20 July 2017
EMA/CHMP/508155/2017
Committee for Medicinal Products for Human Use (CHMP)

CHMP assessment report on extension(s) of marketing authorisation and an extension of indication variation

Signifor

International non-proprietary name: pasireotide

Procedure No. EMEA/H/C/002052/X/0030/G

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Administrative information

Name of the medicinal product:	Signifor
MAH:	Novartis Europharm Ltd Frimley Business Park Camberley GU16 7SR UNITED KINGDOM
Active substance:	Solution for injection pasireotide disapartate Powder and solvent for suspension for injection PASIREOTIDE PAMOATE
International Non-proprietary Name/Common Name:	pasireotide
Pharmaco-therapeutic group (ATC Code):	hypothalamic hormones, somatostatin and analogues (H01CB05)
Therapeutic indication(s):	Solution for injection Treatment of adult patients with Cushing's disease for whom surgery is not an option or for whom surgery has failed. Powder and solvent for suspension for injection Treatment of adult patients with acromegaly for whom surgery is not an option or has not been curative and who are inadequately controlled on treatment with another somatostatin analogue. Treatment of adult patients with Cushing's disease for whom surgery is not an option or for whom surgery has failed. The 60 mg strength is only to be used in the treatment of acromegaly.
Pharmaceutical form(s):	Solution for injection // Powder and solvent for suspension for injection
Strength(s):	Solution for injection

	0.3 mg, 0.6 mg, 0.9 mg Powder and solvent for suspension for injection 10 mg, 20 mg, 30 mg, 40 mg and 60 mg
Route(s) of administration:	Solution for injection Subcutaneous use Powder and solvent for suspension for injection Intramuscular use
Packaging:	Solution for injection ampoule (glass) Powder and solvent for suspension for injection Powder: vial (glass); Solvent: pre-filled syringe (glass)
Package size(s):	Solution for injection 6 ampoules, 18 ampoules, 30 ampoules, 60 ampoules Powder and solvent for suspension for injection 1 vial + 1 pre-filled syringe + 1 vial adapter + 1 needle and 3 x 1 vial + 1 pre-filled syringe + 1 vial adapter + 1 needle (multipack)

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List of abbreviations

24h-UFC	24-hour urinary-free cortisol
ACTH	Adrenocorticotropic hormone
ADM	Anti-diabetic medication
ADR	Adverse drug reaction
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the curve of blood/plasma concentration versus time
AUC,ss	Area under the concentration-time curve at steady state
bid	Twice daily
BMI	Body mass index
CDS	Core Data Sheet
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
Cmax,ss	Maximum concentration at steady-state
Ctrough	Trough concentration
DDI	Drug-drug interaction
ECG	Electrocardiogram
Emax	Maximum possible effect
EMA	European Medicines Agency
FAS	Full analysis set
FDA	Food and Drug Administration
FPG	Fasting plasma glucose
GI	Gastrointestinal
GGT	Gamma-glutamyltransferase
HbA1c	Glycosylated hemoglobin
im	Intramuscular
LOCF	Last observation carried forward
MedDRA	Medical Dictionary for Drug Regulatory Activities
MID	Minimally important difference
mUFC	Mean urinary free cortisol
PD	Pharmacodynamic
PK	Pharmacokinetic
q28d	Every 28 days
QTcB	Corrected QT interval (according to Bazett)
QTcF	Corrected QT interval (according to Fridericia)
SAE	Serious adverse event
sc	Subcutaneous
SBP	Summary of Biopharmaceutic Studies and Associated Analytical Methods
SSA	Somatostatin analog
TBIL	Total bilirubin
UFC	Urinary free cortisol
ULN	Upper limit of normal

1. Background information on the procedure

1.1. Submission of the dossier

Novartis Europharm Ltd submitted on 30 November 2016 a group of variation(s) consisting of an extension of the marketing authorisation and the following variation(s):

Variation(s) requested		Type
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

The MAH applied for the addition of two new strengths (10 mg and 30 mg) of the long acting intramuscular powder and solvent for suspension for injection pharmaceutical form.

In addition, the MAH proposed a type II variation (C.I.6.a) to extend the indication to include 'Treatment of adult patients with Cushing's disease for whom surgery is not an option or for whom surgery has failed' to the intramuscular injection formulations.

Furthermore, the PI is brought in line with the latest QRD template version 10.0

The legal basis for this application refers to:

Article 7.2 of Commission Regulation (EC) No 1234/2008 – Group of variations

Signifor, was designated as an orphan medicinal product (EU/3/09/671) on 08 October 2009 in the following condition: Treatment of Cushing's disease.

The new indication, which is the subject of this application, falls within the above mentioned orphan designation.

Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/75/2009 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 MAH did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

Scientific Advice

The MAH received Scientific Advice from the CHMP on 18 December 2008. The Scientific Advice pertained to clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Kristina Dunder

- The application was received by the EMA on 30 November 2016.
- The procedure started on 23 December 2016.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 13 March 2017. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 12 March 2017. The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on 13 March 2017.
- During the meeting on 6 April 2017, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP.
- During the meeting on 21 April 2017, the CHMP agreed on the consolidated List of Questions to be sent to the MAH.
- The MAH submitted the responses to the CHMP consolidated List of Questions on 18 May 2017.
- The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on 26 June 2017.
- During the meeting on 20 July 2017, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for an extension(s) of the marketing authorisation for Signifor on 20 July 2017.
- The CHMP adopted a report on similarity of Signifor with Ketoconazole HRA on 20 July 2017 (Appendix 1)

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The new claimed therapeutic indication for the long-acting intramuscular (i.m.) formulation of Signifor is:

“Treatment of adult patients with Cushing’s disease for whom surgery is not an option or for whom surgery has failed.”

2.1.2. Epidemiology

Cushing’s disease is a very rare, debilitating, and life-threatening disease. The prevalence of Cushing’s disease is 0.4 per 10000 individuals in the EU. The disease is 3.5 times more frequent in women than men, and it is usually diagnosed in patients 25 to 45 years of age.

2.1.3. Aetiology and pathogenesis

Cushing’s disease is caused by an adrenocorticotropic hormone (ACTH)-secreting pituitary adenoma. The tumours are usually microadenomas (≤1 cm in diameter); macroadenomas are rare. The elevated levels of ACTH stimulate the adrenal glands to produce excess cortisol, thereby leading to the subsequent development of the clinical signs and symptoms of hypercortisolism.

2.1.4. Clinical presentation, diagnosis

The disease is characterised by the development of the clinical signs and symptoms of hypercortisolism. The normal circadian rhythm of cortisol production is usually lost. Most patients are obese or overweight, with abdominal visceral adiposity and facial fullness (moon face). More than 70% have hypertension, around 80% have impaired glucose tolerance or diabetes (often due to insulin resistance), and dyslipidaemia is seen in around 20% of patients. Changes in physical appearance commonly include hirsutism, thinning of skin with easy bruising, purplish striae, reddening of the cheeks, and ulceration of the skin. Hypercortisolism is also associated with muscular atrophy, generalized weakness and fatigue, osteopenia/osteoporosis, menstrual disorders in women, decreased fertility and/or libido, and immune deficiency with an increased risk for infections. In addition, patients with large pituitary tumours may have evidence of mass effect, including headache or visual impairment as a result of impingement on the optic apparatus.

The physiological and physical changes resulting from chronic hypercortisolism have significant impact on the patients' quality of life: many patients suffer from depression, emotional instability, and sleeping difficulties, 80% of patients report interference with family life and relations with their partner, and more than half with school or work performance.

Patients with Cushing's disease have increased morbidity and a mortality rate 4 times higher than age- and gender-matched subjects.

2.1.5. Management

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. Currently ketoconazole is approved for the treatment of Cushing's syndrome which includes a number of conditions with increased cortisol production, including Cushing's disease. Ketoconazole is an 11β-hydroxylase and 17α-hydroxylase inhibitor, which leads to a decrease in cortisol production. 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.

Other available pharmacological treatments are metyrapone and mitotane which like ketoconazole inhibit cortisol production. Mifepristone is a synthetic steroid that appears to inhibit glucocorticoid receptor activation. Cabergoline, which is a dopamine receptor agonist has also been used, since some corticotroph pituitary adenomas express dopamine receptors. There is however only 1 prospective study on the use of cabergoline as monotherapy.

None of the available pharmacological treatment options listed, apart from cabergoline, targets the cause of the disease, i.e. the pituitary adenoma. Thus there is an unmet medical need in the treatment of patients with Cushing's disease.

Pasireotide, in the short-acting formulation for subcutaneous use, has already been shown to be effective in the treatment of Cushing's disease and limited data indicate that pasireotide not only lowers cortisol production but also result in a decrease in pituitary tumour volume.

2.1.6. About the product

Pasireotide is a cyclohexapeptide analog of the natural hormone somatostatin. Pasireotide was first developed as an immediate release formulation for subcutaneous (s.c.) injection. The pasireotide s.c. formulation was first approved for the treatment of hypercortisolism in Cushing's disease in 2012.

A long-acting release formulation ("pasireotide longacting"; "pasireotide LAR") for intramuscular (i.m.) injections was developed to improve the convenience of administration by reducing the number of injections from twice a day to once a month. The pasireotide long-acting formulation was first approved for the treatment of acromegaly.

2.1.7. The development programme/compliance with CHMP guidance/scientific advice

There are no specific regulatory guidelines for the development of medicinal products intended to treat Cushing's disease. The design of the Phase 3 study supporting this application reflects current scientific and clinical knowledge.

In the EU, Scientific Advice was sought on the development program for the pasireotide long-acting formulation in Cushing's disease. The CHMP considered the study design, which mimics that of Study B2305, acceptable (EMA Scientific Advice 2008). The Applicant incorporated the suggestion to evaluate a high and a low dose of the long-acting formulation versus the initially proposed doses of 40 mg and 60 mg to offset the lack of a control arm

in the trial. In addition, following Rapporteur/Co-Rapporteur feedback received in July 2015 in response to the communication regarding the error in the methodology of determination of the UFC reference range at the central lab, the statistical analysis plan was revised to include analyses that evaluated the impact of the new ULN on study conduct (enrolment, dose up-titration) and response rates.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as powder and solvent for suspension for injection containing 10 and 30 mg of pasireotide pamoate as active substance.

Other ingredients are poly(D,L-lactide-co-glycolide) (50-60:40-50) and Poly(D,L-lactide-co-glycolide) (50:50) in the powder; and carmellose sodium, mannitol, poloxamer 188 and water for injections in the solvent, as described in section 6.1 of the SmPC.

The finished product is available in a brownish glass vial with chlorobutyl rubber stopper containing the powder, and a colourless glass pre-filled syringe containing the solvent, packaged together with a vial adapter and a safety injection needle as described in section 6.5 of the SmPC.

2.2.2. Active Substance

The active substance used in the manufacture of the proposed Signifor 10 mg and 30 mg powder and solvent for suspension for injection is the same as that being used for the already approved Signifor 20 mg, 40 mg and 60 mg powder and solvent for suspension for injection strengths. No new information on the active substance has been provided within this line extension application.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

The finished product is presented as powder and solvent for suspension for injection. The formulation is a long acting release (LAR) dosage form for parenteral (intramuscular) administration. It consists of pasireotide pamoate loaded poly(D,L-lactide-co-glycolide) microparticles which should be suspended in an aqueous vehicle prior to injection. The lyophilised powder is a slightly yellowish to yellowish powder packaged in a 6 ml glass vial.

The solvent (solution composed of commonly used excipients and water for injections) is a 2 ml clear, colourless to slightly yellow or slightly brown solution filled into 3 ml prefilled syringes. The solvent for these two new strengths is the same used in the already authorised strengths. No further information regarding the manufacture, specifications and stability has been presented in the context of this line extension application.

The objective of the pharmaceutical development was to develop two new dosage strengths, namely 10 and 30 mg, of Signifor powder and solvent for suspension for intramuscular (im) injection to support the extension of indication for Cushing's disease, in addition to the already approved 20 mg and 40 mg strengths.

The two new strengths were developed with the same long release formulation, employing microencapsulation of the active substance in biodegradable polymers, as the currently approved strengths, for administration once a month. The active substance is uniformly distributed within the microparticles from which the active substance is continuously released (primarily by diffusion and hydrolysis/erosion).

The formulation development and manufacturing process for pasireotide pamoate powder for suspension for injection, as well as the pharmaceutical development for the vehicle and the devices was established and presented during the original submission of the current approved strengths of 20 mg, 40 mg and 60 mg.

The 10 mg and 30 mg strengths are derived from the same bulk powder as the marketed strengths. They only differ in the fill weight and the colour of the flip-off cap. Therefore, the pharmaceutical development information of the already approved strengths (including pasireotide salt selection studies, excipient selection and compatibility studies, design of the microparticles manufacturing process and pharmacokinetic profile studies for different formulation variants) is applicable to all developed dosage strengths. Several process improvements were conducted to optimize the filling accuracy and robustness for the 10 mg strength. The successful implementation of the adaptations was proved during process validation.

The composition and configuration of clinical batches has been presented. The switch from the clinical presentation to commercial presentation was supported by comparative analytical data on 'uniformity of delivered dose'. In summary all data for the clinical as well as the commercial presentation comply with the specifications criteria and the specified limits. Each vial contains a justified overfill which allows removal of the labelled content from the vial.

The same terminal sterilization method by gamma irradiation is used for all the strengths. Therefore, no additional information has been provided for the 10 mg and 30 mg dosage strengths.

The excipients used for the new strengths are the same as those employed for the currently approved strengths. They are all well-known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards.

The primary packaging for pasireotide pamoate powder for suspension for injection 10 mg and 30 mg is the same as for the already approved strengths. It consists of colourless 6 ml glass vials (Type I glass) complying with the requirements of Ph. Eur. and USP, closed with a grey rubber stopper (chlorobutyl rubber) and covered with a coloured flip-off cap (aluminum/polypropylene). The cap does not come into contact with the finished product. Due to the final gamma irradiation process a slight change in the vial's appearance from colourless to brownish occurs, which was not a new finding. It was also observed with the already approved strengths and has no impact on the chemical and physical properties of the glass (except colour and light transmission). The choice of the container closure system has been validated and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process for Signifor 10 mg and 30 mg powder for suspension for injection is a standard process for parenteral formulations which comprises the following main steps: preparation of the organic and the aqueous phases separately; preparation of microparticules; washing, drying and sieving of the microparticules; filling and stoppering of the vials and terminal sterilization by gamma-irradiation.

The manufacturing process has been described in sufficient detail. The manufacturing process for the bulk powder and the gamma irradiation sterilization process is the same for all dosage strengths and it is covered by the process validation performed for the manufacture of the already approved 20 mg, 40 mg and 60 mg strengths.

As the powder for suspension for injection for the 10 mg and 30 mg strengths is derived from the same bulk powder as the marketed strengths and the new dosage strengths only differ from those already approved in the fill weight and colour of the flip-off cap, the manufacturing process development and validation of the process for these new strengths were focused on the filling process. The validation of the manufacturing process for the bulk powder and the terminal sterilization process is covered by the process validation performed for the manufacture of the commercial 20 mg, 40 mg and 60 mg strengths. The filling step of the process for the 10 mg and 30 mg powder for suspension for injection has been validated using three full-scale production batches of

each strength. Details on the process validation for the filling of the bulk material into vials for the 10 mg and 30 mg strength have been provided and fully meet the specifications.

The critical steps, which have been defined and are controlled by in-process controls (IPCs), have been adequately justified. The overall control strategy ensures that the manufacturing process consistently delivers a product that meets the defined criteria for all release specifications.

A holding time for the intermediate has been established and the compatibility of its packaging material has been demonstrated by stability studies.

In conclusion, based on process validation data and adequacy of in-process controls, it is considered that the manufacturing process of the finished product (pasireotide powder and solvent for suspension for injection, 10 mg, and 30 mg) is sufficiently robust to provide assurance of consistent quality, complying with the proposed specification.

Product specification

The specification for batch release and shelf-life for Signifor 10 mg and 30 mg powder for suspension for injection includes the following tests: appearance of the vial, its contents and the reconstituted suspension (visual inspection), identification (TLC and HPLC), pH value (Ph. Eur.), particle size distribution (laser diffraction), molecular mass of the polymer (GPC), suspendability (visual inspection), drug burst release (HPLC), tightness of container (dye intrusion), water (KF), degradation products (HPLC), drug release (HPLC), microbial limit tests (Ph. Eur.), uniformity of deliverable dose (HPLC), uniformity of dosage units (HPLC), bacterial endotoxins test (Ph. Eur.), sterility (surface and core) (Ph. Eur.) and assay (HPLC).

Adequate specifications for control of the finished product at release and during shelf-life have been established. The analytical methods used have been adequately described and validated in accordance with the ICH guidelines. These are the same used for the already approved strengths (20 mg, 40 mg and 60 mg). Satisfactory information regarding the reference standards has been presented.

Appropriate data have been presented to justify the specifications for each quality characteristic that is controlled. The specifications established for control ensure the identity, safety, and purity of the 10 mg and 30 mg powder and solvent for suspension for injection, throughout the proposed finished product shelf life.

Batch analysis results are provided from six commercial scale batches of the 10 mg strength and three commercial scale batches for the 30 mg s strength, confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification. All results comply with the proposed specification.

Stability of the product

Stability data of three commercial scale batches of the 10 mg strength stored under long term conditions at 5ºC (inverse and upright storage)/ambient RH for 60 months and for up to 6 months under accelerated conditions at 25ºC (inverse storage)/60% RH according to the ICH guidelines were provided. The batches of Signifor 10 mg are representative of those proposed for marketing and were packed in the primary packaging proposed for marketing.

For the 30 mg strength, a bracketing approach was followed and the registration stability study provided for the commercialized strengths (i.e. 20 mg, 40 mg and 60 mg) was used. This is in line with ICH requirements, as the different dosage strengths are obtained by filling different amounts of microparticles (powder for suspension for injection) into glass vials of the same size and they only differ in the fill weight.

The stability parameters studied were assay, degradation products, appearance of the contents, appearance of the constituted suspension, pH value of the constituted suspension, particle size distribution, molecular mass of the polymer, suspendability, drug burst, drug release, water content and microbial tests. The methods used were the same as those for release and are stability indicating.

All the results from the long term stability study were within the proposed specifications limits. Although some out of specification results were observed they have been attributed to laboratory errors and not to product failure. No difference was observed between inverted and upright storage. Overall the data demonstrate good product stability profile at 5°C/ambient RH.

Under accelerated condition, all chemical and physical data met specification limits except for one result for water content after 3 months of storage in inverted position. After 6 months storage, the water content was within the specifications, but showing variability. In addition, a slight trend for total of degradation products, drug burst and water content towards increasing values was observed.

Additional stability testing was performed on one commercial scale batch stored for up to 6 months at -20°C (inverse storage)/ambient RH and three commercial scale 10 mg stored for up to 6 months at 30°C (inverse storage)/75% RH. All the data generated met specifications in both conditions except the water content after 3 and 6 month under the 30°C/75% RH storage conditions that exceed the specification limit. Additionally, stress studies were carried out at freeze and thaw conditions and included a photostability test, which was carried in one commercial batch in accordance with the ICH Q1B guideline. The results show that the finished product is not sensitive to low temperatures and neither to light.

The stability of the reconstituted suspension was studied on two pilot scale batches after storage of the powder at 5°C/ambient RH for up to 60 months. Following reconstitution, the suspension was kept for 3 hours at room temperature and analysed. The data generated showed that the suspension is stable over the investigated period and supports the SmPC instruction in section 4.2 “Signifor suspension must only be prepared immediately before administration”.

Based on the provided stability data, the proposed shelf life of 36 months when stored at 2°C to 8°C as stated in the SmPC (section 6.3 and 6.4) is acceptable.

Adventitious agents

No excipients of human or animal origin have been used in the manufacture of the finished product Signifor 10 mg and 30 mg powder and solvent for suspension for injection.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

No new information on the active substance has been provided within this line extension application.

The development of the 10 mg and 30 mg strengths was based on the already authorised Signifor 20 mg, 40 mg and 60 mg powder and solvent for suspension for injection. The solvent for these two new strengths is the same used in the already authorised strengths. No further information regarding the manufacture, specifications and stability of the solvent has been presented. All strengths are prepared from the same bulk powder. They only differ in fill weight and flip-off cap. Information on development, manufacture and control of the finished product has been presented in a satisfactory manner. The results of test carried out indicate 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 clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendation for future quality development

None.

2.3. Non-clinical aspects

No non-clinical documentation was provided by the Applicant. Both the indication and the formulation are already approved in the EU for Signifor. This line extension adds two product strengths (10mg and 30mg) to the currently approved product strengths (20mg, 40mg and 60mg), and extends the treatment of the currently approved Cushing’s disease indication to a once-monthly formulation. No additional non-clinical data has been generated, as all relevant non-clinical aspects have already been addressed in the original submission (for the indication) and the previous line extension procedure X-10 (for the formulation). This is acceptable.

2.3.1. Ecotoxicity/environmental risk assessment

According to the guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00 corr 2), an environmental risk assessment (ERA) should be prepared if there is an increase in the environmental exposure. Since the use of the once-monthly intramuscular formulation in Cushing's disease (maximum dose 40mg q28d, i.e. 1.43 mg/day) will target the same indication and population as the currently approved subcutaneous formulation (maximum dose in Cushing's disease: 900mcg bid, i.e. 1.8 mg/day), no increase in environmental exposure relative to the originally submitted ERA for pasireotide diaspartate and pasireotide pamoate is anticipated. Therefore, no new ERA has been submitted. This is acceptable.

2.3.2. Conclusion on non-clinical aspects

There is no objection to an approval of Signifor from a non-clinical point of view.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- **Tabular overview of clinical studies**

Study / purpose / formulation	Description	Patients treated	Status of the study	Clinical study report (Data cut-off or LPLV)
Study G2304 Registration study Pasireotide long-acting formulation	Randomized, double-blind Phase 3 study of pasireotide 10 mg and 30 mg in patients with Cushing's disease, consisting of a 12-month core phase and an open-ended, optional extension.	Total: 150 10 mg q28d: 74 30 mg q28d: 76	Core completed; Extension ongoing	Core analysis at Month 12: [Study G2304] (10-Nov-2015)
Study B2305 Supportive study Pasireotide sc formulation	Randomized, double-blind Phase 3 study of pasireotide sc 600 µg bid and 900 µg bid in patients with Cushing's disease, consisting of a 12-month core phase and an open-ended, optional extension.	Total: 162 600 µg bid: 82 900 µg bid: 80	Completed	Primary analysis: [Study B2305-primary analysis] (17-Mar-2010) Final report: [Study B2305-final analysis] (21-May-2014)

LPLV = last patient last visit

2.4.2. Pharmacokinetics

Introduction

The current submission of pasireotide LAR 10 and 30 mg is primarily based on one pivotal phase 3 study. Supportive data from earlier studies following sc administration for treatment of Cushing's disease and im injection in treatment of patients with acromegaly are also included (Table 1).

