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Efficacy and safety of once-monthly pasireotide in patients with Cushing's disease: results from a 12-month clinical trial

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Background: Cushing's disease is a rare, deleterious condition in which few prospective, interventional studies have been conducted. This manuscript reports results of the first Phase III study evaluating long-acting intramuscular pasireotide in patients with Cushing's disease.

Methods: Patients with persistent/recurrent or *de novo* (non-surgical candidates) Cushing's disease and mean urinary free cortisol (mUFC; of three 24-hour samples) ≥1·5–5·0x upper limit of normal (ULN; N=150) were randomised (double blind) using an interactive-response-technology system to pasireotide 10mg or 30mg every 4 weeks. Randomisation was stratified by screening mUFC (1·5–<2·0xULN and 2·0–5·0xULN). The dose could be up-titrated (10 to 30mg/30 to 40mg) at month 4 if mUFC>1·5xULN and/or months 7, 9, 12 if mUFC>1·0xULN. Primary endpoint: patients achieving mUFC≤ULN at month 7 regardless of dose titration. Efficacy analyses were based on intention to treat. This trial is registered with ClinicalTrials.gov: NCT01374906.

Findings: Between 28 December 2011 and 9 December 2014, 150 patients were randomised to receive pasireotide 10mg (n=74) or 30mg (n=76). The primary efficacy endpoint (mUFC≤ULN at month 7) was met by 31/74 (41·9%; 95%CI:30·5,53·9) patients in the 10mg group and 31/76 (40·8%; 95%CI:29·7,52·7) patients in the 30mg group. The most common adverse events (10mg and 30mg groups, respectively) were hyperglycaemia (36/74 [48·6%] and 36/76 [47·4%]), diarrhoea (26/74 [35·1%] and 33/76 [43·4%]), cholelithiasis (15/74 [20·3%] and 34/76 [44·7%]), diabetes mellitus (14/74 [18·9%] and 18/76 [23·7%]), and nausea (15/74 [20·3%] and 16/76 [21·1%]). Serious adverse events suspected to be study drug related were reported in 8/74 (10·8%) and 4/76 (5·3%) of patients in the 10mg and 30mg groups. Two patients died during the study (pulmonary artery thrombosis; cardiorespiratory failure); neither was judged to be related to study drug.

Interpretation: Long-acting pasireotide normalised mUFC in ~40% of patients with Cushing's disease at month 7 and had a similar safety profile to that of twice-daily subcutaneous pasireotide. Long-acting pasireotide is an effective treatment option for some

patients with Cushing's disease who have failed or are not candidates for surgery and provides a convenient monthly administration schedule.

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Introduction

Cushing's disease is a rare condition characterised by adrenal overproduction of cortisol secondary to an adrenocorticotropic hormone (ACTH)-secreting pituitary tumour (corticotropinoma).[1] Prolonged exposure to supraphysiological cortisol levels is associated with multisystem morbidity, which contributes to impaired quality of life and excess mortality.[2,3] Prompt treatment and long-term control of cortisol excess is crucial in preventing clinical complications and reducing mortality associated with Cushing's disease.[1–5]

Surgical resection of the causative pituitary adenoma is the first-line treatment of choice for most patients with Cushing's disease, which leads to remission in over 75% of patients if performed by an expert pituitary surgeon.[6] However, surgery is not always successful and disease recurrence can occur several years after initial remission, while some patients refuse or are not candidates for surgery.[6] As a result, many patients require additional treatment options for the management of Cushing's disease. Owing to its rarity (estimated incidence and prevalence: 1·2–2·4 and 39 per million population, respectively),[7,8] few prospective studies of medical therapies have been conducted in patients with Cushing's disease. All currently approved medical therapies for Cushing's disease require daily administration, either orally or by injection,[2] which can represent a burden for patients with chronic diseases.[9]

Pasireotide is a multireceptor-targeted, second-generation somatostatin analogue with highest affinity for somatostatin receptor subtype 5 (SSTR5), the most abundantly expressed SSTR in corticotropinomas.[10] Twice-daily, subcutaneous pasireotide (Signifor®) is approved in many countries worldwide, including the USA and EU, for treatment of adults with Cushing's disease.[6] An intramuscular long-acting formulation suitable for once-monthly administration has been developed.[11] While long-acting pasireotide has been approved for the treatment of acromegaly,[12,13] it had not yet been tested in patients with Cushing's disease. This manuscript describes results of the first Phase III study of long-acting pasireotide in patients with Cushing's disease.

Methods

Study design

This was a prospective, multicentre, randomised-dose (double-blind), Phase III study (Clinical Trial Registration Number: NCT01374906) comprising a 12-month core phase and an optional, open-ended extension. The study was conducted at 57 sites (19 countries) in accordance with the Declaration of Helsinki; an independent ethics committee/institutional review board for each site approved the study protocol. Patients provided written informed consent to participate.

Patients

Key inclusion criteria: age ≥18 years and confirmed diagnosis of persistent, recurrent, or *de novo* (if not surgical candidates) Cushing's disease with: mean 24-hour urinary free cortisol (mUFC) ≥1·5–5·0x upper limit of normal (ULN), calculated from three 24-hour samples collected within 2 weeks before study entry; normal/above-normal morning plasma ACTH; confirmed pituitary source of Cushing's syndrome (Supplementary Methods).

Key exclusion criteria: any previous pasireotide treatment; mitotane therapy within 6 months; pituitary irradiation within 10 years (Supplementary Methods).

Randomisation and blinding

After a 30-day screening period and washout of Cushing's disease medications, patients were randomised 1:1 (using an interactive-response-technology system) in a double-blind manner to intramuscular pasireotide 10mg or 30mg every 28 days (Novartis Pharma AG, Basel, Switzerland) administered by site personnel (Supplementary Methods); see Supplementary Methods for dose-selection rationale. Randomisation to one of the two pasireotide dose regimens was stratified by screening mUFC (stratum 1: mUFC 1·5–<2·0xULN; stratum 2: mUFC 2·0–5·0xULN). The dose was up-titrated (10 to 30mg/30 to 40mg) at month 4 if mUFC>1·5xULN and/or at months 7, 9, or 12 (maximum: 40mg) if mUFC>1·0xULN, provided there were no tolerability issues. One dose-level reduction was permitted during the first 7 months for tolerability. Patients were returned to their randomised dose once the tolerability issue resolved, or discontinued treatment if the issue

persisted. Further dose reductions were permitted after month 7; if a dose of 5mg was not tolerated, the patient discontinued treatment.

