 µg/L post-oral glucose tolerance test, and IGF-1 >ULN) were eligible for enrollment into the 12-month core study.
- Patients were randomized to pasireotide LAR 40 mg/28 days or octreotide LAR 20 mg/28 days. Dose titration to pasireotide LAR 60 mg/28 days or octreotide LAR 30 mg/28 days permitted, but not mandatory, at month 3 or 7. Dose decreases were permitted for tolerability issues (**Figure 1**).

Figure 1. Study Design



- A protocol amendment implemented shortly after the trial had begun, established a double-blind extension phase whereby patients could either remain on their randomized therapy or crossover to the opposite treatment.
- Prior to the protocol amendment, patients who were inadequately controlled with octreotide LAR could switch to pasireotide LAR at month 12, but not vice versa.
- Following this amendment, patients with GH <2.5 µg/L and IGF-1 ≤ULN at month 12 could continue on their randomized therapy as could patients considered by the investigator to be achieving clinical benefit.
- Patients entering the extension were followed up to month 26 (core plus extension).
  - Last assessment of GH, IGF-1, and tumor volume was performed at month 25
  - Last assessment of safety and monthly acromegaly symptom scores was performed at month 26
- Dose escalation to pasireotide LAR 60 mg or octreotide LAR 30 mg was permitted, but not mandatory, at any time during extension if GH ≥2.5 µg/L and/or IGF-1 >ULN. Dose decreases were permitted for tolerability issues.

Study Objectives and Endpoints

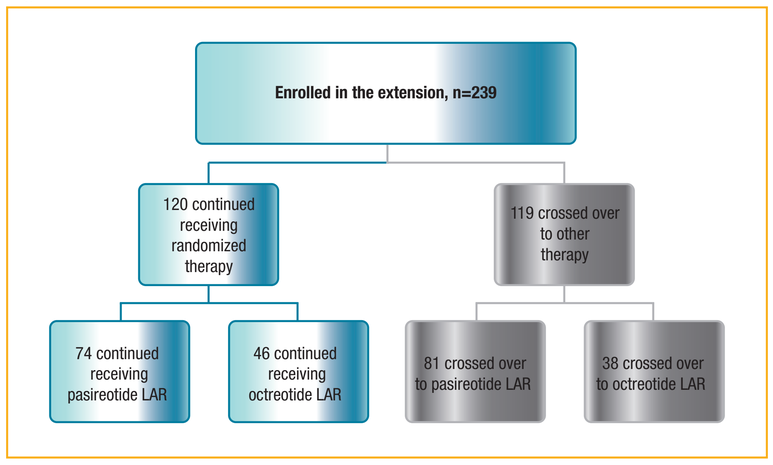
- The primary objective of the core study was to demonstrate the superiority of pasireotide LAR over octreotide LAR in providing GH <2.5 µg/L and normal IGF-1 at month 12.
- The objective of the extension study was to assess the effect of pasireotide LAR and octreotide LAR as long term treatment on the following efficacy endpoints.
  - Proportion of patients with a reduction of mean GH level to <2.5 µg/L and normalization of IGF-1 (age and sex related) at months 16 and 25
  - Proportion of patients achieving GH <2.5 µg/L at months 16 and 25
  - Proportion of patients achieving normal IGF-1 at months 16 and 25
  - Change from core baseline in (i) GH levels (ii) IGF-1 levels, (iii) tumor volume, and (iv) severity scores (0 to 4 scale) of acromegaly symptoms (headache, fatigue, perspiration, paresthesia, and osteoarthralgia), over time
- Safety and tolerability of pasireotide LAR and octreotide LAR as long term treatment was evaluated. Safety assessments included monitoring of adverse events (AEs), as well as hematology, blood chemistry and urinalysis parameters.

RESULTS

Patients

- Of the 358 patients who entered the core phase, 120 patients entered the extension in their randomized arm and continued receiving randomized treatment (**Figure 2**).

