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Pasireotide LAR Maintains Biochemical Control in Patients With Acromegaly: Results From the Extension of Randomised, Phase III, PAOLA Study

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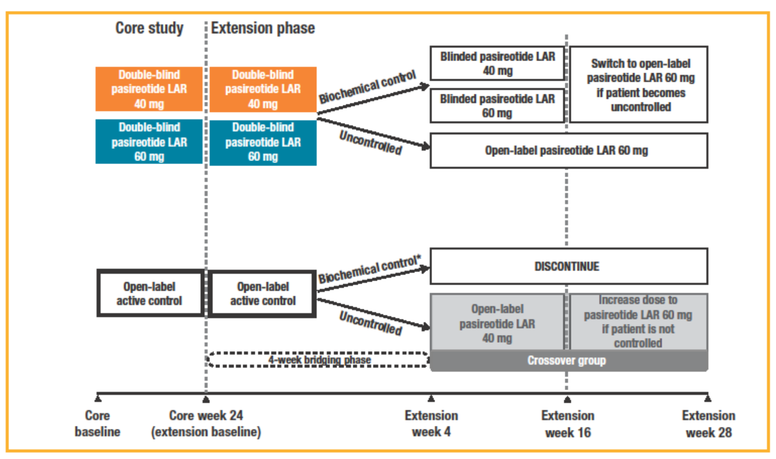
INTRODUCTION

- Somatostatin analogues (SSA) are the current standard of medical management in acromegaly; the first-generation SSA, octreotide long-acting repeatable and lanreotide Autogel preferentially bind to somatostatin receptor subtype 2 (sst_2).[1,2]
- Pasireotide is a next-generation SSA which binds to 4 of the 5 somatostatin receptor subtypes and has greater binding affinity for sst_5 than either octreotide or lanreotide.[2] Pasireotide long-acting release (LAR) was recently approved for the treatment of acromegaly by both the FDA and EMA.[3,4]
- Patients aged ≥ 18 years who had inadequately controlled acromegaly (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 limit of normal) despite receiving octreotide long-acting repeatable 30 mg or lanreotide Autogel 120 mg monotherapy for ≥ 6 months were enrolled in a prospective, multicentre, randomised, phase III, parallel-group, PAOLA study
  - Patients in active control group continued treatment with octreotide long-acting repeatable 30 mg/lanreotide Autogel 120 mg
  - Biochemical control was defined as GH levels < 2.5 µg/L and normalised IGF-1.[5]
- At the end of the core phase (week 24), a significantly greater proportion of patients achieved biochemical control with pasireotide LAR 40 mg and 60 mg than with active control (15.4% [P =.0006] and 20.0% [P < .0001] vs 0%, respectively).[5]
- Patients who completed the core study (except active control patients who were biochemically controlled at the end of the core phase) were eligible for the extension phase.
- Here we report a preliminary analysis from week 28 of the extension phase of this study, which assesses the efficacy and safety of pasireotide LAR over an extended period of time.

METHODS

Figure 1. Study Design



*None of the patients in the active control group were biochemically controlled at the end of the core phase, so none of them discontinued at this time point. LAR, long-acting release.

Endpoints and Analysis – Data Cut-off at June 3, 2013

- Patients who had reached 28 weeks of treatment in the extension phase or discontinued before week 28 of the extension were included in this analysis.
- Key efficacy endpoints included:
  - Proportion of patients at extension week 28 at the time of data cut-off with (i) biochemical control, (ii) GH level < 2.5 µg/L and (iii) normal IGF-1 levels
  - Overall changes in GH and IGF-1 levels from core baseline
  - Overall change in acromegaly symptom scores (headache, fatigue, perspiration, paraesthesia and osteoarthralgia) from core baseline.
- Safety and tolerability was assessed and analysed for all the treatment groups.

