Assessment report

Signifor

pasireotide

Procedure No.: EMEA/H/C/002052

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Product information

Name of the medicinal product:	Signifor
Applicant:	Novartis Europharm Ltd. Wimblehurst Road Horsham, W Sussex RH12 5AB United Kingdom
Active substance:	pasireotide (as diaspartate)
International Nonproprietary Name:	pasireotide
Pharmaco-therapeutic group (ATC Code):	Somatostatin and analogues (H01CB05)
Therapeutic indication:	Treatment of adult patients with Cushing's disease for whom surgery is not an option or for whom surgery has failed.
Pharmaceutical form:	Solution for injection
Strengths:	0.3 mg, 0.6 mg, 0.9 mg
Route of administration:	Subcutaneous use
Packaging:	Ampoules (glass)
Package sizes:	6 ampoules, 18 ampoules, 30 ampoules, 60 ampoules

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List of abbreviations

ACTH	Adrenocorticotropic hormone
AE	Adverse Event
b.i.d.	bis in die/twice a day
BMI	Body mass index
CI	Confidence interval
CRH	Corticotropin-releasing hormone
HRQL	Health related quality of life
IPSS	Inferior petrosal sinus sampling
ITT	Intent to treat
LLN	Lower limit of normal
MRI	Magnetic resonance imaging
mUFC	Mean urinary free cortisol
PD	Pharmacodynamics
PK	Pharmacokinetics
PT	Prothrombin time
PTT	Partial thromboplastin time
s.c.	Subcutaneous
SD	Standard deviation
SE	Standard error
SOC	System organ class
SOM230	Pasireotide
sst	Somatostatin receptor
t.i.d.	ter in die/three times a day
UFC	Urinary free cortisol
ULN	Upper limit of normal

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Novartis Europharm Limited submitted on 30 September 2010 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Signifor, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 29 September 2009.

Signifor was designated as an orphan medicinal product EU/3/09/671 on 8 October 2009 in the following indication: Treatment of Cushing's disease.

The applicant applied for the following indication: "Treatment of adult patients with Cushing's disease for whom surgery is not an option or for whom surgery has failed."

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision EMEA-00464-PIP01-08 on the granting of a (product-specific) waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Applicant's request(s) for consideration

New active Substance status

The applicant requested the active substance pasireotide (as diaspartate) Novartis Europharm Ltd. contained in the above medicinal product to be considered as a new active substance.

Scientific Advice

The applicant received Scientific Advice from the CHMP on 27 July 2006. The Scientific Advice pertained to non-clinical and clinical aspects of the dossier.

Licensing status

The product was not licensed in any country at the time of submission of the application.

1.2. Manufacturers

Manufacturer of the finished product

Novartis Pharma Stein AG

Schaffhauserstrasse

4332 Stein

Switzerland

GMP compliance of all manufacturing sites has been confirmed.

Manufacturer responsible for batch release

Novartis Pharma GmbH

Roonstrasse 25

D-90429 Nürnberg

Germany

1.3. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:

Rapporteur: **Kristina Dunder** Co-Rapporteur: **Philippe Lechat**

- The application was received by the EMA on 30 September 2010.
- The procedure started on 20 October 2010.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 07 January 2011. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 11 January 2011.
- During the meeting on 17 February 2011, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 18 February 2011.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 19 May 2011.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of Questions to all CHMP members on 1 July 2011.
- During the CHMP meeting on 21 July 2011, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 25 August 2011.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the list of outstanding issues to all CHMP members on 7 September 2011.
- During the CHMP meeting on 22 September 2011, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.

- The applicant submitted the responses to the CHMP List of Outstanding Issues on 5 December 2011.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the list of outstanding issues to all CHMP members on 5 January 2012.
- During the meeting on 19 January 2012, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Signifor.

2. Scientific discussion

2.1. Introduction

Signifor contains the new chemical entity pasireotide and is a novel somatostatin analogue (SSA) exerting its pharmacological activity through binding to somatostatin receptors. Pasireotide is a novel cyclohexapeptide containing the amino acids lysine, tryptophane, phenylglycine, aminoethylcarbamoyl-hydroxyproline, phenylalanine and O-benzyltyrosine.

Pasireotide is provided as pasireotide diaspartate and has been has been formulated as 0.3 mg/1 ml, 0.6 mg/1 ml and 0.9 mg/1 ml solution for injection in ampoules.

The marketing authorisation application concerns the following indication:

- *Signifor is indicated for the treatment of patients with Cushing's disease for whom surgery is not an option or for whom surgery has failed.*

Signifor is intended for subcutaneous injections twice daily by self injection. The recommended initial dose is 0.6 mg s.c. twice daily. A dose increase to 0.9 mg may be considered based on the response to the treatment, as long as the 0.6 mg dose is well tolerated by the patient. There are no dose adjustments recommended in the elderly or in renal impairment. The recommended initial dose for patients with moderate or severe hepatic impairment is 0.3 mg twice a day, with a maximum recommended dose of 0.6 mg twice a day.

Cushing's disease

Cushing's disease is a very rare, debilitating, and life-threatening disease that is caused by an adrenocorticotropic hormone (ACTH)-secreting pituitary adenoma most commonly affecting adult females. The tumours are usually microadenomas (≤ 1 cm in diameter); macroadenomas are rare. The elevated levels of ACTH secreted by these tumours stimulate the adrenal glands to produce excess cortisol, thereby leading to the subsequent development of the clinical signs and symptoms of hypercortisolism. In patients with Cushing's disease, most adenomatous cells develop a high set-point for feedback inhibition of ACTH secretion by cortisol, which may lead to loss of tumour differentiation to the point where increased cortisol levels can no longer suppress ACTH production and release.

The most common pathologic finding in Cushing's disease patients is bilateral hyperplasia of the adrenal cortex due to excessive stimulation of the adrenal glands by uncontrolled ACTH secretion by the pituitary adenoma. The primary clinical symptoms of Cushing's disease are due to hypercortisolism. As a result, patients with Cushing's disease have increased morbidity and a mortality rate 4 times higher than age- and gender-matched subjects.

Pituitary resection of the adenoma is the current first-line therapy for Cushing's disease, but surgical failure rates range between 8 to 31% even in the hands of the most experienced neurosurgeons, and post-operative recurrence rates are between 5 and 34%. Repeat pituitary surgery may be undertaken

if disease persists after initial surgery, although there is an overall lower rate of success than that seen after the first operation.

For patients not cured by pituitary surgery (either 1 or multiple attempts), irradiation (fractionated external beam radiotherapy or stereotactic radiosurgery) of the pituitary or bilateral adrenalectomy are the remaining non-medical treatment options.

Available medical options generally fill a short-term, palliative role and are rarely used alone as long-term therapy. The use of these drugs is based on limited data; their safety and efficacy profiles are not well established.

In the following section, the efficacy and safety of commonly used medications are summarised.

Ketoconazole is an anti-fungal agent that inhibits the synthesis of cortisol, adrenal and gonadal androgens. It is an 11β-hydroxylase and 17α-hydroxylase inhibitor, which leads to a decrease in cortisol production. Published studies on the use of ketoconazole in Cushing's syndrome are small and/or retrospective. The initial efficacy with ketoconazole (normalization of UFC) is up to 81% of patients with Cushing's disease, but escape is possible requiring continued dose escalation with an increased risk of side effects.

Metyrapone is a pyridine which acts by blocking 11β-hydroxilase, thus inhibiting aldosterone biosynthesis. There are no large prospective studies on the efficacy of metyrapone as monotherapy. Treatment with metyrapone in combination with radiation therapy or other drugs normalised plasma cortisol in up to 74% of patients with Cushing's disease and Cushing's syndrome. Reduction of cortisol levels may induce an increase in pituitary ACTH secretion. Therefore, like with other steroidogenesis directed therapies, escape phenomenon is common.

Mitotane is a compound with similar chemical structure as the insecticide DDT. It has been used in the treatment of adrenocortical carcinomas due to its adrenolytic action. It also is an inhibitor of 11β-hydroxylase, 18-hydroxylase and 3β-hydroxysteroid dehydrogenase. There are no reported large prospective studies on the use of mitotane in patients with Cushing's disease. In combination with radiation therapy, remission rates have been seen in up to 81% of patients. Nevertheless, 60% of these patients subsequently relapsed and needed additional courses of drug or radiation therapy.

Mifepristone is a synthetic steroid that has high affinity for the glucocorticoid and progesterone receptors, acting as a competitive antagonist. Mifepristone appears to inhibit glucocorticoid receptor activation. The safety and efficacy of mifepristone is currently being studied in a clinical development programme in Cushing's syndrome; results have not yet been published. Mifepristone acts very quickly in decreasing some of the signs of hypercortisolism, specially the psychotic manifestations. Mifepristone causes ACTH levels to increase causing an exacerbation of hypercortisolism.

Cabergoline is a dopamine receptor agonist used for the treatment of prolactinomas and (at high doses) Parkinson's disease. The rationale for the use of cabergoline in Cushing's disease is the expression of dopamine receptors in some corticotroph pituitary adenomas. While there are some retrospective studies and case reports in patients with ACTH-dependent Cushing's syndrome, there is only 1 prospective study on the use of cabergoline as monotherapy. In this single center study 20 patients with Cushing's disease were treated with cabergoline. A sustained response (normalization of urine free cortisol) was obtained in 8 patients (40%) after 24 months of treatment, however selection bias (patients with dopamine-receptor positive adenomas) cannot be ruled out. The main safety concern is the association of cabergoline with increased prevalence of irreversible cardiac valve insufficiency.

In summary, while some evidence of efficacy has been reported with these agents in patients with Cushing's disease the data is limited. Furthermore, attenuation of effect and adverse effects limit the

usability of these agents. Thus there is an unmet medical need in the treatment of patients with Cushing's diasease.

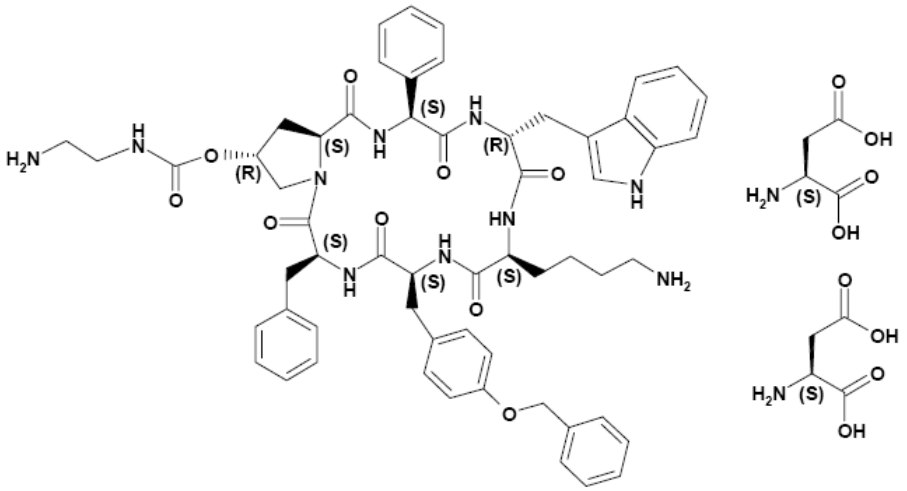
2.2. Quality aspects

2.2.1. Introduction

Signifor contains the active substance pasireotide, as diaspartate. For other ingredients see the SmPC. The product is formulated as a solution for injection in glass ampoules in the concentrations of 0.3 mg/ml, 0.6 mg/ml and 0.9 mg/ml.

2.2.2. Active Substance

Pasireotide is a novel synthetic cyclohexapeptide containing the amino acids lysine, D-tryptophane, phenylglycine, aminoethylcarbamoylhydroxyproline, phenylalanine and O-benzyltyrosine, with molecular formula $C_{58}H_{66}N_{10}O_9 \cdot 2\ C_4H_7NO_4$. Pasireotide free peptide contains 7 assymetric carbon atoms (chiral centres) and there is also one chiral centre in aspartic acid.



The active substance is an amorphous white to slightly greyish powder. Molecular mass is 1313.41. The active substance is freely soluble in water, very slightly soluble in ethanol and acetone, sparingly soluble in methanol and insoluble in acetonitrile and isopropylalcohol.

The structure of pasireotide diaspartate was confirmed by elemental analysis, and several spectroscopic techniques.

Manufacture

Pasireotide diaspartate is manufactured by a solid-phase synthesis. The manufacturing process is well described. The starting materials are sufficiently characterised, specifications and testing procedures being acceptable. For major phases of the synthesis of the active substance, appropriate in-process controls are in place.

Descriptions of the possible impurities which may arise from the route of synthesis and/or storage of the drug substance have been presented. This includes structure, origin and methods of analysis, LOD, LOQ and the proposed limit in the specification for the drug substance.

Specification

The active substance is tested for appearance, clarity and colour of the solution, identity by IR and RP-HPLC, related substances and assay by RP-HPLC, aspartic acid by ion chromatography, amino acid analysis, residual solvents by GC, water, sulphated ash, specific optical rotation, heavy metals, microbial purity and endotoxins. The analytical methods are suitable for testing the chosen specification parameters and were appropriately validated.

Detailed information on impurities was provided. Impurity limits are in line with the Ph.Eur. general monograph for substances for pharmaceutical use, criteria applicable to synthetic peptides. The specification limits for the impurities were also justified by toxicology studies and found safe.

Batch analysis results were provided for development and commercial batches. All results conform to specifications. The reference standard has been appropriately characterised.

Stability

Stability studies have been performed on three batches of the active substance: long term studies, accelerated testing and stress testing.

For the test parameters monitored during the stability studies, the acceptance criteria and methods are the same as for release testing.

Stability results generated under the above long term and accelerated conditions were all within the set specifications. As a result of stressed testing performed, the active substance was found to be sensitive to light and hygroscopic.

Based on stability studies, a retest period for the active substance has been established.

2.2.3. Finished Medicinal Product

Signifor is provided as solution for injection in glass ampoules, 0.3 mg, 0.6 mg and 0.9 mg per ampoule. The volume of the solution in each ampoule is 1 ml. Each ampoule contains an overfill of 0.1 ml, to allow withdrawal of 1 ml of the solution from the ampoule. In addition to the active substance, the product contains mannitol as tonicity agent, tartaric acid as buffering agent, sodium hydroxide for pH adjustment and water for injections as solvent. All excipients are of pharmacopoeial quality.

Pharmaceutical Development

Initial formulations in strengths of 0.15 mg/3 ml (0.05 mg/ml) and 3.0 mg/3 ml (1.0 mg/ml) were prepared as solution for injection in vials. The formulation was optimized after initial Phase 1 studies in strengths 0.1 mg/ml, 0.2 mg/ml, 0.3 mg/ml, 0.6 mg/ml and 0.9 mg/ml as a solution for injection in ampoule. Numerous studies investigating different pasireotide salts, various pH ranges for the formulation and several buffer systems were performed.

Adventitious agents

Pasireotide diaspartate is a fully synthetic active substance. No starting materials, raw materials or reagents are of human or animal origin.

There are no excipients of human or animal origin used in the finished product.

Therefore, there is no risk of BSE/TSE transmission via this product.

Manufacture of the product

The manufacturing process for Signifor 0.3 mg, 0.6 mg and 0.9 mg solution for injection is a standard process for parenteral formulations. In-process controls are in place during manufacture of the product. The manufacturing process has been validated It has been demonstrated that the manufacturing process robustly and consistently yields a product capable of meeting the predefined quality characteristics.

Product specification

The release and shelf-life specification of the finished product covers appropriate parameters for the dosage form. The product is tested for appearance of the container and the solution, identity by TLC and RP-HPLC, assay and degradation products by RP-HPLC, pH, extractable volume, visible and subvisible particles, bacterial endotoxins and sterility. Several degradation products were identified in the product; they are included in the specification, with limits corresponding to ICH Q3B guideline. The shelf-life specification is the same as for release. The specification and control tests are in compliance with general pharmacopoeial standards and ICH/EU guidelines.

The analytical methods have been satisfactorily described and validated.

Batch results on production batches of each dosage strength were presented. All results comply with the specification.

Stability of the product

Stability studies were conducted on several batches of the finished product in glass ampoules. The product was stored at the following conditions: long term (RH), intermediate and accelerated and stress conditions.

No significant changes were observed at long-term conditions The product is sensitive to light.

The results of stability studies support the shelf-life and storage conditions as defined in the SmPC.

2.2.4. Conclusions on the chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and the finished product has been presented in a satisfactory manner. The results of tests carried out indicate satisfactory consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic.

2.2.5. Recommendation(s) for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

The Applicant is recommended to re-assess the limits set for residual heavy metals after more experience in commercial manufacturing is gained. This re-assessment could be envisaged after having data available for additional batches of Pasireotide diaspartate.

Since the current packaging (glass ampoules) is not considered optimal by the CHMP, the Applicant is recommended to further develop and submit an application seeking approval of pasireotide solution for injection in pre-filled syringes as soon as appropriate stability data are available.

2.3. Non-clinical aspects

2.3.1. Introduction

GLP aspects

Safety pharmacology studies were performed according to GLP principles apart from three studies (RD-2010-50430, RD-2010-50370, 0419101), for which sufficient justifications have been provided. Pharmacokinetic (ADME) studies were not GLP-compliant, but in line with standard operation procedures, protocols, and/or current scientific standards. All pivotal non-clinical toxicity studies were performed in accordance with GLP principles except two reproduction toxicity studies (HRA 2914-446 and HRA 2914-447). The absence of GLP compliance does not affect the conclusions that can be drawn from these studies.

2.3.2. Pharmacology

Primary pharmacodynamic studies

Primary pharmacodynamic studies

Binding of pasireotide *in vitro* to somatostatin receptor subtypes, sst1-sst5, as well as functional analysis has been performed using cells expressing human recombinant somatostatin receptor subtypes and mouse pituitary AtT20 cells expressing native somatostatin receptors. Comparisons have been made to octreotide (Sandostatin), a substance that binds primarily to sst2, but also to sst3 and sst5 with lower affinity, while the affinity to sst1 and sst4 is very low, and SRIF-14, which is a natural somatostatin or "somatotropin release inhibiting factor".

In vitro studies

Competition binding experiments showed that pasireotide binds with high affinity to human somatostatin receptor subtypes hsst1, hsst2, hsst3, and hsst5. The affinity for hsst1 and hsst5 is 30 to 40 times higher, and the affinity to hsst3 5 times higher than the affinity of octreotide, while the affinity for hsst2 was somewhat lower to octreotide.

Functional activity at human recombinant somatostatin receptor subtypes showed pasireotide to be a full agonist, with nanomolar or subnanomolar potency at hsst1, hsst2, hsst3 and hsst5 receptor subtypes. Pasireotide had no agonistic activity at the hsst4 receptor subtype, which is in line with the above mentioned binding data. Furthermore, when investigated at somatostatin receptors in mouse pituitary TtT20 cells, a high (nanomolar) affinity for somatostatin receptors and an agonistic action was demonstrated *in vitro*.

The inhibitory effect of pasireotide, SRIF-14 and octreotide on ACTH release was investigated in cell culture experiments using human adenoma tissue and mouse AtT20 corticotroph adenoma cells. Pasireotide and SRIF-14 inhibited ACTH secretion in human adenoma cells and suppressed basal ACTH production in AtT20 cells, whereas octreotide had no effect.

A pivotal study investigated the effect of pasireotide on ACTH secretion and cell proliferation of primary human pituitary corticotroph adenomas obtained from 13 patients with Cushing's disease demonstrating that human pituitary corticotroph adenomas display all somatostatin receptor subtypes except for subtype 3. Furthermore, pasireotide has ability *in vitro* to suppress cell proliferation and inhibit ACTH secretion at concentrations approximately at clinical relevant levels.

In vivo study

There are no relevant animal models available for Cushing's disease. An *in vivo* study on the effect of pasireotide on CRH-stimulated secretion of ACTH and corticosterone has been performed in adult male Sprague-Dawley rats. On day 1, animals were pretreated, i.v., with either pasirotide (1, 3 or 10 µg/kg), octreotide (10 µg/kg) or 0.9% NaCl 0.9% for one hour. The rats were then injected i.v. with CRH 0.5µg/kg to stimulate the secretion of ACTH and corticosterone. The study demonstrates that pasireotide *in vivo* has a stronger inhibitory effect on ACTH and corticosterone secretion than octreotide in rats.

Secondary pharmacodynamic studies

Secondary pharmacodynamic studies demonstrated that consistent with its high *in vitro* binding affinity for sst2 and especially sst5, pasireotide inhibits the GHRH-induced GH release from primary cultures of rat pituitary cells. *In vivo* in rats, pasireotide inhibited unstimulated GH release and caused a dose-dependent decrease in plasma IGF-1 levels following s.c. infusion of 1, 10 or 50 µg/kg/h of pasireotide for 7 days. In rhesus and cynomolgus monkeys, pasireotide is also a strong inhibitor of GH and IGF-1. The ID_{50} of pasireotide for the inhibition of GH in Rhesus monkey was 0.4 µg/kg s.c and thus similar to the values obtained in rats.

Pasireotide caused a marked increase in plasma glucose concentration 1 hour after s.c. injection of ≥10 µg/kg in rats. In contrast, no increase in glucose was observed after injection of the same or even up to 50-fold higher doses of octreotide. Doses of pasireotide ≤1 µg/kg, which inhibit GH *in vivo* (ED50 = 0.2 µg/kg s.c.), did not alter basal glucose levels. The increase in glucose was primarily seen with short term application of pasireotide in rats, but not in monkeys. Transient increases in plasma glucose have also been observed in clinical studies with Cushing's patients.

Safety pharmacology programme

Safety pharmacology studies were performed in accordance with the ICH S7A and S7B guidelines. In a receptor screening assay, low binding affinity was detected to opiate kappa (0.041 µM), ghrelin (0.15 µM), 5HT1A (0.31 µM) and opiate µ (0.42 µM) receptor binding sites which might indicate potential off target effects. However, the binding affinity for sst5 (the main target for Cushing's disease) was 0.16 nM indicating that off target effects of pasireotide via these four receptors at clinical doses of pasireotide is probably of minor importance. Furthermore, there were no findings in the non-clinical safety studies or in clinical trials that can be explained by actions via these receptors.

Cardiovascular *in vitro* studies demonstrated no inhibition of hERG tail currents. No adverse effects on QT interval prolongation, interference with cardiac ion channels, blood pressure or on the electrocardiogram have been observed. Pasireotide when administered subcutaneously in male albino rats had no treatment-related effects on respiratory function. However, safety pharmacology studies carried out to assess the interference with potassium cardiac KCNQ1 and Kv3.4/Kir3., sodium (Nav1.5) and calcium (Cav1.2) channels, as well as the rabbit Purkinje fiber assay were not conducted under GLP conditions. The Applicant warrants that the lack of GLP status did not have an impact on the integrity of the results, a view which is accepted by the CHMP.

Pharmacodynamic drug interactions

No pharmacodynamic drug interaction studies have been performed with pasireotide, which is acceptable.

2.3.3. Pharmacokinetics

The pharmacokinetics or toxicokinetics of pasireotide were determined in mice (CD-1, CB6F1/TgrasH2 and CB6F1/Jic-TgrasH2@Tac), rats (Wistar), rabbits (New Zealand White), dogs (Beagle) and monkeys (Cynomolgus). Absorption, distribution, metabolism and excretion of pasireotide were studied in rats and monkeys using subcutaneous and intravenous dosing.

Pasireotide was rapidly and almost completely absorbed (84-100%) after subcutaneous administration in rats, monkeys and humans. Pasireotide was cleared with half-lives, ranging from approximately 1.3 hours in rats, 59 hours in monkeys and 8 hours in humans. The elimination of the radioactive half-life was much longer in rats, monkeys and humans (39, 187 and 211 hours, respectively), but since the contribution of the terminal phase to the total AUC was only 7-20% (depending on the dose), the effective apparent half-life in human was estimated to be ~12 hours for doses of 0.6-1.5mg. Bioavailability was estimated to be 100% in animals.

Pasireotide related radioactivity was widely and similarly rapidly distributed in pigmented and non-pigmented rats. The highest concentrations were found in the kidney, cartilage (blood vessel wall, ear and esophagus), lymph nodes, spleen and liver. Radioactivity-derived material was eliminated slowly with total radioactivity in the carcass at 1, 3 and 14 weeks post-dose representing 29%, 14% and 2% of the dose, respectively, indicating a potential for drug accumulation. It is also noted that drug-related radioactivity remained at significant levels in several endocrine tissues (in addition to adrenals) where pasireotide is likely to be pharmacologically active (e.g. pituitary gland, pancreas). The passage of the blood-brain barrier was minimal and there was no specific retention in melanin rich tissue. Placental transfer and distribution to the fetus was shown in rats and rabbits. Pasireotide was excreted into milk in rats. Pasiretotide was shown to be moderately bound to plasma proteins in all species tested including human with binding of 94%, 93% and 88% in rat, dogs and humans, respectively.

The metabolism of pasireotide (0.2-0.5 mg protein/mL, 0.15-0.38 µM) was studied *in vitro* using liver microsomes of rat, cynomolgus monkey and human, hepatocytes of rat and human kidney microsomes. The only metabolite shown was a NADPH-dependent metabolite in monkeys, the structure of which could not be determined. The metabolism *in vivo* of pasireotide in rat, monkey, and human following a s.c. dose was very limited with only a few minor metabolites detected. In the monkey, the primary metabolic pathway was formation of metabolite M27, an oxidative product followed by deamination on the lysine moiety of pasireotide. This metabolite was not detected in other species including humans. Unchanged pasireotide was the major circulating component in the plasma of rat (93-95% of AUC), monkey (93% of AUC), and human (100% of AUC).

The main route of excretion in rats and monkeys was via the faecal route (approximately 88%).

2.3.4. Toxicology

Toxicological and toxicokinetic studies have been performed in mice, rats, rabbits and monkeys to support the administration of pasireotide aspartate (tested mostly as base where salt/base ratio is 1.25). These studies include acute, subchronic and chronic toxicity studies, carcinogenicity studies in transgenic mice, local tolerance studies, reproduction studies, as well as *in vitro* and *in vivo* genotoxicity studies. Most of these studies were performed using the subcutaneous route which is the proposed route of administration in patients. In addition, oral and i.v. administration routes were used in rats and monkeys.

Single dose toxicity

Acute toxicity studies were performed in rats and mice via the subcutaneous route with a maximum dose of 30 mg/kg (corresponding to 30 ml/kg as the maximum practical volume) which was non-lethal. In mice, pasireotide only induced crusts at the injection site in one female and no other adverse effects were observed. In rats, sores were noted on the application area of all females at 15 mg/kg and all animals at 30 mg/kg. Loss of body weight was observed during the first week following treatment.

Repeat dose toxicity

Pasireotide has been studied in repeat–dose toxicity studies in mice (up to 4 weeks via the s.c. route), rats (up to 26 weeks, 2 weeks and 1 week via the s.c., i.v. and oral routes), dogs (up to ≤one week via the s.c. route) and monkeys (up to 39 weeks, 2 weeks and 2 weeks via the s.c., i.v. and oral routes). The highest doses chosen in the repeat-dose toxicity studies via the subcutaneous route were 30 mg/kg for 4 weeks in mice (s.c), 4 mg/kg (b.i.d.) for up to 2 weeks in rats, 5 mg/kg (b.i.d.) for 2 weeks in dogs and 8 mg/kg (as salt) up to 4 weeks in monkeys. The mortality rate after subcutaneous doses of pasireotide was low in mice and rats, and none of the monkeys died. Dogs were shown to be the most sensitive species for the adverse effects of pasireotide showing signs of severe GI symptoms. Cynomolgus monkey was used as a non-rodent species further to the results of a 2-week study in dogs showing poor gastro-intestinal tolerability of pasireotide at low exposure levels. According to the Applicant, this is related to an exaggerated pharmacological activity of pasireotide since somatostatin is known to increase intestinal transit, which is endorsed.

Subcutaneous administration of pasireotide by both twice daily (b.i.d.) and once daily (o.d.) regimens caused similar adverse findings and hence the once daily s.c. administration route was chosen in the chronic toxicity studies.

There is some evidence that the dose levels used in repeat-dose toxicity and carcinogenicity studies conducted in rats were rather low since they induced mainly effects related to the pharmacological activity of pasireotide on the neuro-endocrine system at low exposure levels. In addition, they were considerably lower than the dose levels used in reproduction toxicity studies. This issue was discussed by the Applicant and it is still considered by the CHMP that higher doses could have been used in the 6-month rat study, and in the rat carcinogenicity study. Nevertheless, the toxicological profile of pasireotide could be defined from the available toxicity studies. In addition, the concern on dose levels administered to rats is counterbalanced by the high specificity of pasireotide for sst receptors (notably sst5) and high exposure ratios reached in monkeys. Regarding the carcinogenicity study, in spite of rat-to-human exposure ratios reaching 6.5 in females and 13.7 in males, this can be considered acceptable taking also into account the lack of genotoxic potential and results obtained in the short-term mouse carcinogenicity study at higher animal-to-human exposure ratios.