The sponsor study team was blinded to treatment allocation and dose until the month 7 database lock. Investigators, patients, and site personnel were blinded to treatment allocation and dose until the month 12 database lock (ie, after all patients had reached month 12 or were withdrawn from the study).

Study endpoints and assessments

The primary objective was to assess the proportion of patients in each randomised dose group achieving the primary endpoint: mUFC≤ULN (ULN: 166·5nmol/24h [60·3µg/24h]) at month 7, regardless of dose titration at month 4 (classified as responders).

Key secondary objective: to assess the proportion of patients in each group with mUFC≤ULN at month 7 and without dose up-titration at month 4. Other pre-specified secondary objectives reported here were to evaluate for each group during the core study: proportion of patients with mUFC≤ULN at each month; proportion of patients achieving the primary efficacy endpoint according to mUFC stratum; changes from baseline in mUFC at each month; effect on morning plasma ACTH, morning serum cortisol, continuous and categorical measures of clinical signs of hypercortisolism, and health-related quality of life (HRQoL) over time; safety profile and tolerability. The following secondary objectives will be published separately: frequency of controlled mUFC response from baseline to months 7 and 12; predictability of early uncontrolled response to non-response at months 7 and 12; time to first controlled or partially controlled mUFC response; duration of controlled or partially controlled mUFC response; proportion of patients with controlled or partially controlled mUFC (mUFC>ULN but ≥50% reduction from baseline) at each month; pharmacokinetic exposures of long-acting pasireotide in patients with Cushing's disease.

Pre-specified exploratory analyses reported here include: proportion of patients achieving the primary efficacy endpoint by sex; changes from baseline in late-night salivary cortisol and tumour volume for each group during the core study. *Post hoc* analyses included: proportion of patients achieving the primary efficacy endpoint by history of pituitary surgery and maximum tumour diameter at baseline; change in tumour volume by maximum tumour

diameter at baseline; proportion of patients with a ≤20% or ≥20% change (increase or decrease) from baseline in tumour volume according to maximum tumour diameter at baseline; change in mUFC from baseline to month 12 according to tumour volume change from baseline to month 12.

UFC values were determined by high-performance liquid chromatography–tandem mass spectrometry (normal: 15·9–166·5nmol/24h [5·8–60·3µg/24h]) at central laboratories (see Supplementary Methods for assay details). mUFC was calculated as the average of three samples collected over 2 weeks. Systolic and diastolic blood pressure (BP), body weight, waist circumference, and body mass index (BMI) were assessed at every visit. HRQoL (CushingQoL: worst–best QoL, 0–100) was assessed at months 2, 4, 7, 10, 12. Tumour volume was assessed by magnetic resonance imaging (MRI) at baseline and months 7 and 12 and evaluated by a blinded central reader (Supplementary Methods).

Safety analyses were based on adverse events (AEs) reported up to data cut-off (10 November 2015), including data beyond month 12 for some patients. AEs were defined using Medical Dictionary for Regulatory Activities v18·1 and graded per National Cancer Institute Common Terminology Criteria for AEs v3·0. Serious AEs (SAEs) were reported according to standard definitions.[14]

Statistical analysis

Sample-size calculation was based on the primary endpoint. The primary efficacy responder rate for each dosing regimen was hypothesised to be ≥30%. A sample size of 74 patients per dose group would provide 88% power for the lower bound of the respective two-sided 95% confidence interval (95%CI; Clopper–Pearson exact method) to exceed 15%; if the lower bound of the 95%CI was >15%, that group met the pre-specified threshold for the proportion of patients achieving the primary endpoint.

Efficacy analyses were conducted using the intent-to-treat principle (based on randomised dose). For primary/key secondary endpoints, if the mUFC level was missing at month 7, values were imputed using last available measurement between months 4 and 7; patients who discontinued before month 4 were considered non-responders. Dose groups were assessed independently, with no direct between-group comparisons (Supplementary

Methods). Changes from baseline in secondary objectives are summarised descriptively; two-sided 95%CIs were calculated for mean changes in secondary objectives over time.

Safety analyses were conducted according to first dose administered for patients who received ≥1 dose of study drug and had a valid post-baseline safety assessment. For the statistical analyses, SAS software, version 9.4 (SAS Institute) was used.

Role of funding source

Novartis Pharma AG funded the study. Novartis Pharmaceuticals Corporation provided financial support for medical editorial assistance. Study sponsor: designed the trial in collaboration with several investigators; provided funding and organisational support; collected data; performed analyses; aided data interpretation and manuscript preparation. Study steering committee (AL, SP, BMKB, JNP) had unrestricted access to raw data. All authors had access to analysed data, reviewed the manuscript, and had final responsibility for the decision to submit for publication.

Results

Patient population

Between 28 December 2011 and 9 December 2014, 150 patients were randomised to pasireotide 10mg (n=74) or 30mg (n=76) every 28 days (Figure 1).

Altogether, 104/150 (69·3%) patients completed 12 months of treatment (Table 1). At baseline, patient demographics and disease history were balanced between dose groups (Table 1). Approximately two-thirds of patients in each group had mUFC 2·0–5·0xULN at screening. One-hundred and seventeen patients (78%) had a measurable pituitary tumour on MRI; of these, 49 had a pituitary macroadenoma (maximum diameter ≥10mm) [Table 1].

Efficacy

Urinary free cortisol

Most patients in each group had a decrease in mUFC from baseline to month 7 (Figure 2).

The primary efficacy endpoint (mUFC≤ULN at month 7) was met by 41·9% (95%CI: 30·5, 53·9; n=31/74) and 40·8% (95%CI: 29·7, 52·7; n=31/76) of patients in the 10mg and 30mg groups, respectively. Of those patients who met the primary efficacy endpoint, 2/31 (10mg) and 0/31 (30mg) were classified as responders based on imputation of their last available measurement between months 4 and 7. Higher response rates were seen in patients with lower screening mUFC (Figure 3). Partial control was achieved in 4/74 (5·4%; 10mg) and 10/76 (13·2%; 30mg) patients at month 7 (Supplementary Results). Overall, similar response rates were observed between males and females and between patients with and without prior surgery; response rates were numerically higher in patients with a macroadenoma (49·0%; n=24/49) versus a microadenoma (35·3%; n=24/68) at baseline, although this was seen only in the pasireotide 10mg arm (Supplementary Results).

