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Ongoing, Open-Label, Multicentre, Expanded-Access Study Demonstrating the Safety and Efficacy of Pasireotide sc in Patients with Cushing's Disease

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INTRODUCTION

- Pasireotide (Signifor®) is a multireceptor-targeted somatostatin analogue that was initially approved in Europe and the US in 2012 for the treatment of adult patients with Cushing's disease for whom surgery is not an option or has failed.[1,2]
- At the time of approval, pasireotide was the only medical therapy approved for the treatment of Cushing's disease.
- Until regulatory approval was obtained in a specific country, there was no way for patients to receive pasireotide outside the clinical trial setting.

AIMS

- This uncontrolled 'expanded-access' study was designed to provide patients with Cushing's disease the opportunity to receive pasireotide before it was approved in their country, whilst simultaneously collecting further safety and efficacy data. Here we report an interim analysis of this ongoing study.

METHODS

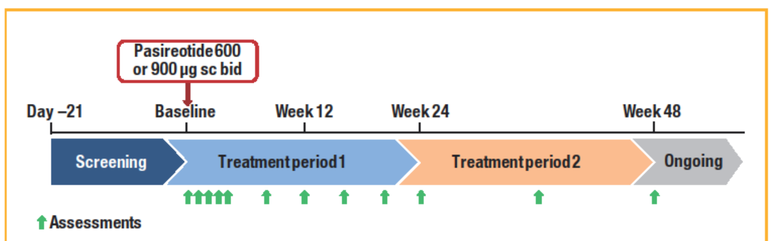
Patient Population

- Patients aged ≥18 years with confirmed persistent/recurrent or *de novo* (if not surgical candidates) Cushing's disease, defined by mean urinary free cortisol (UFC) level above the upper limit of normal (ULN).

Study Design and Dosing

- Open-label, uncontrolled, single-arm, multicentre, international expanded-access study **(Figure 1)**.
- In EU countries, subcutaneously administered (sc) pasireotide was initiated at 600 µg bid in all patients. Pasireotide was initiated at 900 µg bid in countries outside the EU, except for patients with impaired glucose tolerance, whose starting dose was 600 µg bid.
- Pasireotide dose could be decreased in 300-µg increments to a minimum of 300 µg for tolerability issues or sustained UFC normalization (ie UFC ≤ULN on at least two consecutive visits), or increased to a maximum of 900 µg if the patient's UFC was not controlled (ie UFC >ULN).
- Patients will remain in the study until pasireotide becomes commercially available in their country or 31 December 2015, whichever occurs first.

Figure 1. Study Design



Assessments and Endpoints

- During the first 24 weeks of treatment, patients were assessed on a weekly basis up to week 4, then on a 4-weekly basis up to week 24. In the second treatment period, patients were assessed at 12-week intervals until the end of the study.
- Primary endpoint:
  - Proportion of patients experiencing a drug-related grade 3/4 or serious adverse event (AE) during pasireotide treatment. AEs were assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0.
- Secondary endpoints, assessed at weeks 12, 24 and 48, included:
  - Proportion of patients with mean UFC ≤ULN
  - Proportion of patients achieving a reduction in mean UFC of ≥50%
  - Change from baseline in clinical signs and symptoms
  - Change from baseline in patients' quality of life (QoL; measured using the CushingQoL questionnaire[3])
  - Incidence of AEs (assessed throughout the study).
- This interim analysis is based on a data cut-off of 31 July 2014.

RESULTS

- 97 patients had enrolled in the study at the time of data cut-off **(Table 1):**
  - 22 (22.7%) were still in the study
  - 29 (29.9%) had completed the study
  - 46 (47.4%) had discontinued treatment **(Table 2)**.
- Median exposure to pasireotide was 23.6 weeks (range 1–131).

Table 1. Patient Demographics and Characteristics

	Patients (n=97)
Mean age ± SD, years	42.2 ± 12.8
Male:female, n	20:77
Race, n (%)	
Caucasian	74 (76.3)
Black	5 (5.2)
Asian	15 (15.5)
Other	3 (3.1)
Median time since diagnosis (range), months	38.7 (0.7–309.0)
Cushing's disease status, n (%)	
De novo	13 (13.4)
Persistent/recurrent	84 (86.6)
Prior pituitary surgery, n (%)	77 (79.4)
Median time since prior surgery (range), months	31.3 (1.9–306.1)
Prior radiation therapy, n (%)	24 (24.7)
Median time since prior radiation therapy (range), months	30.6 (3.1–169.9)

SD, standard deviation

Table 2. Reasons for Discontinuation

n (%)	Patients (n=97)
AEs*	18 (18.6)
Unsatisfactory therapeutic effect	13 (13.4)
Consent withdrawal	13 (13.4)
Other†	2 (2.1)

*The most common were abdominal pain, diabetes mellitus, hyperglycaemia, decreased blood cortisol and abnormal laboratory values (n=2, 2.1% for each). All other AEs leading to discontinuation occurred in one patient only

†Includes one patient who died

Safety of Pasireotide

- Most AEs were mild or moderate (CTCAE grade 1/2); the most common are shown in **Table 3**.
- 36 patients (37.1%) experienced at least one grade 3/4 or serious AE that was suspected to be drug related
  - The most common were diabetes mellitus (n=9, 9.3%), hyperglycaemia (n=6, 6.2%), nausea (n=5, 5.2%), diarrhoea (n=4, 4.1%), decreased blood cortisol (n=3, 3.1%), type 2 diabetes mellitus (n=2, 2.1%) and adrenal insufficiency (n=2, 2.1%).