<u>Targets of toxicity after subcutanous administration of pasireotide</u>

Generally, decreases in body weight gain and food consumption were noted in mice, rats and monkeys receiving subcutaneous doses of pasireotide. The LOAEL effects for the effects on the body weight in mice and rats were below the expected clinical exposure level based on both Cmax and AUC. These effects were observed in monkeys at exposure levels of 4.6x and 1.1x the expected clinical exposure based on Cmax and AUC, respectively.

The other main target organs of toxicity identified after a subcutaneous dose were local damage of the skin at the injection sites (all species used in the toxicology studies), pituitary (rats and monkeys), thyroid (monkeys), pancreas (mice and rats), bone (rodents), liver (mice and rats), female reproductive organs (mice and rats), lymphoid and hematopoietic organs (mice, rats and monkey), vasculature (rats and monkey) and large intestine (monkey).

Injection site

Irritation of the skin at the injection site was evident in all species used in the repeated dose toxicity studies. These changes consisted of inflammation (chronic partially active dermatitis), fibrotic changes, hyperkeratosis, hypertrichosis, ulceration and necrosis of the skin and underlying tissue at the injection site in mice at the LOAEL of 0.2 mg/kg/day. In rats, subcutaneous redding at the injection site, inflammation scab, alopecia, fibrosis, edema, necrosis, minimal to moderate mineralization and regeneration of skeletal muscle myofibers and regeneration of the panniculus muscle at the injection site and underlying tissues was observed at the LOAEL of 0.008 mg/kg/day. In monkey studies, swelling, redness, edema, inflammation, haemorrhages, granulation tissue, fibroplasias at the injection site and degradation/regeneration of subcutaneous skeletal muscle at the LOAEL of 0.5 mg/kg/day b.i.d.) were also shown. These effects in mice, rats and monkeys are shown at lower exposure levels compared to the roughly estimated clinical exposure. However, effects at injection site have been observed in patients receiving pasireotide and there is a warning for these side effects in the SmPC.

Effects on the neuroendocrine system correlated to the pharmacology of pasireotide

Inhibitory effects on the hypophysis, resulting in lower pituitary weight (rats) and a decrease in size of the somatotrophs or decreased (mice, rats) /increased (monkeys) acidophil cells of the pituitary were shown in the repeat dose toxicity studies. The LOAEL for the effects on the acidophil cells of the pituitary was ≥2.5 mg/kg/day in mice (higher exposure levels than the roughly estimated clinical exposure), 0.008 mg/kg/day in rats (corresponds to lower exposure levels than the roughly estimated clinical exposure) and 1.6 mg/kg/day (monkeys). The LOAEL for the decrease in pituitary weight in rats was 0.8 mg/kg/day.

In the *pancreas* in rats and mice, increased zymogen granules were observed which was not correlated with any other findings in the pancreas. The LOAEL for the effects on pancreas was shown to be 2.5 mg/kg/day for mice and 0.01 mg/kg/day b.i.d in rats. The changes in zymogen content were reversible after dose termination.

In *thyroid* decreased weight was observed in studies where monkeys were treated for 4 and 39 weeks with the LOAEL doses of 2 and 0.5 mg/kg/day, respectively. In both studies these changes were correlated to histopathological changes of attenuated follicular epithelium and small follicles with foamy cytoplasm in follicular epithelium in thyroidea.

The changes in pituitary, pancreas and thyroid are caused by the pharmacology of pasireotide and are known as clinical side effects of somatostatin analogues and are covered in the SmPC sections 4.4 and 4.8.

Effects on *bone growth* including decreased bone formation at the level of the epiphyseal plate of the long bones were observed only in rodents. These effects could be due to the inhibitory effects of pasireotide on the secretion of GH from the pituitary and is thus considered to be a pharmacological effect.

An increase in serum aspartate and alanine aminotransferase activity and a decrease in both total serum protein and globulin were observed in both mice and rats, indicating adverse effects of pasireotide on the *liver*. No histopathological correlates for these changes were found in the liver. Decrease in liver weight and glucagon and bilirubin levels were shown in rats with a LOAEL of 0.05 mg/kg/day (corresponding to 0.5 and 0.05x the roughly estimated clinical exposure levels based on Cmax and AUC, respectively). In rats, an increase in coagulation parameters such as PT, APTT and fibrinogen at LOAEL of 0.024 mg/kg/day (corresponding to 0.2x and 0.09x the roughly estimated clinical exposure levels based on Cmax and AUC, respectively) in females only, were also shown. Decreases in cholesterol, triglycerides and α-1 globulin have also been shown in rats. These effects

could be secondary to the effects of changes of pituitary GH production by pasireotide and resulting in changes in the hepatic lipid metabolism and production of coagulation factor. In any case, a transient increase in the liver enzymes and coagulation factors has been shown in the clinic and measurements of these enzymes are recommended before and during treatment with Signifor, which is reflected in the SmPC section 4.4.

In *female reproductive organs,* prolongation of estrus cycle was observed in females treated with pasireotide for 2 weeks at 5 mg/kg (rabbit) and at doses ≥ 0.08 mg/kg for 26 weeks (rat), which correspond approximately to 60x and 1x the intended clinical exposure based on Cmax and 24x and 0.3X based on AUC, respectively. Morphological changes of the ovary (interstitial cell hyperplasia, minimal to slight decrease in weight and decreased number of corpora lutea) and genital tract (presence of fluid in the uterine horns and uterus dilatation and by hypertrophy with mucification of the superficial cell layers of the vagina) were also observed at the end of 26 weeks.

The reproductive changes were totally or partially reversible. The inhibitory effects seen on the female genital tract and estrus cycles in rat studies are considered to result from the pasireotide-induced decrease in IGF-1 and GnRH and LH, which causes ovulation and estrus not to occur. It is not known whether pasireotide has an effect on human fertility.

Adverse effects in *lymphoid and hematopoietic organs* in the order they developed were decreased lymphoid cellularity in spleen in rats at 0.01 mg/kg/day, decreased WEC in rats at 0.024 mg/kg/day, decreased reticulocytes, thymus weight and bone marrow depression in rats at 0.05 mg/kg/day, decreased hematopoietic activity in spleen in rat at 0.5 mg/kg/day, increased RBC, haemoglobin and hematocrit in rats at 1 mg/kg/day b.i.d, bone marrow depression in monkeys at 2 mg/kg/day, decreaed thymus and spleen weight in rats at 5 mg/kg/day, decreased thymus weights in mice at 10 mg/kg/day and decreased RBC, hematocrit and haemoglobin in mice at 30 mg/kg/day. The first signs of adverse effects on the hematopoietic and lymphoid organs were at doses which gave rise to exposure levels below the intended clinical exposure based on both Cmax and AUC. In monkeys, decreased cellularity in bone marrow was observed starting at 2 mg/kg/day which correspond to 42x and 17x the intended clinical exposure based on Cmax and AUC, respectively. The effects of pasireotide on the lymphoid organs and hematopoiesis are believed to be related to the pharmacological properties of the somatostatin analogues specifically due to the binding of these compounds to the receptors of hematopoietic precursor cells (CD34+ cells), monocytes and lymphocytes inhibiting the proliferation of these cells. The function of lymphoid and hematopoietic organs should be closely monitored in patients, which is reflected in the SmPC.

Vascular effects shortly after administering rats with subcutaneous doses of 5 mg/kg of pasireotide consisted of red tail tip, red feet and ears. After approximately 10 days, swollen ear, muzzle and feet and tail were observed. The effects on muzzle appeared at lower doses in twice daily administration regimen compared to once daily. In monkeys, facial redness was observed after an intravenous dose of 0.135 mg/kg/day. These effects are considered to be secondary to the vasodilatory effects of pasireotide being a somatostatin analogue with release of nitric oxide as the known class effect. Bradycardia has been reported as a common adverse effect for patients receiving pasireotide. Interestingly PK distribution studies with radioactive pasireotide in rats have shown high tissue to blood concentration for the blood vessel wall based on both Cmax and AUC. The SmPC section 4.4 includes a warning for prescribing pasireotide in patients with cardiac disease.

As mentioned above, adverse effects on the *gastrointestinal tract* have been observed in dogs, which showed to be the most sensitive species with signs of severe GI symptoms that ultimately lead to discontinuation of dosing of these animals. Gastrointenstinal disorders such as diarrhea, nausea and vomiting have frequently been reported in patients receiving pasireotide and a warning of these effects are given in the SmPC section 4.8. In monkeys, however, distension of the large intestine with firm

fecal material was present in 1-4 monkeys in each dose group of the 4- and 39-week studies. Hence, the adverse GI effects in monkeys do not correspond directly to the effects reported in patients receiving pasireotide, such as diarrhea (very common) and vomiting (common).

Effects on *kidneys and excretion parameters* consisted of decrease in kidney weight (mice at 10 mg/kg/day) and some minor changes in the excretion parameters (increase in urea, creatinine, phosphorous and decreased pH in the urine) in rats at doses ≥0.24 mg/kg/day and in mice ≥20 mg/kg/day were observed without any histopathological changes in the kidneys. These changes are considered to be prerenal azotemia that occurs when the volume or pressure of blood flow through the kidney drops which ultimately results in a decrease in kidneys filtration rate. The drop in the renal blood flow is a likely effect of pasireotide since somatostatin analogues cause vasodilatation and reduction in blood pressure thus affecting highly perfused organs such as kidneys.

Adverse effects shown using other routes of administration

Intravenous route, rats were dosed up to 4.5 mg/kg (one dose only) and monkeys up to 0.15 mg/kg for 2 weeks). Intravenous administration of pasireotide by bolus injection at a dose of 4.5 mg/kg in one rat only was lethal, due to severe toxicity causing reduced motor activity, recumbency, rapid irregular breathing, cyanosis (at the injection site and generalized, whole body) and the animal was sacrificed 20 minutes after dosing. In the main study, cyanosis was shown to be dose dependent and started at the tip of the tail dose 0.05 mg/kg/day and after 3 doses corresponding to approximately 4x the intended clinical exposure based on Cmax. Cyanosis then progressed to the whole body at the dose 0.15 mg/kg/day which corresponds approximately to 12x and 0.9x the intended clinical exposure based on Cmax and AUC, respectively. Hypoactivity, swelling of snout and transient dyspnea were also shown after 2-3 days of dosing with 0.15mg/kg/day. In addition, erythema in the eye and recumbancy were observed. These effects of pasireotide (cyanosis, irregular breathing, reduced motor activity and recumbency) in rats following intravenous administration are somewhat concerning since the effects start at low exposure levels based on both Cmax and AUC.

The intravenous administration of pasireotide in monkeys did not cause any mortality. A dose of 0.075 mg/kg resulted in redness of the face and recumbancy /immobility immediately post-dose, which corresponds approximately to 19x the intended clinical exposure based on Cmax. At 0.15 mg/kg, excitement (3/3), dilated pupil (1/3) and laboured breathing (1/3) were observed which corresponds approximately to 40x the intended clinical exposure based on Cmax. The reason for pasireotide induced laboured breathing in monkeys is not clear. However, when pasireotide was used in a telemetry study (study 010076, safety pharmacology study) in monkeys given as a single subcutaneous dose of up to 2 mg/kg, no clinical signs were observed. To relate the dose in this study to exposure levels, the results of PK study (DMPK (CH) R01-01556) were used where the exposure level after a subcutaneous dose of 1 mg/kg based was shown to be approximately 1217 ng/mg, which corresponds approximately to 27x the intended clinical exposure based on Cmax. Showing no clinical signs at this high exposure levels is rather unexpected since the cardiovscular effects such as bradycardia and QT prolongation are known clinical pharmacological effect of somatostatin analogues such as lanreotide, octreotide and even pasireotide. The lack of response in monkeys makes the suitability of this species as a non-rodent species for evaluating these types of effects in preclinical studies questionable. The presence of the somatostatin receptor subtype 5 (SS5) in the heart, and the high potency of pasireotide for this receptor, makes this organ a plausible target of toxicity for pasireotide.

Oral route: Generally, doses chosen for the studies via the oral route of administration were much higher than the ones given by the subcutaneous route. The highest dose of pasireotide given by the oral route of administration was up to 300 mg/kg for 4 weeks in rat and up to100 mg/kg for 2 weeks in monkeys. The MTD and lethal doses in rats were ≥80 mg/kg/day and 300 mg/kg/day, respectively

causing decreased body weight, poorly responsive behaviour, recumbency and decreased motor activity. Since the inter-individual variability in the pasireotide concentrations in both clinical and animal studies are very high, the comparison of exposure levels is difficult. However, the exposure levels at MTD in rats (≥80 mg/kg/day) were far below the well tolerated dose of 100 mg/kg in monkeys. Since the oral route of administration is not the intended route for patients, a discussion on the findings of these studies is not considered necessary.

Genotoxicity

Pasireotide has been evaluated for its potential genotoxic effects in bacteria, mammalian cells and in rodents according to guidelines. The studies were performed according to GLP.

In the Ames test, pasireotide was negative in the presence and absence of metabolic activation. Pasireotide did not induce structural chromosomal aberrations in human peripheral blood lymphocytes cells with or without metabolic activation. The Micronucleus test was performed using male rats where the doses in the main study were based on adequate preliminary dose range finding studies in male and female rats. No genotoxic potential was observed in rats treated with pasireotide up to doses of 50 mg/kg (subcutaneous administration). Bone marrow toxicity was observed at the highest tested dose.

Carcinogenicity

A carcinogenicity study in rats and a short-term carcinogenicity study employing TgrasH2 mouse were performed with pasireotide using the clinical administration route.

In rats, doses of 0.01, 0.05 and 0.3 mg/kg/day pasireotide were administered subcutaneously for 24 months. The results of clinical pathology examinations performed are only provided on an individual animal basis in the study report. Pasireotide did not induce tumours in female rats. In male rats a statistically significant treatment-related increase in the incidence of fibroma (whole body) was observed in animals treated with the high dose, 0.3 mg/kg/day. An increased incidence of fibroma/sarcoma was not observed. The NOAEL for the benign fibroma was 0.05 mg/kg/day, which corresponds to an exposure comparable to the intended therapeutic exposure. It is possible that the finding is sporadic as the Applicant proposes, however, considering the three cases of fibroma at the injection site at the high dose group, it is considered more likely that the benign tumours are caused by continuous irritation at the injection site. Irritation of the skin at the injections site is evident in all species in the repeat dose toxicity studies; thus the cases of fibroma at the injection site would not be unexpected. Adequate information has been included in the SmPC to ensure that the patients will not inject themselves at sites where skin reaction/inflammation is present.

In CB6F1/TgrasH2 hemizygous mice doses of 0 (vehicle), 0.5, 1 and 2.5 mg/kg/day pasireotide were administred subcutaneously for 26 weeks. CB6F1 wild-type mice were treated in parallel with 0 (vehicle) and 2.5 mg/kg/day pasireotide. For the CB6F1/TgrasH2 hemizygous mice a positive control, N-methyl-N-nitrosourea (75 mg/kg, single i.p. dose on day 1) was included to ensure test sensitivity. The TgrasH2 mouse short-term carcinogenicity test is acceptable as valid as an alternative for the 24 months mouse carcinogencity study. The design of the study was reasonable and included a positive control which induced neoplatic tumours. The results from the 26 week study with TgrasH2 mice revealed no neoplastic lesions in the pasireotide treated animals. The NOAEL for this 26-week study is >2.5 mg/kg/day, which corresponds approximately to 20x the intended clinical exposure based on Cmax. Similarly to the rat carcinogenicity studies, an increased incidence in subcutaneous inflammation, hemorrhage, fibrosis and regeneration of the panniculus muscle at the injection site were seen in male CB6F1/TgrasH2 mice at pasireotide doses of ≥0.5 mg/kg/day compared to concurrent controls.

Reproduction Toxicity

In the fertility and early embryonic development study in rats, subcutaneous doses of up to 10 mg base/kg/day were administrated. Clinical signs consisted of decreased food consumption and body weight, swollen and red paws and noses and wounds with subsequent hair loss at the injection sites. In females an increased incidence of prolonged estrus cycles/acyclicity and decreased mean numbers of corpora lutea were observed from 0.1 mg/kg. Effects on female reproduction were also seen in the repeat-dose toxicity studies and are an expected pharmacological effect of pasireotide due to an induced decrease in IGF-1. IGF-1 is crucial to the priming actions of estradiol in the female reproductive cycle prior to ovulation. Pasireotide-related impairment of GH-IGF-1 axis may be involved in the induction of female genital tract changes, but there is no clear and absolute understanding of pasireotide's effect on this pathway.

Male reproductive parameters were not affected by treatment. The no adverse effect level (NOAEL) for males was set to 10 mg/kg which corresponds to a margin to human exposure of approximately 10 based on AUC at the maximum human recommended dose (MHRD). No NOAEL was reached for the females.

Embryo-foetal development was studied in rats and rabbits, with subcutaneously administered doses up to 10 mg/kg and 5 mg/kg, respectively. In rats, apart from the previously seen clinical signs, increased absolute number of early/total resorptions, decreased absolute number of viable foetuses and a slight increase in malrotated limbs were observed in combination with maternal toxicity, from 10 mg/kg. A foetal NOAEL was set to 5 mg/kg, corresponding to an $AUC_{(0\text{-}24h)}$ value of 25594 ng*h/mL giving a margin to MHRD based on AUC of approximately 60. In rabbit, clinical signs were obvious from 0.05 mg/kg and consisted of mucoid and/or no stool or urine and decreased food consumption and body weight. Concomitant with maternal toxicity, at 1.0 and 5.0 mg/kg, a decrease in foetal weight and in the absolute number of viable foetuses was noted as well as an increase in unossified forepaw phalanx and talus. Maternal and foetal NOAEL was 0.05 mg/kg/day, corresponding to a $AUC_{(0\text{-}24h)}$ value of 114ng*h/mL, giving no margin to MHRD based AUC.

Prenatal and postnatal development including maternal function was studied in rats, administered subcutaneous doses up to 10 mg/kg. The same clinical signs as observed previously were seen in the dams, however, maternal performance parameters were unaffected. In the F1-generation decreased body weight and a slight retardation in the development of pinna detachment were seen at 2 mg/kg.

There was no effect on visual function, physical development, behavioural performance, macroscopic findings, parental performance or uterine findings for the F1-generation adults. No NOAEL was reached for either generation in this study; the lowest dose of 2 mg/kg gives a margin to human exposure of 2, based on AUC.

No juvenile toxicity study was conducted since Signifor, at present time, is indicated for adults only, and this is acceptable.

Toxicokinetic data

Toxicokinetic data have demonstrated a discrepancy between the exposure levels measured in rats at the high dose levels in the 26-week (0.24 mg/kg/day) and carcinogenicity (0.3 mg/kg/day) studies at the final time-points, i.e. week 22 and week 39, respectively. The exact cause of variability observed between both studies remains unknown. Some inter-study factors could be involved, or possibly other inter-study factors (e.g. variability in pasireotide concentrations in the dosing formulations). Exposure levels were measured in both studies, from which adequate safety margins were determined.

Based on the shown limited biotransformation of pasireotide in all species investigated, the relevance of the use of rat and monkey are supported. However, it should be noted that no GI or cardiovascular effects were seen in these species even at high exposure levels, which might have been expected for this somatostatin analogue.

Local Tolerance

The performed local tolerance studies (ocular irritation and skin irritation/corrosion in the rabbit) demonstrated that pasirotide is non-irritating to rabbit skin but slightly irritating to the eye. However, as was seen in the repeated dose toxicity studies, pasireotide causes irritation at the injection site in all animal species investigated.

Other toxicity studies

A 4-week immunotoxicity study in the rat with pasireotide 0.08, 0.24 and 0.8 mg/kg/day has been performed. In the study lymph node cell counting was performed using a non-validated instrument (Guava automatic counter), thus not in compliance with GLP. The applicant indicates that there is no impact on the integrity of the results based on a comparison assessment with the validated manual method (study no. 27523) performed prior to the main study, a view which is endorsed. Histopathological examination of the bone marrow and lymphoid tissues (spleen, thymus and selected lymph nodes) demonstrated in females at 0.8 mg/kg/day and in males at doses of ≥0.08 mg/kg/day minimal to slight hematopoietic hypocellularity and increased adipose tissue in the bone marrow. Decreases in splenic total lymphocyte counts and absolute counts of all lymphocyte subpopulations analyzed were observed in males dosed at 0.24 and 0.8 mg/kg/day. Neither the anti-KLH IgM nor the anti-KLH IgG responses were affected by pasireotide treatment. The conclusion of the CHMP is that a minimal effect of pasireotide on the immune system was observed in the performed immunotox study.

The Applicant has presented an acceptable argumentation for acceptance of impurities and degradation products and specification limits of pasireotide aspartate, which is endorsed by the CHMP.

The phototoxicity study performed indicated no phototoxic potential for pasireotide. The Applicant in agreement with the OECD test guideline 432 decided that no further investigations were deemed necessary, a view that is shared by the CHMP.

2.3.5. Ecotoxicity/environmental risk assessment

The predicted environmental concentration (PEC) for pasireotide is 0.000035 µg/L, which remains below the trigger value of 0.01 µg/L.

Based on its pharmacological activity, pasireotide should be considered as a potential endocrine disruptor. As such, and in accordance with the guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00), its potential effects on the environment should be addressed irrespective of the quantity released into the environment. Consequently, the fact that phase I PECSURFACEWATER is below the action limit does not preclude the need for additional investigations. The Applicant acknowledges that pasireotide should be tested further in view of its effects on the endocrine system. The Applicant considers that the amphibian metamorphosis assay (OECD TG No. 231) is the most appropriate test to investigate the potential endocrine disruptor activity of pasireotide. This is justified by the drug-induced effects on the hypothalamo-pituitary axis, which were mainly seen on growth. Although pasireotide was shown to affect the growth of rats in a reproducible manner, effects on reproduction cannot be excluded due possibly to drug-induced effects on the GH-IGF-1 pathway.

The amphibian metamorphosis assay is primarily focused on the detection of substances which may interfere with the normal function of the hypotalamo-pituitary-thyroid axis since amphibian metamorphosis is a thyroid-dependent process. Although thyroid findings were not reported in any toxicity study conducted in rodents (including carcinogenicity studies in mice and rats), some were observed in monkeys and were graded minimal to slight (small follicles). Therefore, this assay is considered appropriate to detect any effect related to disruption of the HPT axis. However, this test would be of limited value to detect effects on growth. Therefore, the Applicant is recommended to also perform a juvenile Fish Early Life-Stage study according to OECD 210 to investigate the potential effects on growth, hatchability, fry survival and abnormal change in eggs and fry.

Table 1. Summary of main study results

Substance (INN/Invented Name): Pasireotide			
CAS-number (if available):396091-73-9			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	Directive 92/69/EEC method A.8; OECD107	-2.1	No Potential PBT
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)	0.000035	µg/L	> 0.01 threshold No
Other concerns (e.g. chemical class)			Yes (Potential endocrine disruptor)
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Ready Biodegradability Test	OECD 301E	14.8% within 28 days	Not readily

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

1. The amphibian metamorphosis assay;
2. Fish Early Life-Stage study according to OECD 210;
3. OECD 308 test in line with the ERA guideline.

2.3.6. Discussion on non-clinical aspects

Non-clinical competition binding experiments showed that pasireotide binds with high affinity to human somatostatin receptor subtypes hsst1, hsst2, hsst3, and hsst5. The affinity for hsst1 and hsst5 is 30 to 40 times higher, and the affinity to hsst3 5 times higher than the affinity of octreotide, while the affinity for hsst2 was somewhat lower and equal to octreotide. Thus, the binding data demonstrates that the mechanism of action for pasireotide is somewhat different from that of octreotide, mainly regarding affinity to the hsst5 receptor subtype. Both *in vitro* and *in vivo* data give support for the use of pasireotide in the proposed indication.

The pharmacokinetics of pasireotide is uncomplicated. Rats and monkeys are the species used in the pivotal repeated dose toxicity studies and based on the shown limited biotransformation of pasireotide in all species used, the relevance of the use of rat and monkey are supported by the CHMP. However, it should be noted that no GI or cardiovascular effects were seen in these species even at high exposure levels, which might have been expected for this somatostatin analogue.

Most findings seen in repeated toxicity studies could be attributed to the pharmacology of pasireotide being a somatostatin analogue. The somatostatin neuropeptide family and its receptors have an important physiological role in a wide variety of biological functions in many tissues such as neuroendocrine, vascular, immune, gastrointestinal and reproductive systems. Hence the effects were mostly centered on these systems, which in large also have been noted in clinical trials with pasirotide. Overall, the toxicity profile regarding effects on the neuroendocrine system is expected for this class of compounds. The sensitivity of rats exposed to pasireotide has however been shown to be lower than the known clinical GI effects of somatostatin analogues. In the safety pharmacology and repeated dose toxicity studies, monkeys did not show the typical clinical cardiovascular symptoms of exposure to somatostatin and its analogues, even when the monkeys were exposed to high levels of pasireotide based on Cmax and AUC. Additionally, the adverse GI effects of distention of the large intestine with firm fecal material induced after exposure to pasireotide in monkeys were not typical of those shown in patients who commonly show diarrhea and vomiting. Therefore, the suitability of monkeys as a non-rodent species for evaluating these types of effects in preclinical studies is considered questionable.

The genotoxicity of pasireotide has been adequately studied and the weight of evidence is sufficient to conclude that pasireotide is not genotoxic. Pasireotide is not carcinogenic in mice using the CB6F1/TgrasH2 model or in female rats. In male rats, there were three cases of benign fibroma probably due to sustained toxic irritating effect at the injection site in the high dose group. Irritation of the skin at the injections site is evident in all species in the repeat dose toxicity studies, thus the cases of fibroma at the injection site would not be unexpected. Adequate information has been included in the SmPC to ensure that the patients will not inject themselves at sites where skin reaction/inflammation is present.

Pasireotide did not affect male fertility, but caused prolonged estrus cycles/acyclicity and a decreased mean numbers of corpora lutea in females due to the pharmacological activity. Embryo toxicity at maternally toxic doses was seen in rat and rabbit, but no teratogenic potential was detected in these two species under the study conditions. A slight retardation in the development of pinna detachment and reduced foetal body weight were observed in the prenatal- postnatal development study. In the embryo-foetal study in rabbits and in the prenatal-postnatal study in rats, the effects were seen at similar exposures as reached in humans after MHRD. In the fertility and embryo-foetal studies in rats, the margins to maximum human exposure varied between 10-60 times. These findings have been correctly reflected in the SmPC.

The predicted environmental concentration (PEC) for pasireotide is 0.000035 µg/L, which remains below the trigger value of 0.01 µg/L. Pasireotide cannot be considered as readily biodegradable. Therefore, in accordance with the guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00) the CHMP is recommending the applicant to undertake a study according to OECD 308. Furthermore, based on its pharmacological activity, pasireotide should be considered as a potential endocrine disruptor. In accordance with the guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00), in addition to the amphibian metamorphosis assay suggested by the Applicant, the Applicant is recommended to perform also a Fish Early Life-Stage study according to OECD 210 to investigate the potential effects on growth, hatchability, fry survival and abnormal change in eggs and fry.

2.3.7. Conclusion on the non-clinical aspects

Pasireotide is a somatostatin receptor agonist with a slightly different affinity to somatostatin receptors compared to octreotide. Non-clinical safety data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential, toxicity to reproduction and development. Most findings seen in repeated toxicity studies were reversible and attributable to the pharmacology of pasireotide. Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

Although toxic effects noted in repeat dose toxicity studies in rats could largely be explained by the mechanism of action of pasireotide, monkeys did not show the typical clinical cardiovascular and GI symptoms of exposure to somatostatin and its analogues, which makes the suitability of monkeys as a non-rodent species for evaluating these types of effects in preclinical studies questionable. However, no serious concerns for human safety have been detected in the non-clinical safety studies.

The Applicant is recommended to perform an additional in vitro study assessing the inhibitory effect of pasireotide on a P-gp substrate, preferably with another cell model than Caco-2, with a view to understand the usefulness of performing in vivo studies

The Applicant is recommended to further investigate the potential mechanisms of cardiovascular effects of pasireotide as follows:

1. A study to explore the effects of pasireotide on additional cardiac ion channels using FASTPatch assay.
2. A study examining the expression profile of somatostatin receptor subtypes in cardiac tissues across species.
3. A study to evaluate the effects of pasireotide on hERG-channel trafficking.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Applicant has provided a statement to the effect that all clinical trials that were conducted both within and outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC, which includes compliance with GCP standards.

