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## **Supplementary Appendix**

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

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## Supplementary Methods

### Inclusion criteria

A confirmed pituitary source of Cushing's disease was defined as:

- Magnetic resonance imaging (MRI) confirmation of a pituitary adenoma >6 mm with positive dynamic test (eg, corticotrophin-releasing hormone [CRH] or high-dose dexamethasone test); or
- Inferior petrosal sinus sampling gradient  $\geq 3$  after CRH/desmopressin stimulation or  $\geq 2$  at baseline for patients with a pituitary adenoma  $\leq 6$  mm; or
- Histopathology confirming an adrenocorticotrophic hormone (ACTH)-staining adenoma (in patients who had prior pituitary surgery)

### Exclusion criteria

Key exclusion criteria: patients who were candidates for surgery; pituitary irradiation within 10 years, previous pasireotide therapy, or mitotane therapy within 6 months; compression of the optic chiasm causing any visual field defect requiring surgical intervention; poorly controlled diabetes on antidiabetic medication (defined as glycated haemoglobin [HbA<sub>1c</sub>] >8%); symptomatic cholelithiasis at study entry; liver disease such as cirrhosis, chronic active hepatitis, or chronic persistent hepatitis, or patients with alanine aminotransferase and/or aspartate aminotransferase >2x the upper limit of normal (ULN) or serum bilirubin >1.5xULN; risk factors for torsades de pointes, congestive heart failure, unstable angina, sustained ventricular tachycardia, ventricular fibrillation, advanced heart block, or a history of acute myocardial infarction within 1 year of study entry.

### Dose selection

The selection of the randomised doses of 10 mg and 30 mg was based on the following considerations:

- Efficacy results from the Phase III study of twice-daily (bid) pasireotide in patients with Cushing's disease (CSOM230B2305 [B2305])
- Pharmacokinetic/pharmacodynamic (PK/PD) modelling analyses of the observed pasireotide concentration and mean urinary free cortisol (mUFC) data from the Phase III study (B2305)

- PK/PD plot analysis of the observed pasireotide concentration and serum cortisol and UFC data from the Phase II study of pasireotide bid in patients with Cushing's disease (CSOM230B2208)
- PK simulation for long-acting pasireotide in patients with Cushing's disease based on the observed PK data in healthy volunteer subjects

The 30 mg dose was selected for the higher-dose randomisation group based on its predicted trough plasma concentration ( $C_{\text{trough}}$ ) in patients with Cushing's disease, which is slightly higher than that of the 900 µg bid dose, which was effective in the B2305 study (Supplementary Table 1). The 10 mg dose represented a compromise between being sufficiently low to allow for a robust dose–response assessment in comparison with the 30 mg dose, and being high enough to offer a therapeutic benefit, especially in patients with lower baseline mUFC levels.

**Supplementary Table 1. Simulated PK parameters [mean (95%CI)] at steady state for pasireotide sc and long-acting pasireotide in patients with Cushing's disease**

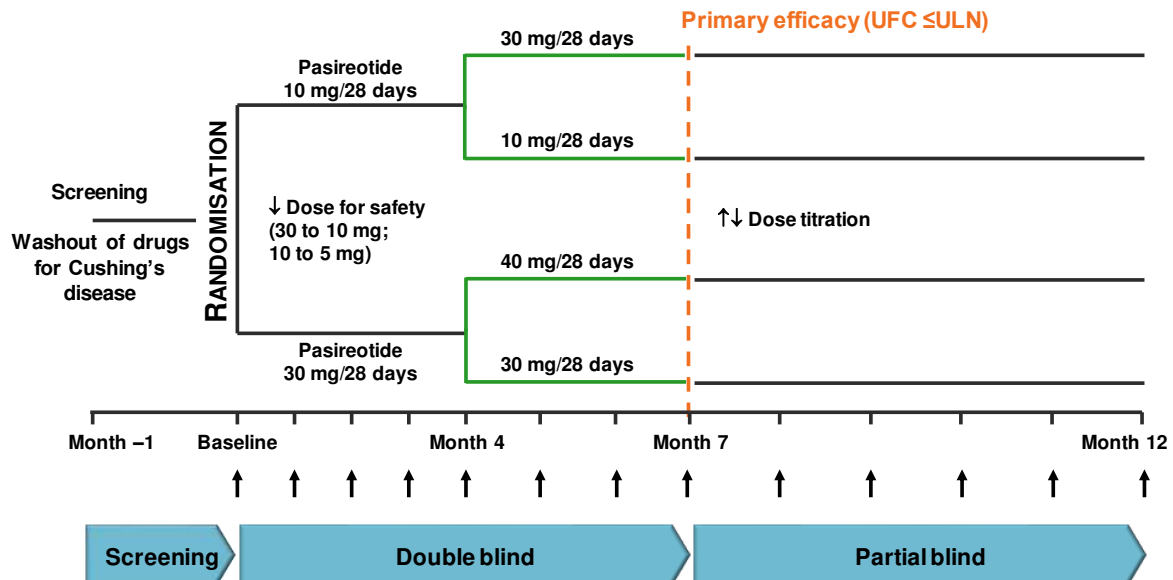
	<b>AUC<sub>0–d28</sub></b> <b>(h·ng/mL)</b>	<b>C<sub>avg</sub></b> <b>(ng/mL)</b>	<b>C<sub>trough</sub></b> <b>(ng/mL)</b>	<b>C<sub>max</sub></b> <b>(ng/mL)</b>
<b>Pasireotide sc dose (µg bid)</b>				
300	4451 (4268–4635)	6·6 (6·4–6·9)	2·8 (2·6–3·0)	18·8 (18·0–19·5)
600	8903 (8536–9269)	13·2 (12·7–13·8)	5·6 (5·3–6·0)	37·6 (36·1–39·0)
900	13,354 (12,804–13,903)	19·9 (19·1–20·7)	8·5 (7·9–9·0)	56·3 (54·1–58·6)
<b>Long-acting pasireotide dose (mg/28 days)</b>				
10	3704 (3488–3920)	5·5 (5·2–5·8)	3·5 (3·3–3·8)	8·6 (8·1–9·2)
20	7407 (6975–7839)	11·0 (10·4–11·7)	7·1 (6·6–7·6)	17·2 (16·1–18·3)
30	11,111 (10,463–11,759)	16·5 (15·6–17·5)	10·6 (9·9–11·4)	25·8 (24·2–27·5)
40	14,814 (13,950–15,678)	22·1 (20·8–23·3)	14·2 (13·2–15·2)	34·5 (32·3–36·6)

