25 September 2014
EMA/CHMP/524716/2014
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Signifor

International non-proprietary name: pasireotide

Procedure No. EMEA/H/C/002052/X/0010

Note

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

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Administrative information

Name of the medicinal product:	Signifor
Applicant:	Novartis Europharm Ltd Wimblehurst Road Horsham West Sussex RH12 5AB UNITED KINGDOM
Active substance:	pasireotide embonate
International Nonproprietary Name/Common Name:	pasireotide
Pharmaco-therapeutic group (ATC Code):	Pasireotide (H01CB05)
Therapeutic indications:	Signifor is indicated for the 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.
Pharmaceutical form(s):	Powder and solvent for suspension for injection
Strengths:	20 mg, 40 mg, 60 mg
Route(s) of administration:	Intramuscular use
Packaging:	Powder: Vial (glass) and Solvent: Pre-filled syringe (glass)
Package sizes:	- 1 vial + 1 pre-filled syringe plus vial adapter and safety injection needle - 3 x 1 vial + 1 pre-filled syringe (multipack) plus vial adapter and safety injection needle

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List of abbreviations

AcroQoL	Acromegaly Quality of Life
ACTH	adrenocorticotropic hormone
ADR	adverse drug reaction
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
bid	twice daily
CAS	crossover analysis set
CV	coefficient of variation
ΔΔQTc	QTc change from baseline compared to placebo
DDI	drug-drug interaction
ECG	electrocardiogram
FAS	full analysis set
FPG	fasting plasma glucose
FR	full response
GGT	gamma-glutamyltransferase
GH	growth hormone
GI	gastrointestinal
GLP-1	glucagon-like peptide-1
HbA1c	glycosylated hemoglobin
IGF-1	insulin-like growth factor-1
im	intramuscular
ITT	intent to treat
LAR	long-acting release (in the context of this application, the product pasireotide powder and solvent for suspension for intramuscular injection is also referred to as pasireotide LAR)
LLN	lower limit of normal
MRI	magnetic resonance imaging
NR	no response
OGTT	oral glucose tolerance test
POC	proof-of-concept
PR	partial response
q28d	every 28 days
QTc	corrected QT interval
QTcB	corrected QT interval (according to Bazett)
QTcF	corrected QT interval (according to Fridericia)
QTcI	corrected QT interval (individual)
SAE	serious adverse event
sc	subcutaneous
SSA	somatostatin analog
SSTR	somatostatin receptor

TB	total bilirubin
TQT	thorough QT
TSH	thyroid stimulating hormone
ULN	upper limit of normal

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Novartis Europharm Ltd submitted on 30 October 2013 an application for a change of an existing Marketing Authorisation (Extension application according to Annex I of Reg. 1234/2008) to the European Medicines Agency (EMA) for Signifor, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004.

Pasireotide was designated as an orphan medicinal product on 8 October 2009 in the following indications: Treatment of Cushing's disease (EU/3/09/671) and treatment of acromegaly (EU/3/09/670).

The applicant applied initially for the following indication:

Signifor is indicated for the treatment of adult patients with acromegaly.
- for whom surgery is not an option or has not been curative.
- who are inadequately controlled on treatment with other somatostatin analogues.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that pasireotide was considered to be a known active substance.

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

Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/181/2010 on the granting of a (product-specific) waiver for the treatment of acromegaly and pituitary gigantism.

Information relating to orphan market exclusivity

Similarity

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

Scientific Advice

The applicant received Scientific Advice from the CHMP on the indication "Acromegaly" on 24 May 2007.

Licensing status

Signifor powder and solvent for suspension for injection (as part of this application) has not been given a Marketing Authorisation in any country so far.

A new application was filed in the following countries: United States of America, Switzerland, Canada, Chile, Indonesia, Colombia, Taiwan, South Africa, Russia, Australia and South Korea.

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

1.2. Manufacturers

Manufacturer(s) of the finished product

Novartis Pharma AG
Lichtstrasse 35
CH-4056 Basel
Switzerland

Novartis Pharma Stein AG
Schaffhauserstrasse
CH-4332 Stein
Switzerland

SANDOZ GmbH
Biochemiestr. 10
6250 Kundl
Austria

Synergy Health Daniken AG
Hogenweidstrasse 2
CH-4658 Daniken
Switzerland

Abbott Biologicals B.V.
Veerweg 12
NL-8121AA Olst
The Netherlands

BSL Bioservice Scientific Laboratories GmbH
Behringstrasse 6-8
D-82152 Planegg
Germany

PharmLog Pharma Logistik GmbH
Siemensstrasse 1
D-69199 Bönen
Germany

Manufacturer responsible for batch release

Novartis Pharma GmbH

Roonstraße 25
90429 Nürnberg
Germany

1.3. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP:

Rapporteur: Kristina Dunder Co-Rapporteur: Philippe Lechat

- The application was received by the EMA on 30 October 2013.
- The procedure started on 20 November 2013.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 7 January 2014. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 11 January 2014 .
- During the meeting on 17 February 2014, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 20 March 2014.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 21 May 2014.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 1 July 2014.
- During the CHMP meeting on 21 July 2014 the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 24 July 2014.
- • During the meeting on 25 September 2014, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive scientific opinion to Signifor.

2. Scientific discussion

2.1. Introduction

Acromegaly

Acromegaly is a rare, serious, and debilitating condition caused by chronic hypersecretion of growth hormone (GH), which, in over 95% of patients, originates from a GH-secreting pituitary adenoma. In patients with acromegaly, basal GH secretion is characterized by a continuous high level with relatively blunted bursts, in comparison to the general population who usually maintain a low GH level during the day, ranging from undetectable to secretory peaks of up to 15 µg/L during sleep. Insulin-like growth factor-1 (IGF-1), which mediates most of the growth-promoting actions of GH, is elevated in parallel with the log of GH concentration.

The clinical manifestations of acromegaly are due to the peripheral actions of GH and IGF-1 and local tumour mass effect. The chronic GH and IGF-1 excess leads to progressive somatic disfigurement due to excessive skeletal growth and soft tissue enlargement. Metabolic complications include increased blood glucose levels, hyperinsulinaemia, diabetes, and dyslipidaemia. Local tumour effects may lead to visual field defects, and in case of large extensive tumours to hydrocephalus or focal epilepsy. Further complications include panhypopituitarism, hypertension, cardiac myopathies, colonic polyps, carpal tunnel syndrome, goiter and respiratory complications (e.g. sleep apnea, upper airway obstruction). Acromegaly can cause a variety of symptoms, such as headache, excessive sweating, arthralgia, paresthesia and severe lethargy. In addition, in patients with adenomas which co-secrete GH and prolactin (approximately 30% of acromegaly patients), the prolactin excess leads to infertility and gonadal and sexual dysfunction.

Patients with acromegaly have a shortened life expectancy, with a mortality rate that is approximately twice that of the general population, and an average reduction in life expectancy of 10 years. The excess mortality is primarily a result of cardiovascular disease and respiratory complications. High GH/IGF-1 levels, arterial hypertension and cardiomyopathy confer a poorer prognosis.

The prevalence of acromegaly is estimated to be 40 to 70 cases per million, with an annual incidence of 3 to 4 new cases per million. Owing to its insidious onset, acromegaly is often diagnosed late (4 to more than 10 years after onset), at an average age of about 40 years.

Clinical diagnosis is suggested by the typical disfigurement of the patient related to progressive acral enlargement and modification of facial appearance. Diagnosis is confirmed biochemically by findings of increased serum GH concentrations that are not suppressed following an oral glucose tolerance test, and by increased IGF-I levels.

The therapeutic goals in acromegaly are to relieve symptoms, to reduce pituitary tumour volume, to avoid tumour relapse, and to reduce mortality to the expected age- and sex-adjusted rates.

Current treatment options

Treatment modalities for acromegaly include surgery, radiotherapy and medical treatment.

Surgery: Transphenoidal surgery is currently the most frequently recommended treatment, except for patients who are poor surgical candidates, have invasive tumours, or who refuse surgery. The surgical effectiveness

varies depending on expertise in pituitary surgery and the size and extension of the anatomic mass. Early remission, defined by target GH levels of <2.5 µg/L, are achieved in about half of all patients. Patients who do not achieve normalization of GH and IGF-1 with surgery require additional treatment, usually with medication. On the other hand, if damage to the surrounding normal pituitary tissue occurs during surgery, the patient may require lifelong pituitary hormone replacement.

Radiotherapy: Radiation is usually reserved for patients who have tumour remaining after surgery, for patients who are poor candidates for surgery, and for patients who do not respond adequately to surgery and/or medication. The main disadvantages of radiotherapy are that normalization of GH secretion may take more than 10 years to occur, and that most patients eventually develop anterior pituitary insufficiency. Complications are now very rare, but concerns have been raised over an association of radiotherapy with premature cerebrovascular disease.

Medical treatment: Currently the medical treatment options for acromegaly include somatostatin analogues (SSAs), GH antagonists, and dopamine agonists.

SSAs are the medical treatment of choice in acromegaly. Currently two different molecular entities, octreotide (Sandostatin) and lanreotide (Somatuline), are available commercially. Octreotide, which has been available for 25 years, is available as a short-acting sc formulation for twice-daily administration, and a long-acting (LAR) microsphere preparation administered by im injection every 4 weeks. Lanreotide is available in a microsphere formulation (sustained release [SR]) and a saturated aqueous solution (Autogel [ATG]); the recommended initial injection frequency is every 2 weeks for the SR formulation and every 4 weeks for the ATG formulation. Current medical management of patients with acromegaly generally employs use of either octreotide LAR or lanreotide ATG (Melmed 2009). In prospective, multicenter, international, controlled, large clinical studies performed with octreotide in patients naive to previous SSA treatment the rate of biochemical control (i.e. GH $\leq$ 2.5 μg/L and normal IGF- 1) in the ITT populations were between 18 and 27% (Mercado et al 2007, Colao et al 2009).

Both octreotide and lanreotide inhibit tumour growth; around 75% of patients experience reduction in tumour volume of at least 20% with octreotide LAR as first-line therapy, whereas the proportion of patients with tumour shrinkage appears to be lower with lanreotide. The administration of SSAs prior to transphenoidal surgery also improves the outcome of surgery and acromegaly-associated morbidity. Known side effects include asymptomatic gallstones and transient gastrointestinal disturbances (e.g. diarrhoea, nausea, abdominal pain) in approximately 30% of patients, and injection site pain and bradycardia have also been reported.

Pegvisomant (Somavert), a pegylated recombinant GH analogue is currently the only commercially available GH antagonist. It is indicated for patients who have had an inadequate response to surgery and/or radiation therapy and/or other medical therapies, or for whom these therapies are not appropriate. The efficacy of pegvisomant in reducing circulating IGF-1 levels is relatively high (around 75% of patients achieved normal IGF-1 levels after 2 years), and is additive with that of SSAs. While pegvisomant antagonizes peripheral action of GH and blocks IGF-1 generation, it does not reduce circulating GH levels and does not impede tumour growth. Transient increases in hepatic transaminase levels are observed in ~5% of patients. Other side effects include injection-site reactions and lipohypertrophy, likely reflecting local adipocyte GH insensitivity.

Dopamine agonists (e.g. bromocriptine, quinagolide, cabergoline) bind to D2 dopamine receptors in the pituitary gland and suppress secretion of prolactin and GH. They have been used in acromegaly both as monotherapy and in combination with an SSA. Their advantage is that they can be administered orally and are of relatively low cost. The efficacy of bromocriptine is low, with about 10% of patients normalizing IGF-1. The second-generation cabergoline is more effective, about half of patients achieving GH levels <2.5 µg/L, a third

normalizing IGF-1, and tumour shrinkage observed in a third of patients. Cabergoline appears to be more effective in patients with tumours co-secreting prolactin and GH, and in patients with lower baseline IGF-1 levels, however the data reported in individual studies is highly variable. Less data is available for quinagolide, with response rates between 17% and 43% reported for normalization of IGF-1. Dopamine agonists are not widely used, as they are associated with an increased risk of cardiac valvular dysfunction, which may be of particular concern in a patient population with cardiac co-morbidities including left ventricular hypertrophy.

Unmet medical need

A significant proportion of patients with acromegaly do not achieve biochemical control with currently available treatment options (surgery, currently available medical treatment options, or radiotherapy). There is, therefore, a significant unmet need for additional, more effective medical treatment options both in newly diagnosed patients with acromegaly for whom surgery is not an option, and in those patients who do not achieve biochemical control post surgery or with currently available therapies.

About the product

Signifor contains pasireotide and is a somatostatin analogue (SSA) exerting its pharmacological activity through binding to somatostatin receptors. Pasireotide is a cyclic hexapeptide (pasireotide embonate; also known as pasireotide pamoate). The pasireotide subcutaneous (sc) formulation (pasireotide diaspartate) was approved in the EU on 24-Apr-2012 for the treatment of Cushing's disease.

The purpose of this application is to obtain marketing authorization for pasireotide powder and solvent for suspension for intramuscular (im) injection (also referred to as pasireotide long-acting release (LAR)) 20 mg, 40 mg and 60 mg.

The following revised indication was proposed by the time of conclusion of the procedure:

Signifor is indicated for the 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.
Pasireotide LAR is provided as pasireotide embonate in vials containing 20 mg, 40 mg and 60 mg.

Pasireotide LAR is intended for deep intramuscular injections every 4 weeks. The recommended initial dose is 40 mg every 4 weeks with a maximum dose of 60 mg every 4 weeks. There are no dose adjustments recommended in the elderly or in renal impairment. In patients with moderate hepatic impairment an initial dose of 20 mg and a maximum dose of 40 mg are recommended. Pasireotide LAR should not be used in patients with in severe hepatic impairment.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as powder and solvent for suspension for injection (i.m.) containing pasireotide embonate as active substance corresponding to 20 mg, 40 mg and 60 mg of pasireotide. It is a long-acting release (LAR) formulation intended to be administered once a month containing microparticles of pasireotide embonate. The active substance in this LAR formulation is a different salt (embonate instead of diaspartate) to the currently authorised Signifor solution for injection.

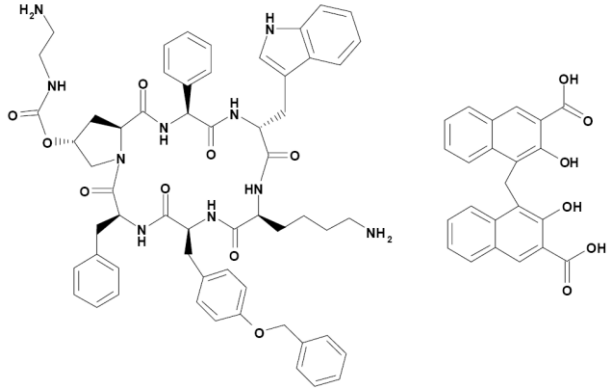
Other ingredients are: poly(D,L-lactide-co-glycolide) in the powder and carmellose sodium, mannitol, poloxamer 188 and water for injections in the solvent, as described in section 6.1 of the SmPC.

The product is available in vials containing the powder and pre-filled syringe containing the solvent, packaged in a blister together with a vial adapter and a safety injection needle as described in section 6.5 of the SmPC.

2.2.2. Active Substance

General information

The active substance pasireotide embonate is a cyclic hexapeptide. Its chemical name is (2-Aminoethyl)carbamic acid (2R,5S,8S,11S,14R,17S,19aS)-11-(4-aminobutyl)-5-benzyl-8-(4-benzyloxybenzyl)-14-(1H-indol-3-ylmethyl)-4,7,10,13,16,19-hexaoxo-17-phenyloctadecahydro-3a,6,9,12,15,18 hexaazacyclopenta cyclooctadecen-2-yl ester pamoic acid salt, corresponding to the chemical structure below. Its molecular formula is $C_{58}H_{66}N_{10}O_9 \bullet C_{23}H_{16}O_6$ and has a relative molecular mass 1047.21 (base), or 1435.58 (embonate salt).



It appears as a white to yellowish, hygroscopic, amorphous powder, practically insoluble in water and in buffers above pH 4 but slightly soluble in 0.1 N HCl. The pKa values for pasireotide base are pKa1 = 10.2, pKa2 = 9.1. However, it has not been possible to evaluate either the pKa nor the Log P and Log D for the embonate salt due to its low solubility in water and n-octanol respectively.
The structure of the active substance is supported has been confirmed by elemental analysis, UV, IR, ^{1}H-NMR, ^{13}C-NMR and MS.
Pasireotide exhibits stereoisomerism due to the presence seven stereocentres. Nevertheless each amino acid used in the solid phase peptide synthesis is a pure stereoisomer of known absolute configuration. Due to the chosen synthetic conditions no changes occur to the amino acids' stereochemistry, which is controlled by appropriate specification, during the peptide chain synthesis and this was demonstrated by analysing sufficient number of batches of active substance. There is also no influence on the established stereochemistry during the formation of the cyclopeptide either, which was demonstrated by analysis results of sufficient number of batches of pasireotide embonate.
No crystalline form was identified and pasireotide embonate is consistently manufactured as an amorphous powder only.

Manufacture, characterisation and process controls

Pasireotide embonate is produced by solid phase peptide synthesis in nine steps. The starting and raw materials used in the synthesis are commercially available or prepared from commercially available materials and are

controlled by suitable specifications. Apart from the first three batches all other subsequent batches during development were manufactured with the commercial process. The critical steps in the synthesis have been identified and reported and controlled by appropriate in-process controls.
The manufacturing process of pasireotide embonate is similar up to salt formation to the currently approved pasireotide diaspartate. Both drug substances share the same bond forming steps, chromatographic purification and only differ in the salt forming agent (embonate instead of diaspartate).
The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities and degradation products have been characterised and toxicologically qualified as appropriate.

As the manufacturing process is fully synthetic and there are no aseptic or sterilisation processes, validation results were not presented. However, validation on three consecutive commercial-scale batches will be performed in accordance with an agreed protocol to confirm the consistency of the manufacturing process.

Specification

The active substance specification includes tests and limits for: appearance (visual), particle size (laser diffraction), specific surface area (nitrogen adsorption), identity (IR, HPLC), sulphated ash (Ph. Eur.), water content (KF), heavy metals (ICP-OES), assay (HPLC), assay of salt forming agent (ion chromatography), amino acid analysis (hydrolysis-separation-derivatisation-photometric detection), related substances (HPLC), residual solvents (GC), specific optical rotation (Ph. Eur.), clarity and colour of the solution (Ph. Eur.), microbiological quality (Ph. Eur.) and bacterial endotoxins (Ph. Eur.).
The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines.
Batch analysis data from four representative development batches manufactured in the production equipment and used in nonclinical, clinical, technical and stability studies have been provided.
Moreover seven production scale batches of pasireotide embonate, manufactured at the proposed commercial production site, have additionally been tested by gas chromatography with flame ionisation detection (FID) method for the absence of residual solvents used in earlier synthetic steps of manufacturing process of the active substance. All the provided results were within the proposed specification for the active substance confirming the consistency of the process.

Stability

Stability data on three production scale batches of active substance from the proposed manufacturer stored in the intended commercial package for up to 24 months under long term conditions at -20 ºC / ambient RH and for up to 12 months under accelerated conditions at 5°C ± 3°C / ambient RH and 25 ºC / 60% RH according to the ICH guidelines were provided.
Two further batches were placed on stability under the same range of conditions to evaluate the impact of elevated heavy metal content and of an alternative packaging type on the active substance stability. Results available up to 60 months in long term have been presented for an alternative type of packaging.
Tests parameters monitored during the stability studies were appearance, identity, related substances, water content, specific optical rotation, clarity of the solution, colour of the solution and assay. Particle size distribution, specific surface area, microbial enumeration test and bacterial endotoxins test were also tested at certain time points, conditions and/or packaging as per the stability protocol. The acceptance criteria and methods were the same as those for release. The analytical methods were shown to be stability indicating.
No significant changes were observed in any physical, chemical and microbiological parameters tested.
Photostability testing following the ICH guideline Q1B was performed on one batch. The results indicate the active substance should be protected from light.
Results on stress conditions (strong acidic, strong alkalic, oxidative, heat, open dish) were also provided on one batch.

Based on presented stability data, the proposed re-test period and storage conditions for pasireotide embonate are acceptable.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

The objective of the pharmaceutical development was to develop a powder and solvent for suspension for intramuscular (im) injection for long-acting release (LAR) of 20 mg, 40 mg or 60 mg of pasireotide. By controlling the release rate, the LAR formulation is expected to produce less peak-to-trough fluctuation than an immediate release subcutaneous formulation thereby potentially minimising adverse events.
Signifor powder and solvent for suspension for injection finished product consists of:

- powder (i.e. microparticles) containing the active substance filled in vials, and a
- solvent (solution composed of commonly used excipients and water for injections) filled in prefilled syringes in which the microparticles are suspended prior to injection.

The embonate salt has been selected for the long acting release formulation based on its low solubility in water as well as superior stability in the selected controlled release polymer system. The active substance is uniformly distributed within the microparticles, which consist of a mixture of two poly (D,L-lactide-co-glycolide) copolymers (PLGA), and from which the active substance is continuously released primarily by diffusion and hydrolysis/erosion. All dosage strengths (20 mg, 40 mg and 60 mg) are derived from the same microparticles, and differ only in the amount of powder filled in the vials. Different variants differing in copolymer composition, ratio and manufacturing process have been developed and tested in Phase I studies. The proposed formulation was selected because of the most favourable PK profile.
The two copolymers, belong to a well-known family of biocompatible poly (D,L-lactide-co-glycolide) copolymers, which have been used for many years in similar commercial products. They are composed of lactide and glycolide building blocks and degrade into lactic and glycolic acid, both of which occur physiologically in the body and are metabolised by normal physiological pathways and are suitable for use in human by the intended route of administration. Both copolymers are controlled prior to their use in the manufacture of microparticles according to in-house appropriate testing monographs.

Drug burst, which determines the release within the first 24 hours, and drug release, which characterises the long term release, are critical quality attributes for the finished product performance. Besides solubility, the active substance particle size distribution (PSD) and specific surface area (SSA) are potential critical physical properties for the product performance and they are therefore routinely controlled. Further experiments on the influence of active substance SSA on the finished product critical quality attributes (e.g. finished product particle size distribution, drug burst, drug release) revealed a relationship between SSA and product PSD and support the proposed specification for these parameters. The influence of particle size on drug burst has been also demonstrated and suitable limits have been established based on batches from clinical trials.
Finally the drug release test is performed at accelerated conditions to obtain complete release within six days qualifying it as a routine quality control test. This accelerated test method has been shown to discriminate batches with different polymeric ratios and molecular masses, and different process parameters. However since the reproducibility of manufacturing process regarding *in vivo* performance in other sites (used during development) has not been demonstrated, any changes in the manufacturing process as well as any future new manufacturing site have to be verified by bioequivalence studies.
The solvent is a 2 ml clear, colourless to slightly yellow or slightly brown solution, filled in prefilled syringes with rubber stoppers, finger grip, hub and cap. It is used to suspend powder to prepare the suspension for injection prior to administration. The solvent development (choice of excipients, selection of manufacturing process, and choice of container closure system) was based on previous experience from other authorised microparticle medicinal products. The solvent was further modified to meet the product specific requirements to provide an

isotonic aqueous solution of physiological pH, and to suspend the dry microparticle powder within short timeframe leading to a homogeneous suspension for parenteral administration. The excipients employed are standard pharmacopoeial excipients commonly used in parenteral formulations. A vial adapter was additionally introduced to allow easy transfer of the solvent into the vial and the transfer of the suspension into the syringe by the user.
All dosage strengths of microparticles must be suspended in the 2 ml solvent and the resulting suspension should be readily injected. This was demonstrated during development and is ensured by a suspendability test being performed as part of the specification. The leachable study results demonstrated that leachable compound levels are below the safety concern threshold (SCT) for any individual compound.
As the drug product is to be used together with the solvent, without any dilution with other products, no compatibility data with other products are required. Satisfactory in-use compatibility data have been presented with the proposed vial adapter.

The sterilisation method was selected taking into account the physicochemical properties of the active substance.The efficiency of the selected sterilisation method has been adequately demonstrated. Also during development the manufacturing process has been successfully scaled-up to the commercial facilities. There were no changes of any critical process parameters observed during up-scaling.
The finished product, primary packed in injection vials, is co-packaged in a protective blister containing the pre-filled syringe of the solvent, vial adapter and safety injection needle. Both the vial adapter and safety injection needle are CE marked.

Manufacture of the product and process controls

The manufacturing process for the powder consists of preparation of organic and aqueous phases, preparation of microparticles, washing; drying and sieving of microparticles, filling and stoppering of the vials and terminalsterilisation. The critical process steps and intermediates have been identified and the proposed in-process controls are adequate for this type of manufacturing process.
Process validation for this non-standard process was performed using full-scale production batches of bulk powder for suspension for injection (microparticles). Each bulk batch has been filled in one vial batch of each strength resulting in overall nine vial batches, three per strength, and terminally sterilized by gamma irradiation. The validation batches have been processed in the same manufacturing facilities, using the same process and the same equipment as for the batches intended for commercial supply. The presented validation data confirm that the manufacture is sufficiently robust to produces product of consistent quality complying with the designated specification.
The manufacturing process for the solvent consists of standard manufacturing processes and employing the dissolving of the excipients in water for injection, filtering and filling into the glass syringes followed by terminal sterilisation. No critical process parameters were identified because although the sterility may be regarded as critical, all contributing factors for achieving a sterile product are validated and well controlled and therefore each single step is regarded as non-critical. Furthermore the process is controlled by appropriate in-process control testing performed during manufacture. The manufacturing method of the solvent for suspension for injection has been validated using three full-scale production batches which have been processed in the same manufacturing facilities, using the same process and the same equipment as for the batches intended for marketing. The validation results were provided and are compliant with specifications.

Product specification

The finished product release specifications include appropriate tests and limits for appearance, (visual examination), suspendability (visual examination), pH of the constituted suspension (Ph. Eur.), identification (HPLC and TLC), water content (KF), degradation products (HPLC), assay (HPLC), particle size (laser light diffraction), uniformity of dosage unit (Ph. Eur.), bacterial endotoxins (Ph. Eur.), drug burst and drug release

(Ph. Eur. –HPLC), molecular mass of the polymer (GPC), tightness of container (dye intrusion), uniformity of deliverable dose (HPLC) and sterility (Ph. Eur.).
Batch analysis results are provided for nine validation and eight clinical batches all of which are considered representative of commercial batches. Results confirm the consistency of the manufacturing process and its ability to manufacture to the intended product specification.
The specifications for the release and stability testing of the solvent include appropriate tests and limits for appearance of the container (visual examination), clarity and colour of the solution (Ph. Eur.), pH (Ph. Eur.), viscosity (Ph. Eur.), extractable volume (Ph. Eur.), subvisible particulate matter (Ph. Eur.), visible particles (Ph. Eur.), bacterial endotoxins (Ph. Eur.), sterility (Ph. Eur.) and tightness of containers (visual by dye intrusion).
Results of analysis of representative stability and production scale batches of the solvent were provided and they comply with the specifications.

All analytical methods used for both the powder and the solvent have been well described and validated according to ICH guidelines.