- **Tabular overview of clinical studies**

Study	Objectives	Dose	No. of subjects
Healthy volunteers			
[B2101]	Safety, tolerability, PK, PD	1, 2.5, 10, 30, 100, 200, 300, 600, 1200 µg single dose	72
[B2102]	Safety, tolerability, PK, PD	50, 200, 600 µg q.d. x 14 days	33
[B2106]	Safety, tolerability, PK	900, 1200, 1500 µg single dose 450, 600, 750 µg twice a day x 1 day	17
[B2107]	Safety, tolerability	150, 300, 600, 900, 1200, 1500 µg q.d. x 8 days 150, 300, 450, 600, 750 µg b.i.d, x 8 days	66
[B2108]	Safety, tolerability, PK	450, 900, 1350, 1800, 2025, 2250 µg/day continuous infusion x 7 days	44
[C2101]	Safety, tolerability, PK	300 µg single dose	78
[B2112]	ADME, PK, safety	600 µg single dose	4
[B2113]	Cardiac safety (QT/QTc), PK, PD	Part I: 900, 1200, 1500, 1800, 1950, 2100 µg b.i.d. x 5 days Part II: 1950 µg b.i.d. x 5 days	128
[B2114]	Hepatic impairment, PK, safety	600 µg single dose	34
[B2216]	Blood glucose, PD, safety	600, 900, 1200 µg b.i.d, x 8 days	38
Cushing's disease patients			
[B2208]	Efficacy, safety, PK, PD	600 µg b.i.d. x 15 days	39
[B2208E1]	Efficacy, safety, PK, PD	300-900 µg b.i.d.; dose titration allowed	19
[B2305]	Efficacy, safety, PK, PD	300, 600, 900, 1200 µg b.i.d.; dose titration allowed	162

q.d.: once daily; b.i.d.: twice a day; QTc: corrected QT interval

2.4.2. Pharmacokinetics

Introduction

The clinical pharmacokinetics (PK) have been investigated in healthy volunteers and in patients (Cushing's disease). In study SOM230C2101, a long acting depot formulation was used, and this study is therefore not assessed in this report. Several population PK models have been developed, one initially on healthy volunteers and eventually two population PK models were developed based on data from patients with Cushing's disease. Of notice is that all healthy volunteer studies with PK assessment included only male subjects, apart from the QTc study (SOM230B2113). Exposure-response models were developed for UFC, QTc and blood glucose.

The pharmacokinetic features of pasireotide have been investigated following subcutaneous administration in healthy volunteers following single (1 to 1500 µg) and repeated doses (50 to 600 µg qd over 14 days, 900 to 2100 µg qd for 5 days). In addition, plasma concentrations were measured in Cushing's disease patients following 600 µg bid up to 15 days using a rich sampling schedule. Sparse data was collected in the phase 3 study (B2305) following 600 and 900 µg bid up to 12 months. Plasma concentrations were measured using a radioimmunoassay method and the data were analysed by means of non-compartmental and/or population PK methods.

Pasireotide solution for injection is an aqueous solution containing the drug substance pasireotide diaspartate formulated in a buffer system. The composition of the product and strengths used in the pivotal study supporting this application is identical to the intended market form.

Absorption

The absolute bioavailability following subcutaneous administration has not been estimated, which is acceptable.

In healthy volunteers, following a subcutaneous dose pasireotide is rapidly absorbed and peak plasma concentration is reached within 0.25-0.5 h. C_{max} and AUC are approximately dose-proportional following administration of single and multiple doses and plasma concentrations decline tri-exponentially. Following the highest recommended dose (900 µg bid) maximum plasma concentrations in patients are predicted to 45 ng/mL on average but due to variability individuals may exhibit levels of 70 ng/mL.

Distribution

In study R99-2082 the protein binding of pasireotide was investigated *in vitro* through ultrafiltration using [14C]pasireotide. The %recovery in the experiments was estimated to be around 70% and independent of the studied concentration, indicating sticking to the filtrate. The bound fraction was found to be on average 88±3% in human plasma from three individuals over the concentration range 25 -10000 ng/mL, without a clear concentrations dependence. The free fraction varied between 8.2 to 16.9%. In the same study, the *in vitro* distribution of [14C]pasireotide to red blood cells was studied in human blood through cell separation by centrifugation and was observed to be very low with fraction in plasma of 91±3% over the concentrations range 100 – 10000 ng/mL. The Cb/Cp was 0.6±0.05.

Thus, in healthy volunteers, pasireotide is widely distributed with large apparent volume of distribution (V_z/F >100 litres). Distribution between blood cells and plasma is concentration independent and shows that pasireotide is primarily located in the plasma (91%). Plasma protein binding is moderate (88%) and independent of concentration.

The available data indicate that the free fraction may be around 0.1 but this value contains some uncertainty. The binding protein in plasma has not been identified.

Based on *in vitro* data pasireotide appears to be a substrate of efflux transporter P-gp (P-glycoprotein). Based on *in vitro* data pasireotide is not a substrate of the efflux transporter BCRP (breast cancer resistance protein) nor of the influx transporters OCT1 (organic cation transporter 1), OATP (organic anion-transporting polypeptide) 1B1, 1B3 or 2B1. Pasireotide is also not an inhibitor of OATP, 1B1 or 1B3.

Elimination

In study SOM230B2112 a single subcutaneous injection of [^{14}C]pasireotide (600 µg) was administered to healthy male subjects (n=4). For all four subjects, >48% of the administered dose radioactivity (56±6.6% of dose) was recovered within 10 days post dose. Pasireotide-related radioactivity was mainly excreted in the faeces, accounting for 38.1–57.2% of the dose elimination (48±8.2% of dose), with renal excretion route accounting for 7.6±2.03% of dose. Based on the metabolite profiling of excreta and plasma, excretion of unchanged pasireotide was considered to be a major elimination route at least within the period 168 hours post dose.

Pasireotide appears to be metabolically stable with little metabolism occurring and no metabolites in the systemic circulation. *In vitro* data show that pasireotide is not a substrate, inhibitor or inducer of any major enzymes of CYP450. In healthy volunteers, pasireotide is predominantly found in unchanged form in plasma, urine and faeces.

The main elimination pathway is hepatic clearance (biliary excretion) and this pathway has been roughly estimated to account for approximately 86% of the dose, predominantly in the form of unchanged drug. The only identified transporter protein involved in the biliary excretion appears to be P-gp. Pasireotide contains 6 chiral carbon atoms and stereochemical inter-conversion *in vivo* is unlikely.

In addition, a small part of the elimination of pasireotide is via the renal route. In a human ADME study 55.9±6.63% of the radioactive dose was recovered over the first 10 days after administration, including 48.3±8.16% of the radioactivity in faeces and 7.63±2.03% in urine.

Pasireotide demonstrates low clearance (CL/F ~6.7 litres/h for healthy volunteers and ~3.8 litres/h for Cushing's disease patients). Based on the accumulation ratios of AUC, the calculated effective half-life ($t_{1/2,eff}$) in healthy volunteers was approximately 12 hours.

Dose proportionality and time dependencies

Over the studied dose range there may be a slight trend of a decreasing apparent clearance at doses above the highest recommended. Over the recommended dose range 600 to 900 μg b.i.d. the lower dose will result in a lower systemic exposure and the decrease is roughly in proportion to dose. On the basis of the healthy volunteer data there is no time dependency indicted and an effective half-life of 12 hours was estimated.

Pharmacokinetic data in patients indicate that patients have a lower apparent clearance, approximately half of that observed in healthy volunteers. No obvious reasons for this difference have been identified. In Cushing's disease patients, pasireotide demonstrates linear and time-independent pharmacokinetics in the dose range of 0.3 mg to 1.2 mg twice a day.

Population pharmacokinetic analysis suggests that based on C_{max} and AUC, 90% of steady state in Cushing's disease patients is reached after approximately 1.5 and 15 days, respectively. Therefore, steady-state is expected to be reached within 2 weeks in patients. The variability in observed pre-dose pasireotide levels in patients ranged from 40-70% CV.

Special populations

Children

No studies have been performed in paediatric patients.

Impaired renal function

There was no effect of mild renal impairment on the systemic exposure of pasireotide. Data in patients with moderate and severe renal impairment are lacking, but an effect is not expected in moderate impairment since the main elimination route is biliary excretion. However, it may not be excluded that the biliary excretion is affected by severe renal impairment.

Impaired hepatic function

A study in hepatic impairment revealed an increase of 60% and 79% in AUC in moderate and severe hepatic impairment, respectively, compared with the control group. A lower initial dose is recommended in patients with moderate and severe hepatic impairment, which is satisfactory.

Elderly

Age has been found to be a covariate in the population pharmacokinetic analysis of Cushing's disease patients. Decreased total body clearance and increased pharmacokinetic exposures have been seen with increasing age. In the studied age range 18-73 years, the area under the curve at steady state for

one dosing interval of 12 hours (AUC_{ss}) is predicted to range from 86% to 111% of that of the typical patient of 41 years. This variation is moderate and considered of minor significance considering the wide age range in which the effect was observed. There is however limited data above the age of 73 years and it is expected that low-weight elderly persons may exhibit higher systemic exposure than patients of higher body weight and lower age.

Gender, race and weight

There is no effect of sex on the systemic exposure of pasireotide. With respect to race, there are no data available. Effects of body weight and age on the systemic exposure were identified in the population PK analyses; pasireotide exposure increased with increasing age and decreasing body weight, respectively. For a range of 60-100 kg the reduction in AUC_{ss} with increasing weight is predicted to be approximately 27%, which is considered moderate and of minor clinical significance. Further, in view of the overall variability, these effects appeared to be of little clinical relevance.

Pharmacokinetic interaction studies

Based on *in vitro* inhibition studies it is considered unlikely that pasireotide would inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4/5 *in vivo*. *In vitro* data are not conclusive concerning inhibition of P-gp by pasireotide, and the Applicant is recommended to complement these data with an *in vitro* study assessing the inhibitory effect of pasireotide on a P-gp substrate, preferably with another cell model than Caco-2. Furthermore, pasireotide is not expected to induce enzymes regulated via the Ah receptor, CAR or PXR.

No drug interaction studies have been performed *in vivo* and in general the interaction potential for pasireotide appears low since there are no strong indications that pasireotide would inhibit or induce enzymes or transporter proteins. Furthermore, pasireotide is mainly excreted unchanged via bile.

P-gp seems to be the only transporter that is likely involved in the distribution and/or elimination of pasireotide. Since biliary excretion is a major elimination pathway for pasireotide, the consequence of an inhibition of this pathway is of importance. From a clinical perspective, the P-gp inhibitor verapamil can be anticipated to be co-administered with pasireotide. Therefore, the Applicant is recommended to perform a clinical interaction study assessing the effect of the strong P-gp inhibitor verapamil on pasireotide pharmacokinetics.

Pasireotide may decrease the absorption of cyclosporine by an unknown mechanism. A cautionary statement suggesting that dose adjustment of cyclosporine may be required upon concomitant administration has been introduced into the SmPC, which is considered sufficient.

Pharmacokinetics using human biomaterials

The clinical pharmacology package contains several human biomaterial studies (permeability in Caco-2 cell monolayers, blood distribution, plasma protein binding, biotransformation and drug-drug interactions using human liver microsome and hepatocytes). The relevant results are discussed above.

2.4.3. Pharmacodynamics

Mechanism of action

Pasireotide (SOM230) is a novel, injectable, somatostatin analogue with a different receptor binding profile than either octreotide or lanreotide.

In contrast to other somatostatin analogues (SRIFa), pasireotide has a high affinity to 4 of the 5 known human sst subtypes (sst 1, 2, 3, and 5), thereby resulting in a binding profile that is closest to date to natural somatostatin. As compared with octreotide, pasireotide exhibits a 30-40 times higher binding affinity for sst1 and sst5, 5 times higher binding affinity for sst3, and a comparable (0.4-fold) affinity for sst2. Pasireotide inhibits ACTH secretion from human corticotropin adenomas *in vitro* with a greater effect than octreotide, potentially due to the higher binding affinity for the sst5 receptor, which is thought to play an important role in Cushing's disease. Several lines of functional pre-clinical data derived from rats, AtT20 cells and human corticotroph adenoma cells support this assumption.

Primary and Secondary pharmacology

Primary pharmacology

Somatostatin is a hormonal peptide that regulates the endocrine system. These principal effects are the inhibition of the release of GH and TSH, the suppression of the release of gastrointestinal hormones (such as gastrin, secretin, cholecystokinin) and pancreatic hormones (inhibition of the insulin and glucagon release). Thus, by its mechanisms of action as analogue of somatostatin, pasireotide may lead to the same inhibition process.

Main efficacy assessments in patients with Cushing's disease were determined by urinary-free cortisol (UFC) as the primary endpoint, while serum cortisol and plasma ACTH were chosen as the secondary endpoints. Since the effect of pasireotide was only investigated in patients with Cushing's disease, these data will be discussed in the efficacy section of this report.

Although the primary target for pasireotide is inhibition of ACTH secretion, ACTH measurement in the evaluation of pasireotide efficacy is not feasible due to the rapid degradation of ACTH in plasma. In patients with Cushing's disease UFC is a surrogate measure for ACTH activity and UFC is accepted as a screening test in Cushing's disease. By applying 24 hour collections and calculation of the mean of two or three consecutive collections the variability is decreased. The choice of UFC was endorsed by the CHMP.

Urinary-free cortisol (UFC) response in Cushing's disease patients

Exposure-response analyses of UFC *versus* measures of pasireotide plasma concentrations revealed a tendency of a relationship, but the analyses do not provide a firm support for the choice of dose.

Secondary pharmacology

Study B2101 was a randomized, double-blind, placebo-controlled, parallel-group, ascending single dose study exploring the tolerability, PK and PD in 72 healthy volunteers. The doses investigated ranged between 1 and 1200 µg.

In this single-dose study, pasireotide did not show any effect on food-induced changes in glucose, CKK, and insulin levels 23 hours post-dose. The GHRH test (performed between 2 to 5 hours post-dose) demonstrated the ability of single doses of pasireotide to suppress the release of GH.

This effect started to be observed at doses of 30 µg, showing a clear suppression in the 200 µg dose group and near maximal effects at 600 to 1200 µg, in which range it approached an upper plateau region in the dose-response and exposure-response curves.

Study B2102 was a placebo-controlled randomized, cross-over, double-blind, dose-escalating study to evaluate safety, tolerability, PK and PD in 33 healthy volunteers. Doses investigated were 50, 200 and 600 µg b.i.d. over 14 days.

When repeated doses were given, glucose levels were elevated both prior to and after a meal in subjects receiving 600 µg pasireotide, but this effect was less prominent on Day 14 than on Day 1. Post-prandial insulin levels until 1 hour post-lunch were elevated after 600 µg.

Glucagon, gastrin, and thyroid hormones were not significantly affected at any dose.

Gallbladder volume was increased post-prandially at both 200 and 600 µg, and this appeared to be correlated with reduced levels of CCK at these doses. Increased stool fat levels were observed in subjects receiving 200 and 600 µg/day. Despite reports of diarrhoea, there was no effect on overall stool weight at any dose.

Pasireotide significantly inhibited GH-RH-stimulated GH secretion at doses of 200 and 600 µg/day, and an average pasireotide concentration of approximately 0.7 ng/mL will yield half of the maximal GH reduction. This effect did not undergo tachyphylaxis after 14 days of treatment, as the effect was similar on Day 1 and Day 14.

These observed effects of pasireotide could be expected considering the mechanism of action.

Blood glucose metabolism in healthy volunteers - Study B2216

In Study B2216, a Phase II, double-blinded, single center study to assess the effects of pasireotide on insulin secretion and glucose metabolism in healthy male volunteers, the mechanistic effects of pasireotide on glucose metabolism was examined in detail. In this study, subjects were randomized into either pasireotide 600 µg b.i.d. s.c. or 900 µg b.i.d. s.c. treatment groups, which they were treated with their respective pasireotide dose level for an 8-day period.

Dose-response data obtained in this study revealed the rapid, transient increase in blood glucose concentration after pasireotide s.c. b.i.d. treatment that was primarily related to a reduction in insulin levels due to a decrease in insulin secretion. No changes in hepatic or peripheral insulin sensitivity were observed. In addition, pasireotide s.c. was also associated with a significant decrease in incretin response (i.e., glucagon-like peptide-1 [GLP-1] and glucose-dependent insulinotropic peptide [GIP]).

Increases in blood glucose occurred with initial pasireotide exposure; however, this effect was followed by a rapid attenuation, after which the normalization of blood glucose levels was reached by Day 7. The effect on post-prandial blood glucose levels, while transient, was more pronounced at doses greater than 600 µg b.i.d. s.c.

QTcF interval – Study B2113 and Study B2125

A thorough clinical QT/QTc evaluation was conducted in 128 healthy volunteers to determine whether pasireotide s.c. at the maximum tolerated dose (MTD) has an effect on cardiac repolarization, as detected by QT/QTc prolongation (study B2113). In this study, a transient QTcF prolongation was observed with pasireotide, when given at supra-therapeutic doses of MTD 1950 µg b.i.d. Pasireotide showed a peak effect on QTcF at 2 hours post-dose. There was a +10.0 ms mean QTcF increase from baseline that equated to a 17.5 ms difference versus placebo. A similar effect was observed on QTcI, but no effect was observed on the QTcB interval. Pasireotide-treated subjects also showed a reduction of the heart rate at 0 to 4 hours post-dose with the maximum change versus baseline of 10.7 bpm. There were no outliers (> 60 ms change from baseline or new QTc > 500 ms) identified in this study.

There was a positive correlation between ΔΔQTcF and pasireotide plasma concentration in the thorough QT study. The maximum plasma concentrations observed in that study may well be observed in the clinical situation in patients following the highest recommended dose.

The results from the thorough clinical QT/QTc study B2125 confirm an effect of pasireotide on QTc interval.

The somatostatin receptor 5 has been shown to be expressed in human heart tissue. After review of the literature the Applicant concluded that no conclusions to support a specific role of SSTR5 in cardiac tissue can be drawn due to paucity of data. The Applicant, however, is recommended to explore whether the cardiac effect of pasireotide (bradycardia, QT prolongation) pertain to any explorable ancillary properties (I_f, somatostatin receptors) by mean of relevant models.

Genetic polymorphism

In several PK/PD and clinical studies, the Applicant has collected blood and urine samples to investigate the potential impact of genetic polymorphism of pasireotide's properties related to the drug target, the somatostatin receptors (sst1-5), genes related to the mechanism of action, such as GH and somatomedin C (IGF-1) and those in drug metabolism genes. The results of these investigations have been submitted by the applicant. No formal relationship can be identified between the responder or non responder status and the genotype. However the Applicant has committed to further explore this issue in the RMP by an adequate complementary programme.

Pharmacodynamics interactions

Considering the effects of pasireotide on the glucose metabolism, interactions with anti-diabetic medications may be foreseen. The Applicant has submitted the results from study B2124 which was designed to define the potential role of different class of anti-hyperglycaemic agents in the management of hyperglycaemia induced by pasireotide. The pharmacodynamic interaction between pasireotide and metformin, nateglinide, vildagliptin and liraglutide was investigated. The most prominent antihyperglycaemic effect was observed with liraglutide and vildagliptin with the least effect observed for metformin. Serum insulin AUC0–4h on Day 7 increased by approximately 71% and 34% after coadministration of pasireotide with vildagliptin and liraglutide, respectively, as compared to pasireotide alone. This effect was mostly achieved during the last 2 hours of the 4-hour postprandial period, whereas almost no reversal of insulin suppression was observed during the first 2 hours. The safety assessment of the combination therapies revealed no unforeseen adverse events and the combinations were moderately well tolerated. Notably increases in hepatic enzymes/bilirubin were more common in the pasireotide + liraglutide arm indicating that this may not be a favourable combination.

With reference to pharmacodynamic interactions, and further to the assessment of the QT studies, a statement on the risk of bradycardia potentiation when this drug is combined with a bradycardic agent has been added to section 4.5 of the SmPC.

2.4.4. Discussion on clinical pharmacology

The provided clinical pharmacokinetic package covers in general the main issues. However, some further studies are recommended concerning drug interactions. The Applicant investigated whether pasireotide would be a substrate for several transporter proteins but the only identified is P-gp. Since co-administration with ketoconazole (P-gp inhibitor) may be expected, the Applicant is recommended to perform an in vivo study with a strong P-gp (verapamil). Furthermore, the results from two in vitro studies concerning the inhibitory effect of pasireotide on P-gp point in different directions and it cannot be concluded that pasireotide is not a P-gp inhibitor. Therefore, the Applicant is recommended to perform an additional in vitro study.

The mechanism of action for pasireotide has been adequately described. The different binding profile of pasireotide compared to other somatostatin analogues together with the data showing that sst5 is expressed by ACTH producing pituitary adenomas, make an effect in Cushing's disease plausible.

The pharmacological effects of pasireotide have been adequately investigated. Pasireotide acts by binding on 4 of the 5 known human sst receptors. The main markers of the pharmacological activity of pasireotide are linked to this mechanism: decrease in level of urinary free cortisol in 24h, serum cortisol or plasma ACTH. Another parameter of pharmacological effect of pasireotide, Growth hormone (GH) activity, has been measured in healthy volunteers by GHRH stimulation test. A careful follow-up of pituitary hormones values before and under treatment should be performed. Adequate information on this issue is mentioned in the SmPC.

Pasireotide in the PD studies has demonstrated an impact on the blood glucose metabolism. In a study investigating the pharmacodynamic interactions between pasireotide and metformin, nateglinide, vildagliptin and liraglutide, respectively, the incretin enhancers were found to be most efficient in the treatment of pasireotide induced hyperglycaemia with the least effect observed with metformin. Hepatobiliary adverse events were, however, more commonly observed with the pasireotide + liraglutide combination.

Two thorough QT/QTc studies have shown a QT prolonging potential of pasireotide. This is reflected in the SmPC; wording has been introduced to highlight the need for monitoring in the clinical setting.

2.4.5. Conclusions on clinical pharmacology

The pharmacokinetic profile of pasireotide has been sufficiently characterised. No major objections are identified regarding the pharmacokinetics, but the Applicant is recommended to perform some further studies for a further characterisation of the clinical pharmacology of pasireotide.

The secondary pharmacodynamic effects observed with pasireotide are in line with what could be expected for a somatostatin analogue. Two thorough QT studies indicate that pasireotide induces QT-prolongation. Adequate warnings in this regard have been included in the SmPC. Warnings regarding effects on glucose metabolism, other hormones such as thyroid hormones and GH as well as cardiac effects are also included in the SmPC. In view of the effects of pasireotide on the glucose metabolism, interactions with anti-diabetic medications have been investigated. The incretin enhancers were found to be most efficient in the treatment of pasireotide induced hyperglycaemia with the least effect observed with metformin. Hepatobiliary adverse events were, however, more commonly observed with the pasireotide + liraglutide combination. The data is not deemed sufficient to make any specific treatment recommendations regarding pasireotide induced hyperglycaemia beyond current guidelines on the treatment of diabetes. The SmPC includes adequate information on hyperglycaemia including recommendations concerning follow-up in pasireotide-treated patients with reference to glucose metabolism, i.e. before and under treatment as well as after discontinuation of treatment.

The Applicant is recommended to perform a clinical interaction study assessing the effect of a strong P-gp inhibitor, preferably verapamil, on pasireotide pharmacokinetics.

2.5. Clinical efficacy

The efficacy claims of this submission are supported by one pivotal study B2305.

The development program supporting this indication (Cushing's disease) consisted of one additional study: a proof-of-concept study B2208 and its extension B2208E1. A summary of these studies is provided in Table 2.

Table 2.

Study ID	No. of study centres / locations	Design	Study Posology	Study Objective	Subjs by arm entered /	Duration	Gender M/F Mean Age	Diagnosis Incl. criteria	Primary Endpoint

					compl.				
B2305	53 (Argentina, Belgium, Brazil, Canada, China, Denmark, Finland, France, Germany, Greece, Israel, Italy, Mexico, Poland, Portugal, Spain, Turkey, USA)	Randomized, double-blind, Phase III trial	Pasireotide 600 µg b.i.d. and 900 µg b.i.d Note: dose reduction to 300 µg b.i.d. and dose escalation to 1200 µg b.i.d. allowed as long as efficacy maintained	Efficacy, safety and PK	N=162	12 months core phase (up to 39 months for data cut-off)	36/126 40 (18-71)	Patients with Cushing's disease	Primary efficacy endpoint: proportion of responders in each dose group (mUFC ≤ ULN, no dose increase) at 6 months after the start of first study medication.
B2208	10 (France, Germany, Italy, United Kingdom, USA)	Proof of concept, open label, non-randomized Phase II study	Pasireotide 600 µg b.i.d	Efficacy, safety and PK	N=39	15 days	10/29 42 (22-73)	Patients with de novo or recurrent Cushing's disease	Primary efficacy endpoint: normalization of UFC levels after 15 days of treatment
B2208E1	8 (France, Germany, Italy, United Kingdom, USA)	Open label extension to study B2208	Pasireotide 300-900 µg b.i.d.; dose titration allowed	Efficacy, PK and safety	N=19	up to 58 months (from 2 months to 4.8 years with three patients ongoing at the time of the data cut-off)	2/17 43 (22-73)	Patients with de novo or recurrent Cushing's disease	Efficacy and safety in patients who completed B2208 and who benefited from pasireotide treatment.

2.5.1. Dose response study(ies)

No formal dose-response study was performed. Instead the pasireotide dose selected in study B2208 was based upon data from healthy volunteer studies, i.e. study B2101, study B2102, study B2106 and study B2107. PK simulation analysis predicted that the peak and trough levels at steady state were approximately 15 ng/mL and 2 ng/mL, respectively, at 600 µg b.i.d. s.c.. A concentration of 1 ng/mL was thought to represent the minimally required level of pharmacologically active octreotide concentration for GH suppression in plasma. The same concentration was assumed to be necessary for suppression of ACTH by pasireotide. However, the higher plasma protein binding of pasireotide (88%) relative to octreotide (65%), which translates into approximately a 3-fold difference in free drug level, suggested that a target plasma level for pasireotide greater than 1-2 ng/mL would be more appropriate. Data from study B2106 in healthy volunteers showed that the tolerability/safety at 600 µg b.i.d. s.c. dose was acceptable; therefore, this dose was used in study B2208. Additionally, the b.i.d. regimen was chosen based on the effective half-life of pasireotide.

Thus dose selection was largely based on assumptions and safety data. Since it is not feasible to study the pharmacological effects of pasireotide on ACTH and cortisol in healthy volunteers and proper dose finding studies in Cushing's disease are not feasible due to the rarity of the disease, this strategy is acceptable.

Results from study B2208 corroborated the theoretical considerations and suggested that a dose of 600 µg b.i.d. or higher was necessary to observe efficacy.

2.5.2. Main study(ies)

Pivotal Study B2305

Study B2305 was a 12-month Phase III, double- blind, randomized, multi-center study of 2 dose levels in Cushing's disease patients performed to assess efficacy, safety, QoL, PK, and PK/PD relationship. Primary efficacy analysis was performed at Month 6. The extension period of the study is currently ongoing.

The study included 165 male and female patients, aged 18 years and above, with a confirmed diagnosis of ACTH-dependent Cushing's disease. Patients with de novo Cushing's disease could be included only if they were not considered candidates for pituitary surgery (e.g. poor surgical candidates, surgically unapproachable tumours, patients who refused to have surgical treatment). For patients on medical treatment for Cushing's disease a washout period had to have been completed before baseline efficacy assessments were performed. Patients with a known history of impaired fasting glucose or diabetes mellitus (DM) could be included. Patients were to be excluded if they had received pituitary irradiation within the last ten years. Patients with symptomatic cholelithiasis, uncontrolled diabetes, significant cardiac disease (including risk factors for torsade de pointes) or liver disease were also excluded.

The study design for study B2305 is outlined in Figure 1 below. Patients were randomized in a 1:1 ratio at baseline to receive pasireotide either 600 µg b.i.d. or 900 µg b.i.d. s.c. Randomisation and blinding procedures were adequate. The study drug was self-administered (subcutaneous injections) by the patients. No comparator was included in the study since there is no approved or universally accepted medical therapy for the treatment of Cushing's disease. Alternative unapproved therapies are inadequate for long-term treatment due to the high incidence of side effects. Furthermore, the availability of the medications used in the management of hypercortisolism is not consistent across countries. Placebo was not deemed ethical for the time required for a clinical trial, given the morbidity associated with extended state of hypercortisolism and other clinical symptoms associated with this disease.

At Month 3, patients continued at the randomised dose until Month 6 (double-blind treatment) if their Month 3 mUFC was a) ≤ 2 x ULN and b) below or equal to their baseline mUFC.