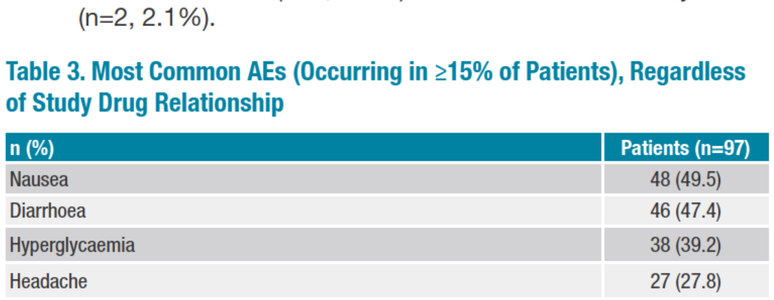
Table 3. Most Common AEs (Occurring in ≥15% of Patients), Regardless of Study Drug Relationship

n (%)	Patients (n=97)
Nausea	48 (49.5)
Diarrhoea	46 (47.4)
Hyperglycaemia	38 (39.2)
Headache	27 (27.8)
Cholelithiasis	25 (25.8)
Fatigue	23 (23.7)
Diabetes mellitus	22 (22.7)
Abdominal pain	18 (18.6)

Effect of Pasireotide on UFC Levels

- At weeks 12, 24 and 48 **(Figure 2)**:
  - 49.3%, 49.0% and 40.7% of patients had UFC ≤ULN, respectively
  - 56.3%, 53.1% and 40.7% had a decrease in UFC of ≥50% from baseline, respectively.

Figure 2. Proportion of Patients with (A) Normalized UFC or (B) ≥50% Decrease from Baseline during Pasireotide Treatment



Note: Data in parentheses are 95% confidence intervals (two-sided)

Effect of Pasireotide on Signs/Symptoms and QoL

- Improvements were observed in various signs and symptoms of Cushing's disease, including facial rubor, supraclavicular/dorsal fat pads, striae, bruising and muscle strength **(Figure 3)**.
- This was accompanied by improvements in patients' QoL **(Table 4)**.

Figure 3. Changes in Signs and Symptoms during Pasireotide Treatment

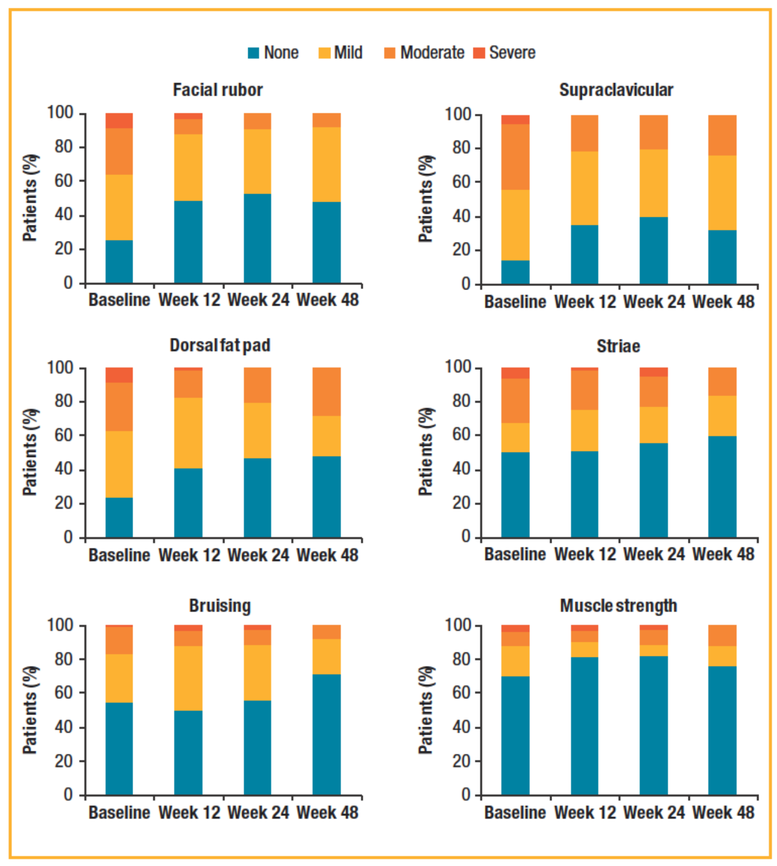


Table 4. CushingQoL Score during Pasireotide Treatment

n (%)	Baseline (n=96*)	Week 12 (n=69)	Week 24 (n=43)	Week 48 (n=25)
Mean ± SD	40.4 ± 19.9	51.4 ± 19.1	51.4 ± 18.2	53.8 ± 15.1
Median (range)	39.6 (2–90)	52.1 (10–96)	52.1 (17–90)	56.3 (8–77)

*Note: One patient did not have CushingQoL assessed at baseline

CONCLUSIONS

- **This expanded-access study shows that pasireotide has a generally favourable safety profile in patients with Cushing's disease.**
- **In line with data from a large Phase III study, it provides further evidence that pasireotide effectively decreases UFC levels,[4] improves clinical signs/symptoms, and improves QoL in patients with Cushing's disease.[5]**
- **Pasireotide is therefore an effective treatment option for patients with Cushing's disease who had unsuccessful pituitary surgery or are not candidates for surgery.**

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