95%CI, 95% confidence interval; AUC<sub>0–d28</sub>, area under the plasma concentration–time curve from day 0 to day 28; C<sub>avg</sub>, average plasma concentration; C<sub>max</sub>, maximum plasma concentration; sc, subcutaneous

## Study design

The study design for the core phase of the study is shown in Supplementary Figure 1.

### Supplementary Figure 1. Core phase study design



The following washouts were required prior to screening assessments: steroidogenesis inhibitors (ketoconazole, metyrapone), 1 week; dopamine agonists (bromocriptine, cabergoline), peroxisome proliferator-activated receptor gamma agonists (rosiglitazone, pioglitazone), mifepristone, 4 weeks; long-acting octreotide, lanreotide sustained release, lanreotide Autogel, 14 weeks; octreotide immediate release, 1 week. mUFC was calculated as the average of three samples collected over 2 weeks; for months 4, 7, 9, and 12, mUFC samples were collected 7–19 days after the previous dose (ie, after the 4<sup>th</sup>, 7<sup>th</sup>, 9<sup>th</sup>, and 12<sup>th</sup> injections, respectively) to allow sufficient time for processing by the central laboratory and to ensure that results were available in time for decisions on dose titrations. At all other visits, samples were collected 14–28 days after the previous dose. Arrows beneath the X axis indicate the timing of long-acting pasireotide injections

## Assay details

UFC values were determined by ultra-performance liquid chromatography–tandem mass spectrometry (LC-MS/MS; Waters Corp., Milford, MA, USA; normal: 15.9–166.5 nmol/24h [5.8–60.3 µg/24h]); intra- and inter-assay coefficients of variation were 2.4–7.1% and 4.5–5.6%, respectively. All samples were analysed by central laboratories (Quintiles, Marietta, GA, USA and Q<sup>2</sup> Solutions [Beijing] Co. Ltd, Beijing, China).

Fasting morning blood samples were tested for serum cortisol by ultra-performance LC-MS/MS (Waters Corp., Milford, MA, USA) and for plasma ACTH (Immulite 2000

ACTH PIL2KAC-15, Siemens Medical Solutions Diagnostics, Los Angeles, CA, USA). Late-night saliva samples were tested for salivary cortisol by ultra-performance LC-MS/MS (Waters Corp., Milford, MA, USA). Intra- and inter-assay coefficients of variation were, respectively: serum cortisol, 1.7–3.9% and 4.6–5.8%; salivary cortisol, 1.8–3.2% and 3.5–4.5%; plasma ACTH, 3.2–4.3% and 3.2–4.7%. All samples were analysed by central laboratories (serum and salivary cortisol: Quintiles, Marietta, GA, USA and Q<sup>2</sup> Solutions [Beijing] Co. Ltd, Beijing, China; plasma ACTH: Quintiles, Marietta, GA, USA, Q<sup>2</sup> Solutions [Beijing] Co. Ltd, Beijing, China, Q<sup>2</sup> Solutions Pte Ltd, Singapore, and Q<sup>2</sup> Solutions, Tokyo, Japan). Serum cortisol and plasma ACTH levels were assessed monthly until month 12. Late-night salivary cortisol was assessed monthly until month 7, and then at months 9 and 12.

Serum insulin-like growth factor 1 (IGF-1) samples were measured using a chemiluminescent immunometric assay (Immulite<sup>®</sup> 2000; Diagnostic Products Corp. [Siemens], Los Angeles, CA, USA) and analysed at central laboratories (Q<sup>2</sup> Solutions, Valencia, CA, USA). Age- and sex-specific reference ranges were used to calculate an IGF-1 standard deviation score (SDS) for each patient (Brabant G *et al.* *J Clin Endocrinol Metab* 2007;92:2604–2609; Brabant G *et al.* *Horm Res* 2003;60:53–60).

### **Tumour volume assessment**

MRI was performed at each study site and the images sent to the central reader. The reading was performed by a single independent radiologist who was blinded to treatment dose and to the time point at which the image was taken. The boundaries of the pituitary tumour were traced to establish the region of interest (ROI). The total volume of voxels included in the ROI was automatically derived for each image and summed by the software to deliver the total tumour volume. In cases of prior pituitary surgery, if the reader determined that post-operative changes had not resolved and that the volume measurements of the pituitary appeared to be affected, the reader would declare the value to be unknown at the given time point. Mean percentage changes in tumour volume from baseline to month 12 were assessed for all patients with evaluable measurements and by maximum tumour diameter at baseline (<6 mm, ≥6–<10 mm, and ≥10 mm).

## Statistical analysis

The primary efficacy responder rate for each of the two long-acting pasireotide dosing regimens was hypothesised to be  $\geq 30\%$ .