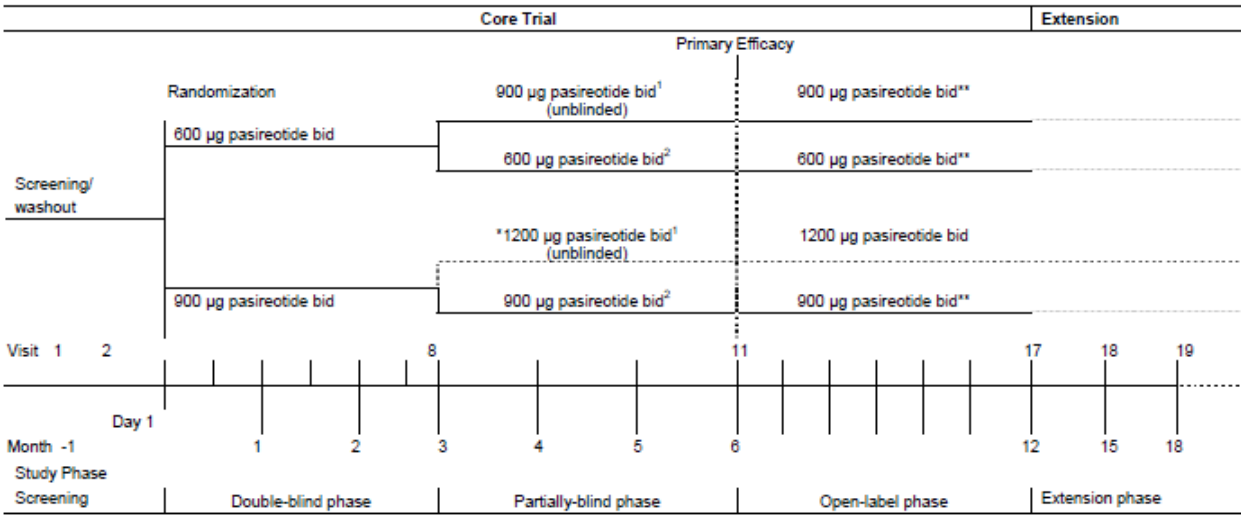
Patients not meeting these mUFC criteria at Month 3 were unblinded and were required to increase their dose by 300 µg b.i.d. with a maximum daily dose of 2400 µg; those whose dose was not increased had to be discontinued from the study. Patients who were unblinded and had dose-escalation at Month 3 were considered non-responders in the primary efficacy analysis, regardless of their UFC levels at Month 6. For patients who were unable to tolerate the protocol-specified dose level, dose reductions were permitted in order to keep the patient on study drug. During the double-blind phase, blinded lower doses were available for blinded dose-reductions.

After six months of treatment, patients entered an open-label treatment period where they remained on their current dose level provided a response was observed. If the patient did not respond, or the response was not maintained during the open-label treatment period, the dose could be increased by

300 µg b.i.d. to a maximum daily dose of 1200 µg b.i.d. Dose decrease by 300 µg b.i.d. was allowed any time for lack of tolerability. The duration of the core study was 12 months, after which patients could enter an open-ended extension.

Allowing dose-titration during the study provides information on the usefulness of up- or down-titration of pasireotide.

Figure 1 Study design



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

Primary objective and endpoint

The primary objective was to assess the efficacy of pasireotide in the treatment of Cushing's disease expressed as the proportion of responders to pasireotide 600 µg s.c. b.i.d. and 900 µg s.c. b.i.d. independently in patients with Cushing's disease as measured by mean UFC ≤ upper limit of normal (ULN) after 6 months of treatment. Thus, no formal comparison between the two doses was planned. The Applicant has justified this change in design as compared to the CHMP Scientific advice provided.

A responder was defined as a patient with Month 6 mUFC ≤ ULN and no dose increase (relative to the randomized dose) prior to Month 6 UFC. If Month 6 mUFC was missing then it was imputed by the last available mUFC (of at least 3 specimens) between (and including) Month 3 up to Month 6.

The proportion of responders in each dose group and overall was summarised using the point estimate and the 95% CIs. If the lower bound of the 95% CI for a dose group was greater than 15% then that dose group was considered to have a significant benefit in terms of UFC reduction. This is acceptable taking into account the seriousness of the disease and the fact that other medications used in Cushing's disease are not suitable for long-term treatment due to an unsatisfactory safety profile.

Based on the null hypothesis of p = 15% and alternative hypothesis of p = 30%, enrollment of 146 patients provided 87% power to demonstrate statistical significance. Based on these calculations a larger sample size than originally proposed was planned.

Prior to the database lock and unblinding, supportive analyses using the following clinical response subgroups were defined in the analysis plan:

Controlled responders: Month 6 mUFC ≤ ULN (regardless of dose increase).

Partially controlled responders: Month 6 mUFC > ULN but mUFC declined by at least 50% from baseline, regardless of dose increase. The choice of 50% was made based on an estimate of the variability of a single sample. This was estimated via the within-patient co-efficient of variation to be 52%. Thus, a 50% reduction from baseline was considered as a reasonable indication of intervention effect.

Uncontrolled: neither controlled nor partially controlled at Month 6**.**

The primary objective was somewhat changed in relation to the CHMP scientific advice in that only patients achieving a normalisation of UFC were considered responders, furthermore the endpoint was measured at six months instead of, as initially proposed, three months. Since these changes are conservative they are acceptable to the Committee.

Secondary objectives and endpoints

The secondary objectives included assessment of reduction of UFC to ≤ 1 x ULN at Month 3 and 12, time to first UFC response, the effect of pasireotide s.c. on plasma ACTH and serum cortisol levels, improvement in clinical signs and symptoms of Cushing's disease, the effect of pasireotide s.c. on tumour volume and Quality of Life. No imputations for missing values were made for the secondary endpoints.

Exploratory efficacy analyses included analysis of response by baseline mUFC category and clinical response status over time

Additional unplanned efficacy analyses included after the Month 12 database lock included predictability of non-response to treatment. Post-hoc analyses explored the relationship between mUFC and clinical signs and symptoms of Cushing's disease by plotting mean mUFC values and the following parameters over time: body mass index (BMI), weight, HDL, LDL, total cholesterol, triglycerides, systolic and diastolic blood pressure, and HRQL scores. Summary statistics for these parameters were also provided.

Results

Participant flow

Overall, 165 patients were randomized into this study, of which 3 did not receive study drug. These 3 patients were screening failures, but were randomised by mistake. Of the 162 patients who were correctly randomized into the study, all were treated. One of the 162 randomized patients had a forced randomization: at the time of randomization, blinded drug packages were only available for one of the two randomized doses at the site. Thus, the IVRS automatically randomized the patient to that dose for which blinded drug was available.

Details of participant flow are given in Table 3. The proportions of the patients who completed Month 12 were similar in both dose groups, but more patients from the 900 µg b.i.d. group entered in the extension phase.

Treatment discontinuations at any time up to data cut-off (including discontinuation prior to as well as after the end of the core study) were similar in both dose groups. The most common reasons for discontinuation were unsatisfactory therapeutic effect, AEs and subject withdrew consent.

Table 3 Patient disposition up to data cut-off by randomized dose group (All randomized set)

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.

Discontinuations due to AEs were most common at the beginning of treatment, whereas lack of effect became more common later on. Patients who discontinued were considered to be non-responders, therefore the discontinuations are not considered to hamper the evaluation of the primary endpoint; however, the outcome of secondary endpoints will be less robust.

Baseline data

Baseline demographic data are presented below (Table 4). Considering the small size of the study, the two study groups were well balanced with regards to the baseline demographic characteristics. The majority of patients were female which is to be expected in this patient group. Very few patients above the age of 65 were included.

Table 4 Baseline demographics by randomized dose group (Full analysis set)

	Pasireotide 600 µg b.i.d. N=82	Pasireotide 900 µg b.i.d. N=80	Overall N = 162
Age (years)			
n	82	80	162
Mean	40.5	39.9	40.2
SD	12.97	10.77	11.90
Median	39.0	41.0	39.0
Min	18	19	18
Max	67	71	71
Age – n (%)			
< 65 years	78 (95.1)	79 (98.8)	157 (96.9)
≥ 65 years	4 (4.9)	1 (1.3)	5 (3.1)
Sex – n (%)			
Male	20 (24.4)	16 (20.0)	36 (22.2)
Female	62 (75.6)	64 (80.0)	126 (77.8)
Race – n (%)			
Caucasian	65 (79.3)	62 (77.5)	127 (78.4)
Black	2 (2.4)	1 (1.3)	3 (1.9)
Asian	10 (12.2)	10 (12.5)	20 (12.3)
Native American	2 (2.4)	2 (2.5)	4 (2.5)
Other	3 (3.7)	4 (5.0)	7 (4.3)
Missing	0 (0.0)	1 (1.3)	1 (0.6)
Ethnicity – n (%)			
Hispanic/Latino	29 (35.4)	22 (27.5)	51 (31.5)
Chinese	10 (12.2)	10 (12.5)	20 (12.3)
Mixed ethnicity	0 (0.0)	1 (1.3)	1 (0.6)
Other	43 (52.4)	46 (57.5)	89 (54.9)
Missing	0 (0.0)	1 (1.3)	1 (0.6)

- Disease history

With the exception of baseline mUFC and previous medication for Cushing's disease, the two treatment groups were well balanced in terms of disease characteristics (Table 5). The median time to the first dose of pasireotide since diagnosis of Cushing's disease was 34 months and ranged from 0.1 to 372 months. The disease status was persistent/recurrent for the majority of patients in both treatment groups (83.3%). Few patients (≤ 5%) in either treatment group had received previous pituitary irradiation. Most patients (79.0%) had previous surgical intervention for the treatment of Cushing's disease. The use of previous medications for Cushing's disease was slightly lower in the 600 µg b.i.d. group than the 900 µg b.i.d. group (43.9 vs. 52.5%).

Table 5 Disease history and baseline characteristics by randomized dose group (Full analysis set – Study B2305)

		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

Time to first pasireotide dose since diagnosis = (First pasireotide dose date – date of diagnosis of Cushing's disease +1)*12/365.25.

The baseline mUFC was considerably higher in the 600 µg b.i.d. group when compared to the 900 µg b.i.d. group and a higher proportion of the patients in the 900 µg b.i.d. group had been previously medically treated. The wash-out periods applied in the study have been adequately justified and it is unlikely that the previous medication had any influence on the outcome.

Primary efficacy results

The primary efficacy results are summarised in Table 6. Only the 900 µg b.i.d. dose met the primary efficacy endpoint as the lower limit of the 95% confidence interval for the pasireotide 900 µg b.i.d. group was greater than the pre-specified null hypothesis of 15%. It has, however, to be taken into account that baseline UFC values were lower in this dose group.

Table 6 Proportion of mUFC responders at Month 6 by randomized dose group - primary efficacy analysis (Full analysis set)

	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 results for the per-protocol set were consistent with those observed in the FAS, thus supporting the results of the primary efficacy analysis.

From a theoretical viewpoint it is not possible to claim that the higher dose met the pre-specified threshold of 15% since the two confidence intervals for the two doses in study B2305 are presented without adjusting (as suggested in the study protocol) for multiplicity issues. The responder rate (26.3 %) in the 900 µg b.i.d. group is, however, considered clinically relevant by the CHMP.

When analysing the primary endpoint, imputations for missing values were made. The Applicant has provided information on the number of values imputed and also provide additional analyses without imputation. The results of the more conservative analysis excluding the imputated data do not change the overall conclusion on a relevant effect of pasireotide. No formal comparison was made between the two doses.

Clinical response subgroup rates at Month 6 – supportive analysis

The results of clinical response subgroup analyses are summarized in Table 7. The proportion of controlled UFC responders was 15.9% and 28.8% in the 600 µg b.i.d. and 900 µg b.i.d. groups, respectively. In this analysis, patients who had had their dose increased at Month 3 were included as opposed to the primary analysis where only patients maintained on the randomized dose were included.

The number of partial responders was higher in the 600 µg b.i.d. group, which indicates that the difference in baseline UFC levels may have affected the outcome.

The proportion of patients who were controlled or partially controlled was 34% in the 600 µg b.i.d. group and 41% in the 900 µg b.i.d group. Thus, a difference is maintained between the two dose levels when also the partial responders are included. These data also indicate that a substantial number of patients may also benefit form the lower dose.

The rate of patients that remained uncontrolled was only slightly higher in the 600 µg b.i.d. group.

Table 7 Proportion of controlled and partially controlled UFC responders at Month 6 by randomized dose group (Full analysis set)

	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)

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

Dose changes among controlled and partially controlled responders

The dose could be increased (by 300 µg b.i.d.) at the Month 3 visit if the patient's mUFC > 2 x ULN or if mUFC was higher than at baseline, and after 6 months if the patient's mUFC > ULN.

Dose titration data indicate that very few patients did benefit from a dose increase above 900 µg b.i.d.. Furthermore, in some of the responders a dose of 300 µg b.i.d. was sufficient to maintain control.

Changes in clinical response subgroup status

Change from Month 1, 2 or 3 to Month 6

Due to the high drop-out rate (which mainly was due to AEs or lack of effect) and dose adjustments during the study period these data are somewhat difficult to interpret.

Overall, most of the patients (> 80%) who were uncontrolled at either Month 1, 2 or 3 were also uncontrolled at Month 6. About 10% shifted from uncontrolled to controlled status at Month 6, and a slightly smaller proportion shifted from uncontrolled to partially controlled status.

The data indicate that non-responders can be identified after 2-3 months of treatment.

Table 8 Shifts in clinical response status from Month 1, 2 or 3 to Month 6 (Full Analysis Set – Study B2305)

		Type of clinical response at Month 6		
		Controlled	Partially controlled	Uncontrolled
		n = 36	n = 25	n = 101
Type of clinical response at:		n (%)	n (%)	n (%)
Month 1	Controlled (n=49)	23 (46.9)	5 (10.2)	21 (42.9)
	Partially controlled (n=27)	4 (14.8)	14 (51.9)	9 (33.3)
	Uncontrolled (n = 86)	9 (10.5)	6 (7.0)	71 (82.6)
Month 2	Controlled (n=34)	22 (64.7)	2 (5.9)	10 (29.4)
	Partially Controlled (n=31)	3 (9.7)	16 (51.6)	12 (38.7)
	Uncontrolled (n=97)	11 (11.3)	7 (7.2)	79 (81.4)
Month 3	Controlled (n=35)	25 (71.4)	4 (11.4)	6 (17.1)
	Partially Controlled (n=30)	3 (10.0)	16 (53.3)	11 (36.7)
	Uncontrolled (n=97)	8 (8.2)	5 (5.2)	84 (86.6)

Percentages presented by rows.
Patients for whom UFC values were not available at a specific time-point were considered to be uncontrolled.

Change from Month 6 to Month 12

The results are generally similar as for the shifts from Months 1, 2 and 3 described above. The proportions of controlled, partially controlled and uncontrolled patients were similar at Month 6 and at Month 12. Most (90.1%) of the patients who were uncontrolled at Month 6 remained uncontrolled at Month 12, whereas more than half of the patients who were controlled at Month 6 remained controlled at Month 12.

Predictability of non-response

The predictive capability of early non-response to identify eventual non-responders at Months 6 and 12 was explored by analyzing shifts in responder status for patients who were uncontrolled at both Month 1 and 2, and at Months 1, 2 and 3 vs response status at Month 6 and Month 12. Of the 72 patients who were uncontrolled at both Month 1 and 2, 66 (91.7%) were uncontrolled at Month 6. Of the 63 patients who were uncontrolled at Months 1, 2 and 3, 60 (95.2%) were uncontrolled at 6 months. The results were similar for analyses of shifts to Month 12.

These data indicate that non-responders can be identified at a relatively early stage of the therapy which is important in the clinical management of the patient. Information that discontinuation of therapy should be considered in patients who have not responded after two months is included in the SmPC.

Change from baseline in mUFC

The mUFC (±SD) at baseline was higher in the 600 µg b.i.d. group than in the 900 µg b.i.d. group (1155.9 ± 2629.78 vs. 781.9± 926.38 nmol/24h). The mean absolute changes from baseline to Month 6 in mUFC were -463.4 and -364.9 nmol/24h, respectively, for the 600 and 900 µg b.i.d. groups. However, due to the higher baseline level the mean percent change from baseline in the mUFC was lower in the 600 µg b.i.d. group (-27.5% in the 600 µg b.i.d. group and -48.4% in the 900 µg b.i.d. group). The median percent change in mUFC was -47.9% in both dose groups. The difference between mean and median percent change from baseline in the 600 µg b.i.d. group was due to a few extreme values influencing the mean (percent changes of up to +542.2% were observed) at Month 6.

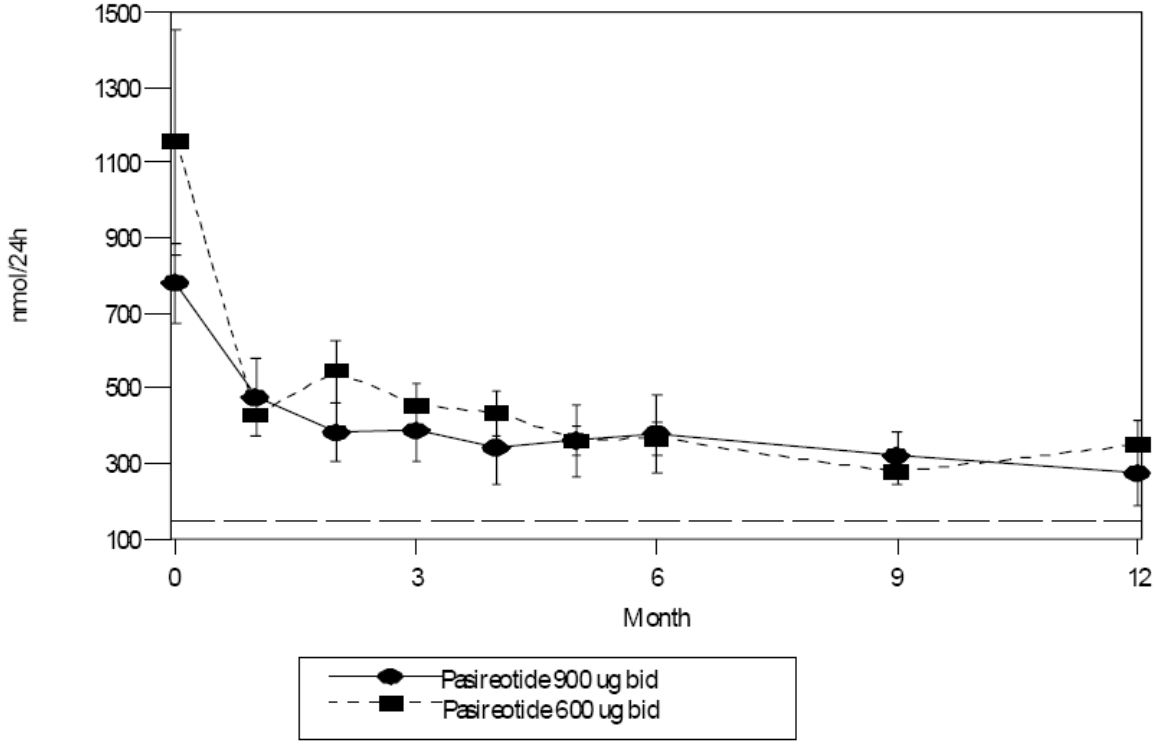
Overall the median percent change from baseline was similar at all time points after Month 1 between the two groups, ranging between -47 and -68%.

At Month 12, the median percent change in mUFC was available for 37 patients in the 600 µg b.i.d. group and for 35 patients in the 900 µg b.i.d. group. The median changes from baseline were -67.6 and -62.4% in the respective groups.

Figure 2 shows the mUFC values (±SE) over time. In both groups there was a robust decrease in the mUFC at Month 1, which appeared to be sustained to Month 12. It is important to note that during the course of the study the number of patients decreased from 162 at the start of treatment to 74 at Month 12. There is no apparent difference in the decrease in mUFC over time between the two doses among patients that completed the study.

Thus the 600 µg b.i.d. dose apparently has an effect although; maybe due to the higher baseline values the primary endpoint was not met for this dose.

Figure 2 Mean (+/-SE) Urinary Free Cortisol (nmol/24h) at time points up to Month 12 by randomized dose group (Full analysis set – Study B2305)

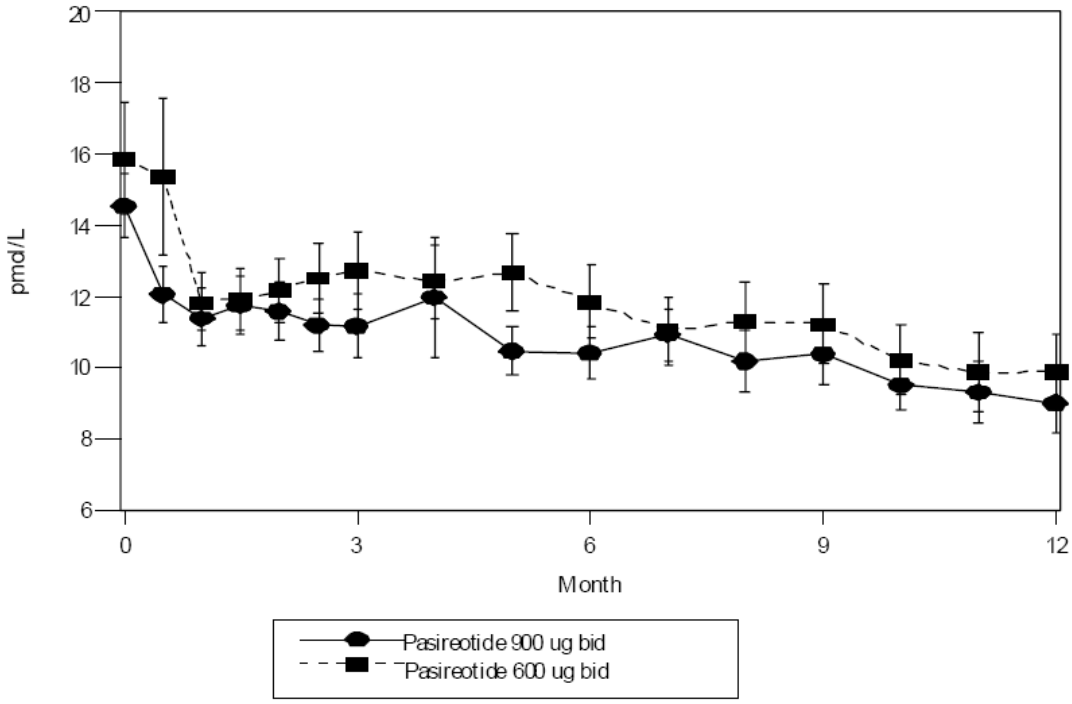


At least three 24h UFC assays contributed to patient mean results at Months 0 (baseline), 3, 6 and 12.
At least two 24h UFC assays contributed to patient mean results at other time points.
+/-Standard errors are displayed.
----- is the ULN for the UFC assay (145 nmol/L)

Plasma ACTH

Mean plasma ACTH levels were below baseline by Month 0.5 in the 900 µg b.i.d. group and by Month 1 in the 600 µg b.i.d. group and remained below baseline levels at all subsequent time-points for both dose groups (Figure 3). The median plasma ACTH levels showed a more robust decrease over time in both treatment arms, which was evident after the first 15 days of treatment.

Figure 3 Mean (+/-SE) plasma ACTH (pmol/L) levels at time points up to Month 12 by randomized dose group (Full analysis set – Study B2305)



+/- Standard Errors are displayed.

However, no imputations for missing values were made for the secondary endpoints and due to the large drop-out rate these data represent a much selected patient group. In order to get a better understanding of the pasireotide effect on ACTH, additional analyses both using imputations (LOCF) for missing values and also an analysis only including the patients that completed the study were provided by the Applicant. These analyses support the original analysis. Baseline values for completers were somewhat lower than observed in the overall population, however, relevant reductions were observed over time for both dose groups with a more prominent effect in the 900 µg b.i.d. group.

Clinical signs and symptoms of Cushing's disease

Continuous parameters

At Month 6, improvements in both treatment groups were observed for several studied signs and symptoms of Cushing's disease (i.e. sitting systolic blood pressure, sitting diastolic blood pressure, BMI, waist circumference, total cholesterol, Beck depression inventory score, Ferriman-Galway hirsutism score and body composition-region fat %). There was a tendency for these to be more pronounced in the controlled subgroup. The changes in triglyceride levels were small. Summary statistics for clinical signs up to month 12 show that the improvements were maintained at Month 12.

Categorical parameters

In both dose groups there were patients with favorable shifts in all the studied signs of Cushing's disease. Facial rubor improved at Month 6 in 36.7% and 59.6% of patients treated with 600 and 900

µg b.i.d., respectively. The greatest proportion of patients with improvement in facial rubor were those in the controlled response subgroups, 57.1% in the 600 µg b.i.d. group and 72.2% in the 900 µg b.i.d. group. More than a third of patients in either treatment group also demonstrated improvement in supraclavicular fat pad and dorsal fat pad, and the rates were more often higher in patients with complete or partial response than in patients who were uncontrolled.

The improvement observed in the clinical signs and symptoms of Cushing's disease supports that pasireotide has clinically relevant effects in patients with Cushing's disease, although data has to be interpreted with caution due to the small number of patients in each subgroup.

Tumour volume

Post-baseline changes in tumour volume were evaluated by MRI. At the Month 12 assessment, both dose groups demonstrated decreases in mean tumor volume (mean decreases were 9.1% and 43.8% for the 600 and 900 µg b.i.d. groups, respectively), showing a trend towards tumour reduction. It is important to note that in this study several patients did not have measurable tumour volume by MRI, and the analysis of mean percent change from baseline in tumour volume is based on a small sample size (14 and 18 patients for the respective dose groups). Thus the data on the effect of pasireotide on tumour volume has to be interpreted with caution. It is, however, reassuring that a trend towards tumour reduction was observed.

Quality of life

A novel single-domain 12 item Cushing's disease health related quality of life (HRQL) questionnaire was implemented in this trial and the significance of the observed changes are difficult to assess. Furthermore, the drop-out rate was very high. Patients that continued in the study are likely to be highly motivated and satisfied with the treatment. Thus the data has to be interpreted with caution and only lend limited support to this application.

Baseline mean and median HRQL scores were similar for the two dose groups. Both dose groups had increases in the scores at Month 6, showing an improvement in the patient's perception of their quality of life. The mean percent changes from baseline in HRQL scores were 31.3% and 73.0%, respectively, for the 600 and 900 µg b.i.d. groups. The median percent changes from baseline were 13.2% and 30.0%, respectively, for the 600 and 900 µg b.i.d. groups. Month 12 HRQL scores showed that patients continued to experience improvement in their quality of life.

Analysis of primary efficacy endpoint by baseline UFC categories

Overall, the highest response rates were seen in patients with baseline mUFC ≤ 5 x ULN (25 of 92 patients, 27.2%). The response rate for patients with baseline mUFC > 5 x ULN was 5 of 61 patients, 8.2%.

Although response is to some extent associated with the baseline value, the basline UFC does apparently not entirely predict response since individual patients with high levels did respond and indeed on the lower dose.

Correlation between mUFC and improvement in clinical signs and symptoms

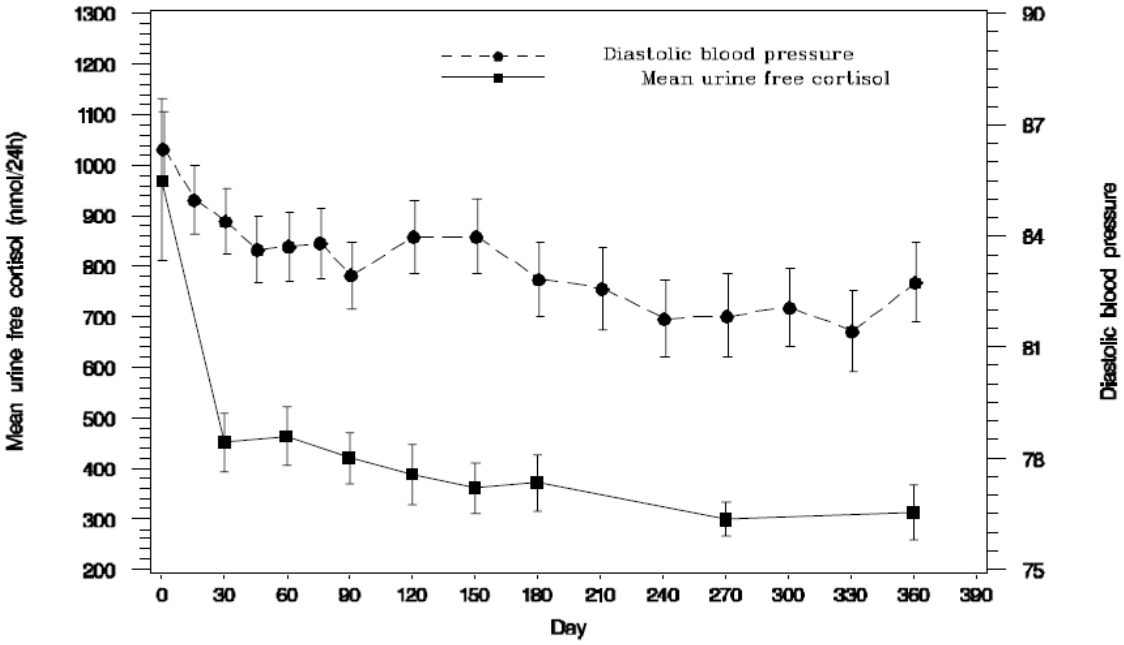
The relationship between mUFC and clinical signs and symptoms of Cushing's disease was explored as post-hoc analyses by plotting mean mUFC values and the following parameters over time: systolic blood pressure, diastolic blood pressure, HDL, LDL, total cholesterol, triglycerides, BMI, weight, and HRQL scores (exemplified in Figure 4 below; diastolic blood pressure).

