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# The Benefits of Pasireotide in Patients with Cushing's Disease Are Not Restricted to Patients with Normalization of UFC: Results from a Large 12-Month Study

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## INTRODUCTION

- Cushing's disease is a debilitating endocrine disorder that is associated with reduced quality of life and increased comorbidities.[1] Patients with uncontrolled Cushing's disease have up to a 5.5-fold increased risk of mortality.[2,3]
- The aims of treatment for Cushing's disease include reversal of clinical features, normalization of biochemical changes with minimal morbidity, and long-term control without recurrence.[4]
- Transsphenoidal adenomectomy is first-line therapy, but although initially successful in 65–90% of cases performed by an expert surgeon, relapse rates are high and in a small proportion of patients, pituitary surgery is not possible.[4]
- Second-line treatments such as steroidogenesis-inhibiting medical therapies can be effective, but they do not target the underlying pituitary tumor or restore normal hypothalamic–pituitary–adrenal axis activity.[4]
- Pasireotide, a multireceptor-targeted somatostatin analogue, was recently approved for the treatment of Cushing's disease based on the positive results from a large double-blind study.[5]
- The current analysis evaluates the effects of pasireotide on the signs and symptoms of Cushing's disease according to the degree of urinary free cortisol (UFC) control.

## METHODS

### Patients

- Patients aged ≥18 years with confirmed persistent/recurrent or *de novo* (if not surgical candidates) Cushing's disease, defined by a mean 24-hour UFC level ≥1.5x the upper limit of normal (ULN).

### Study Design

- This was a randomized, double-blind, multicenter, Phase III study. Patients (n=162) received subcutaneous (sc) pasireotide either 600 or 900 µg bid for 12 months; dose titration to a maximum of 1200 µg bid was allowed after month 3.
- Primary endpoint: proportion of patients with UFC ≤ULN by randomized dose group at month 6 without prior dose increase.
- Secondary endpoints included changes in clinical signs and symptoms, changes in health-related quality of life (HRQoL), and safety.

### Assessment of Signs and Symptoms

- Blood pressure (BP), weight, body mass index (BMI), triglycerides and low-density lipoprotein (LDL)-cholesterol were assessed monthly. Information regarding dose adjustments of antihypertensive or lipid-lowering medication was not collected during the study.
- Waist circumference, HRQoL measured using the CushingQoL questionnaire, and depression status assessed using the Beck Depression Inventory II (BDI-II) were measured at months 3, 6 and 12.
- Signs of hypercortisolism (facial rubor, supraclavicular and dorsal fat pads) were assessed by photograph and scored by a blinded reviewer at baseline and months 3, 6 and 12.
- Bone mineral density and body composition were measured at baseline and months 6 and 12.
- Safety was assessed throughout the study. Hematology, blood biochemistry, urinalysis, electrocardiograms, vital signs and physical condition were assessed at every visit.

### Analysis

- For the analyses of signs and symptoms, only patients still enrolled in the study and who had evaluable measurements at each time point were included.
- Changes from baseline in signs and symptoms are reported at months 6 and 12, stratified by UFC response at month 6.
- The month-6 UFC response subgroups were defined as:
  - Controlled: UFC ≤ULN
  - Partially controlled: UFC >ULN but with ≥50% reduction from baseline
  - Uncontrolled: UFC >ULN and without ≥50% reduction from baseline

## RESULTS

### Effect of Pasireotide Treatment on UFC Levels

- At month 6, 15% (95% CI: 7, 22) of patients in the 600 and 26% (95% CI: 17, 36) of patients in the 900 µg bid groups achieved UFC ≤ULN without prior dose increase.[5]
- When stratified by UFC response at month 6, an overall decrease in UFC from baseline to months 6 and 12 was observed in patients who were controlled and partially controlled. A small decrease was observed in patients with uncontrolled UFC (**Figure 1**).

### Effect of Pasireotide Treatment on Signs and Symptoms

- A decrease in mean UFC was accompanied by improvements in the clinical signs and symptoms of Cushing's disease over the 12-month treatment period.
- When stratified by UFC response at month 6, reductions in systolic BP (SBP), diastolic BP (DBP), BMI and weight were observed at months 6 and 12 regardless of UFC normalization but were greatest in patients with UFC control at month 6 (**Table 1**).
- Reductions in total cholesterol and LDL-cholesterol were seen at months 6 and 12 in patients from all UFC response groups but were greatest in those with controlled UFC at month 6 (**Table 1**).
- Beck depression score (mean [95% CI]) improved from baseline to months 6 (–5.0 [–6.7, –3.3]) and 12 (–4.9 [–7.0, –2.7]), which was significant in all UFC response subgroups (**Table 1**).