Table 1 Overview of phase 3 studies with sparse pharmacokinetic (PK) sampling included in the clinical pharmacology evalaution of pasireotide LAR 10 and 30 mg for treatment of Cushing's disease

Patient	Administration route	Dose	Study no
Cushing's disease	im	10, 30 mg q4w	G2304[b]
Cushing's disease	sc	0.6, 0.9 mg bid	B2305
Acromegaly	im	40 mg q4w	C2305
Acromegaly	im	40, 60 mg q4w	C2402

The Applicant has aimed to achieve similar steady-state exposure after administration of the two starting doses in study G2304 of 10 and 30 mg LAR administered once every 4 weeks as for 300 and 900 µg bid administration of the sc formulation. A similar exposure would allow the extrapolation of data regarding e.g. special populations and drug-drug interactions from the already approved formulations of Signifor.

Pharmacokinetic data

Sparse PK blood samples were taken in the pivotal phase 3 study G2304. PK-samples were taken at the following time points: one blood sample at pre-dose with respect to the LAR intra-muscular injection for each treatment cycle as Ctrough, one blood sample at Day 22 of Month 0, 3 and 6 as Cmax and one blood sample at the end of study treatment as Ctrough. Plasma concentrations of pasireotide were determined with a validated radioimmunoassay (RIA).

Populations Pharmacokinetic Analysis

A population pharmacokinetic (popPK) analysis was undertaken using NONMEM. Development of a base model, i.e., a model without covariates, began with a model previously developed for pasireotide LAR in healthy volunteers and acromegaly patients that accounted for the multiphasic release of pasireotide from the LAR formulation. Sparse sampling could not support estimation of the model's full set of parameters, therefore, absorption parameters were held fixed at their estimates from the previous modeling.

No new information on absorption can be derived from the model and the information on Cmax from is limited. The model's value mainly is to describe the Ctrough values and the model appears adequate for this purpose.

Results

The Ctrough of pasireotide reached an approximately PK steady state after 3 consecutive monthly doses of pasireotide LAR 5 mg, 10 mg, 30 mg and 40 mg in this Cushing's disease patient population, see Table 2 below.

Table 2. Summary of pasireotide Ctrough up to Month 12 by incident doses in study G2304 (PAS).

		Pasireotide							
Day	Month	5 mg (ng/mL)		10 mg (ng/mL)		30 mg (ng/mL)		40 mg (ng/mL)	
		n	Mean (SD)	n	Mean (SD)	N	Mean (SD)	n	Mean (SD)
29	1			65	2.03 (1.25)	64	7.63 (4.58)	-	-
57	2	1	0.83	57	2.35 (1.15)	61	7.82 (4.22)	-	-
85	3	2	1.03 (0.63)	59	2.39 (1.32)	51	8.56 (4.26)	-	-
113	4	3	1.29 (0.237)	51	2.40 (1.11)	49	8.31 (3.87)	-	-
141	5	2	1.04 (0.681)	25	2.47 (0.938)	50	7.88 (4)	20	10.7 (4.91)
169	6	2	2.01 (0.219)	29	2.47 (0.946)	51	8.46 (3.51)	22	12.0 (5.078)
197	7	2	0.72 (0.385)	35	2.88 (1.29)	44	9.13 (4.25)	21	11.9 (5.87)
225	8	3	1.19 (0.429)	22	2.68 (0.975)	28	8.57 (4.7)	34	11.3 (5.18)
253	9	5	1.77 (0.881)	17	2.87 (1.57)	27	9.00 (4.93)	33	12.1 (5.21)
281	10	3	1.24 (0.517)	13	3.36 (1.48)	16	8.18 (4.23)	44	11.4 (5.85)
309	11	1	0.662	23	2.50 (0.988)	19	9.34 (5.61)	43	12.0 (4.58)
337	12	3	1.91 (1.788)	21	3.07 (1.62)	15	8.90 (4.37)	41	12. 6 (6.21)

Note: PK observations with missing concentrations, missing dose, missing elapsed time or an elapsed time from previous injection outside of 28±2 days window were excluded.

The mean Ctrough,ss of 30 mg pasireotide long-acting formulation observed in Study G2304 was 7.88 to 9.34 ng/mL, and it is comparable with the Ctrough,ss of 8.50 ng/mL observed at 900 µg sc bid dose, which was shown to be effective in the Study B2305. The mean Ctrough,ss of the 40 mg pasireotide long-acting formulation observed in Study G2304 was 10.7 to 12.6 ng/mL, and it is higher than the Ctrough,ss observed at 900 µg sc bid dose in the Study B2305. The 10 mg pasireotide yielded a mean Ctrough,ss of 2.40 to 3.36 ng/mL in Study G2304, and it is comparable with 2.80 ng/mL of Ctrough,ss predicted with the 300 µg sc bid dose and with the observed value (ranged from 1.5 to 6.1 ng/mL) from Study B2305 which was shown to maintain response when patients were down-titrated from 600 µg.

The observed mean Cmax at 30 mg ranged from 8.20 to 10.0 ng/mL and the mean Cmax at 40 mg was 12.1 ng/mL, all of which are below the predicted Cmax of 38.5 ng/mL for 600 µg in Cushing patients and observed Cmax of 24.3 ng/mL for 600 µg sc bid dose.

The estimated values of apparent clearance (CL/F) of pasireotide long-acting for typical patients (Cushing disease and acromegaly) and healthy volunteers (based on results from PopPK analysis), are presented in Table 3.

Table 3. Estimated CL/F (L/h) for pasireotide LAR in typical patients and healthy volunteers.

Typical Cushing's Disease Patient		Typical Acromegaly Patient		Typical Healthy Volunteer
Female	Male	Female	Male	Male
Age = 37 y, LBW = 46 kg	Age = 38 y, LBW = 62 kg	Age = 48 y, LBW = 47 kg	Age = 42 y, LBW = 66 kg	Age = 29 y, LBW = 61 kg
4.8	6.5	5.6	8.2	8.4

LBW: lean body weight

Source: This table represents a subset of [Study G2304PopPK Table 6-1]. This table shows only values for the long-acting formulation and where the model was developed on data from the indicated population.

Dose-proportionality was explored for Ctrough,ss (defined as those after the third injection) and Cmax,ss (i.e. C22) of pasireotide by fitting a power model. The point estimate for the slope in dose proportionality analysis was 1.13 (90% CI: 1.08, 1.19) for Ctrough,ss and 0.97 (90% CI: 0.88, 1.06) for Cmax,ss of doses 10 mg to 40 mg.

Special populations

No new data have been submitted in patients with renal or hepatic impairment. Dosage recommendations are based on previous data obtained with pasireotide sc. Gender, race, weight or age were not found to be clinical significant covariates in the popPK model.

Interactions

No additional data were generated for this submission.

2.4.3. Pharmacodynamics

PK/PD analyses evaluated the relationship between pasireotide exposure and response in terms of clinical efficacy and safety in Study G2304.

Mechanism of action

Pasireotide (SOM230), is an injectable cyclohexapeptide analog of natural somatostatin and exerts its pharmacological activity via binding to somatostatin receptors subtypes (SSTR) similar to natural somatostatin and other somatostatin analogs. Five human somatostatin receptor subtypes are known: SSTR 1, 2, 3, 4, and 5. Pasireotide binds with high affinity to four of the five SSTRs (SSTR 1, 2, 3 and 5).

Due to its broad binding profile to somatostatin receptors, pasireotide has the potential to treat diseases characterized by expression of those receptors in the target tissues,such as Cushing'sdisease.

Primary pharmacology

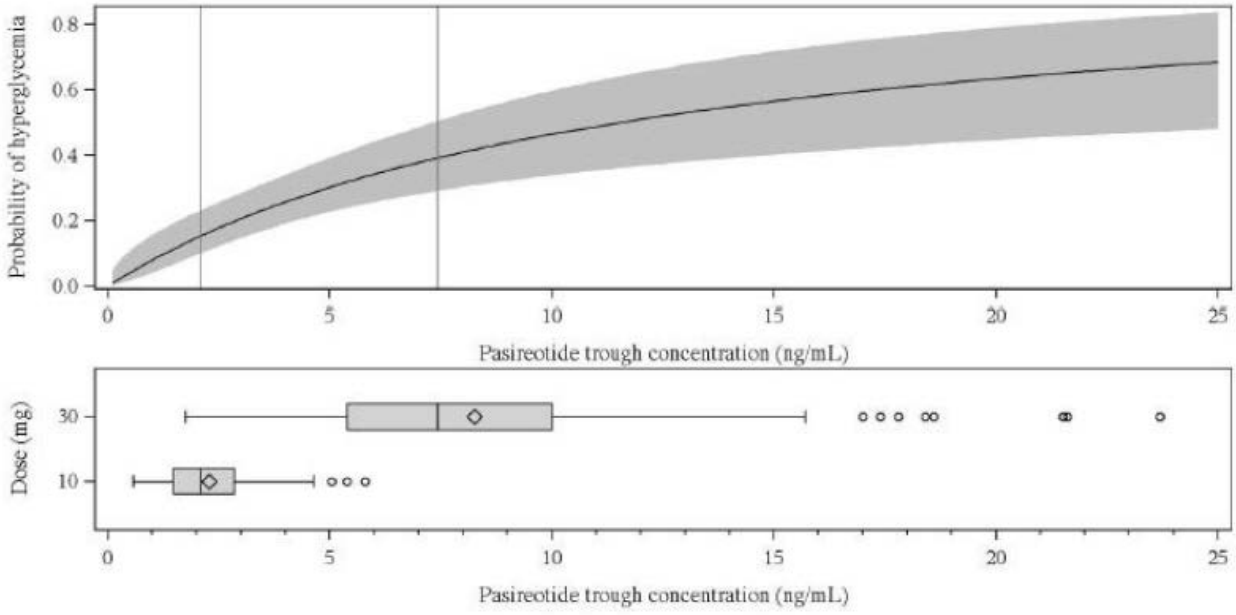
No new data on the pharmacodynamic effect of pasireotide in Cushing's disease have been provided. This is acceptable considering that pasireotide has already been shown to have an effect on the disease when used as subcutaneous injection.

Secondary pharmacology

Hyperglycaemia

The relationship between PK and hyperglycaemia was assessed in several ways. Overall, there was a positive association between $C_{trough,ss}$ and increased probability of developing hyperglycaemia seen across all analyses as exemplified in Figure 2. The risk of developing hyperglycaemia was higher among patients with pre-existing disturbance in glucose metabolism at baseline (i.e. pre-diabetic and diabetic patients).

Figure 1 Repeated measures generalized linear model: pasireotide $C_{trough,ss}$ vs. probability of hyperglycaemia (defined as FPG change from baseline greater than 36 mg/dL) - data up to Month 4 (PAS)



Note: Vertical grey lines represent median Ctrough,ss by incident dose

Cardiac safety: QT intervals

Linear mixed effect model analyses of pasireotide concentration and change from baseline for both QTcF and QTcB suggested a flat, clinically non-significant relationship between pasireotide concentration and change from baseline for both QTcF and QTcB.

Liver safety: hepatic safety parameters

The estimated effect of pasireotide concentration on the hepatic safety parameters aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin (TBIL), gamma-glutamyltransferase (GGT), alkaline phosphatase (ALP) and albumin was investigated based on linear mixed effects models of log-transformed pasireotide concentrations vs. log-transformed laboratory parameters. No clinically significant effects were found between pasireotide concentration and hepatic safety parameters.

Pharmacodynamic interactions with other medicinal products or substances

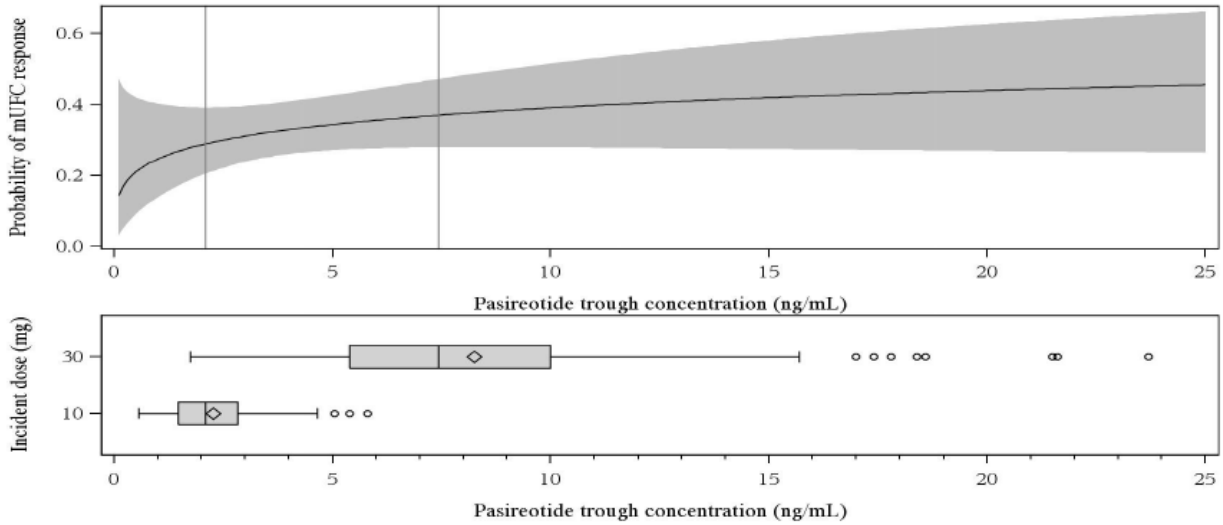
No data on pharmacodynamic interactions have been provided.

Relationship between plasma concentration and effect

The results from two different PK/PD modeling approaches (logistic regression and E_{max} modeling) were consistent, and demonstrated a positive correlation between pasireotide exposure and mUFC response ((i.e. mUFC ≤1.0xULN), and the effect of covariate on the exposure/response relationship). Specifically, the results

from the logistic regression analysis showed that the odds of an mUFC response increased by an estimated 18% for a 3-fold increase in pasireotide $C_{trough,ss}$ (corresponding to a pasireotide dose increased from 10 mg to 30 mg)(Figure 3).

Figure 2 Repeated measures generalized linear model: pasireotide $C_{trough,ss}$ concentrations vs. probability of mUFC response in Study G2304 - data up to Month 4 (PAS)



Vertical lines on the probability plots represent the median concentration at each incident dose.

2.4.4. Discussion on clinical pharmacology

Pharmacokinetics

The pharmacokinetics of pasireotide has previously been investigated in healthy volunteers (sc formulation and LAR), in Cushing's patients (sc formulation) and in acromegaly patients (LAR formulation).

In the current application for two new strengths of pasireotide LAR, 10 mg and 30 mg, pharmacokinetic data has been obtained from sparse sampling in the pivotal phase 3 study in patients with Cushing's disease. This is sufficient given the previous knowledge of the active substance.

The main pharmacokinetic parameters evaluated were Ctrough and plasma concentration at day 22 of months 0, 3 and 6 (C22) which was used as a surrogate for Cmax. Given the large inter-individual variability in the shape of the plasma concentration time profiles previously observed with the LAR formulation, C22 may however not be the true Cmax in all individuals.

Approximate dose-proportionality within the range 10 to 60 mg following single-doses in healthy volunteers has previously been established. In addition, dose-proportionality at steady-state in patients with Cushing's disease was evaluated using sparse sampling in study G2304. Although the results indicate dose-proportionality between 10 and 40 mg for Ctrough,ss and C22,ss the results should be interpreted with caution since the study was not powered to evaluate dose-proportionality.

Mean Ctrough values at steady-state obtained after administration of pasireotide LAR 10-30 mg q4w (study G2304) was approximately comparable to Ctrough,ss obtained after therapeutic doses of pasireotide sc 300-900 µg b.i.d. (study B2305). The 40 mg dose resulted in approximately 30% higher Ctrough concentrations than with the highest recommended sc dose of 900 µg. Since safety has been sufficiently demonstrated for doses up

to 40 mg in the pivotal phase 3 study, this is not a concern. The highest pasireotide LAR dose of 40 mg q4w resulted in C22,ss values which were well below those obtained with 600 µg b.i.d. sc dosing. Even though the use of C22 as a surrogate for Cmax is uncertain, the safety margin between the suggested LAR Cmax and sc Cmax is relatively large. Taken together, the overall plasma exposure at steady state of pasireotide LAR 10-40 mg appears to be approximately comparable to the exposure obtained after therapeutic doses of pasireotide sc. Thus, previous conclusions regarding special populations and drug-drug interactions, from pasireotide sc and pasireotide LAR (acromegaly indication), can be extrapolated to the use of pasireotide LAR in patients with Cushing's disease.

Pharmacodynamics

No new data on the pharmacodynamic effect of pasireotide in Cushing's disease have been provided. This is acceptable considering that pasireotide has already been shown to have an effect on the disease when used as subcutaneous injection.

PK/PD analyses evaluated the relationship between pasireotide exposure and response in terms of clinical efficacy and safety in Study G2304. The data provided indicate a positive exposure/"response" relationship with regards to the risk of developing hyperglycaemia. Notably, pre-existing disturbances in glucose metabolism is an important risk factor for the development of hyperglycaemia. No such correlation with exposure was observed for the risk of QT-prolongation or increases in liver enzymes at the doses investigated.

No data on pharmacodynamic interactions have been provided. Adequate information on pharmacodynamic interactions is included in the SmPC, section 4.5 which is based on the knowledge of the pharmacodynamic effects of pasireotide in combination with the clinical experience in the treatment of both Cushing's disease and acromegaly.

A positive correlation between pasireotide exposure and mUFC response could be demonstrated although the curve is rather flat in the dose range 10 to 30 mg. The odds of mUFC response increased by an estimated 18% whereas the odds of developing hyperglycaemia doubled in this dose range.

2.4.5. Conclusions on clinical pharmacology

The pharmacokinetics has been sufficiently characterised.

The pharmacodynamics of pasireotide has been well characterised.

2.4.6. Clinical efficacy

Dose-response studies and main clinical studies

Dose selection

No dedicated dose-response study was performed. The selection of the two starting doses of pasireotide (10 mg and 30 mg) was based on the following.

The selection of the 30 mg pasireotide dose was guided by PK/PD modelling, which predicted that the C_{trough} at steady-state ($C_{trough,ss}$) would be 10.6 ng/mL in patients with Cushing's disease; this value is slightly higher than the $C_{trough,ss}$ observed clinically with the 900 µg sc bid dose (8.5 ng/mL), which was shown to be effective in Study B2305. The predicted $C_{avg,ss}$ and $AUC_{0\text{-}d28,ss}$ of the 30 mg dose were close to the predicted values of the 900 µg sc bid dose in Study B2305.

The 10 mg pasireotide dose was chosen based on the $C_{trough,ss}$ of 3.5 ng/mL predicted by PK/PD modelling, which was slightly higher than the 2.8 ng/mL $C_{trough,ss}$ observed with the 300 µg sc bid dose in Study B2305. AUC_{ss} and $C_{avg,ss}$ of the 10 mg dose were also close to the corresponding parameters for 300 µg sc bid. The 10 mg dose was expected to offer a better benefit-risk balance in patients with low baseline mUFC; furthermore, the 10 mg dose would allow for a broader dose range together with the 30 mg dose.

Patients whose mUFC was >1.5xULN were up-titrated at month 4 (i.e. at the time steady-state was achieved), unless precluded by safety concerns. Similarly, those randomized to 10 mg were up-titrated to 30 mg, and those randomized to 30 mg were up-titrated to 40 mg, unless precluded by safety concerns. The steady states of AUC, C_{avg}, and C_{trough} predicted for the 40 mg dose were slightly higher than for the 900 µg bid sc dose in Study B2305, and the predicted steady state C_{max} was comparable to the 600 µg bid sc dose. Therefore, the 40 mg dose was considered an appropriate alternative for patients who did not respond to the 30 mg dose.

In Study G2304, a patient's dose could be decreased to a minimum of 5 mg pasireotide in case of tolerability issues.

Considering also the options for dose up-titration and down-titration, the full range of dose levels used in the study was 5 mg to 40 mg, with 10 mg and 30 mg being the starting doses in the study.

Main studies

The efficacy evaluation for this submission is based on the registration Study G2304 (pasireotide long-acting in Cushing's disease). This submission includes data collected up to the cut-off date of 10-Nov-2015, at which time all patients had completed the 12-month Core phase, or discontinued. The study is currently ongoing.

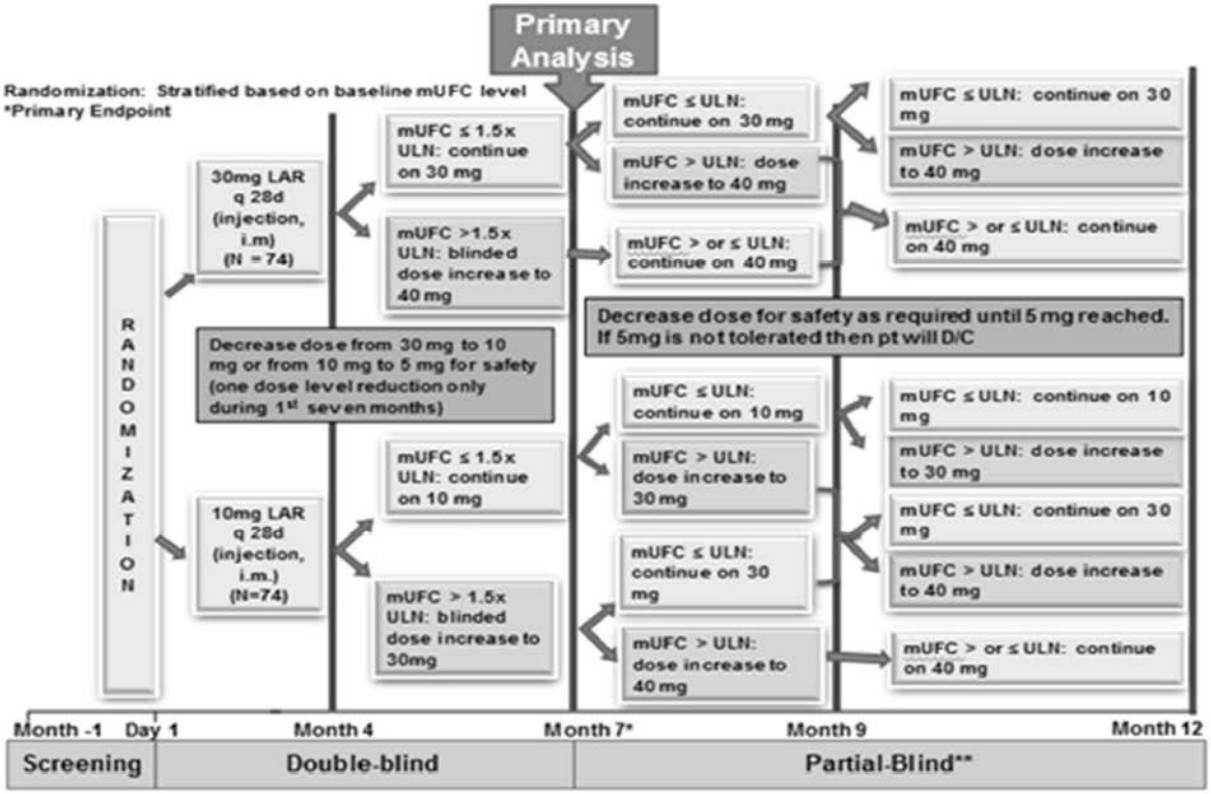
The efficacy of pasireotide in the treatment of Cushing's disease was first established in Study B2305 using the pasireotide s.c. formulation. Data from Study B2305 (including updated long-term data) are also briefly presented in this report to further support the efficacy of pasireotide in Cushing's disease. The original submission for pasireotide sc in Cushing's disease included all data from this study collected up to the cut-off date of 17-Mar-2010, at which time all patients had completed the 12-month core phase or discontinued. The study has now been completed.

