

## ORIGINAL ARTICLE

# A 12-Month Phase 3 Study of Pasireotide in Cushing's Disease

Annamaria Colao, M.D., Ph.D., Stephan Petersenn, M.D.,  
John Newell-Price, M.D., Ph.D., James W. Findling, M.D., Feng Gu, M.D.,  
Mario Maldonado, M.D., Ulrike Schoenherr, Dipl.-Biol., David Mills, M.Sc.,  
Luiz Roberto Salgado, M.D., and Beverly M.K. Biller, M.D.,  
for the Pasireotide B2305 Study Group\*

## ABSTRACT

**BACKGROUND**

Cushing's disease is associated with high morbidity and mortality. Pasireotide, a potential therapy, has a unique, broad somatostatin-receptor-binding profile, with high binding affinity for somatostatin-receptor subtype 5.

**METHODS**

In this double-blind, phase 3 study, we randomly assigned 162 adults with Cushing's disease and a urinary free cortisol level of at least 1.5 times the upper limit of the normal range to receive subcutaneous pasireotide at a dose of 600  $\mu\text{g}$  (82 patients) or 900  $\mu\text{g}$  (80 patients) twice daily. Patients with urinary free cortisol not exceeding 2 times the upper limit of the normal range and not exceeding the baseline level at month 3 continued to receive their randomly assigned dose; all others received an additional 300  $\mu\text{g}$  twice daily. The primary end point was a urinary free cortisol level at or below the upper limit of the normal range at month 6 without an increased dose. Open-label treatment continued through month 12.

**RESULTS**

Twelve of the 82 patients in the 600- $\mu\text{g}$  group and 21 of the 80 patients in the 900- $\mu\text{g}$  group met the primary end point. The median urinary free cortisol level decreased by approximately 50% by month 2 and remained stable in both groups. A normal urinary free cortisol level was achieved more frequently in patients with baseline levels not exceeding 5 times the upper limit of the normal range than in patients with higher baseline levels. Serum and salivary cortisol and plasma corticotropin levels decreased, and clinical signs and symptoms of Cushing's disease diminished. Pasireotide was associated with hyperglycemia-related adverse events in 118 of 162 patients; other adverse events were similar to those associated with other somatostatin analogues. Despite declines in cortisol levels, blood glucose and glycated hemoglobin levels increased soon after treatment initiation and then stabilized; treatment with a glucose-lowering medication was initiated in 74 of 162 patients.

**CONCLUSIONS**

The significant decrease in cortisol levels in patients with Cushing's disease who received pasireotide supports its potential use as a targeted treatment for corticotropin-secreting pituitary adenomas. (Funded by Novartis Pharma; ClinicalTrials.gov number, NCT00434148.)

From the Department of Molecular and Clinical Endocrinology and Oncology, Section of Endocrinology, University of Naples Federico II, Naples, Italy (A.C.); ENDOC Center for Endocrine Tumors, Hamburg, and the Faculty of Medicine, University of Duisburg-Essen, Essen — both in Germany (S.P.); the Department of Human Metabolism, University of Sheffield, Sheffield, United Kingdom (J.N.-P.); the Division of Endocrinology, Metabolism, and Clinical Nutrition, Medical College of Wisconsin, Milwaukee (J.W.F.); the Department of Endocrinology, Key Laboratory of Endocrinology, Ministry of Health Peking Union Medical College Hospital, Beijing (F.G.); Clinical Development, Oncology Business Unit, Novartis Pharma, Basel, Switzerland (M.M., U.S., D.M.); the Division of General Internal Medicine, Hospital das Clínicas, University of São Paulo Medical School, São Paulo (L.R.S.); and the Neuroendocrine Clinical Center, Massachusetts General Hospital, Boston (B.M.K.B.). Address reprint requests to Dr. Biller at the Neuroendocrine Unit, Massachusetts General Hospital, 55 Fruit St., Bulfinch 457B, Boston, MA 02459, or at [bbiller@partners.org](mailto:bbiller@partners.org).

\*Members of the Pasireotide B2305 Study Group are listed in the Supplementary Appendix, available at [NEJM.org](http://NEJM.org).

This article (10.1056/NEJMoa1105743) was updated on August 23, 2012, at [NEJM.org](http://NEJM.org).

N Engl J Med 2012;366:914-24.  
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**C**USHING'S DISEASE IS A RARE DISORDER of chronic hypercortisolism due to a corticotropin-secreting pituitary adenoma. The disorder is associated with central obesity, osteoporosis, arterial hypertension, insulin resistance, glucose intolerance, diabetes mellitus, dyslipidemia, cardiovascular disease, and increased mortality.<sup>1-5</sup>

Transsphenoidal surgery is the primary therapy in most patients, with remission rates of 65 to 90% when an expert pituitary surgeon operates.<sup>6</sup> However, remission definitions vary, and relapse occurs in up to 30% of patients. Second-line options include repeat pituitary surgery, radiation therapy, bilateral adrenalectomy, and medical therapy. However, current medical treatments have not been tested in large prospective, randomized trials.

Corticotroph adenomas express somatostatin receptors, predominantly somatostatin-receptor subtype 5.<sup>7</sup> Activation of this subtype inhibits corticotropin secretion, providing a potential therapeutic target for Cushing's disease.<sup>8-10</sup>

Pasireotide (SOM230) is a somatostatin analogue that targets four of the five somatostatin receptors, with highest affinity for subtype 5.<sup>11</sup> This unique receptor-binding profile and the positive results in a proof-of-concept study<sup>12</sup> provided the rationale for the present study.

