Common Drug Review
Clinical Review Report

August 2015

Drug	pasireotide (Signifor) (0.3 mg/mL, 0.6 mg/mL and 0.9 mg/mL injection)
Indication	Treatment of adult patients with Cushing disease for whom surgery is not an option or for whom surgery has failed, as long as clinical benefit is derived.
Listing request	Treatment of patients with Cushing disease for whom medical therapy is appropriate.
Manufacturer	Novartis Pharmaceuticals Canada Inc.

This review report was prepared by the Canadian Agency for Drugs and Technologies in Health (CADTH). In addition to CADTH staff, the review team included a clinical expert in endocrinology who provided input on the conduct of the review and the interpretation of findings.

Through the CADTH Common Drug Review (CDR) process, CADTH undertakes reviews of drug submissions, resubmissions, and requests for advice, and provides formulary listing recommendations to all Canadian publicly funded federal, provincial, and territorial drug plans, with the exception of Quebec.

The report contains an evidence-based clinical and/or pharmacoeconomic drug review, based on published and unpublished material, including manufacturer submissions; studies identified through independent, systematic literature searches; and patient-group submissions. In accordance with *CDR Update – Issue 87*, manufacturers may request that confidential information be redacted from the CDR Clinical and Pharmacoeconomic Review Reports.

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ABBREVIATIONS

ACTH	adrenocorticotrophic hormone
AE	adverse event
CDR	CADTH Common Drug Review
CI	confidence interval
DB	double-blind
FAS	full analysis set
HRQoL	health-related quality of life
MCID	minimal clinically important difference
OL	open-label
QoL	quality of life
SAE	serious adverse event
UFC	urinary free cortisol

EXECUTIVE SUMMARY

Introduction

Cushing disease is a rare disease caused by persistent exposure to excess glucocorticoid due to abnormal secretion of adrenocorticotrophic hormone (ACTH) from a pituitary adenoma.[1,2,2-8] Major clinical signs and symptoms include obesity, hypertension and cardiovascular disease, glucose intolerance, dyslipidemia, fatigue and muscle weakness, various dermatologic manifestations, neuropsychological changes, bone loss, and limited immune function.[1,2,5,7-9] Cushing disease is associated with a decrease in quality of life (QoL) and increased mortality primarily due to cardiovascular complications.[2,5,7,8] First-line treatment is surgical resection of the pituitary tumour;[1,4,5,10-12] however, remission is not always achieved and even when it is, up to 25% of patients will experience recurrence in the long term.[1,5,11,12] Despite poor evidence of efficacy[5] and significant safety concerns, several drugs that have not been approved by Health Canada to treat Cushing disease have been used in these patients in clinical practice.[12]

Pasireotide is a somatostatin analogue that binds with high affinity to several subtypes of somatostatin receptors that are over-expressed by ACTH-producing adenomas involved in Cushing disease.[8,13,14] Pasireotide has a Health Canada indication for the treatment of adult patients with Cushing disease for whom surgery is not an option or for whom surgery has failed, as long as clinical benefit is derived.[13] The maximum recommended dose is 0.9 mg twice daily. The manufacturer has requested that pasireotide be reimbursed for the treatment of patients with Cushing disease for whom medical therapy is appropriate. The objective of this report was to perform a systematic review of the beneficial and harmful effects of pasireotide for the treatment of Cushing disease in adult patients for whom surgery is not an option or for whom surgery has failed.

Results and Interpretation

Included Studies

One manufacturer-sponsored, partially blinded uncontrolled randomized trial was included in the systematic review. Study B2305 (n = 162)[14-18] evaluated the efficacy and safety of pasireotide 0.6 mg twice daily and 0.9 mg twice daily in patients with Cushing disease who are not candidates for surgery. The primary efficacy outcome was the proportion of responders (response rate) at month 6, where a responder was defined as a patient in whom urinary free cortisol (UFC) levels returned to within the normal range *and* in whom the dose of pasireotide was not increased before month 6. The manufacturer used a pre-specified effectiveness threshold of 15% responders per group, which was agreed upon by the US Food and Drug Administration; CADTH Common Drug Review (CDR) reviewers were unable to determine the rationale for the use of this threshold.

Secondary outcomes included the change from baseline in UFC levels, changes in clinical signs and symptoms of Cushing disease, and changes in QoL assessed using a Cushing syndrome health-related QoL questionnaire. Another secondary outcome was the proportion of patients characterized as being controlled, partially controlled, or uncontrolled responders based on UFC levels at month 6, regardless of dose increases:

- Controlled responders: Month 6 UFC levels were within the upper limit of the normal range.
- Partially controlled responders: Month 6 UFC levels were above the upper limit of the normal range but were decreased by at least 50% compared with baseline.
- Uncontrolled responders: Patients neither controlled nor partially controlled at month 6.

Pasireotide was administered on a double-blind (DB) basis for three months. Patients meeting the pre-specified criteria for improvement moved forward in the study with the same DB dosage for an additional three months (i.e., no dose adjustment); the remaining patients were unblinded at month 3 and were required to increase the dose of pasireotide by 0.3 mg twice daily. All doses were revealed at month 6, at which time the primary outcome was assessed. After month 6, a subsequent six-month-long open-label (OL) phase commenced. The dose of pasireotide could be increased by 0.3 mg twice daily (up to a maximum dose of 1.2 mg twice daily) during the OL phase if the UFC level was above the normal range, or the dose could be reduced in steps of 0.3 mg twice daily at any time throughout the trial in the event of unacceptable toxicity.

A major limitation with Study B2305 was the lack of a control arm; in particular, the absence of a placebo arm makes it difficult to precisely determine the magnitude of the effect size of pasireotide for efficacy and harms. Several other limitations were noted, including high discontinuation rates, variations in dosing, and exclusion of patients with uncontrolled diabetes or clinically significant impairment in cardiovascular or liver function. These limitations could mean that the safety and effectiveness of pasireotide in clinical practice may differ from those observed in the trial.

Efficacy

Changes in Cortisol Levels

The main efficacy outcomes reported in Study B2305 are summarized in Table 1. The response rates after six months were 14.6% (95% confidence interval [CI], 7.0 to 22.3) in the pasireotide 0.6 mg twice daily group and 26.3% (95% CI, 16.6 to 35.9) in the 0.9 mg twice daily group. Therefore, only the 0.9 mg twice daily group met the predefined effectiveness threshold of a 15% response rate. The fact that the 0.6 mg twice daily group failed to meet that threshold might be due to the lower dose used in many patients or high baseline UFC levels (as patients with higher UFC levels do not respond to treatment as well as patients with lower UFC levels). Several patients from both groups had dose adjustments due to inadequate response or unacceptable toxicity, which affects interpretation of the aforementioned results. In addition, high discontinuation rates may also have introduced bias, but the true impact of this limitation on efficacy estimates is uncertain.

Categorization of patients according to clinical response at month 6 revealed that a controlled response (normalized UFC levels regardless of dose increases) was achieved by 15.9% and 28.8% of patients in the 0.6 and 0.9 mg twice daily groups, respectively. Partial control (50% reduction in UFC levels) was achieved by 18.3% and 12.5% of patients in the 0.6 mg and 0.9 mg twice daily groups, respectively. While the normalization of cortisol levels is aligned with clinical treatment goals, the clinical expert consulted by CDR indicated that a 50% reduction in UFC levels is not an appropriate treatment response in clinical practice unless accompanied by meaningful improvements in clinical signs and symptoms of the disease.

There was a substantial decrease in UFC levels in both treatment groups in patients continuing the trial and contributing to this secondary analysis. Specifically, the mean percentage change from baseline in the 0.6 mg twice daily group was –28% (95% CI, –56 to 1) and –41% (95% CI, –66 to –17) at months 6 and 12, respectively. In the 0.9 mg twice daily group, the mean UFC levels were decreased by –48% (95% CI, –57 to –40) and –55% (95% CI, –65 to –44) at months 6 and 12, respectively.

Long-term data were available from the 24-month extension phase of Study B2305. Relatively few (24.7%) patients continued treatment through 24 months. The proportion of patients who met the

criteria for a controlled response decreased from month 12 through month 24 for both groups, and neither group met the pre-specified 15% efficacy threshold at month 24.

Clinical Outcomes

Clinical outcomes were assessed as secondary outcomes in Study B2305, despite these outcomes being of particular importance to patients (based on patient input received by CADTH). The expert consulted by the CDR reviewers indicated that the magnitude of changes in signs and symptoms of Cushing disease observed in Study B2305 would be considered small in clinical practice; however, improvements in blood pressure (–6.8/–4.2 mm Hg in the 0.6 mg twice daily group; –11.4/–5.0 mm Hg in the 0.9 mg twice daily group) and Beck Depression Inventory score (–4.6 ± 9.5 in the 0.6 mg twice daily group; –5.5 ± 8.8 in the 0.9 mg twice daily group), as well as in the Ferriman-Gallwey hirsutism score in the 0.9 mg twice daily group (–2.4 ± 4.7), would likely be considered meaningful to patients. In the 0.6 mg twice daily group, the mean and median change from baseline on the Cushing syndrome health-related QoL questionnaire at month 6 was 6.2 and 7.3, respectively; at month 12, the corresponding values were 9.4 and 10.4. In the 0.9 mg twice daily group, the mean and median change from baseline at month 6 was 12.9 and 8.3, respectively; at month 12, the corresponding values were 12.8 and 9.4. Considering a minimal clinically important difference (MCID) of 10.1 for this instrument,[19,20] patients in the 0.9 mg twice daily group may have achieved clinically meaningful improvements in QoL. However, as noted above, the absence of a control group undermines the rigour of any conclusions regarding the effects of pasireotide on QoL. Moreover, all secondary outcomes were analyzed based on a small number of patients, resulting in substantial variability that limits interpretation of the findings. Finally, it should be noted that how efficacy outcomes related to dosing is somewhat unclear due to the use of a range of doses that varied from 0.3 mg twice daily to 1.2 mg twice daily because of dose adjustments within each group.

Harms

The main harms outcomes are summarized in Table 1. No deaths were reported. A total of 23% and 26% of patients in the 0.6 mg twice daily and 0.9 mg twice daily treatment group experienced serious adverse events (SAEs), respectively; the most common SAEs (< 4% in each treatment group) included pituitary-dependent Cushing syndrome, diabetes mellitus, hyperglycemia, cholelithiasis, and adrenal insufficiency. A total of 98% and 99% of patients in the 0.6 mg twice daily and 0.9 mg twice daily pasireotide treatment groups, respectively, experienced adverse events (AEs); withdrawals due to AEs were 16% and 19% in the 0.6 mg twice daily and 0.9 mg twice daily groups, respectively. While the Health Canada–recommended dose of pasireotide is 0.6 mg twice daily to 0.9 mg twice daily, patients in Study B2305 received dosages that ranged from 0.3 mg twice daily to 1.2 mg twice daily; therefore, the real-world safety profile of pasireotide may differ from what was observed in the trial.

There were several notable safety issues. Glucose metabolism disorders are of particular relevance because these are commonly seen in patients with Cushing disease. Hyperglycemia-related AEs were experienced by 74% and 71% of patients in the 0.6 mg twice daily and 0.9 mg twice daily treatment groups, respectively, despite uncontrolled diabetes at screening being an exclusion criterion. A total of 40% of patients had a last available glycated hemoglobin (A1C) value greater than or equal to 7%, and mean A1C in both groups increased from 5.8% at baseline to more than 7% throughout the trial, which reflects inadequate glycemic control according to the Canadian Diabetes Association Clinical Practice Guidelines[21] and the clinical expert consulted by the CDR review team. More than 40% of patients received concomitant metformin, which was a higher proportion than before the start of the study (18% and 13% of patients in the 0.6 mg twice daily and 0.9 mg twice daily groups respectively). A total of 18% and 25% of patients, respectively, received concomitant sulfonylureas, while 4% of patients in the

0.6 mg twice daily group only received these medications before the trial. There was also a 3.5-fold increase in the proportion of patients using insulin following treatment with pasireotide compared with baseline, where insulin was used by less than 5% of patients overall.

Hepatotoxicity and cardiovascular toxicity were also worthy of note. A total of 33% and 36% of patients in the 0.6 mg twice daily and 0.9 mg twice daily group experienced gall bladder and biliary AEs; 21% and 11% of patients respectively experienced liver safety–related AEs. Bradycardia-related AEs were observed in 18% and 10% of patients randomized to pasireotide 0.6 mg twice daily and 0.9 mg twice daily dosage; the proportions of patients with QT-prolongation AEs reached 7% and 9%, respectively. Hypocortisolism was reported in 9% of patients in the pasireotide 0.6 mg twice daily treatment group and in 8% of patients in the pasireotide 0.9 mg twice daily treatment group; of these, 5% and 6% of patients, respectively, experienced adrenal insufficiency.

Additional safety data from the long-term extension phase of Study B2305 were consistent with the harms observed in the main trial.

Conclusions

The results of a single, partially blinded, uncontrolled study (B2305) indicated that treatment of patients with Cushing disease with pasireotide up to a dose of 0.9 mg twice daily for six months is associated with a response rate that exceeded the predefined effectiveness threshold of a 15% response rate, although the rationale for the use of this threshold is unclear. The 0.6 mg twice daily treatment group in Study B2305 failed to achieve the predefined effectiveness threshold, although patients in this group had high baseline UFC levels and a significant proportion received 0.3 mg twice daily rather than 0.6 mg twice daily pasireotide. Pasireotide treatment was associated with a substantial reduction in UFC levels after 12 months (up to 55% versus baseline), although most patients (60%) discontinued treatment before 12 months. Despite the chronic nature of Cushing disease, whether the efficacy of pasireotide is maintained over the longer term is unclear, because neither treatment group met the effectiveness threshold after 24 months of follow-up and few patients (< 10% after 36 months) continued pasireotide treatment during the long-term follow-up phase of Study B2305. The pasireotide 0.9 mg twice daily treatment group, but not the 0.6 mg twice daily group, had improvements in health-related QoL, which is an outcome that is of particular importance to patients. Pasireotide treatment was also associated with improvement in several of the signs and symptoms of Cushing disease, including a reduction in blood pressure as well as in depression and hirsutism scores. Several notable harms were associated with the use of pasireotide, including hyperglycemia and increased A1C levels, hepatotoxicity, and cardiovascular AEs. The most serious limitations of Study B2305 include the lack of a control arm, high discontinuation rates, and the use of doses that were not in line with the doses recommended for pasireotide.