Methods

Study G2304

This was a randomized, double-blind Phase 3 study of pasireotide 10 mg and 30 mg in patients with Cushing's disease, consisting of a 12-month core phase and an open-ended, optional extension.

Figure 3 Core phase design scheme



**Patients and Investigators were unblinded to the treatment arm only after the analyses at Month 12. Novartis and applicable vendors were unblinded to treatment arm at the time of the primary analysis at Month 7. See Appendix 16.1.1-Section 6.5.3 for further details.
Dose increases at Months 4, 7 and/or 9 visits were only to occur if there were no safety concerns as determined by the Investigator. Following Amendment 4 all Investigators were unblinded to UFC assessments

Extension phase

After completing the 12-month core phase, patients had the option to continue study treatment in the extension phase, based on the following criteria:

- the patient achieved/maintained mUFC ≤ 1.0xULN at Month 12, or if the patient did not achieve/maintain mUFC ≤ 1.0xULN at Month 12, but received significant clinical benefit in the opinion of the Investigator.
- the patient showed acceptable tolerability to pasireotide LAR treatment

With the implementation of Amendment 5, patients who continued to receive clinical benefit, as assessed by the investigator, could continue in the study after Month 24 (i.e. 12 months of core, and 12 months of extension treatment).

Study participants

Main inclusion criteria

A confirmed diagnosis of ACTH-dependent Cushing's disease was required. Male and female patients aged 18 years or older, with persistent or recurrent disease, or de novo patients who were not considered candidates for pituitary surgery, were eligible for the study.

The following criteria for diagnosis were applied (all three bullet points had to be fulfilled):

- The mean of three 24-hour urine samples collected within two weeks ≥ 1.5xULN and ≤ 5xULN (as determined by the central lab of this study)
- Morning plasma ACTH within the normal or above normal range
- Confirmation of pituitary origin of excess ACTH by at least one of the following three:

a. History of MRI confirmation of pituitary adenoma (greater than 6 mm) with positive dynamic test (e.g. CRH or high dose dexamethasone suppression test)

Or

b. History of inferior petrosal sinus sampling in patients with a tumour less or equal than 6 mm that met any of the following criteria with either CRH or DDAVP (desmopressin) stimulation:

- Central to peripheral ACTH ratio ≥ 2 at Baseline, or
- Central to peripheral ACTH ratio ≥ 3 after stimulation by either CRH or desmopressin

Or

c. Prior pituitary surgery with histopathology confirming an ACTH staining adenoma

For patients on medical treatment for Cushing's disease washout periods were defined which should be completed prior to Screening assessments.

Patients with a known history of impaired fasting glucose or diabetes mellitus (HbA1c <8%) were included; blood glucose and antidiabetic treatment were monitored closely throughout the study and adjusted when necessary.

Main exclusion criteria

Patients who were considered for surgical treatment at the time of study entry or who had received prior pituitary irradiation (≤ 10 years prior to visit 1) were excluded.

In addition, patients with risk factors for torsade de pointes or significant cardiovascular disease, patients with liver disease or cholelithiasis and patients who were hypothyroid were excluded.

Treatments

Pasireotide LAR was administered as an intra-muscular depot intragluteal injection once every 28 days (±2 days) by designated study personnel who were blinded to the treatment. Patients were administered pasireotide LAR 10 mg or 30 mg for four months, followed by either continuation of the starting dose, or dose up-titration (if mUFC was still >1.5xULN unless titration was precluded by safety reasons).

The first dose of pasireotide LAR was given after all Baseline assessments (including mUFC and ECG) were performed at Visit 2. Subsequent doses were to be as close as possible to the same time of day as the first dose.

Dose increases and decreases were allowed as per guidelines in the study protocol.

Objectives

Primary objective

To assess the efficacy of two pasireotide LAR regimens (starting doses of 10 mg and 30 mg followed by up-titration if needed or continuation of the same dose) independently in patients with Cushing's disease after 7 months of treatment regardless of up-titration at Month 4.

Key secondary objective

To assess the efficacy of pasireotide LAR 10 mg and 30 mg doses independently in patients with Cushing's disease after 7 months of treatment who did not up-titrate the dose of pasireotide at Month 4 (patients who had their dose up-titrated were counted as non-responders).

Outcomes/endpoints

Primary efficacy endpoint

Proportion of patients with mUFC ≤ 1.0xULN at Month 7 **regardless** of prior dose increase.

Key secondary endpoint

Proportion of patients with mUFC ≤ 1.0xULN at Month 7 and **no dose increase** above the randomized dose prior to Month 7.

Other secondary endpoints/assessments

Actual and percentage change in mUFC from baseline at every month in the core and every three months in the extension.

Other efficacy assessments included plasma ACTH, serum cortisol, late night salivary cortisol, pituitary tumour volume, and a range of clinical signs of hypercortisolism (including blood pressure and body weight).

Health-related Quality of life (HRQoL) was assessed using two patient -reported outcome (PRO) instruments: the single-domain 12-item Cushing's disease quality of life instrument (CushingQoL) and the SF-12v2 General Health Survey (SF-12v2).

Sample size

In Study B2305 the responder rate (defined as Month 6 mUFC≤ 1.0xULN regardless of dose up-titration) for the 900 µg bid group was 33% for patients with Baseline mUFC≤ 5.0xULN. Since the up-titration criterion in this study is looser than that in Study B2305, the primary efficacy responder rate for each of the two randomized dose regimens in this study was expected to be at least 30%. In addition, a primary efficacy response rate higher than 15% in this indication would provide significant clinical benefit to patients. If the true primary efficacy response rate in each of the randomized dose regimens in this study is 30%, then 74 patients in each arm will provide 88% power for the lower bound of the respective 2-sided 95% CI (Clopper Pearson Exact Method) to exceed 15%. Therefore, a minimum of 148 patients were to be recruited in this study.

Randomisation

Patients were randomized to one of the following two dose arms:

- 10 mg pasireotide LAR = 10 mg dose arm
- 30 mg pasireotide LAR = 30 mg dose arm

Randomization was stratified based on screening mUFC to ensure balanced distribution of disease severity in the two dose arms. There were two strata:

- mUFC 1.5xULN to <2xULN
- mUFC 2xULN to 5xULN.

Blinding

At the sites a pharmacist and/or a study nurse, identified prior to start of the study, was unblinded throughout the study and was the only site personnel allowed to reconstitute the study drug. A field monitor identified by the sponsor prior to the start of the study remained unblinded and was responsible for monitoring the patient dosing records. In addition there was an independent unblinded team within Novartis and the data management vendor.

Patients, Investigators, and site personnel remained blinded to the identity of the treatment arm from the time of randomization until all patients had completed Month 12 or discontinued early.

The UFC was only analysed by the central laboratory identified by the sponsor in order to maintain the blind (in situations where patient safety was of concern, investigators were allowed to run a local UFC for quicker results).

Following the primary analysis which occurred after all patients had completed Month 7 or discontinued early, selected Novartis personal were unblinded to dose arms, while Investigators and patients remained blinded until the analyses performed at Month 12.

Statistical methods

The primary efficacy endpoint in Study G2304 was the proportion of patients that attain mUFC ≤1.0xULN at Month 7 in each treatment arm regardless of prior dose increase; the key secondary endpoint was the proportion of patients that attain a mUFC ≤ 1.0xULN at Month 7 without prior dose increase above their randomized dose. For both analyses, LOCF was used for imputation of missing values at Month 7. A treatment was considered effective if the lower bound of the 95% CI was >15%. To ensure that the overall type I error rate is controlled at 5% 2-sided level, a hierarchical testing procedure was employed.

Response rates over time were analysed by calculating the proportion of controlled and partially controlled responders at each visit. The following definitions were used:

- Controlled responder: mUFC≤ 1.0xULN
- Partially controlled responder: at least 50% reduction in mUFC from Baseline, and mUFC >1.0xULN.
- Controlled or partially controlled responder: either of the above
- Uncontrolled: Neither controlled nor partially controlled.

Other efficacy endpoints related to mUFC included analyses of change in mUFC over time, time to and duration of first mUFC response, probability of response, and maintenance of response.

Plasma ACTH, serum cortisol, late night salivary cortisol levels, pituitary tumour volume, and continuous parameters of clinical signs of hypercortisolism were analysed using descriptive summary statistics at each scheduled visit. Categorical measures of clinical signs of hypercortisolism were analysed using shift tables.

The analysis for both PRO instruments was performed using a subset of patients with baseline and at least one post-baseline measurement. This analysis utilized the previously defined minimally important difference (MID)

for CushingQoL as well as correlations between CushingQoL and SF-12v2 scores, and correlation of CushingQoL with mUFC, blood pressure, weight, and clinical symptoms of Cushing's disease.

Selected efficacy parameters were also analysed by Month 7 responder status (i.e. controlled, partial controlled, and uncontrolled).

Subgroup analyses

Subgroup analyses by gender, race, age (<65 and ≥ 65 years) and BMI categories (<25, 25 to≤ 30, and >30 kg/cm^2) were conducted for the primary efficacy endpoint.

The influence of demographic factors (gender, race), BMI, baseline diabetic status, and mUFC randomization strata was also explored using summary statistics for standardized mUFC over time.

Establishing a new ULN for UFC

To minimize variability in the UFC assessment, all measurements of UFC concentration in urine samples were performed at a central laboratory. The central laboratory also established the reference ranges (ULN and LLN) for UFC based on UFC measurements from healthy volunteers. The ULN established at the start of the study was 171.02 nmol/24h. However, due to an error in the methodology used by the central laboratory to calculate the UFC for the reference range, which was discovered by the Applicant during an audit in November 2014, the ULN initially established at the central laboratory was incorrect. Therefore, a new ULN was established and validated at the central laboratory using the correct methodology.

The new ULN was 166.48 nmol/24h, which is only slightly lower than the original ULN of 171.02 nmol/24h. Because all patients had already been enrolled in the study at the time the error was discovered, patient enrolment and stratification was based on the original ULN.

Dose up-titration was based on the original ULN prior to 24-Jul-2015, by which time all patients had reached Month 7; the new ULN was used to guide dose titration decisions from this date onwards.

Several sensitivity analyses were conducted to assess the impact of the difference between the old ULN and the new ULN on study conduct elements impacted by the change (i.e. enrolment, stratification, dose up-titration prior to 24-Jul-2015) and on statistical analyses using the ULN.

The impact of the error in the original ULN is limited, with ≤ 3 patients impacted in any key parameter of the study. The change in UFC ULN had no impact on the efficacy results of the study.

The statistical analyses described in this document are based on the new ULN.

Study B2305 – study design

Study B2305 independently evaluated the efficacy and safety of two dose regimens of pasireotide sc. Patients were randomized 1:1 to receive pasireotide 600 µg bid or 900 µg bid. A patient's dose could be up-titrated (from 600 µg bid to 900 µg bid, and from 900 µg bid to 1200 µg bid) at pre-specified time points during the Core phase (Months 3, 6, and 9), for patients whose mUFC met specific criteria. A patient's dose could be decreased for safety reasons to a minimum of 300 µg bid; patients who could not tolerate 300 µg bid were to be discontinued from the study.

The efficacy assessments included UFC, other hormonal parameters (plasma ACTH, serum cortisol, and late-night salivary cortisol), clinical signs and symptoms of hypercortisolism, pituitary tumour volume, and HRQoL assessed using the CushingQoL instrument.

The primary efficacy endpoint was the proportion of patients who achieved UFC ≤1.0xULN in each of the pasireotide sc treatment arms at Month 6, and who did not have a dose increase (relative to the randomized dose) prior to Month 6.

The original submission for pasireotide sc in Cushing's disease included all data from Study B2305 collected up to the cut-off date of 17-Mar-2010, at which time all patients had completed the 12-month core phase or discontinued. The study has now been completed, and the data have been reported in an updated CSR.

Results

The sections below focus on the results of the registration study G2304 that was conducted with the pasireotide long-acting formulation.

Results from Study B2305 (conducted with the pasireotide s.c. formulation) are presented as well to provide an overview of efficacy of both formulations of pasireotide in patients with Cushing's disease.

Any between-study comparisons must be made with caution due to several key differences in study design (summarized in Table 7) and patient populations.

Table 4 Design characteristics of Study G2304 and Study B2305 – key differences

Characteristic	Study G2304 Pasireotide long-acting	Study B2305 Pasireotide sc
mUFC at study entry	mUFC ≥ 1.5 xULN and ≤ 5xULN	mUFC ≥ 1.5xULN
Stratification at randomization	Yes, based on screening mUFC	No
Pasireotide starting doses	10 mg q28d and 30 mg q28d	sc 600 µg bid and 900 µg bid
First dose increase allowed and blinding	Allowed at Month 4; blinding is preserved	Allowed at Month 3; patients with dose increase are unblinded
Assay for UFC (ULN)	LCMS/MS (166.48 nmol/24h)	HPLC (145 nmol/24h*)
Calculation of mUFC for key time points	Average of at least 2 of 3 planned 24-hour urine samples collected within 2 weeks	Average of at 3 three out of 4 planned 24-hour urine samples collected within 2 weeks
Efficacy endpoints		
Time point for primary efficacy analysis	Month 7	Month 6
Primary efficacy endpoint	Proportion of patients with mUFC ≤ 1.0xULN at Month 7 **regardless** of prior dose increase	Proportion of patients with mUFC ≤ ULN and **no dose up-titration** above the randomized dose prior to Month 6
Key secondary endpoint	Proportion of patients with mUFC ≤ 1.0xULN at Month 7 and **no dose up-titration** above the randomized dose prior to Month 7	None

HPLC = high pressure liquid chromatography, LCMS/MS = liquid chromatography tandem mass spectrometry, q28d = every 28 days

* from Turpeinen et al 1997

Participant flow

Study G2304

Study G2304 enrolled a total of 150 patients; 74 patients were randomized to the 10 mg arm, and 76 patients to the 30 mg arm. As of the cut-off date (10-Nov-2015), all patients had completed the Core phase or discontinued.

Table 5 Patient disposition (randomized set) - Study G2304

	Pasireotide 10 mg N=74 n (%)	Pasireotide 30 mg N=76 n (%)	All Patients N=150 n (%)
Patients randomized	**74 (100)**	**76 (100)**	**150 (100)**
Treated (entered the Core phase)	**74 (100)**	**76 (100)**	**150 (100)**
Treatment ongoing in Core phase	0	0	0
Early discontinuation during the Core phase	24 (32.4)	22 (28.9)	46 (30.7)
Completed the Core phase (at Month 12)	**50 (67.6)**	**54 (71.1)**	**104 (69.3)**
Completed the Core phase and did not enter the Extension phase	10 (13.5)	13 (17.1)	23 (15.3)
Entered the Extension phase (start at Month 12 visit)	40 (54.1)	41 (53.9)	81 (54.0)
Treatment ongoing in the Extension phase	31 (41.9)	20 (26.3)	51 (34.0)
Early discontinuation during the Extension phase	8 (10.8)	21 (27.6)	29 (19.3)
Completed the Extension phase[a]	**1 (1.4)**	**0**	**1 (0.7)**
Primary reason for early discontinuation (up to data cutoff)[b]	**32 (43.2)**	**43 (56.6)**	**75 (50.0)**
Unsatisfactory therapeutic effect	9 (12.2)	19 (25.0)	28 (18.7)
Patient withdrew consent	12 (16.2)	7 (9.2)	19 (12.7)
Adverse event	8 (10.8)	10 (13.2)	18 (12.0)
Protocol deviation	2 (2.7)	2 (2.6)	4 (2.7)
Administrative problems[c]	1 (1.4)	2 (2.6)	3 (2.0)
Death	0	2 (2.6)	2 (1.3)
Abnormal laboratory value	0	1 (1.3)	1 (0.7)

a.One patient in the 10 mg arm had completed the Month 24 assessment in the Extension phase before protocol amendment 5 was implemented; for this patient, the status is therefore listed as "Completed extension phase" (completed the study). Following the implementation of Amendment 5, patients could continue in the extension beyond Month 24 at the investigator's discretion.
b.Patients who completed the Core phase and did not enter the Extension phase are not counted as discontinuations.
c.The 3 patients were randomized at the same site and were discontinued due to Investigator decision.

Study B2305

In Study B2305, the first patient first visit occurred on 22 -Dec-2006. 162 patients received study treatment (82 patients in the 600 µg bid arm, and 80 patients in the 900 µg bid arm). 78 (48.1%) patients completed the 12-month core phase (39 in each arm), and 58 patients (35.8%) entered the long-term extension (26 in the in the 600 µg bid arm, and 32 in the 900 µg bid arm). During the extension phase, 16 patients had the option to enrol in a long-term study or transition to commercially available pasireotide sc. As of 21-May-2014, all patients were off study treatment, and the study was closed.

Overall the most frequent reason for discontinuation of study drug was unsatisfactory therapeutic effect (53 patients, 32.7%), AE (36 patients, 22.2%), and withdrawal of consent (30 patients, 18.5%), and these reasons were balanced between the two treatment arms. Patients who chose not to enter the extension (20 patients), or who transitioned to a long-term study or commercial pasireotide sc (16 patients), are not counted as discontinuations.

Conduct of the study

The study protocol was amended five times. These five amendments were all implemented before the database lock for the primary efficacy analysis at Month 7, and previous sections of this report describe the study conduct as amended.

Modifications to the analysis plan were made after the Month 7 database lock (at which time key efficacy and safety analyses were conducted, but no CSR was prepared), and prior to the Month 12 database.

Protocol deviations

Twelve (8.0%) patients had protocol deviations that excluded them from the per-protocol analyses. The primarily reason for exclusion from per-protocol set was less than two 24-hour UFC samples available at Screening or at Baseline (Table 9).

Table 6 Protocol deviations leading to exclusion from per-protocol set – All patients randomized

	Pasireotide LAR 10 mg N=74 n (%)	Pasireotide LAR 30 mg N=76 n (%)	All Patients N=150 n(%)
Total	**7 (9.5)**	**5 (6.6)**	**12 (8.0)**
Eligibility criteria deviations	1 (1.4)	2 (2.6)	3 (2.0)
mUFC not ≥ 1.5xULN or ≤ 5xULN at study start or missing mUFC	1 (1.4)	1 (1.3)	2 (1.3)
Washout period of prior medication not observed	0	1 (1.3)	1 (0.7)
Other deviations	6 (8.1)	3 (3.9)	9 (6.0)
Only 1 or no 24-hour UFC measurement at Screening or Baseline[a]	6 (8.1)	3 (3.9)	9 (6.0)

A patient may have multiple protocol deviations
a. Per protocol a minimum of 2 samples were required to calculate mUFC for analysis purposes

Baseline data

Study G2304

Demographic and disease characteristics were generally well balanced in the two dose arms (Table 10).

Table 7 Demographic and disease characteristics in Study G2304 (FAS)

		Pasireotide 10 mg N=74	Pasireotide 30 mg N=76	All patients N=150 n (%)
Age (years)	Mean (SD)	38.3 (12.52)	38.6 (12.99)	38.5 (12.72)
	Median	36.0	37.5	37.0
	Min-Max	20.0-71.0	18.0-66.0	18.0-71.0
Age group – n (%)	<65 years	73 (98.6)	74 (97.4)	147 (98.0)
	≥ 65 years	1 (1.4)	2 (2.6)	3 (2.0)
Gender – n (%)	Female	58 (78.4)	60 (78.9)	118 (78.7)
	Male	16 (21.6)	16 (21.1)	32 (21.3)
Race – n (%)	Caucasian	39 (52.7)	44 (57.9)	83 (55.3)
	Asian	27 (36.5)	24 (31.6)	51 (34.0)
	Black	2 (2.7)	0	2 (1.3)
	Other	6 (8.1)	8 (10.5)	14 (9.3)
Cushing's disease status - n (%)	De novo	15 (20.3)	12 (15.8)	27 (18.0)
	Persistent/recurrent	59 (79.7)	64 (84.2)	123 (82.0)
Baseline mUFC (nmol/24h)	Mean (SD)	462.6 (256.41)	477.1 (331.75)	470.0 (296.08)
	Median	409.8	371.6	396.9
	Min-Max	44.7-1432.9	50.8-1670.0	44.7-1670.0
Baseline diabetic status – n (%)	Diabetic	27 (36.5)	33 (43.4)	60 (40.0)
	Pre-diabetic	12 (16.2)	12 (15.8)	24 (16.0)
	Normal glucose tolerance	35 (47.3)	31 (40.8)	66 (44.0)

Diabetic: patients taking antidiabetic medication or prior history of diabetes mellitus or HbA1c ≥ 6.5% or FPG ≥ 126 mg/dL.
Pre-diabetic: patients not qualifying as diabetic and with 100 mg/dL ≤ FPG<126 mg/dL or 5.7% ≤ HbA1c <6.5%.
Normal glucose tolerance: patients not qualifying as diabetic or pre-diabetic and with FPG <100 mg/dL and/or HbA1c <5.7%

As expected in a patient population with Cushing's disease, patients in Study G2304 were on average hypertensive (a substantial proportion of patients was on anti-hypertensive medication at baseline, and the mean blood pressure was 132/86 mmHg), overweight or obese (mean BMI 29 kg/m2, mean waist circumference 102 cm), and had elevated cholesterol levels (mean 5.7 mmol/L).

Study B2305

The demographic characteristics in Study B2305 were similar to those of Study G2304 in terms of age (median 39 years (range 18 to 71) and gender distribution (women accounted for 77.8% of patients). The study enrolled a higher proportion of Caucasian patients (78.4%); Asians accounted for 12.3% of patients. Similar to G2304, the majority of patients (79.0%) had undergone previous pituitary surgery, and entered the study with persistent/recurrent disease (83.3%).