## METHODS

### PATIENTS

Eligible patients in this multicenter, phase 3 study were adults ( $\geq 18$  years of age) with confirmed persistent or recurrent Cushing's disease or newly diagnosed disease, if they were not candidates for surgery. Cushing's disease was defined by a mean 24-hour urinary free cortisol level of at least 1.5 times the upper limit of the normal range, calculated from four 24-hour samples collected within 2 weeks; a morning plasma corticotropin level of 5 ng per liter (1.1 nmol per liter) or more; and a confirmed pituitary source of Cushing's syndrome. Key exclusion criteria were pituitary irradiation within the previous 10 years, compression of the optic chiasm causing visual-field defects, symptomatic cholelithiasis, and a glycated hemoglobin level of more than 8% (for further details, see the Supplementary Appendix, available with the full text of this article at NEJM.org).

### STUDY OVERSIGHT AND SUPPORT

The study was approved by the independent ethics committee, research ethics board, or institutional

review board at each center and complied with the Declaration of Helsinki, the Harmonized Tripartite Guideline for Good Clinical Practice from the International Conference on Harmonization, and local laws. All patients provided written informed consent. The study was funded by Novartis Pharma. Financial support for medical editorial assistance was provided by Novartis Pharma.

The study was designed by the academic investigators and the study sponsor, Novartis Oncology. Data were collected by the site investigators with the use of Novartis data-management systems and were analyzed by the Novartis statistical team. All authors contributed to data interpretation and the writing, reviewing, and amending of the manuscript; the first draft was prepared by one of the academic authors and a medical writer funded by Novartis Pharma. All the authors made the decision to submit the manuscript for publication and vouch for the accuracy and completeness of the data and for the fidelity of the study to the protocol (available at NEJM.org).

### STUDY DESIGN

After screening of 329 patients and appropriate washout of cortisol-lowering medications, 162 patients were randomly assigned to subcutaneous pasireotide at a dose of 600  $\mu\text{g}$  (82 patients) or 900  $\mu\text{g}$  (80 patients) twice daily. Patients with a urinary free cortisol level not exceeding 2 times the upper limit of the normal range and not exceeding the baseline level at month 3 continued to receive their randomly assigned dose, in a double-blind fashion, through month 6. Study assignments were revealed to all other patients at month 3, and the doses were increased by 300  $\mu\text{g}$  twice daily. At month 6, patients entered an open-label phase that lasted through month 12; during this phase, if the urinary free cortisol level was above the upper limit of the normal range, the dose could be increased by 300  $\mu\text{g}$  twice daily (maximum, 1200  $\mu\text{g}$  twice daily) at any time. Throughout the 12-month treatment period, if dose adjustment was required because of adverse events, the dose could be reduced in steps of 300  $\mu\text{g}$  twice daily. After month 12, patients could enter an open-label extension of the trial.

### END POINTS AND ASSESSMENTS

The primary end point of the study was a normalized urinary free cortisol level. Patients were considered to have normalized urinary free cortisol if the level was at or below the upper limit of the normal range at month 6 without a prior dose increase.

Prespecified secondary efficacy end points were a urinary free cortisol level at or below the upper limit of the normal range at months 3, 6, and 12, regardless of dose adjustment; partial control of hypercortisolism (a urinary free cortisol level above the upper limit of the normal range but reduced by  $\geq 50\%$  from baseline); levels of plasma corticotropin, urinary free cortisol, and serum and salivary cortisol over time; changes in clinical signs and symptoms; quality of life; and safety.

The urinary free cortisol level, assessed monthly for 6 months and every 3 months thereafter, was calculated as the mean value of three or four samples, collected within a 14-day period at months 3, 6, and 12 and as the mean value in two consecutive-day samples at other time points. If the measurement at month 6 was missing, the

most recent available value (on the basis of  $\geq 3$  collections) between months 3 and 6 was carried forward. Patients for whom valid measurements were not available and those who discontinued the study medication before month 3 were considered to have uncontrolled hypercortisolism (see the Supplementary Appendix for details of serum cortisol and plasma corticotropin collection and assay).

Systolic and diastolic blood pressure, body weight, body-mass index, and levels of triglycerides and low-density lipoprotein (LDL) cholesterol were assessed monthly. At baseline and at months 6 and 12, a reviewer at each site assessed patients for signs of hypercortisolism (facial rubor and supraclavicular and dorsal fat pads) by scoring photographs on a scale from 0 to 3 (with 0 indicating

**Table 1. Baseline Demographic and Clinical Characteristics of the Overall Study Population and Each Dose Group.\***

Characteristic	Pasireotide 600 $\mu\text{g}$ Twice Daily (N=82)	Pasireotide 900 $\mu\text{g}$ Twice Daily (N=80)	Overall (N=162)
Female sex — no. (%)	62 (76)	64 (80)	126 (78)
Age			
Mean — yr	41	40	40
Range — yr	18–67	19–71	18–71
$\geq 65$ yr — no. (%)	4 (5)	1 (1)	5 (3)
Race or ethnic group — no. (%) <sup>†</sup>			
White	65 (79)	62 (78)	127 (78)
Black	2 (2)	1 (1)	3 (2)
Asian	10 (12)	10 (12)	20 (12)
Native American	2 (2)	2 (2)	4 (2)
Other	3 (4)	4 (5)	7 (4)
Missing data	0	1 (1)	1 (1)
Time since diagnosis — mo			
Mean	53.4	54.7	54.0
Range	0.1–341.8	0.1–372.1	0.1–372.1
Previous treatment — no. (%)			
Surgery	64 (78)	64 (80)	128 (79)
Medication	36 (44)	42 (52)	78 (48)
Pituitary irradiation	3 (4)	4 (5)	7 (4)
Urinary free cortisol			
Baseline measurement — no. of patients (%)	77 (94)	76 (95)	153 (94)
$\geq 3$ samples collected — no. of patients (%)	77 (94)	76 (95)	153 (94)
Level — nmol/24 hr			
Mean	1156	782	970
Median	730	487	565
Range	220–22,944	195–6123	195–22,944