TABLE 1: SUMMARY OF RESULTS

	Study B2305	
	Pasireotide 0.6 mg (N = 82)	Pasireotide 0.9 mg (N = 80)
Proportion of Responders at Month 6 (UFC Within Normal Range; No Dose Increase)		
N (%)	**12 (14.6)**	**21 (26.3)**
95% CI	**7.0 to 22.3**	**16.6 to 35.9**
Change From Baseline in UFC		
Baseline, Mean ± SD (nmol/24 h)	1,156 ± 2,630	782 ± 926
Month 6	**N = 56**	**N = 55**

	Study B2305	
	Pasireotide 0.6 mg (N = 82)	Pasireotide 0.9 mg (N = 80)
Mean value ± SD (nmol/24 h)	366 ± 330	379 ± 753
Mean % change ± SD (%)	–28 ± 104	–48 ± 30
95% CI	–56 to 1	–57 to –40
Month 12	**N = 39**	**N = 38**
Mean value ± SD (nmol/24 h)	352 ± 394	274 ± 555
Mean % change ± SD (%)	–41 ± 77	–55 ± 32
95% CI	–66 to –17	–65 to –44
Change from Baseline in Cushing Syndrome HRQoL Questionnaire		
Month 6	N = 56	N = 55
Mean change ± SD	6.2 ± 16	12.9 ± 14.8
Median change	7.3	8.3
Month 12	N = 36	N = 38
Mean change ± SD	9.4 ± 17.4	12.8 ± 20.4
Median change	10.4	9.4
Key Harms Outcomes		
Mortality, n (%)	0	0
SAEs, n (%)	19 (23.2)	21 (26.3)
AEs, n (%)	80 (97.6)	79 (98.8)
WDAEs, n (%)	13 (15.9)	15 (18.8)
Notable Harms Outcomes		
Hyperglycemia-related AEs, n (%)	61 (74.4)	57 (71.3)
A1C change		
Baseline, mean ± SD	5.83 ± 0.78	5.76 ± 0.79
Month 6, mean ± SD	7.24 ± 1.42	7.34 ± 1.18
Month 12, mean ± SD	7.25 ± 1.32	7.21 ± 1.60
A1C Subgroups, n (%)[a]		
A1C ≤ 6%	20 (24.4)	19 (23.8)
6% < A1C < 7%	26 (31.7)	25 (31.3)
7% ≤ A1C < 9%	27 (32.9)	27 (33.8)
A1C ≥ 9%	5 (6.1)	5 (6.3)
Gall bladder and biliary AEs, n (%)	27 (32.9)	29 (36.3)
Liver safety–related AEs, n (%)	17 (20.7)	9 (11.3)
Bradycardia-related AEs, n (%)	15 (18.3)	8 (10.0)
QT-prolongation AEs, n (%)	6 (7.3)	7 (8.8)
Hypocortisolism, n (%)	7 (8.5)	6 (7.5)

A1C = glycated hemoglobin; AE = adverse event; CI = confidence interval; HRQoL = health-related quality of life; SAE = serious adverse event; SD = standard deviation; UFC = urinary free cortisol; WDAE = withdrawal due to adverse event.
[a] Based on last available value.
Sources: CADTH Common Drug Review submission 2014; Clinical Study Report 2010.[8,18]

1. INTRODUCTION

1.1 Disease Prevalence and Incidence

Cushing syndrome is an endocrine disorder caused by persistent exposure to excess glucocorticoid.[2,5,7,9] This syndrome encompasses a wide range of underlying causes, as well as a broad spectrum of clinical manifestations.[2,5,7,9] This systematic review focuses on Cushing disease, which is characterized by excessive secretion of adrenocorticotrophic hormone (ACTH), usually from a benign pituitary adenoma.[1-6] Such levels of ACTH stimulate the adrenal glands to release excess glucocorticoids, thus resulting in hypercortisolism.[1-5]

Clinical signs and symptoms of Cushing disease are a direct result of chronic exposure to abnormally high cortisol levels[2,5,7,9] and include central obesity; facial plethora; fatigue and muscle weakness; dermatologic manifestations such as skin atrophy, easy bruising, purple striae and hirsutism; hypertension and cardiovascular disease; glucose intolerance; dyslipidemia; neuropsychological changes; bone loss; and limited immune function.[1,2,5,7-9] The clinical manifestations of Cushing disease generally progress slowly but will definitely increase in severity, may vary substantially from one patient to another, and are mostly not specific to the condition, thus complicating diagnosis; however, the simultaneous development of several symptoms is often characteristic of the disease.[1,2,5,7] Cushing disease has been reported to cause substantial decrease in quality of life (QoL), as well as an increase in mortality, predominantly due to cardiovascular complications.[2,5,7,8]

Cushing disease is considered to be rare, with an incidence that may range between 1 and 25 per million per year.[2,7,8]

1.2 Standards of Therapy

The main goal of therapy in Cushing disease is to normalize cortisol secretion in order to reverse the aforementioned clinical signs and symptoms.[4,10] First-line treatment is surgical resection of the pituitary tumour responsible for excessive ACTH secretion.[1,4,5,10-12] Remission rates range between 65% and 90% when surgery is performed by an experienced pituitary surgeon;[1,4,5,10] however, long-term follow-up suggests that up to 20% to 25% of patients will experience a disease recurrence.[1,5,11,12]

In the presence of recurrent disease, second-line treatment options include the following:[1,4,5,10-12]

- repeating pituitary surgery (remission rates ranging from 40% to 70% and a risk of hypopituitarism)
- pituitary irradiation (remission rates around 60% but delayed response up to several years and risk of hypopituitarism)
- bilateral adrenalectomy (very effective with rapid onset of action but requiring lifelong corticoid replacement therapy and risk of Nelson syndrome)
- medical therapy (discussed in the next paragraph).

Some pharmacological treatment options have been used in clinical practice, including the steroidogenesis inhibitors ketoconazole and mitotane, as well as the dopamine receptor agonist cabergoline. However, none of these drugs have a Health Canada indication for the treatment of Cushing disease, and their use is not supported by sound evidence[5] and is associated with significant potential safety concerns.[12] According to clinical expert opinion, ketoconazole appears to be the most frequently used of these drugs in clinical practice. Its key characteristics are presented in Table 2.

1.3 Drug

Pasireotide is a somatostatin analogue binding with high affinity to several subtypes of somatostatin receptors that are overly expressed by ACTH-producing adenomas involved in Cushing disease.[8,13,14] Somatostatin plays a key role in the regulation of endocrine and exocrine secretion, including the release of ACTH.[8] Activation of these receptors inhibits ACTH release and consequently results in decreased adrenal cortisol production.[8,13,14] Pasireotide has a Health Canada indication for the treatment of adult patients with Cushing disease for whom surgery is not an option or for whom surgery has failed, as long as clinical benefit is derived.[13] Clinical benefit (treatment response) is defined as a decrease of at least 50% in urinary free cortisol (UFC) levels, or improvement in signs or symptoms of the disease, or both.[13] The recommended initial dose of pasireotide is 0.6 mg administered twice daily through subcutaneous injection, but it may be increased to 0.9 mg twice daily based on response and tolerance to the treatment.[13] The maximum effect of pasireotide on UFC is typically seen by two months of treatment; it is recommended that patients who do not experience clinical benefit thereafter be considered for discontinuation.[13]

Indication under review
Treatment of adult patients with Cushing disease for whom surgery is not an option or for whom surgery has failed, as long as clinical benefit is derived.
Listing criteria requested by sponsor
Treatment of patients with Cushing's disease for whom medical therapy is appropriate.

TABLE 2: KEY CHARACTERISTICS OF KETOCONAZOLE AND PASIREOTIDE

	Ketoconazole[22,23]	Pasireotide[8,13,14]
Mechanism of Action	Antifungal drug impairing ergosterol synthesis within fungal and yeast cell membranes. At high doses, ketoconazole also impairs the ability of the adrenal gland to produce cortisol by inhibiting several steroidogenic enzymes.[5]	Somatostatin analogue binding to somatostatin receptors overly expressed by ACTH-producing adenomas, impairing the release of ACTH and decreasing adrenal cortisol production.
Indication	Ketoconazole has no Health Canada indication for the treatment of Cushing disease.	Treatment of adult patients with Cushing disease for whom surgery is not an option or for whom surgery has failed, as long as clinical benefit is derived.
Route of Administration	Oral administration	SC
Usual Dose	200 mg to 1,200 mg daily, in divided doses[1,5,10-12]	Initial dose of 0.6 mg SC b.i.d.; may be increased to 0.9 mg SC b.i.d.
Serious Side Effects and Safety Issues	Liver toxicity, including liver failure and death; CYP3A4 inhibitor (high potential for drug interactions)	Glucose metabolism disorders, liver toxicity, cardiovascular adverse events, hypocortisolism
Other	Ketoconazole tablets are indicated for the treatment of serious or life-threatening systemic fungal infections and should not be considered for mild to moderate infections.	Pasireotide should be prescribed and supervised by a qualified physician. Patients must be enrolled in the Access Program for pasireotide.

ACTH = adrenocorticotrophic hormone; b.i.d. = twice daily; SC = subcutaneous injection.

2. OBJECTIVES AND METHODS

2.1 Objectives

To perform a systematic review of the beneficial and harmful effects of pasireotide for the treatment of Cushing disease in adult patients for whom surgery is not an option or for whom surgery has failed.

2.2 Methods

All manufacturer-provided trials considered pivotal by Health Canada were included in the systematic review. Other studies were selected for inclusion based on the selection criteria presented in Table 3: Inclusion Criteria for the Systematic Review.

TABLE 3: INCLUSION CRITERIA FOR THE SYSTEMATIC REVIEW

Patient Population	Adult patients with Cushing disease for whom surgery is not an option or for whom surgery has failed
Intervention	Pasireotide 0.6 mg b.i.d. or 0.9 mg SC b.i.d.
Comparators	Placebo
Outcomes	**Key efficacy outcomes** • Clinical signs and symptoms of hypercortisolism, including blood pressure, body weight, triglycerides, and cholesterol levels • Improvements in HRQoL determined with validated measures • Changes in cortisol levels (e.g., in the mean 24-hour UFC) **Harms outcomes** Mortality SAEs WDAEs AEs including but not limited to: • glucose metabolism disorders • liver toxicity • cardiovascular AEs • hypocortisolism
Study Design	Published and unpublished RCTs

AE = adverse event; b.i.d. = twice a day; HRQoL = health-related quality of life; RCT = randomized controlled trial; SAE = serious adverse event; SC = subcutaneous injection; UFC = urinary free cortisol; WDAE = withdrawal due to adverse event.

The literature search was performed by an information specialist using a peer-reviewed search strategy.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946–) with In-Process records and daily updates through Ovid, Embase (1974–) through Ovid, and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concept was Signifor (pasireotide).

No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year or by language. Conference abstracts were excluded from the search results.

The initial search was completed on September 24, 2014. Regular alerts were established to update the search until the meeting of the Canadian Drug Expert Committee on January 21, 2015. Regular search updates were performed on databases that do not provide alert services.
Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of CADTH's Grey Matters (http://www.cadth.ca/en/resources/finding-evidence-is/grey-matters) checklist: Health Technology Assessment Agencies, Health Economics, Clinical Practice Guidelines, Drug and Device Regulatory Approvals, Advisories and Warnings, Drug Class Reviews, Databases (Free), and Internet Search. Google and other Internet search engines were used to search for additional Web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information about unpublished studies.

Two CADTH Common Drug Review (CDR) clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion. Included studies are presented in Table 4; excluded studies (with reasons) are presented in APPENDIX 3: EXCLUDED STUDIES.

3. RESULTS

3.1 Findings From the Literature

One study was identified from the literature for inclusion in the systematic review (Figure 1). The included study is summarized in Table 4 and described in Section 3.2. A list of excluded studies is presented in APPENDIX 3: EXCLUDED STUDIES.

FIGURE 1: QUOROM FLOW DIAGRAM FOR INCLUSION AND EXCLUSION OF STUDIES

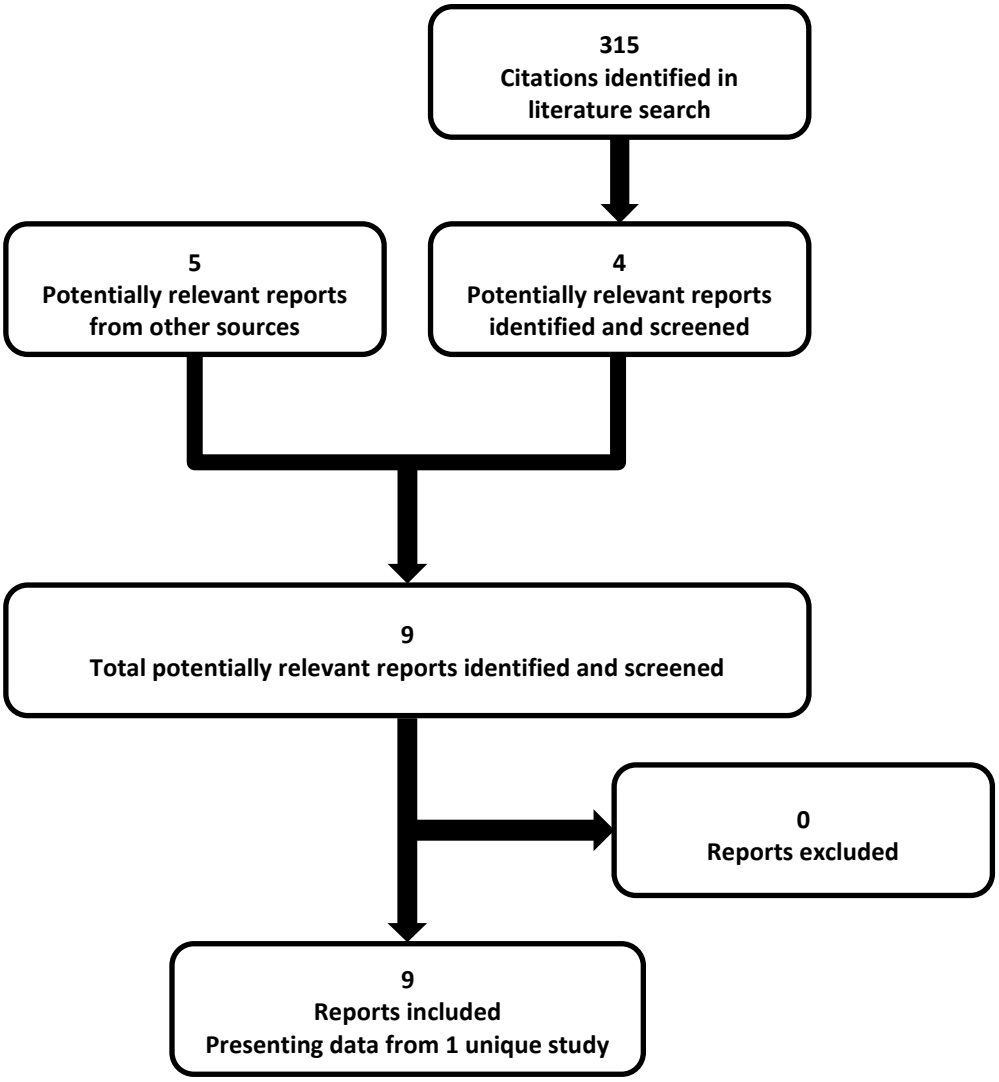


TABLE 4: DETAILS OF INCLUDED STUDIES

		Study B2305
DESIGNS AND POPULATIONS	**Study Design**	DB uncontrolled randomized trial with subsequent OL phase
	Locations	Multi-centre (18 countries): US, Canada (n = 8 Canadians), Europe, South America, Asia
	Randomized (N)	165
	Inclusion Criteria	Patients ≥ 18 years of age with: • confirmed persistent or recurrent Cushing disease[a] or • newly diagnosed Cushing disease and are not candidates for surgery.
	Exclusion Criteria	Diagnostic of Cushing syndrome due to ectopic ACTH secretion or of any other etiology; impairment in cardiovascular or hepatic function; uncontrolled diabetes (A1C > 8%); cholelithiasis; pituitary irradiation within 10 years; recent major surgery.
DRUGS	**Interventions**	**DB Phase** *Months 0 to 3* DB pasireotide 0.6 mg b.i.d. SC ***or*** DB pasireotide 0.9 mg b.i.d. SC **Partially DB Phase** *Months 3 to 6* Responders: DB pasireotide 0.6 mg b.i.d. SC ***or*** DB pasireotide 0.9 mg b.i.d. SC Nonresponders: OL pasireotide 0.9 mg b.i.d. SC ***or*** OL pasireotide 1.2 mg b.i.d. SC **OL Phase** *Months 6 to 12* OL pasireotide 0.6 mg, 0.9 mg, or 1.2 mg b.i.d. SC (dose increases allowed at any time in all groups up to a maximum of 1.2 mg b.i.d.)
DURATION	**Phase**	
	DB	3 months
	Partially DB	3 months
	OL	6 months
	Extension	≥ 12 months
OUTCOMES	**Primary End Point**	Proportion of patients who achieved a UFC level within the upper limit of the normal range in each treatment group at month 6 and who did not have a dose increase before month 6.
	Other End Points	Response to treatment based on change in UFC levels from baseline to month 6; response at months 3 and 12; improvement in clinical signs and symptoms of Cushing disease and in HRQoL.
NOTES	**Publications**	Colao et al. 2012, Pivonello et al. 2014, Webb et al. 2014, Colao et al. 2012[14-17]

A1C = glycated hemoglobin; ACTH = adrenocorticotrophic hormone; b.i.d. = twice daily; DB = double-blind; OL = open-label; HRQoL = health-related quality of life; SC = subcutaneous injection; UFC = urinary free cortisol.