The baseline mUFC levels were higher in Study B2305 (median mUFC 564.5 nmol/24h; 3.9xULN) than in Study G2304 (median mUFC 396.9 nmol/24h; 2.4xULN), reflecting the difference in enrolment criteria (in Study B2305, no upper limit for a patient's mUFC was imposed). The median baseline mUFC was higher in the 600 µg bid arm (730 nmol/24h; 5.0xULN) than the 900 µg bid arm (487 nmol/24h; 3.4xULN); unlike Study G2304, randomization was not stratified by screening mUFC.

Numbers analysed

Study G2304

All patients randomized (150 patients, 100%) received at least one dose of study medication, and all patients received the dose they were randomized to; as a result, the full analysis set and the safety set were identical. The per-protocol analysis set consisted of patients who did not have major protocol deviations. The PK analysis set (PAS) consisted of all patients in the safety set who had at least one valid post-dose PK assessment (Table 11).

Table 8 Analysis sets - All patients randomized

	Pasireotide LAR 10 mg N=74 n (%)	Pasireotide LAR 30 mg N=76 n (%)	All patients N=150 n (%)
Randomized set	74 (100)	76 (100)	150 (100)
Full analysis set	74 (100)	76 (100)	150 (100)
Stratum 1	25 (33.8)	25 (32.9)	50 (33.3)
Stratum 2	49 (66.2)	51 (67.1)	100 (66.7)
Safety set	74 (100)	76 (100)	150 (100)
Per-protocol set	67 (90.5)	71 (93.4)	138 (92.0)
Pharmacokinetic analysis set	68 (91.9)	72 (94.7)	140 (93.3)
Restricted full analysis set	73 (98.6)	73 (96.1)	146 (97.3)
Restricted per protocol set	67 (90.5)	69 (90.8)	136 (90.7)

Original UFC ULN: 171.02 nmol/24h – New UFC ULN: 166.48 nmol/24h
Stratum 1: patients with Screening mUFC 1.5x original ULN to <2.0x original ULN
Stratum 2: patients with Screening mUFC 2.0x original ULN to 5.0x original ULN
Restricted sets: patients with Screening mUFC 1.5x new ULN to 5.0x new ULN

Outcomes and estimation

Study G2304

- *Primary and key secondary endpoint*

In Study G2304, both the 10 mg and 30 mg dose arms met the primary and key secondary endpoints:

- In the primary efficacy analysis, the response rate at Month 7 was similar in both arms: 41.9% (95% CI: 30.5, 53.9) in the 10 mg arm and 40.8% (95% CI: 29.7, 52.7) in the 30 mg arm.
- In the key secondary efficacy analysis, all patients who had a dose increase prior to Month 7 (31 patients in the 10 mg arm, and 28 patients in the 30 mg arm) were considered non-responders. In this analysis, the response rates were 28.4% (95% CI: 18.5, 40.1) and 31.6% (95% CI: 21.4, 43.3) in the 10 mg and 30 mg arms, respectively.

A treatment was considered effective if the lower bound of the 95% CI was >15%.

Table 9 Proportion of responders at Month 7 (primary efficacy analysis) in Study G2304 (FAS)

	Pasireotide 10 mg n/N (%) 95% CI	Pasireotide 30 mg n/N (%) 95% CI
Primary efficacy analysis (all patients)	31/74 (41.9)	31/76 (40.8)
	30.51,53.94	29.65,52.67
By randomization stratum		
1.5xULN to <2xULN	13/25 (52.0)	13/25 (52.0)
	31.3, 72.2	31.3, 72.2
2xULN to <5xULN	18/49 (36.7)	18/51 (35.3)
	23.4, 51.7	22.4, 49.9

Responders: patients with mUFC ≤ 1.0xULN, regardless of dose-titration.
Missing Month 7 mUFC was imputed using LOCF methodology using last mUFC value at or after Month 4. Month 7 mUFC was imputed for 2 responders in the 10 mg arm, and none in the 30 mg arm.

These results also show that dose up-titration allowed additional patients to achieve a response in the primary efficacy analysis, especially in the 10 mg arm, where 10 of 31 patients (32.3%) who were responders at Month 7 had their dose increased to 30 mg prior to Month 7. In the 30 mg arm, 7 of 31 patients (22.6%) who were responders had their dose increased to 40 mg prior to Month 7.

Furthermore, among the subset of patients who were uncontrolled by Month 4 (27 in the 10 mg arm, and 23 in the 30 mg arm), the proportion of patients who achieved mUFC ≤ 1.0xULN at Month 7 was higher among those whose dose was up-titrated (6/17 patients, 35.3%) and 2/12 patients, 16.7% in the 10 mg and 30 mg arms, respectively) than those who were not (1/10 patients, 10.0% and 1/11 patients, 9.1% in the respective arms).

Pre-planned sensitivity analyses and supportive analyses confirmed that the results are robust. These include analyses of the per-protocol set, sensitivity analyses using alternate methods to account for missing values, and analyses performed without LOCF. Of note, for both the primary and key secondary analysis, a missing Month 7 mUFC value was imputed for 2 responders in the 10 mg arm, and none in the 30 mg arm, thus the influence of missing values on the primary and key secondary efficacy results was minimal.

The response rates in **study G2304** are numerically higher than those reported for the corresponding analyses in **study B2305**:

1. The response rates in the primary efficacy analysis were 14.6% and 26.3% in the 600 µg bid and 900 µg bid arms, respectively, at Month 6. In this analysis, patient with prior dose increase were considered non-responders.
    - this analysis corresponds to the key secondary endpoint in G2304 (response rate 28.4% and 31.6% in the 10 mg and 30 mg arms, respectively)

2. The proportion of patients with mUFC ≤ 1.0xULN regardless of prior dose increase was 15.9% and 28.8% in the 600 µg bid and 900 µg bid arms, respectively, at Month 6
    - this analysis corresponds to the primary efficacy endpoint in G2304 (response rate 41.9% and 40.8% in the 10 mg and 30 mg arms, respectively)

- *Other analyses related to mUFC*

Supportive efficacy analysis

As a supportive analysis for the primary endpoint, the proportion of patients who were controlled (mUFC ≤ 1.0xULN), partially controlled (≥ 50% reduction in mUFC from baseline), or a combination of both were calculated for Month 7 (Table 13). Missing mUFC values were imputed using LOCF.

Table 10 Supportive analysis of primary efficacy analysis in Study G2304 (FAS)

Month 7 response category	**Pasireotide 10 mg**	**Pasireotide 30 mg**
	N=74	**N=76**
	N (%)	**n (%)**
Controlled (primary efficacy analysis)	31 (41.9)	31 (40.8)
Partially controlled	6 (8.1)	12 (15.8)
Controlled or partially controlled	37 (50.0)	43 (56.6)

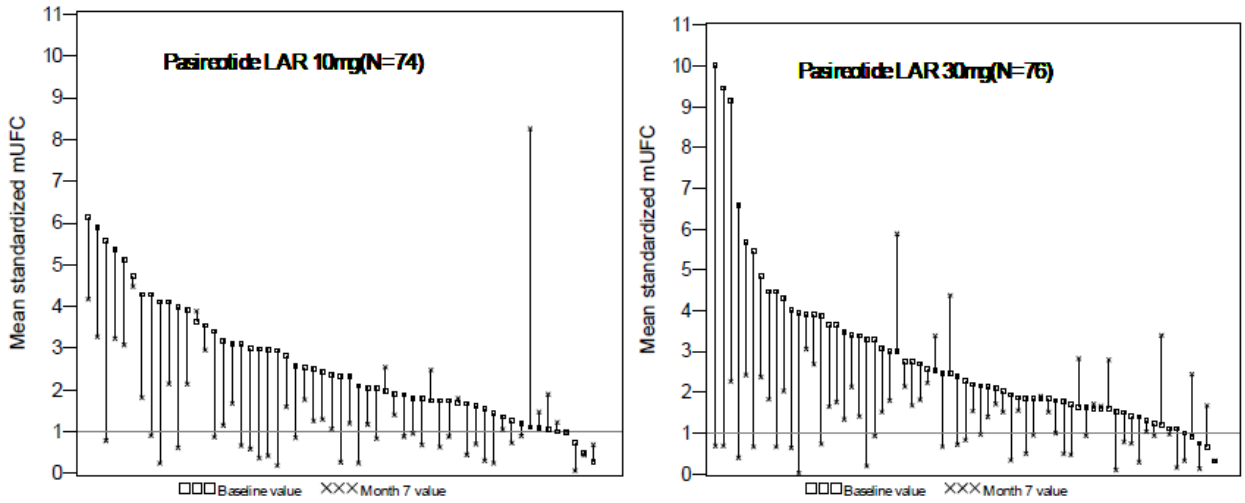
Missing Month 7 mUFC was imputed using LOCF methodology using last mUFC value at or after Month 4.

Response rate and screening/baseline mUFC

In Study G2304, a trend towards higher response rates for patients with lower mUFC levels at study entry was observed: the response rates were higher in the lower mUFC stratum (mUFC 1.5xULN to <2.0xULN), than the higher mUFC stratum (2.0xULN to ≤ 5.0xULN). In the primary efficacy analysis, the response rates in the lower mUFC stratum were 52.0% in both arms, and 36.7% and 35.3% in the 10 mg and 30 mg arms, respectively, in the higher mUFC stratum (see Table 12). In the key secondary efficacy analysis, the response rates in the lower mUFC stratum were 36.0% and 48.0% in the 10 mg and 30 mg arms, respectively, and 24.5% and 23.5% in the respective arms in the higher mUFC stratum,

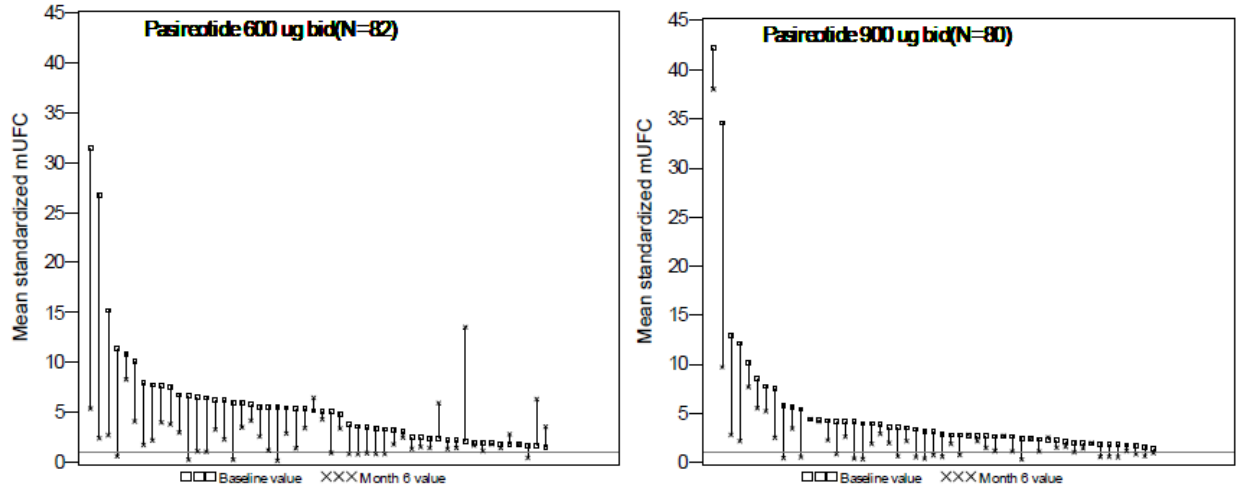
These results are consistent with what was observed in Study B2305, and were as expected considering that for a patient with high baseline mUFC, a relatively larger decrease in mUFC is required to achieve a response. Nevertheless, in both studies, responses were also seen in patients with high baseline mUFC (study G2304, Figure 5; study B2305, Figure 6).

Figure 4 Individual patient standardized mUFC values at Baseline and at Month 7 in Study G2304 (FAS)



The horizontal broken line indicates ULN.
Standardized mUFC = mUFC/ULN, where ULN= 166.48 nmol/24h

Figure 5 Individual patient standardized mUFC values at Baseline and at Month 6 in Study B2305 (FAS)



The horizontal broken line indicates ULN.
Standardized mUFC = mUFC/ULN, where ULN= 145 nmol/24h

Response rates over time

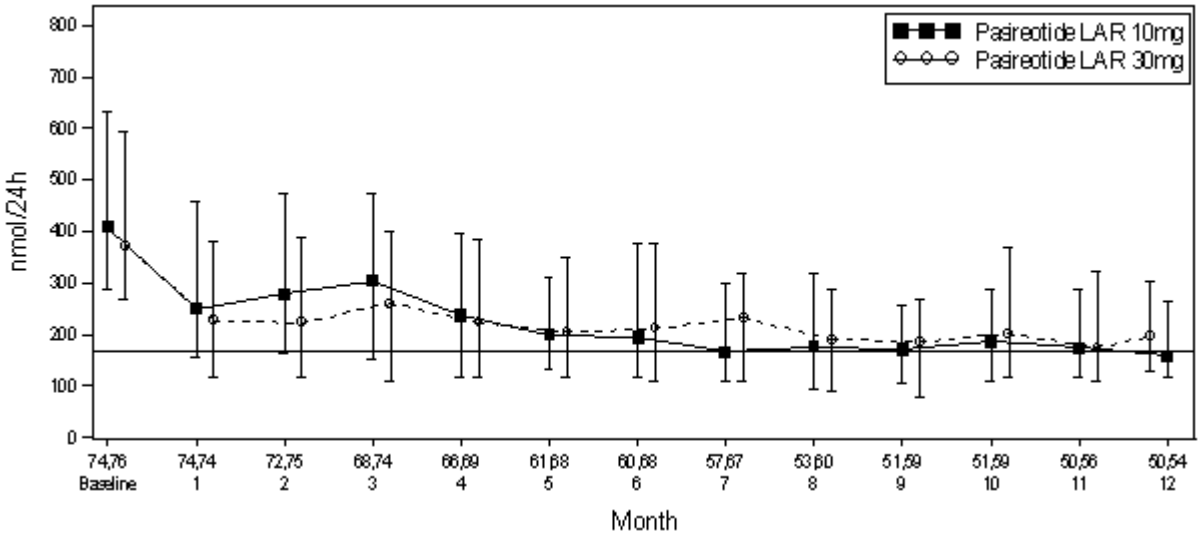
In Study G2304, the proportion of controlled responders (i.e. patients with mUFC ≤1.0xULN) was numerically higher in the 30 mg arm than the 10 mg arm from Month 1 to Month 4 (i.e. before dose up-titration was allowed). At Month 4, the proportion of controlled patients was 31.1% and 36.8% in the 10 mg and 30 mg arms, respectively. After Month 4, the proportion of controlled responders was similar in both arms. The response rates in both arms remained relatively stable over time up to the end of the 12-month core phase.

Change in mUFC levels from baseline

In Study G2304, mean and median mUFC levels decreased within the first month of treatment with pasireotide (Figure 7), consistent with what was observed in Study B2305 with the pasireotide s.c. formulation. At Month 4, the median % decrease in mUFC was 43.3% and 45.3% in the 10 mg and 30 mg arms, respectively. By the time the primary efficacy endpoint was assessed in Study G2304 (Month 7), the median % decrease in mUFC was approximately 48% in both dose arms (Table 14), which is similar to the % median decrease observed in Study B2305 at the corresponding time point (~48%) at Month 6.

In both studies the decrease in mUFC levels was sustained to the end of the 12-month core phase and during the extension phase.

Figure 6 Median (IQR) mUFC (nmol/24h) at time point up to Month 12 in Study G2304 (FAS)



X axis: number of patients in 10/30 mg arms, and scheduled visit timepoint in month.
The dotted line at 166.48 nmol/24h is the ULN for the UFC assay.
IQR=inter-quartile range (25th to 75th percentile)

Table 11 Change from baseline in mUFC in Study G2304 (FAS)

		Pasireotide 10 mg N=74	**Pasireotide 30 mg N=76**
Mean (SD) change in UFC (% from baseline)	Month 7	-29.3% (102.76)	-33.2% (61.37)
	Month 12	-30.3% (79.73)	-31.1% (78.41)
Median (min, max) change in UFC (% from baseline)	Month 7	-47.9% (-94.2, 651.1)	-48.5% (-99.7, 181.7)
	Month 12	-52.5% (-96.9, 332.8)	-51.9% (-98.7, 422.3)

Changes in plasma ACTH and serum cortisol levels from baseline

In Study G2304, baseline mean plasma ACTH levels were 16.3 pmol/L and 15.6 pmol/L in the 10 mg and 30 mg arms, respectively. Mean plasma ACTH levels decreased below baseline levels within the first month of

treatment in both dose arms, and remained below baseline levels thereafter. The mean and median change from baseline were numerically higher in the 30 mg arm at all time points up to Month 4, with no consistent difference observed thereafter up to Month 12 in terms of change from baseline, or mean plasma ACTH levels.

A decrease in mean serum cortisol levels was also apparent within the first month of treatment. Both plasma ACTH and serum cortisol levels remained below baseline levels up to the end of the 12-month core phase.

These results are similar to those seen in Study B2305 for the pasireotide s.c. formulation, where decreases in mean plasma ACTH and serum cortisol levels were observed within the first month of treatment.

Changes in pituitary tumour volume

In Study G2304, reductions in pituitary tumour occurred on pasireotide treatment in both arms. Of the 117 patients who had a visible (assessable by MRI) pituitary tumour at baseline, 33 patients (28.2%) had a reduction (≥ 20%) in pituitary tumour volume at Month 12. Considering only the 73 patients who were assessed for tumour volume both at baseline and at Month 12, the proportion of patients with a ≥ 20% reduction in tumour volume was 45.2% (33/73 patients).

Similar % reductions in pituitary volume were seen in both dose arms. For both arms combined, the % median decrease from baseline was 11.7% at Month 7 (n=90), and 17.2% at Month 12 (n=73). Data from patients in the extension show that pituitary tumour volume continued to decrease, with median % decrease from baseline of 23.3% at Month 18 (n=36), and 25.2% at Month 24 (n=26).

Pituitary tumour volume data were available from a relatively small group of patients in Study B2305, and must therefore be interpreted with caution. In the 600 µg bid arm, analysis of % change from baseline provided clear evidence of tumour shrinkage only after Month 12, whereas in the 900 µg bid arm, pituitary tumour shrinkage was seen from Month 6 onwards.

Changes in clinical signs and symptoms of hypercortisolism

In both dose arms, the decrease in mUFC was paralleled by improvements in clinical signs and symptoms of Cushing's disease, such as SBP, DBP, BMI, waist circumference, weight, LDL, HDL and total cholesterol. The sustained improvement in SBP and DBP may in part be due to improvements in the underlying disease and associated comorbidities, such as obesity, and insulin resistance.

Favourable shifts in categorical parameters were seen as well. At Month 7, the majority of patients had either improvement or no change in all symptoms assessed, compared to baseline (Table 15). Similar results were recorded at Month 12.

Table 12 Patients with improvement or no change in categorical measures of signs and symptoms of Cushing's disease at Month 7 in Study G2304 (FAS)

	Patients with improvement/no change	**Patients with improvement**
	All patients	**All patients**
	n/N (%)	**n/N (%)**
Facial rubor	96/108 (88.9)	47/108 (43.5)
Hirsutism	81/88 (92.0)	23/88 (26.1)

	Patients with improvement / no change All patients n / N (%)	Patients with improvement All patients n / N (%)
Striae	95/107 (88.8)	25/107 (23.4)
Bruising	94/108 (87.0)	21/108 (19.4)
Supraclavicular fat pad	97/108 (89.8)	37/108 (34.3)
Dorsal fat pad	98/107 (91.6)	37/107 (34.6)
Muscle strength	116/122 (95.1)	8/122 (6.6)

In patients who were controlled at Month 7 (i.e. achieved mUFC ≤ 1.0xULN), the improvement in SBP was more pronounced than in patients who were uncontrolled at Month 7. In controlled patients, the mean decrease in SBP at Month 7 was 10.1 mmHg in the 10 mg arm and 8.5 mmHg in the 30 mg arm; in uncontrolled patient, the mean decrease in SBP was 2.3 mmHg and 1.9 mmHg in the respective arms. The improvement in SBP was sustained long term (beyond the 12-month core phase for patients who continued in the extension).

Improvements in body weight (i.e. decrease ≥ 5%) were seen in the 30 mg arm among patients who were controlled at Month 7, with a mean % decrease from baseline in body weight of 7.6% at Month 7, and 9.4% at Month 12. Smaller decreases in mean body weight were seen for uncontrolled patients in the 30 mg arm. The mean % decrease in body weight was smaller in the 10 mg arm for both controlled and uncontrolled patients, compared to those in the 30 mg arm.

Table 13 Patients with at least 5% reduction in supine blood pressure and/or weight - Full analysis set

	Pasireotide LAR 10 mg N=74 n/N (%)	Pasireotide LAR 30 mg N=76 n/N (%)
Supine SBP decrease ≥ 5% from Baseline	58/74 (78.4)	47/75 (62.7)
Supine DBP decrease ≥ 5% from Baseline	47/74 (63.5)	49/75 (65.3)
Weight decrease ≥ 5% from Baseline	46/74 (62.2)	53/75 (70.7)

Total is the number of patients with both Baseline and post Baseline evaluations.
n is the number of patients meeting the criteria at least once.
Baseline is defined as the last available value prior to the first study treatment.
For blood pressure, decrease must occur without an increase in prescribed anti-hypertensive medication.

The results in Study G2304 are consistent with those seen in Study B2305, where similar trends of improvement in continuous measures with decreasing mean mUFC levels were observed as in Study G2304.

Patient-reported outcomes

In Study G2304, the effect of the two pasireotide dosing regimens on patients' quality of life was assessed with the disease-specific patient-reported outcome (PRO) measure CushingQoL, and the generic quality of life

measure SF-12v2. The results for both PRO instruments indicate that patients experienced an improvement in their quality of life with pasireotide treatment. Mean CushingQoL scores improved in both dose arms, similar to what was previously observed in Study B2305. Approximately a third of the patients in both dose arms in Study G2304 had a clinically relevant improvement in CushingQoL scores, defined as a mean change from baseline meeting the established minimal important difference (MID) of 10.1 points. Improvements were seen in the Mental Component Summary (MCS) score of the SF12v2 instrument as well, with the mean change from baseline for both dose arms combined exceeding the established MID of 3.0 points at Month 4 and Month 7.

An association was observed between reduction in mUFC and improvement in SF-12v2 MCS and CushingQoL ($p<0.05$), supporting that improvements in mUFC were associated with benefits in quality of life.

Subgroups of the study population

Subgroup analysis by demographic factors (gender and race) did not reveal any consistent difference in the primary efficacy endpoint between these subgroups in Study G2304.

