Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for Pasireotide (as diaspartate)

Proprietary Product Name: Signifor

Sponsor: Novartis Pharmaceuticals Australia Pty Ltd

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TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <http://www.tga.gov.au>.

About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

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List of abbreviations

Abbreviation	Meaning
AAT	Alanine aminotransferase
ACTH	Adrenocorticotrophic hormone
ADME	Absorption, Distribution, Metabolism and Excretion
AE	Adverse event
AMS	Accelerator mass spectrometry
AST	Aspartate aminotransferase
AUC	Area under curve
BMI	Body mass index
BW	Body weight
CCK	Cholecystokinin
Cmax	Maximum concentration
CL/F	Apparent plasma clearance
CM I	Consumer Medicine Information
CTCAE	Common terminology criteria for adverse events
EGP	Estimated glucose production
EMEA	European Medicines Authority
EU	European Union
FDA	Federal Drug Administration
FPG	Fasting plasma glucose
GDR	Glucose disposal rate
GEP	Gastro entero pancreatic

Abbreviation	Meaning
GGT	Gamma-glutamyltransferase
GH	Growth hormone
GHRH	Growth hormone releasing hormone
GI	Gastrointestinal
HPLC	High-performance liquid chromatography
HV	Healthy volunteers
IGF	Insulin like growth factor
IGFBP	Insulin like growth factor binding protein
IVRS	Interactive voice response system
LAR	Long acting release
LLOQ	Lower limit of quantification
PD	Pharmacodynamic
PI	Product Information
PK	Pharmacokinetic
SAE	Serious adverse event
sc	Subcutaneous
SCS	Summary of Clinical Safety
SD	Standard deviation
SE	Standard error
TGA	Therapeutic Goods Administration
t1/2	Half disappearance time
Tmax	Time to maximum concentration
UFC	Urinary free cortisol
ULN	Upper limit of normal

1. Clinical rationale

The natural hormone somatostatin, the name of which derives from the fact that it was first described as an inhibitor of growth hormone secretion, has widespread physiological functions as an inhibitory regulator of other hormonal functions, one of which is pituitary secretion of ACTH. The extension of this physiological action to a therapeutic analogue of somatostatin inhibiting the secretion of ACTH by functioning pituitary tumours is the basis for the current application.

The first somatostatin analogue to be developed was octreotide which has been registered in Australia since 1993, and in long acting form since 1999, for the treatment of acromegaly and for a number of functioning tumours of the gastro-entero-pancreatic (GEP) endocrine system. A second analogue, lanreotide, has been registered in Australia since 2001 for the treatment of acromegaly and since 2003, in an alternative formulation, also for the treatment of carcinoid tumours. As described in the preclinical part of the application, pasireotide exhibits a profile of binding to the five subtypes of the human recombinant somatostatin receptor (hsst1-5) which renders it more effective in suppressing adrenocorticotrophic hormone (ACTH) secretion and therefore is a potential therapy for pituitary Cushing's disease; the specific point is that corticotroph tumour cells in these patients preferentially express high levels of hsst5, and that pasireotide binds to hsst1, 2, 3, and 5 (most strongly to hsst5), whereas currently available somatostatin analogues listed above bind preferentially to sst2.

Although the sponsor's statement in the letter of application that "there are no medical therapies approved for the treatment of Cushing's disease" is strictly correct in respect of the word approved, a number of other treatments are available, demonstrably effective, and in current use. Most of these act by suppressing cortisol secretion at the adrenal level, which is in principle less desirable than attacking the primary problem of excess pituitary ACTH secretion. There is widespread off-label use of ketoconazole which is also currently recommended as first-line treatment by the widely used clinical guideline program UpToDate [1]. Published evidence of its efficacy or that of fluconazole is limited to small, uncontrolled studies or case reports ([2],[3]). Other drugs which inhibit cortisol biosynthesis and have been used include metyrapone and mitotane. Recently, the glucocorticoid receptor antagonist mifepristone has been approved (17 February 2012) by the United States FDA for use in endogenous Cushing's syndrome, specifically when hyperglycaemia is present ([4]). Again, the rarity of the condition and a lack of commercial initiatives for formal development programs for older drugs with established existing usage for other conditions limits published evidence to relatively small studies ([5],[6]). The only other currently describe treatment acting at the pituitary level is cabergoline, which has been described as being effective either alone or in combination with ketoconazole ([7],[8]).

[1] Nieman LK, 2013, Medical therapy of hypercortisolism (Cushing's syndrome) *UpToDate*, updated, Jan 18, 2013.
[2] Loli P, Berselli ME, Tagliaferri M. J, 1986, Use of ketoconazole in the treatment of Cushing's syndrome. *Clin Endocrinol Metab.* 63(6):1365
[3] Riedl M, Maier C, Zettinig G, Nowotny P, Schima W, Luger A. 2006. Long term control of hypercortisolism with fluconazole: case report and in vitro studies. *Eur J Endocrinol* 154(4):519
[4] FDA approves Korlym for patients with endogenous Cushing's syndrome, Feb 17 2012. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm292462.htm
[5] Castinetti F, Fassnacht M, Johanssen S, Terzolo M, Bouchard P, Chanson P, Do Cao C, Morange I, Picó A, Ouzounian S, Young J, Hahner S, Brue T, Allolio B, Conte-Devolx B. 2009, Merits and pitfalls of mifepristone in Cushing's syndrome. *Eur J Endocrinol* 160(6):1003
[6] Johanssen S, Allolio B, 2007, Mifepristone (RU 486) in Cushing's syndrome. *Eur J Endocrinol* 157(5):561-9
[7] Godbout A, Manavela M, Danilowicz K, Beauregard H, Bruno OD, Lacroix A. 2010, Cabergoline monotherapy in the long-term treatment of Cushing's disease. *Eur J Endocrinol* 163(5):709
[8] Vilar L, Naves LA, Azevedo MF, Arruda MJ, Arahata CM, Moura E Silva L, Agra R, Pontes L, Montenegro L, Albuquerque JL, Canadas V , 2010, Effectiveness of cabergoline in monotherapy and combined with ketoconazole in the management of Cushing's disease. *Pituitary* 13(2):123

The sponsor contends that the current application contains the best evidence so far presented for a medical therapy for Cushing's disease is correct.

2. Contents of the clinical dossier

2.1. Scope of the clinical dossier

The submission contained the following clinical information:

Module 5:

- 12 clinical pharmacology studies, including 11 that provided pharmacokinetic (PK) data and nine that provided pharmacodynamics (PD) data.
- Population PK (PopPK) analyses for healthy volunteers (HV) and the target population of Cushing's disease patients (modelling reports).
- The report of a single pivotal efficacy/safety Study CSOM230B2305 (referred to hereafter as Study B2305), together with ancillary documents detailing protocol amendments and statistical methodology.
- Four other efficacy/safety studies.
- Three bioanalytical reports validating the immunoassay procedures for analysis of pasireotide (sponsor code SOM230). A lower limit of quantification is described of 30 pg/mL, which equates to 150 pg/mL in study samples. These documents have not been reviewed in detail.
- Population safety reports on glucose metabolism, QT/QTc (cardiac safety), and a hepatic safety report

2.2. Paediatric data

The submission did not include paediatric data. The sponsor advises that a relevant product specific waiver was granted by the European Medicines Authority (EMEA) on 6 March 2009, on the grounds that the product "does not represent a significant therapeutic benefit over existing treatments". It appears that this rather odd wording is standard EU terminology for this situation. It is self-evident that the statement is true with particular reference to pituitary surgery as an existing treatment, but equally that the product could confer a significant therapeutic benefit if surgery was contraindicated or had failed, as is the basis of the EU approval and the current application.

An obvious barrier to a paediatric development program is the rarity of the condition in childhood and adolescence and the barrier this would present to developing an evidence base. It appears to the evaluator that the granting of the above referenced waiver should not exclude paediatric use which may have to continue in the occasional case on an off label basis as would be the case at present.

2.3. Good clinical practice

The included studies all appear to have complied with the accepted procedures for Good Clinical Practice.

3. Pharmacokinetics

3.1. Studies providing pharmacokinetic data

Table 1 shows the studies relating to each PK topic.

Table1: Submitted pharmacokinetic studies.

PK topic	Subtopic		Study ID
PK in healthy adults	General PK	Single dose	B2101
			B2107
			C2101
		Infusion	B2108
		Multi-dose	B2102
			B2106
			B2107 B2113 B2125
	Bioavailability (mass balance)		B2112
PK in special populations	Target population §	Multi-dose	B2208
			B2305
	Hepatic impairment		B2114
Population PK analyses	Healthy subjects		Module 5.3.3.5
	Target population		Module 5.3.3.5

§ Subjects who would be eligible to receive the drug if approved for the proposed indication.

None of the PK studies had deficiencies that excluded their results from consideration.

3.2. Summary of pharmacokinetics

Information in the following summary is derived from conventional pharmacokinetic studies unless otherwise stated.

3.2.1. Pharmacokinetics in healthy subjects

3.2.1.1. Absorption

Pasireotide is administered exclusively by subcutaneous injection. From this site, absorption is rapid as shown in single dose Studies B2101 (Table 2), B2106 (Table 3), and C2101 (Table 4), with T_{max} values of 0.25-0.50 hours. These characteristics are confirmed in the acute phase sampling periods of other PK studies in the application, and in the absorption, distribution, metabolism and excretion (ADME) mass balance study described below.

Table 2: Study B2101 summary

Dose (µg)	N	T_{max} (h)	C_{max} (ng/mL)	AUC_{last} (ng.h/mL)	AUC_{inf} (ng.h/mL)	CL/F (L/h)	$t_{1/2}$ (h)
2.5	6	0.25 (0.25-0.50)	0.06 ± 0.01	0.11 ± 0.09	NA*	NA*	2.43 ± 1.29
10	6	0.25 (0.25-0.25)	0.24 ± 0.06	0.66 ± 0.25	NA*	NA*	5.99 ± 3.23
30	6	0.25 (0.25-0.50)	0.72 ± 0.17	2.78 ± 1.02	NA*	NA*	8.62 ± 3.66
100	8	0.50 (0.25-0.50)	2.23 ± 0.45	9.10 ± 2.37	9.59 ± 2.44	11.00 ± 2.67	8.32 ± 1.70
200	4	0.38 (0.25-1.00)	3.73 ± 0.90	16.78 ± 3.65	17.35 ± 3.82	11.90 ± 2.56	9.91 ± 3.75
300	6	0.38 (0.25-1.50)	4.71 ± 1.79	25.95 ± 6.87	27.07 ± 6.98	11.92 ± 3.88	10.74 ± 1.20
600	6	0.50 (0.25-1.00)	15.55 ± 3.25	75.63 ± 11.24	78.60 ± 12.28	7.82 ± 1.39	44.08 ± 46.18
1200	6	0.50 (0.50-1.00)	22.18 ± 5.53	90.35 ± 13.21	93.55 ± 13.60	13.07 ± 2.09	65.92 ± 87.80

* This value was not determined because the number of subjects with available parameters was less than 50% of the total enrolled subjects in this cohort.

Data are median (range) for T_{max} and mean ± standard deviation for all others.

Table 3: Study B2106 summary

Dose (µg)	N	AUC_{inf} (h.ng/mL)	AUC_{last} (h.ng/mL)	$AUC_{(0-24)}$ (h.ng/mL)	C_{max} (ng/mL)	T_{max} (h)	CL/F (L/h)	$T_{1/2}$ (h)
900	9	109.80±28.57	107.49±27.32	89.74±19.13	22.36±4.49	0.50(0.25-1.50)	8.72±2.39	30.21±29.43
1200	8	148.69±41.87	146.14±41.30	121.49±28.15	29.75±6.00	0.50(0.25-1.50)	8.68±2.63	27.65±18.24
1500	8	187.63±51.83	183.13±50.91	152.26±36.86	36.89±5.71	0.50(0.50-1.00)	8.57±2.47	32.44±19.67

Sources: Appendix 4, PT-Table 3.1 and PT-Table 3.2

Values are median (range) for T_{max} and mean ± SD for all other parameters.

Table 4: Study C2101 summary

PK parameter	n	300 µg s.c. dose
C_{max} (ng/mL)	73	6.60 ± 2.14
T_{max} (hr)	73	0.25 (0.2 - 2.0)
AUC_{last} (h.ng/mL)	73	32.7 ± 9.3
AUC_{inf} (h.ng/mL)	71	35.9 ± 9.8
$t_{½}$ (h)	73	8.26 ± 2.72
CL/F (L/h)	71	9.02 ± 2.72
V_z/F (L)	71	103 ± 38

3.2.1.2. Bioavailability

Absolute bioavailability:

The sponsor provided a justification for not submitting an absolute bioavailability study. The sponsor's argument in seeking this waiver is based on the following main points, briefly summarised:

- That the product's physicochemical characteristics favour direct absorption from the injection site into the vascular space as opposed to lymphatic absorption, as is also suggested by its demonstrated PK properties.
- That investigations conducted indicate that degradation or cellular uptake at the injection site is unlikely.
- In particular, that an absolute bioavailability study (comparison of subcutaneous with intravenous absorption) indicating 100% bioavailability has been conducted in the rat, in

which (and in other) species the PK characteristics of absorption from the subcutaneous site is similar to that demonstrated in man by the studies in this application.

The sponsor further argued that their position satisfies the requirements of the EMEA in regard to obtaining such a waiver, and that performance of an absolute bioavailability study was not a requirement in successful applications for registration in the EU, USA or Canada.

On the basis of the above, together with having reviewed the PK data in the submission, this evaluation supports the proposal that such a study is not necessary.

Bioavailability relative to an oral solution or micronised suspension:

Not relevant, as the characteristics of pasireotide do not favour oral absorption and it is proposed for parenteral administration only.

Bioequivalence of clinical trial and market formulations:

The formulation proposed for marketing is identical with that used in pivotal Study B2305, which contains the bulk of the data regarding efficacy, safety and exposure in the proposed indication. There may have been minor differences between this and formulations used in some (not all) of the Phase I and Phase II studies; for example, in some of these a 150 µg product is employed. Given the absorption characteristics of the product, any differences are unlikely to have significant impact on the PK findings.

Bioequivalence of different dosage forms and strengths:

There is only one dosage form, and no clinical studies have been performed to confirm bioequivalence of the three strengths of the proposed formulation. Given that other data indicate rapid and complete absorption from the injection site, formal PK comparison of the strengths is considered unnecessary.

Bioequivalence to relevant registered products:

Bioequivalence with other somatostatin analogues might be considered relevant if there were overlapping indications, but this is not the case.

Influence of food:

Not applicable as the product is administered parenterally by subcutaneous injection.

Dose proportionality:

Although marginally failing a test of statistical significance, dose proportionality was evident in Study B2102 across the dose range 50-600 µg given as single daily injections (Table 5), and likewise across the range 100-1200 µg daily in Study B2101 (Table 2). Dose proportionality was also evident with either once or twice daily administration across the dose range 900-1500 µg daily in Study B2106 (Table 3) and in continuous infusion Study B2108 (Table 6).

Table 5: Study B2102 summary

Dose (µg)	N	$T_{max,ss}$ (h)	$C_{max,ss}$ (ng/mL)	$C_{min,ss}$ (ng/mL)	AUC_{tau} (h.ng/mL)	$C_{avg,ss}$ (ng/mL)	CL/F (L/h)	V/F (L)	$t_{1/2}$ (h)	Accumulation Ratio
50	10	0.35 (0.23, 0.53)	1.39 ± 0.28	0.08 ± 0.06	6.6 ± 1.8	0.27 ± 0.08	8.10 ± 2.14	251 ± 274	10.4 ± 3.4	1.26 ± 0.17
200	8	0.25 (0.25, 0.50)	5.53 ± 1.22	0.25 ± 0.10	22.6 ± 3.5	0.94 ± 0.15	9.03 ± 1.37	1051 ± 774	9.7 ± 3.4	1.20 ± 0.17
600	10	0.50 (0.25, 1.05)	16.76 ± 4.96	0.74 ± 0.33	72.9 ± 14.7	3.04 ± 0.61	8.54 ± 1.76	1091 ± 656	13.1 ± 3.7	1.36 ± 0.22

Sources: Appendix 4, PT-Table 3.1 and PT-Table 3.2
Data are median (range) for $T_{max,ss}$, and arithmetic mean ± SD for all others.