Stability of the product

Stability data were provided for three pilot batches of 20 mg strength and three pilot batches of 80 mg strength stored in both inverted and upright position under long term conditions at 5°C /ambient humidity for up to 36 months and under accelerated conditions at 30°C/75% RH and 25 ºC / 60% RH up to 36 months and under 40 ºC / 75% RH and -20°C/ ambient humidity for up to six months according to the ICH guidelines.

At start of the stability studies program the 80mg strength was considered the highest possible strength. Hence in line with ICH requirements the 40mg and 60mg strengths are bracketed by 20mg and 80mg strengths. However the 80 mg strength was not eventually applied for authorisation. For this reason, two pilot batches of 60 mg strength, in addition, were also studied for stability and data were presented for up to 24 months at 5°C /ambient humidity and at 25 ºC / 60% RH.
The different dosage strengths differ only in filling different amounts of microparticles (powder for suspension for injection) into the primary packaging proposed for marketing therefore they are considered representative to those proposed for marketing and the matrixing approach is deemed acceptable.
Samples were tested as per the release specification test by the same analytical methods which are considered stability indicating. All chemical and physical data generated over 36 months under the proposed storage condition, stored inverted and upright, meet the specifications. No difference was observed between inverted and upright storage.
In addition, two batches (one 20 mg and one 80 mg strength) were exposed to light as defined in the ICH Guideline on Photostability. Results show that exposure to light has no effect on the product quality.
Finally freeze and thaw cycle test showed no trends and all results comply with the specifications.

In-use stability of the suspension
Stability of the suspended solution in vials has also been investigated and the data demonstrate that the suspensions are stable at room temperature over 3 hours.

Based on available stability data, the shelf-life and storage conditions as stated in the SmPC are acceptable.

Adventitious agents

No excipients of human or animal origin are used in the manufacture of Signifor 20mg, 40mg and 60mg powder and solvent for suspension for injection.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The type of formulation drove the choice of the active substance salt and the controlled release formulation system. In addition, the physicochemical properties of the active substance were taken into account in the selection of the manufacturing process. The performance of the long acting formulation has been ensured by appropriate design of the pharmaceutical formulation and the processes and the applied control strategy. The results of tests 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(s) for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

Several studies relevant for this application were submitted and assessed within the frame of the initial MAA for pasireotide (EMEA/H/C/2052).

2.3.2. Pharmacology

A number of in vitro and in vivo pharmacology studies were performed by the Applicant to evaluate the effects of pasireotide on GH and IGF-1 secretion, the two primary biochemical parameters used to evaluate efficacy of treatment for acromegaly. These studies were submitted and assessed within the frame of the initial MAA for pasireotide (EMEA/H/C/2052) and can be summarized as follows:

Functional activity at human recombinant somatostatin receptor subtypes demonstrated pasireotide to be a full agonist, with nanomolar or subnanomolar potency at hsst1, hsst2, hsst3 and hsst5 receptor subtypes. Consistent with its high in vitro binding affinity for sst2 and especially sst5, pasireotide inhibits the GHRH-induced GH release from primary cultures of rat pituitary cells. In vivo in rats, pasireotide inhibited unstimulated GH release and caused a dose-dependent decrease in plasma IGF-1 levels following sc infusion of 1, 10 or 50 µg/kg/h of pasireotide for 7 days. In rhesus and cynomolgus monkeys, pasireotide is also a strong inhibitor of GH and IGF-1. The ID50 of pasireotide for the inhibition of GH in rhesus monkey was 0.4 µg/kg sc and thus similar to the values obtained in rats.

For the present application, a new in vivo study concerning the effect of pasireotide LAR on hormone secretion in rats was submitted. Single sc injection with pasireotide LAR (8 mg/kg) resulted in a pharmacologically active plasma level (49 ng/ml) within 24h and reached peak exposure after 28 days (94 ng/ml). At this dose, a strong (to 40% of control) and long-term (49 days) inhibition of plasma IGF-1 was obtained, which could not be enhanced by increasing the dose. A transient minor increase in plasma glucose was observed on day 1, but showed rapid tachyphylaxis. There were also effects on plasma glucagon levels (transient decrease) and plasma insulin (decrease remaining at 15 days, but after that showing normalization).

It is not clear why the new in vivo study was conducted with sc instead of im injection, which is the intended clinical route of the LAR formulation. However, since plasma levels in a similar range were demonstrated after a single dose, im injection with the LAR formulation (Study R0600360), the study results obtained with sc injection are considered to apply also for im injection.

In conclusion, the results of a number of in vitro and in vivo preclinical pharmacology studies suggest that pasireotide LAR has the potential to inhibit GH and IGF-1 secretion and thus be effective in the treatment of acromegaly. Pharmacodynamic effects of pasireotide are reflcted in section 5.1 of the SmPC.

2.3.3. Pharmacokinetics

A number of pharmacokinetic studies were submitted and assessed within the frame of the procedure for the initial MAA (EMEA/H/C/2052). These studies were conducted in mice, rats, rabbits, dogs and monkeys using sc and iv dosing. Since it is reasonable to assume that pharmacokinetic parameters apart from absorption would be similar for both LAR (long-acting release, im administration) and sc solution formulations, no new PK studies to evaluate distribution, metabolism and excretion have been performed by the Applicant with the LAR formulation, im administration. This is considered acceptable.

The Applicant has conducted a single dose study with two different LAR formulations (2 and 2b), using im injection, to investigate absorption and bioavailability (Study R0600360). The results show that pasireotide embonate was well absorbed after im dosing in rats (absolute bioavailability 85% and 108%, respectively, for formulations 2 and 2b). The interanimal variability was moderate to high; however, a sustained release of pasireotide embonate up to Day 63 after a single im injection in rats could be demonstrated. Both formulations tested caused a local inflammatory reaction at the injection site. Similar local irritative effects have been observed with pasireotide, sc solution, in all animal species investigated.

The Applicant has submitted two new drug transporter studies, studies 1200835 and 1200761, on the assessment of pasireotide as an inhibitor of human organic anion and cation transporters.

2.3.4. Toxicology

Toxicological and toxicokinetic studies using pasireotide aspartate, sc solution, have previously been performed in mice, rats, rabbits and monkeys. These studies include acute, subchronic and chronic toxicity studies, carcinogenicity studies, reproductive toxicity studies, and in vitro and in vivo genotoxicity studies. The results of these studies are considered to be relevant also for pasireotide LAR.

The Applicant has presented an exposure margins table for the carcinogenicity and reproductive toxicity studies conducted with pasireotide, sc solution, using values from the healthy volunteer study with pasireotide LAR, 60

mg. The animal/human exposure margins for pasireotide LAR are within the same range, although slightly lower, than those for pasireotide sc solution.

With regard to carcinogenicity, there were no tumour findings in mice or female rats. In male rats, fibroma was observed at the high dose level (10-fold margin based on AUC). This effect was linked to local irritation at the injection site. It should be noted that daily subcutaneous injection was applied in the rat carcinogenicity study. For pasireotide LAR, there will be only one monthly intramuscular injection and the injection site (as recommended in the SmPC) will be alternated between the left and right gluteal muscle**.** Thus, there will be no continuous inflammatory reaction at the injection site, and the risk for development of fibroma is considered highly unlikely.

For reproductive toxicity, pasireotide did not affect male fertility, but caused prolonged estrus cycles/acyclicity and a decreased mean numbers of corpora lutea in females due to the pharmacological activity (no NOAEL). Embryotoxicity at maternally toxic doses was seen in the rat and rabbit, but no teratogenic potential was detected in these two species under the study conditions. A slight retardation in the development of pinna detachment and reduced foetal body weight were observed in the prenatal-and-postnatal development study (no NOAEL). The wording under section 4.6 in the SmPC is identical to that of pasireotide sc solution and is considered adequate.

To confirm the local and systemic effects of the LAR formulation, the Applicant has conducted local tolerance and repeat-dose toxicity studies in rats. All studies included toxicokinetics and were conducted in accordance with GLP.

Single dose toxicity

No single dose toxicity studies have been performed with the LAR formulation, im administration. The single dose toxicity studies in mice and rats conducted with pasireotide sc formulation are considered sufficient to support the assessment of systemic acute toxicity of pasireotide in general, including the LAR formulation given by im administration. The maximum dose was 30 mg/kg (corresponding to 30 ml/kg as the maximum practical volume) which was non-lethal.

Repeat-dose toxicity

Two repeat-dose toxicity studies (3 cycles/1 injection per month; 6 cycles/1 injection per month) were conducted in rats with the LAR formulation, im administration. The majority of findings in these two studies are considered to reflect the pharmacology of pasireotide, as discussed below:

Decreases in body weight/body weight gain and food consumption; effects on bone growth (inactive growth plates, atrophy of trabecular and compact bone): these effects are most likely related to pasireotide's inhibitory effect on the secretion of GH from the pituitary gland. It is possible that the tibia fracture observed in a rat treated at 3.125 mg/injection pasireotide LAR in the 6-month study was caused by a weakness in the skeleton due to pasireotide's effects on bone growth. Since bone growth is continuous in rodents, but not primates, and no skeletal findings were observed in nonhuman primates treated with pasireotide sc solution, these effects on bone are not considered relevant for adult patients.

Decreased weight of the pituitary gland, correlated with atrophy/decreased acidophilia in pars distalis; increased zymogen granules in the exocrine pancreas; decreased weight of the adrenal gland, correlated with atrophy and cortical vacuolation, and *decreased weight of the thyroid gland, correlated with follicular cell atrophy and attenuation of epithelium,* are all considered to be effects on the neuroendocrine system caused by the pharmacological mode of action of pasireotide.

Effects on the liver, as reflected by a number of changes in clinical chemistry and coagulation parameters (increase in serum aspartate and alkaline phosphatase activity; decrease in total serum protein, globulin and

albumin; increased bilirubin and cholesterol; decreased fibrinogen; increased APTT) might be secondary to the effects of changes of pituitary GH production by pasireotide and resultant changes in the hepatic metabolism and production of coagulation factors. Transient increase in liver enzymes and coagulation factors has been shown in the clinic and measurements of these enzymes are recommended before and during treatment with Signifor in the SmPC section 4.4.

Effects on kidney and excretion parameters (decreased urine volume, increased phosphorus, urea, sodium and chloride; decreased calcium and creatinine) have previously been observed in rat studies with pasireotide sc solution and are thought to be the result of pharmacologically mediated vasodilation, affecting renal blood flow and causing a decrease in the kidney filtration rate.

Effects on hematology parameters and bone marrow: decreased cellularity in the bone marrow, decreased numbers of lymphocytes, white blood cells, and platelets, might be related to the pharmacological properties of somatostatin analogues specifically due to the binding of these compounds to the receptors of hematopoietic precursor cells (CD34+ cells), monocytes and lymphocytes inhibiting the proliferation of these cells.

Injection site erythema and inflammation: similar or more pronounced local irritative effects were previously observed in animal studies with pasireotide sc solution and have also been reported in patients receiving pasireotide. There is a warning for these side effects in the SmPC. The increased numbers of neutrophils noted in some rats injected with pasireotide LAR are most likely related to local inflammatory reactions at the injection site. In the 6-month rat study with pasireotide LAR, muscle atrophy at the injection site occurred at similar incidence and severity in the vehicle and placebo controls as compared to the pasireotide-treated groups.

The only findings in the repeat-dose toxicity studies with pasireotide LAR not previously observed with pasireotide sc solution are adrenal atrophy/cortical vacuolation, decreased platelets and decreased glucose. These findings are most likely related to the pharmacology of pasireotide.

In conclusion, most findings seen in repeat-dose toxicity studies with pasireotide LAR could be attributed to the pharmacology of pasireotide being a somatostatin analogue. There is not a complete overlap between findings in studies using the sc formulation and findings in the two repeat-dose toxicity studies with the LAR formulation; however, no significant new findings were observed with the LAR formulation. All observed findings were fully or partly reversible following cessation of dosing.

Antigenicity

Anti-drug antibodies were measured in the 3-month and 6-month repeat-dose toxicity studies with pasireotide LAR. In both studies, anti-drug antibodies were demonstrated (> 50% of animals in the 3-month study, 44% of animals in the 6-month study). As judged from the pharmacologic effects observed, these antibodies do not appear to have a neutralizing effect on pasireotide.

Formulations and exposure margins

The Applicant used various formulations in the non-clinical studies. Formulations A and B in the 3-month rat study are identical to formulations 2 and 2b, respectively, used in the healthy volunteer study (CSOM230C2101). Higher exposure levels were achieved in animals with formulation 2b/B, which probably explains why clinical chemistry changes were more pronounced in those animals as compared with rats treated with formulation 2/A. However, the incidence and severity of histopathological findings were similar regardless of the formulation used in the 3-month rat study.

Based on TK and immunogenicity data, an impact of anti-drug antibodies on TK data was observed. Immunogenicity in an assay system of the type employed (ELISA) typically leads to artificially high TK values, since the biotinylated pasireotide-tracer is captured by anti-pasireotide antibodies. Because of this, all margin

calculations based on data from the 3-month and 6-month rat studies were performed using the systemic exposure after the 1st injection (presumably less affected by anti-drug antibody interference). At the low dose level of 3 mg/month (study 0770082), rats were 2.4- to 2.7-fold more exposed than humans and most effects were related to the pharmacological activity of pasireotide. There was no NOAEL to these effects, which is in line with the studies conducted in rats by the sc route (based on similar systemic pharmacological effects) whereas margins reached 39-55 in monkeys dosed sc.

Local tolerance

Single doses of pasireotide LAR im injection were generally well tolerated in rats and rabbits. Deposition of test substance as well as local inflammation occurred at the injection site both with placebo formulations and pasireotide LAR. The inflammatory reaction was more pronounced with pasireotide LAR. Recovery was not complete after 92 days, which is not uncommon with a granulomatous type of reaction. Similar local irritative effects have been observed with pasireotide sc solution, in all animal species investigated (see also under Repeat-dose toxicity).

Impurities

The Applicant has presented an acceptable argumentation for acceptance of impurities and degradation products and specification limits of pasireotide embonate.

2.3.5. Ecotoxicity/environmental risk assessment

Pasireotide PEC surfacewater value is below the action limit of 0.01 µg/L and is not a PBT substance as log Kow does not exceed 4.5. However, based on the mechanism of action of pasireotide, potentially indicating endocrine activity, and also on the fact that pasireotide is not readily biodregadable, a tailor-made ERA has been conducted, including a fish early life-stage study and an amphibian metamorphosis assay. No significant toxicity has been observed in these studies and the most sensitive endpoint found was algae growth, leading to a risk ratio of 0.0000532 for surface water. In conclusion, pasireotide is not expected to pose a risk to the environment.

2.3.6. Discussion on non-clinical aspects

Pasireotide LAR has been shown to be pharmacologically active in rats and to produce a similar toxicological profile as pasireotide sc solution following repeat-dose administration up to 6 months (6 cycles of once monthly im injections). There were no significant new findings in the 3- and 6-month repeat-dose toxicity studies in rats with the LAR formulation.

2.3.7. Conclusion on the non-clinical aspects

There was no objection to an approval of Pasireotide LAR from a non-clinical perspective.

2.4. Clinical aspects

2.4.1. Introduction

GCP

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

The applicant 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

Table 1 Tabular overview of clinical studies

Study	Trial design	Efficacy analysis set	Assessment time points	Treatment duration	Dosing regimen
[C2305] (Ongoing)	Phase 3, blinded, active controlled, randomized study of pasireotide im vs. octreotide im in patients with acromegaly to assess efficacy, safety, QoL, PK, and PK/PD relationship	Up to crossover: Pasireotide LAR: 176 Octreotide LAR: 182 After crossover: Pasireotide LAR: 81 Octreotide LAR: 38	GH (5 point mean level) was assessed from a 2 hour profile (120 min, 90 min, 60 min, 30 min and 0 min) prior to LAR injection. IGF-1 was assessed using a single sample taken prior to injection	12 months (core) (completed) 1 year extension phase[1] (completed) open label extension phase (ongoing for patients treated with pasireotide)	Pasireotide LAR: 40 mg q28d Octreotide LAR: 20 mg q28d
[C2402][5] (Ongoing)	Phase 3, multicenter, randomized, parallel-group, three-arm study of double-blind pasireotide LAR 40 mg and pasireotide LAR 60 mg versus open-label octreotide LAR 30 mg or lanreotide ATG 120 mg in patients with inadequately controlled acromegaly	Pasireotide LAR 40 mg: 65 Pasireotide LAR 60 mg: 65 Octreotide LAR or lanreotide ATG: 68	GH (5-point mean GH level) was assessed from a 2 hour profile (120 min, 90 min, 60 min, 30 min and 0 min) prior to injection IGF-1 was assessed using a single sample taken prior to injection	6 months core (completed) extension (ongoing, treatment with pasireotide LAR)	Pasireotide LAR: 40 mg or 60 mg q28d for 24 weeks Active control: Octreotide LAR: 30 mg q28d or Lanreotide ATG: 120 mg q28d for 24 weeks

Study	Trial design	Efficacy analysis set	Assessment time points	Treatment duration	Dosing regimen
[C2110]	Phase 1, open-label, randomized study assessing PK, safety, and tolerability profiles of 3 doses of pasireotide im in patients with acromegaly or carcinoid disease	35 acromegaly* 42 carcinoid	GH and PRL samples were taken at 30 min, 1 h, 1.5h and 2h. IGF-1 was assessed by using a single sample taken at a single time point prior to injection	3 months[2]	Pasireotide LAR q28d[2]: 20 mg, 40 mg, or 60 mg
[C2110E1] (Ongoing)	Open-label extension of Study C2110 to assess long-term safety, tolerability and PK/PD profiles	29 acromegaly 31carcinoid		Dependent on clinical benefit and at the discretion of the Investigator.	Pasireotide LAR q28d[3]: 20 mg, 40 mg, or 60 mg
[B2201]	Phase 2, open-label, randomized, crossover study in patients with acromegaly of multiple doses of pasireotide and octreotide to assess efficacy (biochemical response, tumour volume, symptoms), safety, and PK/PD relationship	60*	GH and PRL samples were taken 30 min and 1 min prior to the first pasireotide dose of the day and 30, 60, 90, and 120 min after the first dose. IGF-1 samples were taken 30 min and 1 min before dosing.	Octreotide sc for 28 days followed by pasireotide 200 µg, 400 µg, or 600 µg bid for 28 days in Period 1; patients progressed to each remaining pasireotide doses in Periods 2 and 3	Pasireotide sc bid: 200 µg bid, 400 µg bid, and 600 µg bid Octreotide: 100 µg tid
[B2201E3] (Ongoing)	Open-label extension of Study B2201 to asses long-term safety, efficacy, and PK	30		Dependent on clinical benefit[4] and lack of safety or tolerability concerns, at the discretion of the Investigator.	Escalation up to pasireotide sc 900 µg bid permitted
[B2103]	Phase 1, double-blind, randomized, crossover study in patients with acromegaly to assess efficacy of single-dose pasireotide vs. octreotide	12	GH and PRL samples were taken 30 min and 1 min prior to dosing, hourly over 24h and at 48h after injection IGF-1 samples were taken 30 min prior to dosing and 24 h and 48 h after dosing	Treatment sequence with 3 single-dose injections of pasireotide sc or octreotide sc each separated by 6-day washout period	Pasireotide sc: 100 µg and 250 µg single dose Octreotide sc: 100 µg single dose

Study	Trial design	Efficacy analysis set	Assessment time points	Treatment duration	Dosing regimen
DBL: database lock; LAR: long-acting release; QoL: Quality of life; PK: pharmacokinetic; PD: pharmacodynamic; im: intramuscular; sc: subcutaneous; q28d: every 28 days; bid: *bis in diem* (twice daily); tid: *ter in die* (three times daily) [1] Extension phase – prior to Amendment 4 the extension phase was not blinded. During the extension phase patients received 14 injections. Following Amendment 4, if patients crossed over they received the first injection of the crossover treatment on Month 13. Whereas prior to amendment 4 the first crossover treatment was received on Month 12. [2] A month was defined as 28 days; For patients who did not previously receive pasireotide, 300 µg pasireotide sc single dose was given, followed by ≥ 5 days washout to ensure patient tolerance. [3] Administered at Investigator's discretion [4] Patients in the extension phase were treated only with pasireotide. [5] The data cut-off for individual patients in Study C2402 was at Month 6 (end of core) * Eight patients who prematurely discontinued [B2201] entered [C2110] [C2110E1] – CSR based on the first DBL of the C2110 extension study [B2201E3] – CSR based on the third DBL of the B2201 extension study					

2.4.2. Pharmacokinetics

Note: Except for absorption, the distribution, metabolism and excretion properties of pasireotide between the Pasireotide sc formulation (EMEA/H/C/002052) and the Pasireotide LAR formulation (this application) were considered to be similar (assuming linear pharmacokinetic processes based on the dose proportionality shown for pasireotide) because the same active entity (pasireotide) is present in both formulations.

Consequently, data from the Pasireotide sc EPAR (EMEA/H/C/002052) and SmPC has been given when relevant.

Regarding interactions, within the approval of Pasireotide sc, it was concluded based on in vitro data that the risk of pasireotide affecting other drugs was low and no in vivo studies were requested. This conclusion must also be considered valid for the LAR formulation given that the expected average maximum plasma concentrations at steady state is lower for the LAR formulation (19 ng/ml) than following Pasireotide sc (45 ng/ml).

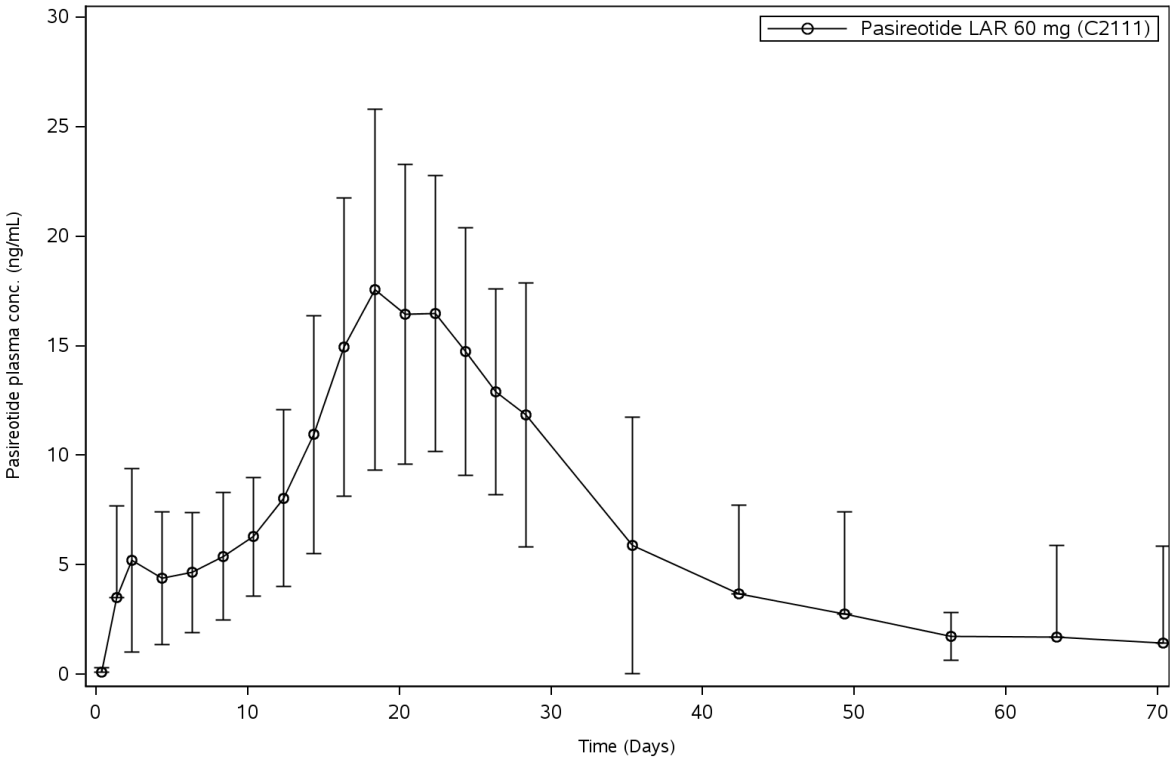
The PK of pasireotide LAR in healthy volunteers was characterized in five Phase I LAR single-dose studies. The PK and PK/PD of pasireotide LAR in acromegaly patients were characterized in one Phase I study and two Phase III studies. Full PK profiles have only been obtained from healthy volunteers whereas sparse sampling was performed in the patient studies.

Absorption:

The average pasireotide PK profile following a single intramuscular LAR dose of 60 mg is shown below. The graph is based on data from a total of 114 healthy volunteers (Study C2111).

Mean (SD) plasma concentration versus time profile for pasireotide LAR 60 mg in healthy volunteers C2111

In most subjects, the PK profile shows an initial burst release on the injection day, followed by a dip from Day 2 to Day 7, then a slow



increase
to maximum concentration around Day 20, and a slow declining phase over the next weeks.

No sign of significant dose dumping (except for the initial burst) was seen across studies.

Absolute bioavailability of pasireotide has not been studied but data on relative bioavailability of pasireotide LAR compared to pasireotide sc was obtained from studies C2101, B2116 and C2112. The relative bioavailability was > 1 in all studies which may suggest that the absorption is higher following administration of LAR relative to that of the sc formulation. However, the difference between pasireotide sc and LAR data may be possibly be explained by difficulties in estimating AUCinf for LAR given the high variability seen in the concentration time curve. Any potential difference in bioavailability between the two formulations/routes of administration is nevertheless accounted for as the LAR formulation has been studied in a comprehensive phase III program.

Regarding formulation development, formulation 2b has been used in all clinical studies, and also is the proposed market form.

Distribution:

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

Elimination:

Across studies, the effective T1/2 was approximately 12 hours and the apparent terminal T1/2 was approximately 16 days.

Across the patient studies, the accumulation ratio ranged between 1 and 2.

The main elimination pathway is hepatic clearance (biliary excretion) and this pathway has been roughly estimated to account for approximately 86% of the dose, predominantly in the form of unchanged drug. In a human ADME study, pasireotide was predominantly found in unchanged form in plasma, urine and faeces. Also in vitro, pasireotide appears to be metabolically highly stable. Pasireotide contains 6 chiral carbon atoms and stereochemical inter-conversion *in vivo* is unlikely. Pasireotide appears to be metabolically stable with little metabolism occurring and no metabolites in the systemic circulation (based on the Signifor sc EPAR).

Across the healthy volunteers studies, the inter-subject variability (CV%) of Cmax,p1 ranged from 21.8% to 73.0%, Cmax,p2 ranged from 20.6% to 53.4% and CV% of AUCinf ranged from 8.2% to 47.2%.

Special populations:

Based on data from the studies performed in patients, the MAH has performed numerous covariate analyses in the general form:

Log (trough pasireotide concentration) = intercept (random subject effect) + covariates + error

Body weight, gender and GGT levels were found to be statistically significant covariates in the final model for pasireotide trough concentration. The effects were not considered large enough to warrant specific dose recommendations.

Interactions (based on the Pasireotide sc EPAR and SmPC, except from the first sentence):
Two new *in vitro* studies demonstrate that pasireotide is not an inhibitor of OAT1, OAT3, OCT1 and OCT2.