The study only enrolled 3 patients who were ≥ 65 years of age, however as responses were seen among these patients as well (one patient was controlled, and one patient was partially controlled at Month 7), the data do not indicate any difference in the efficacy of pasireotide in older patients with Cushing's disease.

Ancillary analyses

Long-term use

In both studies, the decrease in mUFC seen during the 12-month core phase of each study was sustained even beyond Month 12 for patients who continued in the extension phase of the respective studies. In Study G2304, the median % decrease in mUFC was 51.9% at the end of the core phase (Month 12, n=104, both arms combined); the median % decrease in mUFC was 65.9% at Month 24 (n=37), and 91.1% in the single patient who had reached the Month 48 visit. The improvements in clinical signs and symptoms of Cushing's disease observed during the 12-month core phase (e.g. systolic and diastolic blood pressure, weight, BMI, waist circumference, and total cholesterol levels) were maintained in patients for whom data are available in the extension.

Table 14 Proportion of controlled or partially controlled responders over time in Study G2304 (FAS)

Visit	Proportion of responders		
	Controlled	Partially controlled	Controlled and partially controlled
	n/N'* (%) 95% CI	n/N'* (%) 95% CI	n/N'* (%) 95% CI
Month 7	60/150 (40.0)	14/150 (9.3)	74/150 (49.3)
	32.10, 48.31	5.20,15.16	41.08,57.61
Month 12	45/150 (30.0)	21/150 (14.0)	66/150 (44.0)
	22.80,38.01	8.88,20.60	35.91,52.33
Month 18	32/110 (29.1)	8/110 (7.3)	40/110 (36.4)
	20.82,38.52	3.19,13.83	27.40,46.08
Month 24	23/99 (23.2)	6/99 (6.1)	29/99 (29.3)
	15.33,32.79	2.26,12.73	20.57,39.29

Controlled responders: patients with mUFC ≤ 1.0xULN. Partially controlled responder: patient whose mUFC >1xULN but decreased by at least 50% from Baseline.
*. N' excludes patients ongoing who had not reached the analysis time point, patients who did not enter the extension phase after completion of core phase, as well as patients who discontinued due to administrative reason. Discontinued patients were considered as non-responders at timepoints following their discontinuation.

Table 15 Proportion of controlled or partially controlled responders over time in Study B2305 (FAS)

Visit	Proportion of responders		
	Controlled	Partially controlled	Controlled and partially controlled
	n/N'* (%) 95% CI	n/N'* (%) 95% CI	n/N'* (%) 95% CI
Month 6	32/162 (19.8)	21/162 (13.0)	53/162 (32.7)
	13.92,26.73	8.21,19.13	25.56,40.52
Month 12	31/162 (19.1)	15/162 (9.3)	46/162 (28.4)
	13.39,26.05	5.28,14.81	21.60,36.00
Month 18	25/142 (17.6)	11/142 (7.7)	36/142 (25.4)
	11.73,24.88	3.93,13.44	18.43,33.33
Month 24	20/142 (14.1)	5/142 (3.5)	25/142 (17.6)
	8.82,20.91	1.15,8.03	11.73,24.88

Controlled responders: patients with mUFC ≤ 1.0xULN. Partially controlled responder: patient whose mUFC >1xULN but decreased by at least 50% from Baseline.
*. N' excludes patients ongoing who had not reached the analysis time point, patients who did not enter the extension phase after completion of core phase, as well as patients who discontinued due to administrative reason. Discontinued patients were considered as non-responders at timepoints following their discontinuation.

Summary of main efficacy results

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 16 Summary of efficacy for trial G2304

Title: A randomized, double-blind, multicenter, phase III study to evaluate the efficacy and safety of pasireotide LAR in patients with Cushing's disease; Month 12 analysis			
Study identifier	CSOM230G2304		
Design	Randomized, double-blind Phase 3 study of pasireotide 10 mg and 30 mg in patients with Cushing's disease, consisting of a 12-month core phase and an open-ended, optional extension.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		12 months not applicable 12 months (ongoing)
Hypothesis	Exploratory: To assess the efficacy of two pasireotide LAR regimens (starting doses of 10 mg and 30 mg followed by up-titration if needed or continuation of the same dose) independently in patients with Cushing's disease after 7 months of treatment		
Treatments groups	Pasireotide 10 mg		12 months, 74 patients randomised
	Pasireotide 30 mg		12 months, 76 patients randomised
Endpoints and definitions	Primary endpoint	Responders regardless of dose-titration	Proportion of patients that attain a mUFC ≤ 1.0xULN at Month 7 regardless of dose titration
	Key secondary endpoint	Responders without dose-titration	Proportion of patients that attain a mUFC ≤ 1.0xULN at Month 7 and had not had a dose increase at Month 4
Database lock	10-Nov-2015 (data cut-off)		
Results and Analysis			
Analysis description	**Primary Analysis**		

Analysis population and time point description	Full analysis set Month 7			
Descriptive statistics and estimate variability	Treatment group	Pasireotide 10 mg	Pasireotide 30 mg	All patients
	Number of subject	74	76	150
	Responders regardless of dose-titration, n (%)	31 (41.9)	31 (40.8)	62 (41.3)
	95% Confidence Interval	30.51, 53.94	29.65, 52.67	33.36, 49.65
	Responders without dose-titration, n (%)	21 (28.4)	24 (31.6)	45(30.0)
	95% Confidence Interval	18.50, 40.05	21.39, 43.25	22.80, 38.01
Notes	No statistical comparison between groups was made. The outcome was considered clinically relevant if the lower 95% CI > than 15%.			

Clinical studies in special populations

Patients with renal impairment and hepatic impairment were not included in study G2304. Thus, no new data in these populations have been provided.

No separate analysis of the results in the elderly age group has been provided since only three subjects in the study were older than 65 years.

2.4.7. Discussion on clinical efficacy

Design and conduct of clinical studies

With this submission, the Applicant has provided data from two clinical trials, of which G2304 is the pivotal study. Study G2304 was a randomized, double-blind Phase 3 study of pasireotide 10 mg and 30 mg in patients with Cushing's disease, consisting of a 12-month core phase and an open-ended, optional extension. Study B2305 used the subcutaneous formulation of pasireotide and was the pivotal study in the MAA for that formulation comparing two different doses of pasireotide. In both studies, up-titration was done at prespecified time-points whereas down-titration was made when necessary for safety reasons. Study B2305 provides supportive data including long-term data up to 60 months in 15 out of originally 153 subjects. The final study report for B2305 has been provided.

No dose-finding study was performed; instead the dose selection was based on PK/PD data from the development program supporting the approval of the s.c. formulation, together with PK data for the long-acting formulation from healthy volunteers. The rationale for dose selection appears adequate and justifies the lack of dose-finding studies. The doses selected (10-40 mg) corresponds to the dose range investigated in study B2305 with regards to exposure to pasireotide.

Study G2304 compared two different doses of pasireotide, i.e. the study design was similar to that applied in study B2305. In line with the CHMP advice, the doses selected were in the lower and upper range of the dosing interval, based on the data from study B2305. The study investigated a dose-range from 10 to 40 mg, with the option to down-titrate the dose to 5 mg for tolerability reasons. Only down-titrations were allowed during the first four months whereas up-titrations were to be made at month 4, 7 or 9 if treatment target was not met. The study duration of 12 months with assessment of the primary endpoint at 7 months is in line with the CHMP advice. Dose titration and the evaluation of the primary endpoint occurred one month later in study G2304 compared to study B2305. The study design and study objectives were adequate and acceptable.

The inclusion criteria were set in order to ensure that patients with Cushing's disease were included. Additional criteria were applied to ensure that patients with pseudo-Cushing patients were not included taking into account the relatively low mUFC limit of ≥ 1.5xULN. Exclusion criteria were mainly focused on excluding patients with conditions that could worsen due to the known safety profile of pasireotide.

The primary and key secondary endpoints were adequate. The key secondary endpoint in study G2304 corresponds to the primary endpoint in study B2305. The remaining secondary and exploratory endpoints were relevant in order to further assess the efficacy of pasireotide.

Sample size calculations were guided by the outcome of study B2305 and are considered adequate. Patients were stratified by severity of the disease in order to ensure a balanced distribution between groups. Patients, investigators, and site personnel remained blinded until all patients had completed month 12. The statistical methods applied were adequate. The use of LOCF for imputation of missing values is considered conservative in this setting.

During an audit, the Applicant discovered an error in the methodology used for establishing the reference ranges (ULN and LLN) for UFC. The difference between the old (171.02 nmol/24h) and the new ULN (166.48 nmol/24h) was small. All patients were enrolled and dosed based on the old ULN up to month 7 of the study. The Applicant investigated the impact of the change in reference range or UFC. With regards to inclusion criteria the change in reference range only resulted in minor errors: a) 2 patients in the high dose group and 1 patient in the low dose group were assigned to the wrong stratum, and b) two patients were included with mUFC > 5xULN. Three patients in the low dose group missed three potential titrations. However, response rates for both the primary and key secondary endpoints remained unchanged thus the change in reference range did not affect the outcome or interpretation of the study.

The protocol was amended five times and all amendments were implemented before the analysis of the primary endpoint. None of the amendments are considered to affect the outcome or the interpretation of the study. The changes made to the analysis plan did not have any impact on the primary or key secondary endpoints.

The FAS included all randomised patients. Twelve patients (8 %) were excluded from the PP set due to protocol violations. Out of these twelve patients, two patients (one in each group) were stated to have violated the inclusion criterion of mUFC ≥1.5xULN or ≤5xULN and nine patients had only 1 or no 24-hour UFC measurement at screening or baseline.

Efficacy data and additional analyses

The population recruited in study G2304 appears representative of the target population. The majority of patients were female and only three patients were older than 65 years. More than 80% of patients had recurrent of persisting disease. There were no major imbalances between the groups.

The demographics of the patients included in study G2304 were comparable to those included in study B2305, except that in study B2305 no upper limit was imposed for mUFC (patients whose mUFC was ≥ 1.5xULN were eligible) which resulted in a higher mUFC in study B2305 compared to study G2304. This indicates that the population in study B2305 had more severe disease than the population included in study G2304.

The proportion of patients who discontinued was comparable between dose groups (about 30% in the core phase of the study) and the number of patients who entered the extension phase was similar (40 and 41 patients). The reasons for discontinuation however differed with a higher proportion that discontinued due to lack of efficacy in the high dose group (25% vs 12% in the low dose group). This is somewhat unexpected, especially since the mUFC was slightly lower in the 30 mg group compared to the 10 mg group. Discontinuation due to AEs only marginally differed, whereas more patients discontinued due to withdrawal of consent in the low dose group (16% vs 10% in the high dose group). In study B2305 the discontinuation rates and reasons for discontinuation were comparable to those observed in study G2304.

There was no difference between groups with regards to the outcome of the primary endpoint with 42% responders in the low dose group and 41% responders in the high dose group. This may at least partially be explained by the fact that 24% of patients in the 10 mg group had been up-titrated to 40 mg at month 7, compared to 53% of patients in the 30 mg group. Thus dose-titration did recruit more responders since the response rates were lower for the key secondary endpoint, with numerically more responders in the 30 mg dose group (32% vs 28%). The response rate was higher in the stratum with lower mUFC (52% in both groups). These data suggests that the dose titration scheme implemented in the study is effective. Response rates remained stable up to 12 months, indicating that the efficacy of pasireotide is maintained long term.

Higher response rates were observed in study G2304 than in study B2305 where the response rate (NB in patients without up-titration) was 14.6 % and 26.3 % in the 600 µg bid and 900 µg bid arms, respectively. It should however be taken into account that study B2305 recruited patients with higher mUFC at baseline than did study G2304.

The proportion of patients partially controlled was higher in the 30 mg dose group (15.8% vs 8.1% in the low dose group) resulting in a higher proportion of patients controlled or partially controlled in this group (56.6% vs 50% for the 30 mg and 10 mg group, respectively).

Individual data on the change in mUFC for both study G2304 and study B2305 have been presented. These data show that patients in study G2304 in general had a lower mUFC than patients in study B2305. The vast majority showed a decrease in mUFC, but some patients apparently failed on therapy as shown by increased mUFC levels. This finding high-light the importance of monitoring the effect and reconsider treatment in case of treatment failure. This has been adequately reflected in the SmPC,.

The individual data also show that about 5-6 patients in both groups had a mUFC well above 5xULN at baseline. Inclusion was based on mUFC at screening and some patients had been on cortisol-lowering therapy. Therefore further increase in mUFC could possibly be expected between screening and baseline in such patients after the wash-out period. It is noteworthy that, although lower baseline mUFC was associated with a higher response rate, 1 out of 5 patients in the 10 mg group and 4 out of 6 patients in the 30 mg group with a baseline mUFC >

5xULN were responders at month 7 indicating that treatment success is not only due to the mUFC at treatment initiation.

However, notably three patients in the 10 mg group and four in the 30 mg group appear to have had mUFC < 1 at baseline and about 12 patients in the low dose group and about 10 patients in the high dose group appear to have had a mUFC < 1.5xULN at baseline. All these patients fulfilled the inclusion criteria (mUFC at screening). A scatter plot for the screening and baseline values shows that the intrasubject variation is high, with patients both showing higher and lower mUFC at baseline compared to screening. This may in part be explained by the difficulties associated with the collection of (three) 24-hour urine samples. The Applicant has provided additional analyses where patients with a baseline mUFC <1.5xULN were a) excluded or b) considered as non-responders. Exclusion of patients (a) from the analysis resulted in an about 2% reduction in response rates compared to the primary analysis for the primary and key secondary endpoints. When the most conservative analysis (b) was applied, a 10% reduction in the response rate was observed. The physician's decision to treat a patient would possibly be based not only on a (high) pathological UFC but also on the severity of disease symptoms, it is therefore agreed that the protocol-prespecified analysis is the most accurate way to present the data.

The mUFC levels decreased within the first month of treatment and continued to decrease up to month 7 after which the levels remained stable in patients remaining in the study up to month 12. The changes observed for ACTH and s-cortisol were consistent with the changes observed for mUFC. No apparent differences were observed between the two doses.

Change in pituitary tumour volume was an exploratory endpoint and 117 patient had a visible tumour at baseline and 73 of these patients had tumour volume assessed both at baseline and at Month 12. Out of these 73 patients, 33 (45.2%) showed a reduction of tumour volume greater than 20%.

The majority of patients reported stable or improved signs and symptoms of hypercortisolism and about 30% reported an improvement of symptoms. A decrease in SBP was also observed, with the largest decrease observed in controlled patients. A decrease of ≥ 5% was reported by 78% in the 10 mg group and 63% in the 30 mg group. The change was sustained throughout the study. Improvements in body weight (particularly those in the 30 mg arm among patients who were controlled at month 7) were also observed. In the 10 mg group and the 30 mg group respectively, 62% and 71% of patients reported weight decrease of ≥ 5%.

Data from the patient-reported outcome (PRO) measure CushingQoL, and the generic quality of life measure SF-12v2 showed that clinically relevant improvements, defined as changes exceeding the MID, were achieved for both instruments.

Subgroup analyses did not show any apparent differences when data was analysed by sex and race. The response rate was low in the subgroup of males in the 30 mg group, but the number of patients was low, making the estimates uncertain.

Long-term data from the extension of study G2304 is still not complete but support that the effect is maintained in a relevant proportion of patients. These data are supported by the data from study B2305, although it should be noted that the number of patients remaining in the study was very low (16 subjects still ongoing at study closure). In study G2304, at the end of the core phase (i.e. month 12), the proportion of controlled and partially controlled responders was 44.0% (66/150) for both dose arms combined. At month 24, 29.3% of patients (29/99) were controlled or partially controlled responders.

2.4.8. Conclusions on clinical efficacy

Based on the data from study G2304 it can be concluded that long-acting pasireotide (LAR) is efficient in the treatment of Cushing's disease. Although comparisons should be made with caution due to differences in study design and the severity of the disease in the populations included, the effect of pasireotide LAR appears comparable to that of the s.c. formulation. Secondary and exploratory endpoints support the conclusion. Some data has been provided from the ongoing extension phase of study G2304, indicating that the effect is maintained in a relevant proportion of patients up to 24 months.

Currently s.c. pasireotide is approved for treatment of Cushing's disease. With the LAR formulation also approved in this indication, there is a need for recommendations on how to switch from the s.c. formulation to the LAR formulation and vice versa (although the later alternative may be less common). Advice on this has been included in the SmPC.

2.4.9. Clinical safety

In this submission, safety data for pasireotide long-acting formulation in Cushing's disease are available from study SOM230G2304 (hereafter G2304). This submission also includes important safety information from the supportive studies B2305 (which formed the basis of approval of the pasireotide s.c. formulation in Cushing's disease), C2305 and C2402 (which both supported the approval of the long-acting formulation of pasireotide in acromegaly (Table 17).

Study G2304 comprises a 12-month core phase (followed by an optional extension phase). Patients started treatment with either 10 mg or 30 mg pasireotide, followed by dose up-titration (to maximum 40 mg) or continuation of the starting dose after the first 4 months of treatment.

The primary analysis for Study B2305 was conducted when all patients had completed at least 12 months of treatment or discontinued (data cut-off, 17-Mar-2010). Additionally, long-term data from Study B2305, including all data from study start to last patient last visit (data cut-off, 21-May-2014), were reported in a final CSR which is provided as part of this submission.

The primary analysis of study C2305 was conducted when all patients had completed at least 26 months of treatment or discontinued (data cut-off, 29-Dec-2011). In this SCS, the focus is on patients who started treatment with pasireotide from the beginning of the core phase up to at least 12-Month of core phase or early discontinuation (up to crossover).

Table 17 Overview of key studies for the safety analysis and their status

Study / purpose / formulation	Study Objective and Population	Number of treated patients	Status	Clinical study report (Data cut-off or LPLV)
Studies in patients with Cushing's Disease				
G2304 Registration study Pasireotide long-acting in Cushing's disease	Randomized, double-blind Phase III study of pasireotide 10 mg and 30 mg in patients with Cushing's disease, consisting of a 12-month core phase and an optional extension.	Total: 150 10 mg: 74 30 mg: 76	Core completed; extension ongoing	Primary analysis (Month 12): [Study G2304] (10-Nov-2015)
B2305 Supportive; long-term efficacy and safety Pasireotide sc in Cushing's disease	Randomized, double-blind Phase III study of pasireotide sc 600 µg bid and 900 µg bid in patients with Cushing's disease, consisting of a 12-month core phase and an, optional extension.	Total: 162 600 µg bid: 82 900 µg bid: 80	Core and extension completed	Primary analysis (Month 12): [Study B2305-primary analysis] (17-Mar-2010) Final report: [Study B2305-final analysis] (21-May-2014)
Studies in Acromegaly Patients				
C2305 Supportive Pasireotide long-acting in acromegaly.	Randomized, active-controlled, blinded, Phase III study of pasireotide vs. octreotide in patients with acromegaly, consisting of a 12 month core phase and an optional extension	Total: core/extension up to cross over*: Pasireotide : 178 Octreotide; 180 Extension after crossover: Pasireotide: 81 Octreotide: 38	Core and extension completed	Primary analysis (Month 26)**: [Study C2305-primary analysis] (29-Dec-2011)
C2402 Supportive Pasireotide long-acting in acromegaly	Randomized, parallel-group, double-blind, phase III study of pasireotide 40 mg and pasireotide 60 mg versus open-label octreotide or lanreotide ATG in patients with inadequately controlled acromegaly	Total: Pasireotide 40 mg : 65 Pasireotide 60 mg: 65 Active control: 68	Core completed, extension ongoing	Primary analysis (24-weeks): [Study C2402-primary analysis] (22-Jan-2013)

*Up to crossover: refers to data from both core and extension up to data cut-off collected for patients who continued the same treatment as in the core. For patients who crossed over in the extension, includes only data collected before crossover.

**The cut-off for the analysis presented in the CSR was at Month 26. For the analyses generated for this SCS, a cut-off was applied at Month 12.

LPLV = last patient last visit

Patient exposure

In study G2304, exposure of pasireotide LAR in Cushing's disease is available in 150 subjects in doses from 5 mg up to 40 mg (Table 5). Supportive safety data in on use with pasireotide (s.c.) in Cushing's disease is available in 162 subjects in study B2305. Supportive data for use of pasireotide LAR is available from the (pivotal) studies

in approximately 400 Acromegaly patients (C2305 and C2402) (Table 5). Besides the submitted data a considerable number of patients, with different diagnosis, have been exposed to pasireotide in clinical trials. Data from the latest PSUR (DLP 24 Oct 2016) presented an overall exposure of pasireotide in 4036 patients (2779 PYE) in clinical trials (completed, ongoing and IITs).

Dosage

At Month 4, approximately half of the patients in both groups received their randomization dose. In both groups, more than 40% of the patients were up-titrated to a higher dose (Month 4). At Month 12, 27.5% and 17.1% of the patients in the 10 mg group and 30 mg group respectively received their randomization dose. At month 12, 70.7% and 60% of patients in the 30mg group and 10mg group respectively, were up-titrated. The maximum dose (40 mg) was received by 40-50% of all patients from Month 7 to Month 12. Thus safety and tolerability could be judged as have been sufficiently studied also in this population (Table 18).

The doses used in study G2304 result in an exposure to pasireotide which is comparable to the exposure achieved with the doses used with the s.c. formulation (600 µg and 900µg) in subjects with Cushing's disease (see Efficacy section). However, the doses used in study G2304 are lower compared to doses used with the LAR formulation in the clinical study with acromegaly subjects in study C2305 and C2402 (40 mg and 60 mg).

Table 18 Dose administrated in study G2304 (Safety set)

	Pasireotide LAR 10 mg	Pasireotide LAR 30 mg	All patients
	N (patients who completed the visit) n (%)		
Baseline	**74**	**76**	**150**
Received 10 mg	74 (100)	0	74 (49.3)
Received 30 mg	0	76 (100)	76 (50.7)
Month 1	**73**	**75**	**148**
Received 0 mg	0	1 (1.3)	1 (0.7)
Received 5 mg	1 (1.4)	0	1 (0.7)
Received 10 mg	72 (98.6)	3 (4.0)	75 (50.7)
Received 30 mg	0	71 (94.7)	71 (48.0)
Month 4	**65**	**69**	**134**
Received 5 mg	2 (3.1)	0	2 (1.5)
Received 10 mg	32 (49.2)	8 (11.6)	40 (29.9)
Received 30 mg	31 (47.7)	33 (47.8)	64 (47.8)
Received 40 mg	0	28 (40.6)	28 (20.9)
Month 7	**54**	**62**	**116**
Received 0 mg	0	3 (4.8)	3 (2.6)
Received 5 mg	3 (5.6)	0	3 (2.6)
Received 10 mg	22 (40.7)	6 (9.7)	28 (24.1)
Received 30 mg	16 (29.6)	20 (32.3)	36 (31.0)
Received 40 mg	13 (24.1)	33 (53.2)	46 (39.7)
Month 9	**52**	**60**	**112**
Received 0 mg	2 (3.8)	2 (3.3)	4 (3.6)
Received 5 mg	3 (5.8)	1 (1.7)	4 (3.6)
Received 10 mg	18 (34.6)	6 (10.0)	24 (21.4)
Received 30 mg	12 (23.1)	14 (23.3)	26 (23.2)
Received 40 mg	17 (32.7)	37 (61.7)	54 (48.2)
Month 12	**40**	**41**	**81**
Received 5 mg	5 (12.5)	1 (2.4)	6 (7.4)
Received 10 mg	11 (27.5)	4 (9.8)	15 (18.5)
Received 30 mg	13 (32.5)	7 (17.1)	20 (24.7)
Received 40 mg	11 (27.5)	29 (70.7)	40 (49.4)

Duration of exposure

In study G2304, the median number of injections was 14.5 (1-50). Median duration of exposure in days was 398 (28-1393) days. Exposure up-to 12 months was seen in 81/150 (54%) of the patients and up-to 36 months in 11/150 (7%).