In the Phase III study of twice-daily pasireotide (B2305), the response rate (defined as mUFC  $< 1.0 \times \text{ULN}$  regardless of dose up-titration) for the 900  $\mu\text{g}$  bid group was 33% for patients with baseline mUFC  $\leq 5 \times \text{ULN}$ . Since the up-titration criterion in the current study (mUFC  $> 1.5 \times \text{ULN}$  at month 4) was less stringent than in the B2305 study (mUFC  $> 2.0 \times \text{ULN}$  at month 3), the primary efficacy responder rate for each of the two randomised dosing regimens was expected to be  $\geq 30\%$  in this study.

Endpoints were assessed using a hierarchical approach to control the type I error rate at 5%. The key secondary endpoint for a randomised dose group was compared with 15% only if the lower bound of the 95%CI for the primary efficacy responder rate in that dose group exceeded 15%.

In the B2305 study, the response rate (defined as mUFC  $< 1.0 \times \text{ULN}$  at month 6 without dose up-titration) for the 900  $\mu\text{g}$  bid group was 31.5% for patients with baseline mUFC  $< 5 \times \text{ULN}$ . Therefore, the key secondary efficacy responder rate for each of the two randomised dose groups in this study is also expected to be  $\geq 30\%$ .

Mean/median values for mUFC, serum/salivary cortisol, plasma ACTH, clinical signs, and tumour volume were calculated for patients who had evaluable measurements at the specific time point; for calculations of absolute or percentage change, only those patients who had evaluable measurements at baseline and the later time point were included.

The study was neither designed nor powered to detect a difference in efficacy or safety outcomes between dose regimens. Changes in secondary endpoints within dose groups are summarised descriptively; for mean changes from baseline over time for secondary endpoints, two-sided 95%CIs were calculated.



## Definitions of diabetic status

- Diabetic: Prior history of diabetes mellitus *or* receiving antidiabetic medication *or* HbA<sub>1c</sub>  $\geq 6.5\%$  ( $\geq 48$  mmol/mol) *or* fasting plasma glucose (FPG)  $\geq 126$  mg/dL ( $\geq 6.9$  mmol/L)
- Pre-diabetic: Not qualifying as diabetic *and* with FPG  $100$ – $<126$  mg/dL ( $5.5$ – $<6.9$  mmol/L) *or* HbA<sub>1c</sub>  $5.7$ – $<6.5\%$  ( $39$ – $<48$  mmol/mol)
- Normal glucose tolerance: Not qualifying as diabetic or pre-diabetic *and* with FPG  $<100$  mg/dL ( $<5.5$  mmol/L) and/or HbA<sub>1c</sub>  $<5.7\%$  ( $<39$  mmol/mol)

## Supplementary Results: Efficacy

### mUFC $\leq$ ULN response status at month 7 by mUFC stratum

Response status at month 7 by mUFC stratum is shown in Supplementary Table 2.

**Supplementary Table 2. Response status at month 7 by mUFC stratum**

Screening mUFC	mUFC $\leq$ ULN at month 7 (n/N; %)		
	Pasireotide 10 mg/28 days	Pasireotide 30 mg/28 days	All patients
$\geq 1.5$ – $2.0$ xULN	13/25 (52.0)	13/25 (52.0)	26/50 (52.0)
$\geq 2.0$ – $5.0$ xULN	18/49 (36.7)	18/51 (35.3)	36/100 (36.0)

### mUFC response status at month 7 by patient subgroup

Response status at month 7 by sex, pituitary adenoma size, and surgical history are shown in Supplementary Table 3.

**Supplementary Table 3. Response status at month 7 by sex, pituitary adenoma size, and surgical history**

	mUFC $\leq$ ULN at month 7 (n/N; %)		
	Pasireotide 10 mg/28 days	Pasireotide 30 mg/28 days	All patients
Overall	31/74 (41·9)	31/76 (40·8)	62/150 (41·3)
Male	9/16 (56·3)	4/16 (25·0)	13/32 (40·6)
Female	22/58 (37·9)	27/60 (45·0)	49/118 (41·5)
Microadenoma	9/34 (26·5)	15/34 (44·1)	24/68 (35·3)
Macroadenoma	12/20 (60·0)	12/29 (41·4)	24/49 (49·0)
No prior surgery	5/15 (33·3)	6/12 (50·0)	11/27 (40·7)
Prior surgery	26/59 (44·1)	25/64 (39·1)	51/123 (41·4)

### Shift in mUFC response status from month 7 to month 12

Shift in response status between month 7 and month 12 are shown in Supplementary Table 4.

**Supplementary Table 4. Response status at month 7 and month 12**

Month 7 response status	Month 12 response status		
	Responder n (%)	Non-responder n (%)	Discontinued n (%)
10 mg arm			
Responder (n=31)	20 (64·5)	6 (19·4)	5 (16·1)
Non-responder (n=43)	6 (14·0)	18 (41·9)	19 (44·2)
30 mg arm			
Responder (n=31)	15 (48·4)	13 (41·9)	3 (9·7)
Non-responder (n=45)	4 (8·9)	22 (48·9)	19 (42·2)

## Change in mUFC over time

Median mUFC levels at each month of the core study are shown in Supplementary Table 5.