Characteristic	Pasireotide 600 $\mu$ g Twice Daily (N=82)	Pasireotide 900 $\mu$ g Twice Daily (N=80)	Overall (N=162)
Severity of hypercortisolism — no. (%)‡			
Mild	12 (15)	14 (18)	26 (16)
Moderate	26 (32)	40 (50)	66 (41)
Severe	28 (34)	13 (16)	41 (25)
Very severe	11 (13)	9 (11)	20 (12)
Missing data	5 (6)	4 (5)	9 (6)
Months of study completed — no. of patients (%)§			
3	68 (83)	65 (81)	133 (82)
6	54 (66)	53 (66)	107 (66)
12	39 (48)	39 (49)	78 (48)

\* The study was not powered to detect significant differences between dose groups.

† Race or ethnic group was determined by the site investigator and recorded on the case-report forms.

‡ Mild hypercortisolism was defined as an elevated urinary free cortisol level that did not exceed 2 times the upper limit of the normal range (ULN) (145 nmol per 24 hours [52.5  $\mu$ g per 24 hours]), moderate hypercortisolism as a level that was more than 2 times to 5 times the ULN, severe hypercortisolism as a level that was more than 5 times to 10 times the ULN, and very severe hypercortisolism as a level that was more than 10 times the ULN.

§ In the first 3 months, 29 patients discontinued the study: 13 because of adverse events, 4 because of lack of efficacy, 9 because of withdrawal of consent, and 3 because of a protocol violation. By month 6, an additional 26 patients had discontinued the study: 7 because of adverse events, 15 because of lack of efficacy, and 4 because of withdrawal of consent. By month 12, an additional 29 patients had discontinued the study: 6 because of adverse events, 18 because of lack of efficacy, 4 because of withdrawal of consent, and 1 because of a protocol violation.

no signs, 1 mild hypercortisolism, 2 moderate hypercortisolism, and 3 severe hypercortisolism). The reviewers were physicians who were experienced in treating patients with Cushing's disease but who were not involved in other aspects of the study, had no direct contact with the study patients, and were unaware of both the study-group assignments and the timing of the photographs (whether they were taken during or after treatment). Health-related quality of life was measured with the use of the CushingQoL questionnaire (in which scores range from 0 to 100, with higher scores indicating better quality of life).<sup>13</sup> Tumor volume was assessed by magnetic resonance imaging (MRI) at baseline and at months 6 and 12 (or at the time of study-drug discontinuation in the case of early withdrawal from the study) and evaluated by a central reader (see the Supplementary Appendix).

At each visit, hematologic and blood biochemical measurements, urinalysis, and electrocardiography were performed, and vital signs and physical condition were assessed. Ultrasonography of the gallbladder was performed at baseline and at months 3, 6, and 12. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0.<sup>14</sup>

#### STATISTICAL ANALYSIS

The proportion of patients with a urinary free cortisol level at or below the upper limit of the normal range was calculated for the intention-to-treat population at all time points. With a null hypothesis that no more than 15% of patients would meet the primary end point and an alternative hypothesis that 30% would meet the primary end point, we calculated that enrollment of 146 patients would provide 87% power to show statistical significance for each of the two within-group tests. Patients were grouped by randomly assigned dose. If the lower bound of the 95% confidence interval for a dose group was greater than the predetermined 15%, that group was considered to have met the primary end point. Changes in biochemical measures and signs and symptoms over time were assessed according to the number of patients with data that could be evaluated at each time point. Safety was assessed up to the data cutoff date. The study was not powered to detect statistically significant differences between dose groups or changes in secondary end points within dose groups; however, post hoc t-tests were performed without multiplicity adjustment to assess the statistical significance within each study group and in the combined group. Secondary end points are sum-

marized descriptively. All statistical tests were two-sided. The statistical analysis plan is included in the protocol.

## RESULTS

### STUDY PATIENTS

At baseline, 78% of patients had moderate-to-very-severe hypercortisolism (Table 1). The proportion of patients with a baseline mean urinary free cortisol level that was more than 5 times the upper limit of the normal range was higher in the 600- $\mu\text{g}$  group than in the 900- $\mu\text{g}$  group (48% vs. 28%). The median baseline urinary free cortisol level in the 600- $\mu\text{g}$  and 900- $\mu\text{g}$  groups was 730 and 487 nmol per 24 hours, respectively.

The mean treatment duration was 10.8 months (range, 0.03 to 37.8). Seventy-eight patients (48%) completed 12 months of treatment (Table 1). Although discontinuations occurred throughout the study, 71% of patients with fully or partially controlled hypercortisolism at month 1 or 2 continued to receive treatment through month 12, as compared with 25% of those with uncontrolled hypercortisolism at months 1 and 2.