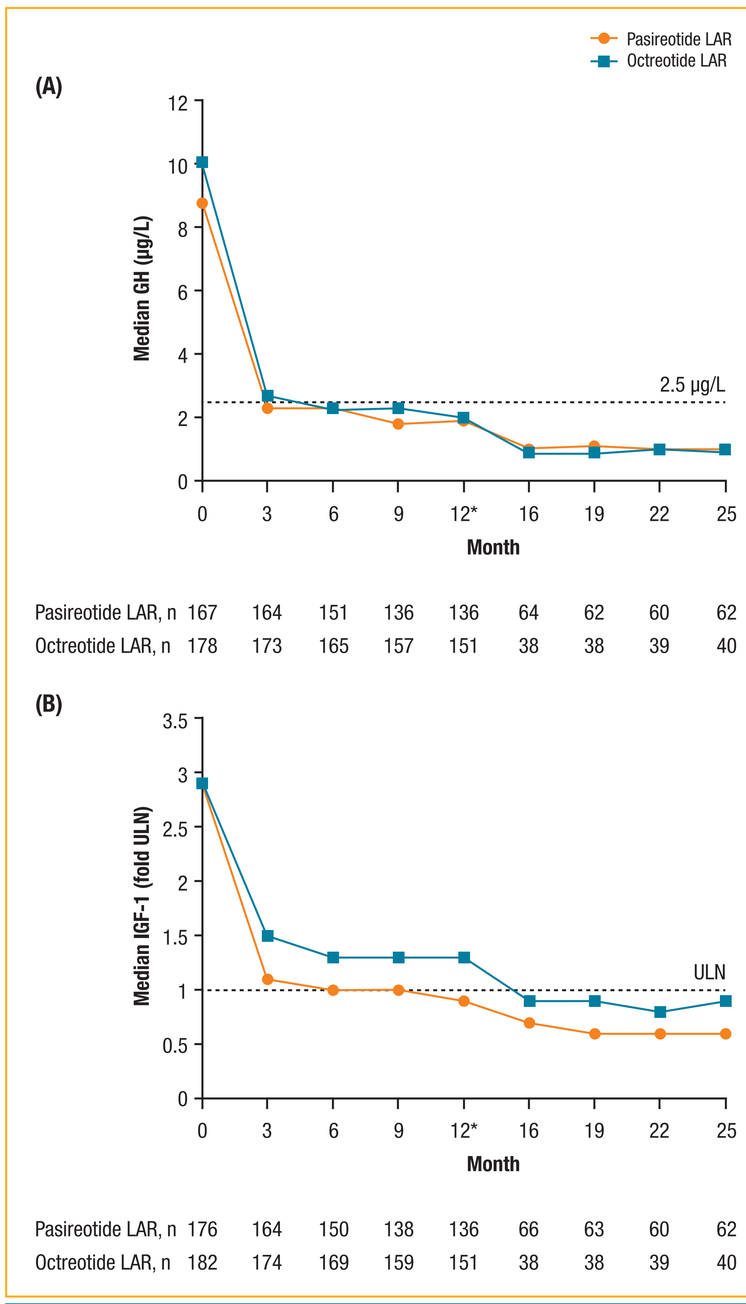
Figure 2. Patient Disposition



Efficacy

- Mean duration of exposure was 527 days in the pasireotide LAR arm and 415 days in the octreotide LAR arm.
- Suppression of GH and IGF-1 was maintained throughout the extension in both the treatment arms (**Figure 3**).

Figure 3. Median (A) GH and (B) IGF-1 Levels During Treatment



*Patients who were in adequately controlled (GH ≥2.5 µg/L and/or IGF-1 >ULN) crossed over to the other treatment - either pasireotide LAR 40 mg/28 days or octreotide IAR 20 mg/28 days at the end of core study (month 13).

- Median percentage change in GH from core baseline to month 25 was –83% in patients in the pasireotide LAR and –86% in patients in the octreotide LAR treatment arm.
- Median percentage change in IGF-1 from core baseline to month 25 was –71% with pasireotide LAR and –64% with octreotide LAR.
- At month 25, 48.6% of pasireotide LAR and 45.7% of octreotide LAR patients achieved GH <2.5 µg/L and normal IGF-1 (**Table 1**).
- At month 25, 60.8% of pasireotide LAR patients and 52.2% of octreotide LAR patients had mean GH levels <2.5 µg/L and IGF-1 ≤ULN.
- Tumor volume decreased from core baseline to month 25 by a mean (SD) of –51.8% (20.8%) in the pasireotide LAR arm and –55.0% (21.3%) in the octreotide LAR arm.
- A significant (≥20%) tumor volume reduction from extension baseline to month 25 was seen in 74.7% of pasireotide LAR and 71.6% of octreotide LAR patients.
- Both the treatments improved severity scores of acromegaly symptoms.