A marked decrease in mean mUFC values was observed within the first month of treatment, after which mean mUFC levels remained stable up to 12 months for those patients who continued in the study. By visual inspection of the graphs, improvements in blood pressure (both systolic and diastolic)

and HRQL were observed within the first 3 months of treatment, concurrent with the decrease in mean mUFC. These improvements were sustained up to 12 months. A trend for improvement in lipids was also noted, as was a trend of decreasing weight and BMI over 12 months.

Although limited due to the high drop-out rates, these data support that pasireotide has a clinically relevant effect in patients with Cushing's disease.

Figure 4 Mean (+/-SE) UFC (nmol/24h) and diastolic blood pressure (mmHg) at time points up to Month 12 (Full analysis set – Study B2305)



Ancillary analyses

Methods of subgroup analyses

The primary efficacy endpoint at Month 6 was analyzed by demographic and disease factors for study B2305 using percentages and 95% CI.

Demographic factors

Primary efficacy

The proportion of responders at Month 6 in the primary efficacy analysis (those with a decrease in mUFC to < ULN and with no dose increase) was analysed by demographic baseline factors. The numbers of patients in the age > 65 years, male, and race subgroups other than Caucasian were relatively small, (especially for the age > 65 years and race subgroups other than Caucasian) and do not allow meaningful conclusions to be drawn.

It is, however, noteworthy that the response rate was very low among males with 15 % responders in the lower dose group and no male responders in the higher dose group. Further analysis of these patients could not reveal any explanation for this finding.

Disease factors

The proportion of responders at Month 6 in the primary efficacy analysis is presented by disease history in Table 9. Benefit was evident irrespective of patients' Cushing's disease status or previous medication. The proportions of patients with de novo disease or previous pituitary irradiation were small, and therefore any comparisons must be interpreted with caution.

The responder rate among patients on previous medication was slightly higher than in the overall analysis for both doses; however, the wash-out periods applied in the study were reassuring.

Table 9 Proportion of UFC responders at Month 6 by randomized dose group and disease history subgroup factors (Full analysis set – Study B2305)

	Pasireotide 600 µg b.i.d. N=82	Pasireotide 900 µg b.i.d. N=80	Overall N=162
Cushings Disease status=De Novo			
Number of patients in analysis	15	12	27
Response: n (%)	2 (13.3)	2 (16.7)	4 (14.8)
95% Confidence Interval	(0.0, 30.5)	(0.0, 37.8)	(1.4, 28.2)
Cushings Disease status=Persistent Recurrent			
Number of patients in analysis	67	68	135
Response: n (%)	10 (14.9)	19 (27.9)	29 (21.5)
95% Confidence Interval	(6.4, 23.5)	(17.3, 38.6)	(14.6, 28.4)
Any Previous Pituitary Irradiation=No			
Number of patients in analysis	79	76	155
Response: n (%)	10 (12.7)	18 (23.7)	28 (18.1)
95% Confidence Interval	(5.3, 20.0)	(14.1, 33.2)	(12.0, 24.1)
Any Previous Medication=Yes			
Number of patients in analysis	36	42	78
Response: n (%)	7 (19.4)	12 (28.6)	19 (24.4)
95% Confidence Interval	(6.5, 32.4)	(14.9, 42.2)	(14.8, 33.9)
Any Previous Medication=No			
Number of patients in analysis	46	38	84
Response: n (%)	5 (10.9)	9 (23.7)	14 (16.7)
95% Confidence Interval	(1.9, 19.9)	(10.2, 37.2)	(8.7, 24.6)

Summary of main study

The following table summarises the efficacy results from the main study supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 10: Summary of Efficacy for trial B2305

Title: Phase III study of pasireotide (SOM230) in Cushing's disease patients		
Study identifier	CSOM230B2305	
Design	Phase III, prospective, randomized, double-blind study to assess the safety and efficacy of different dose levels of pasireotide s.c. in patients with de novo, persistent or recurrent Cushing's disease	
	Duration of main phase: Duration of run-in phase: Duration of extension phase:	12 months not applicable Open-ended extension phase for patients who benefited from the treatment during the main phase.

Hypothesis	Superiority: Lower Bound of 95% CI for primary endpoint within each arm > 15%		
Treatment groups	Pasireotide 0.6mg		Pasireotide 0.6mg twice a day. Dose increase to Pasireotide 0.9mg from month 3 based on UFC response and tolerability to initial dose. Further dose increase to 1.2mg twice a day allowed after month 6. Dose decrease of 0.3mg decrements allowed at any point during treatment based on tolerability. (n= 82)
	Pasireotide 0.9mg		Pasireotide 0.9mg twice a day. Dose increase to Pasireotide 1.2mg from month 3 based on UFC response and tolerability to initial dose. Dose decrease of 0.3mg decrements allowed at any point during treatment based on tolerability. (n= 80)
Endpoints and definitions	Primary endpoint	Normalization of 24-hour UFC at Month 6	Proportion of patients in each arm who achieved normalisation of mean 24-hour UFC levels (UFC ≤ULN) after 6 months of treatment and who did not have a dose increase (relative to randomised dose) during this period.
	Supportive Endpoint	Controlled and Partially Controlled Responder Rates at Month 6	Patients were considered controlled if the Month 6 mUFC ≤ ULN regardless of dose-titration. Patients were considered partially controlled if the mUFC > ULN but decreased by at least 50% from baseline.
	Secondary Endpoint	Change in mUFC	Change in mUFC from baseline to Month 6 and Month 12
	Secondary Endpoint	Controlled Responder Rate at Month 12	Proportion of patients with mUFC ≤ ULN at Month 12
	Secondary Endpoint	Change in serum Cortisol and ACTH	Change from baseline to Month 6 and 12 in Serum cortisol and plasma ACTH
	Secondary Endpoint	Change in Clinical signs and symptoms of Cushing's disease	Change from baseline to Month 6 and 12 in sitting systolic and diastolic blood pressure, body mass index (BMI), weight and total cholesterol
	Secondary Endpoint	Change in HRQL score	Change from baseline to Month 6 and 12 in HRQL score

Database lock	18.May.10			
Results and analysis				
Analysis description	**Primary analysis**			
Analysis population and time point description	Full Analysis Set			
Descriptive statistics and estimate variability	Pasireotide			
Descriptive statistics and estimate variability	Treatment group	Pasireotide 0.6mg	Pasireotide 0.9mg	Overall
	Number of subjects	82	80	162
	Response rate n (%)	12 (14.6)	21 (26.3)	33 (20.4)
	95% CI	7.0 to 22.3	16.6 to 35.9	14.2 to 26.6
Analysis description	**Supportive Analysis**			
Analysis population and time point description	Full Analysis Set			
Descriptive statistics and estimate variability	Treatment group (n)	Pasireotide 0.6mg (82)	Pasireotide 0.9mg (80)	
	Controlled - n(%)	13 (15.9)	23 (28.8)	
	95% CI	7.9 to 23.8	18.8 to 38.7	
	Partially controlled – n(%)	15 (18.3)	10 (12.5)	
	Uncontrolled - n(%)	54 (65.9)	47 (58.8)	
Analysis description	**Secondary Analysis**			
Analysis population and time point description	Full Analysis Set			
Descriptive statistics and estimate variability	Treatment group	Pasireotide 0.6mg	Pasireotide 0.9mg	
	N	82	80	
	% change in mUFC from baseline at			
	Month 6 Mean (n) 95% CI Median	 -27.5 (52) (-55.9, 0.9) -47.9	 -48.4 (51) (-56.6, -40.2) -47.9	
	Month 12 Mean (n) 95% CI Median	 -41.3 (37) (-66.0, -16.6) -67.6	 -54.5 (35) (-65.2, -43.7) -62.4	

	Controlled Responder Rate at Month 12		
	n/N (%) 95% CI	11/82 (13.4) (6.0, 20.8)82	20/80 (25.0) (15.5, 34.5)80
	Change in serum Cortisol from baseline at		
	Month 6 Mean (n) SD	 -70.2 (59) 189.61	 -99.6 (57) 267.69
	Month 12 Mean (n) SD	 -108.6 (39) 230.3982	 -131.7 (38) 200.5780
	Change in ACTH from baseline at		
	Month 6 Mean (n) SD	 -2.6 (58) 6.52	 -3.0 (56) 5.27
	Month 12 Mean (n) SD	 -3.9 (39) 10.34	 -4.1 (39) 5.09
	Change in Sitting SBP from baseline at		
	Month 6 Mean (n) SD	 -6.8 (59) 19.35	 -11.4 (57) 15.92
	Month 12 Mean (n) SD	 -2.8 (39) 18.40	 -9.4 (39) 14.61
	Change in Sitting DBP from baseline at		
	Month 6 Mean (n) SD	 -4.2 (59) 13.54	 -5.0 (57) 11.56
	Month 12 Mean (n) SD	 -2.0 (39) 11.65	 -5.4 (39) 10.86
	Change in BMI from baseline at		
	Month 6 Mean (n) SD	 -1.2 (59) 1.64	 -2.1 (57) 1.72
	Month 12 Mean (n) SD	 -2.1 (40) 2.19	 -2.8 (39) 2.21
	Change in Total Cholesterol from baseline at		

	Month 6 Mean (n) SD	 -0.4 (59) 1.24	 -0.4 (55) 0.98
	Month 12 Mean (n) SD	 -0.5 (40) 1.29	 -0.6 (39) 1.18
	Change in HRQL Score from baseline at		
	Month 6 Mean (n) SD	 6.2 (56) 16.02	 12.9 (55) 14.80
	Month 12 Mean (n) SD	 9.4 (36) 17.38	 12.8 (38) 20.44

Supportive study(ies)

Study B2208

Study B2208 was a multicenter, open-label, single-arm, proof-of-concept study to assess the safety and efficacy of pasireotide 600 µg b.i.d. s.c. for 15 days in patients with Cushing's disease. Patients were accrued into two cohorts following Simon's two-stage design. A cohort of 10 patients was enrolled at the first stage. If there were at least 2 responders among these patients, then a further cohort of 16 patients was to be enrolled into the second stage. A patient was considered a responder if the mean of UFC levels collected from the 24-hour urine samples from Days 14 and 15 (i.e. completed on Days 15 and 16, respectively) were within normal limits. The dose could be reduced by 150 µg per injection in case of drug-related toxicity.

Since this was a short-term study, both de novo Cushing's disease patients who were candidates for pituitary surgery and patients with recurrent Cushing's disease post-pituitary resection who had never received pituitary irradiation were eligible for enrolment.

Diagnosis of ACTH-dependent Cushing's disease must have been verified within two months of study entry by: a) two consecutive urinary free cortisol (UFC) measurements ≥ 2 x ULN (276 nmol/24h); b) morning plasma ACTH within or above normal range; and c) either MRI confirmation of a pituitary macroadenoma (≥ 1 cm) or an inferior petrosal sinus gradient greater than three after CRH treatment for microadenoma (< 1 cm).

Key inclusion criteria included: ≥ 18 years of age, diagnosis of Cushing's disease, and a Karnofsky Performance Status ≥ 60. Key exclusion criteria included hypercortisolism due to ectopic ACTH secretion, adrenal tumours, nodular bilateral adrenal hyperplasia, or genetic causes; active gallbladder disease, poorly-controlled diabetes mellitus, cardiac disease, and patients who had received long-acting somatostatin anagoges within 8 weeks prior to study initiation. Inclusion and exclusion criteria were comparable to those of the pivotal study.

Objectives

The primary objective of the study was to assess the efficacy of pasireotide in patients with Cushing's disease as measured by normalization of 24-hour urinary free cortisol (UFC) after 15 days of treatment. The secondary objectives for efficacy were to assess the effect of pasireotide on the clinical manifestations of excess cortisol (such as blood pressure and blood sugar), to assess the effect of

pasireotide on plasma ACTH and serum cortisol, and to monitor the trough plasma concentrations of pasireotide at steady state.

Results

Thirty-nine patients were enrolled in this study to ensure at least 26 evaluable patients. Of the 39 patients who enrolled, 38 completed the study. Ten patients were excluded from the primary efficacy population due to either having baseline UFC within normal range, or missing UFC at baseline or end-of-study. Thus, 29 patients were included in the primary efficacy population.

The study was considered to have met its primary efficacy endpoint if at least 5 of the first 26 evaluable patients responded. All 5 patients who were responders were in this group. Based on this analysis the response rate was 5/26 (19.2%), and the study met the criteria for success.

Overall, there was a tendency for mean serum cortisol and plasma ACTH levels to decrease. Responders achieved a greater mean reduction in both plasma ACTH and serum cortisol than reducers or non-responders.

Based on sub-group analysis, it appeared that at the same dose level UFC responders had higher pasireotide PK exposure than UFC reducers and non-reducers. These data seemed to suggest a relationship between PK exposure of pasireotide and PD response of UFC.

Therefore, 600 µg b.i.d. and higher doses were recommended for Phase III trial B2305.

Extension study B2208E1

Study B2208E1 was a Phase II extension to the multicenter, open-label study B2208 to assess the safety and efficacy of pasireotide 600 µg b.i.d. s.c. in patients with Cushing's disease who had already received 15 days of pasireotide treatment in the core study and who had either responded or experienced significant clinical benefit, defined as improvement in UFC levels or significant improvement of symptoms of hypercortisolism such as hypertension. Patients who achieved a normalization of UFC levels in the core study could continue on the 600 µg b.i.d. dose. Those who did not achieve normalization, or for those whose UFC levels rose during the extension, the dose could be increased to 900 µg b.i.d. If this was not tolerated a 600 µg t.i.d. schedule could be adopted. As in the core, the dose could be reduced by 150 µg per injection in case of drug-related intolerability.

The primary efficacy variable was the proportion of responders to treatment based on the normalization of UFC levels after 6 months of treatment in the extension phase.

Other efficacy assessments included serum cortisol, and plasma ACTH.

Results

Of the 38 patients who completed the core B2208, 19 patients entered the extension study B2208E1. The majority of patients were female with a mean age of 43 years. Patients remained on treatment from 2 months to 4.8 years with a mean duration of 16 months. Three patients were still on treatment at the time of data cut-off.

Efficacy was evaluated for 18 patients (one patient whose baseline mUFC was within normal range was excluded from the efficacy population). At Month 6, 4 patients (22%, 95% CI: 6.4 to 47.6) were responders and 6 patients (33.3%) were reducers. Eight patients (44.4%) were non-reducers, either because the Month 6 mUFC values were greater than the baseline (2 patients), or the patient discontinued prior to the Month 6 visit (6 patients).

Response status at B2208E1 entry vs response status at 6 months:

- Of the 3 responders in the core study that entered the extension, 1 was still a responder at 6 months and 1 patient became a reducer. The 3rd patient discontinued the study prior to Month 6 and was therefore counted as a non-reducer at 6 months.
- Of the 11 reducers in the core study that entered the extension, 5 maintained their reducer status at 6 months. Two of the reducers became responders at 6 months, and 4 became non-reducers.
- Of the 4 non-reducers in the core study that entered the extension, 1 became a responder at 6 months and 3 remained non-reducers.

Other efficacy results

For all pasireotide doses combined, despite some variability in the mUFC values, a consistent mean reduction in mUFC relative to baseline values was maintained throughout the extension study period. Mean reductions in mUFC from baseline were seen at most visits for the responders and reducer groups. For the non-reducer group, mean reductions were observed at Day 14/Day 15 of the core study and at extension Month 3. Furthermore, there was a consistent trend towards reduction in serum cortisol relative to baseline which was maintained throughout the extension study period.

A sustained reduction in mean plasma ACTH was observed across all patients throughout the extension study as well as for each UFC response subgroup including non-responders at the majority of visits. Generally, the responders showed a greater reduction from baseline in ACTH at every visit compared to the reducers. For the UFC non-reducers, only one patient had a plasma ACTH at Month 6 which showed a reduction at Month 6 relative to core baseline.

There was a decrease in mean systolic and diastolic blood pressure and weight over time relative to core baseline levels.

The extension study provides only very limited data on long-term treatment with pasireotide since very few patients have continued beyond 6 months. The data in the extension study are generally in line with the data from the pivotal study and indicate a maintained effect of pasireotide over time. The clinical data for the 3 patients of study B2208 still on treatment at the cut-off of the study have been provided. All these three patients experienced major decrease and even mUFC/24h normalisation over the 4 years treatment duration. Even if limited in terms of number of patients, these data demonstrate that pasireotide can be used for long term treatment with maintained efficacy in some patients.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The application is based on one pivotal study (B2305). No formal dose-response studies were performed, instead the dose was chosen based on PK data from the phase I studies in healthy volunteers and theoretical assumptions regarding necessary plasma concentrations needed to suppress ACTH levels. These data only lend weak support to the chosen doses. However, due to the rarity of the disease in combination with difficulties in evaluating the primary pharmacology in healthy volunteers, this strategy is acceptable and in line with the recommendations in the CHMP scientific advice.

Standard statistical methods cannot be easily applied and no EU recommendations are available for the development of medicinal products for Cushing's disease. The design of the pivotal study is generally in line with the recommendations given at the CHMP scientific advice. A major difference compared to the study design previously discussed with the CHMP scientific advice working party was the fact that the two doses to be investigated were not compared with each other but each dose was tested against the

hypothesis that at least 15 % responders (the lower bound of the 95 % CI) should be achieved. The absence of statistical comparison between both treatments arms has been sufficiently justified by the Applicant. A responder rate of at least 15 % is considered acceptable.

Furthermore, this cut-off was not modified after the change of the primary endpoint (amendment 6). The modification of the primary endpoint has no major impact on the lower bound of minimal efficacy. Indeed, the conclusions are the same and the lower limit of the 95% CI of the response rate for the higher dose group is greater than 15%.

In the primary analysis imputations for missing values was made by LOCF, whereas no imputations were made for the secondary endpoints. When evaluating the primary endpoint no adjustment for multiplicity issues was made.

Some changes to the originally proposed study protocol were made. The number of patients to be included was increased and the study duration was extended to 12 months, which is welcomed. As dose-titration was allowed during the study after three months of treatment, some information on the usefulness of up- or down-titration of pasireotide is provided.

Inclusion and exclusion criteria were adequate. Some deviations compared to the recommendations given in the CHMP scientific advice were noted. Firstly, the mUFC level was lowered to 1.5 times ULN as compared to 2 times ULN due to difficulties in recruiting patients. Secondly, patients who had undergone pituitary irradiation at least ten years before inclusion could be included. Both these deviations were deemed acceptable by the CHMP.

Since surgery is the primary treatment choice for Cushing's disease patients and given that surgery has a relatively high success rate, patients who were candidates for surgery were not considered eligible for this study, which is acceptable. Patients who were on medical treatment for Cushing's disease were eligible after a wash-out period. The wash-out periods applied for the listed medications have been adequately justified.

The decision not to include an active comparator or a placebo-arm has been adequately justified by the Applicant. The primary objective was somewhat changed in relation to the CHMP scientific advice in that only patients achieving a normalisation of UFC were considered responders, furthermore the endpoint was measured at six months instead of, as initially proposed, three months. Since these changes are conservative they are acceptable. A conservative approach was further taken in that patients who discontinued were regarded as non-responders.

Efficacy data and additional analyses

The drop-out rate in the pivotal study was very high with 34 % of patients having discontinued already prior to or at six months. Since patients who discontinued were considered to be treatments failures, the discontinuations are not considered to hamper the evaluation of the primary endpoint; however, the outcome of secondary endpoints will be less robust. Discontinuations were evenly distributed between the two study groups, both with reference to AEs and lack of effect; however, more patients from the 900 µg b.i.d. group entered the extension phase. Overall, 17 % of patients discontinued due to adverse events and 25 % due to unsatisfactory therapeutic effect. In total, 52% of patients had withdrawn from the study at month 12. However, in the group of patients who were partial or complete responders, the drop-out rate was considerably lower (31.6 % at month 12) compared to the uncontrolled group (69.3 % at month 12).

The proportion and reasons for discontinuations during this study and particularly during the first months (unsatisfactory therapeutic effect and adverse events) should be taken into account for the

efficacy and safety profile of pasireotide. Moreover, the main reasons for unsatisfactory therapeutic effect are linked to biological lack of efficacy.

Considering the small size of the study, the two study groups were well balanced with regards to baseline demographic characteristics. The majority of patients were female, which is to be expected in this patient group. Very few patients above the age of 65 were included. The numbers of protocol deviations were few and evenly distributed between the two study groups, thus a large proportion of the patients were included in the PP-set.

No formal comparison was to be made between the two doses; the data provided therefore does not allow for any conclusions regarding dose-response or whether any of the investigated doses are superior to the other. Only the 900 µg b.i.d. dose met the primary efficacy endpoint, i.e. normalisation of the mUFC in 26.3 % (95 % CI:16.6, 35.9). It should be noted that from a theoretical viewpoint it is not possible to claim that the higher dose met the pre-specified threshold of 15% since the two confidence intervals for the two doses in study B2305 are presented without adjusting (as suggested in the study protocol) for multiplicity issues. The observed response rate is, however, considered clinically relevant in this patient group where long-term treatment options are scarce. However, for both dosages, the observed responder rates were below the expected rate (30%), as initially defined by the Applicant.

The baseline mUFC was considerably higher in the 600 µg b.i.d. group when compared to the 900 µg b.i.d. group and a higher proportion of patients in the 900 µg b.i.d. group had been previously medically treated. These observed differences may have affected the outcome. The wash-out periods applied in the study were, however, chosen with a sufficient margin to preclude a lingering effect of the previous medication.

When analysing the primary endpoint, imputations for missing values were made. In order to evaluate the robustness of the data, the Applicant has provided information on the number of values imputed and has also provided additional analyses without imputation. The results of the more conservative analysis excluding the imputated data do not change the overall conclusion on a relevant effect of pasireotide.

The supportive primary outcome analysis of partial responders showed that the number of partial responders was higher in the 600 µg b.i.d. group, which may again indicate that the difference in baseline UFC levels may have affected the outcome but also that the 600 µg b.i.d. dose has an effect on lowering UFC. The rate of patients that remained uncontrolled was only slightly higher in the 600 µg b.i.d. group. The exploratory analysis of response by baseline mUFC further showed that the response is to some extent associated with the baseline value. The baseline UFC appears, however, not entirely predictive of response since individual patients with high mUFC values did respond and indeed on the lower dose.

Dose titration data indicate that very few patients had benefit from a dose increase above 900 µg b.i.d., whereas an increase from 600 µg b.i.d. to 900 µg b.i.d. did result in an improvement as shown by the Applicant. Furthermore, in some of the responders a dose of 300 µg b.i.d. was sufficient. The efficacy data therefore lend support to the recommendation to start with an initial dose of 600 µg b.i.d. with an option for uptitration to 900 µg b.i.d.

The data on patient shifts between different responder groups is somewhat difficult to interpret due to the high drop-out rate (which mainly was due to AEs or lack of effect) and dose adjustments during the study period. The absence of response to pasireotide was observed rapidly in the majority of non-responders. In fact, of the 72 patients who were uncontrolled at both Month 1 and 2, 91.7% were uncontrolled at Month 6 and of the 63 patients who were uncontrolled at Months 1, 2 and 3, 95.2% were still uncontrolled at 6 months. This indicates that non-responders can be identified at a relatively

early stage in therapy, which is important in the clinical management of the patient. Information that discontinuation of therapy should be considered in patients who have not responded after two months is included in the SmPC.

The ACTH data show a continuous decrease of ACTH levels in both dose groups over time in support of the proposed pharmacodynamic effect of pasireotide. However, no imputations for missing values were made for the secondary endpoint and due to the large drop-out rate these data represent a much selected patient group. In order to get a better understanding of the pasireotide effect on ACTH, additional analyses both using imputations (LOCF) for missing values and also an analysis only including the patients that completed the study were provided by the Applicant. These analyses support the original analysis. Baseline values for completers were somewhat lower than observed in the overall population, however, relevant reductions were observed over time for both dose groups with a more prominent effect in the 900 µg b.i.d. group.

The improvement observed in the clinical signs and symptoms of Cushing's disease supports that pasireotide has clinically relevant effects in patients with Cushing's disease, although data has to be interpreted with caution especially as the drop-out rate was high.

Since the drop-out rate was high and patients that continued in the study are likely to be highly motivated and satisfied with the treatment, the quality of life data are of limited value. Furthermore a new HRQL questionnaire was used in this trial and the clinical significance of the differences observed is difficult to assess. Thus the data has to be interpreted with caution and only lend minor support to this application.

Due to the small sample of patients that had measurable tumour volume the data on the effect of pasireotide on tumour volume has to be interpreted with caution. It is, however, reassuring that a trend towards tumour reduction was observed.

Subgroup analyses based on demographic and disease history were performed. Due to the small numbers, these analyses have to be interpreted with caution. It is, however, noteworthy that the response rate was very low among males with no male responder in the higher dose group. Further analysis of data, including PK data could not identify any explanation for this finding which may be due to chance.

The small supportive and short-term study B2208 showed results that were comparable to the results in the pivotal study and is therefore supportive. Limited efficacy data have been provided from the extension study (B2208E1) up to six months of treatment.

Very few patients (63 in study B2305 and 7 in study B2208E1) have been treated for at least 12 months and only four patients in study B2208E1 have been treated for up to 24 months. Efficacy data up to 12 months indicate that the effect of pasireotide is maintained in responders to treatment.

2.5.4. Conclusions on the clinical efficacy

In the overall population pasireotide globally reduced the 24-hour urinary free cortisol (UFC) and normalised UFC levels in some patients, i.e. 5/29 in Study B2208 after 15 days of treatment and 33/162 patients in Study B2305 after 6 months regardless the dosage received. In the pivotal study, only the high dosage (900 µg) met the primary endpoint, but the rate of responders was low (26.3%) and was even lower for the 600 µg b.i.d. dosage (response rate of 14.6%). Consequently, a large proportion of patients withdrew from the study due to lack of effect. In total, 52% of the patients had withdrawn from the study at month 12. However, in the group of patients who were partial or complete responders, the drop-out rate was considerably lower (31.6 % at month 12) compared to the uncontrolled group (69.3 % at month 12). Both partial and complete responders achieved clinically

relevant effects regarding signs and symptoms of Cushing's disease and thus also patients with partial response should be taken into consideration when evaluating the effect of pasireotide.

The most effective dose has not been clearly defined. An increase in dosage at month 3 in non-responders to the 900 µg b.i.d. dose did not seem to improve the response to treatment whereas some improvement was observed in patients uptitrated from 600 µg b.i.d. to 900 µg b.i.d.. In addition, the study groups were imbalanced with regards to the baseline mUFC (higher values in the group randomised to the 600 µg b.i.d. dose), which may have affected the outcome of the primary endpoint in favour of the higher dose. The results concerning mean reduction of mUFC may indicate that the lower dose may be as effective as the higher dose in some patients. These data support the SmPC recommendation to initiate treatment at the lower dose with an option for uptitration to the higher dose.

Responders to treatment were mainly observed in the two first months of treatment. The study data indicate that individual response may vary and although responder rates were highest in patients with mUFC < 5 x ULN, baseline UFC data are not entirely predictive of response. Available data does not allow characterisation of responders to treatment, however, since non-responders can be detected early and recommendations on treatment discontinuation are given in the SmPC, this issue does not preclude safe use of the product.

Since very limited data are available beyond one year, further post-approval follow-up should be undertaken.