**Supplementary Table 5. Median mUFC level at each month**

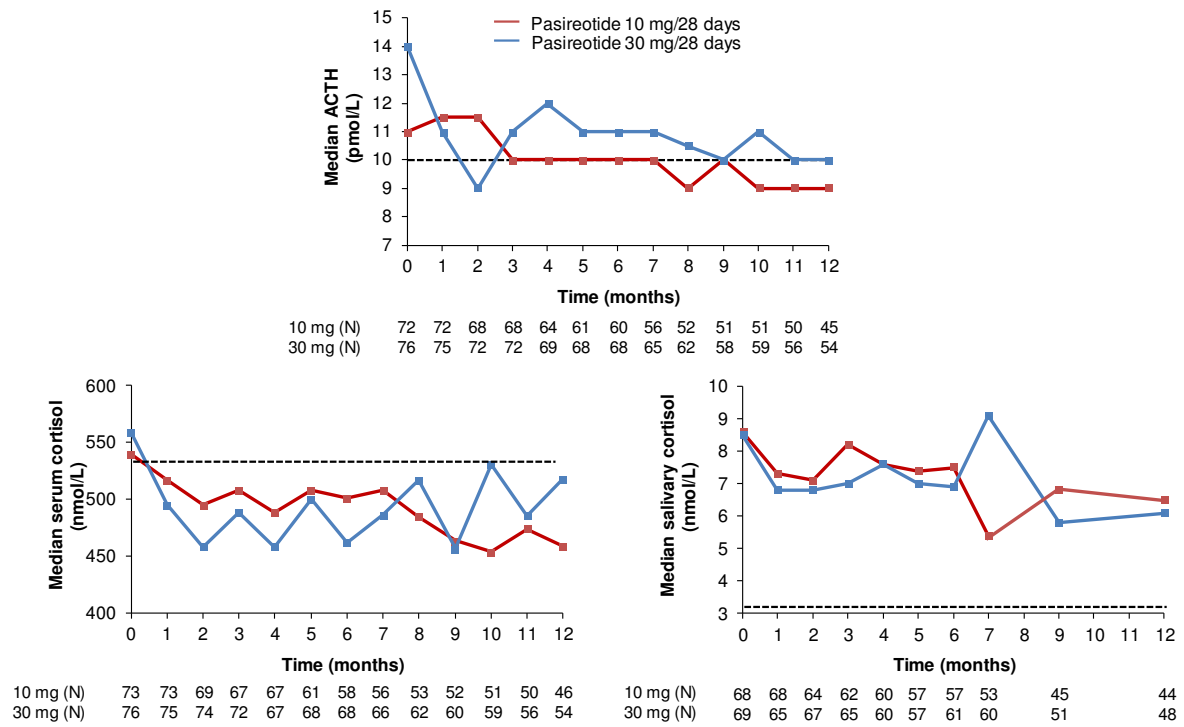
	<b>Pasireotide 10 mg/28 days, nmol/24h (IQR)</b>	<b>Pasireotide 30 mg/28 days, nmol/24h (IQR)</b>
Baseline	409·8 (287·6, 632·5)	371·6 (268·5, 593·7)
Month 1	250·7 (156·5, 459·7)	227·1 (117·0, 379·9)
Month 2	279·5 (164·8, 475·0)	223·0 (118·8, 389·4)
Month 3	304·6 (153·5, 472·8)	260·1 (111·4, 400·1)
Month 4	238·2 (118·1, 395·7)	223·7 (116·9, 385·5)
Month 5	199·6 (131·3, 310·5)	205·4 (116·8, 349·1)
Month 6	194·9 (118·2, 376·1)	211·1 (109·4, 376·8)
Month 7	166·4 (110·0, 298·0)	232·6 (109·5, 317·3)
Month 8	176·5 (94·2, 319·3)	190·5 (89·5, 289·4)
Month 9	172·6 (106·7, 257·1)	185·6 (77·3, 269·4)
Month 10	187·1 (107·8, 287·6)	201·7 (115·6, 370·5)
Month 11	174·5 (119·0, 287·1)	174·6 (111·4, 321·6)
Month 12	158·4 (117·0, 265·2)	196·4 (128·9, 304·9)

IQR, interquartile range

## Change in morning plasma ACTH, morning serum cortisol, and late-night salivary cortisol

Median percentage changes from baseline to month 7 (for patients with evaluable measurements at both time points) in the 10 mg and 30 mg groups were, respectively: plasma ACTH,  $-6.3\%$  ( $n=54$ ) and  $-26.1\%$  ( $n=62$ ); serum cortisol,  $-7.9\%$  ( $n=55$ ) and  $-11.3\%$  ( $n=66$ ); salivary cortisol,  $-33.0\%$  ( $n=50$ ) and  $-5.6\%$  ( $n=58$ ). Median percentage changes from baseline to month 12 were: plasma ACTH,  $-22.5\%$  ( $n=44$ ) and  $-17.4\%$  ( $n=52$ ); serum cortisol,  $-9.2\%$  ( $n=46$ ) and  $+0.1\%$  ( $n=54$ ); salivary cortisol,  $-30.7\%$  ( $n=42$ ) and  $-23.7\%$  ( $n=44$ ). Median plasma ACTH, serum cortisol, and salivary cortisol levels are shown from baseline up to month 12 in Supplementary Figure 2.

**Supplementary Figure 2. Median morning plasma ACTH, serum cortisol, and late-night salivary cortisol from baseline up to month 12**



Dashed lines represent the ULNs. Normal ranges: morning ACTH, 0–10 pmol/L; morning serum cortisol, 146–532.2 nmol/L; late-night salivary cortisol, 0.2–3.2 nmol/L (7.4–116.0 ng/dL). The number of patients contributing to the median is displayed under the X axis

## Change in signs and symptoms of Cushing's disease

Mean changes in clinical signs from baseline up to months 7 and 12 are shown in Supplementary Table 6.

