GP153

Once-Monthly Injection of Pasireotide LAR Reduces Urinary Free Cortisol (UFC) Levels in Patients with Cushing's Disease: Results From a Randomised, Multicentre, Phase III Trial

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INTRODUCTION

- Cushing's disease, a rare condition of hypercortisolism secondary to an adrenocorticotropic hormone (ACTH)-secreting pituitary adenoma, is associated with increased morbidity and mortality[1]
- Pasireotide is a pituitary-directed, multireceptor-targeted somatostatin analogue, which inhibits ACTH secretion by directly acting on pituitary corticotroph adenomas[2,3]
- Twice-daily subcutaneous formulation of pasireotide (Signifor®) is approved in many countries for treating adult patients with Cushing's disease for whom surgery has failed or is not an option[4]
  - In a Phase III study, twice-daily pasireotide controlled mean urinary free cortisol (mUFC) levels in ~20% of patients at month 6[2]
- Here, we present results from a Phase III study designed to evaluate a more convenient, once-monthly long-acting release (LAR) formulation of pasireotide in patients with Cushing's disease

METHODS

Patients

- Adult patients with confirmed persistent, recurrent or *de novo* (non-surgical candidates) Cushing's disease were enrolled. Cushing's disease was defined as mUFC level 1.5–5.0 × ULN (calculated from three 24-hour urine samples collected within 2 weeks), normal/above-normal morning plasma ACTH level, and a confirmed pituitary source of ACTH excess. Patients were required to have completed appropriate pharmacological washout from previous treatments
- Key exclusion criteria included previous pasireotide therapy, pituitary irradiation within the last 10 years, poorly controlled diabetes mellitus on antidiabetic medication (glycated haemoglobin [HbA_{1c}] level >8%)

Study Design

- Randomised-dose, double-blind, multicentre, Phase III study (**Figure 1**)
  - Primary efficacy endpoint was evaluated at month 7
- Patients were stratified by screening mUFC (stratum 1: mUFC 1.5–<2.0 × ULN; stratum 2: mUFC 2–5 × ULN)

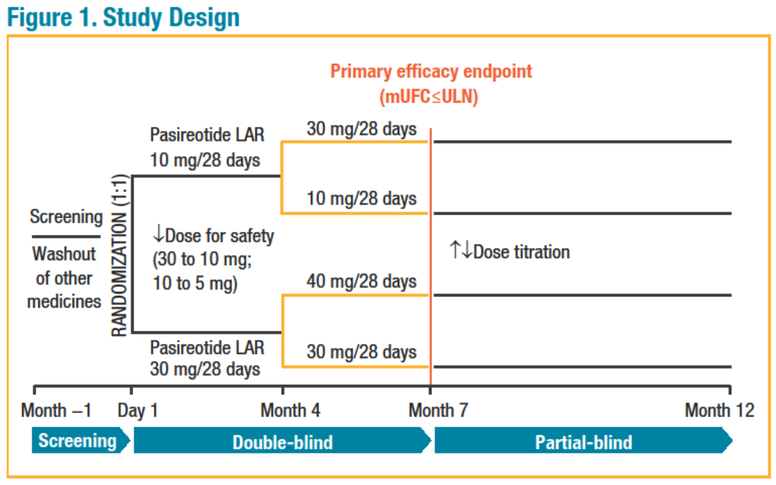
Primary efficacy endpoint:

- Proportion of patients in each pasireotide LAR arm with mUFC ≤ ULN (166.5 nmol/24h [60.3 µg/24h]) at month 7, regardless of dose titration at month 4 (considered as responders)

Secondary endpoints:

- Key secondary endpoint: Proportion of patients in each pasireotide LAR arm with mUFC ≤ ULN at month 7 with no dose up-titration at month 4
- Other secondary endpoints include: Change in mUFC levels over time, change in clinical signs of Cushing's disease (including systolic/diastolic blood pressure [SBP/DBP] and weight) and quality of life over time, and safety

Figure 1. Study Design



Pasireotide LAR dose was up-titrated at month 4 if mUFC >1.5 × ULN, or at months 7, 9, and 12 if mUFC >1.0 × ULN. One dose reduction was allowed during the first 7 months; further dose reduction (up to 5 mg) was allowed after month 7.

Statistical Analysis

- For primary/key secondary efficacy endpoints, proportions of responders and 95% confidence intervals (95% CI) were calculated for each randomised dose group
  - Missing mUFC values at month 7 were imputed using last available values between months 4 and 7; patients who discontinued prior to month 4 were classed as non-responders
  - If the lower bound of the 95% CI for the response rate for a dose group was >15%, that group was considered to have met the primary/key secondary endpoint
  - Dose groups were not compared
- Safety was assessed up to 9 July 2015 (data cut-off), when all patients had either reached month 7 or had withdrawn from the study