The efficacy of pasireotide in the treatment of patients with Cushing's disease has been shown. Taking the low response rate into account, the wording of the indication has, however, been strengthened to clarify that pasireotide is a second line therapy to surgery. Thus, the following wording for SmPC section 4.1 was agreed:

"Signifor is indicated for the treatment of adult patients with Cushing's disease for whom surgery has failed or for whom surgery is no option."

The Applicant is recommended to perform additional biomarker investigations relevant to the mechanism of action of pasireotide (study G2304).

The Applicant is recommended to perform study B2219 to further examine the optimal management of hyperglycaemia. In this regard, the Applicant is recommended to provide a complete protocol to the CHMP before the start of the study and to provide the results when available.

Finally, the Applicant is recommended to perform a post-marketing surveillance study, to further document the safety and efficacy of pasireotide s.c. in patients with Cushing's disease (CSOM230B2410). The final protocol has been included in the RMP and the RMP pharmacovigilance plan has been updated accordingly.

2.6. Clinical safety

The overall safety evaluation is based on 201 Cushing's disease patients who participated in study B2208, its extension B2208E1, and in study B2305 and whom were exposed to pasireotide treatment at various doses. No pooling of data from these studies was performed due to differences in study design and patient populations.

In addition to these datasets, safety data from the acromegaly studies B2103, B2201, and B2201E1, as well as the carcinoid syndrome study B2202, were also evaluated. Seven phase I healthy volunteers studies also support the safety evaluation: 4 single dose, 2 multiple dose studies and one continuous s.c. infusion study (refer to exposure).

Two special safety clinical studies were conducted: one evaluated the QT/QT interval corrected (QTc) profile of pasireotide in healthy volunteers (B2113) and the other the safety of pasireotide in subjects with varying degrees of hepatic function (B2114).

Patient exposure

Exposure to pasireotide was sufficient to allow for an adequate safety assessment in patients representative of the intended target population (Table 11). There were 201 patients in the Cushing's disease safety population. The mean durations of exposure to study drug in study B2305 were comparable between the 2 pasireotide treatment groups (10.77 months) as were the proportions of patients that had at least 6 months' exposure (68% of all patients). The mean duration of exposure to pasireotide in study B2208 was 14.8 days. In study B2208E1, the total treatment duration was between 2 and 58 months, with a mean duration of 16 months; an exposure duration of at least 6 months was observed in 63% of patients.

In total 122 patients with Cushing's disease have been exposed for at least 6 months, 70 patients have been exposed for at least 12 months and 17 patients have been exposed for at least 24 months. Only 6 patients were treated with 600 µg b.i.d. and 7 patients with 900 µg b.i.d. pasireotide for at least 24 months in the pivotal study B2305. One patient with Cushing's disease was treated for 4.8 years in the extension study B2208E1. The long-term experience is thus limited.

Of all patient exposure data obtained from the acromegaly (72 patients), carcinoid syndrome (45 patients), and healthy volunteer populations (294 subjects), study exposure ranged from single s.c. doses to up to 61 months; the longest median duration of exposure in these studies was 22.7 months (range 4 to 61 months) in the acromegaly dataset. In the acromegaly study, 8 patients had more than 3 years of treatment. In the carcinoid syndrome study, the maximal exposure was more than 1 year (85 weeks) for 4 patients.

Table 11 Patient exposure

	Patients enrolled	Patients exposed	Patients exposed to the proposed dose range	Patients with long term* safety data
Double blind [B2305] Cushing's disease	162	150 (> 1m)	80	110 (>6m) 63 (>12m)
[B2103] Acromegaly	12		0	
Open studies [B2208] Cushing's disease	39	38	0	
[B2208E1] Cushing's disease	19	19	7	12 (>6m) 7 (>12m)
[B2202] Carcinoid syndrome	45	45	31	7 (>6m) 4 (>12m)
[B2201] Acromegaly	60		0	
[B2201E1] Acromegaly	30		11	8 (>36m)

* In general this refers to 6 months and 12 months continuous exposure data, or intermittent exposure.

Adverse events

Study B2305

Almost all patients (98.1%) had at least one AE, and the majority of patients (95.7%) had at least one AE considered to be related to study drug. A total of 28 patients (17.3%) discontinued due to an AE.

SAEs were reported for 40 patients (24.7%); of these there were 19 patients that had study drug-related SAEs.

The frequencies of AEs and SAEs were generally similar between both dose groups; however, SAEs related to study drug were slightly more frequent in the 900 µg b.i.d. group. This was mainly due to SAEs related to metabolism and nutrition disorders (predominantly diabetes/hyperglycemia), which occurred more frequently in the 900 µg b.i.d. group. The following table summarises AEs and SAEs observed in the pivotal study.

Table 12 Study B2305. Overview of Adverse Events (AEs) and Serious Adverse events (SAEs)

	Pasireotide	**Pasireotide**	**Overall**
	600 µg b.i.d. N=82 n (%)	**900 µg b.i.d. N=80 n (%)**	**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**
Serious adverse events (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 SOCs with the highest frequencies were gastrointestinal disorders (80.9%), metabolism and nutrition disorders (74.7%), and general disorders and administration site conditions (54.3%). In general, the frequencies of AEs by SOC were comparable between the two groups.

By preferred term, the most frequent AEs overall (> 15% of patients) were diarrhea, nausea, hyperglycemia, cholelithiasis, headache, abdominal pain, fatigue and diabetes mellitus. There were minor differences in frequencies of some preferred terms between the two groups. AEs that were slightly more frequent in the 900 µg b.i.d. group included nausea, hyperglycemia, fatigue, diabetes mellitus, anxiety and insomnia. AEs that were more frequent in the 600 µg b.i.d. group included asthenia, hypoglycemia, type 2 diabetes mellitus, ALT increased, abdominal pain upper, and myalgia.

One patient (B2305-0701/0002) became pregnant during the study and as a result was discontinued from the study. The patient had an abortion.

The most frequent Grade 3/4 AEs were hyperglycemia-related.

Note that multiple preferred terms related to the same abnormality may have been reported. For example, a patient may have had AEs reported for glucose metabolism abnormalities with preferred terms of hyperglycemia, diabetes mellitus or type 2 diabetes mellitus. That patient could therefore have been counted for each of these preferred terms.

AE suspected to be study drug related

A summary of most frequent AEs, which were assessed as related to study drug by the investigator is provided in Table 13. The frequencies of most study drug-related AEs were comparable in the 2 dose

groups. The five most frequently reported drug-related AEs were diarrhea, nausea, hyperglycemia, cholelithiasis and abdominal pain.

Table 13 Frequent (at least 5% overall) study drug-related AEs by preferred term up to data cut-off in (Safety analysis set – Study B2305)

Preferred Term	Pasireotide 600 µg b.i.d. N=82 n (%)	Pasireotide 900 µg b.i.d. N=80 n (%)	Overall N=162 n (%)
Diarrhoea	46(56.1)	43(53.8)	89(54.9)
Nausea	33 (40.2)	43 (53.8)	76 (46.9)
Hyperglycaemia	31 (37.8)	32 (40.0)	63 (38.9)
Cholelithiasis	25(30.5)	23(28.8)	48(29.6)
Abdominal pain	14(17.1)	19(23.8)	33(20.4)
Diabetes mellitus	13 (15.9)	16 (20.0)	29 (17.9)
Fatigue	7(8.5)	12(15.0)	19(11.7)
Glycosylated hemoglobin increased	10(12.2)	7(8.8)	17(10.5)
Type 2 diabetes mellitus	10 (12.2)	5 (6.3)	15 (9.3)
Gamma-glutamyltransferase increased	8(9.8)	7(8.8)	15(9.3)
Alanine aminotransferase increased	9(11.0)	5(6.3)	14(8.6)
Decreased appetite	6 (7.3)	7 (8.8)	13 (8.0)
Headache	5 (6.1)	7 (8.8)	12 (7.4)
Lipase increased	7 (8.5)	5 (6.3)	12 (7.4)
Vomiting	2 (2.4)	8 (10.0)	10 (6.2)
Abdominal pain upper	6 (7.3)	3 (3.8)	9 (5.6)
Adrenal insufficiency	4 (4.9)	5 (6.3)	9 (5.6)
Blood glucose increased	6 (7.3)	3 (3.8)	9 (5.6)
Alopecia	4 (4.9)	5 (6.3)	9 (5.6)

Primary system organ classes are presented in descending order of frequency for the overall group.
A subject with multiple occurrences of an AE under 1 treatment is counted only once in the AE category for that treatment.
N =number of patients in the safety analysis set.

Other notable AEs, which were assessed as drug-related and reported with a frequency of less than 5% and therefore not included in the table were (by preferred terms) QT-prolongation (overall 3.7%); sinus bradycardia (overall 4.3); anemia (overall 0.6%); prothrombin time prolonged (overall 1.2%) and blood amylase increased (overall 2.5%). These AEs were selected either because they could be considered as a class effect for somatostatin analogues (QT-prolongation and sinus bradycardia) or due to their connection to identified and potential risks as identified in the RMP (anemia [identified risk: hematological abnormalities]; prothrombin time prolonged potential [risk: coagulation abnormalities] and blood amylase increased [potential risk: pancreatitis].

AEs in other populations including healthy volunteers

The most frequently reported AEs in acromegaly patients were gastrointestinal disorders (50%) such as nausea, diarrhoea as well as nervous system disorders (30%) and infections and infestations (26.7%). Globally, blood glucose abnormality was reported in fewer patients with acromegaly (11 patients: 18.3%) than in patients with Cushing's disease (40% of hyperglycaemia). Hyperglycaemic-related preferred terms (blood glucose increased, glycosylated haemoglobin increased, diabetes mellitus) were reported in 8.3%, 6.3% and 5% of patients, in 3 treatment groups respectively. In the extension phase of the study, this number increased and even 14 (46.7%) patients reported such hyperglycaemic-related AEs. However, the total number of patients that were included and assessed during this extension phase was rather limited.

The most frequently reported AEs in patients with carcinoid syndrome were also gastrointestinal disorders (75.6%) such as abdominal pain, nausea and diarrhoea. Weight decreased was the most common adverse event in this dataset (19 patients: 42.2%). Hyperglycaemia and diabetes mellitus were reported in 15.6% and 8.9% of patients, respectively. More than 60% of General disorders and

administration site conditions were reported reflecting probably the poor local tolerance. Cardiac disorders were reported in 3 patients (6.7%).

In the phase I studies, gastrointestinal AEs were reported at all doses, for both single doses and multiple doses of pasireotide. Diarrhoea and nausea were the most frequently reported AEs with even reports of severe diarrhoea and abdominal distension. Injection site reactions are also considerable as well as AE of headache.

With regard to hyperglycaemia, both fasting and post-prandial glucose levels were increased after all pasireotide doses. Levels returned to baseline/control values by approximately 10 hours after pasireotide dose.

AEs of special interest – study B2305

AEs of special interest are potential safety concerns identified in the pre-clinical programme, and AEs expected with the somatostatin analogue class and/or in the treatment of Cushing's disease. Twenty groups of AEs of special interest were defined (Table 14). The analysis of AEs of special interest provides an incidence rate for a particular AE in a manner that is more inclusive. For example, all preferred terms related to glucose metabolism abnormalities were captured by this analysis to provide a single incidence rate, as opposed to the individual incidence rates for each preferred term (e.g. hyperglycemia, diabetes mellitus, type 2 diabetes mellitus). This analysis was only performed for study B2305.

Table 14 Adverse events of special interest, regardless of study drug relationship, by category of AE of special interest and randomized dose group, up to data cut-off in pivotal Cushing's disease dataset (Study B2305, Safety analysis set)

	Pasireotide 600 µg b.i.d. N=82 n (%)	**Pasireotide 900 µg b.i.d. N=80 n (%)**	**Overall N=162 n (%)**
Patients with at least one AE of special interest	79 (96.3)	77 (96.3)	156 (96.3)
Category of AE of special interest			
Hyperglycaemia-related AEs	61 (74.4)	57 (71.3)	118 (72.8)
Diarrhoea related AEs	48 (58.5)	46 (57.5)	94 (58.0)
Nausea related AE's	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 AE's	17 (20.7)	9 (11.3)	26 (16.0)
Injection site reaction related AEs	11 (13.6)	13 (16.3)	24 (14.8)
Bradycardia related AEs	15 (18.3)	8 (10.0)	23 (14.2)
Pancreatitis related AE's	11 (13.4)	10 (12.5)	21 (13.0)
Hypocortisolism related AE's	7 (8.5)	6 (7.5)	13 (8.0)
QT-prolongation-related AE's	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 AE's	4 (4.9)	5 (6.3)	9 (5.6)
Hypothyroidism related AE's	4 (4.9)	3 (3.8)	7 (4.3)
Coagulation related AEs	1 (1.2)	2 (2.5)	3 (1.9)
Diabetes insipidus related AE	0 (0.0)	1 (1.3)	1 (0.6)

A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.

The majority of patients (96.3%) in study B2305 reported at least 1 AE of special interest regardless of study drug relationship. Hyperglycaemia-related, diarrhoea-related, nausea-related, and gallbladder and biliary-related AEs were the most commonly reported AEs of special interest.

Of note, the incidences of AEs related to injection site reactions were comparable between the 2 dose groups in study B2305 and were reported by 14.8% of all patients. AEs that were related to injection site reactions and that were considered related to study drug were reported by 13.6% of all patients.

More detailed data on the observed injection site reactions was presented by the Applicant, and the reactions reported are within what could be expected for a medication given subcutaneously. There were no findings correlating to the non-clinical findings of fibromas.

Hyperglycaemia-related AEs

Hyperglycaemia-related AEs (e.g. hyperglycaemia, diabetes mellitus, blood glucose increased) were observed in 72.8% of patients in study B2305 (Table 14, Table 15) and were mostly considered study drug-related.

Table 15 Hyperglycaemia-related AEs of special interest

	AEs regardless of relationship n (%)	**Grade 3 or 4 AEs regardless of relationship n (%)**	**Drug-related AEs n (%)**
All hyperglycaemia-related	**118 (72.8)**	**40 (24.7)**	**114 (70.4)**
Hyperglycemia	65 (40.1)	21 (12.9)	63 (38.9)
Diabetes mellitus	29 (17.9)	12 (7.4)	29 (17.9)
HbA1c increased	18 (11.1)	1 (0.6)	17 (10.5)
Type 2 diabetes mellitus	15 (9.3)	7 (4.3)	15 (9.3)
Hypoglycaemia*	15 (9.3)	3 (1.9)	6 (3.7)
Blood glucose increase	9 (5.6)	0	9 (5.6)
Blood insulin decreased*	5 (3.1)	0	5 (3.1)
Glucose tolerance impaired	4 (2.5)	0	4 (2.5)
Glycosuria	1 (0.6)	0	0

HbA1c: glycosylated haemoglobin
The "all hyperglycaemia-related" row shows the number of patients with at least 1 hyperglycaemia-related AE. A patient may have had more than 1 hyperglycaemia-related event during the study and more than 1 preferred term reported.
*12 of the 15 patients who had an AE of hypoglycemia and 4 of 5 patients who had an AE of blood insulin decrease also had at least 1 AE in the hyperglycaemia category such as diabetes mellitus and hyperglycaemia.

The proportions of patients who experienced these AEs were comparable between the 600 µg b.i.d. and 900 µg b.i.d. groups. Most of these patients (approximately two-thirds) had a maximum Grade 1 or 2 AE. Grade 3 AEs were reported in 38 patients and 2 patients had Grade 4 events. Of the 38 patients with a Grade 3 AE, 21 had a prior history of diabetes or a pre-diabetic condition. Both patients with a Grade 4 AE had impaired glucose tolerance at study baseline. In the majority of the patients with Grade 1 or 2 AEs the event resolved in response to appropriate medical treatment. In fact, initiation of anti-hyperglycaemic therapy resulted in improvement of FPG in 30 patients, and 19 patients also demonstrated improvement in HbA1c. Only 4 patients with Grade 1-2 AEs were discontinued from the study due to the hyperglycaemic event and only 5 patients with Grade 3 events were discontinued due to the event.

Of the 2 patients with Grade 4 hyperglycaemia-related AE (hyperglycaemia and diabetes mellitus), 1 was discontinued due to hyperglycaemia and 1 patient was discontinued from the study due to lack of efficacy. There were no patients with a hyperglycaemic emergency such as diabetic ketoacidosis or hyperglycaemic hyperosmolar state (hyperosmolar coma).

The incidence of hyperglycaemia in study B2208 was similar to that observed in study B2305 (study B2208: 35.9%; study B2305: 40.1%).

In summary, hyperglycaemia-related events were the most frequently reported AEs of special interest. There were no cases of hyperglycaemic emergencies, the majority of the cases were Grades 1 or 2, and there is evidence of improvement upon administration of anti-hyperglycaemic therapy.

The adverse effects of pasireotide on glucose metabolism are expected due to the pharmacodynamic action of pasireotide on insulin and incretin secretion. As glucose metabolism is also affected by the disease per se, a worsening of a diabetic or pre-diabetic state can be expected. It is therefore of importance that patients who experienced hyperglycaemia could be successfully treated by anti-hyperglycaemic therapy, which appears to have been the case. Corresponding warnings and recommendations have been included in the SmPC.

Gastrointestinal AEs

Gastrointestinal AEs (especially diarrhoea, nausea) are the most frequently reported events in patients treated with somatostatin analogues such as pasireotide.

In study B2305, the incidence of diarrhoea-related AEs (preferred term: diarrhea) in the 600 µg b.i.d. and 900 µg b.i.d. treatment groups was similar (58.5% and 57.5%, respectively), and the majority of these patients had events that were suspected to be related to study drug treatment. Of all patients reported with diarrhoea in the Cushing's disease dataset, there were 5 patients with Grade 3 diarrhoea in study B2305 and 1 patient in study B2208.

Nausea was a consistent finding in all safety datasets. The proportions of patients with nausea-related AEs (preferred terms: nausea, vomiting) were higher in the 900 µg b.i.d. group (57.5%) than in the 600 µg b.i.d. group (47.6%). Nausea-related AEs were mostly Grade 1-2 and considered study drug-related. The proportions of patients for whom nausea was reported as an AE were similar in the Cushing's disease studies: 51.9% in study B2305, 30.8% in study B2208 and 63.2% in study B2208E1.

There were 3 patients in study B2305 who discontinued due to diarrhoea-related AEs and two patients discontinued due to nausea. Nausea was more common in the higher dose group. It may therefore be discussed if the lower dose should be recommended as starting dose in order to minimise the risk of discontinuation due to adverse events.

Gall bladder and biliary-related AEs

Gallbladder and biliary-related AEs occurred in 34.6% of all patients and were reported at comparable frequencies in the 600 µg b.i.d. and 900 µg b.i.d. groups. Most of the AEs were suspected to be related to study drug and were Grade 1-2.

Cholelithiasis was the most frequent preferred term and was reported overall for 30.2% of patients in study B2305. Most AEs were asymptomatic, Grade 1 to 2, and were detected during the scheduled ultrasound examinations. One patient discontinued due to this AE. With respect to studies B2208 and B2208E1, 2 patients reported cholelithiasis in the extension study.

In the acromegaly, carcinoid syndrome, and healthy volunteer populations, the incidence of cholelithiasis was lower than that observed in the Cushing's disease dataset.

Cholelithiasis is a well known adverse event with somatostatin analogue treatment.

Cortisol withdrawal syndrome/hypocortisolism

Cortisol withdrawal syndrome (hypocortisolism) was noted at a low frequency in study B2305, with hypocortisolism-related AEs being reported in 13 patients (8%). All but 1 of the cases resolved with a reduction or temporal interruption in pasireotide dose (pasireotide was discontinued in 1 patient), while 3 patients received a short-term course of exogenous steroid treatment. In all patients, marked reductions in UFC level were observed; in patients with a decrease in pasireotide dose, maintenance of UFC normalization in these cases was observed.

Hypocortisolism is a recognized AE associated with any successful pituitary-directed therapy, including surgery. The rapid, complete, or near complete supression of the hypersecretion of ACTH by the adenoma results in decreased circulating levels of cortisol and may potentially lead to transient hypocortisolism/hypoadrenalism, as the normal corticotrophs have been chronically inhibited. Although this is an identified risk, the occurrence further strengthens the notion that a recommendation to introduce therapy with pasireotide at a lower dose than proposed by the Applicant may be preferable. Corresponding warnings and recommendations for monitoring have been added to the SmPC.

Pituitary hormonal deficiency

Except for the pituitary-thyroid axis, deficiencies in pituitary hormonal axes have not been particularly studied in the pasireotide development programme so far but are expected in this population due to previous pituitary surgeries and/or radiation therapy. Additionally, due to the mechanism of action of pasireotide (as for other somatostatin analogues) inhibition of other hormones (i.e. GH and insulin-like growth factor-1 [IGF-1]) has been observed in several studies performed during pasireotide development.

Of particular note, 7 patients had hypothyroidism-related AEs (preferred terms: hypothyroidism, thyroxine-free decreased) in study B2305; all of these patients had a thyroid-stimulating hormone (TSH) level close to the lower limit or at the lower end of normal at study entry. Hypothyroidism was not reported as an AE in study B2208 or its extension B2208E1.

Hypopituitarism is an identified risk with pasireotide treatment. In the studies investigating the pharmacodynamics of pasireotide in healthy volunteers, no effect was observed on thyroid hormone levels whereas suppression of GH could be seen. The SmPC has been amended to include adequate warnings, and long-term effects on GH will be followed as part of the RMP.

QT prolongation

AEs related to QT prolongation were observed in 8.0% of all patients in study B2305, and occurred at comparable frequencies in the 600 µg b.i.d. and 900 µg b.i.d. groups. One patient in study B2305 discontinued due to an AE of QT prolongation. No arrhythmias related to QT prolongation were reported.

The SmPC has been amended with adequate warnings.

Bradycardia-related AEs

In study B2305, bradycardia-related AEs were reported in 14.2% of patients. AEs of bradycardia were not associated with clinical findings and were not associated with adverse clinical outcomes. In study B2208, sinus bradycardia was reported in 1 patient with an SAE of myocardial infarction.

In the acromegaly dataset, sinus bradycardia was reported in 10 patients but was not reported as an AE in any of these cases.

Bradycardia has been described also for other somatostatin analogues and the SmPC has been amended to include adequate warnings in this regard.

Liver safety-related AEs

Liver safety-related AEs occurred in 16.0% of all patients in study B2305. Across all studies in the Cushing's disease dataset, the most commonly reported liver safety-related AE was an increase in γ-glutamyltransferase (GGT) levels.

In study B2305, increases in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were reported as AEs for 17 patients (10.5%) and 9 patients (5.6%), respectively. Liver function abnormalities (primarily GGT level increases) were responsible for the discontinuation of 6 patients. In

studies B2208 and B2208E1, ALT increases were reported for 3 patients (there were no patients with increases in AST), and no patient discontinued due to a liver function. Most of the AEs in both studies were Grade 1-2 and resolved with minimal action taken.

Although six patients discontinued due to increased liver function tests, the adverse events were generally mild. The SmPC has been amended to include adequate warnings.

Haematological abnormalities

In the Cushing's disease dataset, AEs related to low blood cell or coagulation were infrequent, and the majority of these AEs were Grade 1. In study B2305, AEs related to low blood cells (including anemia) were reported for 5.6% of patients, and coagulation-related AEs were reported for 1.9% of patients.

Serious adverse event/deaths/other significant events

The rate of SAEs was comparable between the two study groups with a tendency for more drug-related SAEs in the higher dose group. No deaths were reported within the study period.

Table 16 Deaths, SAEs, and other significant AEs by randomized dose group, up to data cut-off, up to data cut-off (Safety analysis set)

	Pasireotide 600 µg b.i.d. N=82 n (%)	**Pasireotide 900 µg b.i.d. N=80 n (%)**	**Overall N=162 n (%)**
Deaths	0 (0.0)	0 (0.0)	0 (0.0)
Serious adverse events (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)

Serious adverse events

Overall, 24.7% of all patients experienced at least 1 SAE. The frequencies of SAEs were comparable between the two treatment groups. SAEs leading to discontinuation did not cluster in any specific SOC but occurred in several SOCs with maximal 2 patients in each.

The most common SAE in both dose groups was pituitary-dependent Cushing's syndrome (3.7% of all patients); 3 patients in the 600 µg b.i.d. group and 3 patients in the 900 µg b.i.d. group (Table 17).

Minor differences were observed between the two groups in terms of SAE frequencies; in the 900 µg b.i.d. group diabetes mellitus, hyperglycaemia and adrenal insufficiency occurred slightly more often. Conversely, cholelithiasis was reported slightly more frequently in the 600 µg b.i.d. group.

Table 17 Frequent serious adverse events (> 2% in any group), regardless of study drug relationship, by preferred term and randomized dose group, up to data cut-off (Safety analysis set)

	Pasireotide 600 µg b.i.d. N=82 n (%)	**Pasireotide 900 µg b.i.d. N=80 n (%)**	**Overall N=162 n (%)**
Patients with any SAE(s)	19 (23.2)	21 (26.3)	40 (24.7)
Preferred term			
Pituitary-dependent Cushing's syndrome	3 (3.7)	3 (3.8)	6 (3.7)
Diabetes mellitus	1 (1.2)	3 (3.8)	4 (2.5)
Hyperglycaemia	1 (1.2)	3 (3.8)	4 (2.5)
Cholelithiasis	3 (3.7)	1 (1.3)	4 (2.5)
Pituitary tumour benign	1 (1.2)	2 (2.5)	3 (1.9)
Adrenal insufficiency	0 (0.0)	2 (2.5)	2 (1.2)

Due to the small numbers no firm conclusion can be drawn with regards to differences between the two doses. No unexpected SAEs were reported.

Cushing's disease reported as a SAE

There were 9 patients for whom a SAE of "Pituitary-dependent Cushing's syndrome", "Pituitary tumour benign" or "Secretory adenoma of pituitary" was reported. Eight of these patients were discontinued from the study and then had surgical interventions (pituitary surgery or bilateral adrenalectomy) for the treatment of Cushing's disease, for which they were hospitalized within 30 days of treatment discontinuation; these events were considered as SAEs due to the hospitalization. For 1 patient, the SAE "Pituitary tumour benign" was the underlying reason for an SAE of nerve paralysis and was thus reported as a SAE as well.

None of these SAEs were considered related to the study drug by the investigator.

The Cushing's disease SAEs reported indicate that some patients were included that eventually were reconsidered for pituitary surgery; furthermore these SAEs indicate that in some patients the effect of pasireotide was not satisfactory. However, these SAEs appear not to be related to the study drug.

SAEs suspected to be study drug-related

A total of 19 patients (11.7%) had study drug-related SAEs; 7 patients (8.5%) in the 600 µg b.i.d. group and 12 patients (15.0%) in the 900 µg b.i.d. group. No SAE was reported for more than 4 patients (2.5%) in total.

The most frequent study drug related SAEs were related to glucose-metabolism (9 patients) and cholelithiasis (4 patients). SAEs related to glucose metabolism occurred slightly more frequently in the 900 µg b.i.d. group, whereas cholelithiasis was slightly more frequent in the 600 µg b.i.d. group as described below.

Cholelithiasis was reported for 3 patients (3.7%) in the 600 µg b.i.d. group and 1 patient (1.3%) in the 900 µg b.i.d. group.

A total of 8 patients had SAEs leading to discontinuation; 3 patients (3.7%) in the 600 µg b.i.d. group and 5 patients (6.3%) in the 900 µg b.i.d. group. No SAE leading to discontinuation was reported for more than one patient and SAEs did not cluster in any specific SOC (maximal 2 patients reported SAEs in any given SOC). SAEs leading to discontinuation in the 600 µg b.i.d. group were lipase increased, diabetes mellitus, and pregnancy, and in the 900 µg b.i.d. group were adrenal insufficiency, pituitary-dependent Cushing's syndrome, ECG QT prolonged, hyperglycemia, pituitary tumour benign, cranial nerve paralysis, and tongue paralysis.

None of the SAEs that were considered to be study drug related were unexpected but were mostly related to the pharmacodynamic effect of pasireotide. It should be noted that one patient in the high

dose group discontinued due to adrenal insufficiency, which further support the recommendation of a lower starting dose.

Deaths

No deaths were reported in the clinical database. However, two cases of death were reported to the sponsor's safety department. One patient died during the screening period due to dementia, pituitary tumour and hypotension. The patient had not received any treatment with pasireotide. The other patient died approximately 2 months after the last dose of pasireotide due to post-surgical complications after bilateral adrenalectomy. SAE narratives have been provided for both cases. None of the reported deaths were related to the study drug.

In the remaining clinical development programme, one death was reported from the phase II study in carcinoid syndrome [Study B2202] due to tumour progression (neoplasm) and liver failure. The patient experienced progressive liver failure with hyperbilirubinemia and cholestasis. The cause of death was reported to be due to disease progression; a relationship to study drug was not suspected.