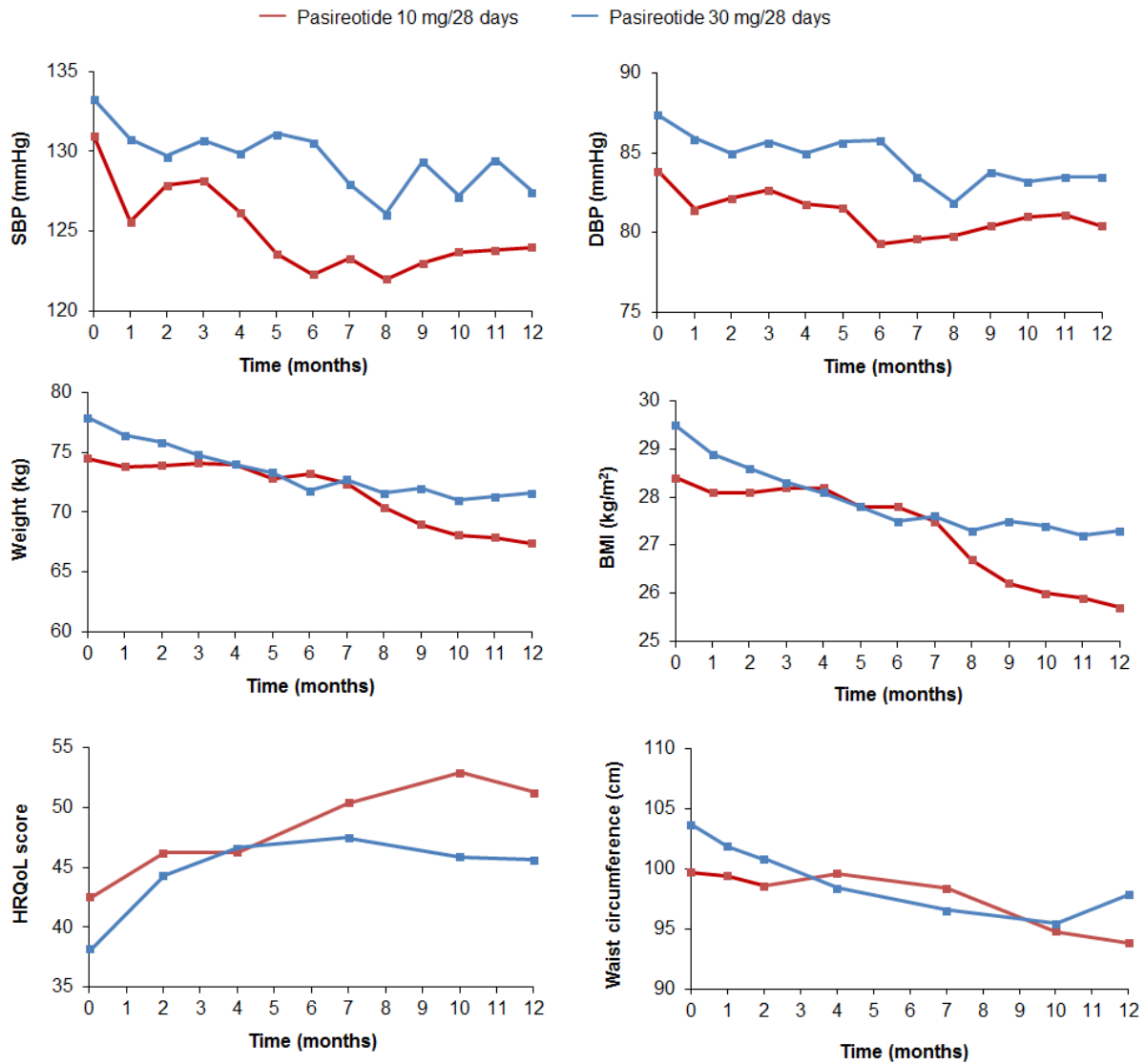
**Supplementary Table 6. Mean change (95%CI) from baseline in clinical signs of Cushing's disease by randomised dose group at months 7 and 12**

	Month 7		Month 12	
	10 mg/28 days	30 mg/28 days	10 mg/28 days	30 mg/28 days
SBP, mmHg	-6.8 (-10.9, -2.6)	-4.6 (-8.1, -1.1)	-4.6 (-9.9, 0.7)	-5.0 (-8.8, -1.3)
DBP, mmHg	-4.8 (-8.0, -1.6)	-3.0 (-6.0, -0.1)	-3.4 (-7.3, 0.4)	-3.1 (-5.7, -0.5)
Weight, kg	-1.8 (-2.9, -0.7)	-4.6 (-5.9, -3.4)	-3.4 (-4.8, -2.0)	-6.5 (-8.3, -4.7)
Waist circumference, cm	-1.6 (-4.0, 0.7)	-7.1 (-10.0, -4.1)	-4.5 (-7.2, -1.8)	-6.2 (-8.7, -3.6)
BMI, kg/m <sup>2</sup>	-0.7 (-1.1, -0.3)	-1.8 (-2.3, -1.3)	-1.3 (-1.8, -0.8)	-2.6 (-3.3, -1.9)
Total body composition, % fat	-1.0 (-1.9, -0.2)	-1.8 (-2.9, -0.6)	-1.8 (-2.9, -0.6)	-2.1 (-3.2, -1.1)
LDL-c, mmol/L	-0.4 (-0.6, -0.1)	-0.4 (-0.6, -0.2)	-0.3 (-0.6, 0.0)	-0.4 (-0.7, 0.0)
HDL-c, mmol/L	-0.1 (-0.2, 0.0)	0.0 (-0.1, 0.0)	-0.1 (-0.2, 0.0)	0.0 (-0.1, 0.1)
Total-c, mmol/L	-0.5 (-0.8, -0.2)	-0.4 (-0.7, -0.2)	-0.4 (-0.7, -0.1)	-0.3 (-0.7, 0.0)
Triglycerides, mmol/L	0.0 (-0.2, 0.1)	-0.2 (-0.4, 0.0)	0.0 (-0.2, 0.2)	-0.1 (-0.4, 0.1)
HRQoL score	5.7 (1.4, 10.0)	7.8 (4.9, 10.7)	6.4 (1.3, 11.6)	7.0 (3.0, 10.9)