In the final analysis of study B2305, median duration of treatment with pasireotide sc was 10.37 months (minimum-maximum: 0.03-76.6 months). 40 (24.7%), 22 (13.6%), 18 (11.1%), 14 (8.6%) and 6 (3.7%) patients had been treated with pasireotide s.c. for at least 24, 36, 48, 60, and 72 months, respectively.

Overall, a robust safety dataset is available both with the s.c. and LAR formulation up to 12 months, considering that both Cushing's disease and acromegaly are rare diseases. Data beyond 12 months have also been presented for the s.c. formulation by the final analysis of study B2305 and results from the extension of study G2304 will provide further long-term data.

Adverse events

Common adverse events

In study G2304, almost all patients (99.3%) reported at least one AE. In total, 93.3% of the patients experiencing AEs suspected to be related to pasireotide. The proportion of patients with AEs leading to study discontinuation was 12.7%. The overall during the 12 Months the most common AEs were *hyperglycaemia* (48.0%), *diarrhoea* (39.3%) and *cholelithiasis* (32.7%). *Diabetes mellitus* was reported in 21.3% (Table 19). All these events were also the most frequently events reported by the investigator as possible related to study drug (Table 20).

Table 19 Common AEs (more than 10% in study G2304) by preferred term compared to frequencies in study B2305 and C2305

	Study G2304 All Patients N=150 n (%)		Study B2305 All Patients N=162 n (%)		Study C2305 Pasireotide N=178 n (%)	
	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4
Total	**149 (99.3)**	**86 (57.3)**	**159 (98.1)**	**80 (49.4)**	**169 (94.9)**	**55 (30.9)**
Hyperglycemia	72 (48.0)	9 (6.0)	65 (40.1)	20 (12.3)	53 (29.8)	6 (3.4)
Diarrhoea	59 (39.3)	0	92 (56.8)	5 (3.1)	70 (39.3)	1 (0.6)
Cholelithiasis	49 (32.7)	4 (2.7)	49 (30.2)	2 (1.2)	52 (29.2)	1 (0.6)
Diabetes mellitus	32 (21.3)	24 (16.0)	31 (19.1)	14 (8.6)	39 (21.9)	9 (5.1)
Nausea	31 (20.7)	1 (0.7)	84 (51.9)	4 (2.5)	25 (14.0)	1 (0.6)
Headache	28 (18.7)	1 (0.7)	46 (28.4)	3 (1.9)	36 (20.2)	2 (1.1)
Nasopharyngitis	28 (18.7)	0	21 (13.0)	0	30 (16.9)	0
Fatigue	26 (17.3)	0	31 (19.1)	3 (1.9)	18 (10.1)	1 (0.6)
Abdominal pain	22 (14.7)	2 (1.3)	39 (24.1)	3 (1.9)	33 (18.5)	1 (0.6)
Hypertension	22 (14.7)	14 (9.3)	16 (9.9)	0	18 (10.1)	2 (1.1)
Hypoglycemia	21 (14.0)	4 (2.7)	15 (9.3)	3 (1.9)	10 (5.6)	0
Oedema peripheral	21 (14.0)	0	13 (8.0)	0	7 (3.9)	0
Influenza	18 (12.0)	0	14 (8.6)	0	15 (8.4)	1 (0.6)
Dizziness	17 (11.3)	1 (0.7)	15 (9.3)	2 (1.2)	21 (11.8)	0
Urinary tract infection	17 (11.3)	0	6 (3.7)	0	9 (5.1)	1 (0.6)
Asthenia	15 (10.0)	0	19 (11.7)	4 (2.5)	1 (0.6)	0
Back pain	15 (10.0)	0	10 (6.2)	2 (1.2)	19 (10.7)	0

Table 20 Frequents AEs (more than 10% in study G2304) suspected to be study drug related compared to study B2305 and C2305

Preferred term	Study G2304 All Patients N=150 n (%)	Study B2305 All Patients N=162 n (%)	Study C2305 Pasireotide N=178 n (%)
Total	**140 (93.3)**	**155 (95.7)**	**150 (84.3)**
Hyperglycaemia	70 (46.7)	63 (38.9)	49 (27.5)
Diarrhoea	48 (32.0)	87 (53.7)	58 (32.6)
Cholelithiasis	47 (31.3)	48 (29.6)	49 (27.5)
Diabetes mellitus	31 (20.7)	31 (19.1)	34 (19.1)
Nausea	22 (14.7)	76 (46.9)	15 (8.4)
Abdominal pain	17 (11.3)	33 (20.4)	23 (12.9)
Fatigue	15 (10.0)	19 (11.7)	8 (4.5)

Dose differences

The largest difference in AE frequencies, between the two treatment-groups (starting dose 10 mg and 30 mg respectively), was noted for the common reactions *cholelithiasis* and *diarrhoea* both at Month 4 and after 12 months. Events of *hyperglycaemia* and *diabetes mellitus* were reported in slightly higher frequency in the 30 mg group at Month 4 but in comparable frequencies after 12 months and events of *headache* were reported more frequently in the 10 mg group compared to the 30 mg group both after 4 and 12 months). The frequencies of events judged as severe and/or life-threatening were slightly higher at Month 4 in the 30 mg group (30.3%) compared to 10 mg group (21.6%) but reported in comparable frequencies after 12 months. As discussed above, it should be noted that after Month 4 the doses were adjusted to treatment effect, both in the 10 mg and 30 mg groups, making a direct comparison between the two treatment groups difficult to perform after this visit.

Cushing's disease: pasireotide LAR compared (G2304) to s.c. pasireotide (B2305)

Events from the SOC GI disorders such as *diarrhoea, nausea* and *abdominal pain* were reported with less frequency with the LAR formulation (SOC GI disorders study G2304: 63%) compared to the s.c formulation (SOC GI disorders study B2305: 81%). Events from the SOC metabolism and nutrition disorders such as *hyperglycaemia* and *diabetes mellitus* (82% in study G2304 and 75% in study B2305) as well as events of *cholelithiasis* (33% in study G2304 and 30% in study B2305) were presented in comparable frequencies with the LAR formulation compared to s.c. formulation in patients with Cushing's disease (Table 19).

Pasireotide LAR: use in Cushing's disease G2304) compared to use in Acromegaly (C2305)

Events from the SOC metabolism and nutrition disorders such as *hyperglycaemia* were presented with higher frequencies in the population with Cushing´s disease (82% in study G2304) compared to the acromegaly population (61% in study C2305). However, frequencies events from the SOC GI disorders (63% in both studies) and *cholelithiasis* (33% in study G2304 and 29% in study C2305) were reported in comparable frequencies between the two indications treated with pasireotide LAR.

As a conservative approach, no term frequencies have been decreased in the proposed SmPC (e.g., QT prolongation which was uncommon in G2304 is maintained as "common" in the combined table), and no terms were removed. All 22 terms that were already present in the acromegaly SmPC have been maintained. For two terms (nausea and the grouped term abdominal pain), the ADR frequency category was higher in the G2304 study (14.7% and 11.3%, respectively) and the higher overall frequency category was therefore assigned in the

grouped table for both terms (“very common” instead of “common”). While some minor differences in underlying disease-related morbidities is acknowledged, no adverse drug reaction frequencies diverged sufficiently between indications to warrant a footnote in the table.

For all other terms that were previously not present in the acromegaly SmPC, a three-step approach has been adopted to update the ADR table for the intramuscular formulation with the findings of study G2304, as described by the Applicant in the clinical overview.

AEs suspected to be drug related

In study G2304, *Hyperglycaemia, diarrhoea, cholelithiasis* and *diabetes mellitus* were the most common AEs judged with a causal relationship to study drug by the investigator (Table 20).

When comparing the studies in subjects with Cushing’s disease on pasireotide LAR (G2304) with s.c. pasireotide (B2305) events of *hyperglycaemia* were reported with a slightly higher frequency compared to s.c. formulation and GI events (*diarrhoea, nausea* and *abdominal pain)* with lower frequencies (Table 20).

When comparing the studies in subjects with Cushing’s disease on pasireotide LAR (G2304) with pasireotide LAR in Acromegaly (C2305) events of *hyperglycaemia, nausea and fatigue* were reported in higher frequencies compared to the Acromegaly population.

Adverse events of special interest (AESI)

Thirteen categories of AESI were defined in the clinical development program for pasireotide (Table 21).

Table 21 Overview of AESI by categories in study G2304, B2305 and C2305

	G2304 All patients N=150 n (%)		B2305 All patients N=162 n (%)		C2305 Pasireotide N=178 n (%)	
	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4
Hyperglycemia related AEs	115 (76.7)	35 (23.3)	116 (71.6)	39 (24.1)	107 (60.1)	16 (9.0)
Gallbladder and biliary related AEs	52 (34.7)	6 (4.0)	56 (34.6)	4 (2.5)	64 (36.0)	3 (1.7)
Liver safety related AEs	30 (20.0)	11 (7.3)	26 (16.0)	7 (4.3)	19 (10.7)	2 (1.1)
Bradycardia related AEs	13 (8.7)	0	22 (13.6)	3 (1.9)	26 (14.6)	0
Hypocortisolism related AEs	13 (8.7)	3 (2.0)	13 (8.0)	4 (2.5)	6 (3.4)	1 (0.6)
Low blood cell related AEs	13 (8.7)	2 (1.3)	8 (4.9)	0	17 (9.6)	1 (0.6)
Hypotension related AEs	9 (6.0)	0	11 (6.8)	0	0	0
Pancreatitis related AEs	6 (4.0)	3 (2.0)	12 (7.4)	3 (1.9)	9 (5.1)	0
QT-prolongation related AEs	6 (4.0)	2 (1.3)	13 (8.0)	4 (2.5)	12 (6.7)	2 (1.1)
Hypothyroidism related AEs	5 (3.3)	0	7 (4.3)	0	9 (5.1)	0
Injection site reaction related AEs	4 (2.7)	1 (0.7)	28 (17.3)	0	14 (7.9)	0
Growth hormone deficiency related AEs	2 (1.3)	0	0	0	1 (0.6)	0
Coagulation related AEs	1 (0.7)	0	3 (1.9)	0	2 (1.1)	0

Hyperglycaemia related AESI

In study G2304, a large proportion (77%) of the subjects on pasireotide develop hyperglycaemia related AEs. A tendency toward a slightly greater risk with the higher dose of pasireotide LAR could be noted during the first four months of treatment. Overall, only very few (n=2) of the events were defined as SAEs.

The frequency of hyperglycaemia related AEs with LAR in Cushing's disease (77%) is comparable to previous the studies with s.c. pasireotide in subjects in this population (72% in study B2304). However, the frequencies of these events are slightly higher in Cushing's disease (77% in study G2304) compared to subjects with acromegaly (60% in study C2305). Table 21

Glucose metabolism disorders are reflected in section 4.4, 4.5 and 4.8 in the SmPC. *Hyperglycaemia* is also reflected below in the section Special safety topics.

Gallbladder and biliary related AESI

A dose difference in the incidence of gallbladder and biliary related AESIs could be noted in study G2304 especially during the first 4 months (10 mg group: 24% and 30 mg group: 45%). However, the overall incidence (35% in study G2304) of these events is comparable to previous studies with s.c pasireotide in subjects with Cushing's disease (35%) and the LAR formulation in subjects with acromegaly (36%) (Table 21).

Gallbladder and related events are considered adequately reflected in the SmPC section 4.4 and 4.8.

Liver safety related AESI

Liver safety related AESIs were reported equally in the two treatment arms (approximately 20% in both arms). Most of the AEs were related to increased liver enzymes. The incidence was similar as in previous study in Cushing patients treated with s.c. pasireotide (16%) but slightly higher compared to subjects treated with pasireotide LAR in the population with Acromegaly (11%) (Table 21). One patient, in study G2304, met biochemical criteria for Hy's law: However, the patients suffered from with concurrent SAE of cholelithiasis, acute cholecystitis and oedematous pancreatitis.

The effect of pasireotide on the liver is considered adequately reflected and covered in the SmPC section 4.4 (monitoring with liver function test) and section 4.8 (increased liver enzymes).

Bradycardia related AESI

Bradycardia is a known phenomenon during treatment with pasireotide. Higher frequencies of bradycardia related AEs were noted with higher dose regime (10 mg group: 5% and 30 mg group: 12%). The difference was persistent over time.

The risk for bradycardia during treatment with pasireotide is considered adequately reflected in the SmPC section 4.4, 4.5 and 4.8.

Hypocortisolism related AESI

In study G2304, hypocortisolism-related AESIs were reported in 13 (9%) patients including adrenal insufficiency in 10 patients (7%). SAEs of hypocortisolism related events (adrenal insufficiency) were reported in 3 patients. The SAEs were all judged as related to study drug. No dose difference was noted.

Adrenal insufficiency (including blood cortisol decreased) is considered adequately labelled in SmPC section 4.8.

Low blood cell related AESI

The risk of haematological abnormalities is known in association to use of pasireotide and includes both decreases in haemoglobin and decrease in lymphocytes (see section Laboratory findings).

In study G2304, low blood cell related AESI was reported in 9% (n=13). *Anaemia* was reported in 8 cases (5%) and in five cases (3%) leukopenia, lymphopenia and/or neutropenia were reported (Table 22).

Two patients (1.3%) reported grade 3 AEs, no grade 4 AEs or AEs leading to discontinuation were reported. SAE was reported in one patient – the patient had anemia. In four (2.6%) of the 13 patients low with blood cell related AESI, the events were judged as related to pasireotide long-acting treatment. In all four cases the events were *anemia* and all four events were occurred in close correlation with UFC decreases.

Additional analyses for study G2304 showed that decreases in mUFC levels also were associated with decreases in WBC and neutrophil counts. However, none of the five cases reporting leukopenia, lymphopenia and/or neutropenia were judged as related to treatment with pasireotide by the investigator.

"Hematological abnormalities" is characterized as an important potential risk in the RMP and the clinical relevance of decreased haemoglobin (anaemia) is well characterised and reflected in the SmPC section 4.8. However, no information regarding decrease in WBC and neutrophils are reflecting in the SmPC. It is not considered that the findings in study G2304 warrant any up-date of the SmPC at present. However, in the latest pasireotide PSUSA (EMEA/H/C/PSUSA/00009253/201610) it was agreed with the MAH to present a cumulative review of cases on patients with AEs related to decreased in WBC in the coming PSUR.

Table 22 Low blood cell related AESI

	Pasireotide LAR 10 mg N=74 n (%)	Pasireotide LAR 30 mg N=76 n (%)
Any AESI	**6 (8.1)**	**7 (9.2)**
Anaemia	4 (5.4)	4 (5.3)
Leukopenia	1 (1.4)	1 (1.3)
Haemoglobin decreased	0	1 (1.3)
Lymphopenia	1 (1.4)	0
Neutropenia	1 (1.4)	0
Platelet count decreased	0	1 (1.3)
Grade 3-4	1 (1.4)	1 (1.3)
SAE	0	1 (1.3)
AE leading to discontinuation	0	0
AE requiring dose adjustment/interruption	0	0

Hypotension related AESI

Hypotension related AESIs were reported in 9 (6%) patients; all were grade 1 or grade 2 AEs and none were SAEs. The mechanism of action and the clinical significance of this finding have not been established. Therefore, hypotension is characterised as an important potential risk in the RMP.

Hypotension is part of symptoms associated with hypocortisolism and reflected SmPC section 4.8.

Pancreatitis related AESI

The PT in all cases (n=6) of pancreatitis related AESIs reported in study G2304 related AESIs were events of *increased lipase*. No pancreatitis related SAE was reported. *Lipase and amylase increased* is considered adequately reflected in SmPC section 4.8.

QT-prolongation related AEs

QT prolongation related AESIs were reported in 6 (4%) patients. The most frequent AE in this category was "electrocardiogram QT prolonged" in three (2%) patients with all these events being either grade 1 or 2. There was one SAE cardiac arrest (fatal case) Day 431 (after the first dose of pasireotide LAR). The patient died due to the cardiopulmonary failure and the Investigator reported that cardiopulmonary failure caused cardiac arrest. See also section -Serious adverse events and deaths (subject G2304-3403-00018) below.

QT-prolongation is a known risk with pasireotide reflected in the SmPC section 4.4 and 4.8. The incidence of QT-prolongation related AEs in study G2304 was not higher compared to previous studies.

Injection site reaction related AESI

In study G2304, injection site reaction related AESI were reported in 4 patients (3 %) and similar between the two doses. As previous demonstrated (study C2305) injections site reactions with LAR were reported with a lower frequency compared to the s.c. formulation (Table 21).

"Injection site reactions" is listed in SmPC section 4.8 for Signifor LAR.

Hypothyroidism related AESI (hypothyroidism)

In study G2304, five events of hypothyroidism were reported (3%), all were grade 1 events and none were SAEs or AEs that led to discontinuation.

Monitoring of pituitary function (e.g. TSH/free T4) is recommended in SmPC section 4.4.

Hypothyroidism is also listed as an important potential risk in the RMP for pasireotide.

Growth hormone related AESI

In study G2304, Growth hormone related AESI (insulin-like growth factor decreased) were rare events reported in 2 patients (1.3%), both were grade 1 events.

Coagulation related AESI

Patients with abnormal coagulation (PT or PTT elevated by 30% above normal limits) were excluded in study G2304 as was patients who received anticoagulants that affect PT or PTT. Lack of safety data in patients with severe coagulation abnormalities is reflected in SmPC section 4.4.

Prothrombin time prolonged is labelled in SmPC section 4.8.

Serious adverse events and deaths

SERIOUS ADVERSE EVENTS

In study G2304, SAEs were reported in 38 (25%) patients, including 12 (8%) patients who had SAEs suspected to be related to pasireotide. The most common SAEs regardless of study drug relationship were *cholelithiasis* (3%; n=4) and *pituitary-dependent Cushing's syndrome* (2%, n=3). The safety profile regarding SAEs in study G2304 was comparable to that observed in previous studies.

In total 12 SAEs were judged as related to study drug. All are labelled in the SmPC section 4.8 (*cholelithiasis, blood cortisol decreased, adrenal insufficiency, diabetes mellitus* and *hyperglycaemia*).

Table 23 Frequent SAEs (more than 1% in any study) regardless of study drug relationship in studies G2304, B2305 and C2305 (Month 12 analyses)

	Study G2304 All Patients N=150 n (%)	Study B2305 All Patients N=162 n (%)	Study C2305 Pasireotide N=178 n (%)
	All Grades	All grades	All grades
Total	38 (25.3)	42 (25.9)	32 (18.0)
Cholelithiasis	4 (2.7)	5 (3.1)	3 (1.7)
Pituitary-dependent Cushing's syndrome	3 (2.0)	6 (3.7)	0
Blood cortisol decreased	2 (1.3)	0	0
Endometrial cancer	2 (1.3)	0	0
Pulmonary embolism	2 (1.3)	0	0
Stress fracture	2 (1.3)	0	0
Diabetes mellitus	1 (0.7)	4 (2.5)	3 (1.7)
Hyperglycaemia	1 (0.7)	4 (2.5)	1 (0.6)
Adrenal insufficiency	1 (0.7)	2 (1.2)	0
Pituitary tumor benign	0	3 (1.9)	0
Disease progression	0	2 (1.2)	0
Drug ineffective	0	2 (1.2)	0
Hypotension	0	2 (1.2)	0
Uterine polyp	0	2 (1.2)	0
Nephrolithiasis	1 (0.7)	0	2 (1.1)
Acromegaly	0	0	2 (1.1)
Concomitant disease progression	0	0	2 (1.1)

DEATHS

Study G2304

Two patients died on-treatment (i.e. within 56 days of last pasireotide dose), both in the pasireotide 30 mg group. Neither of the deaths was suspected to be related to study treatment.

- Subject G2304-3403-00018, a 45 year-old female, died of *cardiopulmonary failure* approximately 15 months (Day 447) after receiving her first dose of pasireotide (last dose of pasireotide received on Day 431). The Investigator reported that cardiopulmonary failure caused *cardiac arrest*.
- Subject G2304-3802-00005, a 63 year-old female, died of *pulmonary artery thrombosis* and *sepsis* a month (Day 31) after her first dose of pasireotide.

Study C2305

In the Month 26 analysis, two on-treatment deaths occurred on pasireotide. None of the deaths were considered related to study drug by the investigator.

- Subject C2305-0912-00008, died on day 361 (24 days after receiving 13th injection - extension phase). Cause of death was reported as *psychotic depression* that was precipitated by external circumstances.
- Subject C2305-0102-00001, died 23 days after receiving the 20th injection of crossover treatment (extension phase – crossover to pasireotide treatment). Cause of death was reported as *aortic aneurysm rupture*.

Laboratory findings

Haematology

In the 12-month analysis of study G2304, the most commonly reported worst post-baseline abnormalities were *absolute lymphocytes decreased* (33%) and *haemoglobin decreased* (27%). The majority of haematological abnormalities were grade 1 or 2. Shifts to grade 3 abnormalities were reported in three patients: absolute lymphocytes decreased (10 mg group), haemoglobin decreased (30 mg group) and patient with prothrombin increased (30 mg group). No grade 4 post baseline abnormalities were reported.

Decrease in haemoglobin and absolute lymphocytes reported in study G2304 is in accordance with results from previous studies with pasireotide and somatostatin.

Low blood cell related AESI are also described in the section "Adverse events of special interest".

Clinical chemistry

In study G2304**,** a transient elevation in mean AST and mean ALT was observed shortly after the initiation of treatment with pasireotide LAR. Following these initial increases, mean AST and mean ALT return to values close to those observed at Baseline. AST or ALT values above 5 ULN noted in 7 patients (5%) and one patients noted ALT or AST above 8 ULN (**Table 24**).