No other deaths were reported from any of the other studies included in this submission.

Laboratory findings

Glucose metabolism report

Summary of Results

Patients with Cushing's disease have a known predisposition for hyperglycaemia, which was observed in this study.

Following the initial increase in FPG (peaking at month 1) the FPG levels decreased in both groups. HbA1c increased within 2 months and remained stable at that level for the duration of the study.

At Month 12, the adjusted mean change (95% CI) from baseline in FPG was 27.98 mg/dL (14.57 to 41.39) in the 600 µg b.i.d. group and 25.09 mg/dL (11.73 to 38.45) in the 900 µg b.i.d. group. The adjusted mean change from baseline were similar between the two groups, except for the Day 15, Month 1 and Day 45 time points where the adjusted mean difference tended to be higher in the 900 µg b.i.d. group.

At Month 12, the adjusted mean change (95% CI) from baseline in HbA1c was 1.61% (1.31 to 1.91) in the 600 µg b.i.d. group and 1.55% (1.25 to 1.86) in the 900 µg b.i.d. group. The adjusted mean change from baseline was similar between the two groups.

Patients who achieved mUFC ≤ ULN in the 600 µg b.i.d. randomized dose group had lower increases in glycaemic measures (FPG and HbA1c) than any other clinical response subgroup.

In patients with Cushing's disease whose baseline HbA1c level <7% and were not receiving any antidiabetic medication at baseline treatment with pasireotide s.c. for a year results in moderate increases in FPG and HbA1c with no differences between dose groups. In contrast, there was a tendency for all other 'diabetic' patients at study entry (N=42) to experience more noticeable increases, particularly in HbA1c, following treatment with the 900 µg b.i.d. dose.

Following treatment with anti-diabetic medication, FPG levels showed a decrease, whilst HbA1c levels did not. The HbA1c increases should, however, be viewed with caution due to several limitations in the way the data were collected which preclude any firm conclusions.

Hyperglycaemia related AEs were frequently reported in both treatment groups. No clear dose dependency was observed.

Table 18 Summary of mean FPG (mg/dL) by randomized group and visit for patients whose baseline HbA1c was <7% and did not receive any anti-diabetic medication at baseline (Safety analysis set – Study B2305)

	Pasireotide 600 µg b.i.d. N=58		Pasireotide 900 µg b.i.d. N=62	
Visit	N	Mean (SD) mg/dL	n	Mean (SD) mg/dL
Baseline	56	91.8 (12.42)	61	92.0 (13.69)
Month 0.5	54	117.8 (38.7)	58	127.2 (43.55)
Month 1	54	121.6 (36.46)	55	134.2 (58.50)
Month 1.5	53	124.8 (49.88)	53	130.0 (47.34)
Month 2	49	124.3 (47.34)	52	130.1 (60.05)
Month 3	49	111.4 (24.64)	51	116.0 (40.03)
Month 4	48	112.7 (25.79)	47	114.3 (28.36)
Month 5	44	115.8 (27.91)	44	118.7 (32.65)
Month 6	40	117.4 (27.77)	43	113.4 (38.87)
Month 9	33	122.6 (33.61)	38	114.9 (30.74)
Month 12	27	114.4 (30.64)	31	103.3 (17.62)

Table 19 Summary of mean HbA1c (%) by randomized group and visit for patients whose baseline HbA1c was <7% and did not receive any anti-diabetic medication at baseline (Safety analysis set – Study B2305)

	Pasireotide 600 µg b.i.d.		Pasireotide 900 µg b.i.d.	
	N=58		N=62	
Visit	n	Mean (SD) %	n	Mean (SD) %
Baseline	58	5.50 (0.42)	62	5.47 (0.39)
Month 2	52	6.89 (1.39)	51	6.96 (1.12)
Month 4	48	6.93 (1.18)	47	6.83 (0.98)
Month 6	41	7.03 (1.19)	44	6.99 (0.93)
Month 8	36	7.15 (1.36)	36	6.92 (1.06)
Month 10	30	7.13 (1.17)	37	6.72 (0.89)
Month 12	27	7.05 (1.24)	30	6.64 (0.87)

Conclusions

It is estimated that glucose intolerance and frank diabetes affect 20-60% of patients with Cushing's disease. The following comments are assessed from the submitted documentation on glucose metabolism and hyperglycaemia-related events:

- Hyperglycaemia was reported in preclinical studies in rats;
- Hyperglycaemia-related events are related to inhibition of insulin secretory capacity and occur with increasing doses;
- Hyperglycaemia is more significant in patients with a history of hyperglycaemia and diabetes mellitus prior to pasireotide treatment;
- During phase 2 and phase 3 studies, hyperglycaemia was an AE frequently reported, notably grade 1 and 2 with relatively few grade 3 and 4; SAE and discontinuations due to AE related to hyperglycaemia were also reported.

- In a phase 3 study, the increase in FPG and HbA1c is to be noticed: adjusted mean changes in FPG: 27.98 mg/dl in 600 µg and 25.09 mg/dl in 900 µg b.i.d. group; HbA1c: 1.61% and 1.55%, respectively, in two groups of treatment. It can be agreed that the adjusted mean changes from baseline in FPG and HbA1c levels were similar between 2 groups of treatment, however, with regard to the mean values, neither mean FPG nor mean HbA1c returned to the levels before treatment in any group of patients (those whose baseline HbA1c was <7% and did not receive any anti-diabetic medication at baseline and those whose FPG was >100 mg/dL at baseline and whose HbA1c was >7%). The levels of FPG and HbA1c remained increased after the discontinuation of the study drug.
- The applicant has performed a study (B2124) to define potential role of different class of anti-hyperglycaemic agents in the management of hyperglycaemia. Although the study duration of only one week is clearly insufficient, this study gives some insight on the different responses to these anti-diabetic medications in the treatment of pasireotide induced hyperglycaemia. At least in HV (with normal insulin sensitivity) metformin showed a very modest effect, whereas the secretagogue nateglinide and the incretin enhancers vildagliptin and liraglutide showed more prominent effects with high reporting of gastrointestinal adverse events for liraglutide.
- Hyperglycaemic effect was less pronounced in patients with acromegaly and carcinoid syndrome than in Cushing's patients.

Overall, hyperglycaemia-related AEs were frequently reported during the development programme of pasireotide. These AEs were observed in 118 (72.8%) patients in the pivotal study and were more significant in patients with a history of hyperglycaemia and diabetes mellitus prior to pasireotide treatment. The percentage of patients taking anti-diabetic treatment significantly increased during the pivotal study. However, no collection of data on concomitant medications was performed. This is of concern notably for the assessment of information on anti-diabetic treatment of patients who reached the FBG threshold for treatment intervention.

In the pivotal study, the increase in FPG and HbA1c levels is notable without return to the levels before pasireotide treatment in any group of patients. Hyperglycaemia appears to stabilise over time and the observed improvement in other risk factors may in part out-weigh the risk connected with the increased HbA1c. The optimal therapy in pasireotide induced hyperglycaemia remains to be established, however, current guidelines for the management of diabetes are considered sufficient. The Applicant has proposed specific precautions for use that appear necessary in these patients. No situations where the use of pasireotide should be contraindicated have been identified. The SmPC has been amended to guide prescribers in the management of hyperglycaemic events, including recommendations on the follow-up required with regard to glucose metabolism.

Moreover, long-term risk of hyperglycaemia and risks for ketoacidosis or coma are not known as well as risk of use of pasireotide in a larger population; these issues will be followed as part of the RMP.

Clinical chemistry

In the Cushing's disease dataset, GGT, ALT, AST, and lipase increases were frequently noted as newly occurring laboratory abnormalities; most of these abnormalities were Grade 1 or 2. No newly occurring or worsened Grade 4 biochemistry abnormalities were observed in study B2305, but there were 1 patient in study B2208 and 2 patients in study B2208E1 with Grade 4 values. There were no patients with concurrent elevations ALT or AST > 3 x ULN and bilirubin ≥ 2 x ULN.

In the acromegaly dataset a Grade 4 increase was reported for 1 patient in study B2201 (triglycerides) and 3 patients in study B2201E1 (alpha-amylase, glucose, and lipase). In the carcinoid syndrome population, Grade 4 abnormalities were noted for calcium increase (1 patient), AST elevation (1 patient) and glucose elevation (2 patients). While laboratory abnormalities in these populations were typically Grade 1-2, they were sporadic in occurrence and did not require treatment for resolution. In

the healthy volunteer dataset, three subjects showed liver test abnormalities fulfilling the Hy's law criteria. All subjects were asymptomatic and the events resolved upon discontinuation of medication.

Elevations of liver enzymes have been observed throughout the clinical study programme. The observed changes appear manageable, however, monitoring of liver function is warranted. Warnings in this regard have been included in the SmPC as well as a contraindication in patients with severe hepatic impairment. Lipase increases are expected due to the pharmacodynamic action of pasireotide.

Fasting blood glucose and HbA1c

Elevations in glucose levels were the most frequently reported Grade 3 laboratory abnormality study B2305; the frequency of Grade 3-4 fasting blood glucose and HbA1c abnormalities was slightly higher in the 900 µg b.i.d. treatment group than that reported for patients receiving 600 µg b.i.d. pasireotide.

Diabetic patients tended to have larger increases in FPG and HbA1c relative to non-diabetic patients and tended to have larger increases in FPG and HbA1c on 900 µg b.i.d. relative to 600 µg b.i.d. Although the 600 and 900 µg b.i.d. 'diabetic' groups contain a relatively small number of patients, the tendencies for larger increases in glycaemic parameters with 900 µg b.i.d. appeared to be clinically meaningful. Within the limitations of the analysis, there is clear evidence for improvement in these measures as detailed in the shift tables and effect on FPG after intervention with anti-hyperglycaemic medications.

The increase in blood glucose is expected due to the pharmacodynamic action of pasireotide. This is of concern due to the fact that this patient group is prone to have a high prevalence of diabetes due to long-standing hypercortisolism. Warnings in this regard have been included in the SmPC.

Hematology

Abnormalities in hemoglobin were frequently seen in studies B2305, B2208, and B2208E1; these were mostly Grade 1. In both acromegaly and carcinoid patients, the most commonly occurring abnormalities were in hemoglobin and absolute lymphocytes. In study B2305, hemoglobin abnormalities were more frequent in the 900 µg b.i.d. group than in the 600 µg b.i.d. group. With the exception of 1 patient in study B2305 who had Grade 3 hemoglobin abnormality, no further Grade 3 or 4 hemoglobin abnormalities were reported in any of the Cushing's studies presented in this submission.

In study B2305, Grade 4 abnormalities were only reported for lymphocytes (1 patient) and neutrophils (2 patients); infrequent Grade 3 abnormalities in hemoglobin and were also noted. The most frequently reported abnormalities were partial thromboplastin time and international normalized ratio (INR), of which a Grade 1 abnormality was reported for 33.3% and 20.0% of all patients, respectively. In the 600 µg b.i.d. group there were 5 patients with a Grade 3 partial thromboplastin time. Three of these patients also had Grade 3 INR. In the 900 µg b.i.d. group 1 patient had a Grade 3 INR, and none had Grade 3 partial thromboplastin time. There were no patients in either group with Grade 4 partial thromboplastin time or INR.

No Grade 3-4 laboratory abnormalities were noted in studies B2208 and B2208E1.

While no Grade 3 or 4 hematology abnormalities were noted in the acromegaly and healthy volunteer populations, there were 2 patients with Grade 3 absolute lymphocyte count at higher dose ranges (i.e. between 900 and 2400 µg b.i.d. pasireotide) in the carcinoid syndrome patient population.

No clinically significant hematology changes were evident in any of the healthy volunteer studies.

Urine analysis

No clinically relevant findings for any of the clinical studies included in this submission were observed.

ECGs

The complete evaluation of the QT prolongation across the entire pasireotide development programme included central re-reading of all (available) locally read (i.e. machine derived values) ECGs. The percentage of healthy volunteers with notable post-baseline QTcF interval values was low. Overall, the percentage of patients with notable post-baseline QTcF interval values was low: new QTcF > 480 ms=1.2% (3/257); new QTcF > 500 ms=0.8% (2/257) and QTcF change from baseline > 60 ms=1.9% (5/258). No episodes of Torsade de Pointes were observed in the Cushing's disease studies or in any other patient populations.

The QTcF outlier analysis for study B2305 revealed similar findings relative to that observed across the pasireotide development programme i.e. few outlier values (n=3 events > 480 ms; n= 2 events > 500 ms, and n=5 events for changes from baseline of > 60 ms)(note that the exclusion criteria allowed patients with baseline QTcF of up to 480 ms to enrol). None of the QTcF values > 480 ms were associated with any reported AEs nor required any medical intervention or interruption of study medication. In addition, these events appeared to be sporadic (not related to duration of exposure) and asymptomatic. In addition, no discernable pattern of AEs was evident, and no dose dependency was observed.

Therefore, the central tendency changes in QTcF observed from study B2113 did not appear to correlate with a higher occurrence of categorical outliers in either B2305 or across the entire pasireotide development program as might be expected from a drug that prolonged QT/QTc.

In the supportive Cushing's disease studies B2208 and B2208E1, no patients with a QTcF or QTcB value > 480 ms were observed.

In the acromegaly carcinoid syndrome, and healthy volunteer populations, no clinically significant ECG abnormalities were reported.

Since the target population can be expected to be at a high cardiovascular risk due to longstanding hypercortisolism the prescriber has to be made aware of this potential risk. Appropriate warnings have been included in the SmPC.

Vital signs, body weight, and physical examinations

Minor fluctuations in blood pressure and body weight were noted, but there were no abnormalities that were considered to be clinically relevant. As discussed in the efficacy section, the majority of the observed changes were related to improvement of the clinical symptoms of the disease.

Gallbladder ultrasonography

Gallbladder ultrasonography was performed in a number of studies supporting the current submission. No clinically relevant observations with respect to gallstone or sludge frequency were observed. However, gallstones or sludge were observed during the ultrasound evaluation at a slightly higher frequency after pasireotide treatment compared to baseline in the Cushing's disease dataset and the acromegaly population. No gallbladder ultrasonography was performed in the carcinoid dataset. No clinically relevant changes were seen in the healthy volunteer population. Gallstones and sludge formation is a well known adverse effect of somatostatin analogue treatment.

Safety in special populations

Demographics

Population pharmacokinetic (PK) analyses of pasireotide suggest that race, ethnicity, gender, and liver function do not influence PK parameters. The covariate effects of age and body weight are found to influence PK parameters, but considered not to be clinically relevant.

Elderly patients

Age has been found to be a covariate in the population PK analysis of Cushing's disease patients. Decreased total body clearance and increased PK exposures have been seen with increasing age. The AUC at steady state for one dosing interval of 12 hours (AUCss) is predicted to be increased moderately (25%) when age increased from 18 to 73 years. This increase is moderate and considered of minor significance considering the wide age range in which the effect was observed. Data on Cushing's disease patients older than 65 years of age are limited but do not suggest any clinically significant differences in safety in relation to younger patients.

Paediatric patients

No studies have been performed in pediatric patients.

Patients with renal impairment

Clinical studies have not been performed in patients with impaired renal function. However, renal clearance has a minor contribution to the elimination of pasireotide in humans. Renal function is not expected to significantly impact the circulating levels of pasireotide.

Patients with hepatic impairment

In study B2114 in subjects with impaired hepatic function (Child-Pugh A, B and C), statistically significant differences were found only in subjects with severe hepatic impairment. These results indicate that hepatic impairment has a moderate impact on the PK profile of pasireotide and is unlikely to require dose modification.

Regarding patients with hepatic impairment, one specific safety study was performed in patients with different levels of hepatic impairment. This study (B2114) showed significant differences only in patients with severe hepatic impairment. Results of PK data indicate that hepatic impairment has a moderate impact on the PK profile of pasireotide and is unlikely to require dose modification. However, in the pivotal B2305 Study, 6 patients discontinued treatment due to hepatic adverse events. Based on these overall data, appropriate warnings have been added to the SmPC as well as a contra indication in patients with severe hepatic impairment.

Patients with established glucose metabolism disorders

In the pivotal study in patients with Cushing's disease, patients who had either baseline HbA1c ≥ 7% or were taking an anti-diabetic medication prior to randomization tended to have higher mean elevations in FPG and HbA1c relative to patients with a baseline HbA1c < 7% and not taking any anti-diabetic medication prior to randomization.

Patients with disorder of pituitary function

Deficiency of pituitary secreted hormones is common sequelae of transsphenoidal surgery and even more frequently post-radiation therapy of the pituitary gland. Cushing's disease patients with persistent or recurrent disease might therefore present with deficiency of multiple pituitary hormones. As the pharmacological activity of pasireotide mimics that of somatostatin, inhibition of pituitary hormones, other than ACTH, cannot be disregarded. In study B2305 in patients with Cushing's disease, hypothyroidism was reported for 7 patients but all presented with a TSH close to the lower limit or at the lower end of normal at study entry which precluded establishing a direct causal effect with pasireotide.

Pregnancy, lactation and fertility

Regarding experimental data, effects on female fertility were observed. In the peri-post-natal toxicity study, a slight retardation in the development of rats was noted.

The potential risk for humans is unknown since there is no clinical experience. Only 2 pregnancies have been reported.

Immunological events

The presence of antibodies was reported in preclinical studies in rats. No analysis on immunological events or research on antigenicity has been conducted in humans. However, in clinical studies, hypersensitivity and allergic reactions were reported. Injection site reactions were also reported very frequently in the pivotal Study B2305 (13.6% of patients). With regard to immunological events in Cushing's disease, 3 patients had an AE: 1 grade 1 allergy to chemicals, and 2 grade 2 drug hypersensitivity, not considered as related to study drug. With regard to injection site reactions reported, they are within what could be expected for a medication given subcutaneously. There were no findings correlating to the non-clinical findings of fibromas. Injection site reactions will be followed as outlined in the RMP.

Safety related to drug-drug interactions and other interactions

Drug-drug interactions are discussed in the clinical pharmacology part of this report.

Discontinuation due to adverse events

There did not appear to be a difference in the incidence of AEs leading to discontinuation in study B2305 between the 2 doses (15.9% and 18.8%, respectively, for the 600 and 900 µg b.i.d. groups). The most common AEs leading to discontinuation overall were GGT increased (3 patients [3.7%] in the 600 µg b.i.d. group and 2 patients [2.5%] in the 900 µg b.i.d. group), hyperglycaemia (2 patients [2.4%] in the 600 µg b.i.d. group and 3 patients [3.8%] in the 900 µg b.i.d. group), and diabetes mellitus (2 patients [2.4%] in the 600 µg b.i.d. group and 2 patients [2.5%] in the 900 µg b.i.d. group).

In the other studies comprising the Cushing's disease dataset, there were 2 patients who discontinued due to an AE, and in both cases these were related to glucose metabolism: 1 patient in study B2208 (hyperglycaemia) and 1 patient in study B2208E1 (type 2 diabetes mellitus). The data from study B2124 indicate that incretin enhancers may be more efficient than insulin secretagogues or biguanides in the treatment of pasireotide induced hyperglycaemia.

In the acromegaly patient population, AEs related to glucose metabolism were the most frequent AEs leading to study discontinuation: 2 patients in study B2201 and 3 patients in study B2201E1 discontinued as a result of a glucose-metabolism-related AE. In contrast, AEs related to gastrointestinal disorders were the most common AEs leading to discontinuation in the carcinoid syndrome population (hyperglycaemia was reported as an AE leading to discontinuation for only 1 patient).

Nine subjects had AEs leading to study discontinuation in the healthy volunteer dataset; however, these were distinct from those reported in all other datasets.

AEs requiring dose adjustment or interruption

Nausea, diarrhoea, hyperglycaemia, and adrenal insufficiency were the most common AEs requiring dose adjustment or interruption in study B2305. A total of 55 patients had at least 1 AE requiring dose adjustment or study drug interruption; 31 patients (37.8%) in the 600 µg b.i.d. group and 24 patients (30.0%) in the 900 µg b.i.d. group. Apart from adrenal insufficiency, these findings were consistent with observations in study B2208; however, each AE was only reported for 1 or 2 patients.

The most commonly occurring adverse events were often of a magnitude calling for dose adjustments. The treatment should be started at lower dose levels in order to increase tolerability.

2.6.1. Discussion on clinical safety

The safety data available indicate that the safety profile is largely similar to that seen with other somatostatin analogues with a predominance of gastrointestinal adverse reactions. No unexpected adverse events have been detected during the development programme.

The safety assessment is limited by the rather small number of patients treated with pasireotide. Out of the 201 patients with Cushing's disease treated with pasireotide, 122 patients were exposed for at least 6 months, 70 patients were exposed for at least 12 months and 17 patients were exposed for at least 24 months. The long-term experience is thus limited. In addition, safety data from studies in patients with acromegaly and carcinoid syndrome have been provided by the Applicant. The main focus of this assessment is however on the Cushing's disease safety population.

Almost all patients experienced an adverse event, 159 out of 162 studied patients with a majority of AEs that were study drug-related (95.7%). The number of Grade 3 or 4 AEs was high occurring in one half of patient population (48.8%). The number of serious AEs occurred also in high number of patients (40 patients: 24.7%).

Gastrointestinal and glycaemia related adverse events were most common as could be expected compared with other somatostatin analogues. Notably not only hyperglycaemia but also hypoglycaemia was reported. There was no apparent relationship with dose but adverse events were comparable between the two doses.

Twenty adverse events of special interest based on potential safety concerns identified in the non-clinical programme as well as adverse events expected with the somatostatin analogue class were defined by the Applicant. One of these selected adverse events was injection site reactions, and it may be concluded that these events were within the range that could be expected for a subcutaneously injected drug.

The adverse effects of pasireotide on glucose metabolism are expected due to the pharmacodynamic action of pasireotide on insulin secretion and incretins. Hyperglycaemia was also one of the most common reasons for discontinuation due to adverse events both in the Cushing and acromegaly populations. This is of concern due to the fact that the target patient group is prone to have a high prevalence of diabetes due to long-standing hypercortisolism. It is therefore of importance that patients who experienced hyperglycaemia could be successfully treated by anti-hyperglycaemic therapy which appears to have been the case. The data from study B2124 indicate that incretin enhancers may be more efficient than insulin secretagogues or biguanides in the treatment of pasireotide induced hyperglycaemia. However, hepatobiliary adverse events were observed with the combination of liraglutide and pasireotide. The available data does not allow for any recommendations beyond those already given in current guidelines on the treatment of diabetes. Warnings concerning hyperglycaemic events have been included in the SmPC.

Octreotide, another somatostatin analogue already authorised, was used in the study B2201 involving 60 patients with acromegaly. However, this study was not comparative; it was an open-label, randomized, crossover study in patients treated with octreotide 100 µg t.i.d. for 28 days following by pasireotide 200, 400 and 600 µg b.i.d. for 28 days each. Total treatment duration was 16 weeks. Even though no direct comparison between octreotide and pasireotide was provided as the treatment periods were different, it can be pointed out that more AEs were reported during the phases with pasireotide treatment than during the phase with octreotide: 86.7% vs 60%; hyperglycaemia was

reported in 8.3% of patients treated with pasireotide vs 1.7% (1 pts) with octreotide; increase of HbA1c was reported in 6.7% et diabetes mellitus in 5% of patients vs 0% with octreotide.

As known from the use of other somatostatin analogues, diarrhoea and nausea were common and may limit the use of pasireotide. Nausea was more common in the higher dose group. Cholelithiasis is a well known adverse event with somatostatin analogue treatment and was also observed with pasireoide.

Hypocortisolism was reported in almost 10 % of patients and is an identified risk with pasireotide treatment, however, only one patient discontinued due to hypocortisolism.

Hypopituitarism is another identified risk with pasireotide treatment. In the studies investigating the pharmacodynamics of pasireotide in healthy volunteers, no effect was observed on thyroid hormone levels whereas suppression of GH could be seen. Adverse events related to hypothyroidism were reported in patients with low or normal thyroid function at study entry. However, the impact of pasireotide therapy on this and other pituitary axes has not been discussed. The potential impact on the safety profile of inhibition of pituitary hormones other than ACTH has been explored by the Applicant. Pasireotide does not seem to alter the levels of thyrotropin or free T4. However, long-term effects on GH and IGF-1 levels in patients with Cushing's disease have not been studied and thus cannot be ruled out. The issue of long-term inhibition of pituitary hormones is adequately covered in the SmPC with recommendations for periodical monitoring of pituitary function.

The SmPC has been amended to include adequate warnings regarding potential effects on TSH and GH; however, long-term effects on GH should be followed as part of the RMP.

In the thorough QT study an effect of pasireotide on QT was observed, however, although the evaluation of ECGs with regard to QT prolongation revealed sporadic cases of QT prolongations no events with arrhythmias were reported. Bradycardia has been described for other somatostatin analogues and was observed in about 15 % of patients; however, in no case the bradycardia was associated with clinical symptoms. Since the target population can be expected to be at a high cardiovascular risk due to longstanding hypercortisolism, the prescriber has to be made aware of this potential risk. Warnings in this regard have been included in the SmPC.

The rate of SAEs was comparable between the two study groups with a tendency for more drug-related SAEs in the higher dose group. However, due to the small numbers, no firm conclusion can be drawn with regard to differences between the two doses. No unexpected SAEs were reported.

There were SAEs related to Cushing's disease, apart from lack of effect, these SAEs appear not to have been related to the study drug.

Among the SAEs that were considered to be study drug related none was unexpected and they were mostly related to the pharmacodynamic effect of pasireotide. It should be noted that one patient in the high-dose group discontinued due to adrenal insufficiency.

None of the two reported deaths were related to the study drug.

With regard to laboratory parameters, elevations of liver enzymes have been observed throughout the clinical study programme. Although six patients discontinued treatment due to increased liver function tests, the adverse events were generally mild. In the healthy volunteer dataset, three subjects showed liver test abnormalities fulfilling the Hy's law criteria. All subjects were asymptomatic and the events resolved upon discontinuation of medication. The observed changes appear manageable, however, monitoring of liver function is warranted. Warnings in this regard have been included in the SmPC. The SmPC, has been amended to include recommendations on actions to take if elevated liver enzymes are detected. The use of pasireotide in patients with severe hepatic impairment has been contraindicated.

Lipase increases were also observed and are expected due to the pharmacodynamic action of pasireotide. Changes in hematology parameters were observed but were generally mild. No clinically relevant changes in clinical chemistry parameters or urine analysis were observed.

Due to the size of the study, no meaningful analysis of safety related to gender, age or ethnicity could be made. A single dose of pasireotide given to patients with hepatic impairment did not reveal any unexpected adverse reactions. Hyperglycaemia was the most commonly reported event in this population.

In the pivotal study a rather large proportion of patients discontinued treatment due to adverse events. Furthermore, the efficacy data indicate that some patients may respond to lower doses than the recommended starting dose of 900 µg b.i.d. In order to minimise the risk of discontinuations due to adverse events a lower starting dose is now recommended in the SmPC.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

2.6.2. Conclusions on the clinical safety

The safety data-base is limited due to the small size of the pivotal study. The safety profile, however, appears comparable to that of other somatostatin analogues and thus this limitation could be acceptable. The most important adverse reactions observed were gastrointestinal events and hyperglycaemia. In the pivotal study, the increase in FPG and HbA1c is noteworthy. With regards to the mean values, neither mean-FPG nor mean-HbA1c returned to the levels before pasireotide treatment in any group of patients. The levels of FPG and HbA1c remained increased after discontinuation of the study drug. Long-term risk of hyperglycaemia and risks of ketoacidosis or coma are not known as well as the risks of use of pasireotide in a larger population. Further data on the management of pasireotide induced hyperglycaemia from study B2124 indicate that incretin enhancers may be the best option in the treatment of pasireotide induced hyperglycaemia; however the safety profile of the combinations has to be taken into account.

Other important identified risks that need further observation are the effects on QT prolongation as well as the observed increased incidence of bradycardia. The potential long-term effect on pituitary hormones, especially GH suppression, could be followed in post-approval studies. Treatment has been shown to cause hypocortisolism in some cases which may be handled by dose reduction or temporary discontinuation.

The Applicant is recommended to perform a post-marketing surveillance study, to further document the safety and efficacy of pasireotide s.c. in patients with Cushing's disease (CSOM230B2410). The final protocol has been included in the RMP and the RMP pharmacovigilance plan has been updated accordingly.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management Plan

The applicant submitted a risk management plan.