Table 6: Study B2108 summary

Dose (µg/day)	C_{ss} (ng/mL)	AUC_{inf} (ng*h/mL)	CL_{ss}/F (L/h)	V_{ss}/F (L)	$t_{1/2}$ (h)
450 (N=6)	1.75 ± 0.39	319 ± 56	11.19 ± 2.55	125 ± 70	27.8 ± 3.2
900 (N=6)	5.07 ± 2.11	839 ± 353	8.31 ± 2.70	129 ± 38	15.5 ± 2.5
1350 (N=6)	8.10 ± 6.32	1327 ± 976	9.92 ± 5.48	140 ± 41	19.6 ± 6.6
1800 (N=12)	11.73 ± 3.47	2013 ± 532	7.14 ± 2.88	83 ± 40	19.3 ± 3.0
1800[R] (N=5)	17.26 ± 0.93	2634 ± 95	4.36 ± 0.23	79 ± 38	19.8 ± 3.8
2025 (N=6)	11.98 ± 6.39	2013 ± 930	9.13 ± 5.40	109 ± 38	20.8 ± 5.8
2250 (N=6)	16.17 ± 4.05	2543 ± 693	6.09 ± 1.37	141 ± 71	16.3 ± 2.2

Bioavailability during multiple-dosing:

Multiple doses within the therapeutic range were given over 14 day periods in Study B2102 (Table 5) and both once and twice daily in Study B2106 (Table 3). In both studies, steady state as reflected by trough pasireotide levels was achieved after three to four days. Drug accumulation at steady state, as reflected by the ratio of exposure (AUC) at Day 14 by comparison with Day 1, was between 20-36% in study B2102 (36% at 600 µg daily). Values for t½ and apparent plasma clearance (CL/F) were similar, following multiple dosing, to the estimates after single doses.

Steady state was also achieved between Days 3 and 4 in continuous infusion Study B2108; steady state pasireotide concentration on 900 µg daily was 5.1+2.1 ng/mL.

Effect of administration timing:

The effect of giving the total daily dose as a single injection at 9 am by comparison with two injections at 9 am and 9 pm was examined in Study B2106 (Table 3), for total daily doses of 900, 1200 and 1500 µg. Total exposure (AUC) was similar between the two regimens, although C_{max} was about double with the single daily administration, as might be expected from the dose proportionality studies. Other PK parameters were similar.

Comment: Clinical studies subsequent to this, including the efficacy studies, were conducted with the twice daily dosing schedule. This relates to safety rather than PK parameters: while similar drug exposure was achieved with the once daily schedule, the twice daily schedule was much better tolerated, presumably reflecting the lower C_{max}.

3.2.1.3. Distribution

In the submitted PK studies for which summaries are given below, the plasma concentration-time profiles for pasireotide appear mono-exponential at lower dosage but become more

complex with increasing dosage, a tri-exponential pattern being evident at therapeutic dosage in the 600-1500 µg range. The final elimination phase contributes little to the total exposure as reflected by AUC. Half elimination time (t½) varies somewhat amongst the various studies, averaging approximately 12 hours. CL/F is likewise variable; an overall estimate for the HV population is 6.7 L/h.

Volume of distribution:

The summary of clinical pharmacology states that in Studies B2101 and B2106 apparent total volume of distribution (Vz/F) was estimated to be > 100 L. Vz/F data are presented in Study B2101 report (see Table 2). The estimated value increases progressively with dosage to a maximum of 1190 litres in the 1200 µg group. The significance of this apparent dose dependence is not discussed in the submission or clearly understood by this evaluator, but may be related to the accuracy of estimations during the terminal elimination phase, when plasma levels of pasireotide are very low, being critically dependent on the lower limit of quantification (LLOQ) of the assay.

At steady state during a continuous pasireotide infusion of doses within and above the proposed therapeutic range (Study B2108, Table 6), volume of distribution was estimated (mean values for the dosage groups) at between 79 and 141 litres, with no evidence of dose dependence. This is probably a more valid estimate.

Plasma protein binding:

In a preclinical study on human plasma, the fraction bound to plasma proteins was found to be 88+3%.

Erythrocyte distribution:

Intravascular distribution is mainly to plasma rather than red cells. A fractionation study on human blood showed pasireotide distribution to the plasma to be 91+3%.

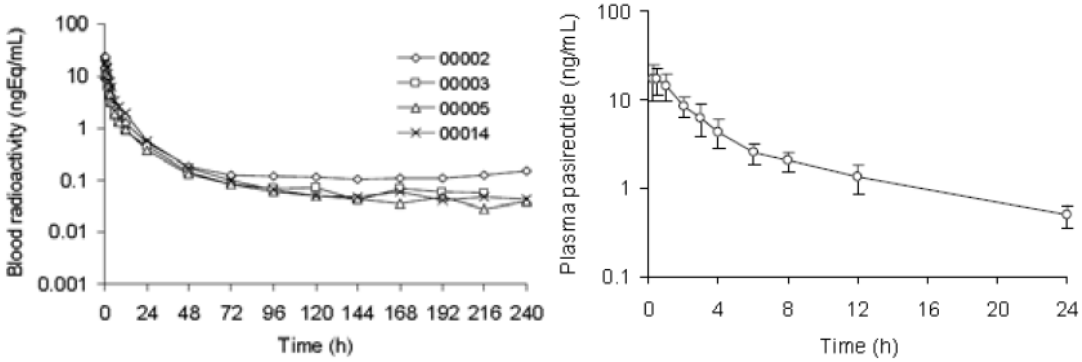
Tissue distribution:

There is no direct evidence on this subject in the submitted studies.

3.2.1.4. Metabolism

In vitro (IV) studies referred to in the submission, including the Summary of Clinical Pharmacology, indicate that pasireotide is highly metabolically stable, and this is supported by clinical evidence specifically from mass balance Study B2112 (Table 7).

Table 7: Study B2112 summary



Non-renal clearance:

The majority of pasireotide elimination occurs by means of hepatic clearance of unchanged pasireotide, with renal excretion playing a minor part.

Metabolites identified in humans:

Mass balance Study B2112 identified metabolites to be responsible for a small but apparently variable (based on three subjects) proportion of recovered radioactivity from labelled pasireotide which had been administered, and for some 15% of urinary recovery. The structural identity and other PK properties of these metabolites, and whether they might be active, has as yet not been identified.

Consequences of genetic polymorphism:

Samples for pharmacogenetic were collected from the subjects in mass balance Study B2112 and in some of the other studies, but results are not presented in this application.

3.2.1.5. Excretion

Routes and mechanisms of excretion:

As already indicated, the majority of pasireotide excretion takes place through the liver, with a minor renal component. In each case, the majority of excretion is as unchanged drug. The exact mechanisms of excretion are, to the knowledge of this evaluator, unidentified.

Mass balance studies:

Study B2112, using 14C-labelled pasireotide (Table 7) showed that the majority (86%) of radioactivity recovered after 10 days was found in the faeces and the remaining 14% in the urine, in both cases mostly as unchanged pasireotide. In the faeces, a metabolite of unknown structure designated P28 accounted for 8.1+10.2% of recovery, the large variance being due to its mainly having been present in one of the four subjects studied. Of the radioactivity recovered in the urine, most was in the form of unmodified pasireotide with approximately 15% being accounted for by metabolites. The study did not identify the structural nature of metabolites recovered in the excreta.

The PK aspect of the study did demonstrate that after 12 hours plasma exposure to unmodified pasireotide represented 100% of the total drug-related exposure, suggesting rapid absorption and distribution into the plasma space from the subcutaneous injection site.

In this study, overall recovery of radioactivity was only 56%, suggesting considerable retention in organs and tissues. The investigators speculate that given the cyclohexapeptide structure of pasireotide, there is a possibility of its having been degraded, with amino acid derivatives being incorporated into cell structures and subsequently being eliminated very slowly. They cite a rat tissue distribution study, presumably part of the preclinical development program, in which radioactivity after intravenous dosing with pasireotide was still observed at 14 weeks in various organs, with 14% remaining in the carcass after three weeks; and a further rat ADME study in which 8.3% of the dose was retained in the carcass at 72 hours, corresponding to unchanged pasireotide residing in liver and kidney. They also cite the possibility of radioactivity having been lost by non-specific binding to containers and bags during the study, quoting prior experience of the sponsor's development group that pasireotide has such properties. If that is the case, it is a possible design flaw in the study that the containers were not included in the accounting process for tracer distribution. In particular, it is noted that the accuracy of the administered dose was checked by weighing the syringe before and after administration, rather than by counting the syringe for residual radioactivity. It is recognised that technical procedures for measuring minute quantities of radiocarbon in such devices may have made this difficult.

Renal clearance:

This has not been formally measured.

Comment: As reviewed above, evidence supports the majority of pasireotide elimination being by the hepatic route, and it is understood that this has also been shown in animal studies. Renal clearance would, therefore, only become a limiting factor and therefore potentially important from a safety standpoint, in situations in which hepatic elimination is compromised by impaired liver function. The

impact of impaired renal function on pasireotide PK, whether in the presence or absence of impaired hepatic function, has not been studied.

3.2.1.6. Intra- and inter-individual variability of pharmacokinetics

In all of the submitted studies, this appears within reasonable limits for the type of investigations undertaken, based on the experience of this evaluator.

3.2.2. Pharmacokinetics in the target population

In pivotal efficacy Study B2305, trough pasireotide levels (ng/mL) were measured prior to the morning dose at baseline, every 15 days for the first three months and every month thereafter. These data are shown below, by dosage group:

Table 8: Trough pasireotide levels

Day	300 µg b.i.d.		600 µg b.i.d.		900 µg b.i.d.		1200 µg b.i.d.	
	N	Mean ± SD	N	Mean ± SD	N	Mean ± SD	N	Mean ± SD
15	2	1.46 ± 0.67	75	5.15 ± 3.30	64	8.22 ± 5.91	0	n/a
30	5	3.02 ± 1.34	77	5.84 ± 3.56	56	9.06 ± 5.22	0	n/a
45	6	4.06 ± 2.67	72	5.72 ± 3.36	58	7.97 ± 4.44	0	n/a
60	5	3.09 ± 0.91	72	5.89 ± 3.23	49	8.49 ± 4.34	0	n/a
75	4	2.62 ± 0.91	70	6.14 ± 3.15	53	8.20 ± 3.71	0	n/a
90	6	5.72 ± 7.29	69	6.60 ± 4.38	49	8.82 ± 4.35	0	n/a
120	6	2.94 ± 0.99	42	6.08 ± 3.21	58	8.48 ± 3.91	11	11.70 ± 4.28
150	7	3.25 ± 1.19	31	6.47 ± 4.09	59	8.65 ± 5.42	13	14.01 ± 5.40
180	8	6.09 ± 7.78	29	7.09 ± 4.76	58	8.94 ± 5.02	14	14.48 ± 5.43
210	8	3.38 ± 0.76	16	9.15 ± 7.03	53	8.73 ± 4.86	19	13.83 ± 6.27
240	8	3.50 ± 0.90	14	10.01 ± 8.01	45	8.95 ± 4.11	19	13.21 ± 7.47
270	6	4.17 ± 1.77	17	7.37 ± 5.44	44	8.12 ± 3.28	20	12.11 ± 5.49
300	7	4.00 ± 1.49	16	9.82 ± 7.45	42	8.36 ± 3.14	19	11.97 ± 5.32
330	7	3.73 ± 1.87	18	8.63 ± 7.48	35	8.79 ± 3.91	18	10.64 ± 3.78
360	5	4.67 ± 3.89	14	7.58 ± 4.77	33	8.22 ± 5.91	19	12.01 ± 5.41

There is no evidence of accumulation beyond 15 days, and visual inspection of the data suggests dose proportionality consistent with that described in the studies in HV.

A Cushing's disease PopPK model and analysis provided by the sponsor suggests that dose specific exposure is approximately twofold higher than in HV. It is difficult to confirm this by reference to data from the specific study reports (for example, trough levels at steady state which would be comparable with the data in Table 1 above are not given for the twice-daily cohort in the study report for B2106), but the population analysis attributes the difference to reduce CL/F figures approximating 3.8 L/h for the Cushing's disease population by comparison with approximately 6.7 L/h for healthy subjects. The population analysis does identify age and lean body weight (BW) as covariates. The study population in B2305 was older (mean 40 years) than in the HV PK studies in which mean age range from 26-30 years. This, together with the reduced proportion of lean body mass characteristic of all forms of Cushing's syndrome, may explain the observation.

Comment: Whatever the mechanism, the prediction and observation of increased drug exposure in the target population of Cushing's disease is important as it suggests that any exposure related safety signals in the Phase I studies (of which there are some) are likely to be amplified in clinical use.

3.2.3. Pharmacokinetics in other special populations

3.2.3.1. Pharmacokinetics in subjects with impaired hepatic function

PK of pasireotide in relation to hepatic function is addressed in Study B2114, in which single doses of pasireotide 600 µg were administered to HV and to cohorts of subjects with mild, moderate or severe hepatic dysfunction. The results are included in Table 9.

Table 9: Study B2114 summary

PK Parameter (unit)	Normal (N = 12)	Mild (N = 6)	Moderate (N = 7)	Severe (N = 6)
AUC_{inf} (ng.hr/mL)	88.9 (33.8)	100.0 (24.8)	138.9 (31.3)	125.9 (41.5)
AUC_{last} (ng.hr/mL)	83.2 (33.4)	91.9 (28.9)	120.2 (32.1)	116.3 (40.0)
C_{max} (ng/mL)	11.4 (48.4)	11.8 (29.2)	16.6 (42.4)	15.2 (46.1)
T_{max} (hr)	0.76 (0.25 - 2.00)	1.00 (0.50 - 2.00)	0.67 (0.47 - 2.00)	1.00 (0.50 - 1.00)
$T_{1/2}$ (hr)	15.4 (71.7)	22.1 (42.8)	36.4 (73.4)	29.1 (74.3)
CL/F (L/hr)	6.7 (33.7)	6.0 (24.8)	4.3 (31.4)	4.8 (41.4)
V_z/F (L)	149.6 (54.8)	191.3 (24.7)	226.3 (49.0)	199.8 (42.5)
λ_z (1/hr)	0.045 (71.7)	0.031 (42.6)	0.019 (73.6)	0.024 (74.4)

The unadjusted data showed statistically significant increases in $AUCi_{nf}$ of 56% and 42% for the moderate and severe cohorts respectively and a statistically significant increase of 45% in C_{max} for the moderate cohort. Following adjustment for age and BMI, the only significant finding was an increase in AUC_{inf} of 38% in the severe cohort. These data are reproduced below in Table 10.

Table 10: Pharmacokinetic parameters from Study B2114, by grade of impaired hepatic function

PK Parameter (unit)	Cohort	n*	Age- and BMI-adjusted Geo-mean	Comparison (s)	Comparison: Geo-mean Ratio	Comparison: 90% CI Lower	Comparison: 90% CI Upper
AUC_{inf} (ng.hr/mL)	Control	12	95.6				
	Mild	6	97.6	Mild : Control	1.02	0.79	1.32
	Moderate	6	117.6	Moderate : Control	1.23	0.92	1.65
	Severe	6	131.9	Severe : Control	1.38	1.07	1.78
AUC_{last} (ng.hr/mL)	Control	12	88.3				
	Mild	6	90.3	Mild : Control	1.02	0.78	1.34
	Moderate	7	105.8	Moderate : Control	1.20	0.89	1.61
	Severe	6	121.7	Severe : Control	1.38	1.06	1.79
C_{max} (ng/mL)	Control	12	11.5				
	Mild	6	11.7	Mild : Control	1.02	0.72	1.46
	Moderate	7	15.9	Moderate : Control	1.39	0.94	2.05
	Severe	6	15.8	Severe : Control	1.38	0.98	1.94
CL/F (L/hr)	Control	12	6.3				
	Mild	6	6.2	Mild : Control	0.98	0.76	1.27
	Moderate	6	5.1	Moderate : Control	0.81	0.61	1.09
	Severe	6	4.5	Severe : Control	0.73	0.56	0.93
T_{max} (hr)	Control	12	0.76				
	Mild	6	1.00	Mild : Control	0.26	0.00	1.00
	Moderate	7	0.67	Moderate : Control	0.00	-0.33	0.48
	Severe	6	1.00	Severe : Control	0.00	-0.02	0.50

n* = number of subjects with non-missing values

Control is the hepatic function normal cohort

PK parameters were analyzed separately on the log scale by means of an ANOVA model including cohort as a fixed effect, and age and BMI as covariates

For T_{max}, median is presented under 'Adjusted Geo-mean', Hodges Lehmann estimate for the difference between the hepatic impairment cohort and the control cohort under "Geo-mean ratio", and the corresponding 90% distribution free CI under "Lower" and "Upper".

Source: PT-Table 14.2-1.1b

Despite the limitation of statistically significant change to the exposure data for the severe cohort, there is a clear trend in the point estimates towards increasing abnormality in the PK parameters as hepatic function deteriorates beyond the mild category, in which there are clearly no changes of significance. AUC_{inf} is increased by 23% in the moderate group and 38% in the severe group; C_{max} is increased by 39% and 38% respectively, and CL/F reduced by 19% and 27% respectively. Viewed collectively, these data suggest a definite change increasing drug exposure by means of reduced clearance in both the moderately and severely impaired groups, although more pronounced in the latter.

The difference between the unadjusted and age/BMI adjusted data is explained by the moderately affected patients being older, on average 63 years compared with 55 years for the entire group.

