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# Long-Term (5 Years) Treatment of Cushing's Disease with Pasireotide

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## INTRODUCTION

- Cushing's disease is a rare disorder of chronic hypercortisolism, which is caused by an adrenocorticotropic hormone (ACTH)-secreting pituitary adenoma.[1]
- Untreated, Cushing's disease is associated with significant clinical burden, increased mortality and impaired quality of life.[1]
- In a randomized, 12-month, Phase III study (B2305), the multireceptor-targeted somatostatin analogue pasireotide (Signifor®) led to a rapid and sustained decrease in mean urinary free cortisol (UFC) and provided clinical benefit in patients with persistent, recurrent or *de novo* Cushing's disease[2]
  - Based on the results of this study, pasireotide was approved in the US and EU for the treatment of adult patients with Cushing's disease for whom surgery has failed or is not an option.[3,4]
- Here, we report long-term efficacy and safety data from the B2305 study following an open-ended extension.

## METHODS

### Study Design

- Randomized Phase III study with an open-ended, open-label extension
  - 12- and 24-month results have been reported previously.[2,5]
- During the extension, patients continued with the same dose of pasireotide they were on at month 12
  - Dose increases and decreases were permitted at the investigators' discretion (maximum dose, 1200 µg sc bid).
- The study ended when all of the patients had discontinued from the extension.

### Patients

- 162 adult patients with persistent/recurrent or *de novo* Cushing's disease were initially randomized to pasireotide 600 or 900 µg bid.
- Patients who had UFC levels up to the upper limit of normal (ULN) or were achieving clinical benefit at month 12 could enter the extension.

### Assessments and Statistical Analyses

- Efficacy data are presented for patients who received ≥1 dose of pasireotide (overall population) and for patients who reached month 60.
- All patients who received ≥1 dose of pasireotide were included in the analysis of safety and adverse events (AEs), regardless of whether they entered the extension, unless otherwise stated
  - AEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 3.0
  - Kaplan–Meier estimates of cumulative event rate for first occurrence of AEs of special interest were calculated.

## RESULTS

### Patient Disposition

- Seventy-eight of the 162 patients who received pasireotide completed 12 months of treatment; 58 of these patients continued into the extension
  - 39, 19, and 16 patients reached the month 24, 48, and 60 visits, respectively
  - The maximum duration of exposure to pasireotide was 76.6 months.
- The main reasons for patient discontinuation (≥5% of patients) from baseline (month 0) up to study end were: unsatisfactory therapeutic effect (32.7%), AEs (22.2%), consent withdrawal (18.5%), and administrative problems (9.9%).