Based on in vitro data pasireotide appears to be a substrate of efflux transporter P-gp (P-glycoprotein). Based on in vitro data pasireotide is not a substrate of the efflux transporter BCRP (breast cancer resistance protein) nor of the influx transporters OCT1 (organic cation transporter 1), OATP (organic anion-transporting polypeptide) 1B1, 1B3 or 2B1. At therapeutic dose levels pasireotide is also not an inhibitor of UGT1A1, OATP, 1B1 or 1B3, P-gp, BCRP, MRP2 and BSEP.

Based on in vitro inhibition studies it is considered unlikely that pasireotide would inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4/5 in vivo. Furthermore, pasireotide is not expected to induce enzymes regulated via the Ah receptor, CAR or PXR.

In general the interaction potential for pasireotide appears low since there are no strong indications that pasireotide would inhibit or induce enzymes or transporter proteins. Furthermore, pasireotide is mainly excreted unchanged via bile.

2.4.3. Pharmacodynamics

Mechanism of action

Natural somatostatin is a peptide hormone that is widely distributed in the neural, endocrine and immune system. Somatostatin action is mediated through five different somatostatin receptor (SSTR) subtypes (SSTR1 through SSTR5). All SSTRs belong to the superfamily of G-protein coupled receptors. They are expressed throughout the body in different tissues and cell types, with single cells expressing one or more subtypes at different densities.

The physiological actions of natural somatostatin are diverse. It is an important inhibitory regulator of endocrine and exocrine secretion of various organs, including the pituitary, pancreas, gastrointestinal (GI) tract, thyroid,

kidney, and adrenal glands. It modulates GI function (including bowel motility and absorption of nutrients), inhibits gallbladder contractility and bile flow, and stimulates GI water and electrolyte absorption. It also inhibits cell proliferation and activated immune cells, and promotes apoptosis.

Pasireotide (SOM230) is a second-generation SSA. It has a broader SSTR binding profile than the first-generation SSAs octreotide and lanreotide, with high affinity to four of the five receptors (SSTR1, 2, 3 and 5). Thus its binding profile is closer to that of natural somatostatin, which has similar affinity to all five receptor subtypes. Compared to octreotide, the binding affinity of pasireotide is 30-40 times greater for SSTR1 and SSTR5 and 5 times greater for SSTR3, whereas the affinity for SSTR2 is similar. Based on this SSTR binding profile, pasireotide is expected to be more efficacious than octreotide or lanreotide in acromegaly, both in patients with de novo disease and in those resistant to prior SSA.

Primary pharmacology

The main efficacy assessments were performed by normalization of GH and IGF-1 levels. Exposure-response relationship between pasireotide LAR concentrations and GH/IGF-1 levels in medically naïve acromegaly patients or inadequately controlled acromegaly patients are discussed in later parts of this report.

Secondary pharmacology

Hyperglycaemia: HbA1c and FPG

A summary of the 3 key mechanistic studies conducted in healthy volunteers to investigate the mechanism of pasireotide-induced hyperglycaemia and its management is provided below.

Study B2107, a single-center, open-label, dose escalation study conducted in male healthy volunteers evaluated the effect of repeated administration of pasireotide sc (single and multiple doses) on glucose, insulin and glucagon profiles. Results showed that in the fasting state, pasireotide induced a marked decrease in insulin, a smaller decrease in glucagon and an increase in FPG. When pasireotide was given after a breakfast meal, the decrease in insulin was smaller than in the fasting state. There appeared to be attenuation of the effects of pasireotide as glucose values on Day 7 tended to be lower relative to corresponding values of Day 1.

Study B2216 was an investigator-initiated phase 2, double-blinded, single-center study conducted in male healthy volunteers. Results demonstrated that the hyperglycaemia is primarily a consequence of decreased secretion of insulin and incretins (glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), with no changes in hepatic or peripheral insulin sensitivity. No dose related effects were observed.

The hyperglycaemic effect is in line with receptor binding profile of pasireotide. In humans, inhibition of insulin secretion from pancreatic islet cells is mediated mainly by SSTR2 and SSTR5, whereas the inhibition of glucagon secretion is mediated almost entirely by SSTR2. Higher affinity of pasireotide to SSTR5 than SSTR2 leads to relatively stronger inhibition of insulin than glucagon, which explains the stronger hyperglycaemic effect observed with pasireotide compared to other somatostatin analogues that bind avidly to SSTR2, but have lower binding affinity for SSTR5.

Study B2124, a randomized, single-center, open-label phase 1 study conducted in male healthy volunteers was initiated to better understand the effects of different anti-hyperglycaemic agents used in combination with pasireotide. The results confirmed that the underlying mechanisms of hyperglycaemia following pasireotide sc treatment in humans are mainly due to decreased insulin secretion and reduced GLP-1 and GIP incretin secretion with no changes in hepatic or peripheral insulin sensitivity. Results demonstrated that incretin based

therapies (i.e. GLP-1 analogues and DPP-4 inhibitors) are the most promising agents in the management of pasireotide-induced hyperglycaemia.

PK/PD analyses of pasireotide concentration and FPG and HbA1c levels indicated that the risk that a patient develops hyperglycaemia increases with higher pasireotide exposure; a 1.5-fold increase (corresponding to dose increase from 40 mg to 60 mg) in trough concentration increased the odds of hyperglycaemia (defined as FPG change from baseline >36 mg/dL) by 21% in medically naïve patients and 36% in inadequately controlled patients. Higher baseline HbA1c was found to increase the risk of hyperglycaemia.

Cardiac safety: QT intervals

Healthy volunteers – sc bid doses

Two TQT studies, Study B2113 and Study B2125 were conducted with the pasireotide sc formulation in healthy volunteers. Study B2113 was conducted to determine whether pasireotide sc, at the maximum tolerated dose (MTD), has an effect on cardiac repolarization. The study showed a maximum placebo-subtracted QTcF change from baseline of 17.5 ms at the supratherapeutic dose of 1950 µg bid. Pasireotide treatment was associated with heart rate (HR) decreases up to 4 hours post-dose (maximum change from baseline of 10.7 bpm).

A second TQT study Study B2125 was conducted to further characterize the impact of pasireotide on QTc. Given the observed bradycardia effect with pasireotide in Study B2113, an individual QT correction for HR (QTcI) was used. Study B2125 encompassed 2 pasireotide dose levels (a therapeutic dose of 600 µg bid and a supra-therapeutic dose of 1950 µg bid).

The results from Study B2125 were consistent with those from Study B2113, and confirmed that pasireotide is associated with QT interval prolongation and bradycardia in healthy volunteers at therapeutic and supra-therapeutic doses. The maximal placebo-subtracted change from baseline in QTcI was 13.19 ms (600 µg bid) and 16.12 ms (1950 µg bid) at 2 hours post dose, ~1.5 hours later than the peak in pasireotide concentration which was observed at ~0.5 hour. This delay between maximal drug concentration and QT effect suggests that pasireotide does not interact directly with cardiac ion channels, which is consistent with the absence of a signal for QT prolongation in preclinical studies.

The dose-response effect for QTc prolongation was relatively flat between pasireotide doses 600 µg bid and 1950 µg bid. The small difference between the 2 doses in terms QTcI prolongation (i.e. 13 vs. 16 ms) suggests that the pasireotide QTcI effect is reaching a plateau in this dose range (corresponding to a concentration range of 25 to 90 ng/mL).

For pasireotide sc formulation, the observed Cmax,ss (mean±SD) at the supra-therapeutic dose of 1950 µg bid (as MTD; maximum tolerated dose) was comparable between Study B2113 and Study B2125: 80.3±15.8 ng/mL (Study B2113; Part I, n=6) and 67.5±27.5 ng/mL (Study B2113; Part II, n=84), versus 80.6±25.3 ng/mL (Study B2125; n=103). The Cmax,ss for the therapeutic dose of 600 µg bid was 24.3±7.20 ng/mL (Study B2125; n=105).

For pasireotide LAR formulation, the mean values of predicted Cmax,ss for the highest therapeutic doses in acromegaly patients would be 18.8 ng/mL (60 mg for patients with normal liver function) and 19.7 ng/mL (40 mg for patients with moderate hepatic impairment). As such, Cmax,ss 80.6 ng/mL from sc MTD 1950 µg bid in healthy volunteers (Study B2125) has approximately 4-fold coverage for Cmax,ss from the highest therapeutic doses of LAR formulation in acromegaly patients.

Relationship between plasma concentration and effect

GH and IGF-1 response in patients with acromegaly

The PK/PD relationship between pasireotide concentrations and GH/IGF-1 levels was explored using an inhibitory effect Emax model and a repeated measures logistic regression analysis.

The exposure-response analyses demonstrated a positive correlation between pasireotide exposure and efficacy endpoints (GH, IGF-1 and overall GH+IGF-1 response) for both medically naïve and inadequately controlled patients.

2.4.4. Discussion on clinical pharmacology

PK

The applicant has characterized the pasireotide PK profile following LAR administration.

In most subjects, the PK profile shows an initial burst release on the injection day, followed by a dip from Day 2 to Day 7, then a slow increase to maximum concentration around Day 20, and a slow declining phase over the next weeks.

Except for absorption, the distribution, metabolism and excretion properties of pasireotide between the Signifor sc and the LAR formulation are expected to be similar (assuming linear pharmacokinetic processes based on the dose proportionality shown for pasireotide) because the same active entity (pasireotide) is present in both formulations.

Regarding interactions, within the approval of pasireotide sc, it was concluded based on in vitro data that the risk of pasireotide affecting other drugs was low and no in vivo studies were requested. This conclusion must also be considered valid for the LAR formulation given that the expected average (based on simulations of single dose data from healthy volunteers) maximum plasma concentrations at steady state is lower for the LAR formulation (26 ng/ml) than following pasireotide sc (45 ng/ml).

The pharmacokinetic documentation for pasireaotide LAR is considered sufficient.

PD

The physiological actions of somatostatin are well known. Pasireotide is a somatostatin analogue with affinity to four of the five described somatostatin receptors (SSTR), thus the binding profile differs somewhat from the somatostatin analogues octreotide and lanreotide currently approved in the treatment of acromegaly. The difference in binding profile makes it plausible that a difference in both efficacy and secondary pharmacological characteristics can be expected compared to octreotide and lanreotide.

Somatostatin analogues are known to affect the glucose metabolism through their effects on the pancreatic islets. The data presented with the MAA for the sc formulation of pasireotide show that pasireotide decreased insulin secretion and reduced GLP-1 and GIP incretin secretion with no changes in hepatic or peripheral insulin sensitivity. Further data was presented indicating that incretin based therapies may be the most promising agents in the treatment of hyperglycaemia. With the current application, PK/PD analyses have been provided, indicating a dose-related risk of hyperglycaemia.

The two thorough QT studies were assessed with the MAA for the sc pasireotide formulation. In this assessment it was concluded that there was a positive correlation between ΔΔQTcF and pasireotide plasma concentration. Pasireotide-treated subjects also showed a reduction of the heart rate. The Applicant has provided relevant

arguments that the results from the two TQT studies conducted with the sc formulation are adequate and sufficient to characterize the potential effect of the LAR formulation on QT intervals. An exploratory dynamic QT beat-to-beat analysis was provided with the new submission indicating that pasireotide may have a low arrhythmia liability. However, due to the exploratory nature of this analysis, no firm conclusions can be drawn. The effect of pasireotide LAR on QT was evaluated in the clinical studies and is further discussed in the safety section of this report.

Exploratory exposure–response analyses were performed. An inhibitory E_{max}-model was used to describe the dependence of GH and IGF-1 on pasireotide concentrations assuming a direct relationship between plasma concentrations and the effect. Based on the presented data it may be concluded that higher exposure is associated with greater GH and IGF-1 suppression. Different EC50-estimates were found for the different studies which may be a reflection of the different underlying disease status. The results from the exposure-response analysis support the approach of dose escalation in patients not achieving sufficient treatment response.

Considering the effects of pasireotide on the glucose metabolism, interactions with anti-diabetic medications may be foreseen. Study B2124, which was submitted with the MAA for the sc pasireotide formulation, was designed to define the potential role of different class of anti-hyperglycaemic agents (metformin, nateglinide, vildagliptin and liraglutide) in the management of hyperglycaemia induced by pasireotide. The most prominent antihyperglycaemic effect was observed with liraglutide and vildagliptin with the least effect observed for metformin. The safety assessment of the combination therapies revealed no unforeseen adverse events and the combinations were moderately well tolerated. Notably increases in hepatic enzymes/bilirubin were more common in the pasireotide + liraglutide arm indicating that this may not be a favourable combination. These data are, however, not considered sufficient to allow any specific recommendations with regards to pasireotide-induced hyperglycaemia. A study investigating the management of pasireotide-induced hyperglycaemia in patients with Cushing's disease and acromegaly is planned and the study protocol has been assessed by the CHMP. The study is further included in the RMP (category 3).

With reference to pharmacodynamic interactions, and further to the assessment of the QT studies, a statement on the risk of bradycardia potentiation when this drug is combined with a bradycardic agent is included in section 4.5 of the SmPC. Furthermore, information on the need for dose adjustments of insulin and antidiabetic medicinal products is included in section 4.5 of the SmPC.

2.4.5. Conclusions on clinical pharmacology

The CHMP considers all relevant aspects on the pharmacodynamic effects of pasireotide LAR to be adequately covered.

2.5. Clinical efficacy

The clinical efficacy studies are summarized in Table 1 (see section clinical aspects – introduction).

The efficacy and safety of pasireotide LAR in acromegaly are primarily derived from two Phase 3, randomized studies comparing pasireotide LAR with active controls, Study SOM230C2305 and Study SOM230C2402. Supportive efficacy and safety data in the acromegaly indication are available from Study SOM230C2110 with its

extension Study SOM230C2110E1 using the LAR formulation, and from Study SOM230B2103 and Study SOM230B2201 with its extension Study SOM230B2201E3 using the sc formulation.

No pooling of data was performed due to significant differences in study design.

2.5.1. Dose response studies

The choice of the pasireotide LAR dose regimen in Study C2305 and Study C2402 was based on the PK and PK/PD analysis results from Study B2201 and Study C2110.

In Study B2201, pasireotide sc was tested at 200, 400 and 600 µg bid dose levels in patients with acromegaly. The response rates appeared to be dose-dependent for pasireotide sc at 200 µg bid (14.3%), 400 µg bid (11.8%) and 600 µg bid (30.0%), suggesting pasireotide sc 600 µg bid and higher dose levels should be tested in further clinical development.

In Study C2110, pasireotide LAR was tested at 20, 40 and 60 mg q28d in patients with acromegaly. Interim analysis of PK data from this study showed that the trough concentrations of pasireotide at steady-state (Day 84) were 2.74 ± 1.33, 5.92 ± 2.85, and 8.87 ± 4.53 ng/mL following three monthly im injections of 20 mg, 40 mg, and 60 mg LAR, respectively. The mean values of pasireotide trough concentrations after 40 mg dose (5.92 ng/mL) and 60 mg dose (8.87 ng/mL) from Study C2110 were above the mean value of $C_{effective}$ (5.09 ng/ml) from pasireotide sc on GH reduction <2.5 µg/L in Study B2201. In addition, in terms of monthly dose loading, the LAR formulation 40 mg monthly (q28d) dosing is the closest dose strength to the sc formulation 600 µg bid (i.e. 1.2 mg/day x 28 days = 33.6 mg every 28 days). Based on these results, a 40 mg pasireotide LAR dose was chosen as the starting dose for Phase 3 Study C2305.

Due to inter-patient variability in PK exposures, PD (GH and IGF-1) response, and safety/tolerability, it is expected that some patients may require lower or higher doses of pasireotide LAR. In Study C2305, for patients who did not respond to pasireotide LAR 40 mg after three months of treatment, when it was considered that the trough concentration was close to steady state, a dose increase to 60 mg was permitted. In Study C2402, a dose decrease in 20 mg increments and in Study C2305 a dose reduction to pasireotide LAR 20 mg or octreotide LAR 10 mg was permitted at any time in the event of tolerability issues.

2.5.2. Main studies

Medically naïve patients - Study C2305

Study C2305 is a large prospective randomized study conducted in patients with acromegaly. This was a Phase 3, multicenter, randomized, blinded study of pasireotide LAR vs. octreotide LAR in patients with active acromegaly who had not received previous medical treatment.

Inadequately controlled patients - Study C2402

Study C2402 is a Phase 3, multicenter, randomized, parallel-group, three-arm study of double-blind pasireotide LAR 40 mg and pasireotide LAR 60 mg versus open-label octreotide LAR 30 mg or lanreotide ATG 120 mg in patients with inadequately controlled acromegaly.

Methods

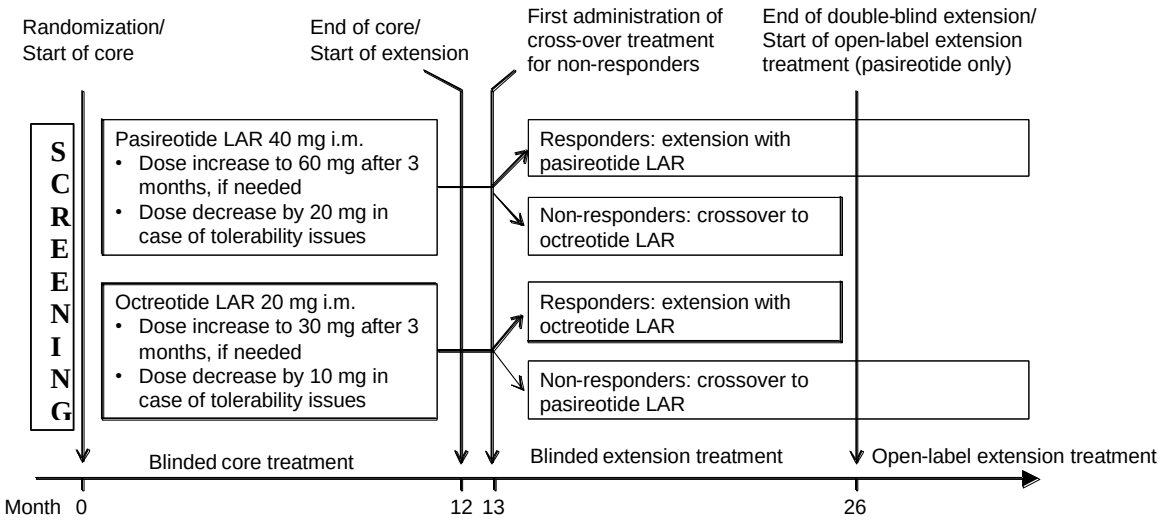
Study C2305

This Phase 3, multicenter, randomized, blinded study assessed the safety and efficacy of pasireotide LAR 40 mg vs. octreotide LAR 20 mg in 358 patients with active acromegaly who had not received previous medical treatment.

Enrollment was stratified by the following two strata: 1) patients who had undergone one or more pituitary surgeries but had not been treated medically and 2) de-novo patients presenting a visible pituitary adenoma on MRI and who refuse pituitary surgery or for whom pituitary surgery was contraindicated.

The study consisted of two blinded study phases: a 12 month core phase and an optional extension (Figure 1).

Figure 1 C2305 Study design (incorporating Amendment 4)



Core phase: Treatment in the core was blinded for all patients. Patients were randomized 1:1 to receive either pasireotide LAR 40 mg im or octreotide LAR 20 mg im depot injections every 28 days for a total of 12 injections in the core. The total duration of the core was 12 times 28 days, i.e. 12 study months. All patients had to have follow-up evaluations 28 days after the End of Study visit (56 days after the last dose of study medication).

Extension phase: At the discretion of the Investigator, patients who did not respond to their randomized treatment (i.e. pasireotide LAR or octreotide LAR) at the end of the core (Month 12) were allowed to switch to receive the other treatment in the extension, and those who were responders continued with the same treatment as in the core.

Data from Study C2305 are presented in three categories:

- ***Core phase:*** includes all data from the core phase up to Month 12 (primary efficacy analysis).
- ***Up to crossover:*** includes 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 switched medication only data collected before crossover is included.

- ***After crossover:*** includes all data in the extension collected after the crossover time point for patients who crossed over (efficacy and safety for patients who did not achieve biochemical control with previous SSA treatment in the core phase). These analyses correspond to inadequately controlled patients.

Study C2402

This was a Phase III, multicenter, randomized, parallel-group, three-arm study of double-blind pasireotide LAR 40 mg and pasireotide LAR 60 mg versus open-label octreotide LAR 30 mg or lanreotide ATG 120 mg in patients with inadequately controlled acromegaly. The study consisted of a core and extension phase (Figure 2). The originally submitted clinical study report presents data of the core phase. With the responses to the Day 120 LoQ, interim data from the extension phase was submitted with a data cut-off date of 03-Jun-2013.

Core phase

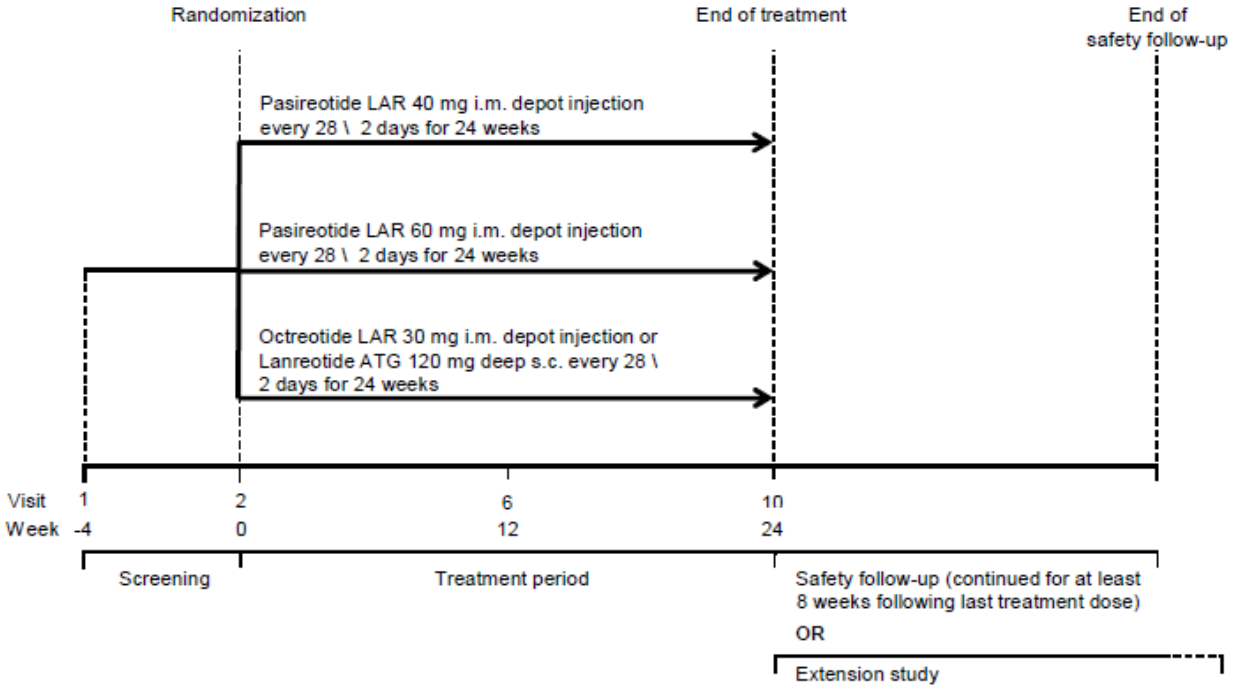
After a 4-week screening period where inclusion and exclusion criteria were assessed, patients were randomly allocated to receive either pasireotide LAR 40 mg or pasireotide LAR 60 mg (in double-blind fashion) or to continue on the same treatment on the maximum indicated dose of octreotide LAR 30 mg or lanreotide ATG 120 mg as before randomization (in an open-label, active control arm).

Patients were stratified according to previous treatment (octreotide LAR, lanreotide ATG) and GH levels at Visit 1 (screening, >2.5 µg/L and ≤ 10 µg/L; and >10 µg/L). The total treatment duration with pasireotide LAR 40 mg or pasireotide LAR 60 mg or with octreotide LAR 30 mg or lanreotide ATG 120 mg was 24 weeks. The total study duration was 28 weeks, including the screening phase.

Extension phase

The purpose of the extension study is to collect additional efficacy and safety data with pasireotide LAR. Available data from the extension study with a data cut-off date of 03-Jun-2013 has been submitted. In this interim analysis of data 83 % of patients included had reached Week 28 of the extension.

Figure 2 Study design of core and extension phase



- **Study participants**

Study C2305

Main inclusion criteria

1. Patients with active acromegaly demonstrated by
    - a lack of suppression of GH nadir to <1 µg/L after an oral tolerance test with 75 g of glucose (OGTT) (not applicable for diabetic patients) **or**
    - a mean GH concentration of a 5-point profile within a 2 hour time period of >5 µg/L
    - elevated circulating IGF-1 concentration (age and sex adjusted)
2. Patients who have undergone one or more pituitary surgeries, but have not been treated medically, or de-novo patients presenting a visible pituitary adenoma on MRI and who refuse pituitary surgery or for whom pituitary surgery is contraindicated
3. Patients with a known history or new diagnosis of impaired fasting glucose or diabetes mellitus could be included, however blood glucose and anti-diabetic treatment had to be monitored closely throughout the trial and adjusted as necessary

Main exclusion criteria

1. Patients who were being or were treated with octreotide, lanreotide or dopamine agonists with the exception of a single dose of short-acting octreotide or short –acting dopamine agonists. In case of a single dose of short-acting octreotide, the dose should not be used to predict the response to the octreotide treatment. The single dose of short acting octreotide or short-acting dopamine agonists should not have been administered in the 3 days prior to randomization.
2. Patients who were being or were treated with GH antagonists
3. De-novo patients not having a visible pituitary adenoma on MRI
4. Patients who had received pasireotide prior to randomization
5. Patients with compression of the optic chiasm causing any visual field defect for whom surgical intervention was indicated
6. Patients who required a surgical intervention for relief of any sign or symptom associated with tumour compression
7. Patients who had received pituitary irradiation within the last 10 years prior to Visit 1
8. Patients who were hypothyroid and were not adequately treated with stable doses of thyroid hormone replacement therapy
9. Diabetic patients on anti-diabetic medications whose fasting blood glucose was poorly controlled as evidenced by HbA1c >8%
10. Patients with symptomatic cholelithiasis
11. Patients with abnormal coagulation (prothrombin time (PT) and/or activated partial thromboplastin time (APTT) elevated by 30% above normal limits) or patients receiving anticoagulants that affect PT or APTT

12. Patients who had congestive heart failure (NY Heart Association Class III or IV), unstable angina, sustained ventricular tachycardia, ventricular fibrillation, clinically significant bradycardia, advanced heart block or a history of acute myocardial infarction within the six months preceding enrollment

13. Patients with risk factors for torsade de pointes, i.e. patients with a baseline QTc >450 ms, hypokalemia, hypomagnesaemia, hypocalcaemia, family history of long QT syndrome, or patients receiving a concomitant medication known to prolong QT interval.

14. Patients with confirmed central hypothyroidism, central hypoadrenalism and diabetes insipidus, unless they are adequately treated with stable doses of hormone replacement therapy for a minimum of three months prior to study entry (first dose of study medication). Patients with confirmed central hypogonadism unless they are adequately treated with stable doses of hormone replacement therapy for a minimum of three months prior to study entry (first dose of study medication) except in cases where hormones replacement therapy is not indicated.