The proportion of patients achieving mUFC≤ULN at month 7 with no prior dose up-titration was 28·4% (95%CI: 18·5, 40·1; n=21/74) and 31·6% (95%CI: 21·4, 43·3; n=24/76) in the 10mg and 30mg groups. Thirty-one (10mg) and 28 (30mg) patients received dose up-titration at month 4; of these, 10/31 (32·3%) and 7/28 (25·0%) had mUFC≤ULN at month 7.

At month 12, 35·1% (95%CI: 24·4, 47·1; n=26/74) and 25·0% (95%CI: 15·8, 36·3; n=19/76) of patients in the 10mg and 30mg groups had mUFC≤ULN; partial control was achieved in 8/74 (10·8%; 10mg) and 13/76 (17·1%; 30mg) patients. Of patients who were classified as responders at month 7, 20/31 (64·5%; 10mg) and 15/31 (48·4%; 30mg) had mUFC≤ULN at month 12. Six of 31 (19·4%; 10mg) and 13/31 (41·9%; 30mg) responders at month 7 had mUFC>ULN at month 12 (Supplementary Results); two of these patients (both in the 30mg arm) received a lower dose of long-acting pasireotide at month 11 compared with month 6.

Median mUFC decreased within 1 month of treatment in both groups and remained below baseline to month 12 for ongoing patients (Figure 4). Median percentage change from baseline in mUFC was –47·9% (10mg) and –48·5% (30mg) at month 7, and –52·5% and –51·9% at month 12.

Plasma ACTH and salivary and serum cortisol

Sustained reductions were seen in both groups for median morning plasma ACTH and late-night salivary cortisol (Supplementary Results). Median percentage changes from baseline to month 12 in the 10mg and 30mg groups were, respectively: plasma ACTH, –22·5% and –17·4%; late-night salivary cortisol, –30·7% and –23·7%. At baseline, 13·2% (n=9/68) and 4·3% (n=3/69) of patients in the 10mg and 30mg arms, respectively, had normal late-night salivary cortisol levels compared with 30·2% (n=16/53) and 15·0% (n=9/60) of patients at month 7, and 25·0% (n=11/44) and 20·8% (n=10/48) of patients at month 12.

Changes in serum cortisol levels were generally consistent with those seen for morning plasma ACTH and late-night salivary cortisol (Supplementary Results). Median percentage changes from baseline to month 12 for serum cortisol were –9·2% and 0·1% in the 10mg and 30mg groups, respectively; for the 30mg group, median percentage changes of –8.0% to
–16.1% were seen at all other time points between months 7 and 11.

Clinical signs and symptoms

Clinical improvements were present at month 7 and improved further to month 12 (Supplementary Results). Mean changes (95%CI) from baseline to month 12 in the 10mg

and 30mg groups were, respectively: systolic BP, –4·6mmHg (–9·9, 0·7) and –5·0mmHg (–8·8, –1·3); diastolic BP, –3·4mmHg (–7·3, 0·4) and –3·1mmHg (–5·7, –0·5); waist circumference, –4·5cm (–7·2, –1·8) and –6·2cm (–8·7, –3·6); BMI, –1·3kg/m^2 (–1·8, –0·8) and –2·6kg/m^2 (–3·3, –1·9); weight, –3·4kg (–4·8, –2·0; 4.6% decrease) and –6·5kg (–8·3, –4·7; 8.6% decrease); CushingQoL, 6·4 (1·3, 11·6) and 7·0 (3·0, 10·9). Improvements were also seen in facial rubor, fat pads, and other clinical signs of Cushing's disease from baseline to months 7 and 12 (Supplementary Results).

Tumour volume

From baseline to month 12, median tumour volume decreased by 17·8% (10mg; n=35) and 16·3% (30mg; n=38) (Supplementary Results). For patients with a macroadenoma (maximum diameter ≥10mm) at baseline, median tumour volume decreased by 14·6% (10mg; n=15) and 11·6% (30mg; n=13) at month 12. Of these patients, 40·0% (10mg; n=6/15) and 38·5% (30mg; n=5/13) experienced a ≥20% tumour volume reduction at month 12; one patient per group experienced a ≥20% increase (Table 2). Median mUFC levels decreased from baseline to month 12 in patients regardless of tumour volume change (Supplementary Results).

Safety

By data cut-off, the median treatment duration was 449 (10mg; range: 28–1393; interquartile range: 197–756) and 381 days (30mg; range: 28–1294; interquartile range: 280–532). Overall, 73/74 (98·6%; 10mg) and 76/76 (100%; 30mg) patients experienced ≥1 AE. Most commonly reported AEs were hyperglycaemia, diarrhoea, cholelithiasis, diabetes mellitus, and nausea (Table 3); most were of mild-to-moderate severity (grade 1–2). The most frequent grade 3–4 AE was diabetes mellitus.

Nine of 74 (12·2%; 10mg) and 10/76 (13·2%; 30mg) patients discontinued treatment because of an AE (Supplementary Results). Two patients in the 30mg group died during the study: pulmonary artery thrombosis, n=1 (30 days after first injection); cardiorespiratory failure, n=1 (16 days after 16th injection [during extension phase]); neither was suspected to be drug related. SAEs were reported in 21/74 (28·4%) and 17/76 (22·4%) patients in the 10mg and 30mg groups; the most commonly reported SAE was cholelithiaisis (10mg, 2·7%

[n=2/74]; 30mg, 2·6% [n=2/76]). Eight of 74 (10·8%) and 4/76 (5·3%) patients in the 10mg and 30mg groups, respectively, experienced an SAE that was suspected to be related to study drug.

Hyperglycaemia-related AEs occurred in 53/74 (71·6%; 10mg) and 62/76 (81·6%; 30mg) patients; 17/74 (23·0%) and 18/76 (23·7%) experienced grade 3–4 events. Four patients per group (10mg, 5·4%; 30mg, 5·3%) discontinued treatment because of hyperglycaemia-related AEs. No instances of diabetic ketoacidosis or hyperosmolar hyperglycaemic non-ketotic syndrome were reported.

Mean fasting plasma glucose (FPG) and glycated haemoglobin (HbA_{1c}) increased within 1–2 months of treatment. Mean (SD; range) HbA_{1c} increased from 5·7% (0·6%; 4·5–7·4%) and 5·7% (0·7%; 4·5–7·6%) in the 10mg and 30mg groups at baseline, respectively, to 6·4% (0.9%; 5·0–8·7%) and 6·8% (1·3%; 5·2–12·3%) at month 4, and to 6·9% (1·4%; 5·1–10·2%) and 7·0% (1·4%; 4·8–11·7%) at month 12. At month 12, 58·3% (28/48) and 60·4% (32/53) of patients in the 10mg and 30mg groups, respectively, had HbA_{1c}<7·0%.