Table 20 Summary of the risk management plan

Safety issue	Agreed pharmacovigilance activities	Agreed risk minimization activities
Hypocortisolism/ Cortisol withdrawal syndrome	Routine pharmacovigilance activities Targeted follow-up of all SAE reports using a targeted checklist.	This item is appropriately communicated through current labeling: SPC Section 4.4 Special warnings and precautions for use. Treatment with pasireotide leads to rapid suppression of ACTH (adrenocorticotropic hormone) secretion in Cushing's disease patients. It is therefore necessary to monitor and instruct patients on the signs and symptoms associated with hypocortisolism (e.g. weakness, fatigue, anorexia, nausea, vomiting, hypotension, hyperkalaemia, hyponatraemia, hypoglycaemia). In the event of documented hypocortisolism, temporary exogenous steroid (glucocorticoid) replacement therapy and/or dose reduction or interruption of pasireotide therapy may be necessary. Adrenal insufficiency is included as ADR in SPC Section 4.8 Undesirable effects.
Hyperglycemia	Routine pharmacovigilance activities Targeted follow-up of all SAE reports using a targeted checklist.	This item is appropriately communicated through current labeling: SPC Section 4.4 Special warnings and precautions for use. Hyperglycaemia and, less frequently, hypoglycaemia, were observed in subjects participating in clinical studies with pasireotide. The degree of hyperglycaemia appeared to be higher in patients with pre-diabetic conditions or established diabetes mellitus. During the pivotal study, HbA_{1c} levels increased significantly and stabilised but did not return to baseline values. More cases of discontinuation and a higher reporting rate of severe adverse events due to hyperglycaemia were reported in patients treated with the dose of 0.9 mg twice daily. Glycaemic status (fasting plasma glucose/haemoglobin A_{1c} [FPG/HbA_{1c}]) should be assessed prior to starting treatment with pasireotide. FPG/HbA_{1c} monitoring during treatment should follow established guidelines. Self monitoring of blood glucose and/or FPG assessments should be done every week for the first two to three months and periodically thereafter, as clinically appropriate. In addition, monitoring of FPG 4 weeks and HbA_{1c} 3 months after the end of the treatment should be performed. If hyperglycaemia develops in a patient being treated with pasireotide, the initiation or adjustment of antidiabetic treatment is recommended, following the

Safety issue	Agreed pharmacovigilance activities	Agreed risk minimization activities
		established treatment guidelines for the management of hyperglycaemia. If uncontrolled hyperglycaemia persists despite appropriate medical management, the dose of pasireotide should be reduced or pasireotide treatment discontinued. In patients with poor glycaemic control, diabetes management and monitoring should be intensified prior to initiation and during pasireotide therapy. Hyperglycaemia and glucose metabolism disorders are included as ADRs in SPC Section 4.8 Undesirable effects SPC section 4.5 Interaction with other medicinal products and other forms of interaction *Insulin and antidiabetic medicinal products*
Bradycardia	Routine pharmacovigilance activities	This item is appropriately communicated through current labeling: SPC Section 4.4 Special warnings and precautions for use. Bradycardia has been reported with the use of pasireotide. Careful monitoring is recommended in patients with cardiac disease and/or risk factors for bradycardia, such as history of clinically significant bradycardia or acute myocardial infarction, high-grade heart block, congestive heart failure (NYHA Class III or IV), unstable angina, sustained ventricular tachycardia, ventricular fibrillation. Dose adjustment of medicinal products such as beta blockers, calcium channel blockers, or medicinal products to control electrolyte balance, may be necessary. Sinus bradycardia is included as ADR in SPC Section 4.8 Undesirable effects. Section 4.5 Interaction with other medicinal products and other forms of interaction *Bradycardic medicinal products.* Clinical monitoring of heart rate, notably at the beginning of treatment, is recommended in patients receiving pasireotide concomitantly with bradycardic medicinal products, such as beta blockers (e.g. metoprolol, carteolol, propranolol, sotalol), anticholinergics (e.g. ipratropium bromide, oxybutynin), certain calcium channel blockers (e.g. verapamil, diltiazem, bepridil), certain antiarrhythmics.
QTc interval prolongation	Routine pharmacovigilance activities Targeted follow-up of all SAE reports using a targeted checklist.	This item is appropriately communicated through current labeling: SPC Section 4.4 Special warnings and precautions for use. Pasireotide has been shown to prolong the

Safety issue	Agreed pharmacovigilance activities	Agreed risk minimization activities
		QT interval on the ECG. Pasireotide should be used with caution and the benefit risk carefully weighed in patients who are at significant risk of developing prolongation of QT, such as those: With congenital long QT syndrome; with uncontrolled or significant cardiac disease, including recent myocardial infarction, congestive heart failure, unstable angina or clinically significant bradycardia; taking antiarrhythmic medicinal products or other substances that are known to lead to QT prolongation, with hypokalaemia and/or hypomagnesaemia. Monitoring for an effect on the QTc interval is advisable and ECG should be performed prior to the start of pasireotide therapy, one week after the beginning of the treatment and as clinically indicated thereafter. Hypokalaemia and/or hypomagnesaemia must be corrected prior to administration of pasireotide and should be monitored periodically during therapy. 4.5 Interaction with other medicinal products and other forms of interaction Medicinal products that prolong the QT interval Pasireotide should be used with caution in patients who are concomitantly receiving medicinal products that prolong the QT interval. QT prolongation is included as ADR in SPC Section 4.8 Undesirable effects.
Cholelithiasis	Routine pharmacovigilance activities	This item is appropriately communicated through current labeling: SPC Section 4.4 Special warnings and precautions for use. Cholelithiasis is a recognised adverse reaction associated with long-term use of somatostatin analogues and has frequently been reported in clinical studies with pasireotide. Ultrasonic examination of the gallbladder before and at 6 to 12 month intervals during pasireotide therapy is therefore recommended. Cholelithiasis is included as ADR in SPC Section 4.8 Undesirable effects.
Hematological abnormalities	Routine pharmacovigilance activities	This item is appropriately communicated through current labeling: Anaemia is included as ADR in SPC Section 4.8 Undesirable effects.
Liver enzymes increased	Routine pharmacovigilance activities	This item is appropriately communicated through current labeling: SPC Section 4.2 Posology and method of administration: Pasireotide should not be used in patients with severe hepatic

Safety issue	Agreed pharmacovigilance activities	Agreed risk minimization activities
		impairment (Child Pugh C). Section 4.3 Contraindications: Severe hepatic impairment (Child Pugh C). Section 4.4 Special warnings and precautions for use, Liver tests: Mild transient elevations in aminotransferases are commonly observed in patients treated with pasireotide. Rare cases of concurrent elevations in ALT (alanine aminotransferase) greater than 3 x ULN and bilirubin greater than 2 x ULN have also been observed. Monitoring of liver function is recommended prior to treatment with pasireotide and after one, two, four, eight and twelve weeks during treatment. Thereafter liver function should be monitored as clinically indicated. Patients who develop increased transaminase levels should be monitored with a second liver function evaluation to confirm the finding. If the finding is confirmed, the patient should be followed with frequent liver function monitoring until values return to pre-treatment levels. Therapy with pasireotide should be discontinued if the patient develops jaundice or other signs suggestive of clinically significant liver dysfunction, in the event of a sustained increase in AST (aspartate aminotransferase) or ALT of 5 x ULN or greater, or if ALT or AST elevations greater than 3 x ULN occur concurrently with bilirubin elevations greater than 2 x ULN. Following discontinuation of treatment with pasireotide, patients should be monitored until resolution. Treatment should not be restarted. Gamma-glutamyltransferase increased, and alanine aminotransferase increased are included as ADRs in SPC Section 4.8 Undesirable effects.
Injection site reactions	Routine pharmacovigilance activities	This item is appropriately communicated through current labeling: Injection site reaction is included as ADR in SPC Section 4.8 Undesirable effects.
Gastrointestinal disorders	Routine pharmacovigilance activities	This item is appropriately communicated through current labeling: Diarrhoea, abdominal pain, nausea, vomiting, and abdominal pain upper are included as ADRs in SPC Section 4.8 Undesirable effects.
GH/IGF-I Decrease	Routine pharmacovigilance activities	This item is appropriately communicated through current labeling: SPC Section 4.4 Special warnings and precautions for use. Pituitary hormones:

Safety issue	Agreed pharmacovigilance activities	Agreed risk minimization activities
		As the pharmacological activity of pasireotide mimics that of somatostatin, inhibition of pituitary hormones other than ACTH cannot be ruled out. Monitoring of pituitary function (e.g. TSH/free T_4, GH/IGF-1) before and periodically during pasireotide therapy should therefore be considered, as clinically appropriate.
Hypothyroidism	Routine pharmacovigilance activities	This item is appropriately communicated through current labeling: Hypothhyroidism is covered by 'Pituitary hormones' and included as ADR in SPC Section 4.8 Undesirable effects.
Pancreatitis	Routine pharmacovigilance activities	This item is appropriately communicated through current labeling: SPC Section 4.8 Undesirable effects. Pancreatic enzymes: Asymptomatic elevations in lipase and amylase were observed in patients receiving pasireotide in clinical studies. Pancreatitis is a potential adverse reaction associated with the use of somatostatin analogues due to the association between cholelithiasis and acute pancreatitis. Lipase increased and blood amylase increased are included as ADRs in SPC Section 4.8 Undesirable effects.
Coagulation abnormalities	Routine pharmacovigilance activities	This item is appropriately communicated through current labeling: Prothrombin time prolonged is included as ADR in SPC Section 4.8 Undesirable effects.
Hypotension	Routine pharmacovigilance activities	This item is appropriately communicated through current labeling: Hypotension is included as ADR in SPC Section 4.8 Undesirable effects.
Hypocalcemia	Routine pharmacovigilance activities	Currently available data do not support the need for risk minimization.
Gastrointestinal erosions/bleedings	Routine pharmacovigilance activities	Currently available data do not support the need for risk minimization.
Potential interactions with cyclosporine, drugs metabolized by CYP3A4, bromocriptine, antiarrhythmic medicines and antidiabetics	Routine pharmacovigilance activities	This item is appropriately communicated through current labeling: SPC Section 4.5 Interaction with other medicinal products and other forms of interaction; *In vitro*, pasireotide has been shown to be a P-gp substrate. There is potential for strong P-gp inhibitors, e.g. ketoconazole, ciclosporin, verapamil, clarithromycin, to increase concentrations of pasireotide
Off-label use in children and other indications	Routine pharmacovigilance activities	This item is appropriately communicated through current labeling: SPC Section 4.2 Posology and method of Administration, Special populations, Paediatric population:

Safety issue	Agreed pharmacovigilance activities	Agreed risk minimization activities
		The safety and efficacy of pasireotide in children and adolescents aged 0 to 18 years have not been established. 5.2 Pharmacokinetic properties; Special populations, Paediatric population: No studies have been performed in paediatric patients.
Allergic reactions/immunogenicity	Routine pharmacovigilance activities	Currently available data do not support the need for risk minimization.
Tumor expansion	Routine pharmacovigilance activities	Currently available data do not support the need for risk minimization.
Pregnancy and Breast-feeding	Routine pharmacovigilance activities	This item is appropriately communicated through current labeling: SPC Section 4.6 Fertility, pregnancy and lactation There are no adequate data from the use of pasireotide in pregnant women. Studies in animals have shown reproductive toxicity. The potential risk for humans is unknown. Pasireotide should not be used during pregnancy unless clearly necessary. It is unknown whether pasireotide is excreted in human milk. Available data in rats have shown excretion of pasireotide in milk. Breast-feeding should be discontinued during treatment with pasireotide. 5.3 Preclinical safety data Pasireotide did not affect fertility in male rats but, as expected from the pharmacology of pasireotide, females presented abnormal cycles or acyclicity, and decreased numbers of corpora lutea and implantation sites. Embryo toxicity was seen in rats and rabbits at doses that caused maternal toxicity but no teratogenic potential was detected. In the pre- and postnatal study in rats, pasireotide had no effects on labour and delivery, but caused slight retardation in the development of pinna detachment and reduced body weight of the offspring.
Elderly patients	Routine pharmacovigilance activities	This item is appropriately communicated through current labeling: SPC Section 4.2 Posology and method of administration, Special populations, Elderly patients (≥65 years): Data on the use of pasireotide in patients older than 65 years are limited, but there is no evidence to suggest that dose adjustment is required in these patients; 5.2 Pharmacokinetic properties, *Elderly patients (≥65 years):* Decreased total body clearance and increased pharmacokinetic exposures have been seen with increasing age.

Safety issue	Agreed pharmacovigilance activities	Agreed risk minimization activities
Patients with cardiac disorders	Routine pharmacovigilance activities	This item is appropriately communicated through current labeling: SPC Section 4.4 Special Warnings and precautions Careful monitoring is recommended in patients with cardiac disease and/or risk factors for bradycardia, such as history of clinically significant bradycardia or acute myocardial infarction, high-grade heart block, congestive heart failure (NYHA Class III or IV), unstable angina, sustained ventricular tachycardia, ventricular fibrillation. Dose adjustment of medicinal products such as beta blockers, calcium channel blockers, or medicinal products to control electrolyte balance, may be necessary. Section 4.5 Interaction with other medicinal products and other forms of interaction *Medicinal products that prolong the QT interval* Pasireotide should be used with caution in patients who are concomitantly receiving medicinal products that prolong the QT interval. *Bradycardic medicinal products* Clinical monitoring of heart rate, notably at the beginning of treatment, is recommended in patients receiving pasireotide concomitantly with bradycardic medicinal products.
Children and adolescents (patients < 18 years)	Routine pharmacovigilance activities	This item is appropriately communicated through current labeling: SPC Section 4.2 Posology and method of Administration, Special populations, Paediatric population The safety and efficacy of pasireotide in children and adolescents aged 0 to 18 years have not been established. 5.2 Pharmacokinetic properties; Special populations, Paediatric population: No studies have been performed in paediatric patients.
Patients with liver disease	Routine pharmacovigilance activities	This item is appropriately communicated through current labeling: SPC Section 4.2 Posology and method of administration, Special populations, Hepatic impairment Dose adjustment is not required in patients with mildly impaired hepatic function (Child Pugh A). The recommended initial dose for patients with moderate hepatic impairment (Child Pugh B) is 0.3 mg twice a day (see section 5.2). The maximum recommended dose for these patients is 0.6 mg twice a day.

Safety issue	Agreed pharmacovigilance activities	Agreed risk minimization activities
		Pasireotide should not be used in patients with severe hepatic impairment (Child Pugh C). Section 4.3 Contraindications: Severe hepatic impairment (Child Pugh C). Section 5.2 Pharmacokinetic properties, Patients with hepatic impairment In a clinical study in subjects with impaired hepatic function (Child-Pugh A, B and C), statistically significant differences were found in subjects with moderate and severe hepatic impairment (Child-Pugh B and C). In subjects with moderate and severe hepatic impairment, AUC_{inf} was increased 60% and 79%, C_{max} was increased 67% and 69%, and CL/F was decreased 37% and 44%, respectively.
Long-term safety in patients	Routine pharmacovigilance activities Non-interventional study for the generation of long term safety and efficacy data of pasireotide s.c. in patients with Cushing's disease CSOM230B2410	Currently available data do not support the need for risk minimization.

The CHMP, having considered the data submitted, was of the opinion that the below pharmacovigilance activity in addition to the use of routine pharmacovigilance is needed to investigate further some of the safety concerns:

Description	Due date
StudyCSOM230B2410: Non-interventional study for the generation of long term safety and efficacy data of pasireotide s.c. in patients with Cushing's disease. [European Registry on Cushing's syndrome ('ERCUSYN'): Generation of long term safety and efficacy data of pasireotide s.c. in patients with Cushing's disease].	Efficacy and safety data will be submitted on a yearly basis as of 2014 Final CSR due 2018

No additional risk minimisation activities were required beyond those included in the product information.

2.8. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Benefit-Risk Balance

Benefits

Beneficial effects

In Cushing's disease, hypercortisolism is caused by ACTH producing pituitary adenomas. The first line therapy is pituitary surgery; however, the recurrence rate is high also in the hands of experienced neurosurgeons. Another option is pituitary irradiation which has the disadvantage of slow onset of effect in combination with effects on all other pituitary hormones, eventually causing panhypopituitarism. There is currently no medical therapy available across the EU. The drugs currently used in the treatment of hypercortisolism all share a negative safety profile, making them less suitable for long-term treatment. Thus there is an unmet medical need for new medical therapies for the treatment of Cushing's disease.

Pasireotide is a new somatostatin analogue with a different binding pattern to the somatostatin receptors compared to the currently available somatostatin analogues octreotide and lanreotide. In the pivotal study (B2305) 162 patients were randomised to receive either 600 µg b.i.d. or 900 µg b.i.d. The primary endpoint was responder rates, where responders were defined as patients who had normalised their mean UFC evaluated after six months of treatment with the hypothesis that a lower bound of the 95 % CI above 15 % response rate would represent a clinically relevant effect. Normalisation of mean UFC is an important measure as it is expected to translate into alleviation of the clinical signs and symptoms of Cushing's disease. Responder rates are therefore considered a clinically relevant measure of efficacy.

The response rates in the pivotal study were 26.3 % (95 % CI; 16.6, 35.9) and 14.6 % (95 % CI; 7.0, 22.3) for the 900 and 600 µg b.i.d. doses, respectively. Since hypercortisolism, whatever UFC value, leads to an increase in morbidity and mortality the aim of treatment should be the normalisation of mUFC. However, also partial response is expected to be of clinical relevance. When partial responders (showing at least 50 % reduction of their mUFC compared to baseline) were included, the response rate was 41 % for the higher dose and 34 % for the lower dose.

All secondary and exploratory endpoint outcomes supported the primary endpoint including beneficial and clinically relevant effects on objective parameters such as blood pressure, weight and Quality of Life as well as data suggesting that pituitary tumour volume decreases during treatment. This was seen both in patients who were complete and partial responders. Thus, the efficacy of pasireotide is considered to have been adequately shown.

Uncertainty in the knowledge about the beneficial effects.

Efficacy data is only available up to 12 months of treatment, although these data indicate that the effect is maintained. The rate of discontinuation was particularly high in the pivotal trial. Only 48% of the randomised patients completed the study at 12 months with the main cause of discontinuation being unsatisfactory therapeutic effect (25.3%). However, in the group of patients who were partial or complete responders, the drop-out rate was considerably lower (31.6 % at month 12) compared to the non-responder group (69.3 % at month 12).

The long-term effects will have to be followed as post-authorisation measures. The Applicant will perform a post-marketing surveillance study, to further document the safety and efficacy of pasireotide s.c. in patients with Cushing's disease (CSOM230B2410). The final protocol has been included in the RMP and the RMP pharmacovigilance plan has been updated accordingly.

Due to the relatively high rate of non-responders it is considered important that non-responders could be detected early. The data shows that more than 80 % of patients who had not responded at 2-3 months of treatment were still non-responders at month 6; therefore patients that do not benefit from treatment can be identified early. This issue is adequately reflected in the SmPC and recommendations on when to discontinue treatment are provided.

Due to the statistical design of the study no formal comparison was made between the two doses investigated. The study groups were imbalanced with regard to the baseline mUFC (higher values in the group randomised to the 600 µg b.i.d. dose), which may have affected the outcome of the primary endpoint. The totality of data indicates that the lower dose may be as effective as the higher dose in some patients. Further, the increase in pasireotide dosages did not translate into better efficacy especially when increasing the dose beyond 900 µg b.i.d. Among the 36 patients concerned by dose increases only 3 experienced UFC normalization, however, additional reductions of mUFC was observed when the dose was increased from 600 µg b.i.d to 900 µg b.i.d. Based on the fact that some patients did respond to the lower dose, this dose is now recommended as the starting dose in the SmPC with an option to uptitrate to the higher dose.

Factors that could differentiate patients, who may or may not respond to treatment, have not been established at the present time. The characteristics (biological or clinical) of patients who would benefit from pasireotide treatment are still unknown but will be further explored in the non-interventional post-marketing study.

Risks

Unfavourable effects

The safety profile of pasireotide appears comparable to that seen for other somatostatin analogues. The most common adverse events were gastrointestinal (diarrhoea and nausea, 54.9 % and 46.9 %, respectively) and metabolic (hyperglycaemia, 38.9 %). The adverse events clearly affect the tolerability and caused a rather large number of discontinuations (15.9 % and 18.8 % of patients in the low and high dose, respectively). Hyperglycaemia is of concern due to the fact that the target patient group is prone to have a high prevalence of diabetes due to long-standing hypercortisolism. The data suggests that hyperglycaemia in most cases can be successfully managed by anti-diabetic treatment. A short-term study (B2124) has investigated different anti-diabetic therapies in pasireotide induced hyperglycaemia. However, the importance of the high incidence of hyperglycaemia needs to be followed. The Applicant is recommended to perform study B2219 to further examine the optimal management of hyperglycaemia. In this regard, the Applicant is recommended to provide a complete protocol to the CHMP before the start of the study, and to provide the results when available.

Cholelithiasis is a well known adverse reaction of somatostatin analogue treatment and was also observed with pasireotide in 30 % of the patients.

Hypocortisolism was reported for almost 10 % of the patients and is an identified risk with pasireotide treatment.

Hypopituitarism is another identified risk with pasireotide treatment. In the studies investigating the pharmacodynamics of pasireotide in healthy volunteers, no effect was observed on thyroid hormone levels whereas suppression of GH could be seen. Adverse events related to hypothyroidism (4.3 %) were reported in patients with low or normal thyroid function at study entry.

Two thorough QT studies have been performed, both indicating that pasireotide may cause QT-prolongation and sporadic cases were observed also in the clinical programme. QT-prolongation and bradycardia have been described also for other somatostatin analogues.

Increases in liver function tests were observed for 16 % of patients in the pivotal study; however these increases were generally mild. Increases in liver functions test were also observed in asymptomatic healthy volunteers, all these events resolved once medication was discontinued. A PK study was performed in patients (without Cushing's disease) with different levels of hepatic impairment on the effects of pasireotide on hepatic function. Results showed significant differences only in patients with severe hepatic impairment. Moreover, in the pivotal study B2305, 6 patients discontinued treatment due to hepatic adverse events. Based on these overall data, a dose adjustment for patients with moderate hepatic impairment as well as recommendations regarding monitoring of liver function have been included in the SmPC. Adequate recommendations regarding actions to take if elevated liver enzymes are observed have been included. Furthermore, the use of pasireotide in patients with severe hepatic impairment has been contraindicated.

Injection site reactions, of a type and severity to be expected with a subcutaneously injected drug, were reported by 13.6 % of the patients in the pivotal study.

No unexpected adverse events were reported in the clinical programme.

The identified risks are all considered possible to handle by following the information in the SmPC; the risks should further be followed as outlined in the RMP.

Uncertainty in the knowledge about the unfavourable effects

Due to the fact that Cushing's disease is a rare disease the safety database is small comprising of only 201 patients with Cushing's disease, whereof only 70 patients have been treated for up to 12 months. Thus it is not possible to detect uncommon adverse events. Therefore post-approval follow-up will be needed.

The long-term effects of pasireotide on GH suppression are not known and will have to be followed as a post-authorisation measure. The Applicant will perform a post-marketing surveillance study, to further document the safety and efficacy of pasireotide s.c. in patients with Cushing's disease (CSOM230B2410). The final protocol has been included in the RMP and the RMP pharmacovigilance plan has been updated accordingly.

No drug interaction studies have been performed and in general the interaction potential for pasireotide appears low from a pharmacokinetic point of view but there are some issues identified that may necessitate complementary *in vivo* interaction studies. Furthermore, interactions with antidiabetic agents are expected from a pharmacodynamic perspective. Data from the study B2124 indicate that incretin enhancers may be the best choice in the treatment of pasireotide induced hyperglycaemia, and that the combinations tested are tolerated. However, hepatobiliary adverse events were seen with the combination pasireotide and liraglutide and the available data are not deemed sufficient to make recommendations regarding this combination. The data from B2124 also indicate that metformin may not be efficient in the treatment of pasireotide induced hyperglycaemia. Available data, however, is insufficient to give any recommendations that go beyond current guidelines for the treatment of diabetes. Adequate information in this regard is given in the SmPC.

Non-clinical competition binding experiments showed that pasireotide binds with high affinity to human somatostatin receptor subtypes sst1, sst2, sst3, and sst5. The affinity for sst1 and sst5 is 30 to 40 times higher, and the affinity to sst3 is 5 times higher than the affinity of octreotide, while the affinity for sst2 was somewhat lower and equal to octreotide. Thus, the binding data demonstrates that the mechanism of action for pasireotide is somewhat different from that of octreotide, mainly regarding affinity to the sst5 receptor subtype, which has a fairly large distribution in the heart. Therefore, pharmacodynamically mediated adverse cardiac reactions different from those observed with octreotide may be expected. Currently available published data does not allow for any conclusions on

this issue. The Applicant is recommended to further explore whether the cardiac effect of pasireotide (bradycardia, QT prolongation) pertain to any explorable ancillary properties (I_f, somatostatin receptors) by means of relevant models and to report the outcome to CHMP as post-authorisation measures.

No specific study was performed in specific populations such as elderly, patients with renal and hepatic failure, children, pregnant and breast feeding women.

Pasireotide antibodies were detected in an antigenicity study of pasireotide LAR in the 6-cycle rat. No investigations of antibodies and thus their potential impact on efficacy have been conducted in humans. Thus, no formal conclusion can be drawn, but with regard to the injection site reactions reported, they are within what could be expected for a medication given subcutaneously.

Benefit-risk balance

Importance of favourable and unfavourable effects

Cushing's disease is a rare and life-threatening disorder associated with an increase of mortality and morbidity. At the present time, no medicinal treatment is registered that could be helpful especially in the event of recurrence or persistence of the disease after surgery, or when surgery is impossible. Reducing the hypercortisolism in these patients is of outmost importance in order to protect them from the co-morbidities associated with this condition such as cardiovascular disease, diabetes and osteoporosis. In that context, the development and approval of a new therapy is important.

The overall clinical programme showed that pasireotide, due to its pharmacological properties as somatostatin analogues, is effective in reducing UFC and even normalising UFC in a relevant proportion of patients suffering from Cushing's disease. These effects have also been observed on other biological parameters considered as markers of the disease and its evolution. Pasireotide seems to be also effective in improving signs and symptoms and Quality of Life in some patients.

Further characterisation of responders to treatment is not possible based on the available data; however, responders to treatment could be identified after the two first months of treatment after which treatment can be discontinued in non-responders.

With regard to the risks of this new treatment, the safety profile of pasireotide was partly the same as the safety profile of other somatostatin analogues; hypocortisolism, hyperglycaemia, bradycardia, cholelithiasis, haematological abnormalities, liver enzymes increased and injection sites reactions. Further, a QT prolongating effect of pasireotide has been observed. The SmPC has been amended to adequately cover these identified risks. Taking into consideration that the target population is expected to be under close surveillance by specialists in endocrinology, liver safety could be handled by routine pharmacovigilance and will also be followed in the planned post-marketing study. Appropriate warnings have been added to the SmPC as well as a contraindication in patients with severe hepatic impairment.

Hyperglycaemia events were reported with high rates. These events, however, are manageable if current treatment guidelines are applied and in view of the fact that adequate information has been included in the SmPC. The long-term evolution and management will have to be followed as part of the RMP.

Taking the low response rate into account the wording of the indication has been strengthened to clarify that pasireotide is a second line therapy to surgery.

The initial marketing authorisation application for Signifor was submitted for a product in pre-filled syringes. However, during the procedure, translucent, "flake like" visible particles were found in pre-filled syringes, for which the initial application was submitted. The cause of forming the particles was

identified as combination of silicone coating of the syringes and stoppers and damage of the stoppers by gamma-irradiation. The applicant decided to replace the pre-filled syringes by ampoules. As all data submitted for the ampoules were satisfactory, this solution was accepted.

However, since the current packaging (glass ampoules) is not considered optimal by the CHMP, the Applicant is recommended to submit an application seeking approval of pasireotide solution for injection in pre-filled syringes as soon as appropriate stability data are available, and to keep the CHMP informed on the progress of these stability studies.

Benefit-risk balance

Discussion on the benefit-risk balance

From a clinical point of view the benefits of Signifor (pasireotide) in the treatment of Cushing's disease are considered to outweigh the risks. Thus, the benefit-risk balance of Signifor is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Signifor in the treatment of adult patients with Cushing's disease for whom surgery is not an option or for whom surgery has failed, is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Conditions and requirements of the Marketing Authorisation

Risk Management System

The MAH must ensure that the system of pharmacovigilance, presented in Module 1.8.1 of the marketing authorisation, is in place and functioning before and whilst the product is on the market.

The MAH shall perform the pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in version 2 of the Risk Management Plan (RMP) presented in Module 1.8.2 of the marketing authorisation and any subsequent updates of the RMP agreed by the CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted:

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- at the request of the EMA

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Not applicable

New Active Substance Status

Based on the CHMP review of data on the quality, non-clinical and clinical properties of the active substance, the CHMP considers that pasireotide(as diaspartate) is to be qualified as a new active substance.