RESULTS

Patients

Table 1. Patient Disposition and Analysis Groups

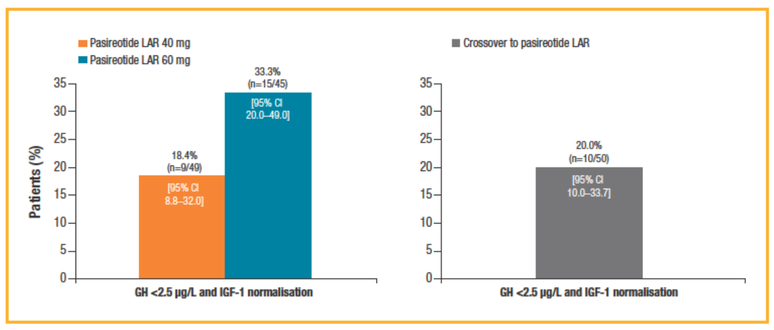
Patient population	PAS LAR 40 mg	PAS LAR 60 mg	Crossover	Total
Enrolled in core phase	65	65	68	198
Completed core phase	59	57	65	181
Entered ext phase	57	54	62	173
Not reached ext wk 28 at the time of the data cut-off (excluded from current analysis)	8	9	12	29
Included in current analysis	49	45	50	144
On treatment at ext wk 28	40	36	47	123
Discontinued before ext wk 28	9	9	3	21

Note: Treatment groups are based on randomised dose at core baseline.
Ext, extension; LAR, long-acting release; PAS, pasireotide; wk, week.

Biochemical Control

- At extension week 28, 18.4%, 33.3% and 20.0% of patients in the pasireotide LAR 40 mg, 60 mg and crossover groups, respectively, had biochemical control **(Figure 2 and Table 2).**

Figure 2. Proportion of Patients With Biochemical Control at Extension Week 28



Note: Data for pasireotide LAR 40 mg/60 mg cohorts are based on 52 weeks of treatment in total; data for the crossover cohort are based on 28 weeks of treatment. Calculations are based on patients who entered the extension phase and either had available extension week 28 data at the time of data cut-off, or discontinued before week 28 of the extension (considered uncontrolled). CI, confidence interval; GH, growth hormone; IGF-1, insulin-like growth factor 1; LAR, long-acting release.

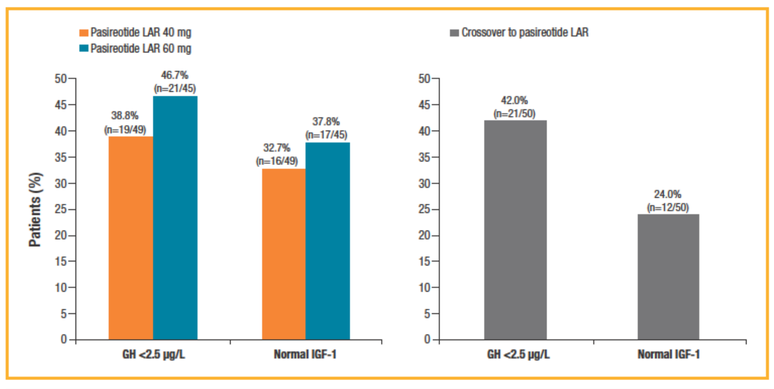
Table 2. Biochemical Control at Extension Week 28

Patient population	PAS LAR 40 mg	PAS LAR 60 mg
Patients on treatment at ext wk 28	40	36
Biochemically controlled at ext baseline	10	8
Maintained biochemical control at ext wk 28	4	5
Uncontrolled at ext wk 28	4*	3†
Missing IGF-1 or GH values	2	-
Uncontrolled at ext baseline	30	28
Achieved biochemical control at ext wk 28	5	10

Note: Treatment groups are based on randomised dose at core baseline.
*One patient had normal IGF-1 only and remaining 3 had GH levels < 2.5 µg/L only; †Two patients had GH levels < 2.5 µg/L only. Ext, extension; GH, growth hormone; IGF-1, insulin-like growth factor 1; LAR, long-acting release; PAS, pasireotide; wk, week.

GH and IGF-1 Levels

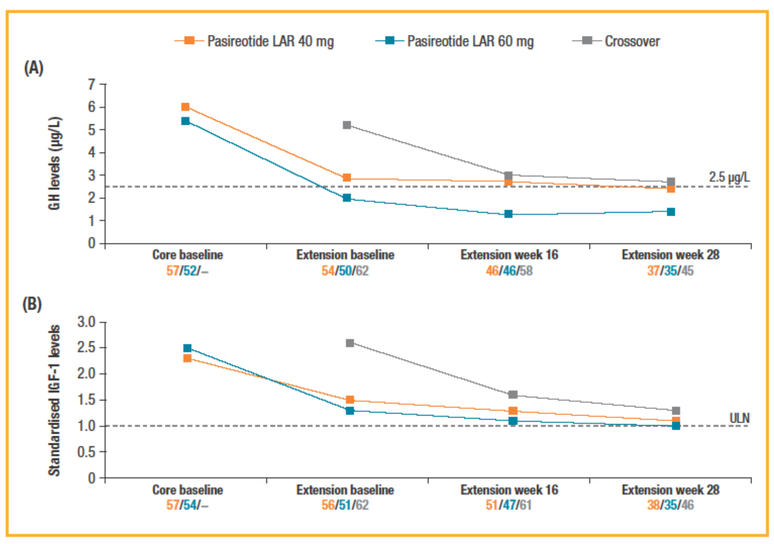
Figure 3. Proportion of Patients with GH < 2.5 µg/L and Normal IGF-1 at Extension Week 28