At baseline, 27/74 (36·5%; 10mg) and 33/76 (43·4%; 30mg) patients were diabetic, 12/74 (16·2%) and 12/76 (15·8%) were pre-diabetic, and 35/74 (47·3%) and 31/76 (40·8%) had normal glucose tolerance (see Supplementary Methods for definitions). Of patients with normal glucose tolerance at baseline in the 10mg and 30mg arms, 13/35 (37·1%) and 7/31 (22·6%) had a worst-reported value in the pre-diabetic range, and 19/35 (54·3%) and 21/31 (67·7%) had a worst-reported value in the diabetic range. Seven of 12 (58·3%) and 11/12 (91·7%) patients in the 10mg and 30mg arms who were pre-diabetic at baseline had a worst-reported value in the diabetic range. Of patients with normal glucose tolerance at baseline, 8/35 (22·9%; 10mg) and 13/31 (41·9%; 30mg) had last available HbA_{1c}≥6·5%; 9/12 (75·0%) and 7/12 (58·3%) patients who were pre-diabetic at baseline had last available HbA_{1c}≥6·5% (Supplementary Results). Of patients with normal glucose tolerance or pre-diabetes at baseline, 18/47 (38·3%; 10mg) and 22/43 (51·2%; 30mg) were receiving antidiabetic medication (ADM) at last assessment; 8/11 (72·7%) and 14/14 (100%) diabetic patients not receiving ADM at baseline were receiving ADM at last assessment. Nine of 16 (56·3%) and 10/19 (52·6%) patients on ADM at baseline were receiving ≥1 additional agent at last assessment (see Supplementary Results for HbA_{1c} changes by ADM status).

Gallbladder/biliary-related AEs occurred in 18/74 (24·3%; 10mg) and 34/76 (44·7%; 30mg) patients; four underwent cholecystectomy. Of patients with normal baseline ultrasound results, 8/64 (12·5%; 10mg) and 24/67 (35·8%; 30mg) had detectable sludge/gallstones at last assessment. Fifteen patients per group experienced liver-safety-related AEs (10mg, 20·3%; 30mg, 19·7%); 6/74 (10mg, 8·1%) and 5/76 (30mg, 6·6%) experienced grade 3–4 AEs, most commonly increased gamma-glutamyltransferase. Two patients per group (10mg, 2·7%; 30mg, 2·6%) discontinued treatment because of liver-safety-related AEs; alanine aminotransferase levels remained elevated at last observation (42 [82U/L] and 54 [166U/L] days after last pasireotide dose). No instances of jaundice or other symptoms of hepatic dysfunction were reported.

Two patients in the 10mg arm experienced a grade 1 AE of decreased insulin-like growth factor 1 (IGF-1) without any associated symptoms; one of these patients initiated growth hormone (GH) replacement 2·5 years after AE onset. Another patient had an AE of GH deficiency (IGF-1 and GH below the normal range); no associated symptoms were reported and treatment was not adjusted (Supplementary Results). IGF-1 levels decreased during pasireotide treatment. The initial decrease, seen at months 1 and 3 (prior to any dose up-titration), was greater in the 30mg arm. By month 7 (3 months after first permitted dose up-titration), mean IGF-1 SD score (SDS) was similar in both arms and remained stable to month 12. Mean (SD) IGF-1 SDS in the 10mg and 30mg groups, respectively, was: 0.3 (1.4) and 0.3 (1.2) at baseline; –0.6 (1.5) and –1.5 (1.4) at month 3; –1.2 (1.6) and –1.6 (1.4) at month 7; –1.0 (1.5) and –1.4 (1.6) at month 12 (Supplementary Results). Newly occurring QTcF prolongation of >480ms occurred in two patients in the 30mg arm; events were sporadic and resolved without treatment interruption. No patients with QTcF prolongation of >480ms experienced arrhythmias or clinical symptoms associated with episodes of QTcF prolongation. Two patients per group experienced injection-site-related AEs; one event required temporary treatment interruption and medication for pain.

Discussion

This first prospective trial of monthly pasireotide in Cushing's disease met the pre-specified threshold for the proportion of patients achieving the primary and key secondary endpoints; pasireotide normalised mUFC levels in approximately 40% of patients at month 7. Excluding patients who received a dose increase at month 4, around 30% of patients attained normal mUFC at month 7. Normal mUFC was more likely to be achieved in patients with a lower screening mUFC level (1·5–<2·0xULN). Nevertheless, pasireotide normalised mUFC in more than one-third of patients with higher screening mUFC (2·0–5·0xULN).

The similar between-group response rates at month 7 may be due to dose up-titration at month 4; the proportion of patients with mUFC≤ULN was consistently higher in the 30mg group at each month up to month 4, but tended to be similar thereafter. Dose up-titration may be beneficial for some patients who do not achieve normalised mUFC levels at lower doses.

In the Phase III study of twice-daily pasireotide, normal mUFC was achieved by 22·2% of patients with Cushing's disease at month 6 (regardless of prior dose titration). Mean/median baseline mUFC levels were higher in that study (entry criterion, mUFC≥1·5xULN; baseline mean/median, 6·5xULN/3·9xULN) than in the current study (entry criterion, mUFC≥1·5–5xULN; baseline mean/median, 2·8xULN/2·4xULN).[15] As patients with lower baseline mUFC were more likely to attain normal mUFC in both studies, the higher response rates observed for long-acting pasireotide may have resulted from exclusion of patients with mUFC >5xULN.

In both dose groups, reductions in mUFC were seen rapidly (within 1 month), with median levels remaining below baseline and close to ULN for the study duration. Decreases in mUFC were accompanied by reductions in morning plasma ACTH and late-night salivary cortisol.

Assessment of late-night salivary cortisol levels has high sensitivity (>90%) for the diagnosis of Cushing' disease.[16,17] Consistent with these findings, 91% of patients in this study had elevated late-night salivary cortisol levels at baseline. Few studies have

investigated the value of late-night salivary cortisol in monitoring response to medical treatment in patients with Cushing's disease, with varying outcomes.[18–21] As such, the potential role of late-night salivary cortisol during monitoring of medical treatment remains to be determined. In this study, normal late-night salivary cortisol levels were seen in 22–23% of patients at months 7 and 12. Further study is required to determine the effect of medical therapies on the restoration of normal circadian cortisol secretion in patients with Cushing's disease.