Comment: This study does not fully address the potential for significant overexposure to pasireotide in patients with moderately impaired, as well as severely impaired, liver function for the following reasons:

- § It is only a single dose study. PK studies in HV, reviewed above, clearly show drug accumulation with achievement of steady state at three to four days. Exposure at steady state is what is important from a safety standpoint.
- § To draw the rather fine distinction between the moderately and severely affected groups, the subject numbers are small: seven with moderate and six with severe hepatic impairment.
- § With the reduction in clearance which is apparent, and given that hepatic clearance is the major route of excretion, it is at the very least likely that accumulation will be exaggerated and prolonged in moderately impaired patients, resulting in higher steady state drug levels. This should either be assumed or excluded by appropriate studies.
- § While the adjustment for age and BMI is scientifically valid, the observation that a statistically significant increase in exposure occurred in an older group of moderately hepatic impaired subjects cannot be ignored. Age has already been identified as a potential factor for increased exposure in the target population, and it is plausible that older patients may be particularly vulnerable to the impact of impaired liver function on pasireotide exposure.

3.2.3.2. Pharmacokinetics in subjects with impaired renal function

No clinical data submitted.

3.2.3.3. Pharmacokinetics according to age

Not specifically studied, but the results of PopPK modelling as already referred to above suggest a relationship with a between increasing age and reduced clearance.

3.2.4. Pharmacokinetic interactions

3.2.4.1. Pharmacokinetic interactions demonstrated in human studies

No clinical data submitted.

3.2.4.2. Clinical implications of in vitro findings

IV studies described in the Clinical Overview, Summary of Clinical Pharmacology and other summary documents showed that pasireotide was a weak inhibitor of a variety of CYP 450 enzymes with IC 50 values in the 10-100 μM range, and a moderate inhibitor of CYP2C9 and CYP2D6, with IC 50 approximating 5 μM. It also failed to induce CYP 450 enzymes at concentrations up to 1 μM. Pasireotide is also described as being highly metabolically stable in the kidney microsomes and to be metabolised only slowly by recombinant CYP 3A4 and CYP 3A5. Therapeutic levels of plasma pasireotide are two to three-fold lower (approximately 0.1 μM) than the concentrations described above. The clinical evaluator therefore accepted the sponsor's conclusion that, based on these findings, there is a very low likelihood of pasireotide being implicated in interactions with drugs which are inhibitors, inducers or substrates of CYP 450 enzymes.

IV findings similarly lead to a conclusion that there is a low likelihood of drug-drug interactions between pasireotide and drugs which are inhibitors, inducers or substrates of P-gp (see Summary of Clinical Pharmacology). Similar conclusions are made in the Clinical Overview in relation to the likelihood of pasireotide inhibiting the metabolic clearance of co-medications metabolised by UGT1A1 or affecting the conjugation of bilirubin in-vivo; or of drug-drug interactions based on inhibition of the bile salt export pump or being a substrate for breast cancer resistance protein or organic anion-transporting polypeptides. All of these conclusions appear soundly based, presuming that the studies leading to them have been evaluated in the nonclinical evaluation report(s) for this application.

3.3. Evaluator's overall conclusions on pharmacokinetics

The PK profile of pasireotide has been well characterised, both in HV and the target population, in respect of its intended use by subcutaneous injection for patients with Cushing's disease. Rapid and complete absorption with dose proportionality across the proposed therapeutic range, absence of significant interference by metabolites, and major dependence on hepatic excretion have all been established.

Increased exposure in the target population is identified and appears largely due to the covariate of age. This should be made clearer in information on PK in the draft PI and the clinical evaluator made a comment about this.

As discussed above, the data on single dose PK exposure in hepatically impaired patients is accurate as it stands but does not adequately assess the potential for hazardous exposure with multiple dosing. This has implications for relevant sections of the contraindications, precautions and dosing sections of the draft PI.

4. Pharmacodynamics

4.1. Studies providing pharmacodynamic data

Table Table11 shows the studies relating to each pharmacodynamic (PD) topic. Note that a number of these studies also appear in Table 1 as many of the Phase I studies include both PK and PD data; also that there are no clinical studies relating to the primary PD action of pasireotide for the purpose of this application, which is its action in suppressing ACTH release from the pituitary, and from pituitary tumour cells in particular. This has been established in IV studies.

Table 11: Submitted pharmacodynamic studies.

PD Topic	Subtopic	Study ID
Secondary Pharmacology	Effect on growth hormone release	B2101
	Effect on glucose homoeostasis	B2102
		B2102*
		B2106*
		B2107*
		B2216
	Cardiac repolarisation	B2113
		B2125
PD Interactions	Metformin, vildagliptin, liraglutide and nateglinide	B2124
Population PD and PK-PD analyses	Target population with pituitary Cushing's disease	Module 5.3.3.5

None of the PD studies had deficiencies that excluded their results from consideration.

4.2. Summary of pharmacodynamics

The information in the following summary is derived from conventional PD studies in humans unless otherwise stated.

4.2.1. Mechanism of action

As described above, the mechanism of action in the proposed indication is for pasireotide to inhibit ACTH secretion by pituitary corticotroph tumours by means of binding to the specific receptor subtype (hsst5) expressed in those tumours and thus inhibiting ACTH release, with consequent reduction in cortisol hyper-secretion which is responsible for the clinical manifestations of Cushing's disease. Evidence supporting this PD action is based on IV studies, briefly summarised by the sponsor in the following statement copied from the draft PI:

IV studies have shown that corticotroph tumour cells from Cushing's disease patients display a high expression of hsst5 whereas the other receptor subtypes are either not expressed or are expressed at lower levels. Pasireotide binds and activates the hsst receptors of the corticotrophs in ACTH producing adenomas resulting in inhibition of ACTH secretion.

Accompanying this statement is the following table displaying the binding affinities of native somatostatin, pasireotide, and other somatostatin analogues to the various hsst subtypes:

Table 12: binding affinities of native somatostatin, pasireotide, and other somatostatin analogues to the various hsst subtypes

Compound	hsst1	hsst2	hsst3	hsst4	hsst5
Somatostatin (SRIF-14)	0.93±0.12	0.15±0.02	0.56±0.17	1.5±0.4	0.29±0.04
Pasireotide	9.3±0.1	1.0±0.1	1.5±0.3	> 1000	0.16±0.01
Octreotide	280±80	0.38±0.08	7.1±1.4	> 1000	6.3±1.0
Lanreotide	180±20	0.54±0.08	14±9	230±40	17±5

These data are expressed as the inhibitory concentration 50 (IC50) (nmol/L) required for inhibition. Note that the value for pasireotide in respect of hsst5 is very low, indicating a high affinity of binding to this receptor subtype.

Evidence supportive of this PD action in man is necessarily based on efficacy studies, the first which to be conducted was proof-of-concept Study B2208.

It should also be noted from Table 11 that pasireotide exhibits binding to hsst2 of the same order of magnitude as octreotide and lanreotide, which are used as treatments for acromegaly. This is the basis for its action in suppressing growth hormone (GH) release, which for the purpose of this application is discussed as a secondary PD action along with its other secondary actions on insulin glucagon secretion, which is of particular significance for this application.

4.2.2. Pharmacodynamic effects

4.2.2.1. Secondary pharmacodynamic effects

In many of the submitted studies, the PD effect of pasireotide on growth hormone secretion was measured as a parameter of primary interest in relation to the potential use of pasireotide as a treatment for disorders of growth hormone excess. For the purpose of this submission, any effect on pituitary secretion of growth hormone is of secondary importance and should be regarded as a safety issue. Relevant data from individual studies are briefly summarised below.

In Study B2101, suppression of the GH response to growth hormone releasing hormone (GHRH) given intravenously (1 µg GHRH/kg BW) was measured, to gain an early indication of the dosage threshold at which such effects would be observed. Evidence of suppression was evident following single subcutaneous (sc) doses of 30-100 µg with near maximal effects at 200 µg (79% suppression), 300 µg (87%) 600 µg (83%) and 1200 µg (96%).

Table 13: The distribution of baseline characteristics between the randomised dosage groups

		Pasireotide 600 µg b.i.d. N=82	Pasireotide 900 µg b.i.d. N=80	Overall N=162
Time (months) to first pasireotide dose since diagnosis				
n		82	80	162
Mean (SD)		53.38 (63.79)	54.70 (62.79)	54.03 (63.11)
Median		35.48	29.70	33.99
Min –Max		0.10-341.78	0.10-372.14	0.10-372.14
Cushing's Disease Status – n (%)	De novo	15 (18.3)	12 (15.0)	27 (16.7)
	Persistent/recurrent	67 (81.7)	68 (85.0)	135 (83.3)
Any previous surgery – n (%)	No	18 (22.0)	16 (20.0)	34 (21.0)
	Yes	64 (78.0)	64 (80.0)	128 (79.0)
Any previous pituitary irradiation – n (%)	No	79 (96.3)	76 (95.0)	155 (95.7)
	Yes	3 (3.7)	4 (5.0)	7 (4.3)
Any previous medication – n (%)	No	46 (56.1)	38 (47.5)	84 (51.9)
	Yes	36 (43.9)	42 (52.5)	78 (48.1)
Baseline mean UFC				
n		77	76	153
Mean (SD)		1155.94 (2629.779)	781.90 (926.384)	970.14 (1979.020)
Median		730.00	487.00	564.50
Min-Max		219.50-22943.75	195.00-6122.75	195.00-22943.75

Comment: Clearly, the dose threshold for this action (that is, EC50) is much lower than that for its therapeutic action in reducing cortisol (via ACTH) secretion in Cushing's disease; of note, however, what is being described here is suppression of physiological hormonal secretion, not pathological hypersecretion.

In Study B2102, a number of PD parameters were measured including 24-hour gastric pH monitoring, GHRH stimulation test, stool fat excretion, glucose, cholecystokinin (CCK), gastrin, insulin, total insulin-like growth factor-1 (IGF-1), free IGF-1, IGF-binding protein (IGFBP)-1, IGFBP-2, and IGFBP-3. The results for gastric pH were very variable and difficult to interpret. There was some evidence of an increase in stool fat of around 5% at the higher dose levels. Pre- and post-prandial glucose levels, and also insulin levels, were elevated in the 600 µg pasireotide group but the effect on glucose was less evident on Day 14 than on Day 1. Statistical significance was not demonstrated due to the small numbers. There was no evidence of an effect on glucagon, gastrin or thyroid hormones. There was an increase in gallbladder volume at the 200 and 600 µg dose levels, corresponding with reduced levels of CCK at these doses. The expected effect on inhibition of GHRH stimulated GH secretion was observed at 200 and 600 µg but not at 50 µg; half maximal GH reduction was associated with a mean pasireotide concentration of approximately 0.7 ng/mL. There was no evidence of tachyphylaxis comparing the results on Day 14 with Day 1.

Effects on glucose homoeostasis:

Inhibition of both insulin and glucagon secretion is a known effect of somatostatin which can be reproduced by somatostatin analogues and the overall effect of pasireotide on glucose, insulin and glucagon homoeostasis is therefore an important secondary PD effect with potential safety implications.

Exploratory observations in Studies B2101 (Table 2) and B2102 (Table 5) showed both pre-and post-prandial hypoglycaemia. Further observations in B2106 (Table 3) showed hyperglycaemia during a fasting period following pasireotide administration to be accompanied by reduced insulin levels. Post-prandial hyperglycaemia was also observed and appeared to be dose

dependent and accompanied by insulin levels which were higher than on a control day, although the latter observation is of little significance because the insulin levels have to be interpreted in relation to the prevailing plasma glucose. Study B2107 was conducted specifically to examine the effects on glucose homoeostasis of the range of doses from 150 to 1500 µg, given as either single or divided daily doses for 8 days, but as noted in Table 14 below, the quality of the data obtained and analysis thereof permits only descriptive comments of the outcomes.

Table 14: The effects on glucose homoeostasis of the range of doses from 150 to 1500 µg

Dose	Day 1 Pre-dose FG Mean (SD)	Day 1 Peak FG Mean (SD)	Day 1 Peak PPG Mean (SD)	Day 7 Peak FG Mean (SD)	Day 7 Peak PPG Mean (SD)	Day 2 Pre-dose FG Mean (SD)	Day 2 Peak PPG Mean (SD)	Day 8 Pre-dose FG Mean (SD)	Day 8 Peak PPG Mean (SD)
1 x 150 µg	84.0 (7.0)	130.7 (15.4)	142.2 (32.0)	115.5 (10.6)	118.8 (14.4)	94.0 (4.9)	180.0 (42.1)	87.0 (4.7)	156.8 (14.8)
1 x 300 µg	97.5 (3.9)	163.2 (12.8)	175.7 (23.8)	133.5 (10.2)	145.2 (30.6)	97.8 (5.4)	208.2 (22.3)	95.0 (3.3)	201.5 (20.0)
1 x 600 µg	95.8 (8.9)	164.5 (22.5)	207.2 (45.1)	130.2 (19.4)	156.8 (29.6)	99.8 (9.3)	200.2 (38.5)	88.5 (9.6)	165.8 (21.4)
1 x 900 µg	98.0 (5.7)	171.7 (26.8)	225.0 (35.2)	130.3 (17.3)	153.0 (30.3)	91.2 (6.9)	209.2 (37.7)	93.0 (6.5)	194.8 (38.9)
1 x 1200 µg	94.0 (6.3)	166.2 (21.2)	266.2 (63.7)	144.7 (21.3)	208.8 (27.5)	88.5 (10.1)	213.0 (45.8)	100.2 (12.8)	189.8 (26.2)
1 x 1500 µg	101.3 (9.6)	174.8 (15.0)	293.8 (64.8)	141.5 (29.3)	227.0 (27.1)	105.7 (9.5)	217.0 (36.1)	98.0 (15.9)	207.3 (27.7)
2 x 150 µg	90.7 (6.7)	132.8 (10.5)	111.0 (30.1)	118.3 (7.6)	127.5 (17.7)	97.0 (8.4)	185.0 (28.9)	91.8 (5.6)	163.8 (14.3)
2 x 300 µg	96.0 (7.5)	154.3 (15.5)	165.2 (30.6)	125.2 (10.3)	125.2 (27.8)	104.5 (6.4)	187.5 (30.7)	96.8 (7.2)	181.7 (19.0)
2 x 450 µg	98.2 (4.8)	153.0 (19.5)	194.7 (22.5)	126.7 (10.2)	129.7 (15.8)	101.2 (5.7)	172.2 (12.9)	91.0 (9.1)	173.7 (13.1)
2 x 600 µg	91.7 (7.3)	156.5 (27.6)	209.8 (44.7)	125.3 (16.4)	154.2 (27.1)	96.3 (10.3)	174.2 (12.8)	94.0 (10.2)	188.2 (22.2)
2 x 750 µg	99.2 (5.6)	174.7 (22.7)	229.3 (36.6)	135.3 (7.4)	145.5 (35.5)	104.3 (5.0)	180.3 (26.9)	102.7 (11.5)	184.2 (20.0)

In summary, these were:

- A substantial increase in glycaemia approximating 60-70% at peak over the four hours following administration of pasireotide in the fasting state, for all doses >300 µg.
- Elevation of post-prandial glucose at all doses, in a dose-dependent fashion with the greatest increases following the larger single morning doses; the highest mean (SD) peak plasma glucose value observed was 294+65 mg/dL (16.3+3.6 mmol /L) in the 1500 µg dosage group
- The fasting hyperglycaemia was associated with quite marked suppression of insulin secretion, particularly during the first hour after pasireotide administration with many of the groups showing mean plasma insulin values of 0-2 pmol/L during this time, compared with fasting values of approximately 30-50 pmol/L. The extent and duration of suppression was dose-related but not markedly so except that suppression was clearly less than for the 150 µg dosage group. This of course indicates that the effect is quite definite and similar across the proposed therapeutic dosage range.
- Suppression of fasting glucagon secretion was mild (by about 20% of baseline), and transient.
- There was a clear trend for both the post-prandial and particularly the fasting hyperglycaemia to be less evident, by approximately 10-15%, on Days 7 and 8 of the treatment period than on Days 1 and 2.

Very similar findings to the above were reported in Study B2108 in which doses of 450-2250 µg pasireotide daily were infused for seven days (Table 6).

The above data shows that pasireotide suppresses insulin secretion and to a lesser extent glucagon secretion in the fasting state, from quite a low dosage threshold (no higher than 150 µg). To assess the effect of pasireotide in the fed state, that is, the mechanism of the post-prandial hypoglycaemia, a glucose clamp study was required and this was performed in Study B2216. The response to oral glucose, including measurement of incretin hormones, insulin secretion during a hyperglycaemic clamp, and measurements of hepatic and peripheral insulin sensitivity during a hyperinsulinaemic clamp, were assessed on consecutive days in a control sequence and secondly during pasireotide administration. For convenience, the summary of the results, with the addition of graphic illustrations, is shown as follows:

Following glucose loading, a delayed and excessive rise in plasma glucose was seen, peaking at two hours and accompanied by marked suppression of insulin response. Fasting glucagon was also suppressed. There was virtual abolition of the incretin effect (response of GLP-1 and GIP) following oral glucose. The time course of the various parameters observed during the glucose tolerance tests prior to (Day 1) and following (Day 8) pasireotide administration is shown in the following grahics. Note that in all these displays, data for both 600 and 900 µg bd dose levels are shown.