15. Patients with liver disease such as cirrhosis, chronic active hepatitis or chronic persistent hepatitis, or patients with alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) more than 2 x ULN, serum creatinine >2 x ULN, serum bilirubin >2 x ULN, serum albumin <0.67 x lower limit of normal (LLN), [Chinese patients need to have normal serum creatinine level (China only)].

16. Patients with white blood cell (WBC) $<3 \times 10^9$/L; hemoglobin <90 % LLN; platelets $<100 \times 10^9$/L

Study C2402

Main inclusion criteria

1. Male and female patients ≥ 18 years of age

2. Patients with inadequately controlled acromegaly as defined by:

    - a mean GH concentration of a 5-point profile over a 2-hour period >2.5 µg/L

    - and sex- and age-adjusted IGF-1 >1.3 × upper limit of normal (ULN)

3. Patients treated with maximum indicated doses of octreotide LAR or lanreotide ATG given as monotherapy for at least 6 months prior to Visit 1 (Screening) (the maximum indicated doses were 30 mg for octreotide LAR and 120 mg for lanreotide ATG)

4. Patients with diagnosis of pituitary micro- or macro-adenoma (patients could have been previously submitted to surgery)

Main exclusion criteria

In general, exclusion criteria were similar to those in study 2305. Criteria different to those in study 2305 are given in the following:

1. Concomitant treatment with growth hormone receptor (GHR)-antagonist or dopamine agonists, unless concomitant treatment was discontinued 8 weeks prior to Visit 1 (Screening) (8-week wash-out period). Such patients must have been treated with octreotide LAR 30 mg or lanreotide ATG 120 mg monotherapy continuously for a minimum of 6 months prior to starting combination therapy and they should have been inadequately controlled on monotherapy

- **Treatments**

Study C2305

Core phase

For the core phase of the study, patients were randomized to one of the following 2 treatment arms in a ratio of 1:1:

- Pasireotide LAR 40 mg im depot injection, blinded, once every 28 days (± 2 days) for 12 months.
- Octreotide LAR 20 mg im depot injection, blinded, once every 28 days (± 2 days) for 12 months.

Dose increase and decrease were permitted.

Extension phase

The starting dose in the extension for patients who crossed over was pasireotide LAR 40 mg or octreotide LAR 20 mg. Patients who entered the extension without crossing over continued the same dose as they were receiving in the core.

Permitted dose adjustments and interruptions of study treatment

A patient's dose could be increased one dose level during the core or the extension if central laboratory results showed mean GH level ≥ 2.5 µg/L and/or IGF-1 >ULN (age and sex related). The permitted dose increases were from 40 mg to 60 mg for pasireotide LAR, and from 20 to 30 mg for octreotide LAR.

Dose decrease to pasireotide LAR 20 mg or octreotide LAR 10 mg was permitted at any time in the event of tolerability issues.

For patients who were unable to tolerate the protocol-specified dosing scheme, dose adjustments and interruptions were permitted in order to keep the patient on study drug. Guidelines for dose adjustments/interruptions for patients experiencing adverse events (AEs) or QTc prolongation were in place. Further guidance on treating patients in case of hyperglycaemia and QT-related cardiology was provided.

Study C2402

For the core phase, patients were randomized to one of the following three treatment arms in a ratio of 1:1:1:

- Double-blind pasireotide LAR 40 mg intramuscular (i.m.) injection, once every 28±2 days for 24 weeks
- Double-blind pasireotide LAR 60 mg i.m. injection, once every 28±2 days for 24 weeks
- Active, open-label control arm: Continuation on the same treatment that was received for at least 6 months prior to randomization with either octreotide LAR 30 mg i.m. injection or lanreotide ATG 120 mg subcutaneous (s.c.) once every 28±2 days for 24 weeks.

For the extension, patients originally randomized to pasireotide arms who achieved biochemical control at the end of the core phase could continue on the same dose of double-blind pasireotide LAR as long as biochemical control was maintained. Patients who were not biochemically controlled at the end of the core phase (following treatment with either pasireotide LAR 40 mg or 60 mg) were offered to continue on open-label pasireotide LAR 60 mg in the extension. Patients originally randomized to the active control arm in the core period who did not achieve biochemical control at the end of the 24-week treatment period were started on open-label pasireotide LAR 40 mg in the extension. The dose could then be increased to 60 mg should biochemical control not be achieved after 3 months.

Permitted dose adjustments and interruptions of study treatment

For patients who were unable to tolerate the protocol-specified dosing schedule in the pasireotide LAR treatment arms, dose adjustments were permitted in order to keep the patients on study drug. Patients randomized to the pasireotide LAR treatment arms who did not tolerate the assigned 40 mg or 60 mg dose were permitted to decrease their dose by 20 mg.

As octreotide LAR 30 mg and lanreotide ATG 120 mg were already used in their maximum indicated doses for at least 24 weeks prior to randomization, no further dose adjustments were expected.

- **Objectives**

Study C2305

The **primary objective** of the study was to compare the proportion of patients with a reduction of mean GH level to < 2.5µg/L and the normalization of IGF-1 to within normal limits (age and sex related) between pasireotide LAR vs octreotide LAR at 12 months.

Key **secondary objectives** were to compare the effect of pasireotide LAR vs octreotide LAR on reduction of GH to < 2.5 µg/L, tumour volume and normalization of IGF-1 at 12 months.

Study C2402

The **primary objective** of this study was to compare the proportion of patients achieving biochemical control (defined as mean GH levels <2.5 µg/L and normalization of sex- and age-adjusted IGF-1) at 24 weeks with pasireotide LAR 40 mg and pasireotide LAR 60 mg separately versus continued treatment with octreotide LAR 30 mg or lanreotide autogel (ATG) 120 mg.

Key **secondary objective** were to compare the effect of pasireotide LAR (40 mg and 60 mg separately) versus continued treatment with octreotide LAR 30 mg or lanreotide ATG 120 mg on the proportion of patients achieving normalization of sex- and age adjusted IGF-1 at 24 weeks.

- **Outcomes/endpoints**

Study C2305

GH (5-point mean GH level): A patients' 5-point mean GH level was assessed from a 2-hour profile after one hour at rest at the hospital and before the LAR injection, if applicable. All GH 2 hour profiles prior to glucose intake were to be taken at the same time (morning at around 8 am).

As all GH assessments were based on the mean of a 5-point 2-hour profile, the term "GH" is used to denote "mean GH (based on a 5-point 2 hour profile)".

IGF-1: A patient's total IGF-1 levels were assessed at specified time points. Sampling for IGF-1 was performed immediately before the LAR injection, if applicable.

The GH and IGF-1 samples were analyzed by the central laboratory.

Magnetic Resonance Imaging (MRI) using gadolinium as contrast material*:* An MRI of the pituitary was performed at screening, at Month 6, at Month 12 (core study completion) and then every 6 months in the extension. For de-novo patients an adenoma had to be visible on screening MRI. The MRIs were evaluated by a blinded central reader.

To ensure consistency throughout all participating sites, the MRIs were performed and processed following the guidelines from the central reader facility.

***Symptoms of acromegaly**:* Ring size and symptoms of acromegaly were collected monthly in the core, the first 6 months in the extension, and every 3 months thereafter in the extension. The investigator also asked the patient to score the following symptoms of acromegaly: headache, fatigue, perspiration, paresthesias, osteoarthralgia according to a five-point score scale (0=absent, 1=mild, 2=moderate, 3=severe, 4=very severe)

***Quality of Life**:* Health related quality of life information was collected monthly in the core and every 6 months in the extension using the Acromegaly Quality of Life Questionnaire (AcroQoL). The questionnaire is unidimensional and contains 22 items divided in two scales: one that evaluates physical aspects (eight items) and another one that evaluates psychological aspects (14 items). This last one is also divided in two 7-item sub-scales: one evaluates physical appearance, and the other evaluates the impact of the disease on the personal relationships of the patient.

***Prolactin**:* PRL levels were assessed every 3 months in the core and extension. Sampling for PRL was performed immediately before the LAR injection, if applicable.

The PRL samples were analyzed by the central laboratory.

Study C2402

Primary efficacy assessments

GH (5-point mean GH level): The 5-point mean GH was assessed from a 2-hour profile after one hour at rest at the hospital at Visit 1 (Screening), Visit 2 (baseline), Visit 6 (Week 12), and Visit 10 (Week 24, study completion). All GH assessments were based on such a profile.

The 5-point mean GH profile was done within a 2-hour time period prior to glucose intake when an OGTT was required.

All GH 2-hour profiles were taken at the same time in the morning. The samples for GH were analyzed by the central laboratory.

IGF-1: Total IGF-1 levels were assessed with one pre-dose sample at the same visits as GH. Blood sampling for IGF-1 was done prior to the administration of both study drug/active control and glucose, when applicable. This sample was taken together with the first sample of the GH profile. The samples for IGF-1 were analyzed by the central laboratory.

All IGF-1 assessments are reported as standardized IGF-1, adjusted for sex and age.

Secondary efficacy assessments

GH and IGF-1: Both values (in combination or alone) were used to assess secondary efficacy parameters at different time points.

Magnetic Resonance Imaging using gadolinium as contrast material: An MRI of the pituitary was performed during the screening period if possible only after patient's eligibility for the study was confirmed and at Visit 10 (study completion). The MRIs were sent to a central reader for evaluation. To ensure consistency throughout all participating sites, the MRIs were performed and processed following the guidelines from the central reader facility.

Symptoms of acromegaly: At all visits (except Visits 3 and 7), the Investigator measured the patient's ring size using a provided gauge. The Investigator also asked the patient to score the following symptoms of acromegaly: headache, fatigue, perspiration, paresthesias, and osteoarthralgia according to a five-point score scale (0=absent, 1=mild, 2=moderate, 3=severe, 4=very severe).

Health-related quality of life: Health-related quality of life was assessed at Visit 2 (baseline), 4, 5, 6, 8, 9, and 10 using the AcroQoL instrument. The AcroQoL instrument was comprised of 22 questions divided into two scales: one evaluating physical aspects (8 items) and one addressing psychological aspects (14 items). The psychological scale was further divided into a subscale evaluating physical appearance and a subscale focusing on the impact of the disease on personal relationships of the patient (7 items each).

- **Sample size**

Study C2305

In previous clinical studies with octreotide LAR in patients with newly diagnosed acromegaly (CSMS995B2401, CSMS995B2402), a 25% response rate (GH <2.5 µg/L and IGF-1 within the age and sex adjusted normal range) was observed along with a 95% CI of 10.2%, 39.8%.

In the current study patients who were medical treatment naïve after first surgery were also eligible and the response rate data in this stratum is not known from previous studies, however comparable response rates are expected. Considering the relatively wide confidence interval of the response rate from the previous studies and the potential of early withdrawal to dilute the treatment effect, a lower overall response rate for the octreotide group (20%) is assumed in both strata.

A Phase II cross-over study in acromegaly (CSOM230B2201) showed a 39% response rate across pasireotide sc doses ranging from 200 µg bid to 600 µg bid. At the 600 µg bid dose level, the response rate was 36% across all time periods in this study. Therefore, a 35% response is assumed as the minimal response rate for the pasireotide LAR group. It was assumed that 75 % and 25 % of patients, respectively, would enroll in the strata of treatment naïve after first surgery and newly diagnosed acromegaly patients. To detect an increase of 15% in response rate from 20% in octreotide LAR group to a 35% in pasireotide LAR group within each stratum (equivalently odds ratio equals 2.154), a sample size of 151 patients per group would be adequate based on a two-sided CMH test at the 0.05 level with 80% power. Considering a possible 9% dropout rate in this study, a sample size of 330 (165 patients/group) was needed.

Study C2402

Response rate data (GH <2.5 µg/L and IGF-1 within the age and sex adjusted normal range) in this patient population were not available from previous studies with pasireotide. However, since patients recruited were inadequately controlled from prior treatment, the response rate was expected to be lower than in medically-naïve or newly diagnosed patients with acromegaly. The expected response rates and their difference (considered clinically significant) for this study were conjectured by a medical expert.

The sample size calculation was based on the primary efficacy variable (GH <2.5 µg/L and IGF-1 within the age and sex adjusted normal range at 24 weeks). The assumptions for the sample size calculation were as follows:

- Response rates at Week 24 for pasireotide LAR groups (40 mg and 60 mg separately) were assumed to be 25%
- Response rate at Week 24 for the active control group (continuing on same treatment) was assumed to be 5%

The statistical null hypotheses of the primary efficacy variable were:

A sample size of 62 patients per treatment group (pasireotide LAR 60 mg, pasireotide LAR 40 mg, and active control (octreotide LAR 30 mg or lanreotide ATG 120 mg)) achieved 90% power to detect a difference of 20% in response rate between active control (5%) and pasireotide LAR (40 mg and 60 mg separately) (25%) with a family-wise error rate of 2.5% (one-sided).

- **Randomisation**

Study C2305

At Visit 2, all eligible patients were randomized using an interactive voice recognition system (IVRS) to one of the treatment arms according to the specified strata. The unblinded independent nurse/study coordinator called the IVRS after the investigator had confirmed that the patient fulfilled all the inclusion/exclusion criteria. The IVRS identified the treatment assigned to the patient based on a randomization list. The IVRS communicated only the treatment the patient was assigned to, but did not reveal the randomization number.

Randomization was stratified by 2 strata (i.e. patients who had prior pituitary surgery (but had not been treated medically) and patients with de novo disease). Within each stratum block randomization was used. Treatment assignment was balanced by country.

Study C2402

In order to randomize the patient to one of the three treatment arms an Interactive Voice Response System/Interactive Web Response System (IVRS/IWRS) was used. The IVRS/IWRS assigned a randomization number to the patient, which was used to link the patient to a treatment arm.

The randomization number in either situation was not communicated to the caller.

A specific procedure was used to ensure that treatment assignment was unbiased and concealed from patients and investigator staff.

- **Blinding (masking)**

Study C2305

Due to the different appearance of the pasireotide and octreotide LAR formulations, a true double-blind treatment was not feasible. Blinding was achieved by having a dedicated independent nurse/coordinator call the IVRS, prepare and administer the LAR treatment and complete the Unblinded Dosage Administration Record case report form (CRF). This nurse/coordinator was not blinded to the treatment assignment. The patient, investigator, and sponsor were blinded to treatment assignment. The nurse/study coordinator was not to discuss treatment assignment with the patient or the investigator or the sponsor’s clinical monitor.

Also the persons performing the central assessments and data analyses remained blinded to the identity of the treatment.

For patients not continuing in the extension phase of the study, the treatment was unblinded after Month 12. Patients who entered the extension before Amendment 4 was implemented received unblinded treatment in the extension (from Month 12). Amendment 4 extended blinding to patients' treatment from Month 12 (end-of-core) to Month 26 in the extension. For patients continuing in the extension phase of the study after Amendment 4 was implemented, the treatment was unblinded at Month 26.

Blinded and open-label data

All data in the core phase was collected in a blinded manner. Following implementation of Amendment 4, treatment in the extension was blinded up to Month 26, after which patients on pasireotide could continue on open-label treatment. In addition, patients who entered the extension prior to Amendment 4 received open-label pasireotide. Data from both the blinded and open-label treatment were pooled in the analyses that included extension data for patients continuing on the same treatment.

Study 2402

The patient, Investigator, site staff, monitor, and data manager were unblinded to the treatment arm assignment but were blinded to the treatment dose in the double-blind pasireotide LAR treatment arm during the core phase. The extension phase of the study was unblinded.

- **Statistical methods**

Study C2305

Interim analyses

An early safety interim analysis was performed after 30 patients had completed the Month 6 assessment. These interim data were analyzed by an independent statistician and the results reviewed by the DMC in order to identify any early safety signal and make recommendations to Novartis.

Analysis of the primary efficacy variable

The analysis of the primary efficacy variable includes all data from the FAS. Last observation data at or after Month 6 were carried forward (last observation carried forward; LOCF) when a Month 12 assessment was not available. A patient who never received study drug was considered as a non-responder in the primary efficacy analysis.

If a patient had less than three samples for the assessment of the 5-point mean GH from the 2- hour profile, then the mean GH was considered as missing. In addition, if GH and IGF-1 measurements were taken after 35 days from the date of any injection of study drug, the values were considered as missing. Missing mean GH and/or IGF-1 were imputed using data obtained at or after Month 6 by the LOCF method, otherwise patients were considered as a non-responder.

Statistical hypothesis, model, and method of analysis

The null hypothesis was that there is no difference in the response rate between pasireotide LAR and octreotide LAR. The alternative hypothesis was that the response rates are different between the two groups. A two-sided Cochran-Mantel-Haenszel (CMH) test adjusting for randomization stratification factor was used to test the null hypothesis at the significance level of 0.05.

In addition, the point estimate of odds ratio along with the two-sided 95% confidence interval was provided for each randomization stratum as well as overall. The response rate was also calculated with the two-sided 95% exact (Clopper-Pearson) confidence interval (CI) by randomization stratum and treatment group.

Supportive/sensitivity analyses for the primary efficacy variable

The primary analysis was also performed on the PP set.

As a sensitivity analysis to the primary efficacy endpoint on the FAS, a patient with missing GH or IGF-1 at Month 12, or who had discontinued prior to Month 12, was considered a non-responder.

In addition, following a GCP audit conducted by Novartis at 2 sites in Mexico (730 and 731), additional sensitivity analyses excluding the 22 patients from the two sites were conducted. These changes were made prior to the Month 26 database lock and unblinding of the study.

Analysis of secondary and exploratory efficacy variables

The 3 key secondary variables are the proportion of patients with GH <2.5µg/L, with normalization of IGF-1 and the change from baseline in tumour volume at Month 12.

Study 2402

Analysis of the primary variable

The primary efficacy analysis was performed on the FAS.

The statistical null hypotheses of the primary efficacy variable were:

H1: The response rate in the pasireotide LAR 40 mg group was less than or equal to the active control group.

H2: The response rate in the pasireotide LAR 60 mg group was less than or equal to the active control group.

Each null hypothesis was tested against the one-sided alternative; that the response rate in the pasireotide LAR group was greater than in the active control group.

An exact logistic regression model that adjusts for the randomization stratification factors (Hirji et al 1987) was used to test the null hypothesis. The exact two-sided 95% and 97.5% confidence intervals (CI) for the common odds ratio (OR) were calculated. A common OR >1 indicated an increased odds for the pasireotide LAR (40 mg or 60 mg) group compared to the active control group.

The procedure to control the family-wise type I error rate at significance level α for the multiple comparisons on the primary and key secondary efficacy variable is described below after the key secondary endpoints are discussed.

Handling of missing values

If a patient had less than three samples for the assessment of the 5-point mean GH from the 2- hour profile, then the mean GH was considered as missing. In addition, if GH and IGF-1 measurements were taken after 35 days from the date of any injection of study drug, the values were considered as missing. A patient with missing values of mean GH or IGF-1 at 24 weeks or who withdrew earlier from the study was considered as a non-responder.

Analysis of secondary variables

The key secondary efficacy variable was the proportion of patients achieving normalization of sex- and age-adjusted IGF-1 at 24 weeks.

Results

- **Participant flow and numbers analysed**

Study C2305

Table 2 Patient disposition by treatment - Core phase-C2305 (FAS)

	Pasireotide LAR N=176 n (%)	Octreotide LAR N=182 n (%)	All patients N=358 n (%)
Patients randomized	176 (100.0)	182 (100.0)	358 (100.0)
Treated	176 (100.0)	182 (100.0)	358 (100.0)
Patients treated, completed Month 12 (core phase)	141 (80.1)	156 (85.7)	297 (83.0)
Did not enter extension	29 (16.5)	29 (15.9)	58 (16.2)
Entered extension, crossed over	38 (21.6)	81 (44.5)	119 (33.2)
Entered extension, continued same treatment	74 (42.0)	46 (25.3)	120 (33.5)
Discontinued prior to Month 12	35 (19.9)	26 (14.3)	61 (17.0)
Adverse Event(s)	14 (8.0)	6 (3.3)	20 (5.6)
Protocol deviation	7 (4.0)	8 (4.4)	15 (4.2)
Unsatisfactory therapeutic effect	5 (2.8)	8 (4.4)	13 (3.6)
Subject withdrew consent	5 (2.8)	3 (1.6)	8 (2.2)
Administrative problems	2 (1.1)	0	2 (0.6)
Abnormal laboratory value(s)	1 (0.6)	0	1 (0.3)
Lost to follow-up	1 (0.6)	0	1 (0.3)
Death	0	1 (0.5)	1 (0.3)

Death includes only those patients for whom death was reported as the primary reason for discontinuation of therapy.

Table 3 Patient disposition by treatment – Extension phase between Month 12 and Month 26 for patients continuing the same treatment - Study C2305 (FAS)

	Pasireotide LAR N=176 n (%)	Octreotide LAR N=182 n (%)	All patients N=358 n (%)
Patients entered extension and continued the same treatment	**74 (100.0)**	**46 (100.0)**	**120 (100.0)**
Completed study at Month 26	NA	31 (67.4)	
Continued beyond Month 26*	51 (68.9)	5 (10.9)	56 (46.7)
Discontinued between Month 12 and prior to Month 26	23 (31.1)	10 (21.7)	33 (27.5)
Subject withdrew consent	9 (12.2)	2 (4.3)	11 (9.2)
Unsatisfactory therapeutic effect	3 (4.1)	3 (6.5)	6 (5.0)
Administrative problems	3 (4.1)	2 (4.3)	5 (4.2)
Lost to follow-up	3 (4.1)	1 (2.2)	4 (3.3)
Adverse Event(s)	2 (2.7)	1 (2.2)	3 (2.5)
Abnormal laboratory value(s)	2 (2.7)	0	2 (1.7)
Death	1 (1.4)	1 (2.2)	2 (1.7)

* Patients who received octreotide in extension phase were not followed further in the study after Month 26.
Percentage is based on the number of patients who entered extension and continued the same treatment.
Death includes only those patients for whom death was reported as the primary reason for discontinuation of therapy.
NA=not applicable (patients in pasireotide arm were not considered as completers per protocol)

Table 4 Patient disposition by treatment – from start of crossover to Month 26 - Study C2305 (CAS)

	Crossed over to pasireotide LAR N=81 n (%)	Crossed over to octreotide LAR N=38 n (%)	All patients N=119 n (%)
Patients entered extension and crossed over	**81 (100.0)**	**38 (100.0)**	**119 (100.0)**
Completed study at Month 26	NA	25 (65.8)	25 (21.0)
Continued beyond Month 26*	50 (61.7)	0	50 (42.0)
Discontinued after crossover and prior to Month 26	31 (38.3)	13 (34.2)	44 (37.0)
Adverse Event (s)	12 (14.8)	1 (2.6)	13 (10.9)
Subject withdrew consent	8 (9.9)	4 (10.5)	12 (10.1)
Unsatisfactory therapeutic effect	7 (8.6)	4 (10.5)	11 (9.2)
Subjects condition no longer requires study drug	2 (2.5)	0	2 (1.7)
Abnormal laboratory value (s)	1 (1.2)	0	1 (0.8)
Administrative problems	1 (1.2)	4 (10.5)	5 (4.2)

* Patients who received octreotide LAR in extension phase were not followed further in the study after Month 26.
Death includes only those patients for whom death was reported as the primary reason for discontinuation of therapy.
NA=not applicable (patients in pasireotide arm were not considered as completers per protocol)

Patients who underwent pituitary surgery after discontinuing from the study

Twenty-six de novo patients underwent pituitary surgery after withdrawing from the study (core or extension), or after choosing not to enter into the extension. The actual surgery date was available for 12 patients, and another 14 patients expressed interest in surgery but a surgery date was not available in the database. The treatments that patients were on at the time of discontinuation were as follows: pasireotide seven patients; octreotide five patients; crossed over to octreotide seven patients; crossed over to pasireotide seven patients.

Study C2402

Table 5 Patient disposition by treatment - Core phase-Study C2402 (FAS)

Disposition Reason	Pasireotide LAR 40 mg N=65 n (%)	Pasireotide LAR 60 mg N=65 n (%)	Active control N=68 n (%)
Patients randomized			
Untreated	2 (3.1)	1 (1.5)	1 (1.5)
Treated*	63 (96.9)	64 (98.5)*	67 (98.5)*
Completed 24-week core phase	59(90.8)	57(87.7)	65(95.6)
Not continuing into extension	3 (4.6)	4 (6.2)	3 (4.4)
Continuing into extension	56 (86.2)	53 (81.5)	62 (91.2)**
Discontinued core phase	6(9.2)	8(12.3)	3(4.4)
Adverse event(s)	2 (3.1)	4 (6.2)	0
Subject withdrew consent	2 (3.1)	2 (3.1)	2 (2.9)
Administrative problems	2 (3.1)	1 (1.5)	0
Protocol deviation	0	1 (1.5)	1 (1.5)

Disposition Reason	Pasireotide LAR 40 mg N=65 n (%)	Pasireotide LAR 60 mg N=65 n (%)	Active control N=68 n (%)

* Two patients (one in active control arm and one patient in pasireotide LAR 60 mg) did not receive any study medication but had incorrect data entered in the Dosing CRF. These patients are incorrectly counted in the Treated row, instead of the Not treated row.
** For patients who switched from active control to pasireotide in the extension, this may be considered a crossover period.

Table 6 Patient disposition - Extension phase-Study C2402 (FAS)

Disposition Reason	Pasireotide LAR 40 mg N=65 n (%)	Pasireotide LAR 60 mg N=65 n (%)	Active control arm (Cross-over to pasireotide) LAR*N=68 n (%)
Completed core period	59 (90.8)	57 (87.7)	65 (95.6)
Entered extension phase	**57 (87.7)**	**54 (83.1)**	**63 (92.6)**
Discontinued during bridging period	3 (4.6)	2 (3.1)	1 (1.5)**
Adverse event	2 (3.1)	0	0
Unsatisfactory therapeutic effect	1 (1.5)	1 (1.5)	0
Patient withdrew consent	0	1 (1.5)	1 (1.5)
Discontinued during extension phase (after Month 7/Week 4)*	17 (26.2)	13 (20.0)	12 (17.6)
Adverse event	1 (1.5)	3 (4.6)	3 (4.4)
Unsatisfactory therapeutic effect	9 (13.8)	2 (3.1)	6 (8.8)
Subject withdrew consent	4 (6.2)	5 (7.7)	3 (4.4)
Lost to follow-up	0	1 (1.5)	0
Administrative problem	0	1 (1.5)	0
Death	1 (1.5)	0	0
Protocol deviation	2 (3.1)	1 (1.5)	0

* Patients in the active control arm crossed-over to pasireotide LAR 40 mg in the extension phase.
** One patient randomized to active control at study entry entered the extension phase but withdrew consent during the bridging period and therefore was not dosed with pasireotide LAR.
Source: Table 14.1-1.1.1

- **Conduct of the study**

Study C2305

During the conduct of Study C2305, 2 sites were closed for critical GCP violations. To evaluate the potential impact of these violations on the outcome of the study, additional sensitivity analyses were conducted for efficacy and safety, in which the 22 patients from these sites were excluded. The results of these analyses are consistent with the main analyses, indicating that these GCP violations did not affect the validity of the study results.