[a] Cushing disease is characterized as persistent if first-line therapy, usually surgical resection of the pituitary tumour,[1,4,5,10-12] has failed. Even when first-line surgery is successful, a disease recurrence may nevertheless happen in the longer term.[1,5,11,12]

Note: 5 additional reports were included.[8,18,24-26]

Sources: CADTH Common Drug Review submission 2014;[8] Colao et al. 2012;[14] Pivonello et al. 2014;[15] Webb et al. 2014;[16] Colao et al. 2012;[17] Clinical Study Report 2010.[18]

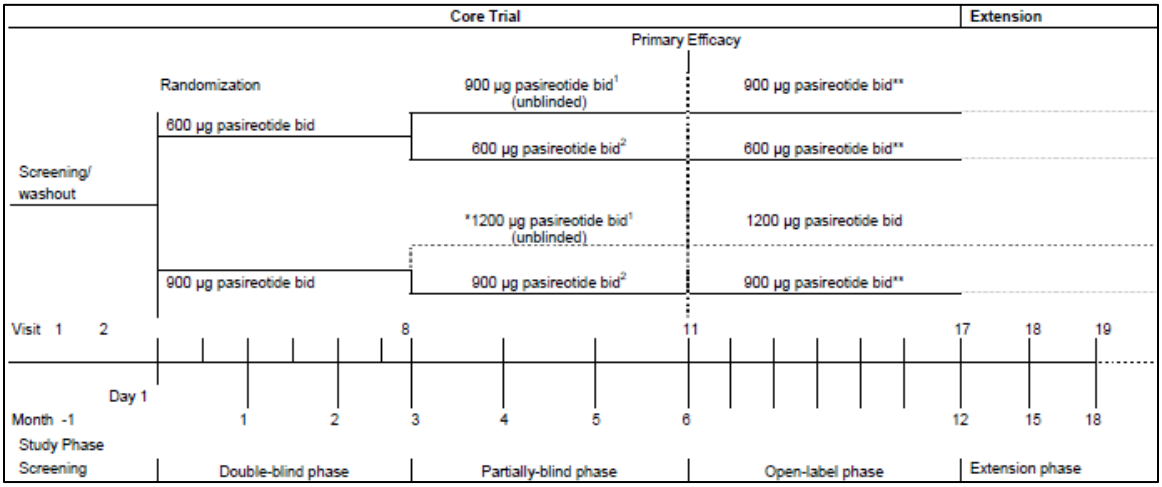
3.2 Included Studies

3.2.1 Description of Studies

One published, manufacturer-sponsored, double-blind (DB) and open-label (OL) uncontrolled randomized trial was included in the systematic review. Study B2305 (n = 162)[14-18] evaluated the efficacy and safety of different dose levels of pasireotide in patients with de novo, persistent, or recurrent Cushing disease who are not candidates for surgery.

As presented in Figure 2, after a washout period of cortisol-lowering medications, pasireotide was administered subcutaneously at a dose of either 0.6 mg twice daily or 0.9 mg twice daily, on a DB basis, for the first three months. At month 3, patients with a mean UFC level within twice the upper limit of the normal range and not exceeding the baseline level moved forward in the study with the same DB dosage for an additional three months. Patients not meeting these criteria were unblinded and were required to increase their dose by 0.3 mg twice daily on an OL basis or to be discontinued from the study. After six months in the study, doses were revealed as patients moved to an additional six-month OL phase, where the dose could be increased by 0.3 mg twice daily (up to a maximum of 1.2 mg twice daily) at any time if the UFC level was above the normal range. Throughout the whole study duration, the dose could be reduced in steps of 0.3 mg twice daily in the event of unacceptable toxicity.

FIGURE 2: STUDY DESIGN SCHEMATIC[8]



bid = twice daily; UFC = urinary free cortisol.
[1] Patients with a UFC exceeding twice the upper limit of the normal range or exceeding baseline levels after 3 months.
[2] Patients with a UFC not exceeding twice the upper limit of the normal range and not exceeding baseline levels after months.
* Permitted dose increase only if patient had tolerated 0.9 mg bid.
** During open-label phase, doses could be increased by 0.3 mg bid. at any time during the study if response was lost.
Source: CADTH Common Drug Review submission 2014.[8]

3.2.2 Populations

a) Inclusion and Exclusion Criteria

Patients were eligible for the trial if they were at least 18 years of age with a confirmed diagnosis of Cushing disease that was persistent or recurrent despite previous surgical treatment or who were not candidates for surgery. Cushing disease was evidenced by a mean UFC greater than or equal to 1.5 times the upper level of the normal range, a morning plasma ACTH level within or above normal range, and a confirmed pituitary source of the disease (ACTH-producing adenoma). Patients on medical treatment for Cushing disease had to complete a washout period before baseline efficacy measurements were

performed. Inclusion of patients with impaired fasting glucose or controlled diabetes mellitus was allowed, with close monitoring and adequate antidiabetic treatment.

Key exclusion criteria included diagnoses of Cushing syndrome due to ectopic ACTH secretion or of any other etiology; uncontrolled diabetes mellitus (defined in the study as A1C > 8%) or hypothyroid; congestive heart failure (Class III or IV), unstable angina, myocardial infarction within one year before starting the study, or any other clinically significant impairment in cardiovascular function; abnormal liver function or liver disease such as cirrhosis or chronic acute or persistent hepatitis; symptomatic cholelithiasis; and coagulation disorders. Patients were also excluded if they had received pituitary irradiation within the last 10 years, as the onset time of the radiation effects might be delayed and could not be determined, or if they had undergone major surgery within one month before starting the study.

b) Baseline Characteristics

Details regarding baseline characteristics are provided in Table 5. Patients enrolled in the trial had a mean age of 40 years, with the overall trial population ranging from 18 to 71 years; however, only 3% of patients were 65 years of age or older. There was a predominance of females and Caucasians in the patient population. Overall, baseline demographics were balanced between treatment groups.

The mean time since diagnosis was 54 months, but there was substantial variation within both treatment groups as expressed by the wide range (0 to 31 years). As for previous treatments for Cushing disease, the majority of patients (79%) had undergone surgery, 48% of patients had received medication, and prior pituitary irradiation was rare (4%). These clinical characteristics were balanced between treatment arms.

Patients assigned to the pasireotide 0.6 mg twice daily treatment group had a median UFC level of 730 nmol/24 h (ranging from 220 up to 22,944), while patients assigned to the pasireotide 0.9 mg twice daily treatment group had a median UFC level of 487 nmol/24 h (ranging from 195 up to 6,123). The severity of hypercortisolism was also less pronounced in the latter.

TABLE 5: SUMMARY OF BASELINE CHARACTERISTICS

Baseline Characteristics	Study B2305		
	Pasireotide 0.6 mg (N = 82)	Pasireotide 0.9 mg (N = 80)	Overall (N = 162)
Age			
Mean, years ± SD	41 ± 13	40 ± 11	40 ± 12
Range, years	18 to 67	19 to 71	18 to 71
≥ 65 years, n (%)	4 (5)	1 (1)	5 (3)
Sex, n (%)			
Male	20 (24)	16 (20)	36 (22)
Female	62 (76)	64 (80)	126 (78)
Race, n (%)			
Caucasian	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 (3)	4 (3)
Other	3 (4)	4 (5)	7 (4)
Missing	0	1 (1)	1 (1)

Baseline Characteristics	Study B2305		
	Pasireotide 0.6 mg (N = 82)	Pasireotide 0.9 mg (N = 80)	Overall (N = 162)
Cushing Disease Status, n (%)			
De novo	15 (18)	12 (15)	27 (17)
Persistent or recurrent	67 (82)	68 (85)	135 (83)
Time Since Diagnostic, Months			
Mean ± SD	53.4 ± 63.8	54.7 ± 62.8	54.0 ± 63.1
Range	0.1 to 341.8	0.1 to 372.1	0.1 to 372.1
Previous Treatment, n (%)			
Surgery	64 (78)	64 (80)	128 (79)
Medication	36 (44)	42 (52)	78 (48)
Pituitary irradiation	3 (4)	4 (5)	7 (4)
UFC			
Level, nmol/24 h	N = 77	N = 76	N = 153
Mean ± SD	1156 ± 2629.8	782 ± 926.4	970 ± 1979.0
Median	730	487	565
Range	220 to 22,944	195 to 6,123	195 to 22,944
Severity of Hypercortisolism			
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)

SD = standard deviation; UFC = urinary free cortisol.
Sources: CADTH Common Drug Review submission 2014; Colao et al. 2012; Clinical Study Report 2010.[8,14,18]

3.2.3 Interventions

Study B2305 evaluated the use of pasireotide administered at a dose of either 0.6 mg twice daily or 0.9 mg subcutaneously twice daily. According to the study design, if response was unsatisfactory, the dose could be increased by 0.3 mg twice daily after three months of treatment and at any time during the OL phase, from months 6 to 12, up to a maximum of 1.2 mg twice daily. Throughout the whole study duration, the dose could be reduced in increments of 0.3 mg twice daily due to adverse events (AEs) without any impact on blinding.

The manufacturer considered the use of placebo as a comparator unethical given the morbidity associated with chronic exposure to hypercortisolism and the known clinical signs and symptoms of Cushing disease. The absence of an active comparator is explained by the lack of approved medical therapy for Cushing disease and by the fact that there is no broadly accepted single drug or combination therapy regimen among the available non-approved therapies.

The use (but not the dose) of concomitant medication and significant non-drug therapies was reported.

3.2.4 Outcomes

The primary efficacy outcome for Study B2305 was the proportion of patients who achieved a UFC level within the upper limit of the normal range (defined in the study as 52.5 mcg/24 h or 145 nmol/24 h)[14] in

each treatment group at month 6 and who did not have a dose increase before month 6. These patients are referred to as responders.

As a supportive analysis, patients were also characterized as being controlled, partially controlled, or uncontrolled based on UFC levels at month 6, regardless of dose increases.

- Controlled responders: Month 6 UFC levels were within the upper limit of the normal range, regardless of whether a patient had a dose increase.
- Partially controlled responders: Month 6 UFC levels were above the upper limit of the normal range but were decreased by at least 50% compared with baseline.
- Uncontrolled responders: Patients neither controlled nor partially controlled at month 6.

Other secondary outcomes included UFC response at months 3 and 12, change from baseline in cortisol levels, time to first response, as well as improvement in clinical signs and symptoms of Cushing disease and in QoL using a Cushing syndrome health-related QoL (HRQoL) questionnaire.

The evaluation of UFC levels was based on the mean of four 24-hour urine collections for UFC; samples were taken within 14 days of each other, within the last 21 days before the start of study for baseline values and immediately before the visit at other time points.

Safety outcomes included AEs, serious adverse events (SAEs), withdrawals due to adverse events, clinical laboratory results, and vital signs.

3.2.5 Statistical Analysis

Sample size was determined based on a null hypothesis of a response rate of 15% and an alternative hypothesis of a response rate of 30%. Indeed, the manufacturer considered that while a response rate of 30% was achievable, a response rate of 15% in this indication would provide significant clinical benefit to patients. Based on these assumptions, enrolment of 146 patients would provide 87% power to demonstrate statistical significance for the within-group testing of the null hypothesis. The trial did not have sufficient power to detect statistically significant differences within groups for any secondary outcomes.[14]

The primary efficacy outcome was summarized using point estimates and 95% confidence intervals (CI). Each dose of pasireotide was considered effective if the lower bound of the 95% CI of the response rate at month 6 was greater than the pre-specified null hypothesis of 15%.

Patients who discontinued before month 3 evaluation were considered nonresponders in the primary outcome analysis. If the month 6 UFC level was missing, it was imputed by the last available measurement between month 3 and month 6. In order to be valid, all UFC measurements had to be based on at least three urine sample collections.

a) Analysis Populations

The manufacturer indicated that efficacy analyses were performed using the full analysis set (FAS) population, which was defined according to the intention-to-treat principle and consisted of all randomized patients who received at least one dose of the study drug. However, this appears to be the case only for the primary outcome; for several secondary outcomes, few patients contributed to the analyses. Patients were analyzed within the treatment group they were assigned to at randomization. The primary efficacy outcome was also analyzed using the per-protocol population, which consisted of a subset of patients in the FAS population who did not have any major protocol deviation before month 6.

The safety population included all randomized patients who received at least one dose of study drug and was identical to the FAS population.

3.3 Patient Disposition

A total of 329 patients were screened for Study B2305, and 165 patients were randomized. However, three patients had no intake of study medication and therefore were not included in the analysis population. Discontinuation rates throughout the trial duration reached 60% of patients in both treatment groups; the most frequent reasons for discontinuation were unsatisfactory therapeutic effect (25% of patients overall) and AEs (17% of patients overall). A total of 34% of patients discontinued from the study before month 6, when the primary outcome was measured. Further details regarding patient disposition are provided in Table 6.

TABLE 6: PATIENT DISPOSITION

Patient Disposition	Study B2305		
	Pasireotide 0.6 mg	Pasireotide 0.9 mg	Overall
Screened, N	329		329
Randomized	83	82	165
Randomized and Treated, n (%)	82 (100)	80 (100)	162 (100)
Discontinued, n (%)	49 (60)	48 (60)	97 (60)
Most Frequent Reasons for Discontinuation, n (%)			
Unsatisfactory therapeutic effect	19 (23)	22 (28)	41 (25)
Adverse events	13 (16)	15 (19)	28 (17)
Patient withdrew consent	13 (16)	11 (14)	24 (15)
Protocol deviation	4 (5)	0	4 (3)
Time of Discontinuation, n (%)			
≤ Month 6	28 (34)	27 (34)	55 (34)
Between months 6 and 12	15 (18)	14 (18)	29 (18)
Analysis Sets			
ITT, N	82	80	162
PP, N	77	76	153
Safety, N	82	80	162

ITT = intention-to-treat population; PP = per-protocol population.
Sources: CADTH Common Drug Review submission 2014; Colao et al. 2012; Clinical Study Report 2010.[8,14,18]

3.4 Exposure to Study Treatments

Exposure to study treatments is presented in Table 7. While the mean daily dose remained similar in the 0.9 mg twice daily pasireotide group, the mean daily dose increased over time in the 0.6 mg twice daily treatment group. Overall, a total of 19 patients were receiving pasireotide at the maximum dose of 1.2 mg twice daily at month 12.[8] The mean duration of exposure was 11 months in both treatment groups.