Increase in liver safety parameters (ALT, AST and total bilirubin) reported in study G2304 were consistent with the previous reported data. One patient met the biochemical criteria for Hys law this event was associated with concomitant SAEs and further described in the section "Adverse events of special interest".

Table 24 Patients with elevations of liver enzymes - Safety set

	Pasireotide LAR 10 mg N=74 n (%)	Pasireotide LAR 30 mg N=76 n (%)
Worst post-Baseline values		
ALT or AST >3xULN	10 (13.5)	11 (14.5)
ALT or AST >5xULN	4 (5.4)	3 (3.9)
ALT or AST >8xULN	0	1 (1.3)

The effect of pasireotide on the liver is considered adequately reflected and covered in the SmPC section 4.4 (monitoring with liver function test) and section 4.8 (increased liver enzymes).

Severe hepatic impairment is a contraindication for pasireotide (SmPC section 4.3). Use of pasireotide in subjects with hepatic impairment is covered in SmPC section 4.2.

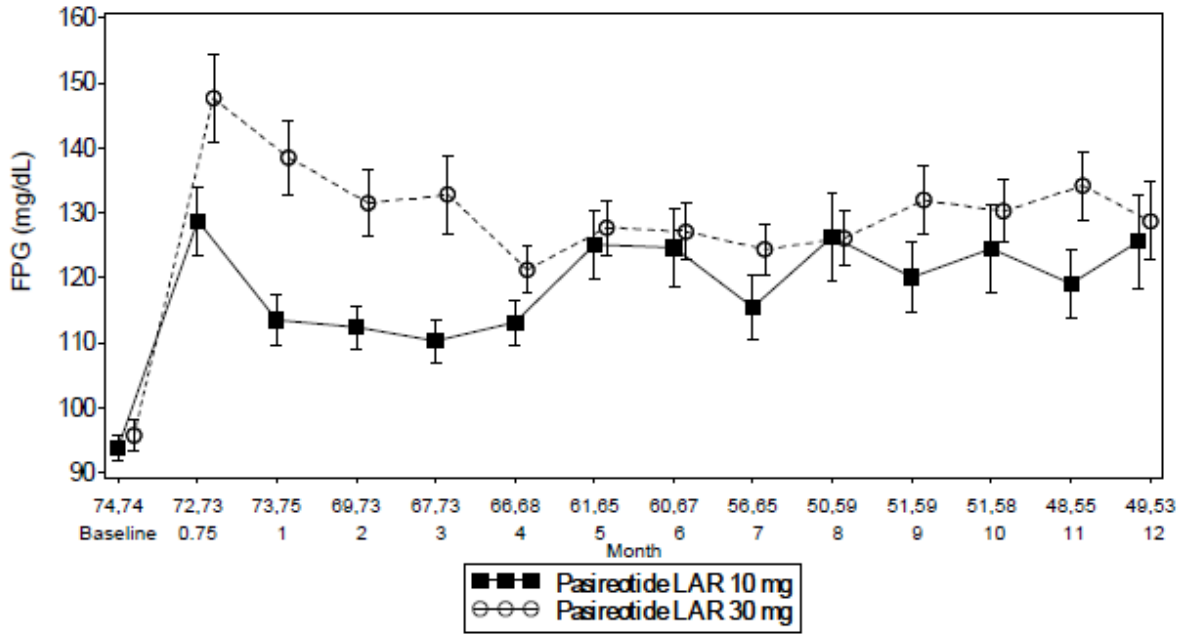
Analyses of glycaemic parameters

Fasting plasma glucose

Mean FPG levels increased following the first dose of pasireotide LAR, with a peak seen at 3 weeks. The increase was dose dependent and more pronounced in patients with diabetes or pre-diabetes at base-line. Overall, in subjects with diabetes at baseline (n=60) the FPG increased by 29% at month 12 compared to baseline and by 54% in subjects with pre-diabetic status (n=23). In subjects with normal b-glucose status at baseline (n=65) the FPG had increased by 39% at month 12 compared to baseline. The flattening of the curve might well be a

result of anti-diabetic treatment in all groups but more pronounced in the group of patients with diabetes at baseline (**Figure 8**).

Figure 7 Mean (SE) FPG during the core phase – safety set

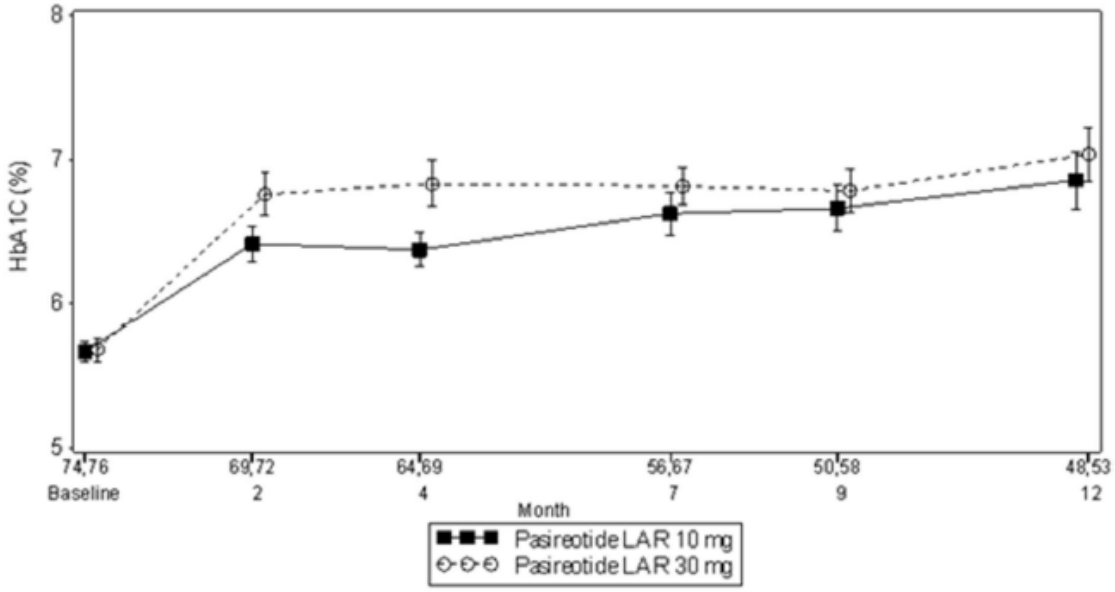


HbA1c

At Baseline, a majority of patients in study G2304 (56.7%) had HbA1c <5.7% (62.2% in the 10 mg arm and 51.3% in the 30 mg arm), and none had HbA1c ≥ 8% (HbA1c >8% at Screening was an exclusion criterion). During the study, almost all patients (93.3%) shifted to a worst post-baseline HbA1c value ≥ 5.7% (Figure 9). HbA1c followed a similar trend in the supportive pasireotide studies (B2305, C2304 and C2402).

At baseline, the mean HbA1c levels were < 6% in both dose groups (10mg and 30mg). During treatment, at all time points, the mean HbA1c levels were ≤ 7%. There was an initial increase from baseline in HbA1c levels in both 10mg and 30mg groups up to month 2, after which the HbA1c remained stable. HbA1c levels were slightly higher in the 10 mg group compared to the 30 mg group throughout the core phase of the study (Figure 9). These data suggest that hyperglycaemia associated with pasireotide is manageable with commonly used therapies.

Figure 8 Mean (SE) change in HbA1c (%) during the Core phase in study G2304



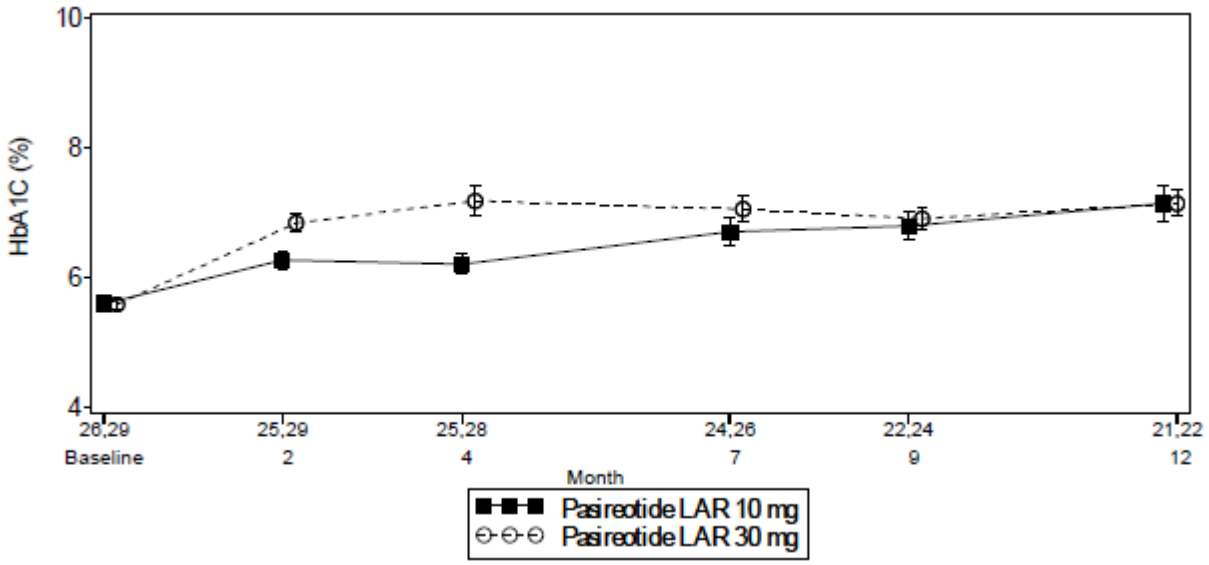
The number of patients contributing to the mean and standard error(SE) for each month are displayed under the X axis.
This analysis includes scheduled visits only.

Time to first hyperglycaemia and time to achievement of HbA1c <7% for patients without diabetes at baseline

Approximately 50% of the patients without diabetes at baseline develop hyperglycaemia (HbA1c ≥ 6.5% or FPG ≥ 126 mg/d).

Time to first hyperglycaemia in subjects with normal FPG at baseline (study G2304) had a wide range and the median time was significant shorter for the high starting dose (30 mg; 57 days [range: 21-469]) compared to the lower starting dose (10 mg: 141 days [range: 21-1149 days]). Introduction of antidiabetic treatment in subjects with normal FPG at baseline but later hyperglycaemia reduced HbA1c to < 7% within 1-3 months.

Figure 9 Patients not on ADM when entering the trial, and prescribed insulin either with or without oral ADM



In summary it is of importance to highlight that even Cushing subjects with normal glucose tolerance are at high risk to develop hyperglycaemia during treatment with pasireotide LAR. Thus a careful monitoring of blood glucose levels is of great importance. This is reflected in SmPC section 4.4.

Vital signs, physical findings and other observations related to safety

Overall, there was no new safety concerns observed based on analysis of vital signs Blood pressure, Pulse, Electrocardiogram – QT prolongation and Gallbladder ultrasound measured in study G2304.

Blood pressure

Supine systolic BP (mmHg) was changed from normal at baseline (n=149) to high as worst post-baseline value in 3 subjects (2%) and diastolic BP (mmHg) was increased to high as worst post-baseline value in 15/140 subjects (10.7%).

Hypertension is part of symptoms of Cushing's disease and therefore a causal relationship to study drug is difficult to assess. From the efficacy assessment it is noted that some patients showed an increase in UFC during the study (Figure 5). Overall, an association between mUFC changes and BP changes was observed in study G2304. Hypertension, reported as AE, occurred in 21 instances out of a total of over 2700 individual measurements. No clear trend between UFC changes and BP changes could be determined at the individual patient level. Thus, no apparent causal relationship to study drug is observed.

Pulse

Supine Pulse (bpm) was changed from normal at baseline to low as worst post-baseline value in 14 patients (9.5%).

Electrocardiogram – QT prolongation

The incidence of QTcF >480 ms was <1.5% (n=2) and no episodes of QTcF >500 ms were observed. The two patients with isolated QTcF elevations >480 ms were both randomized to 30 mg, with no associated symptoms reported during these episodes (Table 25).

Table 25 Categorical QTcF changes in study G2304

ECG variable (QTcF)	All patients N=150 n (%)
New QTcF >450 ms	18 (12.0)
New QTcF >480 ms	2 (1.3)
New QTcF >500 ms	0
QTcF increase >30 ms	58 (38.7)
QTcF increase >60 ms	5 (3.3)

New = Newly occurring post Baseline value.

Safety in special populations

Renal impairment

Patients with renal impairment were not included in study G2304.

Hepatic impairment

Patients with hepatic impairment were not included in study G2304. Thus, no new data have been submitted in patients with renal or hepatic impairment. Dosage recommendations are based on previous data obtained with pasireotide sc.

Elderly patients

Analyses were not conducted by age in study G2304 since only three of the 150 patients were ≥ 65 years. Thus, no new data have been submitted in elderly patients. Dosage recommendations are based on previous data obtained with pasireotide.

Immunological events

Immunogenicity/anti-pasireotide antibodies

No clinical samples have been collected to evaluate immunogenicity of the pasireotide long-acting formulation in the pivotal Study G2304. According to pharmacological data, the observed exposure profiles over time for pasireotide s.c. and long-acting formulation in Cushing's disease patients and acromegaly patients were as expected. No abnormal accumulation or elimination was observed after multiple dosing of pasireotide s.c. or long-acting formulation in Cushing's disease patients or in acromegaly patients, suggesting immunogenicity did not occur in these patient studies.

Allergic reactions

Allergic reactions/immunogenicity is defined as an important potential risk in the RMP.

In total, 37.3% (n=56) of the subjects in study G2304 experienced a reaction (PT) that described a potential risk of allergic reactions/immunogenicity. Three of the events were classified with CTC grade 3 or 4. In 11 cases (7.3%) the events were judged as related to pasireotide. The PTs included in these cases were skin exfoliation

(n=6 [4%]), pruritus (n=4 [2.7%]), oedema peripheral (n=2 [1.3%]), hypotension (n=1 [0.7%]), erythema (n=1 [0.7%]) and injection site hypersensitivity (n=1 [0.7%]).

Pruritus is labelled in the SmPC section 4.8 for the s.c formulation and also for the i.m. formulation pasireotide LAR.

The frequencies of allergic reaction were similar in study B2305 (40.7%) but lower in the studies conducted in acromegaly subjects (12.8% and 27% in study C2402 and C2305, respectively).

Injection site reactions

Injection site reactions are a known risk for pasireotide (reported in 2.7% in study G2304) and further handled in the section regarding adverse events of special interest above.

Safety related to drug-drug interactions and other interactions

No additional data were generated for this submission.

Discontinuation due to AES

In study G2304 AEs leading to discontinuation were reported in 13% with a similar proportion in the two arms. The only AEs leading to discontinuation reported in more than two patients were diabetes mellitus, cholelithiasis and hyperglycaemia. AEs leading to discontinuation were slightly higher for the population with Cushing's disease (13%) compared to acromegaly patients on pasireotide LAR (8 %), but lower compared to subjects with Cushing with s.c. pasireotide treatment (20%).

2.4.10. Discussion on clinical safety

The safety data set in this submission is based on study G2304, studying two (new) strengths (10 mg and 30 mg) of the LAR formulation in subjects with Cushing disease. Supportive data from the pivotal study for the s.c. formulation in Cushing's disease (B2305) and the two studies included in the submission of the LAR formulation in patients with acromegaly (C2304 and C2402) were also submitted.

In study G2304, the median number of injections was 14.5 (1-50). Median duration of exposure in days was 398 (28-1393) days. Exposure up-to 12 months was seen in 81/150 (54%) of the patients and up-to 36 months in 11/150 (7%).

The dose adjustment at Month 4 makes a direct comparison between the two initial treatment groups (10mg and 30 mg respectively) difficult to perform. The maximum dose (40 mg) was received by 40-50% of all patients from Month 7 to Month 12. Thus safety and tolerability could be judged as have been sufficiently studied also in the population using doses of 40 mg.

Common adverse events

In study G2304, almost all patients (99%) reported at least one AE in comparable frequencies between the both treatment groups. In total, 93% of the patients experiencing AEs suspected to be related to pasireotide. The proportion of patients with AEs leading to study discontinuation was 13%.The most common AEs were *hyperglycaemia* (48.0%), *diarrhoea* (39.3%) and *cholelithiasis* (32.7%). *Diabetes mellitus* was reported in 21.3%. All these events were also the most frequently events reported by the investigator as possible related to study drug.

Both at Month 4 and at data cut-off (12 months) AEs of *cholelithiasis* were reported in a greater proportion of patients randomized to the 30 mg arm (18% and 45%) compared to in 10 mg (0% and 20%). Events of *hyperglycaemia* were reported in slightly higher frequency in the 30 mg group at Month 4 (10 mg: 31% and 30 mg: 42% respectively) but in comparable frequencies after 12 months (47-48%).

When comparing the studies in subjects with Cushing's disease on pasireotide LAR (G2304) with s.c. pasireotide (B2305) the frequencies of events reported in the SOC Metabolism and nutrition disorders (including *Hyperglycaemia* and *diabetes mellitus)* were comparable (82% in study G2304 vs 75% in study B2305). On the other hand events in the SOC Gastrointestinal disorders (*diarrhoea, nausea* and *abdominal pain)* were reported with less frequency with the LAR formulation (63% in trial G2304) compared to the s.c. formulation (81% in trial B2305).

When comparing the studies in subjects with Cushing's disease on pasireotide LAR (G2304) with pasireotide LAR in Acromegaly (C2305) events from the SOC metabolism and nutrition disorders such as *hyperglycaemia* were presented with higher frequencies in the population with Cushing´s disease (82% in study G2304) compared to the acromegaly population (61% in study C2305). GI events were reported in similar frequencies.

Events of cholelithiasis were reported in equally high (approximately 30%) in all three studies.

SAEs and deaths

In study G2304, SAEs were reported in 38 (25.3%) patients, including 12 (8.0%) patients who had SAEs suspected to be related to pasireotide. The only SAEs that were reported in more than two patients were cholelithiasis (n=4) and pituitary-dependent Cushing's syndrome (n=3). No dose difference was noted in study G2304. The safety profile regarding SAEs in study G2304 was comparable to that observed in previous studies.

Two patients died on-treatment (cardiopulmonary failure; pulmonary artery thrombosis and sepsis). Both patients were in the pasireotide 30 mg group. Neither of the deaths was judged as suspected to be related to study treatment by the investigators. No new safety concerns are evoked by these cases. Cushing's syndrome (CS) causes metabolic abnormalities that determine an increased cardiovascular risk and cardiovascular complications in patients with CS cause a mortality rate higher than that observed in a normal population.

AEs leading to discontinuation were noticed in 13% of the patients. The main reason for discontinuation was AEs related to hyperglycaemia, cholelithiasis and/or acute cholecystitis.

AEs of special interest (AESI)

Thirteen categories of AESI were defined in the clinical development program for pasireotide and further assessed in study G2304. Results of the following AE of special interest were presented in study G2304 as expected (known risks with pasireotide) and in accordance with results from the supportive studies: AEs related to bradycardia, hypocortisolism, hypotension, pancreatitis, QT-prolongation, hypothyroidism, growth hormone deficiency and coagulation.

Hyperglycaemia and related AEs: In study G2304, mean FPG levels increased following the first dose of pasireotide LAR, with a peak seen at 3 weeks. The absolute increase in FPG was greater in patients with diabetes at baseline, followed by pre-diabetic patients and it was more pronounced in patients in the 30 mg group as compared to patients in the 10 mg group, particularly during the first 3 months of treatment.

Median time to first hyperglycaemia (defined as HbA1c ≥ 6.5% or FPG ≥ 126 mg/dL) was 84 days with a wide range (21-1149 days). A dose difference was noted with shorter time to the event for the 30 mg group (57 days) compared to the 10 mg group (141 days).

Approximately 50% of the patients with normal glucose tolerance at baseline developed hyperglycaemia during the study. Introduction of antidiabetic treatment in subjects with normal FPG at baseline, who developed hyperglycaemia, normally reduced HbA1c to < 7% within 1-3 months.

In summary, results in study G2304 demonstrated that also Cushing subjects with normal glucose tolerance are at high risk of developing hyperglycaemia during treatment with pasireotide LAR and that time to first hyperglycaemia ranged from a few weeks up to years. As reflected in SmPC section 4.4, it is of importance to ensure careful monitoring of blood glucose levels during treatment with pasireotide.

Gallbladder and biliary related AEs: A dose difference in the incidence of gallbladder and biliary related AESIs could be noted in study G2304 especially during the first 4 months (10 mg group: 24% and 30 mg group: 45%). However, the overall incidence (35% in study G2304) of these events is comparable to previous studies.

Liver safety and related AESI: In study G2304, AESIs related to liver safety were reported in 20% of patients and events were distributed equally in the two treatment arms. The reactions were all PTs related to increase in liver enzymes. The occurrence of AEs related to liver safety are in accordance with results from laboratory findings in study G2304.

Haematology and Low blood cell related AESI: In study G2304, low blood cell related AESI was reported in 9% (n=13). *Anaemia* was reported in 8 cases (5%) and in five cases (3%) leukopenia, lymphopenia and/or neutropenia were reported.

The risk of haematological abnormalities is known in association to use of pasireotide and includes both decreases in haemoglobin and decrease in lymphocytes (see section Laboratory findings). The clinical relevance of decreased haemoglobin (i.e. *anaemia*) is well characterised and reflected in the SmPC section 4.8. It is not, at present, considered that the findings in study G2304 warrant any up-date of the SmPC regarding decrease in WBC and neutrophils.

Injection site reaction related AESI**:** In study G2304, the frequency of injection site reactions related to AESI was reported in 2.7% (similar between the two doses 10 mg and 30 mg) and lower compared to the use in subjects with Cushing's diseases treated with pasireotide s.c. formulation in study B2305 (17.3%) and study C2305 (7.9%)**.**

Safety in special populations

Patients with renal impairment and hepatic impairment were not included in study G2304. Thus, no new data in these populations have been provided. Neither has no new results in the elderly age group been provided since only three subjects in the study were older than 65 years.

No clinical samples have been collected to evaluate immunogenicity of the pasireotide long-acting formulation in the pivotal Study G2304.

No separate presentation of AEs related to *allergic reactions* has been presented from study G2304 and is requested.

In summary, no new safety concern was detected with pasireotide LAR in subjects with Cushing´s disease based results from study G2304.

2.4.11. Conclusions on clinical safety

Overall, the safety profile of pasireotide LAR in subjects with Cushing's disease was in line with previous studies with the substance and no new safety concerns were raised with the results from study G2304. Adverse events

were reported in almost all subjects (99%), with the reactions *hyperglycaemia* (48%), *diarrhoea* (39%) and *cholelithiasis* (33%) as the most common. The largest difference in AE pattern with the LAR formulation compared to treatment with s.c. pasireotide for the population with Cushing's disease was lower frequencies of GI events with pasireotide LAR. When comparing the studies in subjects with Cushing's disease and acromegaly patients on pasireotide LAR the overall frequencies of AE were comparable. However, the AE pattern differed somewhat and reactions including *hyperglycaemia* were reported with higher frequencies in the population with Cushing's disease compared to acromegaly patients.