The mean daily dose of pasireotide in the 600- $\mu\text{g}$  and 900- $\mu\text{g}$  groups at months 3, 6, and 12 was 1165  $\mu\text{g}$  and 1701  $\mu\text{g}$ , 1353  $\mu\text{g}$  and 1875  $\mu\text{g}$ , and 1569  $\mu\text{g}$  and 1813  $\mu\text{g}$ , respectively. At month 12, 19 patients were receiving pasireotide at a dose of 1200  $\mu\text{g}$  twice daily.

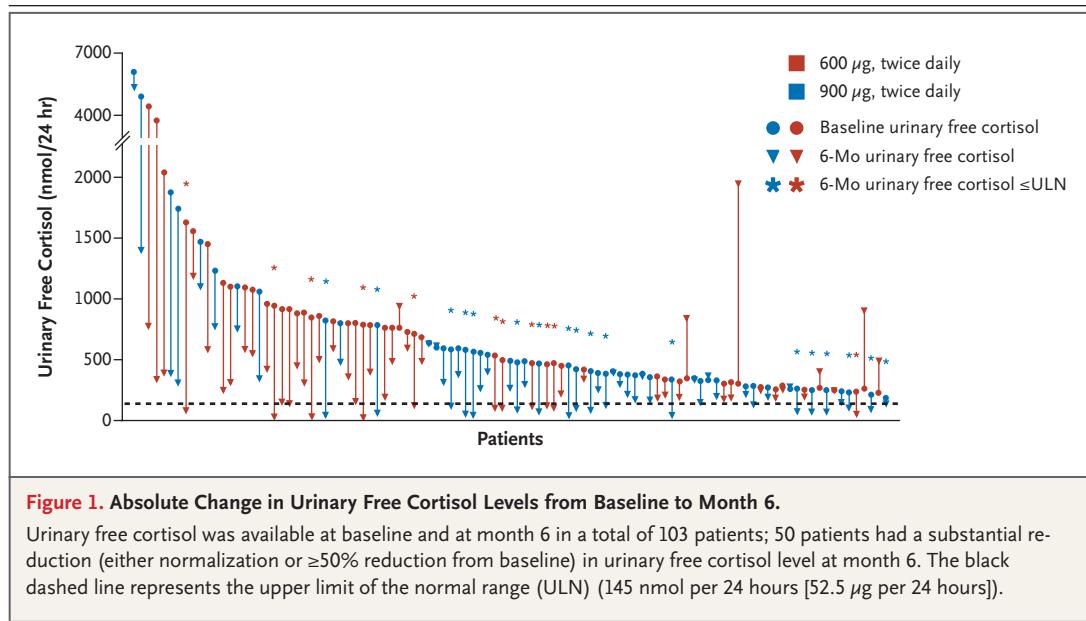
### EFFICACY

#### Urinary Free Cortisol

In the majority of patients, the urinary free cortisol level decreased from baseline to month 6 (Fig. 1). At month 6, 15% (95% confidence interval [CI], 7 to 22) of patients in the 600- $\mu\text{g}$  group and 26% (95% CI, 17 to 36) of those in the 900- $\mu\text{g}$  group had urinary free cortisol levels at or below the upper limit of the normal range without a prior dose increase. The null hypothesis was rejected in the 900- $\mu\text{g}$  group (i.e., the lower bound of the 95% confidence interval for the response rate in the 900- $\mu\text{g}$  group was >15%).

At month 3, 16% (95% CI, 8 to 24) of patients in the 600- $\mu\text{g}$  group and 28% (95% CI, 18 to 37) of those in the 900- $\mu\text{g}$  group had urinary free cortisol levels at or below the upper limit of the normal range; 45 patients (28%) had their dose increased: 29 (35%) in the 600- $\mu\text{g}$  group and 16 (20%) in the 900- $\mu\text{g}$  group. With the inclusion of patients who had an increased dose at month 3, 16% (95% CI, 8 to 24) of patients in the 600- $\mu\text{g}$  group and 29% (95% CI, 19 to 39) of those in the 900- $\mu\text{g}$  group had normalized urinary free cortisol levels at month 6.

At month 12, 13% (95% CI, 6 to 21) of patients in the 600- $\mu\text{g}$  group and 25% (95% CI, 16 to 35) of those in the 900- $\mu\text{g}$  group had urinary free cortisol levels at or below the upper limit of the normal range. In 20 of the 36 patients with normalized urinary free cortisol levels at month 6,



the levels remained normal at month 12. Patients whose dose was reduced to 300  $\mu\text{g}$  twice daily (5 patients) or 600  $\mu\text{g}$  twice daily (6 patients) continued to have normal urinary free cortisol levels. Partial control of hypercortisolism was achieved in 18% and 13% of patients in the 600- $\mu\text{g}$  and 900- $\mu\text{g}$  groups at month 6 and in 16% and 3% at month 12, respectively. Patients with lower baseline urinary free cortisol levels ( $\leq 5$  times the upper limit of the normal range) had a higher rate of response (Fig. 2).

The reduction in mean urinary free cortisol levels was rapid and sustained (Fig. 2, and the Supplementary Appendix). Among the 72 patients with uncontrolled hypercortisolism at months 1 and 2, hypercortisolism remained uncontrolled in 66 patients (92%) at month 6 and in 64 patients (89%) at month 12.