Protocol amendments

The study protocol was amended 7 times. Previous sections describe the study conduct as amended. The key amendment is described below:

Amendment 4 (23-Apr-2009) was implemented after 34 patients had entered the extension and introduced the following important changes:

- Patients randomized to octreotide, who responded to treatment at Month 12, were offered to enter a 14-month extension phase with the same medication to have a benchmark for the evaluation of the long-term safety and efficacy of pasireotide.
- Patients not responding to either pasireotide or octreotide at Month 12 were to be offered to be switched to the other study medication in order to explore the safety and efficacy of switching from pasireotide to octreotide and from octreotide to pasireotide. Patients who crossed over to the other treatment arm at Month 13 were to follow the same schedule of evaluations as patients continuing in the extension phase in the same arm.
- Blinding to patients' treatment was extended from Month 12 to Month 26.

Protocol deviations

Core phase

Protocol deviations leading to exclusion from the PP set were reported for 15 patients (8.5%) in the pasireotide arm and 11 patients (6.0%) in the octreotide arm. The most common deviation was that patient did not complete 3 months of treatment (10 patients in the pasireotide arm and 8 patients in the octreotide arm). Deviations of inclusion criteria (all pertaining to GH assessment) were reported for 6 patients in the pasireotide arm and 4 patients in the octreotide arm, whereas exclusion criteria (prior medical treatment for acromegaly) was reported for 2 patients in the pasireotide arm.

Extension

Protocol deviations leading to exclusion from the second PP set were reported for 6 patients (7.4%) among those who crossed over to pasireotide, and 1 patient (2.6%) among those who crossed over to octreotide. The most common deviation was that patient did not complete 3 months of crossover treatment (4 patients on pasireotide, none on octreotide arm).

Patients who received octreotide in the extension were not followed after Month 26 in the study, and were to receive their last injection at Month 25. There were 5 patients who were randomized to octreotide and who were recorded as receiving one or more injections of octreotide after this time point within the study.

Ten patients crossed over in the extension with treatment switch not per protocol.

Study 2402

Protocol amendments

The study protocol was amended 5 times. Previous sections describe the study conduct as amended. None of the amendments affected the analysis of the primary endpoint, thus the amendments are not considered to affect the outcome or the interpretation of the study.

Protocol deviations

Protocol deviations leading to exclusion from the per-protocol set were reported for 11 patients (16.9%) in the pasireotide LAR 40 mg arm, 14 patients (21.5%) in the pasireotide LAR 60 mg arm, and 8 patients (11.8%) in the active control arm. Four patients had a protocol deviation of GH 5pt mean ≤ 2.5 µg/L or IGF-1 ≤ 1.3 × ULN. For one of these patients in the pasireotide LAR 60 mg arm, the protocol deviation was reported in error. The remaining three patients had screening GH or IGF-1 missing or below these criteria. At baseline, these patients had GH values above 2.5 µg/L and IGF-1 above 1.3 × ULN.

- **Baseline data**

Study C2305

Table 7 Demography by treatment – Study C2305 (FAS)

	Pasireotide LAR N=176	Octreotide LAR N=182	All patients N=358
Age (years)			
n	176	182	358
Mean (standard deviation)	45.1 (12.37)	45.6 (12.97)	45.4 (12.67)
Median	46.0	45.0	46.0
Range	18 to 80	19 to 85	18 to 85
Age category (years)			
<65	168 (95.5%)	167 (91.8%)	335 (93.6%)
≥ 65	8 (4.5%)	15 (8.2%)	23 (6.4%)
Sex			
Male	85 (48.3%)	87 (47.8%)	172 (48.0%)
Female	91 (51.7%)	95 (52.2%)	186 (52.0%)
Race			
Caucasian	105 (59.7%)	111 (61.0%)	216 (60.3%)
Asian	39 (22.2%)	43 (23.6%)	82 (22.9%)
Other	23 (13.1%)	19 (10.4%)	42 (11.7%)
Native American	6 (3.4%)	5 (2.7%)	11 (3.1%)
Black	3 (1.7%)	4 (2.2%)	7 (2.0%)
BMI (kg/m^2)			
n	175	181	356
Mean (standard deviation)	28.8 (4.58)	28.7 (5.17)	28.7 (4.88)
Median	28.1	27.8	28.0
Range	19.0 to 44.4	19.5 to 55.8	19.0 to 55.8

Similar to the FAS, baseline demographic characteristics in the cross-over analysis set (CAS) were balanced between the treatment arms. The mean age was 45.2 years, with equal proportions of men and women. The largest race groups were Caucasian (52.1%) and Asian (28.6%).

Baseline characteristics and disease history

Baseline characteristics and disease history were balanced between the treatment arms. Median time since diagnosis was six months, and the majority of patients (>80%) had been diagnosed within 24 months of study start. Less than half (42.2%) of all patients underwent prior surgery (40.3% in the pasireotide LAR arm and 44.0% in the octreotide LAR arm). One patient had received radiation therapy 89.9 months (7.5 years) prior to study entry; this was recorded as a protocol deviation.

Mean GH levels at core Baseline were 21.9 µg/L in the pasireotide LAR arm and 18.8 µg/L in the octreotide LAR arm. Mean standardized IGF-1 levels at core Baseline were 3.1 in both arms.

For the crossover population, mean GH at extension Baseline was 5.9 µg/L for patients who crossed over to pasireotide LAR and 7.1 µg/L for patients who crossed over to octreotide LAR. Mean standardized IGF-1 level at extension Baseline was 1.9 for those who crossed over to pasireotide LAR and 2.1 for those who crossed over octreotide LAR.

Medical history and continuing medical conditions were as expected for a patient population with active acromegaly of this age.

Disease history and baseline characteristics for the crossover analysis set (CAS) were generally comparable with those of the FAS. The proportion of patients who had previous surgery was lower among patients who crossed over to octreotide LAR (26.3%) than in patients who crossed over to pasireotide (43.2%).

Study C2402

Table 8 Demographic summary by treatment group – Study C2402 (FAS)

Demographic variable	Pasireotide LAR 40 mg N=65	Pasireotide LAR 60 mg N=65	Active control N=68
Age (years)			
n	65	65	68
Mean (SD)	42.9 (14.05)	45.8 (14.07)	46.2 (13.11)
Median	46.0	45.0	46.5
Range	18 – 80	20 – 83	18 – 74
Age category (years) – n (%)			
<65	62 (95.4)	57 (87.7)	63 (92.6)
≥ 65	3 (4.6)	8 (12.3)	5 (7.4)
Gender – n (%)			
Female	38 (58.5)	35 (53.8)	38 (55.9)
Male	27 (41.5)	30 (46.2)	30 (44.1)
Race -n (%)			
Caucasian	53 (81.5)	52 (80.0)	56 (82.4)
Black	3 (4.6)	8 (12.3)	4 (5.9)
Asian	3 (4.6)	1 (1.5)	0 (0)
Other	4 (6.2)	3 (4.6)	7 (10.3)
Native American	2 (3.1)	1 (1.5)	1 (1.5)
Body mass index (kg/m^2)			
n	62	64	67
Mean (SD)	29.1 (4.97)	29.8 (6.20)	29.5 (5.69)
Median	28.4	27.5	28.2

Demographic variable	Pasireotide LAR 40 mg N=65	Pasireotide LAR 60 mg N=65	Active control N=68
Min-Max	20.0 - 42.1	21.8 - 49.9	19.2 - 48.0

Baseline characteristics and disease history

Baseline characteristics and disease history were well balanced between the treatment arms (Table 9). Median GH levels at Baseline were 7.1 µg/L, 5.3 µg/L, and 6.1 µg/L in the pasireotide LAR 40 mg arm, 60 mg arm and active control arms, respectively; median standardized IGF-1 levels were 2.3, 2.6 and 2.9 in the respective treatment arms.

Table 9 Disease history and baseline characteristics by treatment – Study C2402 (FAS)

Demographic Variable	Pasireotide LAR 40 mg N=65	Pasireotide LAR 60 mg N=65	Active control N=68
Time since diagnosis of acromegaly (months)*			
n	65	65	68
Mean (SD)	66.4 (60.98)	75.0 (65.46)	80.1 (75.59)
Median	50.0	54.5	53.8
Minimum- Maximum	10-337	8-357	8-357
Time category – n (%)			
≥ 6 to <12	6 (9.2)	3 (4.6)	4 (5.9)
≥ 12 to <24	14 (21.5)	6 (9.2)	11 (16.2)
≥ 24 to <60	19 (29.2)	26 (40.0)	22 (32.4)
≥ 60	26 (40.0)	30 (46.2)	31 (45.6)
Time since last previous surgery (months)*			
n	50	41	41
Mean (SD)	58.3 (64.85)	73.9 (51.34)	69.9 (66.26)
Median	32.0	66.0	43.7
Minimum- Maximum	3-337	21-229	5-240
Time category – n (%)			
≥ 2 to <6	1 (1.5)	0 (0)	2 (2.9)
≥ 6 to <12	10 (15.4)	0 (0)	2 (2.9)
≥ 12 to <24	10 (15.4)	4 (6.2)	7 (10.3)
≥ 24 to <60	14 (21.5)	16 (24.6)	13 (19.1)
≥ 60	15 (23.1)	21 (32.3)	17 (25.0)
Missing	15 (23.1)	24 (36.9)	27 (39.7)
Previous radiation – n (%)			
External beam radiation	2 (3.1)	2 (3.1)	5 (7.4)
Gamma-knife therapy	0 (0)	1 (1.5)	0 (0)
Randomization stratification factors – n (%)			
Octreotide LAR	50 (76.9)	50 (76.9)	51 (75.0)
Lanreotide ATG	15 (23.1)	15 (23.1)	17 (25.0)
GH > 2.5 to ≤ 10 µg/L	47 (72.3)	47 (72.3)	48 (70.6)

Demographic Variable	Pasireotide LAR 40 mg N=65	Pasireotide LAR 60 mg N=65	Active control N=68
GH > 10 µg/L	18 (27.7)	18 (27.7)	20 (29.4)

Months = (date of first dose−date of diagnosis/surgery+1)/30.4375."

- **Outcomes and estimation**

Study C2305

Primary efficacy results

The study met its primary endpoint showing a statistically significant result (p=0.007) in favour of pasireotide LAR (Table 10). The proportion of responders (i.e. patients with GH below 2.5 µg/L and normalized IGF-1 at Month 12) was 31.3% (95% CI 24.5, 38.7) in the pasireotide LAR arm, and 19.2% (95% CI 13.8, 25.7) in the octreotide LAR arm, with an odds ratio (95% CI) of 1.942 (1.190, 3.168) in favour of pasireotide LAR.

When analyzed by post-surgery vs de novo stratum, the response rates were slightly higher for patients who were post-surgery relative to de novo patients for both pasireotide LAR and for octreotide LAR, with response rates remaining higher in the pasireotide LAR arm than in the octreotide LAR arm for both strata (Table 10).

GH and IGF-1 at Month 12 were imputed by carrying the last observation forward (LOCF) for four and three responders in the pasireotide LAR and octreotide LAR arms, respectively. Analyses of response rates without imputation showed a response rate of 29% in the pasireotide group and 17.6% in the octreotide LAR group.

Table 10 Proportion of patients with a reduction of GH level to below 2.5 ug/L and normalization of IGF-1 at Month 12 by stratum and treatment – LOCF-Study C2305 (FAS)

	Pasireotide LAR	Octreotide LAR	Between treatment	
Stratum	n/N (%) (95% CI)	n/N (%) (95% CI)	Odds ratio (95% CI)	P-value
Post-surgery	28/71 (39.4) (28.0, 51.7)	17/78 (21.8) (13.2, 32.6)	2.337 (1.140, 4.790)	
De novo	27/105 (25.7) (17.7, 35.2)	18/104 (17.3) (10.6, 26.0)	1.654 (0.846, 3.234)	
Overall	55/176 (31.3) (24.5, 38.7)	35/182 (19.2) (13.8, 25.7)	1.942 (1.190, 3.168)	0.007

Post surgery = medically naïve after surgery; De novo = treatment naïve.
P-value was based on two-sided Cochran-Mantel-Haenszel test.
GH assessment was based on mean of a 5-point 2-hour profile.

Supportive analysis for primary efficacy endpoint

The results of the analysis of the primary efficacy endpoint for the PP set (the subset of patients in the FAS who did not have any major protocol deviation by Month 12 and completed 80% of randomized treatment during the core study) were consistent with the primary efficacy analysis and show a treatment effect statistically significantly in favour of pasireotide LAR (33.5%) vs octreotide (19.9%) (p=0.004; odds ratio 2.056 with 95% CI (1.247, 3.389)).

The results of the analysis of the primary efficacy endpoint where patients with missing values were considered as non-responders were consistent with the primary efficacy analysis, and show a treatment effect statistically

significantly in favour of pasireotide LAR (29.0%) vs octreotide 17.6% (p=0.009; odds ratio 1.939 with 95% CI (1.173, 3.206)). This analysis was based on the FAS.

Analysis of key secondary efficacy variables - Study C2305 core phase

Patients with a GH response at Month 12

The proportion of patients with reduction of GH to below 2.5 µg/L at Month 12 was comparable in both treatment arms, with 48.3% of patients in the pasireotide LAR arm and 51.6% of patients in the octreotide LAR arm achieving this response (Table 11). By post-surgery vs de novo strata, the response rates for post-surgery patients were 52.1% for pasireotide LAR and 51.3% for octreotide LAR; for de novo patients, the response rates were 45.7% for pasireotide LAR and 51.9% for octreotide LAR.

The GH value at Month 12 was imputed for nine responders in the pasireotide LAR arm, and eight responders in the octreotide LAR arm. Response rates without imputation showed 43.2% and 47.3% of patients in the pasireotide LAR and octreotide LAR arms respectively, with GH levels below 2.5 µg/L at Month 12.

Table 11 Proportion of patients with a reduction of GH level to below 2.5 ug/L at Month 12 by stratum and treatment – LOCF - Study C2305 (FAS)

	Pasireotide LAR N=176	Octreotide LAR N=182	Between treatment		
Stratum	n/N (%) (95% exact CI)	n/N (%) (95% exact CI)	Odds ratio (95% CI)	p-value	Adjusted p-value
Post surgery	37/71 (52.1) (39.9, 64.1)	40/78 (51.3) (39.7, 62.8)	1.034 (0.543, 1.967)		
De novo	48/105 (45.7) (36.0, 55.7)	54/104 (51.9) (41.9, 61.8)	0.780 (0.453, 1.343)		
Overall	85/176 (48.3) (40.7, 55.9)	94/182 (51.6) (44.1, 59.1)	0.877 (0.579, 1.328)	0.536	0.838

Post surgery = medically naïve after surgery; De novo = treatment naïve.
P-value was based on two-sided Cochran-Mantel-Haenszel test, adjusting for randomization stratification factor.
Adjusted p-value was based on equally weighted Simes test.
GH assessment was based on mean of a 5-point 2-hour profile.

Patients with IGF-1 response at Month 12

The proportion of patients with normalization of IGF-1 at Month 12 was significantly higher in the pasireotide LAR arm than in the octreotide LAR arm (Table 12). The proportion of patients with normalized IGF-1 was 38.6% in the pasireotide LAR arm, and 23.6% in the octreotide LAR arm, with an odds ratio (95% CI) of 2.087 (1.316, 3.308) in favour of pasireotide LAR (Simes test adjusted p=0.007).

The proportion of patients with IGF-1 levels in the normal range or below the normal range (over-response) at Month 12 was 44.3% for pasireotide LAR and 25.8% for octreotide LAR. Ten patients in the pasireotide LAR arm and four patients in the octreotide LAR arm were not considered IGF-1 responders in the per-protocol analysis because their IGF-1 levels decreased to below the LLN.

The IGF-1 at Month 12 was imputed for five responders in the pasireotide LAR arm and three responders in the octreotide LAR arm. Without imputation, response rates at Month 12 were 35.8% and 22.0% for pasireotide LAR and octreotide LAR, respectively.

Table 12 Proportion of patients with normalization of IGF-1 at Month 12 by stratum and treatment – LOCF - Study C2305 (FAS)

	Pasireotide LAR N=176	Octreotide LAR N=182	Between treatment		
Stratum	n/N (%) (95% exact CI)	n/N (%) (95% exact CI)	Odds ratio (95% CI)	p-value	Adjusted p-value
Post surgery	36/71 (50.7) (38.6, 62.8)	21/78 (26.9) (17.5, 38.2)	2.792 (1.410, 5.528)		
De novo	32/105 (30.5) (21.9, 40.2)	22/104 (21.2) (13.8, 30.3)	1.634 (0.872, 3.061)		
Overall	68/176 (38.6) (31.4, 46.3)	43/182 (23.6) (17.7, 30.5)	2.087 (1.316, 3.308)	0.002	0.007

Post surgery = medically naïve after surgery; De novo = treatment naïve.
P-value was based on two-sided Cochran-Mantel-Haenszel test, adjusting for randomization stratification factor
Adjusted p-value was based on equally weighted Simes test.

Change from Baseline in tumour volume

Baseline tumour volume was comparable in both treatment arms and between post-surgery and de novo strata (Table 13).

A marked decrease in tumour volume was seen at Month 12 in both treatment arms . The mean decrease was 987.1 mm^3 (39.7%) in the pasireotide LAR arm, and 801.2 mm^3 (38.0%) in the octreotide LAR arm. Similar decreases were observed with both treatments in both post-surgery and de novo strata.

The proportion of patients with decrease or no change in tumour volume was high in both treatment arms, however it was slightly higher for pasireotide vs. octreotide, both for post-surgery patients (100% vs. 94.2%), and for de novo patients (96.1% vs. 94.4%).

Table 13 Change from Baseline in tumour volume (mm^3) at Month 12 by stratum and treatment - Study C2305 (FAS)

	Pasireotide LAR N=176		Octreotide LAR N=182		P-value	Adjusted p-value
Stratum	n	Mean (SD)	n	Mean (SD)		
Post surgery						
Baseline value	70	2185.2 (2861.09)	74	2196.5 (3922.08)		
Value at Month 12	45	1464.6 (1989.87)	58	1407.9 (2659.69)		
Change at Month 12	44	-873.7 (1282.06)	55	-713.8 (1708.20)		
% Change at Month 12	44	-39.5 (20.60)	52	-39.0 (23.81)		
De novo						
Baseline value	96	2592.4 (4901.99)	95	2308.1 (2930.84)		
Value at Month 12	80	1492.3 (2596.99)	80	1377.7 (1771.05)		
Change at Month 12	77	-1051.9 (2919.18)	73	-867.1 (1661.24)		
% Change at Month 12	76	-39.9 (22.65)	72	-37.2 (25.07)		
Overall						
Baseline value	166	2420.7 (4159.21)	169	2259.2 (3390.20)	0.838	0.838
Value at Month 12	125	1482.4 (2387.88)	138	1390.4 (2179.93)		
Change at Month 12	121	-987.1 (2448.14)	128	-801.2 (1676.62)		

Stratum	Pasireotide LAR N=176 n	Mean (SD)	Octreotide LAR N=182 n	Mean (SD)	P-value	Adjusted p-value
% Change at Month 12	120	-39.7 (21.83)	124	-38.0 (24.47)		

Only patients who had value at Month 12 are included in the analysis.
Post surgery = medically naïve after surgery; De novo = treatment naïve.
P-value was based on ANCOVA model for change at Month 12 with treatment as the fixed effect and tumour volume at Baseline and randomization as covariates.
Adjusted p-value was based on equally weighted Simes test.

Reduction in tumour volume of at least 20%: The proportion of patients who achieved a reduction of at least 20% in tumour volume during core plus extension treatment (up to crossover) was comparable in both treatment arms (74.7% for pasireotide LAR vs. 71.6% for octreotide LAR). The median time to this event was also comparable (25.0 weeks for pasireotide LAR vs. 24.3 weeks for octreotide LAR). The probability estimates for this event at 48 weeks was slightly higher for pasireotide LAR (21.8%) than for octreotide LAR (17.4%). The results were comparable across strata (post-surgery and de novo).

Other secondary efficacy results – Study C2305 core phase

Shifts from Baseline in GH during core phase

Baseline GH categories (<1 µg/L, 1 to <2.5 µg/L, 2.5 to <5 µg/L, ≥ 5 µg/L) were comparable between the pasireotide LAR and octreotide LAR arms, with more than 70% of all patients having baseline GH in the ≥ 5 µg/L category. Shifts to lower GH categories occurred on both treatments, but the proportion of patients with a shift was slightly higher in the pasireotide LAR arm than the octreotide LAR arm. Among patients with baseline GH ≥ 5 µg/L, 84 of 125 patients (67.2%) in the pasireotide LAR arm shifted to a lower category, compared to 84 of 134 patients (62.7%) in the octreotide LAR arm.

Note also that the proportion of patients who had GH below 1 µg/L as last value in the core was marginally higher in the pasireotide LAR arm (27.3%) than in the octreotide LAR arm (23.6%); conversely the proportion of patients with GH ≥ 5 µg/L as last value was higher in the octreotide LAR arm (26.9%) than the pasireotide LAR arm (22.2%).

Other efficacy results – core phase and up to crossover- Study C2305

The sections below present analyses of data for the core phase (i.e. up to Month 12), and up to crossover (i.e. including core and extension data up to data cut-off for patients who continued the same treatment in the extension). For patients who crossed over, data are included up to the time point of crossover (note that for analyses of response rates these patients are considered non-responders for time points after crossover). The evaluation of efficacy in the sections below focuses on assessments up to Month 25, as this was the last visit at which efficacy parameters were assessed in the octreotide arm.

The time point for crossover was at Month 12 for patients who entered the extension prior to Amendment 4 (n=31), and at Month 13 for patients who entered the extension after Amendment 4 (n=228). In addition, three patients who entered the extension prior to Amendment 4, and seven patients who entered the extension after Amendment 4, had their treatment changed at a later time point in the extension.

Because the decision regarding a patient's treatment in the extension was at the discretion of the investigator, patients who did not meet the GH and IGF-1 response criteria at Month 12 could continue in the extension on the same treatment if the investigator felt that the patient benefited from the randomized treatment. The number

of patients who continued the same treatment in the extension was 74 (42.0%) for pasireotide and 46 (25.3%) for octreotide. Among these patients, the majority had full or partial response in terms of GH and IGF-1 at the Month 12 assessment. Thirteen of the 74 patients (17.6%) on pasireotide and 8 of the 46 patients (17.4%) on octreotide were non-responders at Month 12.

Based on these results, the Applicant concluded that no bias was evident with respect to investigator's choice of treatment for the extension (i.e. randomized treatment vs. crossover) between the treatment arms.

Patients with GH and IGF-1 response over time

The proportions of patients who were responders (i.e. GH below 2.5 µg/L and normalized IGF-1) were consistently higher in the pasireotide LAR arm than in the octreotide LAR arm throughout the core and extension for patients who remained on the same treatment. Odds ratios indicated a treatment effect in favour of pasireotide LAR at all time points up to Month 25. Results at Month 12 for this population are consistent with those of the primary efficacy analysis (Table 14).

The results of analyses evaluating response rates in the blinded extension (Month 12 to Month 25), using as a denominator the number of patients who entered the extension and remained on the same treatment in the core (n=74 for pasireotide LAR, and n=46 for octreotide LAR) showed a persistent treatment effect in both arms. The response rates were comparable in both arms.

Table 14 Proportion of patients with a reduction in mean GH level to below 2.5 ug/L and normalization of IGF-1 by visit and treatment – FAS with data up to crossover Study C2305 (FAS)

	Pasireotide LAR, N=176		Octreotide LAR, N=182		Between treatment
Visit	n/N (%)	95% exact CI	n/N (%)	95% exact CI	Odds ratio (95% CI)
Month 3	53/176 (30.1)	(23.4, 37.5)	39/182 (21.4)	(15.7, 28.1)	1.605 (0.992, 2.596)
Month 6	53/176 (30.1)	(23.4, 37.5)	36/182 (19.8)	(14.3, 26.3)	1.758 (1.082, 2.857)
Month 9	49/176 (27.8)	(21.4, 35.1)	42/182 (23.1)	(17.2, 29.9)	1.291 (0.803, 2.074)
Month 12	51/176 (29.0)	(22.4, 36.3)	32/182 (17.6)	(12.3, 23.9)	1.939 (1.173, 3.206)
Month 16	37/147 (25.2)	(18.4, 33.0)	19/153 (12.4)	(7.6, 18.7)	2.425 (1.314, 4.476)
Month 19	34/147 (23.1)	(16.6, 30.8)	21/153 (13.7)	(8.7, 20.2)	1.891 (1.039, 3.442)
Month 22	37/147 (25.2)	(18.4, 33.0)	25/153 (16.3)	(10.9, 23.2)	1.733 (0.984, 3.054)
Month 25	36/147 (24.5)	(17.8, 32.3)	21/153 (13.7)	(8.7, 20.2)	2.058 (1.135, 3.730)

Odds ratios are adjusted for randomization stratification factor.
Denominator for time points up to Month 12 is the FAS. Denominator for time points after Month 12 excludes patients who did not enter the extension.
Patients who discontinued were considered non-responders for the time points after discontinuation, patients who crossed over were considered non-responders after Month 12.
GH assessment was based on mean of a 5-point 2-hour profile.

The proportion of responder was higher in the pasireotide LAR arm than the octreotide LAR arm throughout the core and extension. Note that the denominator changes over time: for time points up to Month 12 it is the FAS, for time points beyond Month 12 patients who did not enter the extension after completion of core were excluded (unless they crossed over or discontinued early).

At Month 12, 29.0% of patients in the pasireotide arm achieved both, GH and IGF-1 response. GH response only was achieved by additional 14.2% and IGF-1 response only was achieved by additional 6.8% of patients in the pasireotide LAR arm. In the octreotide arm GH and IGF-1 response was achieved by 17.6% of patients, GH

response only was achieved by additional 29.7% and IGF-1 response only was achieved by additional 4.4% of patients.

Patients with GH response over time

The proportion of patients who achieved GH below 2.5 µg/L was comparable in the pasireotide LAR and octreotide LAR arms throughout the core up to Month 12 (Table 15).

During the extension up to Month 25, the proportion of patients with a GH response was slightly higher in the pasireotide LAR arm than in the octreotide LAR arm. Odds ratios indicated a treatment effect in favour of pasireotide LAR at all visits in the extension; with lower bound of 95% CIs above 1 at all time points up to Month 25.