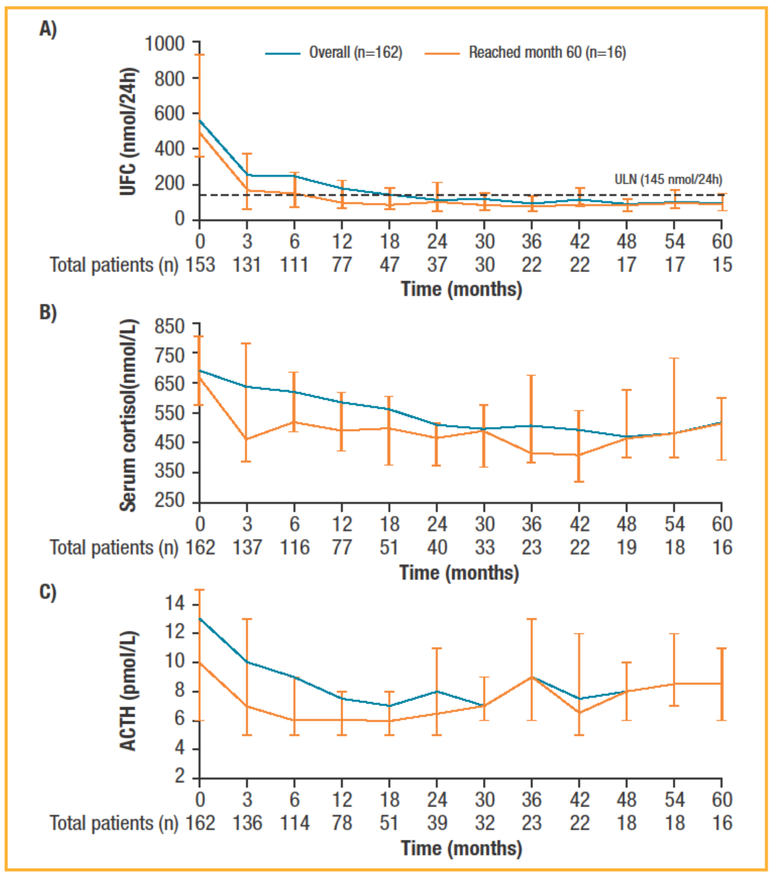
### Long-Term Efficacy of Pasireotide

- At baseline, median (95% confidence interval [CI]) UFC level was 564.5 nmol/24h (483–662; normal range, 30–145 nmol/24h) in the overall population and 488.3 nmol/24h (358–931) in the 16 patients who reached month 60.
- In the overall population, a reduction in median UFC from baseline was observed by month 3
  - Median UFC continued to decrease up to month 24 and plateaued thereafter (**Figure 1**).
- For patients who reached month 60, median UFC decreased during the first 3 months of treatment and continued to do so until month 12, after which median UFC stabilized (**Figure 1**).
- For patients who reached month 60, 10/16 and 11/16 had UFC ≤ULN at month 12 and month 60, respectively.
- At baseline, median (95% CI) serum cortisol and ACTH levels were 691 nmol/L (660–729) and 13 pmol/L (11–14), respectively, in the overall population and 668 nmol/L (577–804) and 10 pmol/L (6–15), respectively, in patients who reached month 60 (**Figure 1**).
- Reductions in median serum cortisol and plasma ACTH levels were observed by month 3 in the overall population, as well as in patients who reached month 60 (**Figure 1**).
- Serum cortisol and plasma ACTH remained below baseline levels up to month 60, with variations noted in median plasma ACTH levels beyond month 30 (**Figure 1**).

### Clinical Signs of Cushing's Disease

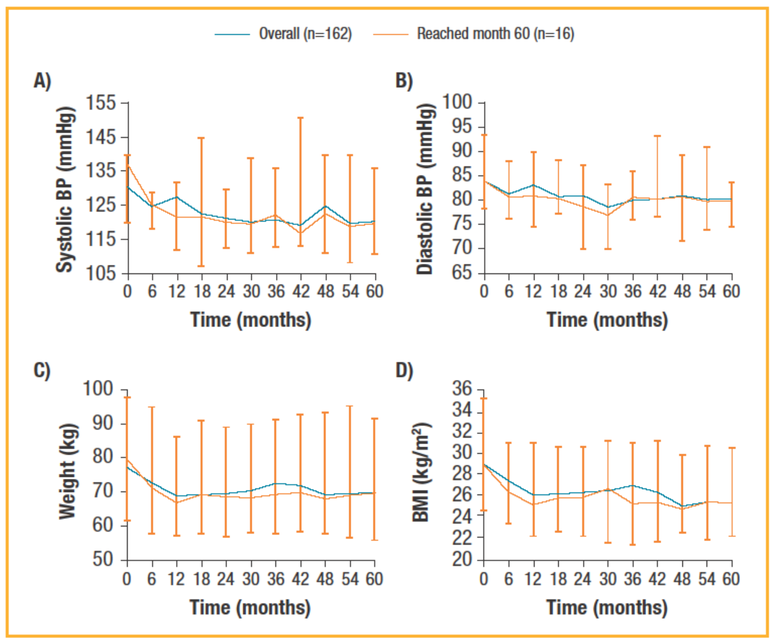
- Median systolic and diastolic blood pressure, weight and body mass index (BMI) decreased during the first 12 months of treatment in the overall population, as well as in patients who reached month 60.
- These improvements in clinical signs of Cushing's disease were sustained up to month 60 (**Figure 2**).