Table 1. Biochemical Response Rates in Patients who Continued Receiving Their Randomized Dose up to Month 26

	Pasireotide LAR, N=74		Octreotide LAR, N=46	
	n (%)	95% CI	n (%)	95% CI
GH levels <2.5 µg/L and normal IGF-1				
Month 16	37 (50.0)	38.1, 61.9	19 (41.3)	27.0, 56.8
Month 25	36 (48.6)	36.9, 60,6	21 (45.7)	30.9, 61.0
GH levels <2.5 µg/L				
Month 16	49 (66.2)	54.3, 76.8	34 (73.9)	58.9, 85.7
Month 25	52 (70.3)	58.5, 80.3	37 (80.4)	66.1, 90.6
Normal IGF-1				
Month 16	44 (59.5)	47.4, 70.7	21 (45.7)	30.9, 61.0
Month 25	38 (51.4)	39.4, 63.2	22 (47.8)	32.9, 63.1

Safety

- Overall, 23/74 (31.1%) and 10/46 (21.7%) patients in the pasireotide LAR and octreotide LAR arms who continued receiving their randomized treatment in the extension phase discontinued treatment between months 12 and 26.
  - Most common reason for discontinuation was consent withdrawal (12.2% and 4.3%)
- Two deaths were reported during the extension phase (major depression in a pasireotide LAR patient, sepsis in an octreotide LAR patient). Both were considered to be unrelated to study drug by the investigator (**Table 2**).

Table 2. Most Commonly Reported Adverse Events (>15% in Total in Either Treatment Arm) From Core Baseline to Month 26

	Pasireotide LAR (N=178*)		Octreotide LAR (N=180*)	
	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)
Diarrhea	71 (39.9)	1 (0.6)	81 (45.0)	5 (2.8)
Cholelithiasis	58 (32.6)	3 (1.7)	71 (39.4)	3 (1.7)
Headache	41 (23.0)	2 (1.1)	49 (27.2)	5 (2.8)
Abdominal pain	33 (18.5)	1 (0.6)	44 (24.4)	0
Hyperglycemia	55 (30.9)	6 (3.4)	18 (10.0)	1 (0.6)
Alopecia	34 (19.1)	0	36 (20.0)	0
Nasopharyngitis	32 (18.0)	0	29 (16.1)	0
Nausea	27 (15.2)	1 (0.6)	41 (22.8)	0
Diabetes mellitus	39 (21.9)	9 (5.1)	8 (4.4)	0

*Two patients randomized to the octreotide LAR treatment arm received pasireotide LAR in error. These two patients are included in the pasireotide LAR treatment arm for the purposes of the safety analysis.

- Mean glucose and glycosylated hemoglobin (HbA_{1c}) increased in the first 3 months after initiation of pasireotide LAR therapy and remained stable to 26 months. In octreotide LAR arm, a smaller and more gradual increase in mean glucose and HbA_{1c} was observed, which peaked at months 9 to 12 and remained relatively stable up to month 26.
- Hyperglycemia-related AEs (including but not limited to hyperglycemia, hypoglycemia, diabetes mellitus, and increased HbA_{1c}) was the only category that was more frequent with pasireotide LAR than octreotide LAR.
- Proportion of patients with grade 3 or 4 hyperglycemia-related AEs was higher with pasireotide LAR than octreotide LAR (16/178 [9.0%] vs 3/180 [1.7%]), and similar to that reported in the core phase.

CONCLUSIONS

- **Pasireotide LAR was significantly superior to octreotide LAR in providing biochemical control in the 12-month core phase of the study. During the extension phase, suppression of GH and IGF-1 levels was maintained in both the treatment arms.**
- **No new safety findings were reported during the extension phase compared with the core study.**
- **The safety profile of pasireotide LAR and octreotide LAR was similar, except for the degree of hyperglycemia.**
- **These results suggest that pasireotide LAR and octreotide LAR provide long-term inhibition of GH and IGF-1 in patients with acromegaly.**

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