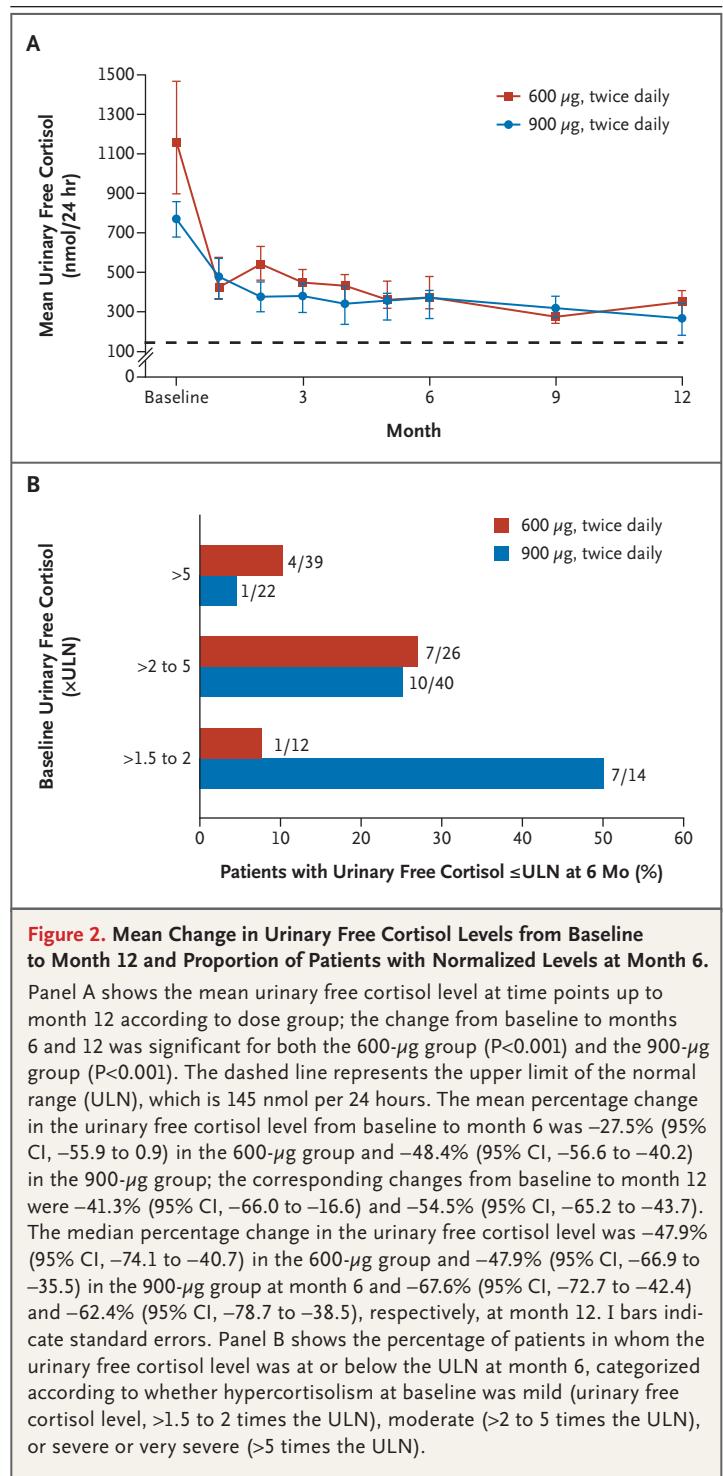
#### Plasma Corticotropin and Serum and Salivary Cortisol