Table 15 Proportion of patients with a reduction in GH level to below 2.5 ug/L by visit and treatment - Study C2305 (FAS)

	Pasireotide LAR, N=176		Octreotide LAR, N=182		Between treatment
Visit	n/N (%)	95% exact CI	n/N (%)	95% exact CI	Odds ratio (95% CI)
Month 3	87/176 (49.4)	(41.8, 57.1)	79/182 (43.4)	(36.1, 50.9)	1.274 (0.841, 1.930)
Month 6	80/176 (45.5)	(37.9, 53.1)	87/182 (47.8)	(40.4, 55.3)	0.912 (0.603, 1.380)
Month 9	75/176 (42.6)	(35.2, 50.3)	84/182 (46.2)	(38.8, 53.7)	0.870 (0.574, 1.321)
Month 12	76/176 (43.2)	(35.8, 50.8)	86/182 (47.3)	(39.8, 54.8)	0.851 (0.561, 1.291)
Month 16	49/147 (33.3)	(25.8, 41.6)	34/153 (22.2)	(15.9, 29.6)	1.744 (1.048, 2.904)
Month 19	54/147 (36.7)	(28.9, 45.1)	33/153 (21.6)	(15.3, 28.9)	2.104 (1.266, 3.496)
Month 22	52/147 (35.4)	(27.7, 43.7)	34/153 (22.2)	(15.9, 29.6)	1.918 (1.156, 3.181)
Month 25	52/147 (35.4)	(27.7, 43.7)	37/153 (24.2)	(17.6, 31.8)	1.725 (1.046, 2.843)

Odds ratios are adjusted for randomization stratification factor.
Denominator for time points up to Month 12 is the FAS.
Denominator for time points beyond Month 12 excludes patients who did not enter the extension.
Patients who discontinued were considered non-responders for the time points after discontinuation, patients who crossed over were considered non-responders after Month 12.
GH assessment was based on mean of a 5-point 2-hour profile.

The results of analyses evaluating GH response rates in the extension (Month 12 to Month 25) including only patients who entered the extension on the same treatment as in the core (74 patients in the pasireotide LAR arm and 46 patients in the octreotide LAR arm) showed that the response rates for GH were similar between the pasireotide LAR and octreotide LAR arms from Month 12 to Month 25, and ranged between 66.2 to 78.4% for pasireotide and from 71.7% and 80.4% for octreotide.

GH values over time

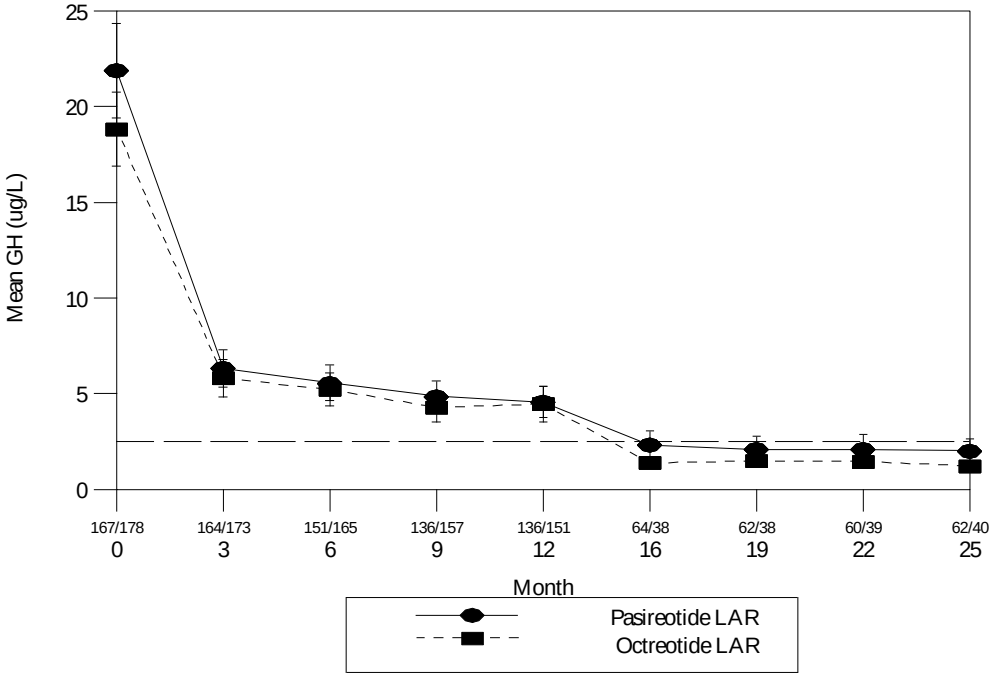
As shown in Figure 3, by Month 3 a marked decrease in mean GH was observed in both arms (percent decrease from Baseline was 63.4% for pasireotide LAR and 61.4% for octreotide LAR), with a slight further decrease observed up to Month 12 for patients who remained in the study. Between-treatment comparison for change from Baseline did not reveal any statistically significant differences between the treatment arms up to Month 12.

As expected, the mean GH levels of patients who continued the same treatment were below 2.5 µg/L at the first assessment in the extension (Month 16) in both treatment arms.

The treatment effect was consistent across strata in both arms. Patients who were post-surgery had slightly lower baseline GH levels (mean 16.1 µg/L and 13.3 µg/L for pasireotide LAR and octreotide LAR, respectively) than patients with a de novo tumour (mean 25.9 µg/L and 22.9 µg/L, respectively). Robust decreases in GH

levels were observed in both treatment arms for both strata by Month 3: percent decrease from Baseline was 63.8% and 51.9% (pasireotide LAR and octreotide LAR, respectively) for patients who were post-surgery, and 63.1% and 68.1% for patients who were de novo. GH levels at Month 12 were slightly lower for patients who were post-surgery (2.6 µg/L and 3.3 µg/L for pasireotide LAR and octreotide LAR, respectively) than for patients who were de novo (5.8 µg/L and 5.3 µg/L). A slight difference between the strata was also evident at Month 25; mean GH values for post-surgery patients were 1.3 µg/L and 1.0 µg/L for pasireotide LAR and octreotide LAR, whereas for de novo patients mean GH values were 2.9 µg/L and 1.4 µg/L, respectively.

Figure 3 Mean (+/- SE) of GH level by visit and treatment – FAS with data up to crossover - Study C2305



Numbers shown between the x-axis tick mark and the numeral indicating the month represent the numbers of patients in pasireotide/octreotide treatment group. This analysis includes scheduled visits only. At least three samples contributed to patient mean GH at each time point. ± standard errors are displayed. Reference line is 2.5 ug/L.
GH was based on mean of a 5-point 2-hour profile.

Patients with IGF-1 response over time

The proportion of patients who achieved normalization of IGF-1 was higher in the pasireotide LAR than the octreotide LAR arm throughout the core and extension (Table 16).

Odds ratios indicated a treatment effect in favour of pasireotide LAR at all visits in the core and extension, with lower bound of 95% CIs above 1 at all time points except Month 9 and Month 22.

Table 16 Proportion of patients with normalization of IGF-1 by visit and treatment - Study C2305 (FAS)

	Pasireotide LAR, N=176		Octreotide LAR, N=182		Between treatment
Visit	n/N (%)	95% exact CI	n/N (%)	95% exact CI	Odds ratio (95% CI)
Month 3	62/176 (35.2)	(28.2, 42.8)	46/182 (25.3)	(19.1, 32.2)	1.640 (1.036, 2.595)
Month 6	63/176 (35.8)	(28.7, 43.4)	44/182 (24.2)	(18.1, 31.1)	1.764 (1.116, 2.790)
Month 9	60/176 (34.1)	(27.1, 41.6)	51/182 (28.0)	(21.6, 35.1)	1.328 (0.849, 2.077)
Month 12	63/176 (35.8)	(28.7, 43.4)	40/182 (22.0)	(16.2, 28.7)	2.018 (1.262, 3.226)
Month 16	44/147 (29.9)	(22.7, 38.0)	21/153 (13.7)	(8.7, 20.2)	2.795 (1.552, 5.031)
Month 19	37/147 (25.2)	(18.4, 33.0)	24/153 (15.7)	(10.3, 22.4)	1.803 (1.018, 3.194)
Month 22	38/147 (25.9)	(19.0, 33.7)	26/153 (17.0)	(11.4, 23.9)	1.709 (0.978, 2.988)
Month 25	38/147 (25.9)	(19.0, 33.7)	22/153 (14.4)	(9.2, 21.0)	2.092 (1.168, 3.748)

Odds ratios are adjusted for randomization stratification factor.
Denominator for time points up to Month 12 is the FAS.
Denominator for time points beyond Month 12 excludes patients who did not enter the extension.
Patients who discontinued were considered non-responders for the time points after discontinuation, patients who crossed over were considered non-responders after Month 12.

Mean standardized IGF-1 values over time

Baseline mean standardized IGF-1 was comparable in the pasireotide LAR and octreotide LAR arms (mean 3.1 in both arms). Standardized IGF-1 values were calculated by dividing the actual IGF-1 value by the ULN of the normal range reported by local laboratory providing the patient data. By Month 3, there was a marked reduction in IGF-1 levels in both treatment arms (mean percent decrease from Baseline was 49.5% for pasireotide LAR and 45.1% for octreotide LAR). At Month 12, mean IGF-1 was 1.4 in the pasireotide LAR arm, and 1.5 in the octreotide LAR arm. The decrease from Baseline at Month 12 was slightly larger in the pasireotide LAR arm (55.2%) than the octreotide LAR arm (45.4%).

As expected, standardized IGF-1 levels were close to 1 (actual IGF-1 value/local lab ULN) at the first assessment in the extension (Month 16) in both treatment arms, and remained stable thereafter in both treatment arms. At Month 25, mean IGF-1 was 0.8 vs. 0.9 for pasireotide LAR vs. octreotide LAR, and the mean decrease from Baseline was 67.2% vs. 61.2%, respectively.

The treatment effect was consistent across strata in both arms. Patients who were post-surgery had slightly lower baseline IGF-1 levels (mean 2.6 and 2.8 for pasireotide LAR and octreotide LAR, respectively) than de novo patients (mean 3.3 in both arms). There were robust decreases in IGF-1 levels in both treatment arms for both strata by Month 3 in the core: mean percent decrease from Baseline was 54.9% vs. 40.0% (pasireotide LAR vs. octreotide LAR) for patients who were post-surgery, and 46.0% vs. 48.8% for de novo patients. Mean IGF-1 levels at Month 12 were slightly lower for patients who were post-surgery (1.0 vs. 1.5 for pasireotide LAR vs. octreotide LAR) than for de novo patients (1.6 in both arms). A slight difference between the strata was also evident at Month 25; mean IGF-1 for post-surgery patients was 0.7 for both pasireotide LAR and octreotide LAR, whereas for de novo patients mean IGF-1 was 0.9 vs. 1.0 for pasireotide LAR vs. octreotide LAR.

Time to first response and persistence of efficacy

Time to first response

Median time to first response in terms of combined GH and IGF-1 criteria (i.e. GH below 2.5 µg/L and normalized IGF-1) during core and extension treatment (up to crossover) was comparable in the two treatment arms: 12.6

weeks for pasireotide, and 12.4 weeks for octreotide LAR. The results were similar for both strata (post-surgery and de novo).

Time to first GH response (i.e. GH below 2.5 µg/L) and time to first IGF-1 response (i.e. normalization of IGF-1) were also similar in both treatment arms and strata.

Duration of first response

The median duration of first response for patients who achieved response was twice as long in the pasireotide arm (51.6 weeks, 95% CI 24.1, 64.1) than in the octreotide LAR arm (24.1 weeks, 95% CI 12.3, 36.0). Patients who lost response at one visit in both treatment arms often regained response at later visits.

The number of patients with a response based on GH and IGF-1 criteria (i.e. GH below 2.5 µg/L and normalized IGF-1 at any time point) using up to crossover data was higher in the pasireotide arm (81 patients) than in the octreotide LAR arm (63 patients). By data cut-off (or crossover for patients who crossed over), 30 patients in pasireotide LAR arm and 12 in octreotide LAR arm maintained response at all subsequent time points. The remaining 51 patients in the pasireotide LAR and 48 patients in the octreotide LAR lost response at least once. The abnormal values for these patients were very close to the normal limits and returned to normal at subsequent evaluations. Additionally, some patients were recorded to have lost response due to IGF-1 values below LLN. The loss of response was defined as GH ≥ 2.5 µg/L and/or any IGF-1 above or below normal. At Month 12, 4.5% of patients in the pasireotide arm and 1.6% of patients in the octreotide arm had over response defined as GH below 2.5 µg/L and IGF-1 below LLN.

Duration of response achieved at Month 12

The number of patients who achieved a response at Month 12 (i.e. GH to below2.5 µg/L and normalized IGF-1) was 51 in the pasireotide arm, and 32 in the octreotide LAR arm. The response was maintained for 64.4 weeks for pasireotide, and 64.6 weeks for octreotide LAR and was comparable in the two treatment arms (Table 17). About half of all patients with response were censored for this analysis.

Based on review of individual patient data, most patients who lost response after Month 12 did so due to small variations in GH and IGF-1 levels (of note, some patients lost response because their IGF-1 decreased to below LLN). In both arms, the GH and IGF-1 levels tended to remain close to the criteria for biochemical control: tachyphylaxis was not evident.

Table 17 Duration of response (weeks) for patients achieving a reduction in GH level to below 2.5 ug/L and normalization of IGF-1 at Month 12 by treatment – FAS with data up to crossover - Study C2305

	Pasireotide LAR N=176	Octreotide LAR N=182
Responders	51	32
No. of patients losing response	28 (54.9%)	16 (50.0%)
No. of censoring	23 (45.1%)	16 (50.0%)
Median duration of response (95% CI)	64.4 (52.1, 100.4)	64.6 (40.0, 92.0)

Percentage is based on the responders.
Median and corresponding 95% CI were obtained using Kaplan-Meier method.
GH assessment was based on mean of a 5-point 2-hour profile.

Tumour volume

Tumour volume data collected beyond Month 12 showed that mean tumour volume continued to decrease for patients who continued the same treatment in the extension. Mean percent decrease from core Baseline at Month 25 was 51.8% (n=54) for pasireotide and 55.0% (n=34) for octreotide. As mentioned previously, the mean percentage decrease at Month 12 was 39.7% for pasireotide and 38.0% for octreotide. Most of the data after Month 25 is from patients receiving pasireotide, who remained on study longer. For these patients, tumour volume continued to decrease.

Change from Baseline in PRL levels

Mean baseline PRL levels were higher in in the pasireotide LAR arm (20.6 µg/L) than the octreotide LAR arm (15.8 µg/L), but median values were similar (median 8.0 µg/L in both arms). PRL levels decreased with treatment in both arms, but did so more rapidly in the pasireotide LAR arm than in the octreotide LAR arm. At Month 12, mean PRL was 8.9 µg/L in the pasireotide LAR arm and 11.7 µg/L in the octreotide LAR arm, and median PRL was the same (6.0 µg/L) in both arms.

There was a statistically significant difference (p=0.006) between the two treatment arms in change in PRL from Baseline to Month 12.

Mean and median PRL levels decreased further during the extension for patients who continued the same treatment, with levels decreasing further in the pasireotide LAR than the octreotide LAR arm. At Month 25, mean PRL was 5.4 µg/L in the pasireotide LAR arm and 6.7 µg/L in the octreotide LAR arm; the mean decrease from Baseline was 31.1% vs. 25.9% for pasireotide LAR vs. octreotide LAR.

In addition, changes in PRL levels were analyzed for those patients with hyperprolactemia (PRL level above the upper limit of normal) at study entry. Mean baseline values were higher in the 29 patients in the pasireotide LAR arm (83.5 µg/L) than for the 30 patients in the octreotide LAR arm (55.9 µg/L). Over time the decrease in PRL levels was greater in the pasireotide LAR arm compared to the octreotide LAR arm. At Month 12, median decrease was −31.5 µg/L, with an actual median value of 11.0 µg/L in the pasireotide LAR arm and −25.5 µg/L, with an actual median value of 25.0 µg/L in the octreotide LAR arm. This trend remained for patients who continued on the same treatment; at Month 25, the median decrease was −27.0 µg/L, with an actual median value of 5.0 µg/L in the pasireotide LAR arm and -30.0 µg/L, with an actual median value of 12.5 µg/L in the octreotide LAR arm.

Symptoms of acromegaly and ring size

Symptoms of acromegaly (headache, fatigue, perspiration, paresthesias, osteoarthralgia) were recorded monthly in the core phase and in the first 6 months in the extension and every three months thereafter according to a five-point score scale (0=absent, 1=mild, 2=moderate, 3=severe, 4=very severe). Improvements in severity scores of acromegaly symptoms were noted in both treatment arms at Month 12. No relevant differences were observed between the treatment arms in the core phase and for those who continued on the same treatment.

Ring size was measured at the fourth digit of the non-dominant hand. In the case a patient had a fourth digit size exceeding the highest size of the measuring device, the fifth digit of that hand was used for initial and follow-up investigation. Assessments were recorded at the same time-points as signs and symptoms of the disease. A small decrease in mean ring size was observed in both treatment arms at Month 12, however, differences between treatment arms were not statistically significant (p=0.219). Mean ring size remained below baseline levels throughout the extension for patients who continued the same treatment.

Acromegaly quality of life

Improvements in AcroQoL scores (total and individual sub-scores) were noted in both treatment arms, but the changes from Baseline were larger in the pasireotide LAR arm than the octreotide LAR arm throughout the study period. At Month 12, the mean percentage increase from Baseline in total AcroQoL score was +28.4% for pasireotide LAR and +15.8% for octreotide LAR. AcroQoL scores remained higher in the pasireotide LAR than the octreotide LAR arm throughout the extension for patients who continued the same treatment; at Month 25, the change from Baseline was +41.4% for pasireotide LAR and +12.1% for octreotide LAR.

The results for between-treatment comparison for change from Baseline in AcroQoL at Month 12 showed that the changes from Baseline were numerically higher in the pasireotide LAR arm than in the octreotide LAR arm for the total score (least square mean change of 7.2 for pasireotide LAR vs. 4.8 for octreotide LAR) as well as the four sub-scores. The difference between pasireotide LAR and octreotide LAR was not statistically significant for the total score (p=0.158) or for any of the sub-scores (p-values ranged from 0.072 to 0.405). However, it must be noted that the study was not powered to detect a significant difference in this analysis.

Study C2402

Primary efficacy results for Study C2402

Study C2402 met its primary efficacy endpoint. In both the pasireotide LAR 40 mg and 60 mg treatment arms, the proportion of patients who achieved biochemical control was significantly higher compared to the active control arm (Table 18).

In the pasireotide LAR 40 mg arm, 10 patients (15.4%) achieved biochemical control at Week 24 compared with none in the active control arm (odds ratio=16.63 with 95% CI: [3.32, infinity]; adjusted p-value=0.0006).

In the pasireotide LAR 60 mg arm, 13 patients (20.0%) achieved biochemical control at 24 weeks (odds ratio=23.03 with 95% CI: [4.72, infinity]; adjusted p-value<0.0001).

Table 18 Proportion of patients with a reduction in mean GH level to below 2.5 ug/L and normalization of IGF-1 at Week 24 by treatment - Study C2402 (FAS)

Category	Pasireotide LAR 40 mg N=65	Pasireotide LAR 60 mg N=65	Active control N=68
n (%)	10 (15.4)	13 (20.0)	0
95% CI for %	[7.63, 26.48]	[11.10, 31.77]	[0.00, 5.28]
OR vs. Active control	16.63	23.03	
95% CI for OR	[3.32, infinity]	[4.72, infinity]	
p-value*	0.0006	<0.0001	
adjusted p-value**	0.0006	<0.0001	

The 95%CI for % is two-sided and calculated based on the Clopper-Pearson method.
The 95% CI for the OR is two-sided and calculated using the stratified exact logistic regression with treatment included as a covariate and the randomization stratification factors as the stratification variables.
*The p-value is one-sided and calculated using stratified exact logistic regression.
**Adjusted p-value computation based on trimmed version of the weighted Simes test
Discontinued patients are considered non-responders.

The proportion of patients with mean GH below 2.5 ug/L and normalization of IGF-1 at Week 12 was similar to Week 24: 15.4% and 18.5% in the pasireotide LAR 40 mg and 60 mg arms, and 0% in the active control arm.

Supportive analysis for primary efficacy endpoint

The proportion of patients who achieved biochemical control at Week 24 in the PP set (i.e. patients with no protocol deviations) was similar to that observed in the FAS; in the PP set, seven patients (13%) in the 40 mg arm, nine patients (18.0%) in the 60 mg arm, and no patients (0%) in the active control arm achieved biochemical control at Week 24. The difference from the rate in the active control arm was statistically significant in both the 40 mg (p=0.0051) and 60 mg (p=0.0007) treatment arms.

The results of a sensitivity analysis of the primary endpoint using LOCF were in line with those of the primary analysis (Table 19).

Table 19 Proportion of patients with a reduction in mean GH level to below 2.5 ug/L and normalization of IGF-1 at Week 24 by treatment – Sensitivity analysis using LOCF - Study C2402 (FAS)

	Pasireotide LAR 40 mg N=65	Pasireotide LAR 60 mg N=65	Active Control N=68
n (%)	11 (16.9)	15 (23.1)	0
95% CI for %	[8.76, 28.27]	[13.53, 35.19]	[0.00, 5.28]
OR (vs. Active control)	19.00	28.35	
95% CI for OR	[3.83, infinity]	[5.86, infinity]	
p-value*	0.0002	<0.0001	

* The p-value is one-sided and calculated using stratified exact logistic regression.
Last observation carried forward (LOCF) was used. Baseline value was not carried forward.

Response rates by randomization strata

Both pasireotide arms were superior to active control in patients previously inadequately controlled on octreotide. Among patients in the stratum prior octreotide LAR, the proportion of patients who achieved biochemical control at Week 24 was consistent with the primary analysis. For the stratum prior lanreotide, low sample size prevents any definite conclusions from being drawn.

Both pasireotide arms were superior to active control in patients with a baseline GH level below 10 µg/L. Among patients with a baseline GH level below 10 µg/L, the proportion of patients who achieved biochemical control at Week 24 was consistent with the primary analysis. No meaningful conclusions can be drawn for patients with a baseline GH level above 10 µg/L due to the low sample size.

Analysis of the key secondary efficacy variable – Study C2402

The proportion of patients who achieved normalization of IGF-1 at Week 24 (key secondary efficacy variable) was significantly higher in both pasireotide arms (24.6% and 26.2% in the pasireotide LAR 40 mg and 60 mg arms, respectively) compared to the active control arm (no responders) (Table 20).

The response rates in terms of IGF-1 normalization at Week 12 (24.6% in each pasireotide LAR arm, and 1.5% in the active control arm) were similar to those at Week 24.

Table 20 Proportion of patients with normalization of IGF-1 at Week 24 by treatment - Study C2402 (FAS)

Category	Pasireotide LAR 40 mg N=65	Pasireotide LAR 60 mg N=65	Active control N=68
n (%)	16 (24.6)	17 (26.2)	0 (0)
95% CI for %	[14.77 , 36.87]	[16.03 , 38.54]	[0.00 , 5.28]
OR vs. Active control	30.12	32.66	
95% CI for OR	[6.28, infinity]	[6.84, infinity]	
p-value*	<0.0001	<0.0001	
Adjusted p-value**	0.0006	<0.0001	

The 95% Confidence Interval (CI) for % is two-sided and calculated based on the Clopper-Pearson method.
The 95% CI for the Odds Ratio (OR) is two-sided and calculated using the stratified exact logistic regression with treatment included as a covariate and the randomization stratification factors as the stratification variables.
*The p-value is one-sided and calculated using stratified exact logistic regression.
**Adjusted p-value computation based on trimmed version of the weighted Simes test
Discontinued patients are considered non-responders.

Analysis of other secondary efficacy variables – Study C2402

Patients with GH response

The proportion of patients with mean GH below 2.5 ug/L at Week 24 was highest in the pasireotide LAR 60 mg arm (43.1%), followed by the 40 mg arm (35.4%) and the active control arm (13.2%) (Table 21).

The results for GH response at Week 12 were similar to those at Week 24, with 33.8%, 49.2% and 4.4% of patients in the pasireotide LAR 40 mg, 60 mg and active control arms achieving GH below 2.5 µg/L at Week 12, respectively.

The proportion of patients with a reduction of GH to below 1 µg/L at Week 24 was also highest in the pasireotide LAR 60 mg arm (18.5%), followed by the pasireotide LAR 40 mg arm (12.3%), and the active control arm (2.9%). Similar results were seen at Week 12, with 7.7%, 21.5% and 1.5% of patients in the pasireotide LAR 40 mg, 60 mg and active control arm achieving GH below 1 µg/L at Week 12, respectively.

Table 21 Proportion of patients with a reduction in mean GH level to below 2.5 ug/L at Week 24 by treatment - Study C2402 (FAS)

	Pasireotide LAR 40 mg N=65	Pasireotide LAR 60 mg N=65	Active Control N=68
n (%)	23 (35.4)	28 (43.1)	9 (13.2)
95% CI for %	[23.92, 48.23]	[30.85, 55.96]	[6.23, 23.64]
OR (vs. Active control)	3.62	5.05	
95% CI for OR	[1.42, 9.94]	[2.01, 13.77]	
p-value*	0.0024	0.0001	

* The p-value is one-sided and calculated using stratified exact logistic regression.
Discontinued patients are considered non-responders.

Change from Baseline in GH at Week 24

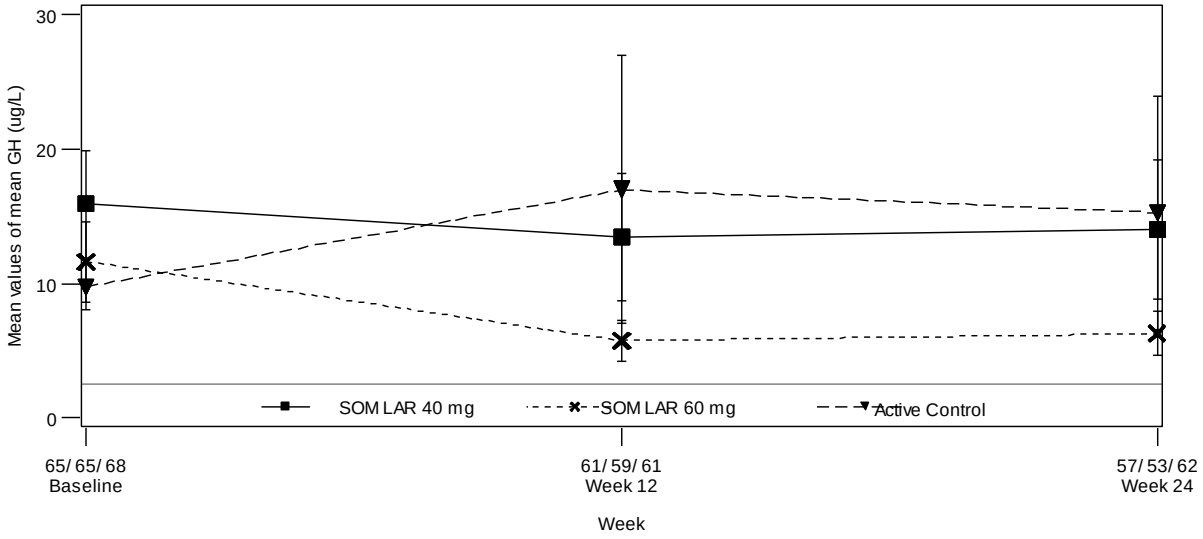
Both doses of pasireotide LAR were more efficacious than active control in suppressing GH levels; suppression of mean GH was achieved by Week 12 and was well maintained thereafter (Figure 4).

Most patients entered the study with a median GH level below 10 µg/L. The median absolute change in GH from Baseline to Week 24 was −3.10 µg/L and −2.88 µg/L in the pasireotide LAR 40 mg and 60 mg arms, and −0.88 µg/L in the active control arm.