TABLE 7: EXPOSURE TO STUDY TREATMENT

	Study B2305	
	Pasireotide 0.6 mg (N = 82)	Pasireotide 0.9 mg (N = 80)
Mean Daily Dose, mcg[a]		
Month 3	1,165	1,701
Month 6	1,353	1,875
Month 12	1,569	1,813
Treatment Duration, Months		
Mean ± SD	11 ± 8	11 ± 8
Range	0 to 31	0 to 38

SD = standard deviation.
[a] No standard deviations reported.
Sources: CADTH Common Drug Review submission 2014; Clinical Study Report 2010.[8,18]

3.5 Critical Appraisal

3.5.1 Internal Validity

a) Study Design, Intervention, and Comparator

Study B2305 was an uncontrolled trial, as there is no other approved medical therapy or broadly accepted non-approved drug for Cushing disease and as the manufacturer considered the use of placebo as a comparator unethical. Cushing disease is indeed associated with substantial morbidity due to chronic exposure to high cortisol levels; however, the absence of placebo-controlled data reduces the strength of evidence.

Due to the trial design, secondary outcome conclusions have to be drawn on a range of doses rather than on the two planned group doses of 0.6 mg twice daily and 0.9 mg twice daily. Indeed, the dose of pasireotide could be increased or decreased as needed within treatment groups. While this is consistent with clinical practice, it affects interpretation of the findings. Patients were analyzed within the dose group they were assigned to at randomization, but results show that several of them actually received pasireotide at a higher or at a lower dosage than the group label. Patients with an increased dose are likely to have an increased response to treatment but are also more likely to experience AEs. The opposite is true for patients with a reduced dose. The impact of dose adjustment on the primary outcome differs in that patients with dose increases were considered nonresponders; for the primary outcome, a responder was defined as a patient in whom UFC levels returned to within the normal range *and* in whom the dose of pasireotide was not increased before month 6. Therefore, patients achieving a controlled response in the primary efficacy analysis received either the pasireotide dose assigned at randomization or a reduced dose if they experienced unacceptable toxicity.

A possible source of bias is the use of concomitant medications, especially prohibited medications that could impact cortisol levels. Overall, 98% of patients received concomitant medication, significant non-drug therapies, or both. Prohibited medications were taken by 17% of patients in both groups; the most common were corticosteroids and ketoconazole (no data shown).[18] According to the manufacturer, the use of these prohibited medications may have influenced the response analysis in 21 patients; 8 of these patients were excluded from the per-protocol analysis since the impact was considered major. The issue appears to have been managed by the manufacturer, but the possibility remains that the use of concomitant medication may have confounded the results.

b) Selection, Allocation, and Disposition of Patients

Patients were randomized to treatment groups using a centrally generated allocation sequence. Investigators, assessors, and patients were blinded to treatment allocation for the first three months (DB phase). It is unlikely that patients or the medical team could discover treatment allocation due to differential AEs or changes in response following randomization, as both groups were receiving active treatment with the same drug. Patients meeting the criteria for dose increase at month 3 were unblinded (partially blinded phase), and treatment allocation was revealed for all patients at month 6 (OL phase). It is unlikely that unblinding compromised the evaluation of treatment response for the objective outcomes such as UFC; however, it may have had some impact on the assessment of subjective measures such as QoL.

Baseline UFC levels were higher in the 0.6 mg twice daily treatment group, and patients assigned to this lower pasireotide dosage group appeared to have hypercortisolism that was more severe. Experience from clinical practice suggests that patients with higher UFC levels do not respond to treatment as well as patients with lower UFC levels and are more likely to have their medication titrated.

Discontinuation rates reached 60% in both treatment groups throughout the trial; 34% of patients discontinued from the study before primary outcome measurement at month 6. This is an important limitation to interpretation of the findings, considering that such discontinuation rates may induce clinically significant bias in the effect estimates of pasireotide. The direction of bias is uncertain; however, the fact that discontinuations before month 3 were treated as nonresponders mitigates concerns regarding the primary efficacy outcome analysis.

c) Outcome Measures

The UFC measurement is an accepted method used to assess treatment response for Cushing disease, especially considering the use of four urine samples to obtain mean UFC levels. The Cushing QoL questionnaire is valid, reliable, and easy to use; therefore, the choice of outcome measures is appropriate.

d) Statistical Analysis

The trial had sufficient power to demonstrate statistical significance for the within-group testing of the primary outcome. However, the choice of a 15% response rate threshold seems somewhat arbitrary, as no appropriate justification was provided by the manufacturer.

Imputation of missing data seems appropriate. Nevertheless, several secondary analyses were conducted based on a small number of patients, resulting in substantial variability as expressed by wide 95% CIs and large standard deviations. This issue limited interpretation of the findings.

3.5.2 External Validity

a) Patient Selection

Inclusion and exclusion criteria appeared relevant and reasonable; however, patients with uncontrolled diabetes mellitus were excluded. In addition, various groups of patients with comorbid conditions were excluded as well, including those with clinically significant impairment in cardiovascular function and abnormal liver function. Therefore, the findings from Study B2305 are not generalizable to these categories of patients. Baseline characteristics seem representative of real-life patients according to the clinical expert consulted by CDR reviewers.

b) Treatment Regimen and Length of Follow-Up

The fact that the dose of pasireotide could be increased or decreased as needed within treatment groups is consistent with clinical practice; however, it complicates interpretation of the secondary outcome findings as they are based on a range of doses rather than on the two planned group doses of 0.6 mg twice daily and 0.9 mg twice daily. The maximum study dose of 1.2 mg twice daily is higher than the Health Canada–recommended maximum dosage of 0.9 mg twice daily; overall, 19 patients were receiving pasireotide 1.2 mg twice daily at month 12, which is not aligned with Canadian clinical practice.

There is currently no other approved medical therapy or broadly accepted non-approved drug for Cushing disease, therefore limiting the ability to perform a comparative trial with appropriate treatment in this indication.

Follow-up of six months was considered of appropriate duration in order to see changes in UFC levels and in clinical signs and symptoms of Cushing disease.

c) Outcome Measures

The definition used in Study B2305 for treatment response, i.e., UFC levels within normal range, is consistent with the goals set in clinical practice for UFC levels reduction. The clinical expert consulted indicated that normalization of UFC levels is what clinicians aim for, although it is not easily achieved.

3.6 Efficacy

Only those efficacy outcomes identified in the review protocol are reported here (Section 2.2, Table 3). See APPENDIX 4: DETAILED OUTCOME DATA for detailed efficacy data.

3.6.1 Changes in Cortisol Levels

The primary efficacy outcome in Study B2305 was the proportion of responders, defined as patients who achieved a UFC level within the upper limit of the normal range in each pasireotide dose group at month 6 and who did not have a dose increase before month 6. Treatment was considered effective if the lower bound of the 95% CI was greater than the pre-specified threshold of 15%. Pasireotide 0.6 mg was associated with a response rate of 14.6% at six months (n = 12; 95% CI, 7.0 to 22.3), while the use of pasireotide 0.9 mg was associated with a response rate of 26.3% (n = 21; 95% CI, 16.6 to 35.9). Therefore, the only dosage meeting the pre-specified effectiveness threshold was 0.9 mg twice daily. Results for the FAS population are consistent with those for the per-protocol population.

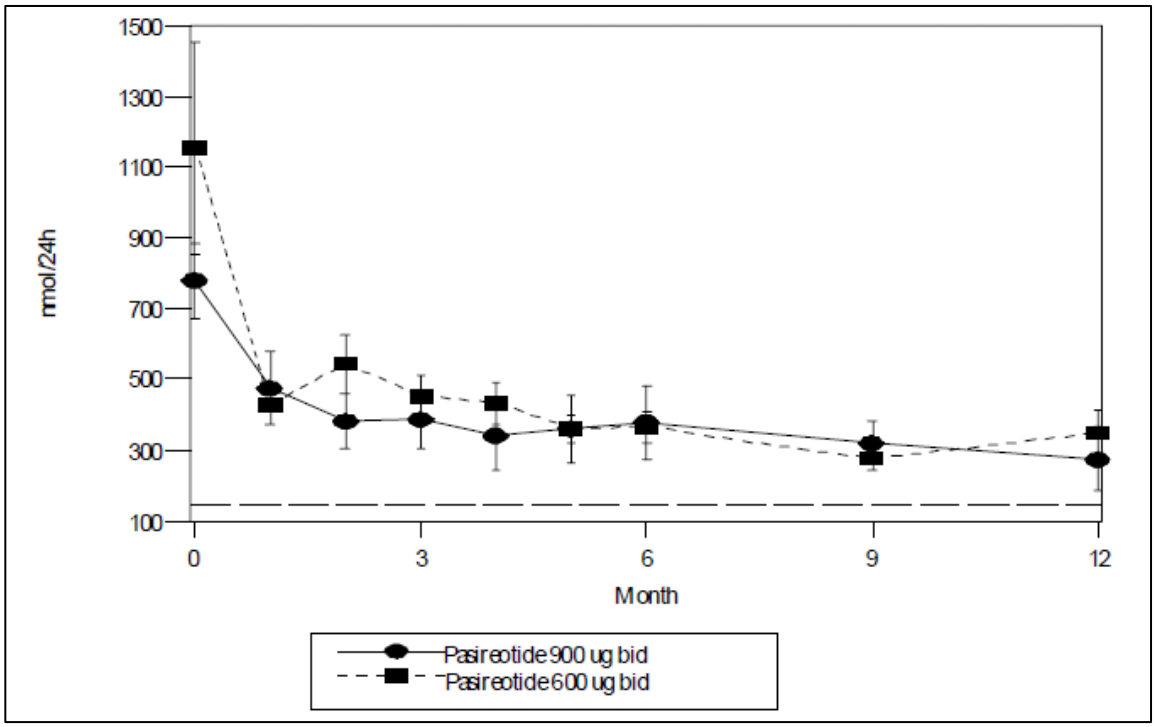
As a supportive analysis, patients were categorized according to clinical response subgroups at month 6, regardless of dose increases. In this analysis, the proportions of patients who achieved a controlled response, i.e., UFC within normal range, was 15.9% (n = 13; 95% CI, 7.9 to 23.8) in the 0.6 mg twice daily treatment group and 28.8% (n = 23; 95% CI, 18.8 to 38.7) in the 0.9 mg twice daily group. Results show that 1 patient in the 0.6 mg twice daily treatment group and 2 patients in the 0.9 mg twice daily group achieved control with a dose increase before month 6.[18] Among patients with a controlled response, 5 patients randomized to the 0.6 mg twice daily treatment group and analyzed accordingly were receiving a reduced dose of pasireotide 0.3 mg twice daily (pre-specified dose adjustment in case of unacceptable toxicity); in the 0.9 mg twice daily treatment group, 5 patients were receiving a reduced dose of pasireotide 0.6 mg twice daily.[8]

The proportions of patients who achieved a partially controlled response, i.e., UFC above normal range but decreased by at least 50% compared with baseline, was 18.3% in the 0.6 mg twice daily treatment

group and 12.5% in the 0.9 mg twice daily group (no 95% CI, reported). Results show that eight patients in the 0.6 mg twice daily treatment group and one patient in the 0.9 mg twice daily group achieved partial control with a dose increase before month 6.[18]

The proportions of responders at months 3, 6, and 12 were similar; however, these were not necessarily the same patients at each time point, as the results show that patients shifted in and out of clinical response.[18] Table 11 indicates that 56% of controlled patients at month 6 remained controlled at month 12; however, 90% of uncontrolled patients at month 6 remained uncontrolled at month 12. Figure 3 illustrates the evolution of UFC throughout the trial and shows a substantial decrease in mean UFC levels in both treatment groups within the first three months of treatment. Mean change from baseline in UFC levels in patients randomized to pasireotide 0.6 mg was –28% (95% CI, –56 to 1) after 6 months; median change reached –48%, suggesting that extreme values may have affected the mean. Mean change from baseline at month 12 was –41% (95% CI, –66 to –17). In patients randomized to pasireotide 0.9 mg, mean change from baseline in UFC levels was –48% (95% CI, –57 to –40) at month 6 and –55% (95% CI, –65 to –44) at month 12.

FIGURE 3: MEAN UFC (NMOL/24 H) FOR MONTH 0 THROUGH MONTH 12



b.i.d. = twice daily; UFC = urinary free cortisol.
Note: Standard errors are displayed.
Sources: CADTH Common Drug Review submission 2014; Clinical Study Report 2010.[8,18]

3.6.2 Improvements in Health-Related Quality of Life

Change in QoL was reported using a Cushing syndrome HRQoL questionnaire. Detailed information is provided in Table 14. In the 0.6 mg twice daily group, mean and median change from baseline at month 6 were 6.2 and 7.3 respectively; at month 12, the corresponding values were 9.4 and 10.4. In the 0.9 mg twice daily group, mean and median change from baseline at month 6 were 12.9 and 8.3, respectively; at month 12, the corresponding values were 12.8 and 9.4. Outcome measures including the

Cushing syndrome HRQoL questionnaire are reviewed in Appendix 5. Considering that a minimal clinically important difference (MCID) of 10.1 was estimated for this instrument,[19,20] the clinical significance of the QoL results in Study B2305 is uncertain.

3.6.3 Clinical Signs and Symptoms of Hypercortisolism

Results for various signs and symptoms of Cushing disease were reported separately, in terms of change from baseline or favourable shift from baseline, and may be found in Table 12 and Table 13. Some level of improvement compared with baseline in the majority of the signs and symptoms was reported in both pasireotide treatment groups after six months of treatment, especially in blood pressure (–6.8/–4.2 mm Hg in the 0.6 mg twice daily group and –11.4/–5.0 mm Hg in the 0.9 mg twice daily group), Beck Depression Inventory score (–4.6 ± 9.5 in the 0.6 mg twice daily group and –5.5 ± 8.8 in the 0.9 mg twice daily group) and Ferriman-Gallwey hirsutism score in the 0.9 mg twice daily group (–2.4 ± 4.7). The magnitude of the improvement for other signs and symptoms is considered small.

TABLE 8: KEY EFFICACY OUTCOMES

		Study B2305	
		Pasireotide 0.6 mg (N = 82)	Pasireotide 0.9 mg (N = 80)
Primary Outcome in the Trial			
Proportion of Responders at Month 6 (UFC Within Normal Range; No Dose Increase)			
N (%)		**12 (14.6)**	**21 (26.3)**
95% CI		**7.0 to 22.3**	**16.6 to 35.9**
Secondary Outcomes in the Trial			
A. Clinical Response Subgroups at Month 6 (Regardless of Dose Increases)			
Controlled: UFC within normal range			
N (%)		13 (15.9)	23 (28.8)
95% CI		7.9 to 23.8	18.8 to 38.7
Partially controlled: UFC above normal range but decreased by ≥ 50% compared with baseline			
N (%)[a]		15 (18.3)	10 (12.5)
B. Change from Baseline in UFC			
Baseline, mean ± SD (nmol/24 h)		1,156 ± 2,630	782 ± 926
Month 6		**N = 56**	**N = 55**
Mean value ± SD (nmol/24 h)		366 ± 330	379 ± 753
Mean % change ± SD (%)		–28 ± 104[b]	–48 ± 30[b]
95% CI		–56 to 1	–57 to –40
Month 12		**N = 39**	**N = 38**
Mean value ± SD (nmol/24 h)		352 ± 394	274 ± 555
Mean % change ± SD (%)		–41 ± 77	–55 ± 32
95% CI		–66 to –17	–65 to –44
C. Proportion of Responders at Other Time Points (UFC Within Normal Range)			
FAS population			
Month 3	N (%)	13 (15.9)	22 (27.5)
	95% CI	7.9 to 23.8	17.7 to 37.3
Month 12	N (%)	11 (13.4)	20 (25.0)
	95% CI	6.0 to 20.8	15.5 to 34.5

	Study B2305	
	Pasireotide 0.6 mg (N = 82)	Pasireotide 0.9 mg (N = 80)
D. Change from Baseline in Cushing Syndrome HRQoL Questionnaire		
Baseline, mean ± SD	41.6 ± 20.4	40.5 ± 20.1
Month 6	**N = 56**	**N = 55**
Mean change ± SD	6.2 ± 16.0	12.9 ± 14.8
Median change	7.3	8.3
Month 12	**N = 36**	**N = 38**
Mean change ± SD	9.4 ± 17.4	12.8 ± 20.4
Median change	10.4	9.4

CI = confidence interval; FAS = full analysis set; HRQoL = health-related quality of life; SD = standard deviation; UFC = urinary free cortisol.
[a] No 95% CI was reported.
[b] Median percentage change was –48% in both treatment groups.
Sources: CADTH Common Drug Review submission 2014; Clinical Study Report 2010.[8,18]

3.7 Harms

Only those harms identified in the review protocol are reported here (see 2.2.1, Table 3). See APPENDIX 4: DETAILED OUTCOME DATA for detailed harms data.

