P847

Switching Patients with Acromegaly from Octreotide LAR to Pasireotide LAR Improves Biochemical Control: Crossover Extension to a Randomized, Double-Blind, Multicenter, Phase III Study

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INTRODUCTION

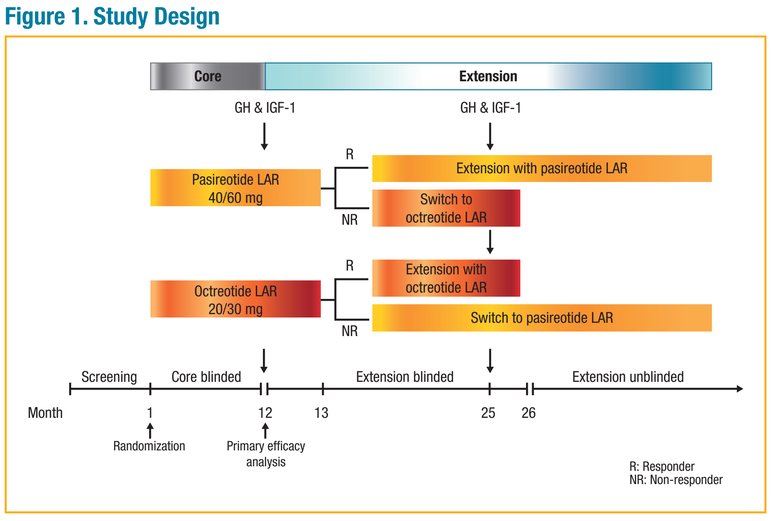
- The therapeutic goal in acromegaly is to reduce morbidity and mortality by removing tumor mass and restoring growth hormone (GH) and insulin-like growth factor-1 (IGF-1) levels to within normal range.[1]
- Somatostatin analogues (SSAs) are the cornerstone of medical therapy in patients with acromegaly in whom surgery is not effective, as well as in those who have a minimal chance of surgical cure (because of extrasellar extension of the tumor) or are not candidates for surgery.[2]
- Pasireotide is a multireceptor-targeted SSA with a broader somatostatin receptor binding profile than currently available SSAs that was developed with the goal of improving biochemical control rates in patients with acromegaly.[3]
- In a large, randomized, double-blind, Phase III trial in medically naïve patients with acromegaly, pasireotide long-acting release (LAR) was significantly superior (P=0.007) to octreotide LAR at providing biochemical control at 12 months.[4]
- An extension phase allowed patients who did not have biochemical control (GH <2.5 µg/L and IGF-1 level within normal limits) to switch over to the other treatment, and those who were controlled or receiving clinical benefit from study drug to continue receiving their randomized therapy beyond month 13.
- Efficacy results for up to 12 months after crossover (last visit at which efficacy parameters were assessed in the octreotide LAR arm) are reported here. Safety results include data up to 13 months after crossover.
- Poster 845 reports the results in patients who continued receiving their randomized therapy.

METHODS

Study Design

- Medically naïve (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) patients with active acromegaly (GH >5 µg/L or GH nadir ≥1 µg/L post-oral glucose tolerance test, and IGF-1 >upper limit of normal [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, with 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 (**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 other 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/or IGF-1 >ULN (age and sex-matched) could switch to the other treatment - either pasireotide LAR 40 mg/28d or octreotide LAR 20 mg/28d at the end of core study (month 13).
- After crossover, dose escalation to pasireotide LAR 60 mg or octreotide LAR 30 mg was permitted, but not mandatory, at month 17 or 20 if GH ≥2.5 µg/L and/or IGF >ULN. Dose decreases were permitted for tolerability.

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 following endpoints were defined for the crossover phase.
  - Proportion of patients in each arm with reductions of mean GH level to <2.5 µg/L and IGF-1 level to within normal limits (age and sex related) at months 3, 6, 9, and 12 after crossover
  - Proportion of patients in each arm with: (i) GH <2.5 µg/L; (ii) IGF-1 within normal limits at time points up to month 12 after crossover
  - Change from extension baseline in GH and IGF-1 levels over time
  - Change from extension baseline in tumor volume over time
  - Safety and tolerability of pasireotide LAR and octreotide LAR after crossover; safety assessments included monitoring of adverse events (AEs), as well as hematology, blood chemistry and urinalysis parameters

Statistical Method

- Extension baseline is defined as the last available assessment within 35 days prior to the first injection after crossover.

RESULTS

Patients

- 141 (80.1%) patients receiving pasireotide LAR and 156 (85.7%) patients receiving octreotide LAR completed the 12-month core study.
- Of the 239 patients who entered the extension, 119 patients crossed over to other therapy - either pasireotide LAR or octreotide LAR; 81 patients were crossed over to pasireotide LAR and 38 to octreotide LAR.
- Median duration of treatment after crossover was 420 days in the pasireotide LAR treatment arm and 364 days in the octreotide LAR treatment arm.
- 31 pasireotide LAR and 13 octreotide LAR patients discontinued within 13 months after crossover.