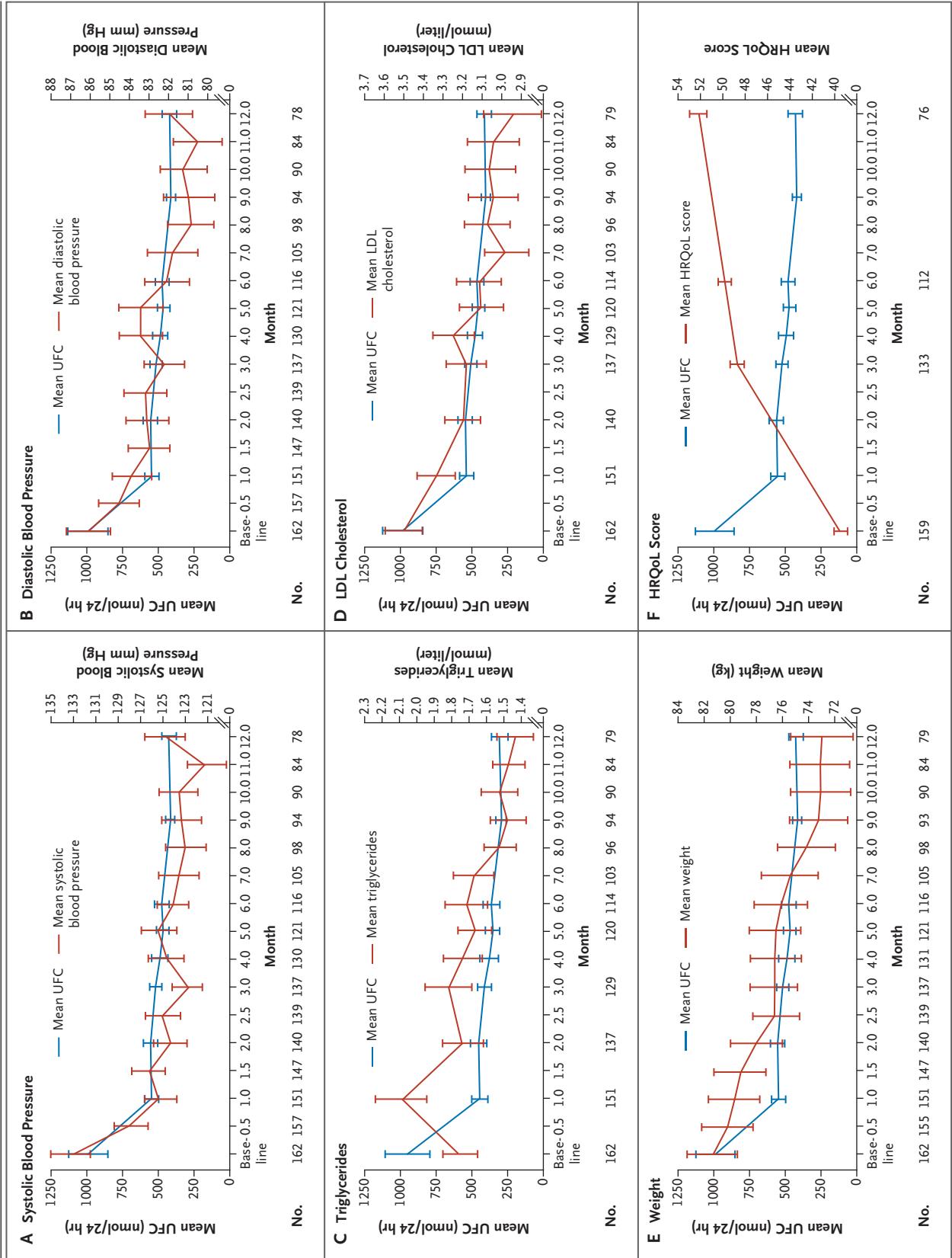
Mean plasma corticotropin and serum and salivary cortisol levels decreased from baseline to month 12 in both dose groups. In the overall population, the mean percentage change in the morning serum cortisol level was  $-7.4\%$  (95% CI,  $-13.4$  to  $-1.5$ ) and  $-13.4\%$  (95% CI,  $-19.7$  to  $-7.0$ ) at months 6 and 12, respectively. The mean percentage change in the midnight salivary cortisol level was  $-3.7\%$  (95% CI,  $-32.5$  to  $25.1$ ) and  $-12.4\%$  (95% CI,  $-32.5$  to  $7.6$ ) at months 6 and 12, respectively. The mean percentage change in the plasma corticotropin level was  $-12.8\%$  (95% CI,  $-20.1$  to  $-5.4$ ) and  $-16.9\%$  (95% CI,  $-27.0$  to  $-6.8$ ) at months 6 and 12, respectively.

#### Signs and Symptoms

As urinary free cortisol levels decreased, clinical improvements were evident at month 6 (see the Supplementary Appendix) and month 12 (Fig. 3). The mean changes from baseline to month 12 were as follows: systolic blood pressure,  $-6.1$  mm Hg (95% CI,  $-9.8$  to  $-2.4$ ;  $P=0.03$ ); diastolic blood pressure,  $-3.7$  mm Hg (95% CI,  $-6.2$  to  $-1.2$ ;  $P=0.03$ ); triglycerides,  $-2$  mg per deciliter ( $-0.2$  mmol per liter) (95% CI,  $-27$  to  $0$  mg per deciliter [ $-0.3$  to  $0.0$  mmol per liter]); LDL cholesterol,  $-15$  mg per deciliter ( $-0.4$  mmol per liter) (95% CI,  $-23$  to  $-8$  mg per deciliter [ $-0.6$  to  $-0.2$  mmol per liter];  $P<0.001$ ); weight,  $-6.7$  kg (95% CI,  $-8.0$  to  $-5.4$ ;  $P<0.001$ ); and health-related quality of life score, 11.1 points (95% CI, 6.8 to 15.5). At months 6 and

12, facial rubor and supraclavicular and dorsal fat pads were diminished in patients with available photographs (see the Supplementary Appendix).





**Figure 3 (facing page). Changes in Signs and Symptoms of Cushing's Disease and Urinary Free Cortisol (UFC) Levels over Time in the Overall Study Population.**

Panel A shows systolic blood pressure, Panel B diastolic blood pressure, Panel C triglycerides, Panel D low-density lipoprotein (LDL) cholesterol, Panel E body weight, and Panel F health-related quality-of-life (HRQoL) score. HRQoL was measured with the use of the CushingQoL questionnaire (in which scores range from 0 to 100, with higher scores indicating better quality of life). The numbers of patients included in analyses of mean UFC levels at various time points were as follows: 153 at baseline, 144 at 1 month, 132 at 2 months, 131 at 3 months, 123 at 4 months, 116 at 5 months, 111 at 6 months, 93 at 9 months, and 77 at 12 months. The corresponding numbers of patients included in analyses of the mean values for signs, symptoms, and quality-of-life scores are shown beneath each graph. I bars indicate standard errors for both UFC level and clinical signs and symptoms. To convert the values for triglycerides to mg per deciliter, divide by 0.01129. To convert the values for LDL cholesterol to mg per deciliter, divide by 0.02586.

#### Tumor Volume

Seventy-five patients (46%) had a measurable pituitary tumor on MRI at baseline. At month 12, the mean percentage change in tumor volume was  $-9.1\%$  (95% CI,  $-46.3$  to  $28.0$ ) in the 600- $\mu\text{g}$  group and  $-43.8\%$  (95% CI,  $-68.4$  to  $-19.2$ ) in the 900- $\mu\text{g}$  group (see the Supplementary Appendix).