3.7.1 Mortality

No deaths were reported in Study B2305.

3.7.2 Serious Adverse Events

A total of 23% and 26% of patients in the 0.6 mg twice daily and 0.9 mg twice daily pasireotide treatment groups respectively experienced SAEs. The most common SAEs reported included pituitary-dependent Cushing syndrome (4% of patients in each treatment group), diabetes mellitus (1% in the 0.6 mg twice daily group and 4% in the 0.9 mg twice daily group), hyperglycemia (1% and 4%, respectively), cholelithiasis (4% and 1% respectively), and adrenal insufficiency (3% in the 0.9 mg twice daily group only). Further details are presented in Table 15.

3.7.3 Adverse Events

The proportion of patients experiencing AEs was 98% in the 0.6 mg twice daily pasireotide treatment group and 99% in the 0.9 mg twice daily pasireotide treatment group. The most common AEs reported included diarrhea, nausea, hyperglycemia, cholelithiasis, headache, abdominal pain, fatigue, diabetes mellitus and hypoglycemia. Further details are presented in Table 17.

A total of 38% and 30% of patients in the 0.6 mg twice daily and 0.9 mg twice daily pasireotide treatment groups, respectively, experienced AEs requiring dose adjustment or study drug interruption[18] (no further data shown). The proportion of patients experiencing AEs requiring significant additional therapy was 87% in the 0.6 mg twice daily pasireotide treatment group and 93% in the 0.9 mg twice daily pasireotide treatment group. Hyperglycemia (27% and 30% respectively) and diabetes mellitus (13% and 19%, respectively) were among the most common reasons[18] (no further data shown).

3.7.4 Withdrawals Due to Adverse Events

WDAEs reached 16% and 19% respectively in the pasireotide 0.6 mg twice daily and 0.9 mg twice daily treatment groups. The most frequent reasons for WDAEs included gamma-glutamyltransferase increase, hyperglycemia, and diabetes mellitus.

3.7.5 Notable Harms

Detailed information pertaining to harms of particular interest is provided in Table 16.

a) Glucose Metabolism Disorders

A total of 74% and 71% of patients in the 0.6 mg twice daily and 0.9 mg twice daily pasireotide treatment groups, respectively, experienced hyperglycemia-related AEs. Mean glycated hemoglobin increased from 5.8% at baseline to greater than 7% when measured at month 6 and month 12 in both treatment groups. A total of 24% of patients in each group had a last available A1C value less than or equal to 6%; 31% of patients between 6% and 7%; 33% of patients between 7% and 9%; and 6% of patients greater than or equal to 9%. Throughout the trial, 45% and 41% of patients in the 0.6 mg twice daily and 0.9 mg twice daily pasireotide treatment groups, respectively, received concomitant treatment with metformin; 18% and 25% of patients respectively, received concomitant sulfonylureas. These proportions include patients who were taking the medications before the start of the study as well as patients who started receiving the medication only after being treated with pasireotide. Prior to the study, 18% and 13% of patients in the 0.6 mg twice daily and 0.9 mg twice daily groups, respectively, received concomitant treatment with metformin; 4% and 0% of patients, respectively, received concomitant sulfonylureas. Information on the dose of concomitant medications was not collected during the study. There was a 3.5-fold increase in the proportion of patients using insulin following treatment with pasireotide compared with baseline, when insulin was used by less than 5% of patients overall (no further data shown).

b) Liver Toxicity

The proportion of patients experiencing gall bladder and biliary AEs was 33% in the 0.6 mg twice daily pasireotide treatment group and 36% in the 0.9 mg twice daily pasireotide treatment group; the most common AE was cholelithiasis (31% and 30%, respectively). Liver safety–related AEs were experienced by 21% of patients in the 0.6 mg twice daily pasireotide treatment group, while the proportion reached 11% of patients in the 0.9 mg twice daily pasireotide treatment group. The most common liver safety–related AEs were alanine aminotransferase increase (13% and 8%, respectively) and gamma-glutamyltransferase increase (12% and 9%, respectively).

c) Cardiovascular Adverse Events

Bradycardia-related AEs were observed in 18% of patients randomized to pasireotide 0.6 mg twice daily and in 10% of patients randomized to the 0.9 mg dosage; the proportions of patients with QT-prolongation AEs reached 7% and 9%, respectively.

d) Hypocortisolism

Hypocortisolism was reported in 9% of patients in the pasireotide 0.6 mg twice daily treatment group and in 8% of patients in the pasireotide 0.6 mg twice daily treatment group; of these, 5% and 6% of patients, respectively, experienced adrenal insufficiency.

TABLE 9: HARMS

	Study B2305	
	Pasireotide 0.6 mg (N = 82)	Pasireotide 0.9 mg (N = 80)
Mortality, n (%)	**0**	**0**
SAEs, n (%)	**19 (23.2)**	**21 (26.3)**
Most common SAEs:		
Pituitary-dependent Cushing syndrome	3 (3.7)	3 (3.8)
Diabetes mellitus	1 (1.2)	3 (3.8)
Hyperglycemia	1 (1.2)	3 (3.8)
Cholelithiasis	3 (3.7)	1 (1.3)
Adrenal insufficiency	0	2 (2.5)
AEs, n (%)	**80 (97.6)**	**79 (98.8)**
Most common AEs:		
Diarrhea	48 (58.5)	46 (57.5)
Nausea	38 (46.3)	46 (57.5)
Hyperglycemia	31 (37.8)	34 (42.5)
Cholelithiasis	25 (30.5)	24 (30.0)
Headache	23 (28.0)	23 (28.8)
Abdominal pain	19 (23.2)	20 (25.0)
Fatigue	12 (14.6)	19 (23.8)
Diabetes mellitus	13 (15.9)	16 (20.0)
Hypoglycemia	12 (14.6)	3 (3.8)
WDAEs, n (%)	**13 (15.9)**	**15 (18.8)**
Most common reasons:		
GGT increase	3 (3.7)	2 (2.5)
Hyperglycemia	2 (2.4)	3 (3.8)
Diabetes mellitus	2 (2.4)	2 (2.5)
Notable Harms, n (%)		
Glucose metabolism disorders		
Hyperglycemia-related AEs, n (%)	**61 (74.4)**	**57 (71.3)**
A1C change		
Baseline, mean ± SD	5.83 ± 0.78	5.76 ± 0.79
Month 6, mean ± SD	7.24 ± 1.42	7.34 ± 1.18
Month 12, mean ± SD	7.25 ± 1.32	7.21 ± 1.60
A1C subgroups, n (%)[a]		
A1C ≤ 6%	20 (24.4)	19 (23.8)
6% < A1C < 7%	26 (31.7)	25 (31.3)
7% ≤ A1C < 9%	27 (32.9)	27 (33.8)
A1C ≥ 9%	5 (6.1)	5 (6.3)
Liver toxicity		
Gall bladder and biliary AEs, n (%)	27 (32.9)	29 (36.3)
Liver safety–related AEs, n (%)	17 (20.7)	9 (11.3)
Cardiovascular AEs		
Bradycardia-related AEs, n (%)	15 (18.3)	8 (10.0)
QT-prolongation AEs, n (%)	6 (7.3)	7 (8.8)
Hypocortisolism, n (%)	7 (8.5)	6 (7.5)

A1C = glycated hemoglobin; AE = adverse event; GGT = gamma-glutamyltransferase; SAE = serious adverse event; SD = standard deviation; WDAE = withdrawal due to adverse event.

[a] Based on last available value.

Source: Clinical Study Report 2010.[18]

4. DISCUSSION

4.1 Summary of Available Evidence

One published manufacturer-sponsored, DB and OL, uncontrolled randomized trial was included in the systematic review. Study B2305 (n = 162)[14-18] evaluated the efficacy and safety of pasireotide 0.6 mg twice daily and 0.9 mg subcutaneously twice daily in patients with Cushing disease who are not candidates for surgery. Pasireotide was administered on a DB basis for three months. Patients meeting the pre-specified criteria for improvement moved forward in the study with the same DB dosage for an additional three months. Others were unblinded and were required to increase their dose by 0.3 mg twice daily. All doses were revealed at month 6 after the primary outcome measurement for the start of a six-month OL phase. The dose could be increased by 0.3 mg twice daily (up to a maximum dose of 1.2 mg twice daily) at any time if the UFC level was above the normal range or reduced in steps of 0.3 mg twice daily in the event of unacceptable toxicity.

Study B2305 was an uncontrolled trial. The manufacturer considered the use of placebo as a comparator unethical given the morbidity associated with chronic exposure to hypercortisolism and the known clinical signs and symptoms of Cushing disease. The lack of a placebo arm nevertheless reduces the strength of evidence. In addition, several limitations affected interpretation of the findings. High discontinuation rates may have induced clinically significant bias in the effect estimates; the direction of bias is uncertain. Since the dose of pasireotide could be increased or decreased as needed within treatment groups, secondary outcome conclusions have to be drawn on a range of doses rather than on the two planned group doses of 0.6 mg twice daily and 0.9 mg twice daily. The maximum study dose exceeded the Health Canada–recommended maximum dosage. Furthermore, patients were excluded if they had uncontrolled diabetes or clinically significant impairment in cardiovascular or liver function. Therefore, the safety and effectiveness of pasireotide in clinical practice may differ from what was observed in the trial.

4.2 Interpretation of Results

4.2.1 Efficacy

Pasireotide at a dose of 0.9 mg, but not the 0.6 mg dosage, met the pre-specified response rate effectiveness threshold of 15% at month 6. The study definition of response to treatment, i.e., normalization of UFC, was consistent with the goals set in clinical practice for UFC levels reduction, which, according to the consulting expert, is not easily achieved in this patient population. Indeed, the UFC measurement is an accepted method to assess treatment response for Cushing disease. However, clinical outcomes such as signs and symptoms of Cushing disease and QoL, which are of particular importance to patients and clinicians, were assessed only as secondary outcomes. The choice of a 15% response rate threshold seems somewhat arbitrary, as no justification was provided by the manufacturer.

Despite failing to achieve the primary outcome, the 0.6 mg twice daily dose was approved by Health Canada. Baseline UFC levels were high in the pasireotide 0.6 mg twice daily treatment group; experience from clinical practice suggests that patients with higher UFC levels do not respond to treatment as well as patients with lower UFC levels and are more likely to have their medication titrated. Several patients from both groups had dose adjustments due to inadequate response or unacceptable toxicity and received pasireotide at a higher or a lower dosage than the group label. Five out of 13 controlled patients randomized to 0.6 mg twice daily and analyzed accordingly were receiving a reduced dose of 0.3 mg twice daily.

Discontinuation rates were high in both treatment groups and may also have induced clinically significant bias in the effect estimates, reaching 34% at month 6 and 60% throughout the trial. Reasons for discontinuation included unsatisfactory therapeutic effect (25% of patients overall), AEs (17% of patients), and withdrawal of consent (15% of patients). Therefore, long-term efficacy data were characterized by a low proportion of patients continually exposed to pasireotide. The true impact of this significant limitation on efficacy estimates is uncertain.

Long-term maintenance of pasireotide effectiveness on UFC levels is uncertain. Proportions of responders at various time points throughout the 12-month trial were similar; however, these were not necessarily the same patients at each time point, as the results show that patients shifted in and out of clinical response. At month 24, the proportion of patients with a controlled response was 10% in the 0.6 mg twice daily treatment group and 15% in the 0.9 mg twice daily treatment group; the lower bound of the 95% CI was below the 15% efficacy threshold for both dose groups.

The most important outcomes according to patient input were related to improvement in clinical features of Cushing disease and in HRQoL. However, the trial was not designed to detect significant changes in these secondary outcomes, and several analyses were conducted based on a small number of patients. There was small improvement in both groups in signs and symptoms of Cushing disease at month 6. Patients in the 0.9 mg twice daily group may have presented clinically meaningful improvements in QoL based on an MCID of 10.1,[19,20] but our level of confidence in the findings is low due to substantial variability in the QoL measurements. Limitations regarding dose titration and high baseline UFC levels in the 0.6 mg twice daily group also limit interpretation of the findings.

4.2.2 Harms

Most patients experienced AEs, leading to treatment discontinuation in several cases. No deaths were reported. Substantial proportions of patients experienced SAEs that were consistent with the known safety profile of pasireotide. Health Canada warnings have been issued with regard to the risks of hepatotoxicity, cardiovascular events, and hyperglycemia,[13] all of which were notable safety issues in the trial. High proportions of patients experienced gall bladder and biliary AEs, as well as liver safety–related AEs. Bradycardia-related AEs and QT-prolongation AEs were also reported in several patients.

Data pertaining to glucose metabolism disorders are of particular relevance, considering that glucose intolerance is commonly seen in patients with Cushing disease. High proportions of patients in Study B2305 experienced hyperglycemia-related AEs, despite patients with uncontrolled diabetes at screening being excluded from the trial. There was also a substantial increase in mean A1C over the trial duration, which reflects inadequate glycemic control according to the Canadian Diabetes Association Clinical Practice Guidelines[21] and the clinical expert consulted by the CDR reviewers; despite that, a high proportion of patients received concomitant antidiabetic treatment.

While the Health Canada–recommended dose of pasireotide is 0.6 mg twice daily or 0.9 mg twice daily, patients in both treatment groups were receiving pasireotide dosages varying between 0.3 mg twice daily and 1.2 mg twice daily. Overall, 19 patients in the study were receiving an increased dose of 1.2 mg twice daily at month 12, which exceeds Health Canada recommendations. This affects generalizability of the results, as these patients are likely to have a better response to treatment but also a higher incidence of AEs. Therefore, the real-world safety profile of pasireotide may differ from what was observed in the trial.

Additional safety data included an extension phase of Study B2305 and showed that the overall frequency and type of AEs observed in the trial did not change over the long term in the few patients who continued pasireotide through 24 months.