**Figure 1. Median (A) UFC, (B) Serum Cortisol and (C) ACTH Levels from Baseline to Month 60**




Note: Error bars show 95% distribution-free confidence limits for median values; numbers of patients with evaluable measurements are shown beneath each time point for the overall population

**Figure 2. Median (A) Systolic Blood Pressure, (B) Diastolic Blood Pressure, (C) Weight, and (D) BMI from Baseline Up to Month 60**




Note: Error bars show 95% distribution-free confidence limits for median values. BP, blood pressure

### Long-Term Safety of Pasireotide

- Almost all patients (98.1%; 159/162) who received pasireotide experienced ≥1 AE and 29.6% (48/162) experienced ≥1 serious AE during the study.
- The most common AEs (≥30% of patients) from baseline up to study end were diarrhoea (58.6%), nausea (53.7%), hyperglycaemia (41.4%), cholelithiasis (32.7%) and headache (30.9%)
  - No deaths were reported during the study.
- Incidences of first-reported AEs that were related to bradycardia, hyperglycaemia, the gallbladder/biliary tract, or the liver were highest in the first 12 months of treatment (**Table 1**)
  - Incremental increases in cumulative event probabilities were noted after month 12 for hyperglycaemia- and gallbladder/biliary-related AEs; smaller increases were observed for liver- and bradycardia-related AEs.

**Table 1. Cumulative Event Probabilities for Time to First Occurrence of AEs Related to Hyperglycaemia, the Gallbladder/Biliary Tract, the Liver, or Bradycardia***

| Months | Hyperglycaemia related | Gallbladder and biliary related | Liver safety related | Bradycardia related |
|---|---|---|---|---|
| 0–12 | 75 (68, 82) | 46 (37, 55) | 18 (12, 25) | 16 (9.3, 22) |
| 0–24 | 82 (74, 90) | 55 (44, 66) | 20 (13, 27) | 21 (13, 30) |
| 0–36 | 87 (79, 96) | 55 (44, 66) | 23 (14, 31) | 21 (13, 30) |
| 0–48 | 94 (84, 100) | 60 (46, 73) | 23 (14, 31) | 26 (14, 37) |
| 0–60 | 94 (84, 100) | 64 (50, 78) | 23 (14, 31) | 26 (14, 37) |
| 0–>60 | Not estimable | 64 (50, 78) | 23 (14, 31) | 26 (14, 37) |

Note: Data show cumulative event probability (%) and 95% CIs

*Common AE terms were grouped, for example, all terms relating to hyperglycaemia (eg, elevated fasting blood glucose/glycated haemoglobin, and diabetes mellitus) or liver safety

- Most patients with AEs related to bradycardia, hyperglycaemia, the gallbladder/biliary tract, or the liver did not experience a worsening of these AEs from first occurrence up to study end (**Table 2**).

**Table 2. CTCAE Grade of AEs Related to Hyperglycaemia, the Gallbladder/Biliary Tract, the Liver, or Bradycardia at First Occurrence and Worst Value**