Figure 1: Dose levels of plasma glucose

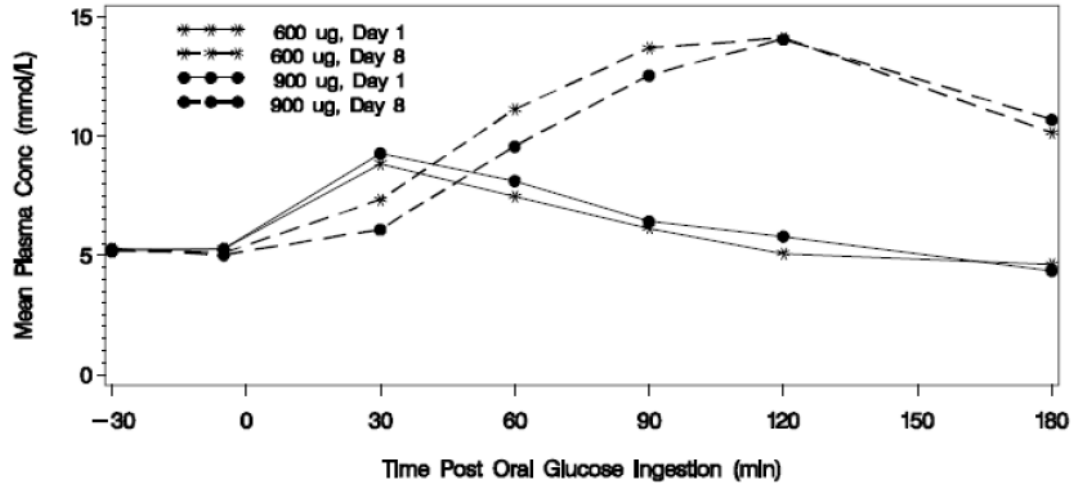
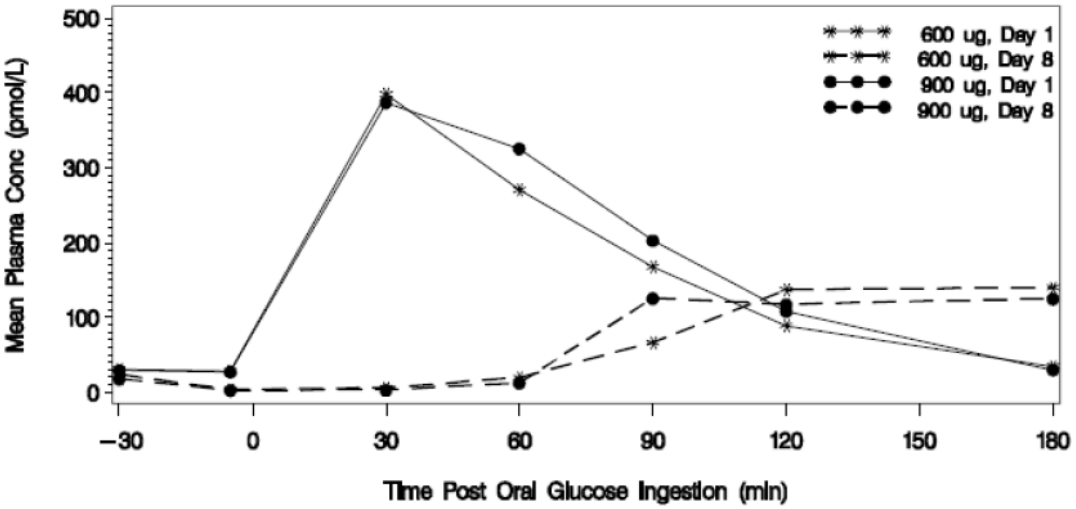
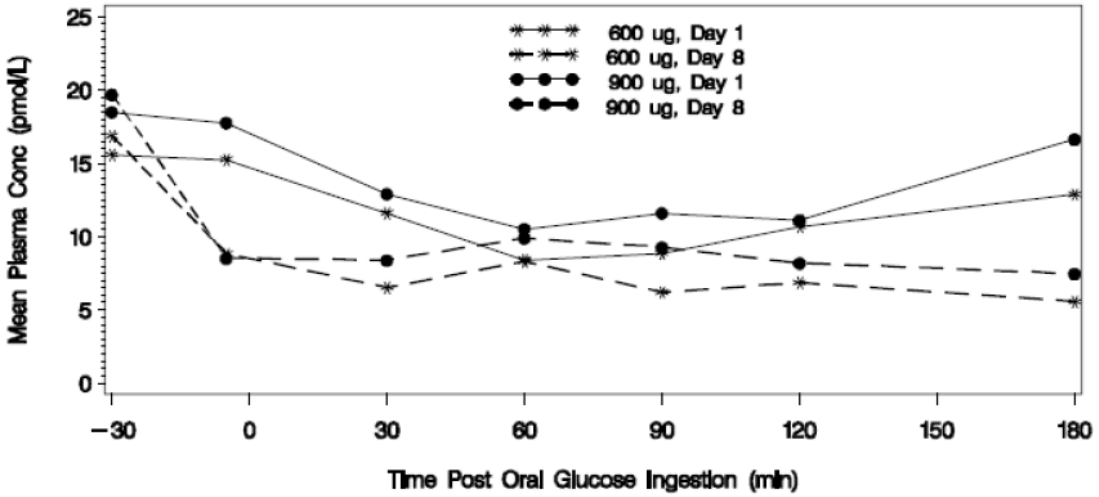


Figure 2: Changes in plasma insulin



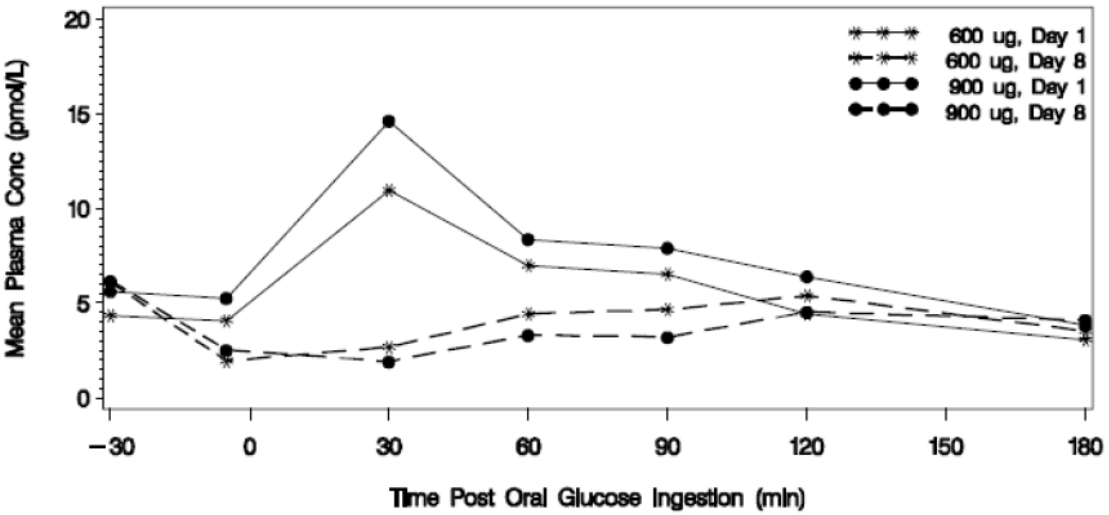
The pattern of time course of changes in C-peptide corresponded closely to those of insulin.

Figure 3: The pattern of change in plasma glucagon



The incretin hormones GLP-1 and GIP were also measured throughout the OGTTs. The results for GLP-1 are shown in Figure 4 below; GIP showed similar suppression

Figure 4: Changes in levels of incretin hormone GLP-1



During the hyperglycaemic clamp study done on pasireotide on Day 10, there was marked suppression of the normal (as seen on Day 3) early and sustained rise of endogenous insulin secretion as reflected by plasma insulin and C-peptide measurement.

During the hyperinsulinaemic clamp studies, measurements of endogenous glucose production (EGP) and glucose disposal rate (GDR) both before and after insulin remained unchanged during pasireotide by comparison with baseline. EGP reflects hepatic and GDR peripheral insulin sensitivity.

Overall, this well-designed study presents robust evidence that the hyperglycaemic effect of pasireotide is the consequence of suppression of insulin secretion, including a component due to suppression of the incretin effect, rather than any effect on hepatic or peripheral insulin sensitivity. Suppression of glucagon in the fasting state also plays a role.

There was no evidence of a dose effect between 600 and 900 µg bd, the doses proposed for therapeutic use; as shown in Study B2107, the dose threshold for effect of pasireotide on fasting glucose is much lower. This is consistent with the observation in relation to its effect on growth hormone, another physiological function, being much lower than that which is observed for therapeutic use on pathological ACTH secretion.

Effect on cardiac repolarisation:

Studies B2113 and 2125 were carried out to assess the potential for therapeutic doses of pasireotide to affect cardiac repolarisation (QT prolongation. Both these studies are classifiable as "thorough QTc studies" for regulatory purposes. The second was done so as to compare any effect observed at a therapeutic dose (600 µg bd) with changes which had been observed in the earlier study at a supra-therapeutic dose of 1950 µg bd. A significant, by comparison with placebo, mean prolongation of QTcI was observed of 13.2 ms for the 600 µg group and 16.1 for the 1950 µg group, comparable with a mean change of 11.1 ms for a group treated with active comparator moxifloxacin, a drug known to prolong QT. The observed changes represent a 2.8-3.5% increase on the maximum allowable QTcF at baseline, which was 470 ms for females and 450 ms for males.

The significance for cardiac safety of these observations is discussed below.

4.2.3. Relationship between drug concentration and pharmacodynamic effects

A detailed PopPK/PD analysis, based on 12 month data from Phase III Studies B2305 and B2208 was presented. The relationship between pasireotide trough concentration and both primary (UFC reduction) and secondary (FPG increase) PD response is analysed. In brief summary, the conclusions were that UFC decreased with increasing pasireotide concentration, but tended to reach a minimum below which it could not go. Likewise, FPG increased on average with increasing pasireotide trough concentration. The pasireotide effect on FPG tended to be higher for patients with baseline FPG and older patients. The effect of baseline FPG was less evident in females.

Comment has already been made in the previous section regarding different dosage thresholds for the primary and secondary PD effects.

4.2.4. Genetic-, gender- and age-related differences in pharmacodynamic response

In the analysis described above, maximum effect on UFC reduction tended to occur at lower trough concentrations of pasireotide in females, but there was no gender difference in the maximum effect (that is, minimum UFC achieved). Age and ethnic group had no effect. As described above, there was a subtle gender effect on the secondary PD response of increasing FPG, but again no influence of other baseline characteristics including age and ethnicity.

4.2.5. Pharmacodynamic interactions

Study B2124 assessed the effectiveness of a variety of oral hypoglycaemic medications coadministered with pasireotide in offsetting its secondary PD effect of inducing hyperglycaemia, the mechanisms for which are described above. The drugs administered in combination with pasireotide were metformin, vildagliptin, liraglutide and nateglinide (a megltinide not registered in Australia: repaglinide belongs to the same class). The greatest degree of inhibition of the hyperglycaemic effect of pasireotide was seen with liraglutide, a GLP-1 agonist, followed by vildagliptin, a DPP4 inhibitor. Metformin was without significant effect.

4.3. Evaluator's overall conclusions on pharmacodynamics

Evidence for the primary PD effects of pasireotide on ACTH and cortisol secretion in patients with pituitary corticotroph tumours rests on IV studies not reviewed in this evaluation, and its effectiveness in the Phase III efficacy studies.

Pasireotide has, as described above, a number of secondary PD actions which reflect the widespread inhibitory role of somatostatin in endocrine physiology. Physiological GH secretion is suppressed at a lower dosage threshold than that found for pasireotide's therapeutic action in Cushing's disease.

The lower dosage threshold also observed for pasireotide's secondary PD effect on glucose homoeostasis, by comparison with its PD effect on cortisol secretion in Cushing's disease, is of practical importance in relation to safety: it implies that maximal effect on parameters of glucose homoeostasis are likely to be seen at any dose within the therapeutic range, so that downward adjustment of dosage would be unlikely to ameliorate hyperglycaemia should this occur as an adverse effect. It is likely that the same applies to the variety of other secondary PD actions assessed in Study B2102 (Table 5), all of which have some potential as the basis for safety issues.

The mechanism for the secondary PD effect on glucose homoeostasis has been extremely well-documented in the included studies. The drug PD interaction Study B2124 suggests that oral diabetes therapies which act through the incretin effect are most likely be to be useful in managing hyperglycaemia should this be necessary. The importance of these observations in relation to safety, particularly in long-term use, is discussed below.

5. Dosage selection for the pivotal studies

The doses used in pivotal Study B2305 were chosen on the basis of the PK/PD data generated by the studies described above as likely to be effective, yet within the tolerated dose range. Particularly in terms of the secondary PD effects on glucose homoeostasis, the doses chosen are closer to the maximum tolerated as opposed to the minimum effective dose. Because of the limited study population available due to the rarity of pituitary Cushing's disease, the sponsor argues that the performance of a formal dose ranging study would be impractical, a position which is acceptable to this evaluation.

6. Clinical efficacy

6.1. Cushing's disease

6.1.1. Pivotal efficacy study

6.1.1.1. Study B2305

Study design, objectives, locations and dates:

This was a Phase III, randomised, double-blind study to assess the efficacy and safety of different doses of subcutaneously administered pasireotide over a six-month treatment period in patients with newly arising, persistent or recurrent Cushing's disease. It was undertaken between December 2006 and March 2010 at 53 international centres in Argentina, Belgium, Brazil, Canada, China, Germany, Denmark, Spain, Finland, France, Greece, Israel, Italy, Mexico, Poland, Portugal, Turkey and the USA. Countries with the largest number of sites (seven each) were France, Italy and the USA. The coordinating investigator was Dr Beverly Biller of the Massachusetts General Hospital, Boston USA.

The study design undertakes comparison of two dosage levels (600 µg bd and 900 µg bd). Following randomisation to one of these two treatment arms, double-blind treatment was to continue for six months unless a 300 µg dose increment was indicated on the basis of pre-established criteria at the three month assessment. Following this there was a further six-month open-label phase. There was no placebo or active control. The sponsor argues that a placebo group would be ethically unacceptable because of the severity of the condition and some of the circumstances of recruitment (for example, failed response to surgery); and that an active control is impractical because there is no alternative approved treatment.

Comment: The argument for not including a placebo group is accepted. With regard to the possibility of an active control, there are other treatments available and in use despite lack of regulatory approval, as summarised above, which could have been used for this purpose. However this would have involved a larger study and potential difficulties in interpretation particularly in the sense that there might be sub-populations more or less likely to respond to one treatment or the other. Furthermore the principal outcome variables are changes in laboratory measurements, for which a placebo response is unlikely to be observed. In summary, the study design is acceptable.

Inclusion and exclusion criteria:

Inclusion criteria: Patients aged 18 years or above with a confirmed diagnosis of Cushing's disease, including a mean urinary free cortisol (mUFC) > one and a half times upper limit of normal (ULN), whose disease had been persistent or occurred after pituitary tumour resection, or for whom, in de novo Cushing's disease, such surgery was not indicated.

In addition to the mUFC on four 24-hour urine samples collected over a two-week period having to satisfy the above criterion, it was required that a non-suppressed plasma ACTH had been demonstrated, and that the presence or prior presence of an ACTH secreting pituitary adenoma had been demonstrated either by inferior petrosal sinus sampling or histological/ mmunohistometric confirmation. Washout periods of four weeks were required for dopamine agonists, of variable periods between one and eight weeks for other somatostatin analogues, depending on the formulation, and for ketoconazole or metyrapone, one week.

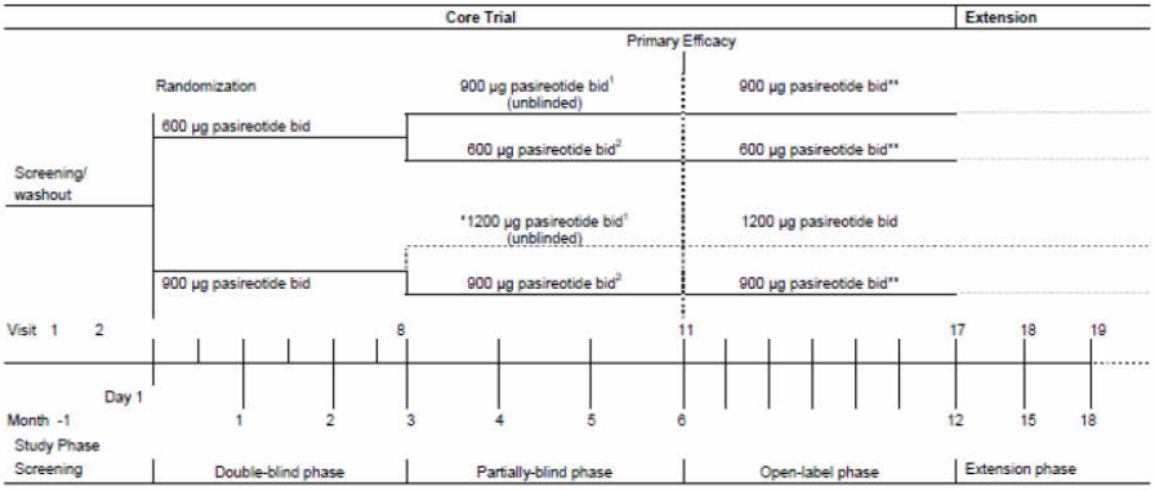
Patients with a known history of diabetes mellitus could be included, with provision for close monitoring during the study.