Body composition and bone mineral density was measured by dual-energy X-ray absorptiometry. BMI, body mass index; DBP, diastolic blood pressure; HDL-c, high-density lipoprotein cholesterol; HRQoL, health-related quality of life; LDL-c, low-density lipoprotein cholesterol; SBP, systolic blood pressure; Total-c, total cholesterol. Bone mineral density was also measured but showed no change from baseline in either group at the reported time points.

Mean changes in clinical signs are shown from baseline up to month 12 in Supplementary Figure 3.

**Supplementary Figure 3. Mean SBP, DBP, weight, BMI, and HRQoL score from baseline up to month 12**



The proportions of patients with an improvement from baseline in other clinical signs of Cushing’s disease at months 7 and 12 are shown in Supplementary Table 7.

**Supplementary Table 7. Proportion of patients with an improvement from baseline in signs of Cushing's disease by randomised dose group at months 7 and 12**

	10 mg/28 days		30 mg/28 days	
	n/N	% (95%CI)	n/N	% (95%CI)
<b>Month 7</b>				
Facial rubor	17/52	32.7 (20.3, 47.1)	30/56	53.6 (39.7, 67.0)
Hirsutism (females)	8/42	19.0 (8.6, 34.1)	15/46	32.6 (19.5, 48.0)
Striae	12/52	23.1 (12.5, 36.8)	13/55	23.6 (13.2, 37.0)
Bruising	13/52	25.0 (14.0, 39.0)	8/56	14.3 (6.4, 26.2)
Supraclavicular fat pad	21/52	40.4 (27.0, 54.9)	16/56	28.6 (17.3, 42.2)
Dorsal fat pad	15/52	28.8 (17.1, 43.1)	22/55	40.0 (27.0, 54.1)
Muscle strength	5/56	8.9 (3.0, 19.6)	3/66	4.5 (1.0, 12.7)
<b>Month 12</b>				
Facial rubor	19/43	44.2 (29.1, 60.1)	19/43	44.2 (29.1, 60.1)
Hirsutism (females)	4/33	12.1 (3.4, 28.2)	14/34	41.2 (24.7, 59.3)
Striae	9/43	20.9 (10.0, 36.0)	8/42	19.0 (8.6, 34.1)
Bruising	11/43	25.6 (13.5, 41.2)	6/43	14.0 (5.3, 27.9)
Supraclavicular fat pad	16/43	37.2 (23.0, 53.3)	17/43	39.5 (25.0, 55.6)
Dorsal fat pad	14/43	32.6 (19.1, 48.5)	19/42	45.2 (29.9, 61.3)
Muscle strength	6/49	12.2 (4.6, 24.8)	3/53	5.7 (1.2, 15.7)

95%CIs are based on normal approximation to the binomial distribution. N is the number of patients in the intention-to-treat population with measurements at month 7 or 12 and baseline. A patient had an improvement from baseline if the sign at month 7 or 12 was less severe than at baseline. Signs of hypercortisolism (facial rubor, supraclavicular and dorsal fat pads) were assessed by photograph and scored on a scale of 0–3 (0=no signs, 1=mild, 2=moderate, 3=severe) at baseline and months 7 and 12. Muscle strength was assessed according to the patient's ability to stand from a low seated position with arms extended (0=can stand easily with arms extended, 1=stands after several efforts without using arms as assistance, 2=can stand by using arms as assistance, 3=completely unable to stand)

### Change in pituitary tumour volume

At baseline, 117 (78%) patients had a measurable pituitary tumour on MRI. Median pituitary tumour volume at baseline was 153.5 mm<sup>3</sup> (n=54) in the 10 mg group and 257.0 mm<sup>3</sup> (n=63) in the 30 mg group. At month 7, median tumour volume was 125.0 mm<sup>3</sup> and 149.0 mm<sup>3</sup> in the 10 mg and 30 mg groups; median percentage decrease for patients with evaluable measurements at baseline and month 7 was 12.0% (n=39) and 11.4% (n=51). At month 12, median tumour volume was 122.0 mm<sup>3</sup> and 140.5 mm<sup>3</sup> in

the 10 mg and 30 mg groups; median percentage decrease for patients with evaluable measurements at baseline and month 12 was 17.8% (n=35) and 16.3% (n=38) [Supplementary Table 8].