Note: Data for pasireotide LAR 40/60 mg cohorts are based on 52 weeks of treatment in total; data for the crossover cohort are based on 28 weeks of treatment. Calculations are based on patients who entered the extension phase and either had available extension week 28 data at the time of data cut-off or discontinued before week 28 of the extension. GH, growth hormone; IGF-1, insulin-like growth factor 1; LAR, long-acting release.

- Median GH and IGF-1 levels decreased during 24-week core study; levels were then maintained to extension week 28 (**Figure 4**).
- In the crossover group, median GH and IGF-1 levels decreased following the switch to pasireotide treatment (**Figure 4**).

Figure 4. Median (A) GH and (B) IGF-1 Levels During Pasireotide Treatment



Note: Overall changes in GH and IGF-1 are shown for patients who entered the extension phase and had available data at each time point. The numbers below each figure represent the patients included at each time point. GH, growth hormone; IGF-1, insulin-like growth factor 1; LAR, long-acting release; ULN, upper limit of normal.

Acromegaly Symptom Scores

- In the pasireotide LAR 40 mg and 60 mg groups, improvements in acromegaly symptom scores that were observed during the core study were maintained in the extension phase.
- In the crossover group, the symptom scores improved from extension baseline.

Safety and Tolerability of Pasireotide LAR

Table 3. Overall AE Profile of Pasireotide LAR in the Extension Phase

	PAS LAR 40 mg (n = 63)	PAS LAR 60 mg (n = 62)	Crossover (n = 62)
Median (range) safety follow-up period, wk	68.1 (11.9-125.0)	61.4 (4.0-126.9)	43.4 (15.4-98.6)
Hyperglycaemia-related AEs, n (%)	47 (74.6)	43 (69.4)	28 (45.2)
Serious AEs, n (%)	11 (17.5)	8 (12.9)	10 (16.1)
AEs leading to discontinuation, n (%)	7 (11.1)	8 (12.9)	4 (6.5)
Death	1*	-	-

*Considered not related to study drug. AE, adverse event; LAR, long-acting release; PAS, pasireotide; wk, week.

Table 4. Most Common AEs (> 15% in Any Treatment Group) Reported During the Core and Extension, Regardless of Study Drug Relationship

n (%)	PAS LAR 40 mg (n = 63)	PAS LAR 60 mg (n = 62)	Crossover (n = 62)
Hyperglycaemia	24 (38.1)	22 (35.5)	12 (19.4)
Diabetes mellitus	14 (22.2)	16 (25.8)	10 (16.1)
Diarrhoea	14 (22.2)	17 (27.4)	8 (12.9)
Cholelithiasis	14 (22.2)	15 (24.2)	8 (12.9)
Headache	13 (20.6)	5 (8.1)	3 (4.8)

LAR, long-acting release; PAS, pasireotide.

- The most frequently reported AEs leading to discontinuation were hyperglycaemia related.
- Notably, a post hoc analysis of the data from the core phase of PAOLA study (see poster **GP-19-09**) demonstrated that pasireotide-induced hyperglycaemia can be managed with proactive monitoring and early intervention.

CONCLUSIONS

- **Preliminary data from the 28-week extension of the PAOLA study indicate that pasireotide LAR maintained biochemical control as well as decreased in GH and IGF-1 in patients with acromegaly.**
  - **Some additional patients randomised to pasireotide LAR 40 mg/60 mg in the core study achieved biochemical control by week 28 of the extension after being uncontrolled at the extension baseline.**
- **Twenty percent of the patients inadequately controlled on octreotide long-acting repeatable/lanreotide Autogel during the core study achieved biochemical control after crossing over to pasireotide LAR in the extension phase.**
- **The safety profile of pasireotide LAR in the extension phase was consistent with that observed in the core study; no new treatment-emergent safety signals were identified during long-term treatment.**
- **These data suggest that pasireotide LAR is a viable, long-term treatment option for patients with acromegaly.**

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