Improvements in weight, waist circumference, BMI, and HRQoL were seen over 12 months, indicating a sustained clinical benefit. Improvements in systolic and diastolic BP were seen in the 30mg arm, with similar trends in the 10mg arm. These changes may be clinically relevant; reductions in diastolic and systolic BP of 2–5mmHg can lower stroke risk by 11·5–13%,[22] while modest weight loss (5–10%) is associated with significant improvement in cardiovascular risk in studies of patients with type 2 diabetes mellitus.[23] Pasireotide treatment is associated with tumour volume reduction in patients with acromegaly and Cushing's disease.[13,24] In this study, over one-third of patients with a macroadenoma experienced a ≥20% reduction in tumour volume at month 12, with two patients experiencing a ≥20% increase. Changes in pituitary microadenoma volume are difficult to assess accurately by MRI and may not be clinically relevant. For optimal outcomes in patients with Cushing's disease, a multidisciplinary team approach to treatment decision making, including an experienced neurosurgeon, is required; in patients who have had failed/are not candidates for surgery, the potential effect of pasireotide-associated tumour shrinkage on any subsequent surgery should be considered.

The observed safety profile of long-acting pasireotide was consistent with that of twice-daily pasireotide in patients with Cushing's disease.[15] Approximately 70% of patients completed ≥12 months' treatment; 13% of patients discontinued because of AEs. Long-acting pasireotide may have more favourable gastrointestinal tolerability than the twice-daily formulation; the incidence of diarrhoea, nausea, and abdominal pain after 12 months was 39%, 21%, and 15%, respectively, for long-acting pasireotide, compared with 58%, 52%, and 24% for twice-daily pasireotide.[15] Gallstones are commonly associated with somatostatin analogue treatment but are rarely symptomatic or require surgery.[15,25] In this

study, 20% (n=15; 10mg) and 45% (n=34; 30mg) of patients had cholelithiasis; four patients underwent cholecystectomy. Gallbladder ultrasound is advised at regular intervals during pasireotide treatment. There was a low incidence of grade 3–4 liver-safety-related AEs during the study, the most common being increased gamma-glutamyltransferase levels.

As previously described for twice-daily pasireotide, hyperglycaemia-related AEs were the most commonly reported AEs of special interest, occurring in 72% and 82% of patients in the 10mg and 30mg groups, respectively, and leading to discontinuation in four patients per group. FPG and HbA_{1c} increased soon after starting pasireotide (within 1–2 months), and approximately 50% of patients required initiation/adjustment of ADM. Of patients with normal glucose tolerance/pre-diabetes at baseline, 41% had last-available HbA_{1c} in the diabetic range (>6.5%). At month 12, ~60% of patients in each group met the goal of HbA_{1c}<7% set by the American Diabetes Association and European Association for the Study of Diabetes.[26,27] Blood glucose levels should be closely monitored in patients treated with pasireotide and action taken, including initiation of glucose-lowering therapy, if necessary. Reductions in mean IGF-1 levels were seen within 1 month of initiating long-acting pasireotide; levels stabilised by month 7. Most (over 80%) patients continued to have IGF-1 levels within the normal range at month 12 and no clinical symptoms were reported. Long-term evaluation of the effects of pasireotide on the GH/IGF-1 axis in patients with Cushing's disease is warranted.

It was not possible to include a control arm in this trial. Owing to the significant morbidity associated with extended periods of hypercortisolism, a placebo-controlled trial was considered unethical. Furthermore, at the time of study start, there was no approved or gold-standard medical treatment for Cushing's disease across all participating countries, which precluded an active comparator arm.

In conclusion, this large Phase III study demonstrated that long-acting pasireotide administered for 12 months can reduce mUFC levels, is associated with improvements in clinical signs and HRQoL, and has a similar safety profile to that of twice-daily pasireotide. Pasireotide is an effective treatment for some patients with Cushing's disease who have failed or are not candidates for surgery and is generally well tolerated, while the long-acting formulation studied here provides a convenient monthly administration schedule.

Research in context

Evidence before this study

We searched PubMed for articles published up to June 2017, using terms related to Cushing's disease to identify relevant research on the management of this debilitating endocrine disorder. Most drugs used in the treatment of Cushing's disease do not target the underlying tumour but either inhibit cortisol synthesis or block the glucocorticoid receptor. Furthermore, most of these agents are not approved for use in Cushing's disease but are used off-label based on small studies or retrospective case series, with varying results. In 2012, the results of a 12-month Phase III study were published, demonstrating the clinical benefits of a twice-daily, subcutaneous formulation of pasireotide in patients with Cushing's disease. Based on the results of that trial, twice-daily pasireotide was approved in the EU, the USA, and other countries worldwide for the treatment of adult patients with this rare disorder. An intramuscular long-acting formulation of pasireotide was developed to allow for a once-monthly administration schedule. Whereas long-acting pasireotide has been recently tested in two Phase III trials in patients with acromegaly, it had not been tested in patients with Cushing's disease prior to the current study.

Added value of this study

This study confirms the efficacy and safety of pasireotide in patients with Cushing's disease, with the long-acting formulation providing a convenient monthly administration schedule.

Implications of all the available evidence

Normalisation of cortisol levels represents a key treatment goal in patients with Cushing's disease, which can improve the mortality rate towards that of the general population. The findings from this study indicate that long-acting pasireotide can normalise cortisol secretion and provide sustained clinical benefit to a significant proportion of patients with this rare, difficult-to-treat, and deleterious condition. Furthermore, a once-monthly administration schedule may allow greater convenience and adherence to treatment than twice-daily subcutaneous self-administration. As such, long-acting pasireotide can represent an effective treatment option for patients with Cushing's disease.

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Author contributions

The study was designed by the academic investigators and the sponsor, Novartis Pharma AG. Data were collected by investigators using Novartis' data management systems and analysed by Novartis' statistical team. The academic investigators enrolled patients into the study. All authors contributed to data interpretation and writing, reviewing, and amending of the manuscript; the first draft was prepared by the study steering committee (AL, BMKB, JNP, SP) and a medical writer funded by Novartis Pharma AG. All the authors made the decision to submit the manuscript for publication and vouch for the accuracy and completeness of the data. MR performed statistical/data analysis.