**Table 1. Changes from Baseline to Months 6 and 12 in the Signs and Symptoms of Hypercortisolism by UFC Response Status at Month 6**

| | Change from baseline to month 6, mean (95% CI), n | | | Change from baseline to month 12, mean (95% CI), n | | |
|---|---|---|---|---|---|---|
| | Controlled | Partially controlled | Uncontrolled | Controlled | Partially controlled | Uncontrolled |
| SBP, mmHg | –13.4 (–20.1, –6.8), 32 | –7.5 (–15.5, 0.4), 22 | –7.3 (–11.4, –3.2), 62 | –11.8 (–18.0, –5.6), 28 | –3.8 (–11.6, 4.1), 17 | –2.5 (–8.0, 3.1), 33 |
| DBP, mmHg | –7.7 (–12.3, –3.2), 32 | –3.9 (–9.8, 2.0), 22 | –3.2 (–6.1, –0.3), 62 | –7.3 (–11.4, –3.2), 28 | –3.2 (–8.7, 2.3), 17 | –0.9 (–4.6, 2.8), 33 |
| BMI, kg/m$^2$ | –2.1 (–2.7, –1.5), 32 | –1.2 (–2.1, –0.4), 22 | –1.5 (–1.9, –1.1), 62 | –2.9 (–3.8, –2.1), 29 | –1.6 (–2.6, –0.6), 17 | –2.5 (–3.3, –1.8), 33 |
| Waist circumference, cm | –2.9 (–5.5, –0.4), 32 | –2.4 (–5.8, 1.0), 22 | –2.6 (–4.3, –0.8), 57 | –4.8 (–8.2, –1.3), 28 | –3.8 (–8.6, 1.1), 16 | –6.1 (–8.8, –3.3), 25 |
| Weight, kg | –5.6 (–7.2, –4.0), 32 | –3.2 (–5.3, –1.1), 22 | –4.1 (–5.2, –3.1), 62 | –8.0 (–10.3, –5.6), 29 | –4.2 (–6.8, –1.6), 17 | –6.9 (–8.9, –4.9), 33 |
| Total cholesterol, mmol/L | –0.6 (–1.0, –0.2), 32 | –0.3 (–0.8, 0.1), 22 | –0.3 (–0.5, 0.0), 62 | –0.7 (–1.2, –0.3), 29 | –0.4 (–1.0, 0.2), 17 | –0.4 (–0.8, 0.0), 33 |
| LDL-cholesterol, mmol/L | –0.4 (–0.7, –0.1), 32 | –0.1 (–0.5, 0.2), 22 | –0.3 (–0.6, –0.1), 62 | –0.5 (–0.9, –0.2), 29 | –0.2 (–0.7, 0.3), 17 | –0.4 (–0.8, 0.0), 33 |
| Hirsutism score | –2.0 (–3.4, –0.5), 28 | –3.4 (–6.1, –0.7), 19 | –0.7 (–1.5, 0.1), 44 | –2.4 (–3.8, –1.1), 27 | –3.6 (–6.6, –0.6), 15 | –1.7 (–2.4, –1.0), 23 |
| HRQoL | 9.6 (4.3, 14.9), 32 | 8.9 (0.7, 17.1), 22 | 9.7 (5.9, 13.4), 61 | 12.8 (7.1, 18.5), 27 | 10.7 (0.8, 20.5), 17 | 9.9 (2.3, 17.6), 23 |
| Beck depression score | –4.9 (–8.4, –1.4), 32 | –5.0 (–8.8, –1.3), 22 | –5.1 (–7.4, –2.7), 60 | –6.2 (–9.2, –3.1), 29 | –2.5 (–6.3, 1.4), 17 | –5.1 (–9.1, –1.1), 33 |

Highlighted orange boxes indicate data where the 95% CI does not hit zero. The use of antihypertensive and lipid-lowering medication was permitted during the study. For conversion from mmol/L to mg/dL, the following conversion factors can be used: total cholesterol (x38.67), LDL-cholesterol (x38.67).