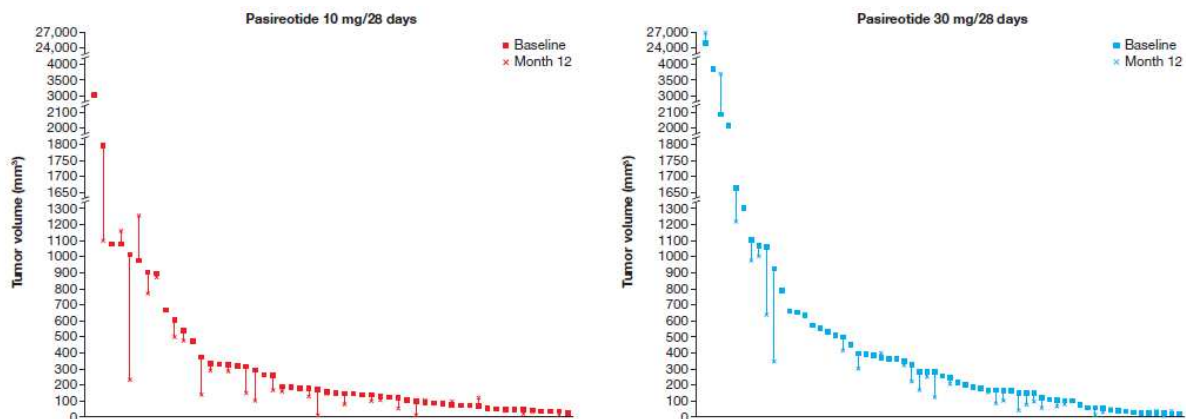
**Supplementary Table 8. Median percentage change in pituitary tumour volume from baseline to month 12 for patients with evaluable measurements at both time points, by maximum tumour diameter at baseline\***

Maximum baseline tumour diameter	10 mg/28 days		30 mg/28 days	
	n	Tumour volume change, % (IQR)	n	Tumour volume change, % (IQR)
<6 mm	8	-12.0 (-39.4, 1.5)	8	+10.9 (-0.8, 36.0)
6-<10 mm	12	-32.7 (-59.4, -3.9)	17	-37.4 (-47.3, -15.4)
≥10 mm	15	-14.6 (-34.6, -4.5)	13	-11.6 (-26.7, -6.2)
Overall	35	-17.8 (-52.2, -3.8)	38	-16.3 (-40.8, 0.0)

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

Absolute changes in tumour volume from baseline to month 12 for individual patients are shown in Supplementary Figure 4.

**Supplementary Figure 4. Absolute change in tumour volume from baseline to month 12 in individual patients**





## Change in mUFC levels by tumour volume change from baseline to month 12

Changes in median mUFC split by tumour volume change from baseline to month 12 are shown in Supplementary Table 9.

**Supplementary Table 9. Median percentage change in mUFC from baseline to month 12, by tumour volume change from baseline to month 12**

Tumour volume change	Pasireotide 10 mg/28 days		Pasireotide 30 mg/28 days	
	n	Median change in mUFC, % (IQR)	n	Median change in mUFC, % (IQR)
≥20% reduction	15	-58.8 (-75.8, -27.8)	18	-64.0 (-93.7, -51.8)
<20% change	17	-54.3 (-70.2, -43.1)	16	-29.6 (-54.6, -17.5)
≥20% increase	3	-31.6 (-73.1, 40.8)	4	-53.6 (-60.8, -48.1)

## Supplementary Results: Safety

### Adverse events

Adverse events (AEs) that led to discontinuation from baseline up to safety cut-off are shown in Supplementary Table 10.

**Supplementary Table 10. AEs leading to discontinuation, regardless of study drug relationship, from baseline up to the 12-month data cut-off\***

AEs leading to discontinuation	Pasireotide 10 mg/28 days (N=74)	Pasireotide 30 mg/28 days (N=76)	Overall (N=150)
Gallbladder related	1 (1.4)	3 (3.9)	4 (2.7)
Hyperglycaemia related	4 (5.4)	4 (5.3)	8 (5.3)
Liver safety related	2 (2.7)	2 (2.6)	4 (2.7)
Other	2 (2.7)	1 (1.3)	3 (2.0)

\*Maximum treatment duration: 1393 days in the 10 mg group and 1294 days in the 30 mg group

### Shift in HbA<sub>1c</sub> level from baseline to highest reported value

Of patients with normal glucose tolerance at baseline, 10/35 (28.6%) and 17/31 (54.8%) in the 10 mg and 30 mg groups had a highest reported HbA<sub>1c</sub> level of ≥6.5%; 9/12 (75.0%) and 10/12 (83.3%) patients who were pre-diabetic at baseline had a highest reported HbA<sub>1c</sub> level of ≥6.5%.

## Change in HbA<sub>1c</sub> levels by ADM status

Mean HbA<sub>1c</sub> levels at baseline, month 7, and month 12 are shown according to antidiabetic medication (ADM) status in Supplementary Table 11.