As demonstrated in previous studies with pasireotide patients in study G2304 presented an, in most cases, mild and reversible elevation of transaminases. Some events of the known risk of bradycardia (9%), QT-prolongation (4%) and anaemia (5%) were also noted.

2.4.12. PSUR cycle

The PSUR cycle remains unchanged.

2.5. Risk Management Plan

Safety concerns

Summary of safety concerns	
Important identified risks	Hypocortisolism/cortisol withdrawal syndrome, Hyperglycemia, Bradycardia, QTc interval prolongation, Cholelithiasis, Hematological abnormalities, Liver enzymes increased, Injection site reactions, Gastrointestinal disorders.
Important potential risks	Clinically significant GH/IGF-I decrease* Hypothyroidism Pancreatitis Coagulation abnormalities Hypotension Hypocalcemia Gastrointestinal erosions/bleedings Potential interactions with cyclosporine, drugs metabolized by CYP3A4, bromocriptine, antiarrhythmic medicines and antidiabetics Off-label use in children and other indications Allergic reactions/immunogenicity Tumor expansion

Missing information	Pregnancy and Breast-feeding Patients with cardiac diseases (such as unstable angina, congestive heart failure, recent myocardial infarction or clinically significant bradycardia) Children and adolescents (patients less than 18 years) Patients with hepatic impairment Long-term safety

*only applicable for Cushing's disease

Pharmacovigilance plan

Study / activity **Type, title and category (1-3)**	**Objectives**	**Safety concerns addressed**	**Status** (planned, started)	**Date for submission of interim or final reports (planned or actual)**
Study CSOM230 2410 (non-interventional, 3)	Non-interventional study for the generation of long term safety and efficacy data of pasireotide (subcutaneous use) in patients with Cushing's disease.	Long term safety and efficacy in patients with Cushing's disease.	Started	Study report and submission of final data Preliminary efficacy and safety data will be submitted to EMA two years after start of the study and on a yearly basis thereafter
Study CSOM230B2219 (interventional, 3)	To evaluate the effect of treatment with incretin based therapy vs insulin on the 16-week glycemic control in patients with Cushing's disease or acromegaly who develop or worsen hyperglycemia on pasireotide, and cannot be controlled by metformin alone or other background anti-diabetic treatments	Hyperglycemia	Started	Study report planned to be submitted by Q2 2018.

Risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Identified risks		
Hypocortisolism/Cortisol withdrawal syndrome	SmPC Section 4.4 Special warnings and precautions for use.	None
Hyperglycemia	Cushing's and Acromegaly SmPC Section 4.4 Special warnings and precautions for use. Cushing's and Acromegaly SmPC Section 4.5 Interaction with other medicinal products and other forms of interaction. Relevant PT included as ADRs in Cushing's and Acromegaly SmPC Section 4.8 Undesirable effects	None
Bradycardia	Pasireotide sc and pasireotide long-acting: SmPC Section 4.4 Special warnings and precautions for use, SmPC Section 4.5 Interaction with other medicinal products and other forms of interaction. Relevant PT included as ADR in SmPC Section 4.8 Undesirable effects	None
QTc interval prolongation	SmPC Section 4.4 Special warnings and precautions for use, SmPC Section 4.5 Interaction with other medicinal products and other forms of interaction. Relevant PT included as ADR in SmPC Section 4.8 Undesirable effects.	None
Cholelithiasis	Pasireotide sc and pasireotide long-acting: SmPC Section 4.4 Special warnings and precautions for use. Relevant PT included as ADR in SmPC Section 4.8 Undesirable effects.	None
Hematological abnormalities	Anaemia is included as ADR in SmPC Section 4.8 Undesirable effects.	None
Liver enzymes increased	SmPC Section 4.4 Special warnings and precautions for use. Relevant PT included as ADRs in SmPC Section 4.8 Undesirable effects.	None
Injection site reactions	SmPC Section 4.2 Posology and method of administration and SmPC Section 4.8 Undesirable effects. Relevant PT included as ADRs in SmPC Section 4.8 Undesirable effects.	None
Gastrointestinal disorders	SmPC Section 4.8 Undesirable Effects. Relevant PT included as ADRs in SmPC Section 4.8 Undesirable effects.	None

Potential risks		
Clinically significant GH/IGF-I Decrease*	SmPC Section 4.4 Special warnings and precautions for use.	None
Hypothyroidism	SmPC Section 4.4 Special warnings and precautions	None
Pancreatitis	SmPC Section 4.8 Relevant PT included as ADRs in SmPC Section 4.8 Undesirable effect	None
Coagulation abnormalities	Prothrombin time prolonged is included as ADRs in SmPC Section 4.8 Undesirable effects.	None
Hypotension	Pasireotide sc: hypotension is included as ADRs in SmPC Section 4.8 Undesirable effects. For pasireotide long-acting, currently available data do not support the need for risk minimization.	None
Hypocalcemia	The potential risk of hypocalcemia is based on preclinical findings that were not confirmed in clinical studies, as evidenced by a lack of major imbalances in clinical studies. Since there is currently insufficient evidence from controlled clinical studies to suggest these to be risks specifically attributable to pasireotide, there is no need for risk minimization activities at this time	None
Gastrointestinal erosions/bleedings	The potential risk of gastrointestinal erosions/bleedings is based on a preclinical finding in dogs that were not confirmed in clinical studies, as evidenced by a lack of major imbalances in clinical studies. Since there is currently insufficient evidence from controlled clinical studies to suggest these to be risks specifically attributable to pasireotide, there is no need for risk minimization activities at this time.	None
Potential interactions with cyclosporine, drugs metabolized by CYP3A4, bromocriptine, antiarrhythmic medicines, and antidiabetics	SmPC Section 4.5 Interaction with other medicinal products and other forms of interaction	None
Off-label use in children and other indications	SmPC Section 4.2 Posology and method of Administration/Special populations/Pediatric population and SmPC Section 5.2 Pharmacokinetic properties/Special populations/Pediatric population.	None
Allergic reactions/immunogenicity	Currently available data do not support the need for risk minimization.	None
Tumor expansion	Currently available data do not support the need	None

	for risk minimization.	
Missing Information		
Pregnancy and Breast-feeding	SmPC Section 4.6 Fertility, pregnancy and lactation and SmPC Section 5.3 Preclinical safety data	None
Patients with cardiac diseases (such as unstable angina, congestive heart failure, recent myocardial infarction or clinically significant bradycardia)	SmPC Section 4.4 Special Warnings and precautions and SmPC Section 4.5 Interaction with other medicinal products and other forms of interaction. Sinus bradycardia and QT prolongation are included as ADRs in SmPC Section 4.8 Undesirable effects.	None
Children and adolescents (patients less than 18 years)	SmPC Section 4.2 Posology and method of administration and SmPC Section 5.2 Pharmacokinetic properties.	None
Patients with hepatic impairment	SmPC Section 4.2 Posology and method of administration, SmPC Section 4.3 Contraindications, SmPC Section 5.2 Pharmacokinetic properties	None
Long-term safety	Currently available data do not support the need for risk minimization.	None

Conclusion

The CHMP and PRAC considered that the risk management plan 5.0 dated 07-Nov-2016 is acceptable.

2.6. Pharmacovigilance

Pharmacovigilance system

The CHMP considers that the pharmacovigilance system summary submitted by the MAH fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.7. Product information

2.7.1. User consultation

With regard to the user consultation with target patient groups on the package leaflet, the bridging for the combined PL submitted by the MAH for the product Signifor powder and solvent for suspension for injection (10 mg, 20 mg, 30 mg, 40 mg and 60 mg) in this procedure EMEA/H/C/2052/X/30/G is considered acceptable.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The new claimed therapeutic indication for the long-acting intramuscular (i.m.) formulation of Signifor is:

"Treatment of adult patients with Cushing's disease for whom surgery is not an option or for whom surgery has failed."

Cushing's disease is a very rare, debilitating, and life-threatening disease caused by an adrenocorticotropic hormone (ACTH)-secreting pituitary adenoma. The elevated levels of ACTH stimulate the adrenal glands to produce excess cortisol, thereby leading to the subsequent development of the clinical signs and symptoms of hypercortisolism. Patients with Cushing's disease have increased morbidity and a mortality rate 4 times higher than age- and gender-matched subjects.

The aim of therapy is primarily to control the increased ACTH levels, thereby reducing the cortisol production. Reduction of cortisol levels diminishes the burden of disease in terms of symptoms of hypercortisolism. A reduction of tumour volume may also be observed.

3.1.2. Available therapies and unmet medical need

Pituitary resection of the adenoma is the current first-line therapy for Cushing's disease, but surgical failure rates range between 8 to 31%. For patients not cured by pituitary surgery, irradiation of the pituitary or bilateral adrenalectomy are the remaining non-medical treatment options.

Available pharmacological treatment options generally fullfill a short-term, palliative role and are rarely used alone as long-term therapy. Currently ketoconazole is approved for the treatment of Cushing's syndrome which includes a number of conditions with increased cortisol production, including Cushing's disease. Other available pharmacological treatments are metyrapone, mitotane, mifepristone and cabergoline. None of the available pharmacological treatment options listed, apart from cabergoline, targets the cause of the disease, i.e. the pituitary adenoma. Thus there is an unmet medical need in the treatment of patients with Cushing's disease.

Pasireotide, in the short-acting formulation for subcutaneous use, has already been shown to be effective in the treatment of Cushing's disease. The long-acting formulation of pasireotide for intramuscular (i.m.) injections was developed to provide improved convenience to patients by reducing the number of injections from twice daily to once every 28 days.

3.1.3. Main clinical studies

Data from two clinical trials, G2304 and B2305 have been provided, of which G2304 is the pivotal study.

Study G2304 was a randomized, double-blind Phase 3 study of pasireotide 10 mg and 30 mg in patients with Cushing's disease, consisting of a 12-month core phase and an open-ended, optional extension. Study B2305 used the subcutaneous formulation of pasireotide and was the pivotal study in the MAA for that formulation comparing two different doses of pasireotide.

Study G2304 compared two different doses of pasireotide (10 mg and 30 mg, every 28 days), i.e. the study design was similar to that applied in study B2305. The study included 150 patients (74 in the 10 mg group and 76 in the 30 mg group). In both groups, patients were up-titrated at month 4 if mUFC was higher than 1.5xULN.

3.2. Favourable effects

There was no difference between groups with regards to the outcome of the primary endpoint (response regardless of up-titration) with 42% (95% CI; 30.51, 53.94) responders in the low dose group and 41% (95% CI; 29.65, 52.67) responders in the high dose group. Since the lower limit of the CI was higher than 15%, the primary endpoint was met for both doses. In the 10 mg group 24% of patients had been up-titrated to 40 mg at month 7, compared to 53% of patients in the 30 mg group. Dose-titration did recruit more responders since the response rates were lower for the key secondary endpoint (response without up-titration), with numerically more responders in the 30 mg dose group (32% vs 28%). The response rate was higher in the stratum with lower mUFC (52% in both groups). Response rates remained stable up to 12 months.

Higher response rates were observed in study G2304 than in study B2305 where the response rate (NB in patients without up-titration) was 14.6% and 26.3% in the 600 µg bid and 900 µg bid arms, respectively. It should however be taken into account that study B2305 recruited patients with higher mUFC at baseline than did study G2304.

The proportion of patients partially controlled was higher in the 30 mg dose group (15.8% vs 8.1% in the low dose group) resulting in a higher proportion of patients controlled or partially controlled in this group (56.6% vs 50% for the 30 mg and 10 mg group, respectively).

Some patients apparently failed on therapy as shown by increased mUFC levels. The importance of monitoring the effect and reconsider treatment in case of treatment failure has been adequately reflected in the SmPC.

The outcome of remaining secondary and exploratory endpoints was consistent with the outcome of the primary and key secondary endpoint. The mUFC levels decreased within the first month of treatment and continued to decrease up to month 7 after which the levels remained stable in patients remaining in the study up to month 12. The changes observed for ACTH and s-cortisol were consistent with the changes observed for mUFC. No apparent differences were observed between the two doses.

Change in pituitary tumour volume was an exploratory endpoint and 117 patients had a visible tumour at baseline and 73 of these patients had tumour volume assessed both at baseline and at Month 12. Out of these 73 patients, 33 (45.2%) showed a reduction of tumour volume greater than 20%.

The majority of patients reported stable or improved signs and symptoms of hypercortisolism and about 30% reported an improvement of symptoms. A decrease in SBP was also observed, with the largest decrease observed in controlled patients. A decrease of ≥ 5% was reported by 78% in the 10 mg group and 63% in the 30 mg group. The change was sustained throughout the study. Improvements in body weight were also observed. In the 10 mg group and the 30 mg group respectively, 62% and 71% of patients reported weight decrease of ≥ 5%.

Data from the patient-reported outcome (PRO) measure CushingQoL, and the generic quality of life measure SF-12v2 showed that clinically relevant improvements, defined as changes exceeding the MID, were achieved for both instruments.

Subgroup analyses did not show any apparent differences when data was analysed by sex and race.

Long-term data from the extension of study G2304 is still not complete but support that the effect is maintained in a relevant proportion of patients up to 24 months. These data are supported by the data from study B2305, although it should be noted that the number of patients remaining in this study was very low (16 subjects still ongoing at study closure). In study G2304, at the end of the core phase (i.e. month 12), the proportion of controlled and partially controlled responders was 44.0% (66/150) for both dose arms combined. At month 24, 29.3% of patients (29/99) were controlled or partially controlled responders.

3.3. Uncertainties and limitations about favourable effects

Currently, s.c. pasireotide is approved for treatment of Cushing's disease. With the LAR formulation also approved in this indication, there is a need for recommendations on how to switch from the s.c. formulation to the LAR formulation and vice versa (although the latter alternative may be less common). The switch situation has not been investigated but adequate recommendations have been included in the SmPC based on available pharmacokinetic and clinical data.

3.4. Unfavourable effects

The safety profile is mainly based on the pivotal study G2304 including 150 subjects with Cushing's disease for treatment with pasireotide LAR up to a maximal dose of 40 mg. Data up to 12 months is available. An extension of the study is ongoing. This submission also includes important safety information from the supportive studies B2305 (which formed the basis of approval of the pasireotide s.c. formulation in Cushing's disease), C2305 and C2402 (which both supported the approval of the long-acting formulation of pasireotide in acromegaly.

In study G2304, 99% reported at least one AE in comparable frequencies between the both treatment groups (10 mg: 98.6% and 30 mg 100%). In total, 93% of the patients experiencing adverse events suspected to be related to pasireotide. The most common AEs were *hyperglycaemia* (48%), *diarrhoea* (39%) and *cholelithiasis* (33%). All these events were also the most frequently events reported by the investigator as possible related to study drug (*hyperglycaemia:* 47%; *diarrhoea* 32% and *cholelithiasis* 31%).

In study G2304, SAEs related to study drug were reported 8% of the patients. All these SAEs were known reactions labelled in the SmPC section 4.8

Mean FPG levels increased following the first dose of pasireotide LAR, with a peak seen at the 3-week time point. In subjects with diabetes at baseline (n=60) the FPG increased 45% at Month 1 compared to baseline and 35% in subjects with pre-diabetic status (n=23). In subjects with normal b-glucose status at baseline (n=65) the FPG had increased 22% at month 1 compared to baseline. Among all patients, 57% had HbA1c <5.7% at baseline. 93% of all patients shifted to a worst post-baseline HbA1c value ≥ 5.7% at month 12. Approximately 50% of the patients with normal glucose tolerance at baseline develop hyperglycaemia (HbA1c ≥ 6.5% or FPG ≥ 126 mg/d).

Increases in transaminases (ALT or AST >3xULN but <5xULN) were reported in 14% of the patients any time during the 12 Months study period. ALT or AST >5xULN but <8xULN were reported in 5%, one patient had ALT >8xULN. Overall, liver related AEs were reported in 20%.

Supine Pulse (bpm) was changed from normal at baseline to low as worst post-baseline value in 14 patients (9.5%) and bradycardia related AEs were reported with the same frequency.

The incidence of QTcF >480 ms (none above 480 ms) was<1.5% and 3% of the subjects reported QTcF increase >QTcF increase >60 ms. QT prolongation related AESIs were reported in 6 (4.0%) patients. The most frequent AE in this category was "electrocardiogram QT prolonged" in 3 (2.0%) patients with all these events being either grade 1 or 2.

Decreased haemoglobin values were reported in 27% of the patients in study G2304 and events of anaemia in 5%.

Overall, the safety profile in study G2304 were in accordance with the supportive studies (B2304 and C2304). The largest difference in AE pattern with the LAR formulation(G2304) compared to treatment with s.c. pasireotide (study B2305) for the population with Cushing's disease was lower frequencies of GI events with pasireotide LAR (events in SOC Gastrointestinal disorders in study G2304 was 63% in 81% in trial B2305). When comparing the studies in subjects with Cushing's disease and acromegaly patients on pasireotide LAR the AE pattern differed somehow and events the SOC metabolism and nutrition disorders such as *hyperglycaemia* were presented with higher frequencies in the population with Cushing´s disease (82% in study G2304) compared to the Acromegaly population (61% in study C2305).

3.5. Uncertainties and limitations about unfavourable effects

There were no new safety concerns, not previously demonstrated with pasireotide, raised by analysis of the results from study G2304. The identified safety issues are all covered in the SmPC and reflected in the RMP (and accordingly followed in the PSURs). Experience regarding safety with use of the formulation of pasireotide Signifor LAR is available from clinical studies and post-marketing since 2015 in patients with Acromegaly. Experience with s.c pasireotide in the population with Cushing's disease is available from clinical trials and post-marketing since 2012. Thus, in summary to date there are few uncertainties and limitations about unfavourable effects.

3.6. Effects Table

Table 26 Effects Table for Signifor i.m. formulation in Cushing's disease (data cut-off: 10-Nov-2015).

Effect	Short Description	Unit	All patients	10 mg/ 30 mg	Uncertainties/ Strength of evidence	References
Favourable Effects						
Reduction in mUFC	Responders regardless of dose-titration	%	41.3	41.9/ 40.8	The rate may be overestimated, see efficacy section	G2304
	Responders without dose-titration	%	30.0	28.4/31.6		G2304
Unfavourable Effects						
AEs of Hyperglycaemia		%	48	49/47		G2304
Cholelithiasis		%	33	20/45		G2304
GI events	Diarreha Vomiting nause	%	63	64/62		G2304

Effect	Short Description	Unit	All patients	10 mg/ 30 mg	Uncertainties/ Strength of evidence	References
Liver enzymes increased	AST and(or ALT increased < 3 ULN	%	19			G2304
Bradycardia related AEs		%	9	5/12		G2304
QT – prolongation related AEs		%	4%	3/5		G2304

Abbreviations: mUFC=Mean urinary free cortisol

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Cushing's disease is a severe and debilitating condition due to an overproduction of cortisol caused by excess production of ACTH from a pituitary tumour. The only curative treatment is surgical removal of the pituitary tumour. All signs and symptoms, except from local symptoms due to tumour growth, are caused by the high cortisol levels. Therefore, the reduction in cortisol levels achieved with pasireotide as reflected by decreases in mUFC and s-cortisol are important favourable effects of pasireotide treatment. The reduction in cortisol levels has further been shown to reduce the clinical signs of the disease, such as the Cushingoid appearance, hypertension and overweight. Available long-term data with pasireotide for subcutaneous use indicate that in patients responding to treatment the effect can be maintained for up to six years. PRO data support that these effects are translated into a better quality of life for the patients.

The response rates are seemingly low (about 40%). However, considering the limited treatment options when pituitary surgery has failed, this is considered clinically relevant. Furthermore, the effect of treatment can be monitored and the treatment be discontinued in case of insufficient response in the individual patient.

The data also indicate a positive effect on tumour size. The clinical relevance of these data is still uncertain and monitoring of tumour size is necessary due to the risk of tumour growth, as an increase in tumour size may have important negative consequences.

The data presented with this submission are consistent with the data supporting the approval of s.c. pasireotide in Cushing's disease. It has been adequately shown that pasireotide LAR has a clinically relevant effect in the treatment of Cushing's disease.

The safety profile of pasireotide is well known, both from the clinical programme for pasireotide but also from the experience with other somatostatin analogues. Hyperglycaemia, which may lead to overt diabetes, is one of the most important unfavourable effects since patients with Cushing's disease are at increased risk of diabetes due to the hypercortisolism per se. Hyperglycaemia is however possible to monitor and the data provided show that the patients do respond to anti-hyperglycaemic treatment. Hyperglycaemia is therefore considered to be manageable and recommendations on monitoring and treatment are given in the SmPC.

The other important group of unfavourable effects are gastrointestinal adverse events (mainly cholelithiasis, diarrhoea, nausea and vomiting) which may limit the use of pasireotide. In this context it should be noted that gastrointestinal events appeared to be milder with the LAR formulation compared to the s.c. formulation of

pasireotide. No new safety concerns have emerged based on the data presented with this application. Although the unfavourable effects may negatively affect the patients well-being, they are easily identified and in most cases manageable.

3.7.2. Balance of benefits and risks

The beneficial effect of pasireotide i.m. formulation on the hypercortisolism in Cushing's disease translates into important improvements in the signs and symptoms of the disease. Taking into account the severity of the disease, these effects outweigh the unfavourable effects. The unfavourable effects can be identified by adequate monitoring, i.e. hyperglycaemia and cholelithiasis, and the unfavourable effects are considered to be manageable.

By starting treatment with the lower dose as currently proposed, with uptitration in case of insufficient response, the risk of hyperglycaemia is minimised while still assuring that the patient achieves maximal effect since dose titration lead to similar outcome in both dose groups.

3.8. Conclusions

The overall B/R of Signifor, including in its new indication, is positive.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Ketoconazole HRA is not similar to Signifor within the meaning of Article 3 of Commission Regulation (EC) No. 847/200. See appendix 1

Outcome

Based on the CHMP review of data on quality and safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Signifor new strengths 10 mg and 30 mg powder and solvent for suspension for injection is favourable in 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 60 mg strength is only to be used in the treatment of acromegaly.

The CHMP therefore recommends the extension(s) of the marketing authorisation for Signifor 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

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

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

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.

In addition, CHMP recommends the variation(s) to the terms of the marketing authorisation, concerning the following change(s):

Variation(s) requested		**Type**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

To extend the indication to include 'Treatment of adult patients with Cushing's disease for whom surgery is not an option or for whom surgery has failed' to the intramuscular injection formulations.

Appendix

1. CHMP AR on similarity dated 20 July 2017