**Figure 1. Mean (±SE) Percentage Change in UFC from Baseline to Months 6 and 12 by UFC Response at Month 6**

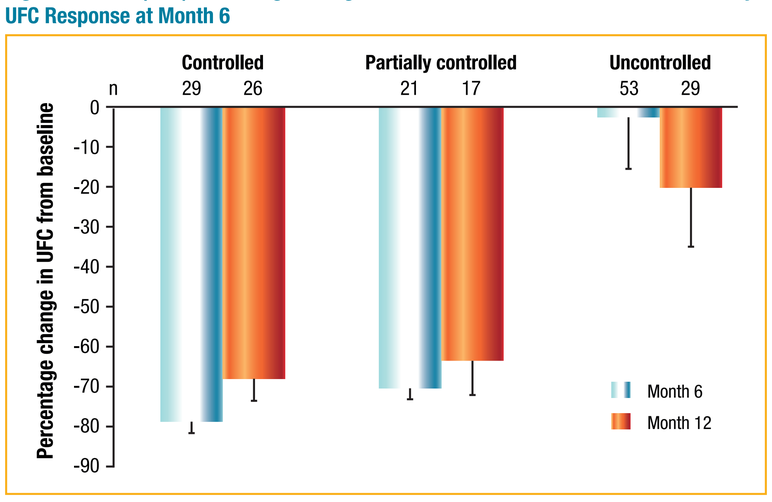
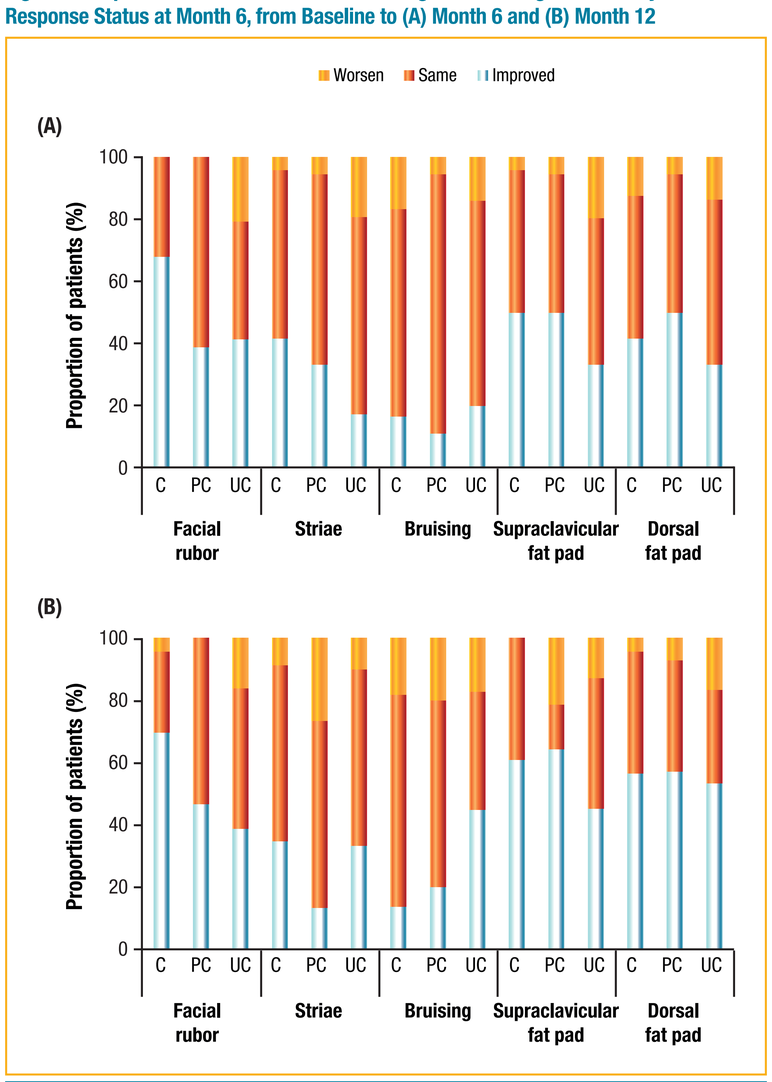



**Figure 2. Proportion of Patients with a Shift in Signs of Cushing's Disease by UFC Response Status at Month 6, from Baseline to (A) Month 6 and (B) Month 12**




Numbers of patients in the full analysis set with measurements from baseline to month 6 and month 12: facial rubor, 96 (25 controlled [C], 18 partially controlled [PC], 53 uncontrolled [UC]) and 69 (23 C, 15 PC, 31 UC), respectively; striae, 94 (24 C, 18 PC, 52 UC) and 68 (23 C, 15 PC, 30 UC), respectively; bruising, 92 (24 C, 18 PC, 50 UC) and 66 (22 C, 15 PC, 29 UC), respectively; supraclavicular fat pads, 93 (24 C, 18 PC, 51 UC) and 68 (23 C, 14 PC, 31 UC), respectively; dorsal fat pads, 93 (24 C, 18 PC, 51 UC) and 67 (23 C, 14 PC, 30 UC), respectively.