Conflict of interest statement

AL has received grants and personal fees as a clinical investigator, study steering committee member and advisory board member for Novartis, personal fees as an editor of UpToDate, and grants as a clinical investigator for Strongbridge. RP has received grants, personal fees and non-financial support from Novartis. PW has received grants and personal fees as a clinical investigator for Novartis and Ipsen, non-financial support (medical editorial assistance) from Novartis, and speaker fees and travel grants from Novartis and Ipsen. RS has received grants and personal fees as a clinical investigator and advisory board member, respectively, for Novartis. LT, MR and SR are all employees of Novartis; SR is a Novartis stockholder. SP has received personal fees as a study steering committee member for Novartis Pharma, and personal fees as a speaker and advisory board member for Novartis Pharma and Ipsen Pharma. BMKB has received grant and personal fees from Novartis, Cortendo, Ipsen and HRA Pharma. JNP received a research grant to University of Sheffield and Sheffield Teaching Hospitals NHS Foundation Trust,

personal fees as a consultant, and is a study steering committee member for Novartis. FG, MB, MY, WG and YY have no conflicts of interest to disclose.

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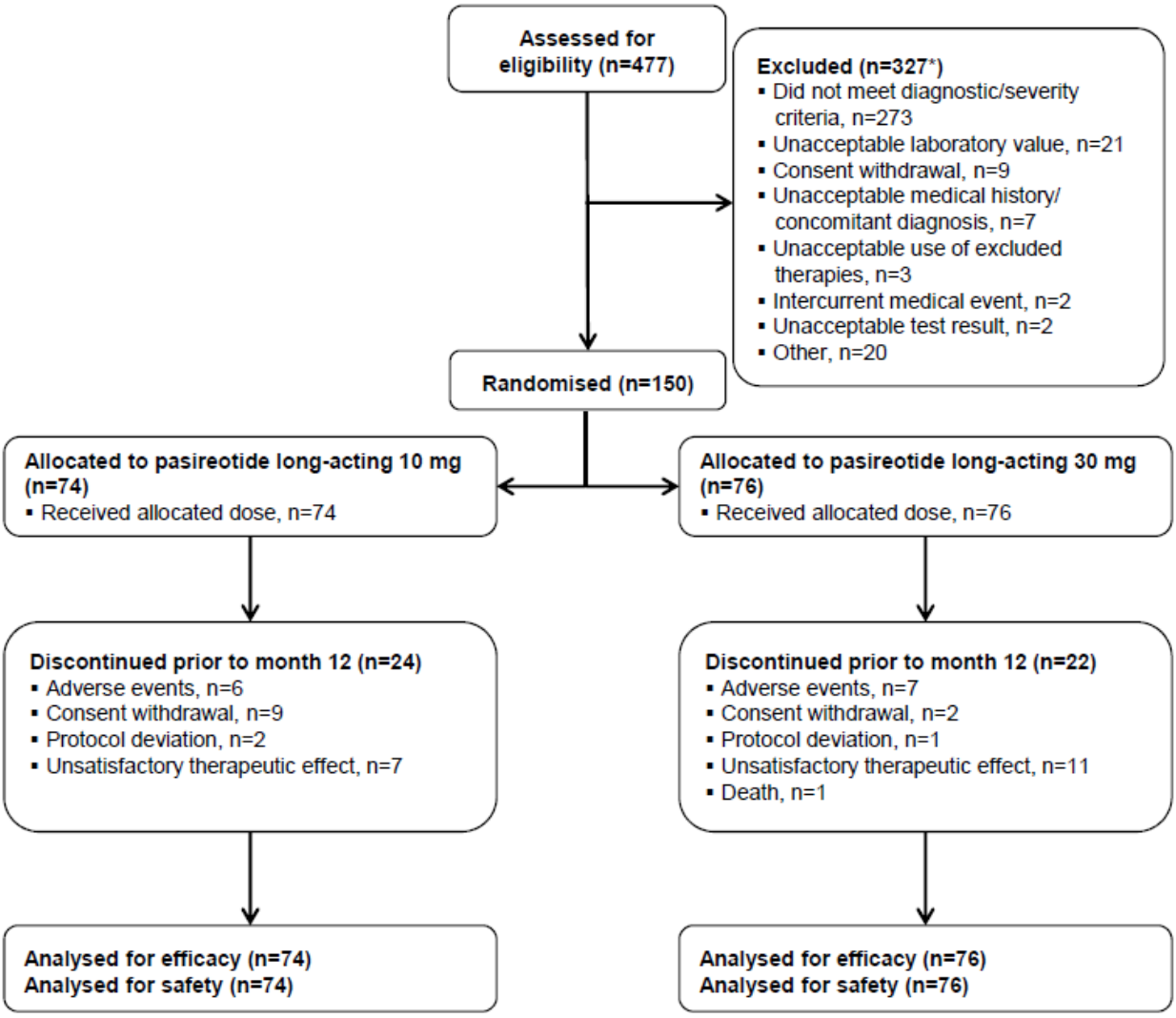
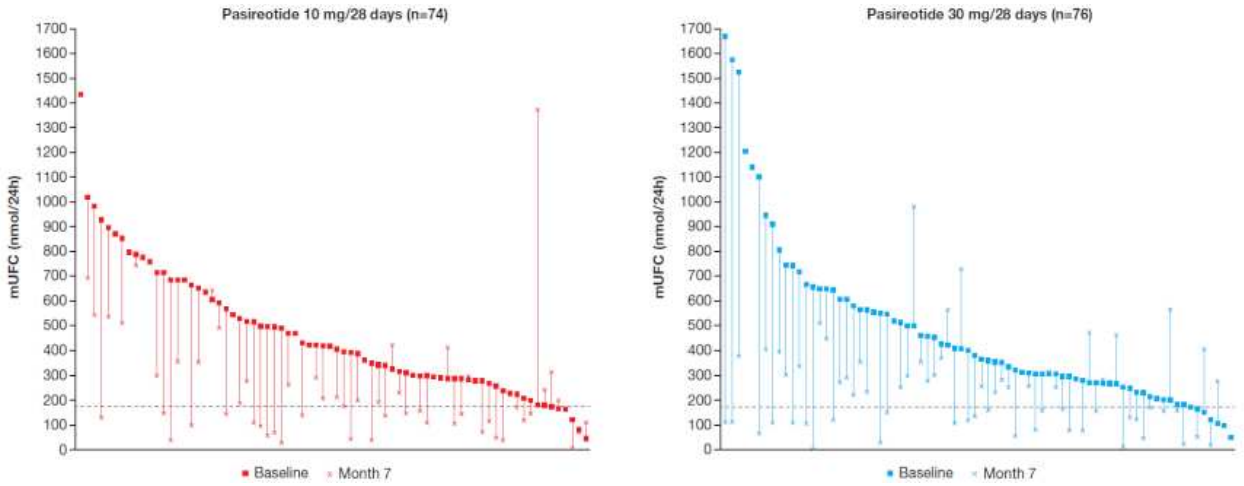
Figures