Efficacy

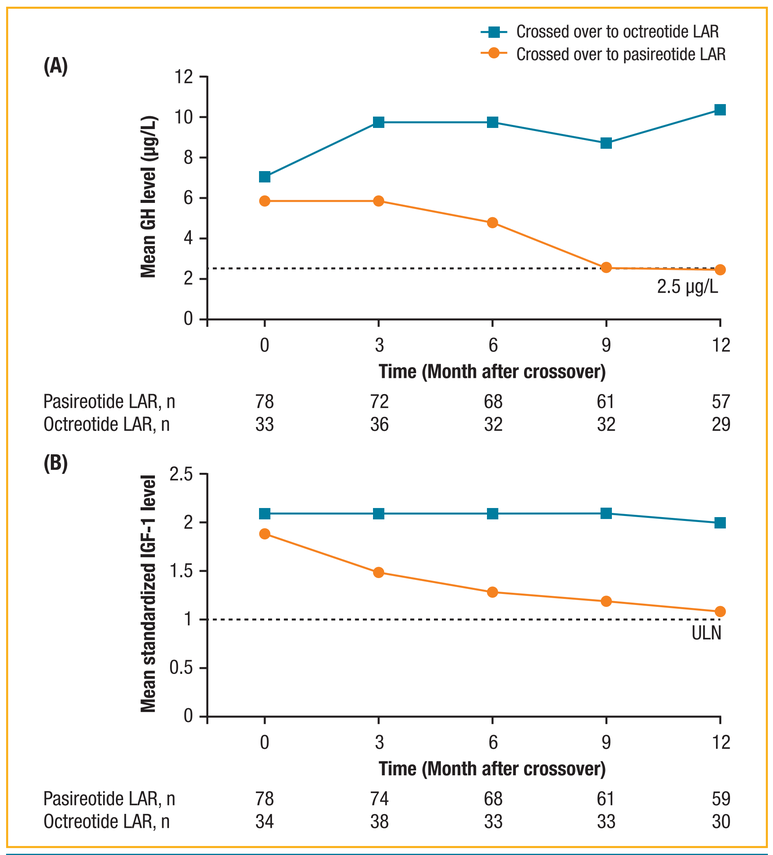
- Of the 81 patients inadequately controlled with octreotide LAR who switched to pasireotide LAR, 14 (17.3%) had biochemical control 12 months after crossover (**Table 1**).
- Of the 38 patients inadequately controlled with pasireotide LAR who switched to octreotide LAR, none had biochemical control 12 months after crossover (**Table 1**).

Table 1. Biochemical Response Rates in Patients After Crossover by Treatment Group

Month after crossover	Crossed over to Pasireotide LAR N=81		Crossed over to Octreotide LAR N=38	
	n (%)	95% exact CI	n (%)	95% exact CI
GH <2.5 µg/L and normal IGF-1				
Month 3	14 (17.3)	9.8, 27.3	1 (2.6)	0.1, 13.8
Month 6	17 (21.0)	12.7, 31.5	1 (2.6)	0.1, 13.8
Month 9	18 (22.2)	13.7, 32.8	2 (5.3)	0.6, 17.7
Month 12	14 (17.3)	9.8, 27.3	0 (0.0)	–
GH levels <2.5 µg/L				
Month 3	40 (49.4)	38.1, 60.7	11 (28.9)	15.4, 45.9
Month 6	35 (43.2)	32.2, 54.7	12 (31.6)	17.5, 48.7
Month 9	44 (54.3)	42.9, 65.4	12 (31.6)	17.5, 48.7
Month 12	36 (44.4)	33.4, 55.9	9 (23.7)	11.4, 40.2
Normal IGF-1				
Month 3	16 (19.8)	11.7, 30.1	3 (7.9)	1.7, 21.4
Month 6	25 (30.9)	21.1, 42.1	3 (7.9)	1.7, 21.4
Month 9	24 (29.6)	20.0, 40.8	4 (10.5)	2.9, 24.8
Month 12	22 (27.2)	17.9, 38.2	2 (5.3)	0.6, 17.7

- Mean GH and standardized IGF-1 levels for both treatment arms at extension baseline and at various timepoints after crossover are shown in **Figure 2**.

Figure 2. Mean GH Level and Standardized IGF-1* Level at Extension Baseline and Months 3, 6, 9 and 12 After Crossover



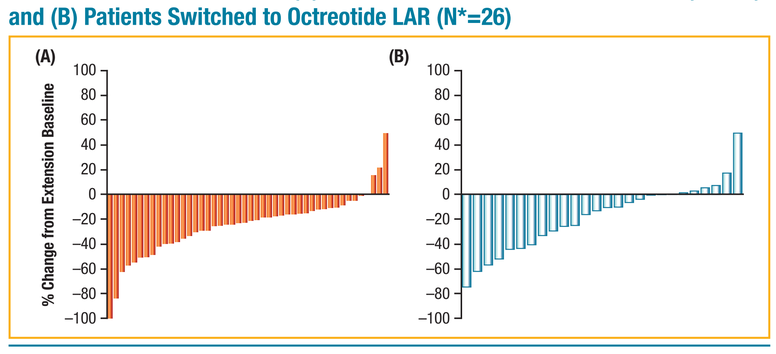
*Standardized IGF-1: patient IGF-1 value / ULN

- Tumor volume decreased from extension baseline to month 12 after crossover by a mean (SD) of 24.7% (25.2%) in the pasireotide LAR arm and 17.9% (27.8%) in the octreotide LAR arm (**Figure 3**).
- A significant (≥20%) tumor volume reduction from extension baseline to month 12 after crossover was seen in 54.3% (25/46) of pasireotide LAR and 42.3% (11/26) of octreotide LAR patients.