- At both 6 and 12 months, the majority of patients had either the same symptom severity or had improved by at least one category. Improvements in supraclavicular and dorsal fat pads were more common in those with controlled or partially controlled UFC levels at month 6 (**Figure 2**).
- No significant changes were observed in bone mineral density.

### Safety

- Detailed safety findings from this study have been reported previously.[5] Pasireotide demonstrated a safety profile similar to that of other somatostatin analogues, with the exception of hyperglycemia.
- Mean fasting plasma glucose (FPG) and $HbA_{1c}$ levels increased from baseline to months 6 and 12 in all UFC response subgroups (**Table 2**).

**Table 2. Changes from Baseline to Months 6 and 12 in FPG and $HbA_{1c}$ Stratified by UFC Response at Month 6**

| | Mean FPG (mg/dL) | | Mean $HbA_{1c}$ (%) | |
|---|---|---|---|---|
| | Mean ± SE (n) | Change from baseline (n) | Mean ± SE (n) | Change from baseline (n) |
| **Controlled** | | | | |
| Baseline | 92.4 ± 2.4 (34) | – | 5.6 ± 0.1 (34) | – |
| Month 6 | 115 ± 7.2 (27) | 24.4 ± 6.9 (28) | 6.8 ± 0.2 (31) | 1.3 ± 0.2 (29) |
| Month 12 | 113 ± 5.8 (29) | 22.9 ± 5.2 (25) | 6.9 ± 0.3 (29) | 1.3 ± 0.2 (27) |
| **Partially controlled** | | | | |
| Baseline | 94.7 ± 4.7 (23) | – | 5.6 ± 0.2 (23) | – |
| Month 6 | 118 ± 6.4 (22) | 21.5 ± 6.7 (20) | 7.0 ± 0.2 (22) | 1.4 ± 0.2 (21) |
| Month 12 | 121 ± 10.8 (17) | 28.8 ± 10.3 (16) | 6.9 ± 0.3 (17) | 1.4 ± 0.2 (16) |
| **Uncontrolled** | | | | |
| Baseline | 100 ± 2.3 (101) | – | 5.9 ± 0.1 (97) | – |
| Month 6 | 135 ± 6.6 (61) | 34.6 ± 5.3 (61) | 7.6 ± 0.2 (62) | 1.7 ± 0.1 (60) |
| Month 12 | 120 ± 7.3 (33) | 19.0 ± 6.2 (33) | 7.7 ± 0.3 (32) | 1.7 ± 0.3 (31) |

FPG, fasting plasma glucose

## CONCLUSIONS

- **Treatment with pasireotide was effective at normalizing UFC in a proportion of patients and improving signs and symptoms during the 12-month study period.[5]**
- **Improvements were observed even without complete UFC normalization, suggesting that partial improvements in UFC produced by pasireotide may be beneficial in improving signs and symptoms in patients with Cushing's disease.**
- **Following treatment with pasireotide, reductions in SBP, DBP, and supraclavicular and dorsal fat pads were greatest in patients achieving UFC control at month 6.**
- **Improvements in BMI and weight at month 12 were observed in the three UFC response groups.**
- **Mean FPG and $HbA_{1c}$ increased from baseline irrespective of decreases in UFC.**
  - **Glycemia should be carefully monitored in patients on pasireotide**
- **These results suggest that treatment with pasireotide provides clinical benefit in patients with Cushing's disease and offers patients a pituitary-directed medical treatment option.**

## REFERENCES

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## ACKNOWLEDGEMENTS

We thank Daniel Webber, Mudskipper Business Ltd. (funded by Novartis Pharmaceuticals Corporation) for providing medical editorial assistance and Hareesh Cheela, Novartis Healthcare Pvt. Ltd. for graphical/poster layout assistance with this poster.