Figure 1. Patient flow



*Multiple reasons for exclusion could be given for individual patients

Figure 2. Absolute change in individual mUFC levels from baseline to month 7



For patients without a mUFC measurement at month 7, only baseline values are shown. Five patients in the 10mg group and six patients in the 30mg group had mUFC≤ULN at baseline (mUFC was ≥1·5xULN [range: 1·6–4·5xULN] at screening, thus meeting the eligibility criterion); of these, 4/5 and 3/6 met the primary efficacy endpoint. Dashed line represents the ULN for UFC (166·5nmol/24h)

Figure 3. Proportion of patients with mUFC≤ULN at month 7, according to mUFC stratum

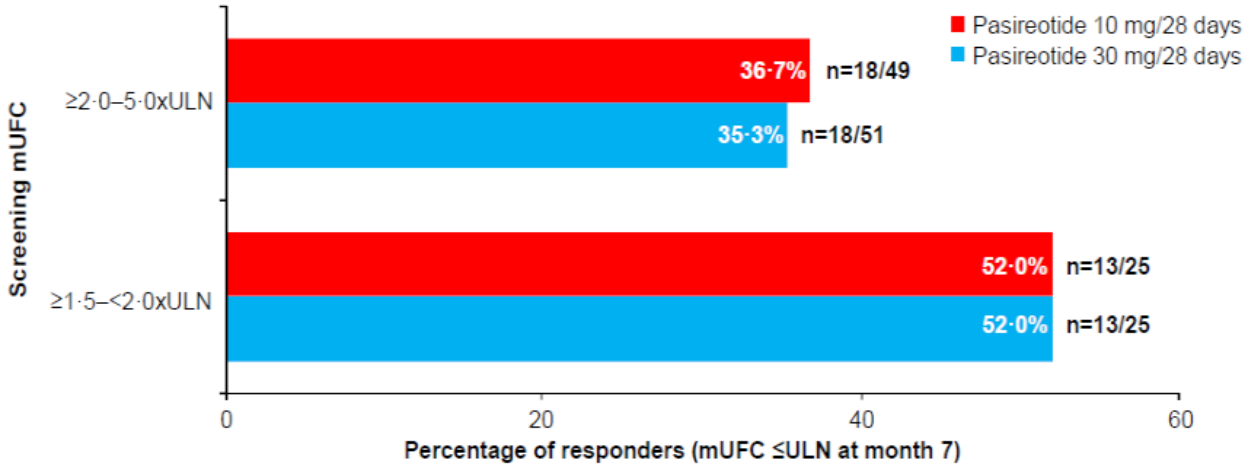
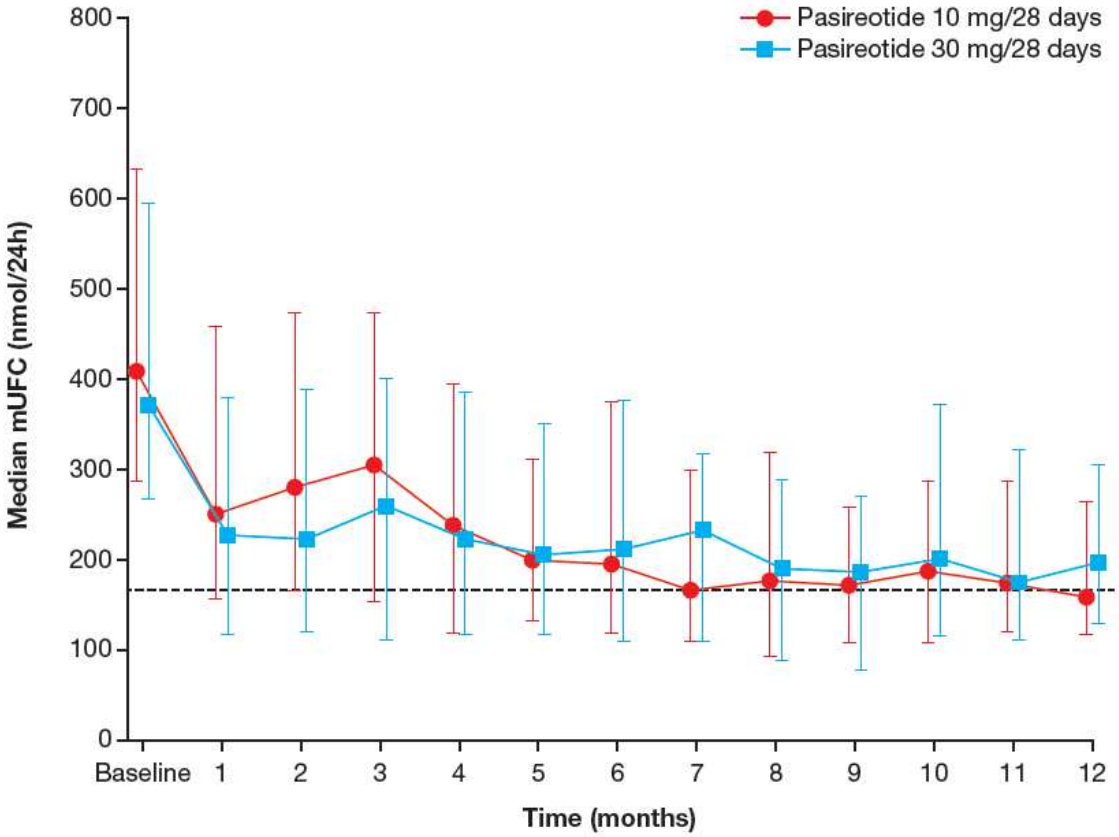


Figure 4. Median mUFC (nmol/24h) from baseline up to month 12



N	74/76	74/74	72/75	68/74	66/69	61/68	60/68	57/67	53/60	51/59	51/59	50/56	50/54
mUFC ≤ULN (n)	5	22	19	19	23	24	24	29	25	25	23	23	26
	6	28	28	26	28	23	28	31	25	27	22	26	19

Bars represent interquartile range. Dashed line represents the ULN for UFC (166·5nmol/24h). The numbers of patients contributing to the median and achieving normal mUFC at each time point are displayed under the X axis (long-acting pasireotide 10mg [red]/30mg [blue])