Exclusion criteria: Significant inclusions in this list are a history of pituitary irradiation within 10 years and a number of cardiac and medication exclusions designed to prevent enrolment of patients at risk for long QT interval disorders.

Study treatments:

Following a 30 day screening period, eligible patients were randomised 1:1 either to 600 µg bd sc 900 µg bd sc in double-blind fashion. The medication was self-administered by the patients at 9 am and 9 pm each day, following instruction by clinic staff at the site. The randomised treatment allocation was not continued for the second three months of the double-blind period if the patient was showing signs of worsening at the three month assessment. Criteria for treatment change were all based on mUFC derived in the same way as for the baseline diagnostic assessment as described above. Full details of the treatment allocation throughout the 12 month study period can be seen from the following diagram.

Figure 4: Treatment allocation throughout the 12 month assessment



[1] For patients who had a baseline mUFC ≥ 2 x ULN with a Month 3 mUFC > 2 x ULN or who had a baseline mUFC < 2 x ULN with a Month 3 mUFC > baseline mUFC

[2] For patients who had a baseline mean UFC ≥ 2 x ULN with a Month 3 mUFC ≤ 2 x ULN or who had a baseline mUFC < 2 x ULN with a Month 3 mUFC ≤ baseline mUFC

* Permitted dose increase only if patient had tolerated 900 µg

** During open-label phase doses could be increased by 300 µg at any time during the study if response was lost

All doses were allowed to be reduced by 300 µg at any time during the study if the doses were not tolerated

China only: patients did not receive doses higher than 900 µg s.c. b.i.d. at anytime during the study

Efficacy variables and outcomes:

The main efficacy variables were:

- Response as determined by normalisation or reduction in urinary free cortisol
- Group response as judged by change in median urinary free cortisol
- Change in plasma ACTH and serum cortisol

The primary efficacy outcome was to achieve mUFC at or below ULN after six months treatment with no increase in pasireotide dosage.

Other efficacy outcomes included:

- Reduction of mUFC to <ULN at Month 3 and Month 12
- Reduction of mUFC by 50% or more
- Time to first response
- Median UFC response
- Improvement in clinical signs and symptoms of Cushing's disease
- Change in pituitary tumour volume on MRI scan
- Effect on quality of life
- Evaluation of safety and tolerability

Further exploratory objectives included evaluation of PK/PD relationship, and evaluation of midnight salivary cortisol levels in relation to serum cortisol and UFC (the latter is not described below as the results were inconclusive).

Randomisation and blinding methods:

Randomisation was managed by a central interactive voice response system (IVRS). Once an eligible patient was ready for randomisation, site staff called the IVRS which randomised the patient to one of the two treatment arms. Study medication was supplied in ampoules all of 1 mL volume containing either 900, 600 or 300 µg pasireotide, of identical appearance, with medication numbers which were linked centrally to the randomisation code, to which the site staff were blind. IVRS continue to provide medication packs on a monthly basis following calls from site staff.

Analysis populations:

146 patients were planned, and 165 patients were randomised. Three patients were erroneously randomised and therefore did not receive study drug. The full analysis set consisted of 162 patients, 82 in the 600 µg bd group and 80 in the 900 µg bd group. Mean age was 40 years (range 18-71); 78% of subjects were female and 78% Caucasian. BW data could not be located.

The per protocol set, consisting of all patients from the FAS without a major protocol deviation, was 153 patients (77 from the 600 µg bd and 76 from the 900 µg bd groups).

The PK analysis set consisted of 159 patients (80 given 600 µg bd and 79 given 900 µg bd), who received at least one dose of pasireotide and had at least one post-dose PK assessment.

Sample size:

Sample size calculations were based on a null hypothesis that any response rate higher than 15% would provide significant clinical benefit, and an alternative hypothesis that 30% response was achievable. Given this, it was calculated that enrolment of 146 patients would provide 87% power to demonstrate statistical significance.

Statistical methods:

Statistical analyses were conducted on date pooled from all study centres. The number of subjects per centre was too small to allow assessment of centre effect.

There was no hypothesis testing to compare the two groups. Between-group comparisons of the major endpoints were based on comparison of the frequencies of response, and other descriptive statistics. Individuals were defined as responders by the criteria listed above, and then point estimates and associated 95% confidence interval (CI) for the proportion of responders in each dosage group were calculated. If the lower bound of 95% CI for a dosage group was greater than 15%, then that dosage group was considered to have derived a significant benefit.

Participant flow:

The disposition of all randomised subjects up to the data cut-off date of 17 March 2010 is shown in the following table. Note that this includes the three subjects erroneously randomised, in addition to the FAS of 162 subjects.

Table 15: Disposition of randomised patients

Disposition Reason	Pasireotide 600 µg b.i.d. N=83 n (%)	Pasireotide 900 µg b.i.d. N=82 n (%)	Overall N = 165 n (%)
Randomized	83 (100.0)	82 (100.0)	165 (100.0)
Randomized but not treated	1 (1.2)	2 (2.4)	3 (1.8)
Randomized and treated	82 (98.8)	80 (97.6)	162 (98.2)
Discontinued at any time*	49 (59.8)	48 (60.0)	97 (59.9)
Reason for discontinuation			
Adverse event(s)	13 (15.9)	15 (18.8)	28 (17.3)
Unsatisfactory therapeutic effect	19 (23.2)	22 (27.5)	41 (25.3)
Subject withdrew consent	13 (15.9)	11 (13.8)	24 (14.8)
Protocol deviation	4 (4.9)	0	4 (2.5)
Discontinued at or prior to Month 6	28 (34.1)	27 (33.8)	55 (34.0)
Discontinued prior to Month 12 but after Month 6	15 (18.3)	14 (17.5)	29 (17.9)
Completed Month 12	39 (47.6)	39 (48.8)	78 (48.1)
Completed Month 12 and did not enter Extension phase*	14 (17.1)	7 (8.8)	21 (13.0)
Completed Month 12 and entered Extension Phase	25 (30.5)	32 (40.0)	57 (35.2)
Ongoing in Extension phase	19 (23.2)	25 (31.3)	44 (27.2)
Discontinued study in Extension phase	6 (7.3)	7 (8.8)	13 (8.0)

Note: % for the first three rows based on N. % for the remaining rows based on randomized and treated subjects. *Patients who completed Month 12 and did not enter extension phase are not counted as discontinuations.

By 12 months, 84 patients (51.9% of those randomised and treated) had discontinued. The most frequent cause given was unsatisfactory therapeutic effect for 16 patients in the 600 µg group and 21 patients in the 900 µg group, followed by adverse events (AE) in 12 and 14 patients respectively.

Major protocol violations/deviations:

As seen above, there were four protocol deviations which resulted in discontinuation, all in the 600 µg bd group. The total number of subjects from the FAS of 162 subjects who were excluded from the per protocol analysis set (n=153) because of protocol deviations was nine. This included three instances of mis-dosing, seemingly due to some breakdown in the system of communication by the investigators with IVRS. The study report also describes nine other protocol deviations sufficient to require exclusion from the per protocol analysis. As the total number of subjects excluded was nine, it is assumed that there were instances of multiple deviations in one or more subjects. The report comments that the inclusion of these patients in the primary efficacy analysis (which was performed on the FAS) had little impact on the results as eight were non-responders. There were no protocol deviations with safety impact.

Baseline data

The distribution of baseline characteristics between the randomised dosage groups is shown below.

Table 16: Distribution of baseline characteristics between the randomised dosage groups

		Pasireotide 600 µg b.i.d. N=82	Pasireotide 900 µg b.i.d. N=80	Overall N=162
Time (months) to first pasireotide dose since diagnosis				
n		82	80	162
Mean (SD)		53.38 (63.79)	54.70 (62.79)	54.03 (63.11)
Median		35.48	29.70	33.99
Min –Max		0.10-341.78	0.10-372.14	0.10-372.14
Cushing's Disease Status – n (%)	De novo	15 (18.3)	12 (15.0)	27 (16.7)
	Persistent/recurrent	67 (81.7)	68 (85.0)	135 (83.3)
Any previous surgery – n (%)	No	18 (22.0)	16 (20.0)	34 (21.0)
	Yes	64 (78.0)	64 (80.0)	128 (79.0)
Any previous pituitary irradiation – n (%)	No	79 (96.3)	76 (95.0)	155 (95.7)
	Yes	3 (3.7)	4 (5.0)	7 (4.3)
Any previous medication – n (%)	No	46 (56.1)	38 (47.5)	84 (51.9)
	Yes	36 (43.9)	42 (52.5)	78 (48.1)
Baseline mean UFC				
n		77	76	153
Mean (SD)		1155.94 (2629.779)	781.90 (926.384)	970.14 (1979.020)
Median		730.00	487.00	564.50
Min-Max		219.50-22943.75	195.00-6122.75	195.00-22943.75

Disease status is evenly distributed between the dosage groups, except for baseline mUFC, an indicator of disease severity, which is markedly higher in the 600 µg bd group as assessed either by mean or median value. The median value for the 900 µg bd group is 3.4 times the ULN range of 30 to 145 nmol/24 hr, whereas that for the 600 µg bd is 5.0 times the upper limit.

Results for the primary efficacy outcome:

The proportion of patients meeting the response criterion for the primary efficacy outcome (normalisation of mUFC at six months) is shown below for the FAS.

Table 17: Proportion of patients meeting the response criteria for the primary efficacy outcome

	Pasireotide 600 µg b.i.d. N=82	Pasireotide 900 µg b.i.d. N=80	Overall N=162
Response – n (%)	12 (14.6)	21 (26.3)	33 (20.4)
95% Confidence Interval	(7.0, 22.3)	(16.6, 35.9)	(14.2, 26.6)

95% confidence intervals are based on normal approximation to the binomial distribution.

The pre-established criteria for significant response (lower bound of 95% CI above 15%) is met for the 900 µg bd but not the 600 µg bd group. A supportive analysis carried out on the PPS showed similar results with the mean (95% CI) percentage of responders being 11.7 (4.5, 18.9) and 26.3 (16.4, 36.2) for the 600 and 900 µg groups respectively.

Results for other efficacy outcomes:

Proportion of partial responders: Partial control in response to treatment was defined as the six-month mUFC remaining above the ULN but having decreased by at least 50% from baseline.

Comment: By definition, such patients must have had a baseline level at least two times ULN and would therefore tend to be amongst those with higher baseline levels in the dataset, that is, those with more severe disease. A decrease of 50% in urinary cortisol would represent a clinically significant response in such patients.

A tabulation of both controlled and partially controlled UFC responders is shown below (Table 18).

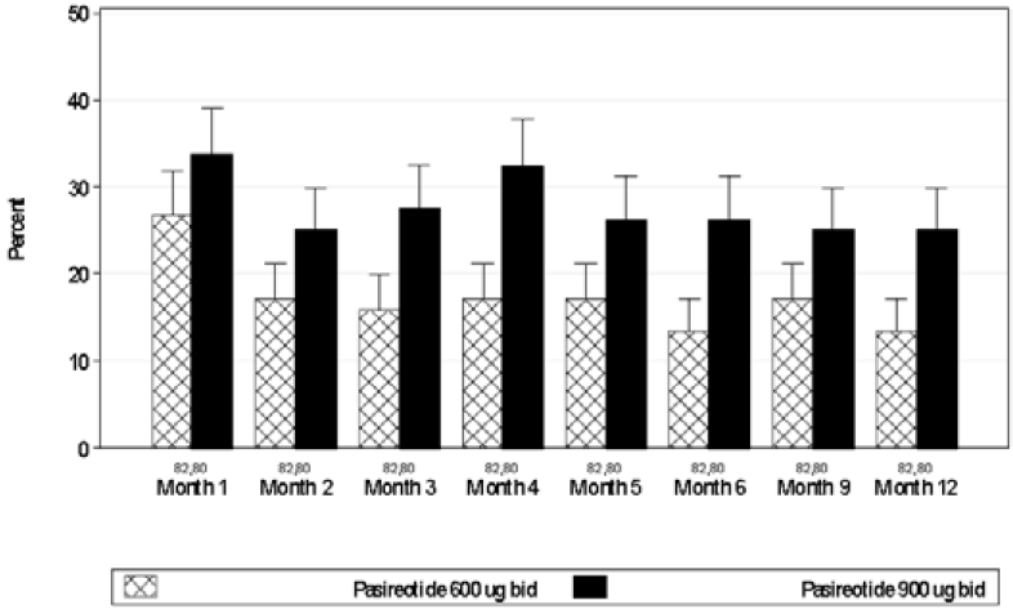
Table 18: Controlled and partially controlled UFC responders

	Pasireotide 600 µg b.i.d. N=82	Pasireotide 900 µg b.i.d. N=80	Overall N=162
Controlled			
Response – n (%)	13 (15.9)	23 (28.8)	36 (22.2)
95% Confidence Interval	(7.9, 23.8)	(18.8, 38.7)	(15.8, 28.6)
Partially controlled			
Response – n (%)	15 (18.3)	10 (12.5)	25 (15.4)
Uncontrolled			
Response – n (%)	54 (65.9)	47 (58.8)	101 (62.3)

Note that this data analysis includes patients whose dosage was adjusted based on the mUFC measurement taken at three months; whereas, the data displayed for the primary efficacy outcome (Table 17) includes only those who remained in double-blind therapy after the three month assessment, as illustrated above in Table 4. Only one 600 µg patient and two 900 µg patients in the controlled category underwent this adjustment, consisting of an increase of 300 µg in both the morning and evening doses. Amongst the partially controlled patients, more underwent this dose increase: eight of 15 patients receiving 600 µg bd and one of 10 receiving 900 µg bd.

Maintenance of response: The proportion of controlled responders (maintenance of normal urinary free cortisol) at time points up till Month 12, for both randomised dosage groups, is shown below.

Figure 5: Proportion of controlled responders at time points up till Month 12



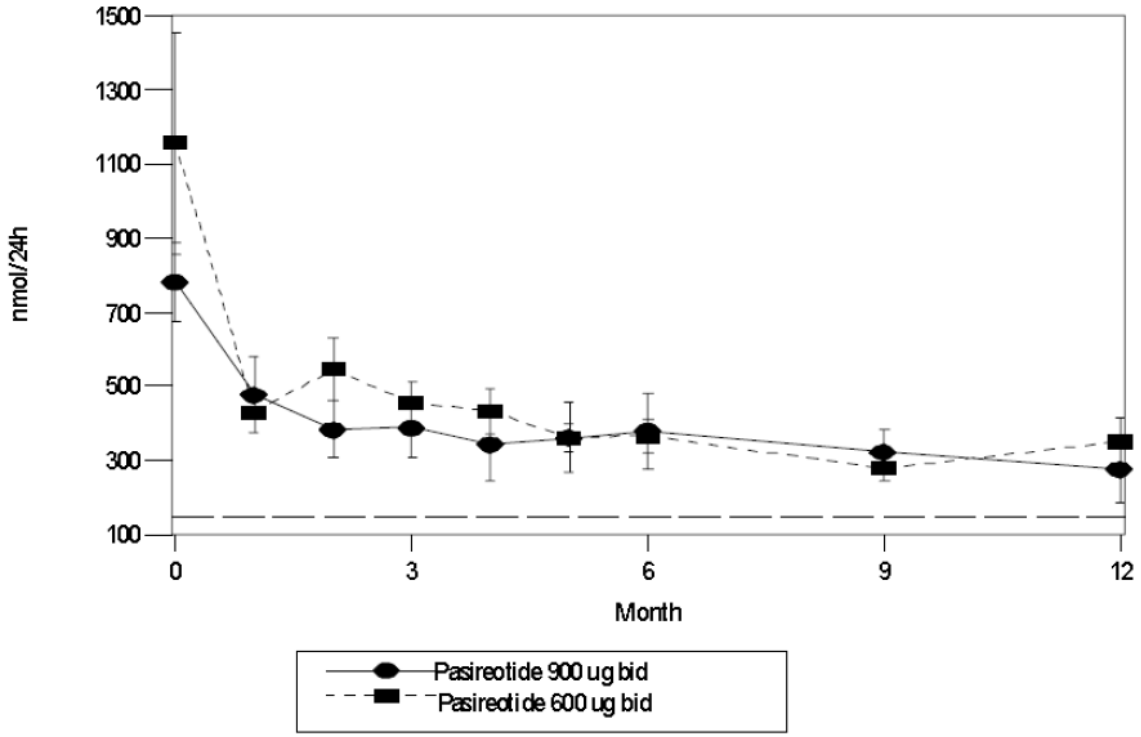
For either dosage group, there is little attenuation in the response rate between Month 6 and Month 12 although as noted above, eight of the 15 responders in the 600 µg dosage group underwent an increase in dosage to 900 µg bd during this time.