RESULTS

Patient Demographics and Disposition

- 150 patients were randomised to pasireotide LAR 10 mg (n = 74) or 30 mg (n = 76) (**Table 1**)
  - Approximately two-thirds of patients in the 10 mg (66.2%) and 30 mg (67.1%) arms had screening mUFC 2.0–5.0 × ULN (stratum 2) (**Table 1**)
- Baseline characteristics were similar between dose groups (**Table 1**)
- Median duration of exposure to pasireotide LAR was 336.5 days (range, 28–1269) and 336.0 days (range, 28–1170) in the 10 mg and 30 mg groups, respectively

Table 1. Summary of Baseline Demographics and Disposition

	Pasireotide LAR		
	10 mg (N=74)	30 mg (N=76)	Overall (N=150)
Mean age, years	38.3	38.6	38.5
Female, n (%)	58 (78.4)	60 (78.9)	118 (78.7)
Mean time since diagnosis, months	42.1	43.7	42.9
Baseline mUFC, × ULN			
Mean	2.8	2.9	2.8
Median	2.5	2.2	2.4
mUFC stratum, n (%)			
≥1.5–<2.0 × ULN	25 (33.8)	25 (32.9)	50 (33.3)
≥2.0–≤5.0 × ULN	49 (66.2)	51 (67.1)	100 (66.7)
Cushing's disease status, n (%)			
Persistent/recurrent	59 (79.7)	64 (84.2)	123 (82.0)
De novo	15 (20.3)	12 (15.8)	27 (18.0)
Previous treatment, n (%)			
Surgery	59 (79.7)	64 (84.2)	123 (82.0)
Medication	32 (43.2)	30 (39.5)	62 (41.3)
Diabetic status, n (%)			
Diabetic	27 (36.5)	32 (42.1)	59 (39.3)
Pre-diabetic	12 (16.2)	13 (17.1)	25 (16.7)
Normal glucose tolerance	35 (47.3)	31 (40.8)	66 (44.0)
Patient disposition, n (%)			
Up-titrated at month 4	31 (41.9)	28 (36.8)	59 (39.3)
Completed month 7	54 (73.0)	62 (81.6)	116 (77.3)

Diabetic, prior history of diabetes mellitus or receiving antidiabetic medication or HbA_{1c} ≥6.5% or fasting plasma glucose (FPG) ≥126 mg/dL; pre-diabetic, not qualifying as diabetic and with FPG ≥100–<126 mg/dL or HbA_{1c} ≥5.7–<6.5%; normal glucose tolerance, not qualifying as diabetic or pre-diabetic and with FPG <100 mg/dL and/or HbA_{1c} <5.7%

Efficacy

- Both pasireotide LAR dose groups met the primary efficacy endpoint; percentage of responders at month 7:
  - 10 mg group: 41.9% (95% CI: 30.5, 53.9)
  - 30 mg group: 40.8% (95% CI: 29.7, 52.7)
- The key secondary efficacy endpoint was met in both pasireotide LAR dose groups; percentage of responders at month 7 without dose titration:
  - 10 mg group: 28.4% (95% CI: 18.5, 40.1)
  - 30 mg group: 31.6% (95% CI: 21.4, 43.3)
- Response rates were higher in patients in stratum 1 (screening mUFC: 1.5–<2.0 × ULN) vs stratum 2 (screening mUFC: 2.0–5.0 × ULN) (**Figure 2**)
- mUFC levels decreased from baseline to month 7 in most patients (**Figure 3**)

Figure 2. Proportion of Responders at Month 7, Regardless of Prior Up-titration, According to mUFC Stratum

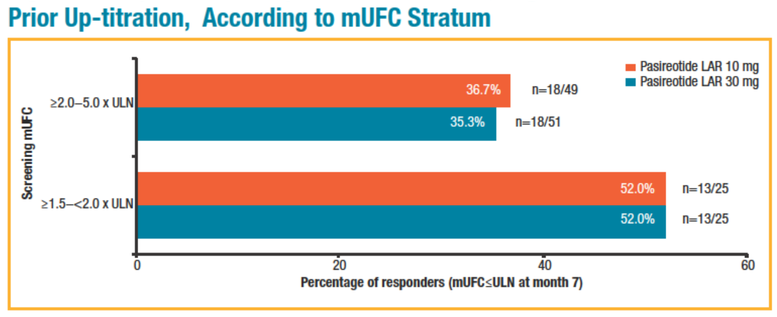
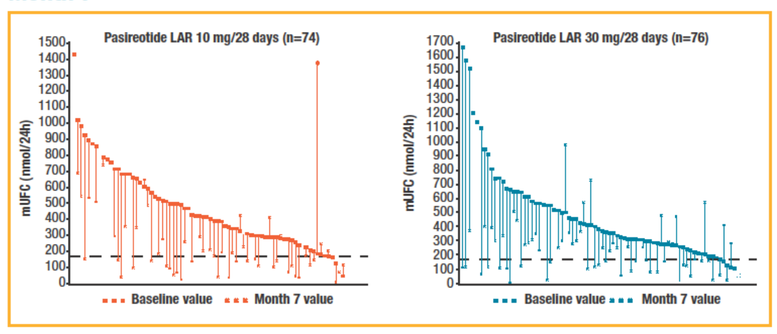