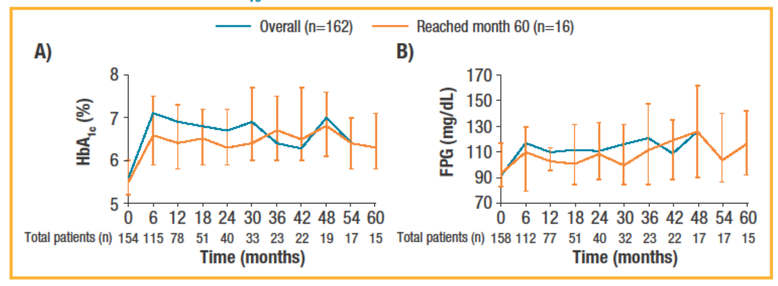
| First reported AE grade | | Worst reported AE grade | | | | |
|---|---|---|---|---|---|---|
| | n | Grade 1 n (%) | Grade 2 n (%) | Grade 3 n (%) | Grade 4 n (%) | Missing n (%) |
| **Bradycardia-related AEs** | | | | | | |
| Grade 1 | 19 | 4 (21.1) | 0 | 1 (5.3) | 0 | 14 (73.7) |
| Grade 2 | 5 | 2 (40.0) | 0 | 1 (20.0) | 0 | 2 (40.0) |
| Grade 3 | 1 | 0 | 0 | 0 | 0 | 1 (100.0) |
| Grade 4 | 0 | 0 | 0 | 0 | 0 | 0 |
| Missing | 0 | 0 | 0 | 0 | 0 | 0 |
| **Gallbladder- and biliary-related AEs** | | | | | | |
| Grade 1 | 48 | 10 (20.8) | 2 (4.2) | 3 (6.3) | 2 (4.2) | 31 (64.6) |
| Grade 2 | 12 | 3 (25.0) | 3 (25.0) | 1 (8.3) | 0 | 5 (41.7) |
| Grade 3 | 1 | 0 | 0 | 0 | 0 | 1 (100.0) |
| Grade 4 | 0 | 0 | 0 | 0 | 0 | 0 |
| Missing | 0 | 0 | 0 | 0 | 0 | 0 |
| **Hyperglycaemia-related AEs** | | | | | | |
| Grade 1 | 56 | 12 (21.4) | 15 (26.8) | 9 (16.1) | 0 | 20 (35.7) |
| Grade 2 | 44 | 5 (11.4) | 8 (18.2) | 11 (25.0) | 0 | 20 (45.5) |
| Grade 3 | 20 | 1 (5.0) | 7 (35.0) | 4 (20.0) | 0 | 8 (40.0) |
| Grade 4 | 2 | 0 | 1 (50.0) | 1 (50.0) | 0 | 0 |
| Missing | 0 | 0 | 0 | 0 | 0 | 0 |
| **Liver-safety-related AEs** | | | | | | |
| Grade 1 | 15 | 7 (46.7) | 1 (6.7) | 0 | 0 | 7 (46.7) |
| Grade 2 | 9 | 1 (11.1) | 3 (33.3) | 3 (33.3) | 0 | 2 (22.2) |
| Grade 3 | 4 | 1 (25.0) | 0 | 2 (50.0) | 0 | 1 (25.0) |
| Grade 4 | 0 | 0 | 0 | 0 | 0 | 0 |

Note: Boxes shaded blue indicate patients with a worse CTCAE grade than at first occurrence

### Changes in Fasting Blood Glucose (FPG) and Glycated Haemoglobin ($HbA_{1c}$)

- In the overall patient population, median $HbA_{1c}$ and FPG increased from baseline to month 6 and stabilized thereafter.
- Similarly, in patients who reached month 60, median $HbA_{1c}$ increased from 5.5% at baseline to 6.6% and 6.3% at months 6 and 60, respectively
  - Median FPG increased from 94 mg/dL at baseline to 110 and 117 mg/dL at months 6 and 60, respectively (**Figure 3**).

**Figure 3. Median (A) $HbA_{1c}$ and (B) FPG from Baseline Up to Month 60**




Note: Error bars show 95% distribution-free confidence limits for median values; numbers of patients with evaluable measurements are shown beneath each time point for the overall population. Concomitant treatment with antidiabetic medication was permitted at the discretion of the investigator

## CONCLUSIONS

- **The findings presented here demonstrate that the reductions in UFC and improvements in clinical signs of Cushing's disease reported after 12 months were maintained for up to 5 years of pasireotide treatment in the 16 patients who remained on treatment.**
- **Median UFC, serum cortisol and plasma ACTH levels were lower at baseline in patients who reached month 60 compared with the overall patient population.**
- **First-reported AEs related to bradycardia, hyperglycaemia, the gallbladder/biliary tract and the liver were most likely to occur during the first 12 months of treatment.**
- **Importantly, most patients with AEs related to bradycardia, hyperglycaemia, the gallbladder/biliary tract or the liver did not experience a worsening of these AEs after first occurrence**
  - **FPG and $HbA_{1c}$ increased within the first 6 months of pasireotide treatment and stabilized thereafter.**
- **Results from this study suggest that pasireotide can be an effective long-term treatment of Cushing's disease.**

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