Change in mean urinary free cortisol: The mean (SD) reduction in mUFC from baseline to Month 6 was 27.5(104)% for the 600 µg dosage group and 48.4(30)% for the 900 µg group. The median reduction for both groups, however, was 47.9%, attributable to some extreme values including marked increases which occurred more in the 600 µg group as is evident from the variance figure (SD=104) of the % change. Inspection of the individual data show some marked

fluctuations from month to month in occasional patients. A potential explanation is irregular medication compliance; while this was monitored, the procedures did not include returning used syringes or ampoules (as opposed to unused ampoules, which was required).

A major and clinically relevant reduction in mUFC, and maintenance over 12 months, is suggested by the following graphic display.

Figure 6: Reductions in mUFC and maintenance over 12 months



In this graphic, mUFC is expressed as mean (SE). It should be noted that the 12 month data is based on 37 patients from the 600 µg dosage group and 35 from the 900 µg group, by comparison with 52 and 51 from these groups respectively for the six month data. Given that the most common reason for discontinuation throughout the study was "unsatisfactory therapeutic effect", this data presentation gives a somewhat false impression of the maintenance of therapeutic response. The same applies to the proportion of controlled responders with time (Figure 5). What can be said is that the mUFC values at 12 months displayed above, along with the described proportion of controlled responders, are those for the 48% of patients who completed 12 months of the study.

Time to first response: By the data cut-off date, 37 of the 600 µg and 46 of the 900 µg dosage groups had returned at least one mUFC measurement indicating response, that is, at or below ULN. The median time to first response was 8.7 months in the 600 µg group at 3.2 months in the 900 µg group.

Serum cortisol and plasma ACTH: Mean serum cortisol level decreased below baseline by Month 0.5 in both dosage groups, and plasma ACTH by Month 0.5 in the 900 µg and by Month 1 in the 600 µg dosage group. Levels of both remained both below baseline at all subsequent time points for both dosage groups. Figures 3 and 4 display a progressive fall over time for both parameters. Again this is a little misleading because of the preferential dropout rate of non-responders as mentioned above.

Comment: A progressive fall in ACTH over 12 months would be a finding of considerable significance in relation to a possible enduring beneficial effect of pasireotide on

the underlying pituitary pathology. An analysis of ACTH levels restricted to those patients completing the 12 month study would be useful.

Pituitary tumour volume: From baseline to Month 6, pituitary tumour volume evaluated by MRI showed a mean increase of 9.3% in the 600 µg dose group and a mean decrease of 19.0% in the 900 µg group; after 12 months, both groups demonstrated decreases in tumour volume of 9.1% and 43.8% respectively.

Comment: Even if not statistically tested and confined to responders only, this finding is of considerable significance in relation to the comment made above regarding ACTH levels.

Clinical changes and quality of life: After six months, improvements in both dosage groups were observed for a variety of clinical parameters, including symptomatic changes, blood pressure (BP) and BMI. The changes tended to be most pronounced in the group of responders as determined by mUFC, and were maintained at 12 months. Improvement in quality of life scores was also noted in both groups but the data were highly variable and as the observations are not placebo-controlled, it is difficult to draw conclusions.

6.1.2. Supportive efficacy study

6.1.2.1. Study B2208/2208E1

Study design, objectives, locations and dates:

This was a Phase II, proof of concept, open-label, uncontrolled study to assess the efficacy and safety of the short term (15 day) administration of pasireotide 600 µg bd to patients with Cushing's disease. The study, which has been published ([9]), was conducted at 10 international centres (France, Germany, Italy, UK and the USA: coordinating investigator Dr Marco Boscaro, University of Ancona, Italy) between April 2004 and June 2006, prior to the initiation of pivotal Study B2305, the design of which it presumably informed. It contains the only clinical data on the use of pasireotide in patients with Cushing's disease apart from the pivotal study, and is submitted in support of it.

Inclusion and exclusion criteria:

Patients with a confirmed diagnosis of pituitary Cushing's disease, whether de novo or recurrent following surgery, were included provided that they had never received pituitary irradiation. The diagnostic criteria were required to include two UFC measurements at least twice the ULN, together with evidence of an ACTH producing pituitary tumour with inappropriate or elevated ACTH secretion. Exclusion criteria included poorly controlled diabetes but were otherwise similar to those for Study B2305.

Study treatments:

All patients were administered pasireotide 600 µg bd sc. Each dose was taken from a 1 mL 900 µg ampoule.

Efficacy variables and outcomes:

The primary efficacy variables were:

- mUFC - in this study, this parameter was derived from two consecutive 24 hour urine collections. Sets of these were collected on Days -2 and -1 as the baseline measurement, and on Days 14 and 15 (completed on Days 15 and 16) as the end of study measurement.
- Changes in serum cortisol
- Changes in plasma ACTH

[9] Boscaro M *et al*. 2009, Report of Study B2208: *J Clin Endocrinol Metab.* 94(1):115-22

The primary efficacy outcome was the proportion of responders. A responder was defined as a subject with mUFC on Days 15-16 within the normal range.

Other efficacy outcomes included evaluation of mean changes in mUFC, serum cortisol and plasma ACTH.

PK data were also collected and are described above.

Randomisation and blinding methods:

Not applicable to this study.

Analysis populations:

The primary efficacy population (29) were all those who had a mUFC reading above the ULN, two urine collections for UFC measurement at baseline and Days 15-16, and completed 15 days treatment with two or less interruptions.

The ITT population (39) consisted of all enrolled subjects, and the safety population (39) all of these who received at least one dose of pasireotide. On the ITT population, 10 subjects were excluded from the primary efficacy population due to protocol violations.

Of the total population of 39 subjects, 20 were female and 37 Caucasian. Mean age was 41.5 years (range 22-73).

Sample size:

A sample size of 26 subjects was planned, using the two-stage enrolment procedure described by Simon ([10]) for situations where limited numbers of subjects are available. This involves preliminary evaluation of the first stage (in this case 10 subjects) before proceeding to the second. Ultimately 39 subjects were enrolled.

Statistical methods:

Data from all centres were combined for statistical analysis, and summary statistics provided for all endpoints. No formal statistical comparisons were necessary for the purpose of this study.

Participant flow:

Of the 39 enrolled patients, one discontinued prior to the study and the remaining 38 received 15 days of pasireotide. 36 remained on stable 600 µg bd sc dosing, with two subjects requiring dose reductions because of intolerance.

Major protocol violations/deviations:

10 subjects were excluded from the efficacy population for protocol violations. These comprised five who had fewer than two UFC samples at baseline or end of study; four who had baseline UFC within the laboratory normal range, and one who discontinued early due to adverse event (AE) and no UFC was available at end of study.

Baseline data:

Of the 39 enrolled patients, six reported previous pituitary surgery and four previous medication for Cushing's disease. This would suggest that 29 were untreated (de novo) cases, although this may be an overestimate as the previous history data was not collected as a protocol requirement.

Baseline mUFC in the efficacy population was 1231 nmol/24 h, over five times the ULN, with a range of 291-5950. The normal range for UFC measurement in this study is given as 55-276 nmol /24 h. This is consistent with the lowest observed baseline measurement of 291 nmol/24

[10] Simon, R, 1989, Optimal two-stage designs for Phase II clinical trials. *Controlled Clin Trials*, 10: 1-10

h just meeting the inclusion criterion for the efficacy population of exceeding the ULN, but is markedly different from the normal range quoted for pivotal Study B2305 (30-145 nmol/24 h), which is confirmed in the graphic display of changes in mUFC in that study (Figure 6).

Comment: This discrepancy is due to this earlier study having utilised a relatively non-specific cortisol assay of a type (electriochemiluminescence immunoassay) which characteristically has a higher reference range than more modern assays utilising HPLC, which have reference ranges consistent with that given for Study B2305 ([11]). The difference between these assay types becomes important when significant qualities of non-cortisol derivatives such as synthetic glucocorticoids are involved. In this case, in which measurements are being made almost exclusively of native cortisol, the difference is relatively unimportant particularly as the primary efficacy outcome is in the form of a responder analysis.

Results for the primary efficacy outcome:

Five (17.2%) of the 29 patients achieved normalisation of mUFC.

Results for other efficacy outcomes:

Change in mean urinary free cortisol: Overall, subjects in the efficacy population showed a mean 24.8% reduction in mUFC with a median, that is, most likely, reduction of 41.2%, as shown in the following table.

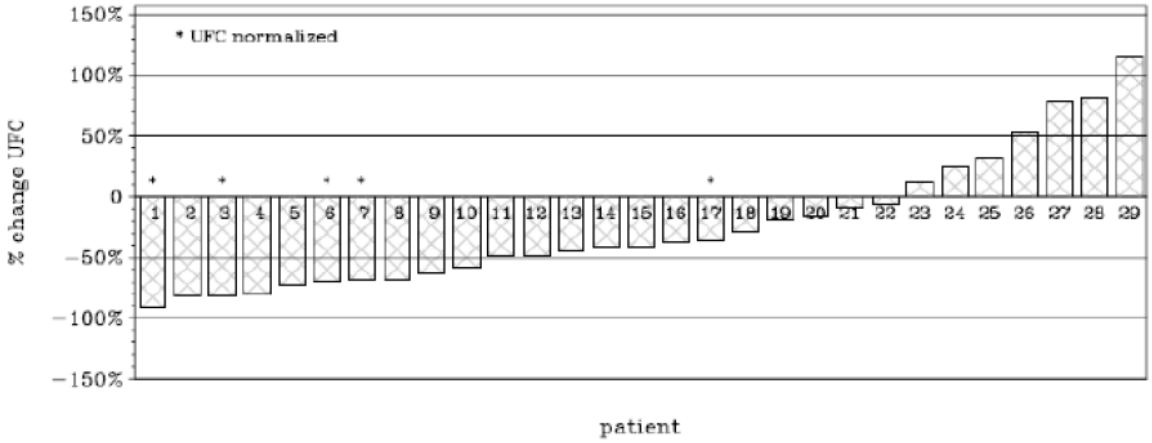
Table 19: Change in mean urinary free cortisol

	Visit	Statistic	Actual (nmol/d)	Change from Baseline† (nmol/d)
All Patients	Baseline*	N	29	-
		Mean (SD)	1230.8 (1140.5)	-
		Range	291,5950	-
		Median	825	-
	End of Study**	N	29	29
		Mean (SD)	683.2 (614.98)	-547.6 (1115.3)
		Range	158, 3364	-4811,1522
		Median	465	-363
		Mean %change (SD)	–	-24.8 (54.32)
		Median % change	–	-41.2

The difference between mean and median response is explained by a group of four subjects whose mUFC increased by more than 50% from baseline to Day 15, as shown below in a display of the individual changes for each of the study subjects.

[11] McCann SJ, Gillingwater S, Keevil, 2005, Measurement of urinary free cortisol using liquid chromatography-tandem mass spectrometry: comparison with the urine adapted ACS:180 serum cortisol chemiluminescent immunoassay and development of a new reference range.. *Ann Clin Biochem* 42(Pt 2):112-8

Figure 7: Increase of mUFC by more than 50% from baseline to Day 15



These data closely mirror those from the pivotal efficacy study confirming that a meaningful degree of response to pasireotide is seen in approximately half of the target population of patients with pituitary Cushing's disease.

Changes in serum cortisol and plasma ACTH: The results for serum cortisol and plasma ACTH measured pre-injection at baseline were compared with those from Day 15. The study report describes these parameters as undergoing "small reductions" of 0.4% and 1.1% respectively. The reality is that there was no significant mean change and that the data was quite variable. There does appear to have been a fall in both ACTH and cortisol in the period of eight hours following the morning pasireotide injection on Day 15. This is consistent with the PD effect of pasireotide on ACTH leading to a reduction in serum and ultimately mean urinary cortisol.

Extension study B2208E1:

Patients who had either been classified as responders or "experienced significant clinical benefit" (which included having shown a reduction in mUFC, but not to normal) in the core 15 day study were permitted to enrol in this 6-month Phase II extension, to continue on the 600 µg bd dose or have it increased to 900 µg bd if UFC levels rose during the extension. As in the original study, the primary efficacy variable was the proportion of responders based on normalisation of mUFC.

18 subjects, comprising three who had been responders in the core study, 11 who had shown a partial reduction of mUFC, and four who had shown no reduction, were evaluated in the extension study and remained on treatment from two months to 4.8 years with a mean duration of 16 months. At the time of data cut-off (March 2010), three patients were still receiving treatment.

The results were somewhat complex and are best summarised as follows:

- Of the three responders in the core study that entered the extension, one was still a responder at six months and one patient became a reducer. The third patient discontinued the study prior to Month 6 and was therefore counted as a non-reducer at six months.
- Of the 11 reducers in the core study that entered the extension, five maintained their reducer status at six months. Two of the reducers became responders at six months, and four became non-reducers.
- Of the four non-reducers in the core study that entered the extension, one became a responder at six months and three remained non-reducers.

Thus, there are similar numbers of responders after six months as at the end of the core study, but they are not the same subjects. Some subjects who responded well early experienced deterioration during the extension, and vice versa.

Comment: The status of the three patients who had been treated for almost five years is of interest. If it can be presumed (latest data not seen) that they are showing a continuing response. The fact that they represent 10% of the original efficacy population is a significant clinical benefit.

6.1.3. Other efficacy studies

No other efficacy studies were included in the application.

6.1.4. Analyses performed across trials (pooled analyses and meta-analyses)

The efficacy data from the above studies has not been subjected to pooled analysis, including the difference in the assay method used for cortisol as noted above.

6.2. Evaluator's conclusions on clinical efficacy for Cushing's disease

A clinically valuable response occurred in approximately half of the patients treated in pivotal Study B2305, and in approximately half of those the urinary cortisol was returned to the normal range. Such a response was significantly more likely to occur if the higher dose of 900 µg bd was employed, by comparison with 600 µg bd. Biochemical evidence of response, when it occurs, is seen within the first month. Some form of reduction of urinary cortisol occurs in approximately two thirds of patients.

Although a higher response rate would obviously be preferred, these outcomes will be valued by clinicians caring for patients with Cushing's disease. Once the option of neurosurgical cure has been exhausted, as in the proposed indication, management becomes difficult and the efficacy outcomes described here are at least equivalent and probably superior to existing treatment options, in so far as the limited data on alternatives allows comparison. The inclusion of an active comparator arm, probably using ketoconazole, in the pivotal trial might have yielded a greater degree of confidence in the relative efficacy of pasireotide with respect to other treatments, but this was not undertaken. The logistics of such a trial would be complex.

The observation of pituitary tumour shrinkage in a significant proportion of patients is an additional treatment benefit.

Reliance on a single pivotal study appears acceptable in this case. The data comes from a wide international spread of specialised centres treating patients with this disorder, which mitigates against treatment or selection bias. Collection of a larger patient population would be difficult. Supporting Study B2208 and its extension contribute little in the way of patient numbers but qualitatively confirm the outcomes observed in B2305.

A significant concern is whether response rates will be maintained with long-term treatment, which would be required by the majority of patients receiving the product for the proposed indication.

If the application is approved, it is likely that the therapeutic benefits of pasireotide will be applied not only alone but in sequence or combination with other therapeutic agents, as has already been described for its use in combination with cabergoline and ketoconazole in one study (.[12]) referred to in the Summary of Clinical Safety.

[12] Feelders RA, de Bruin C, Pereira AM, *et al.* 2010, Pasireotide alone or with cabergoline and ketoconazole in Cushing's disease. *N Engl J Med*; 362(19):1846-8

7. Clinical safety

7.1. Studies providing evaluable safety data

The following studies provided evaluable safety data:

Pivotal efficacy study:

In the pivotal efficacy study, the following safety data were collected:

- AE and serious adverse events (SAE) were recorded and documented according to the study protocol at routine visits by means of historical data and monitoring of vital signs. AE could be spontaneously volunteered or detected by questioning. The severity of AE was assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0, as Grades 1-4 (mild, moderate, severe or life-threatening). Note that these same procedures and criteria for documentation of safety information were employed for all studies in the dossier.
- A number of AEs or safety issues of particular interest were defined for this study, as informed by the preclinical data, Phase I studies, and otherwise known adverse or potential adverse effects of somatostatin analogues. These included changes in blood glucose and related parameters, gallbladder related events, and effects on cardiac repolarisation.
- Laboratory tests, including haematology, blood chemistry and urine tests were performed at all protocol visits.
- Fasting blood glucose and HbA1c at regular intervals.
- ECG performed at all visits.
- Gallbladder ultrasound at baseline and every six months thereafter.

Pivotal studies that assessed safety as a primary outcome:

No such studies are included.

Dose-response and non-pivotal efficacy studies:

There is no dose-response study. The other submitted efficacy Study B2208, together with its long-term extension 2208E1, provided safety data on a relatively small number of patients as shown below in Table 21. As the treatment period in the core study was only 15 days, it safety data has little impact but that from the extension study has been included in the following assessment.

Other studies evaluable for safety only:

The application includes data from three studies performed as part of the development programmes for indications other than Cushing's disease; specifically, acromegaly and carcinoid syndrome which are both amongst the indications already approved for other somatostatin analogues. They have been included to increase the quantum of safety data available for evaluation, as the safety population is otherwise quite small due to the rarity of pituitary Cushing's disease.