Safety

- The safety profile of both agents was similar to that seen in the core study. After crossover, the safety profile of pasireotide LAR was similar to that of octreotide LAR, with the exception of the degree of hyperglycemia (**Table 2**).
- Hyperglycemia-related AEs (including but not limited to hyperglycemia, hypoglycemia, diabetes mellitus, and increased glycosylated hemoglobin [HbA_{1c}]) was the only category that was more frequent with pasireotide LAR (64.2%) than octreotide LAR (21.1%).
- At extension baseline, mean fasting plasma glucose (FPG) and HbA_{1c} levels were higher among patients who crossed over to octreotide LAR than those who crossed to pasireotide LAR (mean FPG: 127 mg/dL vs 104 mg/dL; mean HbA_{1c} levels 6.71% vs 6.19%).

Figure 3. Percentage Change in Tumor Volume (from Extension Baseline) at Month 12 After Crossover for (A) Patients Switched to Pasireotide LAR (N*=46) and (B) Patients Switched to Octreotide LAR (N*=26)



*N is the number of patients with values at both extension baseline and 12-month after crossover.

Table 2. Adverse Events Regardless of Study-Drug Relationship Reported in ≥10% of Patients in Either Treatment Group After Crossover

Preferred term	Crossed over to Pasireotide LAR N=81		Crossed over to Octreotide LAR N=38	
	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)
Total	77 (95.1)	23 (28.4)	34 (89.5)	8 (21.1)
Hyperglycemia	25 (30.9)	4 (4.9)	5 (13.2)	0
Diarrhea	20 (24.7)	0	7 (18.4)	1 (2.6)
Cholelithiasis	19 (23.5)	2 (2.5)	6 (15.8)	1 (2.6)
Headache	17 (21.0)	0	5 (13.2)	0
Diabetes mellitus	15 (18.5)	2 (2.5)	3 (7.9)	0
Nasopharyngitis	13 (16.0)	0	7 (18.4)	0
Arthralgia	10 (12.3)	0	2 (5.3)	0
Blood CPK increased	7 (8.6)	0	6 (15.8)	0
Dizziness	7 (8.6)	0	5 (13.2)	0
Blood triglycerides increased	2 (2.5)	0	4 (10.5)	1 (2.6)

CPK, creatine phosphokinase

- Among patients who crossed over to octreotide LAR, mean FPG and HbA_{1c} levels decreased within 3 months after crossover and stabilized at a lower level thereafter; mean FPG and HbA_{1c} levels were 104 mg/dL and 6.12% at month 3, and 103 mg/dL and 5.98% at month 12 after crossover. By contrast, among patients who crossed over to pasireotide LAR, mean FPG levels peaked 1 month (141.4 mg/dL) and HbA_{1c} levels peaked 3 months after switching from octreotide LAR and stabilized at a slightly lower level thereafter; mean FPG and HbA_{1c} levels were 130 mg/dL and 7.03% at month 3, and 125 mg/dL and 6.68% at month 12 after crossover.
- Eight patients who crossed over to pasireotide LAR and six patients who crossed over to octreotide LAR experienced serious AEs (**Table 3**).

Table 3. Serious Adverse Events (SAEs), Adverse Events (AEs), or Deaths Leading to Discontinuation of Study Drug by Treatment

	Crossed over to Pasireotide LAR N=81	Crossed over to Octreotide LAR N=38
Patients with SAE(s)	**8 (9.9)**	**6 (15.8)**
Study drug related SAE(s)	3 (3.7)	1 (2.6)
Discontinued due to SAE(s)	2 (2.5)	0
Patients with AE(s)	**77 (95.1)**	**34 (89.5)**
Study drug related AE(s)	62 (76.5)	25 (65.8)
Discontinued due to AE(s)	13 (16.0)	0
Grade 3 or 4 AE(s)	23 (28.4)	8 (21.1)
Deaths	**1 (1.2)**	**0**

CONCLUSIONS

- **Pasireotide LAR holds promise as a treatment option for patients with acromegaly inadequately controlled with octreotide LAR.**
- **The safety profile seen with pasireotide LAR after crossover was consistent with the safety profile in the core phase. As observed during the core phase, the safety profile of pasireotide LAR was comparable to octreotide LAR with a higher incidence and degree of hyperglycemia compared with octreotide LAR.**
- **Hyperglycemia associated with pasireotide LAR appeared to be reversible upon discontinuation of pasireotide LAR.**
- **Further randomized studies are warranted to confirm the efficacy of pasireotide LAR in patients inadequately controlled with currently available SSAs. An additional Phase III study assessing this patient population is ongoing (PAOLA; SOM230C2402).**

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