Table 1. Summary of baseline demographics and patient disposition

	Long-acting pasireotide		
	10mg N=74	**30mg 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)
Median time since diagnosis, months (range)	22·3 (0·9–394·7)	22·4 (0·7–231·9)	22·3 (0·7–394·7)
Screening mUFC stratum, n (%)			
≥1·5 *and* <2·0xULN	25 (33·8)	25 (32·9)	50 (33·3)
≥2·0 *and* ≤5·0xULN	49 (66·2)	51 (67·1)	100 (66·7)
Pituitary adenoma, n (%)*			
Microadenoma	34 (45·9)	34 (44·7)	68 (45·3)
Macroadenoma	20 (27·0)	29 (38·2)	49 (32·7)
No visible adenoma	17 (23·0)	12 (15·8)	29 (19·3)
Baseline mUFC, xULN			
Mean (SD)	2·8 (1·5)	2·9 (2·0)	2·8 (1·8)
Median	2·5	2·2	2·4
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)
Medical therapy	32 (43·2)	30 (39·5)	62 (41·3)
Patients completed, n (%)‡			
Month 4	65 (87·8)	69 (90·8)	134 (89·3)
Month 7	54 (73·0)	62 (81·6)	116 (77·3)
Month 12	50 (67·6)	54 (71·1)	104 (69·3)
Patients with dose adjustments, n (%)			
≥1 dose up-titration (up to month 12)	48 (64·9)	51 (67·1)	99 (66·0)
≥1 dose reduction	17 (23·0)	24 (31·6)	41 (27·3)

*Patients with an evaluable tumour measurement at baseline (3 patients in the 10mg arm and 1 patient in the 30mg arm did not have an MRI assessment at baseline); pituitary adenoma size defined by maximum diameter (microadenoma: >0–<10mm; macroadenoma: >10mm); †Twenty-seven patients did not undergo pituitary surgery prior to study entry for the following reasons: patient refused surgery, n=15; poor candidate for surgery, n=11; lack of access to surgical facility, n=1; one patient in the 30mg arm had a documented history of radiotherapy for Cushing's disease 17·1 years before receiving the first dose of long-acting pasireotide; ‡In the first 4 months, 16 patients discontinued treatment (unsatisfactory therapeutic effect, n=5; AEs, n=5; consent withdrawal, n=4; protocol deviation, n=1; death, n=1). By month 7, a further 18 patients had discontinued treatment (unsatisfactory therapeutic effect, n=10; AEs, n=5; consent withdrawal, n=2; protocol deviation, n=1). By month 12, a further 12 patients had discontinued treatment (consent withdrawal, n=5; unsatisfactory therapeutic effect, n=3; AEs, n=3; protocol deviation, n=1). SD, standard deviation

Table 2. Proportion of patients with a ≥20% reduction, ≥20% increase, and <20% change (stable) in tumour volume from baseline to month 12, by maximum tumour diameter at baseline*

	Pasireotide 10mg/28 days				Pasireotide 30mg/28 days			
Maximum baseline tumour diameter	**n**	**≥20% reduction, n (%)**	**<20% change, n (%)**	**≥20% increase, n (%)**	**n**	**≥20% reduction, n (%)**	**<20% change, n (%)**	**≥20% increase, n (%)**
<6mm	8	3 (37·5)	4 (50·0)	1 (12·5)	8	1 (12·5)	4 (50·0)	3 (37·5)
6–<10mm	12	6 (50·0)	5 (41·7)	1 (8·3)	17	12 (70·6)	5 (29·4)	0 (0·0)
≥10mm	15	6 (40·0)	8 (53·3)	1 (6·7)	13	5 (38·5)	7 (53·8)	1 (7·7)
Overall	35	15 (42·9)	17 (48·6)	3 (8·6)	38	18 (47·4)	16 (42·1)	4 (10·5)

*Patients were categorised according to maximum pituitary tumour diameter at baseline (range: 3–54mm). Tumour volume changes were calculated for patients with evaluable measurements at both baseline and month 12

Table 3. Most frequent adverse events (reported in ≥10% of patients overall), regardless of study drug relationship

	Pasireotide 10mg/28 days (N=74)		Pasireotide 30mg/28 days (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 (%)
Hyperglycaemia	36 (48·6)	6 (8·1)	36 (47·4)	3 (3·9)	72 (48·0)	9 (6·0)
Diarrhoea	26 (35·1)	0	33 (43·4)	0	59 (39·3)	0
Cholelithiasis	15 (20·3)	2 (2·7)	34 (44·7)	2 (2·6)	49 (32·7)	4 (2·7)
Diabetes mellitus	14 (18·9)	10 (13·5)	18 (23·7)	14 (18·4)	32 (21·3)	24 (16·0)
Nausea	15 (20·3)	1 (1·4)	16 (21·1)	0	31 (20·7)	1 (0·7)
Headache	18 (24·3)	0	10 (13·2)	1 (1·3)	28 (18·7)	1 (0·7)
Nasopharyngitis	16 (21·6)	0	12 (15·8)	0	28 (18·7)	0
Fatigue	12 (16·2)	0	14 (18·4)	0	26 (17·3)	0
Abdominal pain	10 (13·5)	2 (2·7)	12 (15·8)	0	22 (14·7)	2 (1·3)
Hypertension	10 (13·5)	7 (9·5)	12 (15·8)	7 (9·2)	22 (14·7)	14 (9·3)
Hypoglycaemia	9 (12·2)	2 (2·7)	12 (15·8)	2 (2·6)	21 (14·0)	4 (2·7)
Peripheral oedema	9 (12·2)	0	12 (15·8)	0	21 (14·0)	0
Influenza	12 (16·2)	0	6 (7·9)	0	18 (12·0)	0
Dizziness	9 (12·2)	1 (1·4)	8 (10·5)	0	17 (11·3)	1 (0·7)
Urinary tract infection	8 (10·8)	0	9 (11·8)	0	17 (11·3)	0

Of the 21 patients who experienced an AE of hypoglycaemia, 17 were receiving antidiabetic medication (insulin, n=10; oral antidiabetic medication, n=7); none of these events required hospitalisation or medical intervention. Of the 49 patients who experienced cholelithiasis, four required surgery, 24 required medical treatment, and two had a temporary interruption to long-acting pasireotide treatment. Hypocortisolism-related AEs were reported in six (8·1%) and seven (9·2%) patients in the 10mg and 30mg groups, respectively. Injection-site-related AEs were reported in two patients each in the 10mg (2·7%; pain, n=1; haemorrhage, n=1) and 30mg (2·6%; pain, n=1; hypersensitivity, n=1) groups