7.1.1.1. Study B2201/2201E

This study together with its long-term extension provides further safety data on acromegalic patients exposed to pasireotide at doses of 200, 400, and 600 µg bd. As the upper levels of these doses fall within the dose range proposed for the current application, or at least the lower part of it, the data is appropriately included in the safety database, and for the purposes of this evaluation.

7.1.1.2. Study B2202

This trial was carried out on patients with carcinoid syndrome. Doses given ranged from 300 - 900 µg bd. As shown below (Table 21), most patients were only treated short term (median exposure 12.7 weeks) but 15 received pasireotide for periods of between six and 12 months.

7.1.1.3. Study B2103

This study examined the efficacy and safety of pasireotide in patients with acromegaly. The primary objective was to compare the efficacy of single doses of 100 µg and 250 µg pasireotide with a standard 100 µg dose of octreotide (Sandostatin). The dosages of pasireotide used were employed early in the clinical development program and are not amongst the formulations submitted for market approval. A total of 12 patients received single doses as described above; this exposure does not contribute significantly to that of the safety population and is not included below in Table 21.

7.2. Pivotal studies that assessed safety as a primary outcome

Not applicable. Collection of safety data from the single pivotal Study B2305 is described above.

7.3. Patient exposure

Overall exposure to pasireotide in the studies reviewed for this submission is described below.

Table 20: Exposure to pasireotide and comparators in PK/PD studies.

Study ID	Controlled studies*			Uncontrolled studies	Total Pasireotide
	Pasireotide	Placebo	Moxifloxacin	Pasireotide	
B2101	54	18			54
B2102	28	28			28
B2106				17	17
B2107				66	66
B2108				43	43
B2112				4	4
B2113 part 1	37	18			37
B2113 part 2	95	95	95		95
B2125	112	112	112		112
C2101				78	78
B2114				34	34
B2216				45	45
B2124				90	90
TOTAL	**326**	**271**	**207**	**377**	**703**

*If a crossover study, subjects are counted in all relevant columns

Table21: Exposure to pasireotide in clinical studies according to dose and duration.

Study ID (Indication)	Proposed dose range				Proposed maximum dose***			
	≥ 3 mo.	≥ 6 mo.	≥ 12 mo.	Any dur'n*	≥ 3 mo.	≥ 6 mo.	≥ 12 mo.	Any dur'n*
B2305 (Cushing's)	132	110	63	162	64	55	35	80
B2208 (Cushing's)				39				
B2208E1 (Cushing's)	17	12	7	19				
B2201 (acromegaly)**				62				
B2201E1 (acromegaly)	30	28	23	30				
B2202 (carcinoid)	22	15	7	45				
TOTAL	**201**	**165**	**100**	**357**	**64**	**55**	**35**	**80**

*The amount by which this figure exceeds the 3 month figure indicates patients treated for <3 months; if all columns to the left are blank, then all were treated for <3 months.
**Includes 400 µg bd and 600 µg bd dosage groups.
***A small number of patients included in the proposed dose range section of this table had doses of 1800 µg total daily for periods of their treatment but would not contribute significantly to the totals in this section.

In Study B2305, exposure data is recorded within the proposed dose range for >24 months in 13 patients and >30 months in four patients.

7.4. Adverse events

7.4.1. All adverse events (irrespective of relationship to study treatment)

Pivotal study:

There was an overall high incidence of AE in the pivotal study, as shown below: these are the end of study data reflecting 12 months exposure for completing patients, although note that 52% discontinued prior to 12 months.

Table 22: Incidence of AE in the pivotal study

	Pasireotide 600 µg bid N=82 n (%)	Pasireotide 900 µg bid N=80 n (%)	Overall N=162 n (%)
Adverse events (AEs)	80 (97.6)	79 (98.8)	159 (98.1)
Study drug-related AEs	79 (96.3)	76 (95.0)	155 (95.7)
Discontinued due to AEs	13 (15.9)	15 (18.8)	28 (17.3)
Grade 3 or 4 AEs	39 (47.6)	40 (50.0)	79 (48.8)
Deaths	0	0	0
SAEs	19 (23.2)	21 (26.3)	40 (24.7)
Study drug related SAEs	7 (8.5)	12 (15.0)	19 (11.7)
Discontinued due to SAEs	3 (3.7)	5 (6.3)	8 (4.9)
AEs of special interest	79 (96.3)	77 (96.3)	156 (96.3)

The most frequently reported AE were as shown below.

Table 23: The most frequently reported AE

	Pasireotide 600 µg bid N=82		Pasireotide 900 µg bid N=80		Overall N=162	
	Grades 3 and 4	All Grades	Grades 3 and 4	All Grades	Grades 3 and 4	All Grades
Preferred term	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Diarrhoea	3 (3.7)	48 (58.5)	2 (2.5)	46 (57.5)	5 (3.1)	94 (58.0)
Nausea	1 (1.2)	38 (46.3)	3 (3.8)	46 (57.5)	4 (2.5)	84 (51.9)
Hyperglycaemia	8 (9.8)	31 (37.8)	13 (16.3)	34 (42.5)	21 (13.0)	65 (40.1)
Cholelithiasis	1 (1.2)	25 (30.5)	1 (1.3)	24 (30.0)	2 (1.2)	49 (30.2)
Headache	1 (1.2)	23 (28.0)	2 (2.5)	23 (28.8)	3 (1.9)	46 (28.4)
Abdominal pain	1 (1.2)	19 (23.2)	2 (2.5)	20 (25.0)	3 (1.9)	39 (24.1)
Fatigue	1 (1.2)	12 (14.6)	2 (2.5)	19 (23.8)	3 (1.9)	31 (19.1)
Diabetes mellitus	6 (7.3)	13 (15.9)	6 (7.5)	16 (20.0)	12 (7.4)	29 (17.9)

There is a clear pattern of both upper and lower gastrointestinal (GI) dysfunction and of the anticipated incidence of blood glucose disturbance and gallstones. Events below the above level of frequency were either non-specific or related to other preferred terms corresponding to the GI or diabetes related AE listed above. Liver function abnormalities (AAT, GGT) were reported in 10.5% of patients overall. This is discussed below. There is no evidence of dose relationship of any of these events within the limited range used (600, 900 µg).

Other studies

In supportive Study B2208, the pattern of AE was very similar to that described above. 92% of patients reported at least one AE. Diarrhoea was experienced by 51%, nausea by 31%, and hypoglycaemia by 36%. A similar pattern was seen in the extension study.

In the larger acromegaly dataset (B2201), nausea (32%) and diarrhoea (23%) were the two most commonly reported AE although the incidence was relatively increased in the higher dosage groups. Hyperglycaemia (8.3%) and increased HbA1c (6.7%) were less commonly reported. The pattern of AE reporting was similar to this in the carcinoid syndrome dataset (B2202) with abdominal pain (33%), nausea (30%) and diarrhoea (24%) amongst the five most commonly reported events along with weight loss and fatigue, whereas hyperglycaemia (16%) and a diagnosis of diabetes (9%) were less commonly experienced than in the Cushing's disease datasets.

Comment: This differential in hyperglycaemia related events is not unexpected. Diabetes can occur as a manifestation of both Cushing's syndrome and acromegaly, but is likely to be more florid in the former particularly if it is severe. Carcinoid syndrome is not particularly associated with diabetes. The insulin suppressing effect of pasireotide is therefore more likely to manifest as hyperglycaemia in the Cushing's disease patients.

Details of AE reporting in the Phase I studies conducted in HV are shown in the various study summaries. Throughout these, the most frequently reported events were mild-to-moderate diarrhoea, nausea, abdominal pain and vomiting, together with injection site reactions. Upper GI symptoms occurred more commonly with increasing dose and were the main factor in limiting tolerance, for example in Part 1 of Study B2113 in which the maximum tolerated dose of pasireotide was established as 1950 µg bd, fasting and post-prandial hyperglycaemia were seen, as described in detail above. Again, these abnormalities were less severe than in the Cushing's disease patients.

Throughout the safety assessments in these other studies, no safety signals were observed of a different nature to those seen in the pivotal study.

7.4.2. Treatment-related adverse events (adverse drug reactions)

Pivotal study:

The pattern of AE classified by the investigators as drug-related was similar to that shown above for the overall AE (Table 23). The events most commonly so classified, in order, were diarrhoea (in 55% of subjects), nausea (47%), hyperglycaemia (39%), cholelithiasis (30%), abdominal pain, diabetes mellitus, fatigue, and increased HbA1c.

Other studies:

The pattern of drug related events was not significantly different from that reported for the AE generally. In the acromegaly dataset, no hyperglycaemic events were reported as drug-related. In the HV studies, most reported AE were suspected to be drug-related.

7.4.3. Deaths and other serious adverse events

Pivotal study:

Amongst the recruited patients, two deaths occurred, one during the screening period prior to any administration of study drug and the other two months following study completion, due to surgical complications following adrenalectomy.

Comment: Neither of these deaths is related to study drug, but the second is a vivid illustration of the difficulties which management of pituitary Cushing's disease can present. The patient was aged 47, had failed pituitary surgery, started pasireotide but then developed worsening diabetes so was discontinued from the study and was referred for adrenal surgery with an eventually fatal outcome. The clinical evaluator mentioned this case because it illustrates the level of need for an effective medical treatment, and therefore the level of risk which might be tolerable in achieving such.

SAE were reported overall in 24.7% of patients, with no significant differential between the dosage groups. The pattern of events was similar to that for AE generally with the addition of some instances of "pituitary dependent Cushing's syndrome" and "pituitary tumour benign", clearly related to the underlying disease. Otherwise the most common events are related to blood glucose or gallstone disease. There is no suggestion of any safety issues other than those already recognised.

Other studies:

The only death reported in the remainder of the safety database was that of a single patient in the carcinoid dataset, related to tumour progression.

SAE in the remaining studies were reported in 20-30% of the study populations and most commonly consisted of hyperglycaemia related events, or other AE of known special interest related to the study medication, or incidental disorders such as acute myocardial infarction or pregnancy.

7.4.4. Discontinuation due to adverse events

Pivotal study:

13 (15.9%) and 15 (18.8%) of patients in the 600 µg and 900 µg bd groups respectively experienced AE leading to discontinuation. The most common AE in this category were hyperglycaemia and diabetes mellitus (grouped together) in nine patients and gamma glutamyltransferase (GGT) increase in five patients. The remainder were a wide variety of AE mostly with no obvious relationship to study medication.

Other studies:

Amongst the supportive Cushing's disease safety population and acromegaly dataset, 10 patients discontinued due to AE; seven cases were hyperglycaemia-related. The remaining three were instances of pregnancy, colon cancer and GI symptoms. In the carcinoid dataset, there were 12 discontinuations, six related to GI symptoms and only one to hyperglycaemia, again showing the association of hyperglycaemic events specifically with Cushing's patients.

Amongst the HV population, there were a variety of reasons for discontinuation, mostly diarrhoea or nausea. There was one cardiac SAE leading to discontinuation in Study B2125, an episode of supraventricular arrhythmia occurring shortly after injection of pasireotide. The investigator's opinion that this was not related to the study drug (as opposed to being precipitated by the event of the injection) appears valid.

7.5. Laboratory tests

7.5.1. Liver function

Pivotal study:

Newly occurring or worsening Grade 1 ALT, AST and GGT were reported for 31.8%, 22.6%, and 23.3% of patients, respectively. Grade 2 ALT, AST and GGT abnormalities were less common, and Grade 3 was reported for ALT (one patient in the 600 µg bd group) and GGT (seven patients, 4.5% of all patients). Bilirubin abnormalities were rare. No Grade 3 bilirubin was reported. There were no patients with bilirubin greater than two times ULN. A total of eight patients (5.1%) had an ALT or AST level greater than three times ULN (7.6% in the 600 µg bd group and 2.6% in the 900 µg bd group). There were no patients with ALT or AST greater than three times ULN and bilirubin greater than or equal to two times ULN. The abnormalities are described as being transient. ALT and AST increased at Month 1 but then returned to baseline at Month 4 and remained stable.

Comment: The Hepatic Report states that there were no cases meeting the criteria for Hy's law in the Phase II or Phase III studies. The above data confirms this for the pivotal study as ALT or AST greater than three times ULN together with bilirubin greater than or equal to two times ULN is part of the definition thereof.

Other studies:

In Study B2108, in which doses given by continuous subcutaneous infusion were escalated progressively (Table 6), ALT, AST, or GGT levels were elevated (CTC Grades 1 and 2) by the end of the study in four of six subjects given 1800 µg daily, but the increases were considered not clinically significant. The increases in liver enzymes were generally transient and were not associated with increases in bilirubin or any symptoms. Nevertheless, enrolment at the 2250 and 2700 µg cohorts was temporarily halted and six new subjects were enrolled at the 1800 µg/day dose. One of these subjects also experienced elevated ALT and AST. All subjects who experienced increases in liver enzymes at the 1800 µg/day dose were re-challenged with this dose. The ALT, AST, or GGT laboratory values became elevated again in three subjects, at CTC Grade 1, except for one subject who had an increase of Grade 2.

Data from the remaining studies in the supportive safety set were consistent with the findings of Study B2305, except for those of the carcinoid study in which there were more serious abnormalities of liver function, related to underlying malignant liver disease.

Comment: The data in the previous two sections suggest that biochemical evidence of liver injury occurs commonly at doses within the proposed therapeutic range, but not with sufficient severity to predict the occurrence of clinically significant drug induced liver disease.

7.5.2. Kidney function

Pivotal study:

No significant changes were observed with monitoring of serum creatinine and routine urinalysis.

Other studies:

Findings were similar to those for the pivotal study.

7.5.3. Other clinical chemistry

Pivotal studies:

A frequently occurring finding in these Cushing's disease patients was a Grade 1 rise in serum cholesterol (seen in 51.9% of subjects overall) and triglyceride (46%). A likely possibility is that these may have been associated with the development of hyperglycaemia, but there is no sub-analysis which might confirm this. The observation is otherwise unexplained.

Other studies:

In Study B2201, Grade 1 changes were seen for cholesterol (22%) and triglyceride (15%). The proportion of subjects affected in this acromegaly dataset is less than half of that seen in the Cushing's disease patients, which would support the possibility of the abnormality being hyperglycaemia-related.

There were no other biochemical findings of concern in any of the studies, except of course for hyperglycaemia which is discussed below.

7.5.4. Haematology

Pivotal studies:

There is a relatively high incidence of the development of CTC Grade 1 abnormalities in some parameters, including haemoglobin (11.5%) and partial thromboplastin time (33.3%). However, it is clear on examination of the data that these listings include both increases and decreases; for example, a shift from normal to high in haemoglobin is described for 10.6%, something which is implausible as a consequence of study drug administration. It seems likely that the thresholds for detection of these abnormalities are very sensitive. Furthermore, haemoglobin can vary according to state of hydration. It is not felt that the described abnormalities are of any clinical significance.

Other studies:

The same assessment applies as described above for the pivotal study.

7.5.5. Electrocardiograph results and cardiac safety

Delayed cardiac repolarisation as manifest by prolongation of the QT interval or the heart rate corrected QT interval (QTc) has been observed with other somatostatin analogues. The sponsor has undertaken two studies specifically to evaluate the effect of pasireotide on the QT interval. The first of these was B2113 which employed a maximum tolerated dose defined for the purpose of the study as 1950 µg bd. As a significant mean placebo-corrected increase in QTcF of 17.5 ms was found, a second study (B2125) was performed in which a dose from the therapeutic range, 600 µg bd, was also used. Significant mean placebo corrected increases of QTcI were again found, of 16.1 ms for the 1950 µg and 13.2 ms for the 600 µg group.

Comment: QTcF and QTcI are two different forms of correction which attempt to standardise the QT interval in a more precise way than is achieved by simply adjusting for heart rate. For the present purpose, the difference appears insignificant.

Both of the above referenced studies comply with the requirements for a "thorough QT study" of the relevant FDA Guidance for Industry document ([13]). The findings of the studies are fully documented in the draft PI under the heading "Cardiac Electrophysiology". The degree of prolongation of QT interval falls within the inconclusive category (5-20 ms) as defined by the FDA document.

The clinical significance of these observations is that QT prolongation can be associated with bradycardia but more importantly with the serious and potentially fatal ventricular arrhythmia torsade de pointes. As documented in the draft PI, an overall incidence in the safety population was noted of QT prolongation in 3.7% of subjects (although almost exclusively not in the "notable" category), and of bradycardia in 4.3% of subjects. Throughout the clinical program, no episodes of torsade de pointes have been observed, nor do there seem to have been any possibly associated unexplained serious events, particularly unexplained sudden death. Two serious episodes of cardiac arrhythmia are described amongst the AE, but were defined as atrioventricular block and supraventricular tachycardia respectively, abnormalities not associated with QT prolongation.

The sponsor also includes a QT/QTc Interval Analysis Report. This document reviews, in addition to the clinical data including the above referenced studies, a considerable volume of preclinical data, both in-vivo and IV, which is claimed to not signal a QT prolongation risk in humans. The document argues that a number of disease factors may have contributed to some of the observations, and that a random correction factor in the placebo group of the HV studies may have exaggerated the degree of abnormality.