5. CONCLUSIONS

The results of a single, partially blinded, uncontrolled study (B2305) indicated that treatment of patients with Cushing disease with pasireotide up to a dose of 0.9 mg twice daily for six months is associated with a response rate that exceeded the predefined effectiveness threshold of a 15% response rate, although the rationale for the use of this threshold is unclear. The 0.6 mg twice daily treatment group in Study B2305 failed to achieve the predefined effectiveness threshold, although patients in this group had high baseline UFC levels and a significant proportion received 0.3 mg twice daily rather than 0.6 mg twice daily pasireotide. Pasireotide treatment was associated with a substantial reduction in UFC levels after 12 months (up to 55% versus baseline), although most patients (60%) discontinued treatment before 12 months. Despite the chronic nature of Cushing disease, whether the efficacy of pasireotide is maintained over the longer term is unclear, because neither treatment group met the effectiveness threshold after 24 months of follow-up and few patients (< 10% after 36 months) continued pasireotide treatment during the long-term follow-up phase of Study B2305. The pasireotide 0.9 mg twice daily treatment group, but not the 0.6 mg twice daily group, had improvements in HRQoL, which is an outcome that is of particular importance to patients. Pasireotide treatment was also associated with improvement in several of the signs and symptoms of Cushing disease, including a reduction in blood pressure as well as in depression and hirsutism scores. Several notable harms were associated with the use of pasireotide, including hyperglycemia and increased A1C levels, hepatotoxicity, and cardiovascular AEs. The most serious limitations of Study B2305 include the lack of a control arm, high withdrawal rates, and the use of doses that were not in line with the doses recommended for pasireotide.

APPENDIX 1: PATIENT INPUT SUMMARY

This section was summarized by CDR staff based on the input provided by patient groups. It has not been systematically reviewed. It has been reviewed by the submitting patient groups.

1. Brief Description of Patient Group Supplying Input

The Canadian Pituitary Tumours & Related Disorders Network is a newly created (2014) not-for-profit organization. Their first meeting was held under the auspices of the Canadian Organization for Rare Disorders, which continues to provide administrative support. Since the Network is a newly formed organization, they have not received any funding from any pharmaceutical company; however, the Canadian Organization for Rare Disorders has received unrestricted educational grants and conference support from BIOTECanada, Rx&D, Canadian Institutes of Health Research (CIHR), Care for Rare research program, PRISM (a CIHR-funded project at the University of Alberta), Novartis, and Pfizer.

The author of the submission received travel support and an honorarium from Novartis to present at the Global Pituitary Network meeting in 2013.

2. Condition and Current Therapy–Related Information

Information was gathered through focus groups, individual interviews, and a survey (on Survey Monkey). In addition, two websites based in the US (the Pituitary Network Association and the Cushing's Support and Research Foundation) were used to contact US patients who had experience with Signifor, as the Canadian Network was not aware of patients in Canada who had accessed it either through clinical trials or early access programs.

Overall, the Cushing patients who responded tended to be those who were seriously or very seriously affected: 100% said that they currently or in the past had experienced severe weight gain, with about 60% reporting that the weight gain was "very severe." Between 50% and 60% said that they currently or in the past had experienced "very severe" symptoms of bruising, menstrual or sexual dysfunctions, fatigue or weakness, mood disorders, and cognitive difficulties (thinking or memory). In addition, many had developed secondary conditions: More than half said they had severe high blood pressure, nearly half said they had moderate to severe bone loss leading to fractures, and about one-third had developed mild or moderate hyperglycemia.

Patients reported that the effects of Cushing disease on their lives were "devastating," with the disease having negative influences on their physical, psychological, social, and financial well-being. Some patients were no longer able to work or do the things they were able to do before. In some instances, the psychological impact not only brought on mood disorders and depression but negatively affected the patients' self-image to a point of isolation. In addition, many of the women who responded ended up separated from their spouses or partners following the onset of the disease and, consequently, had to take on new roles to cope as single mothers in addition to managing their disease. As one patient stated, "It has ruined my life in many ways. It has changed the way my body looks and how I feel about my body in a very negative way. I struggle every day not to let this disease get the best of me." Patients also reported challenges in getting an accurate diagnosis. About one-third of patients reported that they were no longer able to work, and one-third said they considerably changed what or how much they did.

Impacts were tremendous on both the caregivers and their families. Many families had come to terms with not having regular family or social lives as the patient experienced problems with their self-image

and tended to self-isolate. Caregivers supported their loved ones through their physical and emotional symptoms, and families often had to change their hopes and dynamics.

Surgery, often accompanied by radiation, is considered the most effective treatment for Cushing disease. All respondents to the survey had undergone surgery to remove their pituitary tumour, their adrenal glands, or both; about one-third had received radiation therapy; and 88% had used mitotane or metyrapone (or both) to control cortisol production. Patients' reports on the effectiveness of their surgery ranged from "very," to "somewhat," to "not at all" effective. Patients who received radiation therapy reported it to be "effective" or "very effective." Less than half of the respondents felt that the medication to reduce cortisol levels was effective. About three-quarters of patients who had had surgery and two-thirds who had received radiation therapy reported serious or very serious adverse effects. Most patients required cortisone therapy to treat resulting (pan) hypopituitarism.

Medications are used to control secondary symptoms associated with Cushing disease. About half of respondents said that their medications to control blood pressure were effective; less than half said that medications for mood disorders were effective; and most reported that medications to regulate glucose levels and sexual dysfunction were mostly ineffective. About 75% of respondents had taken or were taking hydrocortisone (replacement therapy), and 5% were receiving growth hormone therapy.

3. Related Information About the Drug Being Reviewed

None of the Canadian patients who responded to the survey had experience with Signifor but most were aware of the drug and had realistic expectations regarding its potential benefits. Most understood that it would be available only for those for whom surgery was not effective or not an option and were also aware of its potential serious side effects (e.g., development of diabetes, need for liver toxicity monitoring). Some patients commented that Signifor could be an alternative to adrenalectomy, which is currently considered a last resort. "I have hoped that it will help to treat the tumour enough so that we don't need adrenalectomies." Most respondents did not think that Signifor was right for them but said that it was very important or important that it be available as an option.

Of the six American patients who had experience with Signifor, two patients stopped using it during the first six months due to lack of decrease in cortisol levels, another stopped due to AEs (stomach pain, diarrhea, nausea, and high glucose levels), and three other patients reported significant weight loss (or loss of fatty tissue), increased energy, less fatigue, and a more "positive" outlook. Their sense of well-being also increased in that they looked better, felt better, and were up for more socializing.

APPENDIX 2: LITERATURE SEARCH STRATEGY

OVERVIEW	
Interface:	Ovid
Databases:	Embase 1974 to present MEDLINE Daily and MEDLINE 1946 to present MEDLINE In-Process & Other Non-Indexed Citations **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Reference Manager.
Date of Search:	September 24, 2014
Alerts:	Bi-Weekly search updates until January 21, 2015
Study Types:	No search filters were applied
Limits:	No date or language limits were used Conference abstracts were excluded
SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
.sh	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
fs	Floating subheading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
#	Truncation symbol for one character
?	Truncation symbol for one or no characters only
adj	Requires words are adjacent to each other (in any order)
adj#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.ot	Original title
.hw	Heading word; usually includes subject headings and controlled vocabulary
.pt	Publication type
.po	Population group [PsycInfo only]
.rn	CAS registry number
.nm	Name of substance word
pmez	Ovid database code; MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE Daily and Ovid MEDLINE 1946 to Present
oemezd	Ovid database code; Embase 1974 to present, updated daily

MULTI-DATABASE STRATEGY			
Embase 1974 to 2014 September 29			
#	**Searches**	**Results**	**Search Type**
1	*signifor/	197	Advanced
2	(Signifor* or pasireotide* or SOM230 or SOM-230).ti,ab.	363	Advanced
3	1 or 2	378	Advanced
4	Conference abstract.pt.	1597688	Advanced
5	3 not 4	274	Advanced
Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present			
#	**Searches**	**Results**	**Search Type**
1	(Signifor* or pasireotide* or SOM-230 or SOM230).ti,ab,ot,sh,hw,rn,nm.	275	Advanced
2	(I4P76SY3N4 or 820232-50-6 or 981T17066 or 396091-73-9).rn,nm.	0	Advanced
3	1 or 2	275	Advanced

OTHER DATABASES	
PubMed	Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.
Trial registries (Clinicaltrials.gov and others)	Same keywords, limits used as per MEDLINE search.

Grey Literature

Dates for Search:	September 15–18, 2014
Keywords: Signifor, pasireotide or cushing*	
Limits: No date or language limits used	

Relevant websites from the following sections of the CADTH grey literature checklist, "Grey matters: a practical tool for evidence-based searching" (http://www.cadth.ca/en/resources/finding-evidence-is/grey-matters) were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Databases (Free)
- Internet Search.

APPENDIX 3: EXCLUDED STUDIES

All publications marked as potentially relevant met the criteria for inclusion in the systematic review; therefore, there were no excluded studies.

APPENDIX 4: DETAILED OUTCOME DATA

TABLE 10: CHANGES IN CORTISOL LEVELS

	Study B2305	
	Pasireotide 0.6 mg (N = 82)	Pasireotide 0.9 mg (N = 80)
Primary Outcome in the Trial		
Proportion of Responders at Month 6 (UFC Within Normal Range; No Dose Increase)		
FAS population	N = 82	N = 80
N (%)	12 (14.6)	21 (26.3)
95% CI	7.0 to 22.3	16.6 to 35.9
PP population	N = 77	N = 76
N (%)	9 (11.7)	20 (26.3)
95% CI	4.5 to 18.9	16.4 to 36.2
Secondary Outcomes in the Trial		
A. Clinical Response Subgroups at Month 6 (Regardless of Dose Increases)		
Controlled: UFC within normal range		
N (%)	13 (15.9)	23 (28.8)
95% CI	7.9 to 23.8	18.8 to 38.7
Partially controlled: UFC above normal range but decreased by ≥ 50% compared with baseline		
N (%)[a]	15 (18.3)	10 (12.5)
Uncontrolled: neither controlled nor partially controlled		
N (%)[a]	54 (65.9)	47 (58.8)
B. Change from Baseline in UFC		
Baseline value	N = 77	N = 76
Mean ± SD (nmol/24 h)	1156 ± 2630	782 ± 926
Month 6	N = 56	N = 55
Mean value ± SD (nmol/24 h)	366 ± 330	379 ± 753
Mean change ± SD (nmol/24 h)	–463 ± 827	–365 ± 556
Mean % change ± SD (%)	–28 ± 104	–48 ± 30
95% CI	–56 to 1	–57 to –40
Median % change (%)	–48	–48
Month 12	N = 39	N = 38
Mean value ± SD (nmol/24 h)	352 ± 394	274 ± 555
Mean change ± SD (nmol/24 h)	–573 ± 941	–351 ± 380
Mean % change ± SD (%)	–41 ± 77	–55 ± 32
95% CI	–66 to –17	–65 to –44
Median % change (%)	–68	–62
C. Proportion of Responders at Other Time Points (UFC Within Normal Range)		
Month 3		
N (%)	13 (15.9)	22 (27.5)
95% CI	7.9 to 23.8	17.7 to 37.3
Month 12		
N (%)	11 (13.4)	20 (25.0)
95% CI	6.0 to 20.8	15.5 to 34.5

CI = confidence interval; FAS = full analysis set; PP = per-protocol; SD = standard deviation; UFC = urinary free cortisol.
[a] No 95% CI was reported.
Sources: CADTH Common Drug Review submission 2014; Clinical Study Report 2010.[8,18]

TABLE 11: SHIFTS IN CLINICAL RESPONSE STATUS FROM MONTH 6 TO MONTH 12

		Type of clinical response at Month 12		
		Controlled	Partially controlled	Uncontrolled
		n = 31	n = 15	n = 116
Type of clinical response at:		n (%)	n (%)	n (%)
600 µg b.i.d.				
Month 6	Controlled (n=13)	6 (46.2)	2 (15.4)	5 (38.5)
	Partially Controlled (n=15)	1 (6.7)	7 (46.7)	7 (46.7)
	Uncontrolled (n=54)	4 (7.4)	4 (7.4)	46 (85.2)
900 µg b.i.d.				
Month 6	Controlled (n=23)	14 (60.9)	1 (4.3)	8 (34.8)
	Partially Controlled (n=10)	4 (40.0)	1 (10.0)	5 (50.0)
	Uncontrolled (n=47)	2 (4.3)	0	45 (95.7)
Overall				
Month 6	Controlled (n=36)	20 (55.6)	3 (8.3)	13 (36.1)
	Partially Controlled (n=25)	5 (20.0)	8 (32.0)	12 (48.0)
	Uncontrolled (n=101)	6 (5.9)	4 (4.0)	91 (90.1)

b.i.d. = twice daily; UFC = urinary free cortisol.
Percentages presented by row.
Patients for whom UFC values were not available at month 12 were considered to be uncontrolled.
Sources: CADTH Common Drug Review submission 2014; Clinical Study Report 2010.[8,18]

TABLE 12: CHANGE FROM BASELINE IN CLINICAL SIGNS OF CUSHING DISEASE AT MONTH 6

	Study B2305	
	Pasireotide 0.6 mg (N = 82)	Pasireotide 0.9 mg (N = 80)
Sitting Systolic BP		
N	59	57
Mean change ± SD (mm Hg)	–6.8 ± 19.4	–11.4 ± 15.9
Sitting Diastolic BP		
N	59	57
Mean change ± SD (mm Hg)	–4.2 ± 13.5	–5.0 ± 11.6
BMI		
N	59	57
Mean change ± SD (kg/m^2)	–1.9 ± 1.6	–2.1 ± 1.7
Waist Circumference		
N	53	54
Mean change ± SD (cm)	–1.9 ± 8.3	–3.4 ± 5.4
Total Cholesterol		
N	59	55
Mean change ± SD (mmol/L)	-0.4 ± 1.2	-0.4 ± 1.0
Triglycerides		
N	59	55
Mean change ± SD (mmol/L)	0 ± 0.9	0.1 ± 1.0
Beck Depression Inventory Score		
N	56	55
Mean change ± SD	–4.6 ± 9.5	–5.5 ± 8.8

	Study B2305	
	Pasireotide 0.6 mg (N = 82)	Pasireotide 0.9 mg (N = 80)
Ferriman-Gallwey Hirsutism Score		
N	44	47
Mean change ± SD	-0.9 ± 2.9	–2.4 ± 4.7
Lumbar BMD		
N	47	39
Mean change ± SD (mg/cm^3)	0 ± 0.1	0 ± 0
Proximal Femur or Total Hip BMD		
N	46	38
Mean change ± SD (mg/cm^3)	0 ± 0.1	0 ± 0.1
Proximal Femur or Femur Neck BMD		
N	46	38
Mean change ± SD (mg/cm^3)	0 ± 0	0 ± 0.1

BMD = bone mineral density; BMI = body mass index; BP = blood pressure; SD = standard deviation.
Sources: CADTH Common Drug Review submission 2014; Clinical Study Report 2010.[8,18]

TABLE 13: PROPORTIONS OF PATIENTS WITH FAVOURABLE SHIFT FROM BASELINE IN SYMPTOMS OF CUSHING DISEASE AT MONTH 6

	Study B2305	
	Pasireotide 0.6 mg (N = 82)	Pasireotide 0.9 mg (N = 80)
Facial Rubor		
N	49	47
n (%)	18 (37)	28 (60)
95% CI	23 to 50	46 to 74
Striae		
N	49	45
n (%)	15 (31)	8 (18)
95% CI	18 to 44	7 to 29
Bruising		
N	47	45
n (%)	8 (17)	8 (18)
95% CI	6 to 28	7 to 29
Supraclavicular Fat Pad		
N	46	47
n (%)	18 (39)	20 (43)
95% CI	25 to 53	28 to 57
Dorsal Fat Pad		
N	47	46
n (%)	18 (38)	18 (39)
95% CI	24 to 52	25 to 53
Muscle Strength		
N	55	55
n (%)	6 (11)	5 (9)
95% CI	3 to 19	2 to 17