**Supplementary Table 11. Mean HbA<sub>1c</sub> levels at baseline, month 7, and month 12 by ADM status**

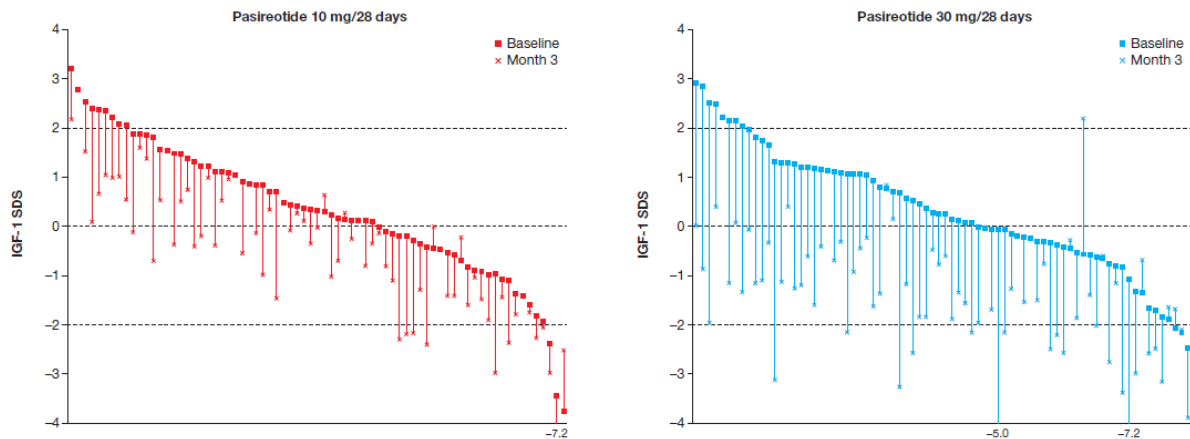
	Mean HbA <sub>1c</sub> , % (SD)	
	Pasireotide 10 mg/28 days	Pasireotide 30 mg/28 days
<b>No ADM at baseline and not prescribed ADM during the trial</b>		
	n=27	n=17
Baseline	5.3 (0.4)	5.1 (0.3)
Month 7	5.7 (0.4)	5.8 (0.4)
Month 12	5.8 (0.5)	5.6 (0.5)
<b>No ADM at baseline and prescribed metformin during the trial</b>		
	n=26	n=29
Baseline	5.6 (0.5)	5.6 (0.4)
Month 7	6.7 (1.0)	7.1 (1.0)
Month 12	7.1 (1.3)	7.1 (1.0)
<b>No ADM at baseline and prescribed incretin (with or without metformin) during the trial</b>		
	n=16	n=17
Baseline	5.9 (0.6)	5.8 (0.5)
Month 7	7.2 (0.9)	7.2 (1.1)
Month 12	7.5 (1.1)	7.4 (1.4)
<b>No ADM at baseline and prescribed insulin (with or without oral ADM) during the trial</b>		
	n=11	n=11
Baseline	5.7 (0.6)	5.6 (0.3)
Month 7	7.4 (0.7)	7.7 (1.4)
Month 12	7.7 (1.5)	8.0 (1.2)
<b>≥1 oral ADM at baseline and prescribed insulin during the trial</b>		
	n=8	n=11
Baseline	6.3 (0.5)	6.6 (0.8)
Month 7	8.1 (1.4)	8.2 (1.0)
Month 12	8.4 (1.8)	8.9 (1.6)

SD, standard deviation

## Change in IGF-1 levels

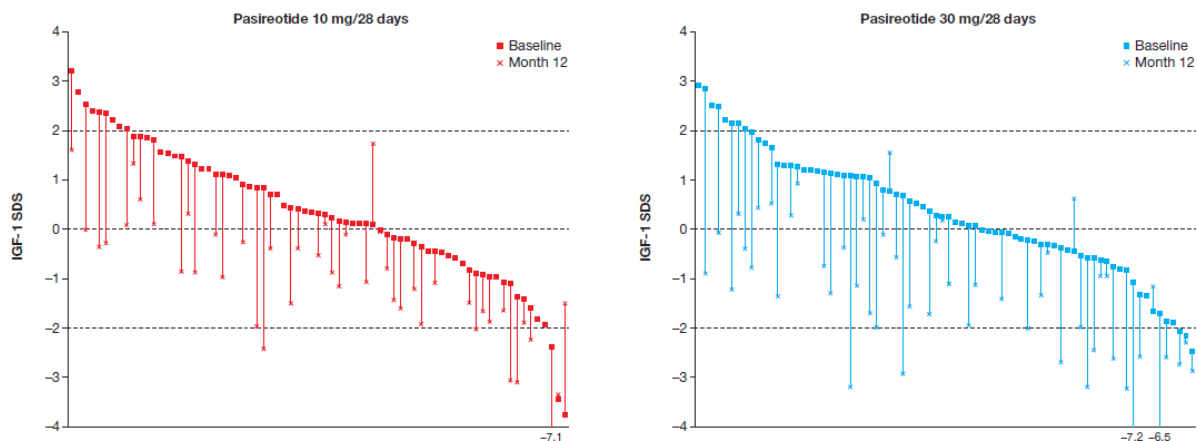
Individual changes in IGF-1 SDS from baseline to month 3 (ie, prior to dose up-titration) and month 12 are shown in Supplementary Figures 5 and 6, respectively.

### Supplementary Figure 5. Absolute change in IGF-1 SDS from baseline to month 3 in individual patients



For patients with an undetectable IGF-1 level, IGF-1 SDS was capped at  $-4.0$ ; for these patients, SDS values are indicated beneath the relevant marker

### Supplementary Figure 6. Absolute change in IGF-1 SDS from baseline to month 12 in individual patients



For patients with an undetectable IGF-1 level, IGF-1 SDS was capped at  $-4.0$ ; for these patients, SDS values are indicated beneath the relevant marker

Of patients in the 10 mg and 30 mg arms, respectively, with measurements at baseline and month 3, IGF-1 was above the normal range at baseline (SDS above  $+2.0$ ) in 8/66 (12.1%) and 7/71 (9.9%) patients, and below the normal range at baseline (SDS below  $-2.0$ ) in 3/66 (4.5%) and 3/71 (4.2%) patients.

In the 10 mg and 30 mg arms, respectively, IGF-1 SDS decreased from within/above the normal range at baseline (SDS above  $-2.0$ ) to below normal in: 8/63 (12.7%) and 18/68 (26.5%) patients at month 3; 9/51 (17.6%) and 18/60 (30.0%) patients at month 7; 5/42 (11.9%) and 12/48 (25.0%) patients at month 12.

It is important to note that the IGF-1 assay used in this study (Immulinite<sup>®</sup> 2000) does not meet the current recommendation of calibration against the World Health Organization International Standard 02/254 and has previously been reported to overestimate IGF-1 levels (Algeciras-Schimmich A *et al. Clin Chem* 2013;59:1187–1194; Bancos I *et al. Endocr Pract* 2014;20:421–426). As such, changes in IGF-1 levels during this study should be interpreted with caution.