Mean percentage change from Baseline in mean GH at Week 24 was −23.10% and −50.86% in the pasireotide LAR 40 mg and 60 mg arms, and −3.16% in the active control arm. The least square mean difference from the active control arm was−6.26 in the 40 mg arm and −13.75 in the 60 mg arm. One patient [C2402-0223-00002] in the active control arm had very high post-baseline GH value, which heavily influenced the mean GH over time in Figure 4. This patient had a GH value of 92.38 µg/L at Baseline, which increased to 573.18 µg/L at Week 12, and then decreased slightly to 527.86 µg/L at Week 24.

Most patients had a decrease in their GH levels on pasireotide LAR treatment.

Figure 4 Mean (+/- SE) of GH level by visit and treatment (FAS)



- The numbers xx/xx/xx are the number of patients with mean GH values at that visit in the SOM LAR 40 mg/ SOM LAR 60 mg/ Active Control treatment group, respectively.
- Includes scheduled visits only.
- Mean GH at each time point is calculated from at least three available GH measurements.
- +/- one standard error are displayed.
- Reference line is 2.5 ug/L.

Change from Baseline in IGF-1 at Week 24

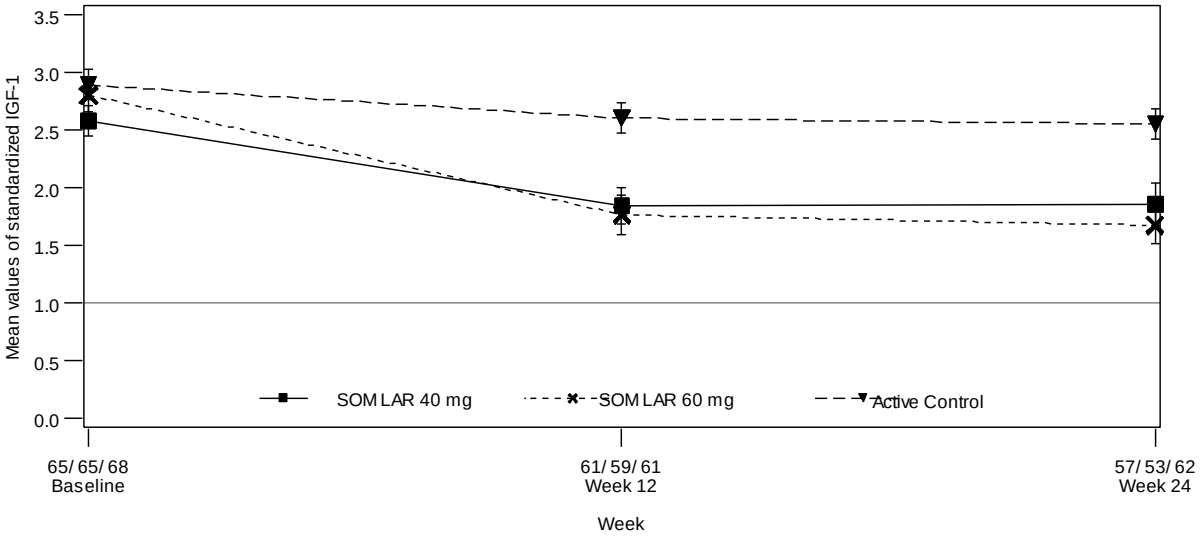
Both doses of pasireotide LAR were more efficacious than active control in suppressing IGF-1 levels; suppression of mean IGF-1 was achieved by Week 12 and was well maintained afterwards (Figure 5).

Mean IGF-1 level at Baseline was similar among the three treatment arms, with a mean standardized IGF-1 level of between 2.5 and 3 in each arm at Baseline. The mean absolute change in IGF-1 from Baseline to Week 24 was −0.650 and −1.116 for pasireotide LAR 40 mg and 60 mg, and −0.327 for active control.

Mean percentage change from Baseline in mean IGF-1 level at Week 24 was −28.0% and −38.6% in the pasireotide LAR 40 mg and 60 mg arms, and −7.2% in the active control arm.

Most patients had a decrease in their IGF-1 levels on pasireotide LAR treatment.

Figure 5 Mean (+/- SE) of standardized IGF-1 level by visit and treatment (FAS)



- The numbers xx/xx/xx are the numbers of patients with IGF-1 values at that visit in the SOM LAR 40 mg/ SOM LAR 60 mg/Active Control treatment group, respectively.
- Includes scheduled visits only.
- Standardized IGF-1 = IGF-1 value / ULN, where ULN is the upper limit of the normal range.
- +/- one standard error are displayed.
- Reference line is 1.

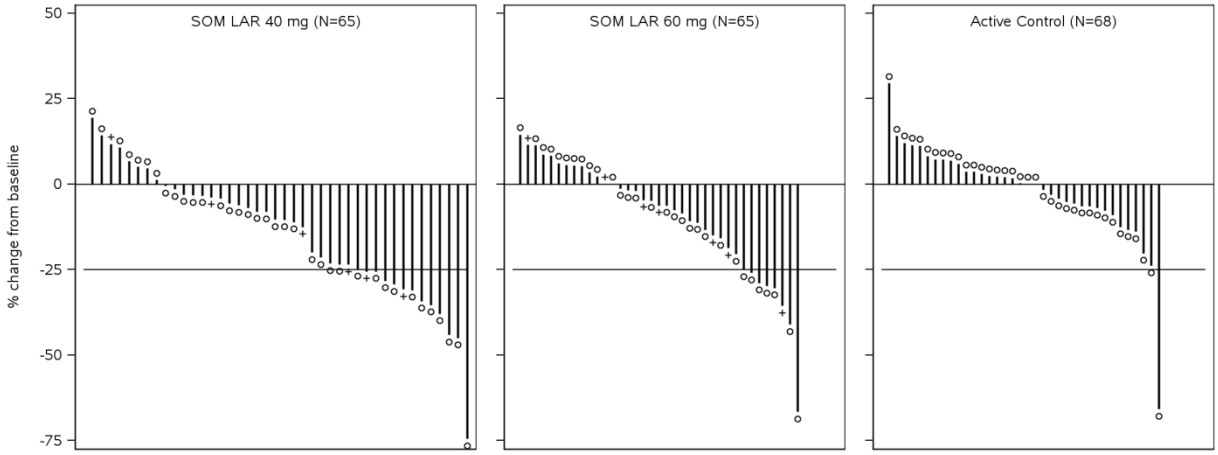
Change in tumour volume

The proportion of patients in the FAS with greater than 25% reduction in tumour volume at Week 24 was 18.5% for pasireotide LAR 40 mg arm, 10.8% for pasireotide LAR 60 mg, and 1.5% for active control.

Approximately 58% of all patients had a tumour assessment performed within the protocol-specified window of ±35 days. Among these patients the mean percentage change in tumour volume from Baseline to Week 24 was greater in the pasireotide arms (−14.38% and −9.45% for 40 mg and 60 mg) than the active control arm (−2.04%).

As shown in Figure 6, the majority (70 to 80%) of patients with tumour volume assessment in the pasireotide LAR arms had tumour shrinkage or no change in tumour volume. In the active control arm, 50% of patients had shrinkage or no change; the remainder had an increase in tumour volume. Greater than 25% reduction in tumour volume was seen for 28.6% and 18.9% of patients in the pasireotide LAR 40 mg and 60 mg arms, and 2.8% of patients in the active control arm.

Figure 6 Percent change from Baseline in tumour volume at Week 24 by treatment (FAS)



Biochemical: O - Non-responder + - Responder

	SOM LAR 40 mg	SOM LAR 60 mg	Active Control
Number of patients included in the analysis	42	37	36
n(%) of patients with decrease/no change in tumor volume	34 (80.95)	26 (70.27)	18 (50.00)
n(%) of patients with decrease from baseline > 25%	12 (28.57)	7 (18.92)	1 (2.78)

- Week 24 is considered as visit 10.

Symptoms of acromegaly

At Baseline, approximately half of all patients had no or mild symptoms of acromegaly (headache, fatigue, perspiration, osteoarthralgia, and paresthesiae), and the proportions were comparable between the treatment arms. Mean scores were slightly decreased for all symptoms at Week 24 in all treatment arms. There was little change in ring size in both pasireotide LAR arms and in the active control arm.

Acromegaly quality of life

At Baseline, mean AcroQoL scores were comparable between the three treatment arms (59.9 in the pasireotide LAR 40 mg arm, 57.2 in the pasireotide LAR 60 mg arm, and 55.5 in the active control arm. At Week 24, mean AcroQoL scores were 61.0, 61.9 and 56.2 in the respective treatment arms.

Interim efficacy results for the extension phase of Study C2402

Twenty-nine patients (17%) had not reached the Week 28 time point (8 patients in the pasireotide LAR 40 mg arm, 9 patients in the pasireotide LAR 60 mg arm, and 12 patients in the cross-over arm) and were ongoing in the study at the cut-off date.

At Week 28 of the extension phase, the proportion of patients with biochemical control was 22.5% (9 patients) in the pasireotide LAR 40 mg arm and 41.7% (15 patients) in the pasireotide LAR 60 mg arm. Among the patients who crossed-over to pasireotide, 10 (21.3%) patients had biochemical control at Week 28, consistent with the results of the primary analysis in the core phase (Table 22).

Table 22 Proportion of patients with GH <2.5 ug/L and normalization of IGF-1 at Week 16 and 28 of the extension by treatment (Extension FAS)

	Pasireotide LAR 40 mg N=57	Pasireotide LAR 60 mg N=54	Cross-over to pasireotide LAR N=62
Week 16			
n	51	48	62
n (%)	11 (21.6)	14 (29.2)	12 (19.4)
95% CI for %	[11.29, 35.32]	[16.95, 44.06]	[10.42, 31.37]
Week 28			
n	40	36	47
n (%)	9 (22.5)	15 (41.7)	10 (21.3)
95% CI for %	[10.84, 38.45]	[25.51, 59.24]	[10.70, 35.66]

n is the number of patients present at Week 16 and Week 28, respectively
For pasireotide arms, Week 16 and 28 of the extension study corresponds to 40 and 52 weeks, respectively, after the start of treatment with pasireotide LAR.
For patients who cross over to pasireotide, Week 16 and 28 of the extension study corresponds to 12 and 24 weeks, respectively, after the start of treatment with pasireotide LAR.
Source: Table 1-1

Compared to the core phase of the study, the total number of responders had increased from 13 to 15 in the pasireotide 60 mg group at week 28 and the responder rate had increased from 20 % to 42 %. The total number of responders in the pasireotide 40 mg group had decreased from 10 to 9 at week 28.

- **Ancillary analyses**

Study C2305

Efficacy results – Study C2305 extension after crossover (inadequately controlled patients)

Patients with GH and IGF-1 response

A higher proportion of patients who crossed over to pasireotide LAR met the GH and IGF-1 response criteria (i.e. GH below 2.5 µg/L and normalized IGF-1), compared to those who crossed over to octreotide LAR. For patients who crossed to pasireotide LAR, the response rate at Month 12 after crossover was 17.3% (14 out of 81 patients); in contrast, none of the 38 patients who crossed over to octreotide LAR met the response criteria at Month 12 (Table 23). The results for the Second PP set were consistent with those of the CAS.

Response rates for patients who crossed to pasireotide LAR were stable for up to two years after crossover, with response rates ranging from 17.8% to 19.4% for Month 15 through Month 24 after crossover.

Table 23 Proportion of patients with a reduction of GH level to below 2.5 ug/L and normalization of IGF-1 by visit and treatment – after crossover - Study C2305 (CAS)

	Crossed over to Pasireotide LAR		Crossed over to Octreotide LAR	
Months after crossover	**n/N (%)**	**95% exact CI**	**n/N (%)**	**95% exact CI**
Month 3	14/81 (17.3)	(9.8, 27.3)	1/38 (2.6)	(0.1, 13.8)
Month 6	17/81 (21.0)	(12.7, 31.5)	1/38 (2.6)	(0.1, 13.8)
Month 9	18/81 (22.2)	(13.7, 32.8)	2/38 (5.3)	(0.6, 17.7)
Month 12	14/81 (17.3)	(9.8, 27.3)	0/38 (0)	-

Months refer to months after crossover
CI - confidence interval

GH response (regardless of IGF-1 response) was achieved at Month 12 by 27.2 % of patients who crossed over to pasireotide LAR and 23.7% of patients who crossed over to octreotide LAR. IGF-1 response (regardless of GH response) was achieved at Month 12 by 9.9% of patients who crossed over to pasireotide LAR and 5.3% of patients who crossed over to octreotide LAR.

Response categories (FR, PR, NR) after crossover

At extension Baseline, the proportion of patients who were non-responders was similar in both crossover arms (74.1% for crossover to pasireotide LAR, and 78.4% for crossover to octreotide LAR). One of the 81 patients who crossed to pasireotide LAR was a responder and 20 of the 81 (24.7%) had PR, while eight of 37 patients (21.6%) who crossed to octreotide LAR had PR.

For patients who crossed over to pasireotide LAR, the proportion of patients with FR was 26.0% at Month 3, and increased to 32.4% at Month 6; and to 36.2% at Month 12. The proportion of patients with PR was 26.0% at Month 3, and remained relatively constant at subsequent time points. At Month 12, the proportion of patients with FR or PR was 67.2%.

In contrast, few patients who crossed over to octreotide LAR achieved FR or PR; at Month 3, one patient (2.7%) had FR, and three patients (8.1%) had PR. Similar values were reported at Month 6. At Month 12, no patient had FR, and four patients (13.3%) had PR.

The proportion of non-responders after crossover to octreotide LAR was high (between 81.8% and 89.2%), whereas after crossover to pasireotide LAR the proportion of non-responders decreased from 47.9% at Month 3 to 32.8% at Month 12.

Over-response was reported only for patients who crossed over to pasireotide LAR. The proportion of patients with over-response varied between 6.8% and 13.1% over the time after the crossover.

Patients with GH response

The response rates for reduction in GH to below 2.5 µg/L were higher for patients who crossed over to pasireotide LAR (43.2% and 44.4% at Months 6 and 12, respectively), compared to those who crossed over to octreotide LAR (31.6% and 23.7% at Month 6 and Month 12, respectively (Table 24). At extension Baseline, two patients who crossed over to pasireotide LAR had a GH response, whereas no patients who crossed over to octreotide LAR had a GH response.

The results for the Second PP set were consistent with those of the CAS.

Table 24 Proportion of patients with a reduction of GH level to below 2.5 ug/L by visit and treatment – after crossover - Study C2305 (CAS)

	Crossed over to Pasireotide LAR		Crossed over to Octreotide LAR	
Extension Visit	**n/N (%)**	**95% exact CI**	**n/N (%)**	**95% exact CI**
Month 3	40/81 (49.4)	(38.1, 60.7)	11/38 (28.9)	(15.4, 45.9)
Month 6	35/81 (43.2)	(32.2, 54.7)	12/38 (31.6)	(17.5, 48.7)
Month 9	44/81 (54.3)	(42.9, 65.4)	12/38 (31.6)	(17.5, 48.7)
Month 12	36/81 (44.4)	(33.4, 55.9)	9/38 (23.7)	(11.4, 40.2)

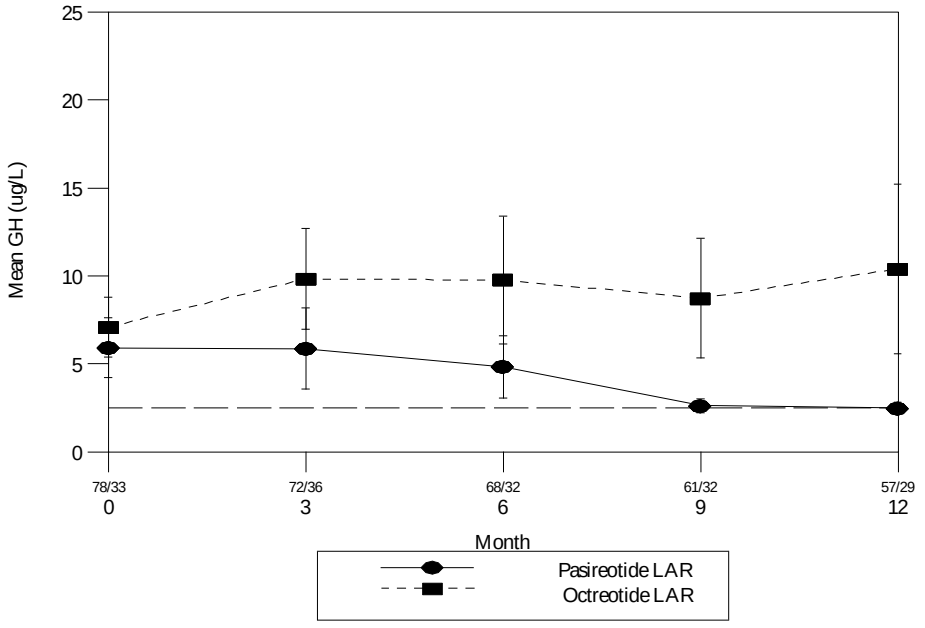
Months refer to months after crossover
CI - confidence interval

While response rates with respect to GH levels, for patients who crossed to pasireotide LAR were stable for the first year after crossover, the proportion of responders decreased over the next year; at Month 24 after crossover, the response rate was 20.4%. However, review of the individual patient data showed that GH levels did not show a large variation over time.

GH values over time

As shown in Figure 7, mean GH decreased for patients who crossed over to pasireotide LAR, whereas mean GH increased among those who crossed over to octreotide LAR. Mean GH at extension Baseline was slightly lower for patients who crossed over to pasireotide LAR (5.9 µg/L, n=78) than for those who crossed over to octreotide LAR (7.1 µg/L, n=33). After crossover to pasireotide LAR, mean GH decreased to 4.8 µg/L at Month 6 (mean decrease from Baseline 5.9%) and to 2.5 µg/L at Month 12 (mean decrease 23.7%); GH levels remained below 2.5 µg/L at all subsequent visits. After crossover to octreotide LAR, mean GH increased to 9.8 µg/L at Month 6 (mean increase 56.4%) and to 10.4 µg/L at Month 12 (mean increase 74.5%).

Figure 7 Mean (+/- SE) of GH level by visit and treatment - after crossover - Study C2305 (CAS)



The numbers xx/xx below the x-axis represent the numbers of patients in pasireotide LAR/octreotide LAR treatment group. This analysis includes scheduled visits only. At least three samples contributed to a patient's GH value at each time point. Reference line is 2.5 µg/L.

Shifts in GH categories from extension Baseline to Month 26 for patients who crossed over

Among patients who crossed over (81 to pasireotide and 38 to octreotide), more than 70% had at extension Baseline a GH that was in the >5 µg/L category. Among these patients 49 of 62 patients (79.0%) on pasireotide LAR and 18 of 30 patients (60.0%) on octreotide LAR shifted to a lower GH category as last value.

Among patients who crossed over to pasireotide LAR, the proportion who achieved GH below 2.5 µg/L was 59.3%, compared to only 31.6% on octreotide LAR. Furthermore, 35.8% of patients who crossed to pasireotide LAR achieved a GH below 1 µg/L, compared to only 5.3% on octreotide LAR.

GH nadir after OGTT

After crossover, GH nadir values after OGTT improved in both treatments arms. After crossover to pasireotide LAR, mean GH nadir improved from 4.0 µg/L (n=28) at extension Baseline to 2.2 µg/L at Month 6 (n=21) and to 2.1 µg/L at Month 12 (n=15). After crossover to octreotide LAR, mean GH nadir improved from 16.1 µg/L (n=4) at extension Baseline to 8.2 µg/L (n=4) at Month 6 and to 4.2 µg/L (n=3) at Month 12. The number of patients with data among those who crossed over to octreotide LAR was low, precluding a meaningful comparison between the treatments.

Patients with IGF-1 response

The response rates for normalization of IGF-1 were much higher for patients who crossed over to pasireotide LAR (30.9% and 27.2% at Months 6 and 12, respectively), compared to those who crossed over to octreotide LAR (7.9% and 5.3% at Months 6 and 12, respectively; Table 25).

The proportion of patients with IGF-1 over-response (i.e. IGF-1 below LLN) at Months 6 and 12 after crossover were 39.5% and 38.3% for pasireotide LAR, and 7.9% and 5.3% for octreotide LAR, respectively.

Response rates for patients who crossed to pasireotide LAR were stable for up to 2 years after crossover, with response rates ranging from 20.4% to 25.8% at Month 15 through Month 24 after crossover.

Table 25 Proportion of patients with normalization of IGF-1 by visit and treatment – after crossover - Study C2305 (CAS)

	Crossed over to Pasireotide LAR		Crossed over to Octreotide LAR	
Extension Visit	**n/N (%)**	**95% exact CI**	**n/N (%)**	**95% exact CI**
Month 3	16/81 (19.8)	(11.7, 30.1)	3/38 (7.9)	(1.7, 21.4)
Month 6	25/81 (30.9)	(21.1, 42.1)	3/38 (7.9)	(1.7, 21.4)
Month 9	24/81 (29.6)	(20.0, 40.8)	4/38 (10.5)	(2.9, 24.8)
Month 12	22/81 (27.2)	(17.9, 38.2)	2/38 (5.3)	(0.6, 17.7)

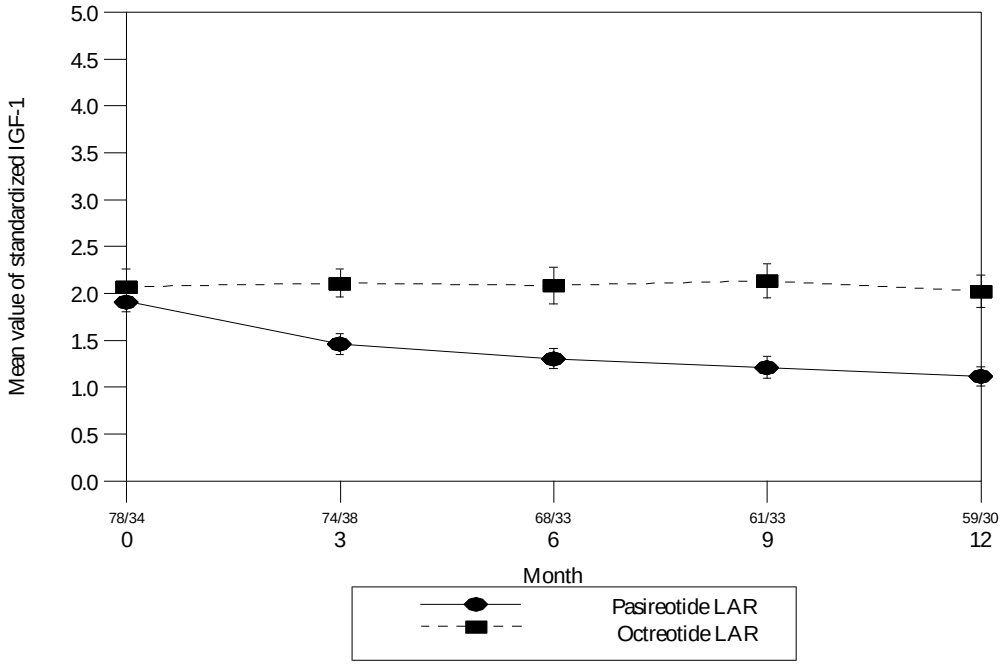
Months refer to months after crossover.

Standardized IGF-1 values over time

As shown in Figure 8, mean standardized IGF-1 decreased for patients who crossed over to pasireotide LAR, but not for those who crossed over to octreotide. Mean IGF-1 at extension Baseline was to some extent lower for patients who crossed over to pasireotide LAR (1.9, n=78) than for those who crossed over to octreotide LAR (2.1, n=34). After crossover to pasireotide LAR mean IGF-1 decreased to 1.3 at Month 6 (mean decrease 28.6%) and to 1.1 at Month 12 (mean decrease 39.9%); after Month 12, mean IGF-1 remained ≤ 1 at all subsequent visits. After crossover to octreotide LAR, mean IGF-1 remained nearly unchanged compared to

Baseline at all visits up to Month 12; mean change from Baseline was +12.5% at Month 6 and +15.9% at Month 12.

Figure 8 Mean (+/- SE) of standardized IGF-1 by visit and treatment - after crossover - Study C2305 (CAS)



The numbers xx/xx below the x-axis represents the numbers of patients in pasireotide LAR/octreotide LAR treatment group. This analysis includes scheduled visits only.

Change in tumour volume

The mean decrease in tumour volume from extension Baseline was slightly higher in patients who crossed over to pasireotide LAR than in patients who crossed over to octreotide LAR (**Table 26**). At Month 12, the mean decrease in tumour volume was 24.7% for crossover to pasireotide LAR and 17.9% for crossover to octreotide LAR. The proportion of patients with a decrease or no change in tumour volume at Month 12 after crossover was higher for pasireotide LAR (91.3%) compared to octreotide LAR (73.1%).

Available data after Month 12 for patients who crossed over to pasireotide LAR, show that tumour volume continued to decrease for these patients. At Month 24 after crossover, the mean decrease in tumour volume was 35.8% for patients with data (n=9), and at Month 30, the mean decrease in tumour volume was 50.6% (n=6).

Table 26 Change from extension Baseline in tumour volume (mm^3) by visit and treatment – after crossover - Study C2305 (CAS)

		Crossed over to Pasireotide LAR N=81		Crossed over to Octreotide LAR N=38	
Extension Visit		**n**	**Mean (SD)**	**n**	**Mean (SD)**
Extension Baseline *	Extension baseline value	73	1420.9 (1914.58)	32	1809.6 (2579.25)
Month 6	Value at Month 6	65	1027.5 (1282.42)	31	1794.9 (2823.08)
	Change at Month 6	60	-241.3 (454.05)	27	-17.9 (803.21)
	% Change at Month 6	59	-18.1 (17.68)	27	-12.3 (24.11)

		Crossed over to Pasireotide LAR N=81		Crossed over to Octreotide LAR N=38	
Extension Visit		**n**	**Mean (SD)**	**n**	**Mean (SD)**
Month 12	Value at Month 12	51	949.0 (1169.49)	30	1610.4 (2666.66)
	Change at Month 12	47	-368.5 (578.62)	26	-1.7 (846.13)
	% Change at Month 12	46	-24.7 (25.20)	26	-17.9 (27.80)

*The extension Baseline was defined as the last assessment prior to administration of the new treatment after crossover.
An extreme value has a greater impact on mean absolute change than mean percentage change.

PRL values over time

PRL values improved over time for patients who crossed over to pasireotide LAR, but not for patients who crossed over to octreotide. After crossover to pasireotide LAR, mean PRL decreased from 11.9 µg/L at extension Baseline to 9.9 µg/L (mean percentage decrease 23.2%) at Month 6 and to 7.5 µg/L (mean percentage decrease 21.7%) at Month 12. Mean PRL values remained below extension baseline levels at all subsequent visits.

After crossover to octreotide, mean PRL decreased from 15.7 µg/L at extension Baseline to 13.6 µg/L at Month 6 (mean percentage increase 1.4%) and increased to 16.1 µg/L (mean percentage increase 13.7%) at Month 12.

Symptoms of acromegaly and ring size

At extension Baseline, severity scores for acromegaly symptoms were comparable between the treatment arms. After crossover, slight improvements compared to extension Baseline in mean severity scores were seen for patients who crossed to pasireotide LAR.