While many of the arguments in this analysis report are accepted, the findings of the included studies do appear scientifically robust and it seems entirely correct that the sponsor has documented them in the draft PI and included a number of appropriate precautionary statements regarding use of pasireotide in patients with recognisable pre-existing cardiac risk factors, or who are taking medications known to cause QT prolongation, or in the presence of hypokalaemia and/or hypomagnesaemia. ECG monitoring is also recommended routinely.

7.5.6. Vital signs

These were routinely monitored in all the studies. There were some predictable changes, such as reduction in BP with improvement in Cushing's disease, but no abnormalities with safety implications were observed.

7.5.7. Glucose homoeostasis (potential for diabetogenic effect)

The pathophysiological basis for the development of hyperglycaemia with pasireotide therapy has been described in detail above.

Pivotal study:

With 12 months exposure to the drug in the target population, Study B2305 provides the largest amount of available information on the long-term effect of pasireotide on blood glucose. This is best described by the following display of fasting plasma glucose (FPG) by duration of administration in the two dosage groups - FPG is inherently stable from day-to-day, and therefore useful for long-term longitudinal comparison.

[13] U.S. Department of Health and Human Services Food and Drug Administration, 2005, E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs: Guidance for Industry,

Table 24: Fasting plasma glucose by duration of administration

	Pasireotide 600 µg b.i.d.		Pasireotide 900 µg b.i.d.	
Visit	n	Mean (SD) mg/dL	n	Mean (SD) mg/dL
Baseline	79	98.6 (23.6)	79	97.0 (18.7)
Month 0.5	78	136.0 (57.0)	76	149.2 (68.1)
Month 1	76	138.8 (68.6)	72	153.4 (71.5)
Month 1.5	74	131.4 (57.0)	69	143.6 (57.0)
Month 2	70	133.7 (51.4)	67	138.4 (60.3)
Month 3	69	122.0 (41.5)	66	124.7 (52.1)
Month 4	68	122.1 (41.8)	61	124.9 (43.1)
Month 5	62	121.3 (33.9)	57	128.5 (46.3)
Month 6	57	125.1 (34.6)	55	128.0 (54.6)
Month 9	46	126.9 (35.9)	48	119.4 (33.1)
Month 12	39	120.9 (40.5)	38	114.4 (36.3)

Following the initial rise to a peak of 153.4 mg/dL (8.5 mmol/L), there appears to be a gradual return towards lower values by the 12 month point. Interpretation of this is impaired by the dropout rate towards the end of the study, and the fact that those who dropped out are likely to have been those more severely affected by Cushing's disease and therefore more likely to be hyperglycaemic. An analysis restricted to completing subjects would have been useful. However, there is clearly a decrease by Month 3, by which time few patients had left the study.

Additionally, HbA1c levels were assessed in this study. From a mean baseline of 5.82% and 5.76% in the 600 and 900 µg groups respectively, HbA1c increased to 7.24% and 7.41% in the two groups respectively by two months and remained stable at subsequent assessments, being 7.25% and 7.21% in the 600 and 900 µg groups respectively at 12 months.

Comment: What this means, in effect, is that the treated group had, at both dose levels, become diabetic. The accepted criterion for diagnosis of diabetes on fasting blood glucose is 7.0 mmol/L, and there is increasing acceptance of a HbA1c reading exceeding 6.5% having diagnostic significance; certainly a level of >7.0% is regarded for therapeutic purposes as representing unsatisfactory control of diabetes. While there was doubtless variation within the group, these data indicate that it is more likely than not that Cushing's disease patients treated with pasireotide will develop diabetes; and that the majority of the patients in the study population would meet criteria for initiation of or intensification of diabetes therapy.

Other studies:

The relatively small amount of data from the extension to Study B2208 is confirmatory of the observations in the previous section. The data from the acromegaly and carcinoid subpopulations have not been taken into account because diabetes is less likely to occur in these groups, with or without exposure to pasireotide.

Pre-existing diabetes and dosage adjustment:

In the draft PI, the sponsor recommends a reduced starting dose of 600 µg bd for patients with pre-diabetes or diabetes mellitus.

Comment: Note that "pre-diabetes" is not a term which they define or which is any longer in general use. Nevertheless the intent is clear.

The evidence presented in the submission, particularly that in Study B2216, does not suggest a differential between the 600 and 900 µg dose levels in inducing these glucose related changes in

the general target population. However it is clear particularly from some of the individual study narratives that patients with pre-existing diabetes may be particularly vulnerable to rapid change, so that some caution here is justified. Amongst all the data presented in the submission, there is one quotation which succinctly summarises the situation; it is the final comment in the conclusions of the PopPK/PD analysis and reads as follows:

> "To balance benefit (UFC reduction) and risk (FPG elevation), the choice of dose might best be informed by a patient's baseline characteristics and by the perceived relative importance of efficacy versus safety".

7.5.8. Adverse events of special interest

In pivotal Study B2305, the sponsor defined 20 AE terms as being of special interest. The incidence of these events in the safety population is included in Table 25.

Table 25: Adverse events of special interest

	Pasireotide 600 µg bid N=82 n (%)	Pasireotide 900 µg bid N=80 n (%)	Overall N=162 n (%)
Patients with any AE(s) of special interest	79 (96.3)	77 (96.3)	156 (96.3)
Category of AE of special interest			
Hyperglycemia-related AEs	61 (74.4)	57 (71.3)	118 (72.8)
Diarrhea related AEs	48 (58.5)	46 (57.5)	94 (58.0)
Nausea related AEs	39 (47.6)	46 (57.5)	85 (52.5)
Gallbladder and biliary related AEs	27 (32.9)	29 (36.3)	56 (34.6)
Liver safety related AEs	17 (20.7)	9 (11.3)	26 (16.0)
Injection site reaction related AEs	11 (13.4)	13 (16.3)	24 (14.8)
Bradycardia related AEs	15 (18.3)	8 (10.0)	23 (14.2)
Pancreatitis related AEs	11 (13.4)	10 (12.5)	21 (13.0)
Hypocortisolism related AEs	7 (8.5)	6 (7.5)	13 (8.0)
QT-prolongation-related AEs	6 (7.3)	7 (8.8)	13 (8.0)
Constipation related AEs	7 (8.5)	4 (5.0)	11 (6.8)
Low blood cell related AEs	4 (4.9)	5 (6.3)	9 (5.6)
Hypothyroidism related AEs	4 (4.9)	3 (3.8)	7 (4.3)
Coagulation related AEs	1 (1.2)	2 (2.5)	3 (1.9)
Diabetes insipidus related AEs	0	1 (1.3)	1 (0.6)
Growth hormone related AEs	0	0	0
Rhabdomyolysis related AEs	0	0	0
Hypotension related AEs	0	0	0
Hypocalcemia related AEs	0	0	0
Gastrointestinal bleeding related AEs	0	0	0

The three most common categories (hyperglycaemia, diarrhoea and nausea) are discussed elsewhere in this section, as are AE related to QT prolongation. Injection site reactions, occurring overall in 14.8% of patients, were mostly mild and of no consequence from the regulatory standpoint. Likewise hypocortisolism is not so much an AE as evidence of excessive efficacy and should be monitored for as advised in the draft PI. Otherwise, AE terms with an incidence of >5% or with significant safety implications are restricted to those relating to the biliary tract and to pancreatitis.

Gallbladder and biliary related AE:

Consistent with the findings for other somatostatin analogues, gallstones occurred commonly in the target population. In the pivotal Study, 137/62 (84.6%) of patients had normal gallbladder

ultrasounds at baseline. By the last assessment, 119 of these 137 patients had a follow-up ultrasound and 27 had gallstones and nine had detectable sludge. There were no cases of intra- or extra-hepatic duct dilatation.

Pancreatitis related AE:

Table 25 lists an incidence of AE relating to this term of 13.4% and 12.5% in the 600 µg and 900 µg bd populations respectively which, even though pancreatitis is a recognised adverse effect of somatostatin analogues, is surprising given that clinical descriptions of pancreatitis do not appear in the event reports, except for a single instance of one severe AE. The explanation appears to be that this classification includes minor (Grade 1) abnormalities of serum enzymes including alpha amylase which became elevated at some stage of the study in 6.8% of all patients, and lipase for which elevations are described in 15.4%. Elevated amylase is also classified as a commonly occurring abnormality in the draft PI.

There is evidence that these biochemical changes, which are presumably a forewarning of clinical pancreatitis, are dose-related. In escalating dose study B2108 (Table 6) at the point when the 2250 µg/day dose given by infusion was reached, pancreatic lipase was increased in five subjects. Two subjects had an increase of CTC Grade 1, two had an increase of CTC Grade 2 and one had an increase of CTC Grade 3. Consequently the next cohort received the reduced dose of 2025 µg/day, and at this and lower levels a similar incidence of these abnormalities was not seen.

7.6. Post-marketing experience

No descriptions of post marketing experience are yet available. A plan for acquisition of such data is described in the form of Clinical Trial Protocol B2410.

7.7. Safety issues with the potential for major regulatory impact

7.7.1. Liver toxicity

Clinically significant liver toxicity appears unlikely except for an unquantified possibility of this being a risk for patients with pre-existing hepatic impairment.

7.7.2. Haematological toxicity

No evidence of concern.

7.7.3. Serious skin reactions

No safety signals evident.

7.7.4. Cardiovascular safety

On currently available evidence and given the cautionary notes included in the PI regarding patients with existing risk factors, QT prolongation does not appear to be a major issue for pasireotide.

7.7.5. Unwanted immunological events

No safety signals evident.

7.8. Other safety issues

7.8.1. Safety in special populations

7.8.1.1. Gender, age and race

A subgroup evaluation of AE by CTC grade to look for any effect of gender, age or race was carried out for the dataset in pivotal Study B2305. The percentage of AE was similar between

male and female patients. The numbers in the other subcategories were small, and it was difficult to draw any conclusions, particularly with regard to an effect of race as most of the subjects were in any case, Caucasian.

7.8.1.2. Hepatically impaired patients

In all of the summary documents, discussion regarding liver toxicity is completely focused on the possibility of hepatic adverse effects occurring in the general target population. There is no data or accompanying discussion on the possibility of this occurring in subjects with pre-existing mild-to-moderate hepatic dysfunction, although the draft PI proposes that use be allowed in such individuals.

Increased pasireotide exposure is seen in the presence of impaired hepatic function, and the sponsor has drawn a distinction between the level to which this occurs in moderately as opposed to severely impaired function based on a statistical test which obscures the observation that a functionally significant level of increased exposure was seen in both these groups, in contrast to those with mildly impaired function (Table 26 below). Furthermore, this distinction is made on the basis of a study which used single doses only, not allowing for the factor of accumulation, and in small numbers of subjects. It is noted that in the draft PI, the sponsor recommends that for patients with moderately impaired hepatic function, a starting dose of 300 µg bd be used and that the maximum dose be limited to 600 µg bd. While the concept of this dose limitation is correct, the quantum chosen appears to be empirical and no evidence has been presented of actual steady state exposure data on this dosage in the particular subpopulation.

Liver toxicity is seen with pasireotide and while this does not appear to cause clinically significant liver disease in the general target population, it might present a hazard for Cushing's disease patients with coexisting liver disease; safe use in such patients has not been demonstrated. Furthermore, there is evidence that liver toxicity is dose (and therefore exposure) dependent; it was the limiting factor in dose escalation Study B2108 (Table 6).

Table 26: PK parameters from Study B2114, by Grade of impaired hepatic function

PK Parameter (unit)	Cohort	n *	Age- and BMI-adjusted Geo-mean	Comparison (s)	Comparison: Geo-mean Ratio	Comparison: 90% CI Lower	Comparison: 90% CI Upper
AUC_{inf} (ng.hr/mL)	Control	12	95.6				
	Mild	6	97.6	Mild : Control	1.02	0.79	1.32
	Moderate	6	117.6	Moderate : Control	1.23	0.92	1.65
	Severe	6	131.9	Severe : Control	1.38	1.07	1.78
AUC_{last} (ng.hr/mL)	Control	12	88.3				
	Mild	6	90.3	Mild : Control	1.02	0.78	1.34
	Moderate	7	105.8	Moderate : Control	1.20	0.89	1.61
	Severe	6	121.7	Severe : Control	1.38	1.06	1.79
C_{max} (ng/mL)	Control	12	11.5				
	Mild	6	11.7	Mild : Control	1.02	0.72	1.46
	Moderate	7	15.9	Moderate : Control	1.39	0.94	2.05
	Severe	6	15.8	Severe : Control	1.38	0.98	1.94
CL/F (L/hr)	Control	12	6.3				
	Mild	6	6.2	Mild : Control	0.98	0.76	1.27
	Moderate	6	5.1	Moderate : Control	0.81	0.61	1.09
	Severe	6	4.5	Severe : Control	0.73	0.56	0.93
T_{max} (hr)	Control	12	0.76				
	Mild	6	1.00	Mild : Control	0.26	0.00	1.00
	Moderate	7	0.67	Moderate : Control	0.00	-0.33	0.48
	Severe	6	1.00	Severe : Control	0.00	-0.02	0.50

n* = number of subjects with non-missing values

Control is the hepatic function normal cohort

PK parameters were analyzed separately on the log scale by means of an ANOVA model including cohort as a fixed effect, and age and BMI as covariates

For T_{max}, median is presented under 'Adjusted Geo-mean', Hodges Lehmann estimate for the difference between the hepatic impairment cohort and the control cohort under "Geo-mean ratio", and the corresponding 90% distribution free CI under "Lower" and "Upper".

Source: PT-Table 14.2-1.1b

7.8.2. Safety related to drug-drug interactions and other interactions

No clinical studies have been done. The sponsor provides evidence based on IV studies that drug-drug interactions are unlikely to be seen with use of pasireotide. The evidence appears acceptable.

7.9. Evaluator's overall conclusions on clinical safety

Pasireotide, similar to other somatostatin analogues, has a significant profile of observed and potential adverse effects. Upper GI symptoms and diarrhoea will be observed in about half of the patients treated with therapeutic doses, although usually improving with time. The high incidence of these adverse effects reflects the fact that the doses required for adequate therapeutic response are close to the maximum tolerated dose. Gallstones will develop in up to 20% of patients.

Hyperglycaemia of some degree develops in most Cushing's disease patients treated with pasireotide, and will meet the criteria for diabetes mellitus in about half of these. If this does

develop, it responds best to those oral agents which act through the incretin mechanism, or could otherwise be treated with insulin.

A minor degree of QT prolongation has been observed but has not been the cause of serious cardiac clinical events.

Abnormalities of liver function have developed with initiation of pasireotide, but have usually been mild and transient. However, there is insufficient evidence of safe use in patients with moderately impaired hepatic function, even at the reduced dosage proposed by the sponsor.

8. First round benefit-risk assessment

Patients with pituitary Cushing's disease who have failed or are otherwise unsuitable for curative pituitary surgery are faced with two equally undesirable alternatives. Therefore, if a treatment offers significant benefits it might justify the taking of significant risks.

8.1. First round assessment of benefits

The benefits of pasireotide in the proposed usage are:

- Reduction of urinary cortisol secretion and consequent improvement in clinical and biochemical manifestations of Cushing's disease.
- Potential avoidance of long-term complications of cortical exposure provided a response is maintained.
- Reduction in pituitary tumour volume.

Although no other medical therapies are currently approved for Cushing's disease, the benefits demonstrated in this application are, on the basis of limited evidence available, equivalent or superior to current off-label use of other medications, as discussed above.

8.2. First round assessment of risks

The risks of pasireotide in the proposed usage are:

- Development of GI adverse effects such as diarrhoea and nausea. These are unpleasant but not permanently injurious to health.
- Development of hyperglycaemia with a significant chance of progression to diabetes mellitus requiring treatment, possibly insulin injections.
- Approximately 20% risk of developing gallstones, but little risk of bile duct obstruction.
- Development of QT prolongation, although with little likelihood of any risk of cardiac compromise except in the case of significant pre-existing comorbidity or co-administration of medications with a similar effect.
- Mild impairment of liver function (raised enzyme levels); the possible impact of this, along with other exposure-related effects of pasireotide, on patients with moderately impaired hepatic function has not been adequately assessed and therefore represents an unquantifiable risk in relation to likely benefit for that subpopulation.

8.3. First round assessment of benefit-risk balance

The benefit-risk balance of pasireotide, given the proposed usage, is favourable with the exception that, in the evaluator’s view, use by patients with moderately impaired hepatic function should not be recommended even at reduced dosage without further evidence that this

is safe. This recommendation is based on the evaluator's assessment that the benefit-risk balance appears, in the absence of definitive data, to be significantly less favourable than for the overall Cushing's disease population.

9. First round recommendation regarding authorisation

It is recommended that the application be approved; pending consideration of the recommendations of this report regarding safety of use in the presence of moderately impaired hepatic function. It is also suggested that the proposed indication be altered to:

> *Treatment of patients with Cushing's disease for whom pituitary surgery is contraindicated or has failed*

as this defines the target population more precisely and is more consistent with the population studied in the pivotal clinical trial.

10. Clinical questions

None requested.

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