CI = confidence interval.
Note: A patient had a favourable shift if the symptom at month 6 was less severe than the symptom at baseline.
Sources: CADTH Common Drug Review submission 2014; Clinical Study Report 2010.[8,18]

TABLE 14: CHANGE IN HRQOL SCORE FROM BASELINE TO MONTH 6 AND MONTH 12

	Study B2305	
	Pasireotide 0.6 mg (N = 82)	Pasireotide 0.9 mg (N = 80)
Baseline Values		
N	81	76
Mean ± SD	41.6 ± 20.4	40.5 ± 20.1
Median	41.7	37.5
Change From Baseline to Month 6		
N	56	55
Mean value ± SD	48.7 ± 21.1	52.0 ± 19.1
Mean change ± SD	**6.2 ± 16.0**	**12.9 ± 14.8**
Median change	**7.3**	**8.3**
Mean % change ± SD (%)	31.3 ± 80.0	73.0 ± 181.1
[95% CI]	[10.4 to 52.3]	[25.2 to 120.9]
Median % change (%)	13.2	30.0
Change From Baseline to Month 12		
N	36	38
Mean value ± SD	50.0 ± 20.3	54.8 ± 18.9
Mean change ± SD	**9.4 ± 17.4**	**12.8 ± 20.4**
Median change	**10.4**	**9.4**
Mean % change ± SD (%)	38.9 ± 77.9	91.8 ± 221.9
[95% CI]	[13.5 to 64.4]	[21.2 to 162.4]
Median % change (%)	26.0	20.6

CI = confidence interval; HRQoL = health-related quality of life; SD = standard deviation.
Note: A Cushing syndrome HRQoL questionnaire was used.
Sources: CADTH Common Drug Review submission 2014; Clinical Study Report 2010.[8,18]

Safety

TABLE 15: MORTALITY AND OTHER SERIOUS ADVERSE EVENTS

Number of Patients With Harms Outcome	Study B2305	
	Pasireotide 0.6 mg (N = 82)	Pasireotide 0.9 mg (N = 80)
Mortality		
n (%)	**0**	**0**
SAEs		
n (%)	**19 (23.2)**	**21 (26.3)**
Most Frequently Reported SAEs: ≥ 2 Patients in at Least One Treatment Group, n (%)		
Pituitary-dependent Cushing syndrome	3 (3.7)	3 (3.8)
Diabetes mellitus	1 (1.2)	3 (3.8)
Hyperglycemia	1 (1.2)	3 (3.8)
Cholelithiasis	3 (3.7)	1 (1.3)
Pituitary tumour benign	1 (1.2)	2 (2.5)
Adrenal insufficiency	0	2 (2.5)
Withdrawal due to SAEs		
n (%)	**3 (3.7)**	**5 (6.3)**

SAE = serious adverse event.
Source: Clinical Study Report 2010.[18]

TABLE 16: NOTABLE HARMS

Number of Patients With Harms Outcome	Study B2305	
	Pasireotide 0.6 mg (N = 82)	Pasireotide 0.9 mg (N = 80)
A. Glucose Metabolism Disorders		
Hyperglycemia-Related AEs, n (%)	**61 (74.4)**	**57 (71.3)**
Diabetes mellitus	13 (15.9)	16 (20.0)
A1C increase	10 (12.2)	8 (10)
Hyperglycemia	31 (37.8)	34 (42.5)
Hypoglycemia	12 (14.6)	3 (3.8)
Type 2 diabetes mellitus	10 (12.2)	5 (6.3)
A1C Change		
Baseline	N = 78	N = 76
Mean ± SD	5.83 ± 0.78	5.76 ± 0.79
Month 6	N = 59	N = 56
Mean ± SD	7.24 ± 1.42	7.34 ± 1.18
Month 12	N = 40	N = 38
Mean ± SD	7.25 ± 1.32	7.21 ± 1.60
A1C Subgroups, n (%)[a]		
A1C ≤ 6%	20 (24.4)	19 (23.8)
6% < A1C < 7%	26 (31.7)	25 (31.3)
7% ≤ A1C < 9%	27 (32.9)	27 (33.8)
A1C ≥ 9%	5 (6.1)	5 (6.3)
Missing	4 (4.9)	4 (5.0)
B. Liver Toxicity		
Gall Bladder and Biliary–Related AEs, n (%)	**27 (32.9)**	**29 (36.3)**
Cholelithiasis	25 (30.5)	24 (30.0)
Liver Safety–Related AEs, n (%)	**17 (20.7)**	**9 (11.3)**
ALT increase	11 (13.4)	6 (7.5)
GGT increase	10 (12.2)	7 (8.8)
C. Cardiovascular AEs		
Bradycardia-Related AEs, n (%)	**15 (18.3)**	**8 (10.0)**
QT-Prolongation–Related AEs, n (%)	**6 (7.3)**	**7 (8.8)**
D. Hypocortisolism		
Hypocortisolism-Related AEs, n (%)	**7 (8.5)**	**6 (7.5)**
Adrenal insufficiency	4 (4.9)	5 (6.3)

A1C = glycated hemoglobin; AE = adverse event; ALT = alanine aminotransferase; GGT = gamma-glutamyltransferase; SD = standard deviation.

[a] Based on last available value.

Source: Clinical Study Report 2010.[18]

TABLE 17: ADVERSE EVENTS

Number of Patients With Harms Outcome	Study B2305	
	Pasireotide 0.6 mg (N = 82)	Pasireotide 0.9 mg (N = 80)
AEs		
n (%)	**80 (97.6)**	**79 (98.8)**
Most Frequently Reported AEs: > 10% in at Least One Treatment Group, n (%)		
Diarrhea	48 (58.5)	46 (57.5)
Nausea	38 (46.3)	46 (57.5)
Hyperglycemia	31 (37.8)	34 (42.5)
Cholelithiasis	25 (30.5)	24 (30.0)
Headache	23 (28.0)	23 (28.8)
Abdominal pain	19 (23.2)	20 (25.0)
Fatigue	12 (14.6)	19 (23.8)
Diabetes mellitus	13 (15.9)	16 (20.0)
Nasopharyngitis	10 (12.2)	11 (13.8)
Alopecia	10 (12.2)	10 (12.5)
Asthenia	13 (15.9)	5 (6.3)
A1C increase	10 (12.2)	8 (10.0)
ALT increase	11 (13.4)	6 (7.5)
GGT increase	10 (12.2)	7 (8.8)
Edema peripheral	9 (11.0)	8 (10.0)
Abdominal pain upper	10 (12.2)	6 (7.5)
Decreased appetite	7 (8.5)	9 (11.3)
Hypercholesterolemia	7 (8.5)	9 (11.3)
Hypoglycemia	12 (14.6)	3 (3.8)
Type 2 diabetes mellitus	10 (12.2)	5 (6.3)
Anxiety	5 (6.1)	9 (11.3)
Influenza	9 (11.0)	5 (6.3)
Insomnia	3 (3.7)	11 (13.8)
Myalgia	10 (12.2)	4 (5.0)
WDAEs		
n (%)	**13 (15.9)**	**15 (18.8)**
Most Frequently Reported Reasons: ≥ 2 Patients in at Least One Treatment Group, n (%)		
GGT increase	3 (3.7)	2 (2.5)
Hyperglycemia	2 (2.4)	3 (3.8)
Diabetes mellitus	2 (2.4)	2 (2.5)
Diarrhea	1 (1.2)	2 (2.5)
ALT increase	0	2 (2.5)

A1C = glycated hemoglobin; AE = adverse event; ALT = alanine aminotransferase; GGT = gamma-glutamyltransferase; WDAE = withdrawal due to adverse event.
Source: Clinical Study Report 2010.[18]

APPENDIX 5: VALIDITY OF OUTCOME MEASURES

1. Objective

To provide information on the characteristics, validity, reliability, and available minimal clinically important differences (MCIDs) of the disease-specific health-related quality of life (HRQoL) questionnaire and the laboratory measurement (primary outcome) used in Study B2305. These include the Cushing Quality of Life (QoL) questionnaire and the 24-hour urinary free cortisol (UFC) measurement.

2. Findings

Currently available outcome measures for Cushing disease or for Cushing syndrome include laboratory or biochemical outcomes (usually primary and secondary outcomes) and those that help describe how the disease affects the Cushing disease patient's HRQoL (secondary outcomes). In past trials or observational studies, either a portion or all of the health dimensions that are negatively associated with HRQoL in Cushing disease (or diseases that mimic Cushing syndrome, e.g., pituitary adenoma) have been measured. Scales that have been used for these assessments include the Short-Form 36-item health survey,[27-29] the Beck Depression Inventory II,[19,20] the Hospital Anxiety and Depression Scale,[27] the World Health Organization Quality of Life Scale–abbreviated version,[29] the Social Adjustment Scale,[27] the EuroQoL-VAS,[29] and the General Health Questionnaire of 28 and 12 items.[29] Subsequent to these generic scales or symptom scales, two Cushing disease–specific HRQoL questionnaires were developed to assess issues of primary concern to these patients: the Cushing QoL and the Tuebingen CD-25 questionnaires.[19] The mean 24-hour UFC measurement and the Cushing QoL questionnaire were the primary and one of the secondary outcomes, respectively, in Study B2305 and have been further summarized here.

Cushing Quality-of-Life Questionnaire

The Cushing QoL questionnaire was developed by Webb et al.[27] to address aspects of Cushing disease and Cushing syndrome (affected by hypercortisolism)[20] that were of greatest concern to these patients. The initial version was developed in Spanish and has since been translated and culturally adapted into a further 16 languages.[19,27] The questionnaire is comprised of 12 items that cover the following areas: sleep issues, wound healing (or bruising), mood (mood swings, irritability, and anger), self-confidence, physical appearance, ability to participate in daily activities, social concerns, memory issues, and future health concerns. It is a self-administered questionnaire that has a four-week recall period. Patients respond on a five-category Likert scale ("Always," "Often," "Sometimes," "Rarely," and "Never" or "Very much," "Quite a bit," "Somewhat," "Very little," and "Not at all") with responses scored on a scale of 1 to 5, whereby 1 corresponds to "Always" or "Very much" and 5 to "Never" or "Not at all." Total scores range from 12 (worst HRQoL) to 60 (best HRQoL) and are subsequently standardized on a 0 (worst HRQoL) to 100 (best HRQoL) scale to facilitate interpretation.[19,20,27,29]

Validity, reliability, and ease of use of the Cushing QoL questionnaire were originally verified in a cross-sectional observational study of patients with both pituitary-dependent and adrenal-dependent Cushing syndrome.[27] Further support for its validity, reliability, and utility were substantiated upon examining patients in a longitudinal phase III study (Study B2305), whereby patients with Cushing disease were treated with two different doses of pasireotide to observe changes in clinical response (primarily measured by mean 24-hour UFC.[19,20] No floor or ceiling effects were identified, good test-retest reliability was observed, and there were moderate correlations between changes in body mass index, weight, and Beck Depression Inventory II and changes in the Cushing QoL scores.[19,20] One caveat observed was the lower-than-anticipated correlation between the Cushing QoL and symptoms,

appearance, and clinical signs.[20] The MCID was estimated (by the half-standard deviation method) at 10.1 using a one-category improvement (in the hypercortisolism subgroup from baseline to month 12) and the distribution-based approach.[19,20]

24-Hour Urinary Free Cortisol Measurement

The UFC measurement is an assessment of the amount of circulating free physiologically active cortisol.[30] For an accurate measurement, urine collection must be obtained from the patient throughout a 24-hour time period, normally between the hours of 0800 on the first day (first urine of the day) to 0800 on the following day (first urine of the next day).[2,30,31] UFC is measured using standardized methods such as tandem mass spectroscopy and high performance liquid chromatography or alternate methods such as unextracted radioimmunoassay or enzyme-linked immunosorbent assay.[30] High performance liquid chromatography has occasionally produced falsely elevated results as carbamazepine, digoxin, and fenofibrate have been observed to co-elute with cortisol, but, in general, both that method and tandem mass spectroscopy have high sensitivities and specificities.[30] In addition, the upper limits of normal for both of these tests are much lower when compared with antibody-based assays, and their use is highly regulated through standard operating procedures.[30] While these methods produce more consistent results, the tests are expensive and require specialized equipment. Unextracted radioimmunoassay and enzyme-linked immunosorbent assay, while significantly less expensive, can be affected by cross-reactivity with both synthetic glucocorticoids and cortisol metabolites.[30] Recent guidelines by the Endocrine Society recommend the use of the UFC upper limit of normal as the criterion for a positive test for Cushing disease or Cushing syndrome confirmation[30] and also recommends at least two 24-hour UFC measurements.[31] Another complementary assay should also be used for Cushing disease and Cushing syndrome diagnosis when clinical suspicion is high (e.g., late-night salivary cortisol test), even though the test has high specificity (91%).[2] Other assays should be used to exclude endogenous Cushing syndrome when clinical suspicion is low (e.g., 1 mg overnight dexamethasone suppression test or late-night salivary cortisol), as the UFC's sensitivity is low, with approximately 15% of results yielding false negatives.[2]

UFC has long been used in the diagnosis of and assessment of treatment for Cushing syndrome or Cushing disease and has the most evidence to support its use; however, it does have shortcomings.[31] The UFC measurement can be affected by drinking excess fluids or any pathological or physiological conditions that can cause increased cortisol production,[30] and there may be compliance issues due to the inconvenient nature of obtaining the urine samples.[2] In one study that examined the treatment of patients classified as having moderate to severe Cushing disease with two different doses of pasireotide (Study B2305), the intra-patient coefficient of variation across two or more UFC samples was approximately 50%.[31] In addition, the variability appeared to increase as UFC levels got higher and over relatively short periods of time (as the urine collection for this study occurred over a two-week period).[31] Therefore, Petersenn et al.[31] determined that the changes in UFC from baseline should be greater than 56% (when averaging two samples) to observe a treatment effect that would be considered beyond the UFC normal variability.[31] In addition, the CIs of the UFC results appeared to narrow when using three separate UFC measurements, thus allowing for more precision with increased measurements.[31] While previous studies had noted that higher UFC levels were associated with severe cognitive impairment, major depression, and risk of serious infection, the authors noted the lack in set study of a correlation between the severity of features of hypercortisolism (e.g., body mass index, blood pressure, fasting glucose or insulin, A1C, or beta-cell function) and mean UFC levels.[31] However, one limitation associated with this study was the exclusion of patients with milder forms of hypercortisolism or mild Cushing disease.[31]

3. Summary

The Cushing QoL questionnaire is valid, reliable, and easy to use. It has good test-retest reliability, and changes in the Cushing QoL appeared to moderately correlate with changes in body mass index, weight, and Beck Depression Inventory II. In addition, the MCID was estimated at 10.1. The UFC measurement is an accepted method to both diagnose and assess treatment for Cushing syndrome and Cushing disease as long as it is applied two or more times; however, it does have some intra-patient variation, may have compliance issues related to the numerous urine collections, and, in patients with moderate to severe Cushing disease, does not appear to correlate with severity of features of hypercortisolism.