#### SAFETY

The safety profile of pasireotide in our study was similar to the safety profile of other somatostatin analogues with respect to adverse events such as gastrointestinal symptoms and gallstones, except that there was a higher frequency of hyperglycemia with pasireotide. Most drug-related adverse events were grade 1 or 2 and resolved without dose modification. The most frequently reported grade 3 or 4 adverse events were hyperglycemia and diabetes mellitus, occurring in 13% and 7% of patients, respectively (Table 2). Overall, 118 of 162 patients (73%) had a hyperglycemia-related adverse event; 6% of patients discontinued treatment because of a hyperglycemia-related adverse event. Preexisting diabetes or impaired glucose tolerance increased the risk of hyperglycemia-related adverse events.

Glucose and glycated hemoglobin levels increased soon after initiation of treatment with pasireotide but stabilized after initiation of glucose-lowering therapy. The mean glycated hemoglobin level increased from 5.8% (in 78 patients) and

5.8% (in 76 patients) in the 600- $\mu\text{g}$  and 900- $\mu\text{g}$  groups, respectively, at baseline to 7.2% (59 patients) and 7.4% (56 patients) at month 6 and to 7.3% (40 patients) and 7.2% (38 patients) at month 12 (see the Supplementary Appendix). At baseline, 55 patients (34%) had diabetes and 39 (24%) had prediabetes (see the Supplementary Appendix for definitions). At study end, 51 (48%) of the 107 patients who did not have diabetes at baseline had a glycated hemoglobin level of 6.5% or more. No cases of diabetic ketoacidosis or hyperosmolar hyperglycemia were reported.

A new antidiabetic medication was initiated in 74 of the 162 patients. In patients not receiving glucose-lowering medications at baseline, at least one medication was started during the study in 53 of 129 patients (41%); 21 of 33 patients (64%) receiving antidiabetic medication at baseline received at least one additional agent. Among patients in whom glucose-lowering therapy was initiated during the study, the mean fasting plasma glucose level fell from 166.2 to 121.5 mg per deciliter (9.2 to 6.7 mmol per liter) in the 600- $\mu\text{g}$  group and from 159.4 to 133.8 mg per deciliter (8.9 to 7.4 mmol per liter) in the 900- $\mu\text{g}$  group.

Hypocortisolism-related adverse events (i.e., clinical symptoms consistent with adrenocortical insufficiency or glucocorticoid withdrawal) were reported in 13 patients (8%). In 11 of the patients, hypocortisolism resolved with a reduction in the pasireotide dose or temporary interruption of treatment, and subsequently, normal urinary free cortisol levels were maintained. Three patients (2%) had a newly occurring prolongation of the corrected QT interval (Fridericia's formula) of more than 480 msec. These events were sporadic, were evident on a single electrocardiogram, and did not require medical intervention or treatment interruption. No patients had a grade 2 or higher arrhythmic disorder. Two patients had syncope, with no notable electrocardiographic changes. Mild (grade 1, or  $<3$  times the upper limit of the normal range) transient elevations in liver enzyme levels were reported in 29% of patients, which in most cases returned to baseline levels with continued pasireotide therapy. No patient had aspartate aminotransferase or alanine aminotransferase levels that were more than 3 times the upper limit of the normal range with a concomitant elevation of the bilirubin level. Of the 137 patients with a normal gallbladder on ultrasonographic examination at baseline, 9 had

**Table 2. Most Frequently Reported Adverse Events (Occurring in  $\geq 10\%$  of Patients in Either Dose Group).\***

Adverse Event	Pasireotide 600 $\mu\text{g}$ Twice Daily (N=82)		Pasireotide 900 $\mu\text{g}$ Twice Daily (N=80)		Overall (N=162)	
	Grade 3 or 4	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4	All Grades
	<i>number of patients (percent)</i>					
Diarrhea	3 (4)	48 (59)	2 (2)	46 (58)	5 (3)	94 (58)
Nausea	1 (1)	38 (46)	3 (4)	46 (58)	4 (2)	84 (52)
Hyperglycemia	8 (10)	31 (38)	13 (16)	34 (42)	21 (13)	65 (40)
Cholelithiasis	1 (1)	25 (30)	1 (1)	24 (30)	2 (1)	49 (30)
Headache	1 (1)	23 (28)	2 (2)	23 (29)	3 (2)	46 (28)
Abdominal pain	1 (1)	19 (23)	2 (2)	20 (25)	3 (2)	39 (24)
Fatigue	1 (1)	12 (15)	2 (2)	19 (24)	3 (2)	31 (19)
Diabetes mellitus	6 (7)	13 (16)	6 (8)	16 (20)	12 (7)	29 (18)
Nasopharyngitis	0	10 (12)	0	11 (14)	0	21 (13)
Alopecia	0	10 (12)	0	10 (12)	0	20 (12)
Asthenia	2 (2)	13 (16)	2 (2)	5 (6)	4 (2)	18 (11)
Glycated hemoglobin elevation	1 (1)	10 (12)	0	8 (10)	1 (1)	18 (11)
ALT elevation	1 (1)	11 (13)	3 (4)	6 (8)	4 (2)	17 (10)
GGT elevation	4 (5)	10 (12)	2 (2)	7 (9)	6 (4)	17 (10)
Peripheral edema	0	9 (11)	0	8 (10)	0	17 (10)
Upper abdominal pain	0	10 (12)	0	6 (8)	0	16 (10)
Decreased appetite	0	7 (9)	0	9 (11)	0	16 (10)
Hypercholesterolemia	0	7 (9)	0	9 (11)	0	16 (10)
Hypoglycemia	3 (4)	12 (15)	0	3 (4)	3 (2)	15 (9)
Type 2 diabetes mellitus	4 (5)	10 (12)	3 (4)	5 (6)	7 (4)	15 (9)
Anxiety	0	5 (6)	0	9 (11)	0	14 (9)
Influenza	0	9 (11)	0	5 (6)	0	14 (9)
Insomnia	0	3 (4)	0	11 (14)	0	14 (9)
Myalgia	1 (1)	10 (12)	0	4 (5)	1 (1)	14 (9)