Figure 3. Absolute Change in Individual mUFC Levels from Baseline to Month 7



- Median mUFC levels decreased within the first month of treatment and remained below baseline values through month 7
  - Median mUFC levels decreased from 409.8 nmol/24h to 166.4 nmol/24h in the 10 mg group, and from 371.6 nmol/24h to 234.4 nmol/24h in the 30 mg group

Changes in Clinical Signs and Quality of Life

- Improvements were seen from baseline to month 7 in mean SBP, weight and Cushing quality of life (CushingQOL) score in both dose groups, and in DBP for the 10 mg group (**Table 2**)

Table 2. Mean Change in Clinical Signs and CushingQOL Score From Baseline to Month 7

Parameter	Pasireotide LAR 10 mg			Pasireotide LAR 30 mg		
	Baseline, Mean (SD)	Month 7, Mean (SD)	% change, Mean (95%CI)	Baseline, Mean (SD)	Month 7, Mean (SD)	% change, Mean (95%CI)
SBP, mmHg	131.0 (16.9)	123.3 (13.1)	-4.3 (-7.4, -1.3)	133.3 (15.8)	128.0 (15.1)	-3.0 (-5.5, -0.5)
DBP, mmHg	83.9 (12.1)	79.6 (11.7)	-4.7 (-8.5, -1.0)	87.4 (10.6)	83.5 (10.1)	-2.6 (-5.9, 0.8)
Weight, kg	74.5 (18.6)	72.4 (19.6)	-2.6 (-4.0, -1.2)	77.9 (19.3)	72.7 (20.3)	-6.1 (-7.8, -4.4)
CushingQOL score*	42.5 (17.6)	50.4 (17.3)	27.3 (10.5, 44.1)	38.2 (17.2)	47.5 (16.3)	34.2 (20.2, 48.2)

*Higher CushingQOL scores are associated with better health-related quality of life[5]

Safety

- Main reasons for patient discontinuation in the 10 mg and 30 mg arms were: consent withdrawal (13.5% [n = 10] and 7.9% [n = 6]), unsatisfactory therapeutic effect (12.2% [n = 9] and 25.0% [n = 19]), and AEs (9.5% [n = 7] and 10.5% [n = 8])
- The safety profile of pasireotide LAR was similar to that of twice-daily pasireotide; hyperglycaemia was the most frequently reported AE in both dose groups (**Table 3**)
- A total of 50 (67.6%) and 61 (80.3%) of patients experienced a hyperglycaemia-related AE in the 10 mg and 30 mg dose groups, respectively
  - Five (3.3%) patients discontinued because of a hyperglycaemia-related AE (10 mg, n=2; 30 mg, n=3)
- Two deaths occurred in the 30 mg arm (cardiorespiratory failure, n=1; pulmonary artery thrombosis, n=1); neither was considered to be drug related

Table 3. Most Frequent AEs (≥15% of Patients Overall), Regardless of Study Drug Relationship

	Pasireotide LAR 10 mg (N=74)		Pasireotide LAR 30 mg (N=76)		Overall (N=150)	
	All Grades n (%)	Grade 3/4 n (%)	All Grades n (%)	Grade 3/4 n (%)	All Grades n (%)	Grade 3/4 n (%)
Hyperglycemia	35 (47.3)	6 (8.1)	35 (46.1)	2 (2.6)	70 (46.7)	8 (5.3)
Diarrhea	25 (33.8)	0	33 (43.4)	0	58 (38.7)	0
Cholelithiasis	13 (17.6)	2 (2.7)	32 (42.1)	2 (2.6)	45 (30.0)	4 (2.7)
Nausea	15 (20.3)	1 (1.4)	15 (19.7)	0	30 (20.0)	1 (0.7)
Diabetes mellitus	12 (16.2)	7 (9.5)	17 (22.4)	12 (15.8)	29 (19.3)	19 (12.7)
Nasopharyngitis	16 (21.6)	0	12 (15.8)	0	28 (18.7)	0
Headache	17 (23.0)	0	9 (11.8)	1 (1.3)	26 (17.3)	1 (0.7)
Fatigue	11 (14.9)	0	14 (18.4)	0	25 (16.7)	0

- Median FPG and HbA_{1c} levels increased soon after initiation of pasireotide LAR. In the 10 mg and 30 mg groups, median FPG increased from 89.0 mg/dL and 88.0 mg/dL at baseline to 105.5 mg/dL and 119.0 mg/dL at month 7. Median HbA_{1c} increased from 5.5% and 5.6% at baseline to 6.3% and 6.5% at month 7

CONCLUSIONS

- **Once-monthly pasireotide LAR normalized mUFC in ~40% of patients with Cushing's disease, with higher response rates seen in patients with less severe mUFC elevations**
- **Pasireotide LAR had a similar safety profile to that of twice-daily pasireotide;[2] 10% of patients discontinued treatment because of AEs**
  - **The most frequently reported AEs were hyperglycaemia-related**
- **These results show that pasireotide LAR is an effective treatment for patients with Cushing's disease while providing a convenient monthly administration schedule**

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