APPENDIX 6: SUMMARY OF EXTENSION STUDY

1. Objective

To summarize the results from the 24-month extension study that included the randomized patients from the phase III uncontrolled Study B2305. The following summary is based on unpublished data the manufacturer provided to the CADTH Common Drug Review.[18]

2. Findings

Study Design

Patients who completed the phase III uncontrolled B2305 study were permitted to continue their treatment by entering the extension phase of this study. Briefly, patients with Cushing disease entered B2305 and were randomized in a 1:1 ratio to receive either a DB subcutaneous dose of 0.6 mg twice daily pasireotide or a double-blind (DB) dose of 0.9 mg twice daily pasireotide. Patients in the 0.6 mg twice daily group who did not meet the required mean urinary free cortisol (UFC) for continuation (described in the main body) at month 3 were unblinded and were required to increase their dose to 0.9 mg twice daily open label (OL). Likewise, patients in the 0.9 mg twice daily group were unblinded and offered OL 1.2 mg twice daily. At six months of treatment, patients entered the OL treatment period, whereby those patients who maintained a response continued on their dose and those who did not achieve or maintain their response could receive a dose increase of 0.3 mg twice daily to a maximum dose of 1.2 mg twice daily. Patients received treatment up to 12 months and then had the option to continue treatment (the extension phase of the study) if they met the following criteria:

- The patient achieved or maintained mean UFC less than or equal to upper limit normal at month 12, or, if patient did not maintain mean mean UFC, the patient was receiving significant clinical benefit (improved signs and symptoms) as determined by the investigator
- Pasireotide was tolerated in the prior 12 months of treatment
- Women of child-bearing age continued oral contraception throughout the extension phase and for one month after the last pasireotide dose
- Male patients continued to use condoms throughout the course of the extension phase and for one month after the last pasireotide dose.

Patients continued on their assigned pasireotide dosing regimens. The first data cut-off was 25 March, 2011, and patient efficacy and harms information was available for the 12 months of core treatment and 12 months of the optional extension phase. This included patients who continued the full length of the extension phase (24 months) along with patients who discontinued treatment throughout both phases.

Results

Patient demographics and disease characteristics were explained at length in the main body of this report. Briefly, three-quarters of the patients were women, the patient mean age was 40 to 41 years, and the majority of patients (78.4%) were Caucasian. Of note, there was a baseline imbalance of mean UFC between the 0.6 mg twice daily and 0.9 mg twice daily of medians of 730 nmol/24 h versus 487 nmol/24 h, respectively. In addition, there was a markedly higher proportion of patients in the 0.6 mg twice daily group who had a baseline mean UFC greater than five times the upper limit normal than in the 0.9 mg twice daily group (47.6% versus 27.5%, respectively).

Patients discontinuing pasireotide treatment at any time during the 24 months ranged from 68% to 69% (0.6 mg twice daily and 0.9 mg twice daily, respectively), with unsatisfactory therapeutic effect being the primary reason for discontinuation (27% to 31%, respectively). Of patients who completed the

first 12 months of Study B2305, 32% in the 0.6 mg twice daily group and 40% in the 0.9 mg twice daily group entered the extension phase. While 5% in the 0.6 mg twice daily group and 9% in the 0.9 mg twice daily group discontinued before month 18 and 6% in the 0.6 mg twice daily group and 4% in the 0.9 mg twice daily group discontinued before month 24 but after month 18, there were still 16% and 23% from the original trial (in the 0.6 mg twice daily group and 0.9 mg twice daily group, respectively) who were still receiving treatment in the ongoing extension phase at the time of this interim analysis. Similar numbers of discontinuations in the extension phase were observed for AEs, unsatisfactory therapeutic results, and withdrawals of consent. Detailed discontinuation results are presented in Table 18.

TABLE 18: PATIENT DISPOSITION UP TO DATA CUT-OFF BY RANDOMIZATION (FULL ANALYSIS SET)

	Pasireotide 0.6 mg b.i.d. (N = 82) n (%)	Pasireotide 0.9 mg b.i.d. (N = 80) n (%)
Discontinued at Any Time[a]	56 (68)	55 (69)
Discontinued before month 12	43 (52)	41 (51)
Completed month 12	39 (48)	39 (49)
Completed month 12 and did not enter extension phase[a]	13 (16)	7 (9)
Completed month 12 and entered extension phase	26 (32)	32 (40)
Discontinued Study in Extension Phase	13 (16)	14 (18)
Reason for Discontinuation in Extension Phase		
AE	3 (4)	2 (3)
Unsatisfactory therapeutic effect	6 (7)	4 (5)
Patient withdrew consent	4 (5)	8 (10)
Discontinued extension phase at or before month 18	4 (5)	7 (9)
Discontinued before month 24 but after month 18	5 (6)	3 (4)
Ongoing in Extension Phase	13 (16)	18 (23)

AE = adverse event; b.i.d. = twice daily.
[a] Patients who completed month 12 and did not enter extension phase are not counted as discontinuations.
Source: Clinical Study Report.[18]

Overall, approximately 24.7% of patients had at least 24 months of exposure to pasireotide, while 40.7% of patients had at least 12 months of exposure. In addition, approximately 6.2% had at least 36 months of exposure. The mean exposure in the 0.6 mg twice daily group was 13.18 months (standard deviation of 11.36) while in the 0.9 mg twice daily group it was 14.13 months (standard deviation of 12.35). Detailed exposures per group are presented in Table 19.

TABLE 19: DURATION OF EXPOSURE TO PASIREOTIDE UP TO DATA CUT-OFF BY RANDOMIZATION (SAFETY ANALYSIS SET)

	Pasireotide 0.6 mg b.i.d. (N = 82)	Pasireotide 0.9 mg b.i.d. (N = 80)
Mean Exposure, Months (SD)	13.18 (11.36)	14.13 (12.35)
Exposure Category in Months, n (%)		
≥ 3	68 (83)	64 (80)
≥ 6	55 (67)	55 (69)
≥ 12	30 (37)	36 (45)

	Pasireotide 0.6 mg b.i.d. (N = 82)	Pasireotide 0.9 mg b.i.d. (N = 80)
≥ 18	22 (27)	24 (30)
≥ 24	18 (22)	22 (28)
≥ 30	9 (11)	9 (11)
≥ 36	4 (5)	6 (8)
≥ 42	2 (2)	2 (3)

b.i.d. = twice daily; SD = standard deviation.
Source: Clinical Study Report.[18]

The proportions of patients in the 0.6 mg twice daily group with controlled UFC response at months 12, 18, and 24 were 13.4%, 14.6%, and 9.8%, respectively, while proportions in the 0.9 mg twice daily group at the same times periods were 25.0%, 16.3%, and 15.0%, respectively. The proportions of patients in the 0.6 mg twice daily group with uncontrolled UFC response at months 12, 18, and 24 were 70.7%, 76.8%, and 87.8%, respectively, while proportions in the 0.9 mg twice daily group at the same time points were 72.5%, 78.8%, and 81.3%, respectively. Detailed proportions of UFC responses are provided in Table 20.

TABLE 20: PROPORTION OF CONTROLLED, PARTIALLY CONTROLLED, AND UNCONTROLLED UFC RESPONDERS BY RANDOMIZED DOSE GROUP (FULL ANALYSIS SET)

	Pasireotide 0.6 mg b.i.d. (N = 82)	Pasireotide 0.9 mg b.i.d. (N = 80)
Controlled[a] UFC Responders, n (%)		
Month 6	11 (13.4)	21 (26.3)
(95% CI)[b]	(6.0 to 20.8)	(16.6 to 35.9)
Month 9	14 (17.1)	20 (25.0)
Month 12	11 (13.4)	20 (25.0)
(95% CI)	(6.0 to 20.8)	(15.5 to 34.5)
Month 15	9 (11.0)	19 (23.8)
Month 18	12 (14.6)	13 (16.3)
(95% CI)	(7.0 to 22.3)	(8.2 to 24.3)
Month 21	10 (12.2)	12 (15.0)
Month 24	8 (9.8)	12 (15.0)
(95% CI)	(3.3 to 16.2)	(7.2 to 22.8)
Partially Controlled[c] UFC Responders, n (%)		
Month 6	13 (15.9)	8 (10.0)
Month 9	17 (20.7)	7 (8.8)
Month 12	13 (15.9)	2 (2.5)
Month 15	11 (13.4)	3 (3.8)
Month 18	7 (8.5)	4 (5.0)
Month 21	5 (6.1)	5 (6.3)
Month 24	2 (2.4)	3 (3.8)
Uncontrolled[d] UFC Responders, n (%)		
Month 6	58 (70.7)	51 (63.8)
Month 9	51 (62.2)	53 (66.3)
Month 12	58 (70.7)	58 (72.5)
Month 15	62 (75.6)	58 (72.5)
Month 18	63 (76.8)	63 (78.8)

	Pasireotide 0.6 mg b.i.d. (N = 82)	Pasireotide 0.9 mg b.i.d. (N = 80)
Month 21	67 (81.7)	63 (78.8)
Month 24	72 (87.8)	65 (81.3)

b.i.d. = twice daily; CI = confidence interval; SD = standard deviation; UFC = urinary free cortisol; ULN = upper limit normal.
[a] Controlled: Mean UFC at month 6 ≤ 1.0 × ULN.
[b] Calculated using four time points (months 1, 2, 3, 6), of which only month 6 is shown. 95% CI provided only for controlled UFC responders.
[c] Partially controlled: Mean UFC at month 6 > 1.0 × ULN but ≥ 50% reduction from baseline.
[d] Uncontrolled: Neither controlled nor partially controlled. If a patient has missing mean UFCs he or she is counted as uncontrolled; no imputation is used.

Mean percentage changes in UFC from month 6 through to month 24 were –27.5% to –70.8%, respectively, in the 0.6 mg twice daily group and –48.4% to –59.5%, respectively, in the 0.9 mg twice daily group. However, it should be noted that the number of patients who continued to receive treatment in both groups continued to fall as the extension study progressed, with 13 patients in the 0.6 mg twice daily group at and 20 patients in the 0.9 mg twice daily group month 24. Details of the mean, median, and mean percentage changes are presented in Table 21.

TABLE 21: CHANGE IN MEAN UFC UP TO MONTH 24 BY RANDOMIZED DOSE GROUP (FULL ANALYSIS SET)

	Pasireotide 0.6 mg b.i.d. (N = 82)	Pasireotide 0.9 mg b.i.d. (N = 80)
Change in Mean UFC (nmol/24 h) From Baseline		
Baseline, n	77	76
Mean value (SD)	1155.9 (2629.78)	781.9 (926.38)
Median (range)	730 (219.5 to 22944)	487 (195 to 6122.8)
Month 6, n	52	51
Mean value (95% CI)	–463.4 (–688 to –239)	–364.9 (–517 to–212)
Median (range)	–368.3 (–3789 to 1649.8)	–217.8 (–3601 to 41.3)
Mean % change (95% CI)	–27.5 (–55.9 to 0.9)	–48.4 (–56.6 to –40.2)
Month 12, n	37	35
Mean value (95% CI)	–572.6 (–876 to –269)	–350.7 (–477 to –225)
Median (range)	–379 (–4386 to 909.8)	–256 (–1619 to 176.8)
Mean % change (95% CI)	–41.3 (–66.0 to –16.6)	–54.5 (–65.2 to –43.7)
Month 18, n	22	22
Mean value (95% CI)	–667.4 (–1046 to –289)	–305.4 (–406 to –205)
Median (range)	–456.3 (–4342 to 16.5)	–266.4 (–1022 to 55.3)
Mean % change (95% CI)	–65 (–78.1 to –51.8)	–59.6 (–70.8 to –48.4)
Month 24, n	13	20
Mean value (95% CI)	–811.8 (–1435 to–189)	–248.7 (–354 to –143)
Median (range)	–415.5 (–4347 to –29.8)	–265.8 (–753.5 to 436.8)
Mean % change (95% CI)	–70.8 (–85.5 to –56.2)	–56.5 (–71.6 to –41.4)

b.i.d. = twice daily; CI = confidence interval; SD = standard deviation; UFC = urinary free cortisol.

By month 24, 97.6% in the 0.6 mg twice daily group and 98.8% in the 0.9 mg twice daily group had experienced at least one AE. Of these the most common by month 24 included diarrhea, nausea (59.8% and 57.5% in the 0.6 mg twice daily and 0.9 mg twice daily groups, respectively), hyperglycemia (34.1% and 30.0% in the 0.6 mg twice daily and 0.9 mg twice daily groups, respectively), and cholelithiasis (34.1% and 30.0% in the 0.6 mg twice daily and 0.9 mg twice daily groups, respectively). Patients experiencing at least one SAE by month 24 reached 23.2% in the 0.6 mg twice daily group and 28.8% in the 0.9 mg twice daily group. No deaths were reported up to and including month 24. Notable harm prevalences by month 24 included metabolism and nutrition disorders (75.6% and 46.3% in the 0.6 mg twice daily and 0.9 mg twice daily groups, respectively), hepatobiliary disorders (40.2% and 36.3% in the 0.6 mg twice daily and 0.9 mg twice daily groups, respectively), and cardiac disorders (17.1% and 8.8% in the 0.6 mg twice daily and 0.9 mg twice daily groups, respectively). Details of the harms are presented in Table 22.

TABLE 22: HARMS (SAFETY ANALYSIS SET)

	Pasireotide 0.6 mg b.i.d. (N = 82) n (%)		Pasireotide 0.9 mg b.i.d. (N = 80) n (%)	
	Month 12	Month 24	Month 12	Month 24
AEs[a]	80 (97.6)	80 (97.6)	79 (98.8)	79 (98.8)
Diarrhea	48 (58.5)	49 (59.8)	46 (57.5)	46 (57.5)
Nausea	38 (46.3)	39 (47.6)	46 (57.5)	46 (57.5)
Hyperglycemia	31 (37.8)	30 (36.6)	34 (42.5)	35 (43.8)
Cholelithiasis	25 (30.5)	28 (34.1)	24 (30.0)	24 (30.0)
Headache	23 (28.0)	24 (29.3)	23 (28.8)	24 (30.0)
Abdominal pain	19 (23.2)	19 (23.2)	20 (25.0)	20 (25.0)
Diabetes mellitus	13 (15.9)	17 (20.7)	16 (20.0)	16 (20.0)
Fatigue	12 (14.6)	12 (14.6)	19 (23.8)	19 (23.8)
Hypoglycemia	12 (14.6)	12 (14.6)	3 (3.8)	4 (5.0)
A1C increased	10 (12.2)	10 (12.2)	8 (10.0)	8 (10.0)
Discontinued due to AE	13 (15.9)	15 (18.3)	15 (18.8)	16 (20.0)
SAEs	19 (23.2)	19 (23.2)	21 (26.3)	23 (28.8)
Discontinued due to SAE	3 (3.7)	3 (3.7)	5 (6.3)	5 (6.3)
Deaths	0	0	0	0
Notable Harms				
Metabolism and nutrition disorders	61 (74.4)	62 (75.6)	60 (75.0)	61 (76.3)
Hepatobiliary disorders	30 (36.6)	33 (40.2)	29 (36.3)	29 (36.3)
Cardiac disorders	14 (17.1)	14 (17.1)	6 (7.5)	7 (8.8)

A1C = glycated hemoglobin; AE = adverse event; b.i.d. = twice daily; SAE = serious adverse event.
[a] All grades; proportion experiencing AE was greater than 10%.

3. Summary

At month 24, the proportion of patients who had been continually exposed to pasireotide was somewhat low, ranging from 22% to 28% of the total study population. Approximately 40% of the total study population completed pasireotide treatment at month 12 and entered the extension phase. Of these patients, 16% to 18% discontinued the extension phase. The proportion of patients who achieved a controlled UFC response by month 24 was on the lower side, ranging from 9.8% to 15.0%, while those

who achieved a partially controlled UFC response ranged from approximately 2% to 4%. By month 24, almost all of the patients included in the original study had experienced at least one AE, with diarrhea, nausea, hyperglycemia, and cholelithiasis being the most frequent. In addition, the proportion of patients experiencing notable harms was quite large for harms categorized as metabolism and nutrition disorders, moderate for hepatobiliary disorders, and less frequent for cardiac disorders.

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