\* Adverse events were classified as grade 1 (mild), grade 2 (moderate), grade 3 (severe), or grade 4 (life-threatening or disabling). ALT denotes alanine aminotransferase, and GGT  $\gamma$ -glutamyltransferase.

detectable sludge and 27 had gallstones at the most recent assessment; 6 underwent cholecystectomy.

There were no deaths during treatment. Forty patients had serious adverse events, as defined in the Supplementary Appendix. Nine patients had a glucose-related serious adverse event (five had diabetes mellitus and four had hyperglycemia). Two patients had a serious adverse event related to hypocortisolism. One patient with a history of hypertension and uncontrolled hypothyroidism had a serious adverse event related to prolongation of the corrected QT interval (Bazett's formula). Four patients had cholelithiasis and underwent intervention or hospitalization.

## DISCUSSION

This randomized, double-blind trial showed that 50 of 103 patients had a substantial reduction (either normalization or  $\geq 50\%$  reduction from baseline) in the urinary free cortisol levels at month 6, including patients with very high baseline values. The majority of patients had moderate-to-severe hypercortisolism at baseline; the mean baseline level was approximately 6.5 times the upper limit of the normal range (78% of patients had a urinary free cortisol level that was more than 2 times the upper limit of the normal range). Normalization of urinary free cortisol was more likely to be

achieved in patients with lower baseline levels than in patients with higher baseline levels; however, pasireotide also decreased the urinary free cortisol level in patients with severe hypercortisolism. Although urinary free cortisol levels remained stable in selected patients whose dose of pasireotide was reduced, the results of this trial cannot be used to determine whether normal cortisol levels could have been achieved with a lower starting dose.

Urinary free cortisol levels decreased quickly, with a median reduction of approximately 50% by month 2, and remained stable in both groups, indicating a continued therapeutic benefit. Patients unlikely to have a response to pasireotide may be identified within the first few months of treatment; in our study, most patients (approximately 90%) whose hypercortisolism was uncontrolled at months 1 and 2 continued to have uncontrolled hypercortisolism at months 6 and 12. Additional medical therapy in combination with pasireotide may be beneficial for patients in whom normal cortisol levels are not achieved. Cabergoline alone or in combination has shown efficacy in small studies,<sup>15-19</sup> including a study in which pasireotide was given alone or in combination with cabergoline with or without ketoconazole.<sup>19</sup>

The reduction in urinary free cortisol levels in response to pasireotide was accompanied by reductions in serum cortisol and plasma corticotropin levels, as well as improvements in signs and symptoms of Cushing's disease. Body weight, systolic and diastolic blood pressure, and LDL cholesterol levels were significantly reduced, and scores for health-related quality of life improved. Improvements in signs and symptoms were not limited to patients in whom a normal urinary free cortisol level was achieved, suggesting that a reduction in the cortisol level may be associated with a long-term clinical benefit. Additional studies are warranted because concomitant medication changes were not monitored in our study, and there was no

placebo group. A placebo-controlled trial of treatment for Cushing's disease was considered to be unethical, and there is no approved medical therapy, which precluded an active comparator group.

As with other somatostatin analogues, the most common adverse events were related to transient gastrointestinal discomfort. Hyperglycemia-related adverse events occurred in 73% of patients, and 6% of patients discontinued the study treatment because of such events. Glucose and glycated hemoglobin levels increased soon after the initiation of treatment with pasireotide, necessitating the administration of medications to manage these complications. Preexisting diabetes or impaired glucose tolerance increased the risk of hyperglycemia-related adverse events. In patients with Cushing's disease, alterations in insulin sensitivity that are associated with hypercortisolism often result in hyperglycemia, diabetes mellitus, or both. Data from studies involving healthy volunteers suggest that pasireotide-induced hyperglycemia is a result of decreased insulin and incretin secretion, whereas insulin sensitivity is unaffected.<sup>20</sup> In the current study, hyperglycemia occurred despite declining cortisol levels. Blood glucose should be monitored in pasireotide-treated patients, with special attention to patients with impaired glucose tolerance or diabetes mellitus. If blood glucose levels increase, appropriate treatment should be initiated promptly.

In conclusion, elevated cortisol levels in patients with Cushing's disease were significantly reduced during treatment with pasireotide, a finding that supports the potential use of this agent as a pituitary-specific treatment for Cushing's disease.

Supported by Novartis Pharma.

Disclosure forms provided by the authors are available with the full text of this article at [NEJM.org](http://NEJM.org).

We thank all the investigators who contributed to the study; the study nurses and coordinators and the patients who participated in the study; and Keri Wellington, Ph.D., for editorial assistance with the manuscript.

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