Summary statistics for decrease in ring size showed improvements for both crossover treatments, with no relevant difference between the arms.

Acromegaly quality of life

Mean AcroQoL total and sub-scores were comparable at extension Baseline in both crossover arms. AcroQoL scores remained stable (total and individual sub-scores) in both crossover arms.

Study C2305 subpopulations

Subgroup analyses were performed for the primary efficacy endpoint by demographic factors of race, ethnicity and age group (<65, ≥ 65 years) using the FAS if the number of patients in the subgroup was large enough. In addition, the primary efficacy endpoint (using LOCF) was summarized by dose up-titration status and treatment.

The results of the analysis of the primary efficacy endpoint across demographic subgroups (race, ethnicity, age) show a treatment effect consistently in favour of pasireotide LAR. No clinically relevant differences were observed between subgroups with regard to age, race and ethnicity. Due to the low number of patients in some subgroups these results should be interpreted with caution.

Study C2402

Subpopulations

Subgroup analyses were performed for the primary efficacy endpoint by the demographic factors, age (<65, ≥ 65 years), ethnicity and race.

No meaningful conclusions can be drawn for subgroups of age and race due to the small number of patients ≥ 65 years (<10% of all patients) and non-Caucasians (<20%). No effect of ethnicity on response rates was evident.

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 27 Summary of efficacy for trial C2305

Title: multicenter, blinded, crossover, active controlled, randomized study comparing pasireotide LAR versus octreotide in patients with active acromegaly who had not received previous medical treatment in the 12 months core phase and after crossover in inadequally controlled in the 13 months extension phase.			
Study identifier	CSOM230C2305		
Design	Randomized, blinded, active-controlled		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		12 months not applicable 13 months blinded phase and open-label phase: unknown duration
Hypothesis	Superiority		
Treatments groups	Pasireotide LAR 40 mg group		Pasireotide LAR 40 mg, one IM per month, 176 patients
	Octreotide LAR 20 mg group		Octreotide LAR 20 mg, one IM per month, 182 patients
Endpoints and definitions	Composite Primary endpoint	GH < 2.5 µg/L and normalization of IGF-1 (adjusted for age and sex)	The proportion of patients with reduction of GH to <2.5 µg/L and normalization of IGF-1 at month 12.
	Secondary endpoint	GH to <2.5 µg/L	Proportion of patients with a reduction of GH < 2.5 µg/L at Month 12
	Secondary endpoint	Normalization of IGF-1	Proportion of patients with normalization of IGF-1 at Month 12
	Secondary endpoint	Tumor volume	Change from baseline in tumor volume at Month 12
Database lock	29.12.2011		
Results and Analysis			
Analysis description	**Primary Analysis** It was performed on the full analysis set **(FAS**) at month 12. The proportion of patients with GH < 2.5 µg/L at month 12 and patients with normalization of IGF-1 at month 12 were analyzed using CMH test adjusting for randomization stratification factor. The analyses were based on the principle of LOCF using the rule of handling missing values. Change of tumor volume at Month 12 from baseline was compared between the two treatment groups using ANCOVA model with treatment as the fixed effect and tumor volume at baseline and randomization stratum as covariates.		

Analysis population and time point description	Intent to treat (Full analysis set) , Per protocol, Month 12			
Descriptive statistics and estimate variability	Treatment group	Pasireotide 40 mg LAR	Octreotide 20 mg LAR	
	Number of subject	176	182	
Primary endpoint	Proportion of responders with GH < 2.5 µg/L and normaliza tion of IGF-1 (adjusted for age and sex) at Month 12	55/176 (31.3%)	35/182 (19.2%)	
	95% CI	(24.5-38.7)	13.8-25.7)	
Secondary endpoints	Proportion of responders with GH <2.5 µg/L at Month 12	85/176 (48.3%)	94/182 (51.6%)	
	95% exact CI	(40.7- 55.9)	(44.1-59.1)	
	Proportion of responders with Normalization of IGF-1 at Month 12	68/176 (38.6%)	43/182 (23.6%)	
	95% exact CI	(31.4- 46.3)	(17.7-30.5)	
	Change from baseline in Tumor volume at Month 12	-987.1	-801.2	
	Mean SD	2448.1	1676.62	
Effect estimate per comparison	Proportion of responders with GH < 2.5 µg/L and normaliza tion of IGF-1 (adjusted for age and sex) at Month 12	Comparison groups	Pasireotide LAR 40 mg	Octreotide LAR 20 mg
Primary endpoint		Odds ratio (FAS)	1.942	1.942
		95% CI	1.190 – 3.168	1.190 – 3.168
		P-value	0.007	0.007
Secondary endpoints	Proportion of responders with GH <2.5 µg/L at Month 12	Odds ratio (FAS)	0.877	0.877
		95% CI	0.579 – 1.328	0.579 – 1.328
		P-value	0.838	0.838
	Proportion of responders with Normalization of IGF-1 at Month 12	Odds ratio (FAS)	2.087	2.087
		95% CI	1.316- 3.308	1.316- 3.308
		P-value	0.002	0.002

	Change from baseline in Tumor volume at Month 12	Difference between treatments	-185.9	-185.9
		P-value	0.838	0.838
		P-value adjusted	0.838	0.838

Table 28 Summary of efficacy for trial C2402

Title: Study C 2402 is a phase III, multicenter, randomized, parallel-group study to assess the efficacy and safety of double-blind pasireotide LAR 40 mg and pasireotide LAR 60 mg versus open label octreotide LAR or lanreotide ATG in patients with inadequately controlled acromegaly			
Study identifier	CSOM230C2402		
Design	Randomized, double-blind, parallel-group versus open-label active control arm		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		24 weeks not applicable extension open-label phase with an unknown duration
Hypothesis	Superiority		
Treatments groups	Pasireotide 40 mg LAR		Pasireotide 40 mg LAR, one IM per month, 65 patients
	Pasireotide 60 mg LAR		Pasireotide 60 mg LAR, one IM per month, 65 patients
	Octreotide 30 mg LAR or Lanreotide 120 mg ATG		Octreotide 30 mg LAR or lanreotide 120 mg ATG, one IM per month, 68 patients
Endpoints and definitions	Composite primary endpoint	Proportion of responders with GH level < 2.5 µg/L and normalization of IGF-1	Proportion of patients with reduction of GH to <2.5 µg/L and normalization of IGF-1 at week 24 (adjusted for age and sex).
	Key Secondary endpoint	Proportion of patients who achieved normalization of IGF-1	Proportion of patients who achieved normalization of IGF-1 at Week 24 (adjusted for age and sex).
	Other Secondary endpoint	Proportion of patients with GH < 2.5 µg/l	Proportion of patients with GH < 2.5 µg/l at week 12 and 24
	Other Secondary endpoint	Proportion of patients with greater than 25% reduction in tumor volume	Proportion of patients achieving a tumor volume reduction > 25% reduction in tumor volume at week 24
Database lock	Janurary,22 2013		
Results and Analysis			
Analysis description	**Primary Analysis** The primary efficacy analysis was performed on the FAS. An exact logistic regression model that adjusts for the randomization stratification factors was used to test the null hypothesis. The exact two-sided 95% and 97.5% confidence intervals (CI) for the common odds ratio (OR) were calculated. A common OR >1 indicated an increased odds for the pasireotide LAR (40 mg or 60 mg) group compared to the active control group.		

Analysis population and time point description	Intent to treat (Full analysis set : FAS), Per protocol 24 weeks			
Descriptive statistics and estimate variability	Treatment group	Pasireotide 40 mg LAR	Pasireotide 60 mg LAR	Active control arm
Primary endpoint	Number of subject	65	65	68
	Proportion of responders with GH level < 2.5 µg/L and normalization of IGF-1	10/65 (15.4%)	13/65 (20%)	0
	95% CI for %	7.63-26.48	11.1-31.77	0-5.28
Secondary endpoints	Proportion of patients who achieved normalization of IGF-1	16/65 (24.6%)	17/65 (26.2%)	0
	95% CI for %	14.77-36.67	16.03-38.54	0-5.28
	Proportion of patients with GH level < 2.5 µg/L at week 24	23/65 (35.4%)	28/65 (43.1%)	9/68 (13.2%)
	95% CI for %	23.92-48.23	2.01-13.77	6.23-23.64
	Proportion of patients with greater than 25% reduction in tumor volume at week 24	12/65 (18.5%)	7/65 (10.8%)	1/68 (1.5%)
	95% CI for %	9.92-30.03	4.44-20.94	0.04-7.92
Effect estimate per comparison	Proportion of responders with GH level < 2.5 µg/L and normalization of IGF-1	Comparison groups	Pasireotide LAR 40 mg	Pasireotide LAR 60 mg
		Odds ratio (OR) versus active control	16.63	23.03
		95% CI for OR	3.32- infinity	4.72-infinity
		P-value	0.0006	< 0.0001
	Proportion of patients who achieved normalization of IGF-1	Odds ratio versus active control	30.12	32.66
		95% CI for OR	6.28-infinity	6.84-infinity
		P-value	< 0.0001	< 0.0001
	Proportion of patients with GH level < 2.5 µg/L at week 24	Odds ratio versus active control	3.62	5.05
		95% CI for OR	1.42-9.94	2.01-13.77
		P-value	0.0024	0.0001
	Proportion of patients with greater than 25% reduction in tumor volume at week 24	Odds ratio versus active control	15.33	8.20
		95% CI for OR	2.14-675.9	1.01-379.7
		P-value	0.0007	0.0245

Clinical studies in special populations

No studies in special populations were conducted.

Analysis performed across trials (pooled analyses AND meta-analysis)

Due to the underlying difference in study design between the studies, no pooling of data was performed for sub-group analysis. The subgroup analyses were performed for the primary efficacy endpoint by age group, race and ethnicity using the FAS and by dose up titration status and treatment for Study C2305, and by age group, race and ethnicity for Study C2402. No such analyses were performed for Study C2110/E1 or Study B2201/E3; due to the relatively small number of patients, such analyses were expected to yield inconclusive results of limited value.

Supportive studies

Supportive studies with LAR formulation - Study C2110 and C2110E1

Study C2110 was an open-label, randomized study assessing PK, safety, and tolerability profiles of 20, 40, and 60 mg doses of pasireotide LAR in patients with acromegaly or carcinoid disease. Following the completion of the core study patients were eligible to enter the extension Study C2110E1.

Thirty-five (35) patients with acromegaly and 42 patients with carcinoid received pasireotide LAR treatment. Only data from patients with acromegaly are included in this regulatory submission. After completion of the three-month core phase, 29 patients with acromegaly entered the open-ended extension study C2110E1.

The primary objectives of C2110 and the extension were related to PK and safety/tolerability. Clinical response was measured by quantitative assessment of PD markers (including GH and IGF-1) and symptoms of acromegaly.

The results from this study showed that pasireotide LAR suppressed GH and IGF-1 concentrations (Figure 9 and Figure 10) as well as PRL in patients with acromegaly. For all three dose groups, the reduction effects of pasireotide LAR on GH levels achieved plateau (steady state) immediately after LAR injection, and were well maintained afterwards; the reduction effects of pasireotide LAR on IGF-1 and free IGF-1 achieved steady state within four weeks, and were well maintained afterwards. Mean GH, IGF-1 and PRL concentrations decreased in all dose groups following the first pasireotide LAR injection. At the end of core phase (Month 3), mean decrease from Baseline in GH was -66.8%, -59.7% and -63.2%, in IGF-1 was-40.2%, -50.7% and -49.8%, and in PRL was -36.0%, -23.8% and -24.4%, for the 20, 40 and 60 mg dose groups, respectively.

Figure 9 Mean (+/- SE) of standardized IGF-1 plasma concentration by week and treatment dose in acromegaly patients (PD population) – Study C2110

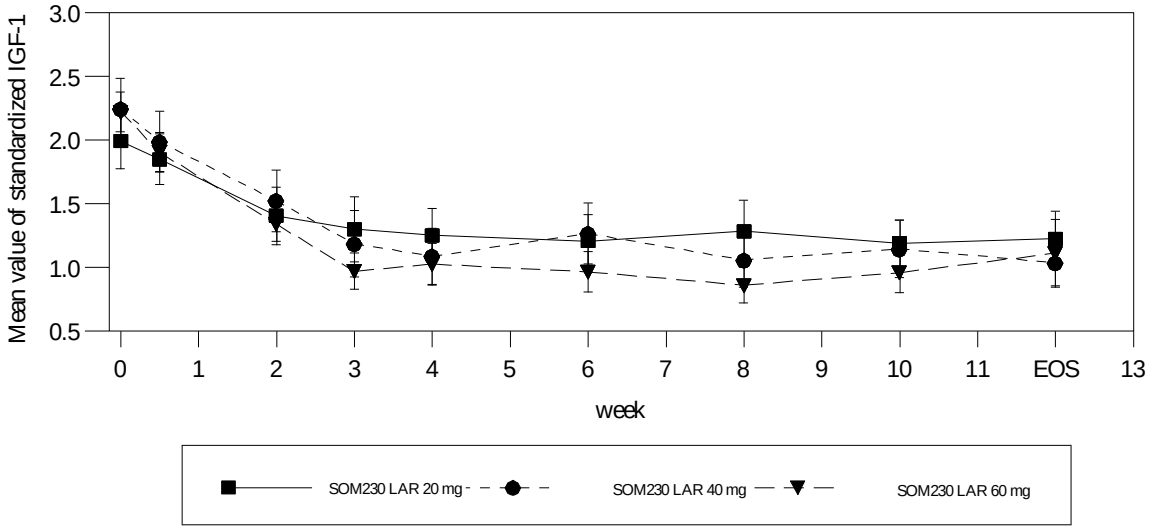
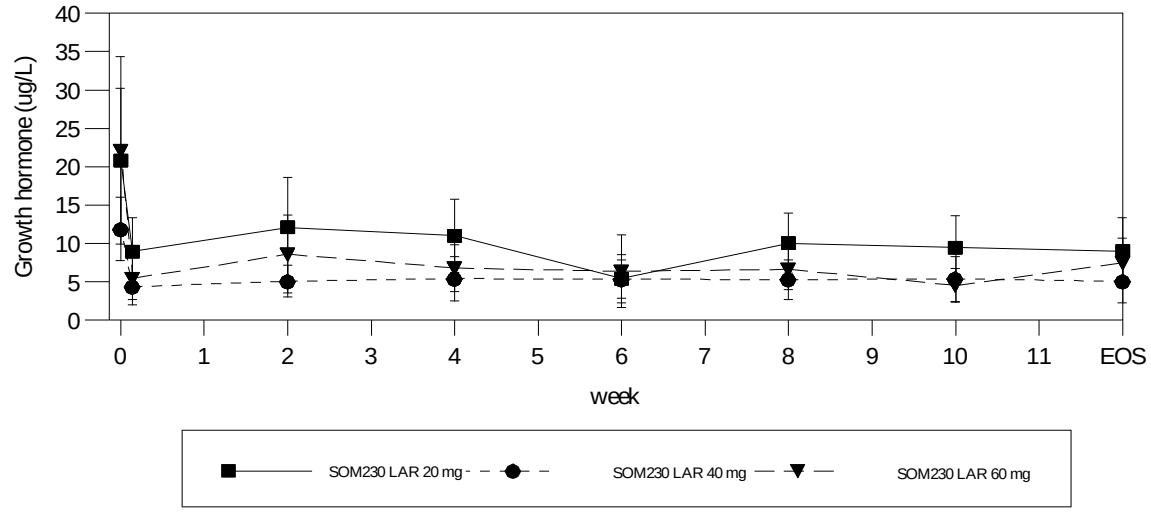


Figure 10 Mean (+/- SE) of GH level by week and treatment in acromegaly patients (PD population) – Study C2110



There were no statistically significant dose effects based on the results of the models fit in terms of the pharmacodynamic (PD) endpoints (GH, IGF-1 and free IGF-1), which may be explained by the small sample size at each dose. Decreases in GH, total IGF-1, free IGF-1, and PRL concentrations were sustained up to Month 48 for those patients who remained on treatment. By Month 36, 12 of the 20 (60%) of patients were considered responders (GH ≤ 2.5 µg/L and IGF-1within normal limits).

Symptoms of acromegaly (headache, fatigue, perspiration, osteoarthralgia, and paresthesia) were present at Baseline for the majority of patients; improvements were seen in all 3 dose groups in both the core and extension phase.

Supportive studies with sc formulation – Study B2201/E and Study B2103

Study B2201/E

Study B2201 was an open-label, randomized, crossover study in patients with acromegaly receiving multiple doses of pasireotide sc and octreotide sc to assess efficacy (biochemical response, tumour volume, symptoms of acromegaly), safety, and PK/PD relationship. After completion of the 16-week core treatment period, patients were allowed to enroll into the extension.

The primary objective of Study B2201 was to assess the effect of a four-week regimen of 100 μg of octreotide sc three times daily followed by a four-week regimen of 200 μg, 400 μg, and 600 μg of pasireotide sc twice daily on circulating GH and IGF-1 concentrations in patients with active acromegaly. All patients received each dose of pasireotide in a different sequence (6 sequences in total); a different dose was administered during each of the 3 treatment periods. In the extension study, patients continued at the lowest dose of pasireotide at which they achieved GH ≤2.5 μg/L and normalization of IGF-1 levels (age and sex related).

In Study B2201 primary efficacy results demonstrated that biochemical markers of the disease improved after 28 days of pasireotide treatment (GH ≤ 2.5 μg/L and normalization of IGF-1). After initial treatment with 28 days of octreotide sc biochemical control was low (8.6%). Following 28 days of pasireotide treatment biochemical control increased to 19.0% (combined results of 3 pasireotide dose groups) with the highest response rate observed with the 600 μg bid dose. At Month 9 (extension study) biochemical control was achieved in 23.1%. Symptoms of acromegaly (headache, perspiration, paresthesia, fatigue, osteoarthralgia, and carpal tunnel syndrome) improved during both the core and extension study. Results demonstrated that from core Baseline to measurements during the core and extension there was an overall increase in the proportion of patients who report symptoms with a score of 0 or 1.

Study B2103

The proof-of-concept study B2103 was a double-blind, randomized, crossover study in patients with acromegaly to assess efficacy of single-dose pasireotide sc vs. octreotide sc.

The primary objective was to assess the efficacy on circulating GH concentrations of single doses of 100 μg and 250 μg of pasireotide compared to that of a single dose of 100 μg of octreotide sc in patients with active acromegaly. Results showed that pasireotide suppresses GH secretion in patients with acromegaly, thus demonstrating a successful proof of concept. Suppression of GH secretion was greater with the pasireotide 250 μg dose than with the 100 μg dose. Using the AUC (0-24h) as a measure of the magnitude of inhibition of GH secretion, the mean change after treatment was 33.4% in the octreotide 100 μg dose group, and 35.4 % in the pasireotide 250 μg dose group compared to 19.0% in the pasireotide 100 μg dose group.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

Studies C2305 and C2402 were considered pivotal for this application. Both studies were multicenter studies including a relevant number of centres in Europe. In addition data from three phase II studies have been submitted.

The choice of the pasireotide LAR dose regimen in Study C2305 and Study C2402 was based on the PK analysis results from Study B2201 and Study C2110. The rationale for dose selection in the phase III studies is acceptable.

Study C2305 is a large prospective randomized study conducted in patients with acromegaly. This was a Phase 3, multicenter, randomized, blinded study of pasireotide LAR vs. octreotide LAR in patients with active acromegaly who had not received previous medical treatment.

The design of Study 2305 was adequate and with a sufficient duration in order to evaluate the effect of pasireotide in medically naïve patients. The core phase of the study was 12 months followed by an extension phase. Data up to two years of treatment is provided. The stratification for patients having undergone surgery and those being totally treatment naïve is adequate. The choice of comparator is acceptable. The study design was further in line with the Scientific Advice given by the CHMP. With Amendment 4, blinding of the extension study was introduced.

In study 2305, two sites were closed due to GCP issues; the handling of these issues was adequate.

Several amendments were made to the study protocol. None of the amendments affected the analysis of the primary endpoint, thus the amendments are not considered to affect the outcome or the interpretation of the study. Amendment 4 was implemented when 34 patients had already been unblinded. The exclusion of responders to octreotide from the extension possibly leads to a slight overestimation of the long-term treatment difference between pasireotide and octreotide. Since the Applicant has not stated how many of the 13 patients in the octreotide arm discontinued due to the fact that they were responders, no estimation can be made but potentially the response rate of about 20 % observed in the core phase would have been maintained. Protocol deviations were relatively few.

Study C2402 is a Phase 3, multicenter, randomized, parallel-group, three-arm study of double-blind pasireotide LAR 40 mg and pasireotide LAR 60 mg versus open-label octreotide LAR 30 mg or lanreotide ATG 120 mg in patients with inadequately controlled acromegaly.

In this study the aim was to investigate the effect of pasireotide in a population inadequately controlled on existing therapies, i.e. maximal dose of octreotide LAR or lanreotide ATG. The study design and duration is considered adequate. Data is only presented for the 6 month core phase of the study. Available data from an interim analysis of the extension study was submitted with the responses to the Day 120 LoQ. This study was never subject for any Scientific Advice by the CHMP.

Several amendments were made to the protocol. None of the amendments affected the analysis of the primary endpoint, thus the amendments are not considered to affect the outcome or the interpretation of the study. Protocol deviations were relatively evenly distributed between groups.

Inclusion and exclusion criteria for both studies were adequate. It should be noted that patients with severe cardiac disease, including a high risk of arrhythmias, were excluded as were patients with poorly controlled diabetes mellitus.

The treatment regimens were adequate. Dose adjustment was allowed and guidance on how and when to adjust the dose was in place. Notably, the long-acting treatment was introduced without any prior test of the patient's tolerance to somatostatin analogue treatment.

The objectives were adequate although the Scientific Advice recommended that a lower cut-off for GH (<2.0) should be considered.

Efficacy assessments were adequate. The use of a 5-point mean GH is endorsed. The QoL questionnaire applied in both studies is acceptable and data to ensure the validation of the instrument has been provided (Badia et al 2004).

Statistical methods and sample size calculations were adequate. Randomisation procedures were adequate.

Due to the different appearance of the pasireotide and octreotide LAR formulations, a true double-blind treatment was not feasible. In study 2305, adequate efforts were made to maintain the blinding of the study taking into consideration the difference in appearance with the study drug and the control.

In study 2402, the patient, Investigator, site staff, monitor, and data manager were unblinded to the treatment arm assignment but were blinded to the treatment dose in the double-blind pasireotide LAR treatment arm. The blinding strategy is acceptable considering that the primary endpoint is based on an objective parameter, i.e. GH and IGF-1.

Efficacy data and additional analyses

In study C2305, dropout rates were slightly higher in the pasireotide treated group (20 %) than in the octreotide treated group (14 %). Slightly more patients in the pasireotide group terminated the study early due to AEs. The proportion of patients who did not enter the extension was similar for both groups. More patients from the pasireotide treated group continued in the extension without crossing over indicating a better effect in this group. However, in the group that crossed over to pasireotide, more patients dropped out due to AEs.

Baseline characteristics including baseline medical history were balanced between groups. Few patients over the age of 65 were included. The majority of patients were Caucasians. The proportion of patients with prior surgery was lower than expected (42 %) but balanced between groups.

The study met its primary endpoint showing that the number of responders with pasireotide LAR (31 %) was significantly higher than for octreotide LAR (19 %; OR 1.94 (1.19, 3.17)). The primary analysis was consistently supported by the sensitivity analyses performed, thus the data appear robust. Response rates in patients that had undergone surgery were higher for both treatments and the overall outcome was mainly driven by this group. Notably, a slightly higher proportion in the pasireotide treated group "over-responded", i.e. GH decreased to <2.5 µg/L and IGF-1 <LLN.

Of note, after initiation of pivotal studies, the GH cut-off associated with efficacy response was revised (GH<1µg/L instead of <2.5µg/L). With the responses to the Day 120 LoQ, the Applicant performed a post-hoc analysis to obtain the proportion of patients who achieved a stricter endpoint (GH <1 µg/L and normal IGF-1, Giustina 2010) at month 12. With pasireotide LAR 40 mg, there was 29/176 (16.5%) of "responders" versus 18/182 (9.9%) with octreotide LAR. The difference was not statistically significant and the lower bound of the 95% CI was below unity (OR [95% CI 1.809 (0.964, 3.392] (p = 0.063)).

The proportion of patients with an adequate GH response did not differ between treatment groups at Month 12 (48 % vs 52 % for pasireotide and octreotide respectively). The difference in GH response was less prominent between post surgery and de novo patients. As shown by the separate analyses for GH and IGF-1 response, the outcome of the primary endpoint was mainly driven by a higher response with regards to IGF-1 with pasireotide LAR (39 %) compared to octreotide LAR (24 %). The difference in IGF-1 response was more prominent between post surgery and de novo patients. As the effect of GH is mediated via IGF-1, the findings support a clinically relevant effect of pasireotide.

Both treatments showed comparable effects on tumour volume with a mean percent reduction of 38-39.7 %. The proportion of patients that achieved at least 20 % reduction was also comparable between treatments. The reduction in tumour size is reassuring since, although surgery is the first line therapy approach, surgery may not always be possible or available.

In keeping with the data on GH reduction, slightly higher proportions of patients in the pasireotide group shifted to a lower GH category. Notably a higher proportion of patients in the pasireotide treated group had GH below 1 µg/L, i.e. were "over-treated".

The data from the extension phase show that the rate of responders decreased somewhat over time, however, responder rates were consistently higher in the pasireotide treated group (24 % vs 14 % at Month 25 for

pasireotide and octreotide respectively; OR 2.1 (1.14, 3.7)). The data support that an adequate effect is maintained at least up to two years of treatment.

In the extension, the proportion of patients that maintained the GH response in the extension up to Month 25 was stable in both groups with at significantly higher proportion in the pasireotide treated groups being responders (35 % vs 24 % for pasireotide and octreotide respectively). GH values over time show that the most prominent effect is observed during the first three months, after which the GH levels remain rather stable. The additional effect observed at Month 16 is most likely due to a selection of patients since non-responders would have crossed over.

Also the proportion of responders with regards to IGF-1 remained stable in both groups with a significantly higher proportion of responders in the pasireotide treated group (26 % vs 14 % for pasireotide and octreotide respectively). Response in IGF-1 and mean standardised IGF-1values over time were consistent with the observations on GH.

Time to first response did not differ between treatments; however, duration of first response was longer in the pasireotide treated arm. When duration of response achieved at Month 12 was compared, no difference between treatments was observed.

Although no adequate comparison can be made between treatments, the long-term data show continuous decrease in tumour volume with continued treatment.

An effect on PRL levels was shown with a more prominent effect of pasireotide compared to octreotide at Month 12. Reduction of PRL levels may restore fertility in female acromegalic patients of childbearing potential. Therefore section 4.4 of the SmPC has been amended with warnings and recommendations that adequate contraception should be used.

Symptoms of acromegaly improved in both treatment groups with no significant differences observed. Improvements with regards to QoL were observed in both groups, with numerically better results in the pasireotide treated group. It is acknowledged that the study was not powered to detect a significant difference in this analysis.

In study C2402, discontinuations were low but slightly higher in the pasireotide treated groups (9 % and 12 % for the pasireotide 40 mg and 60 mg groups compared to 4 % in the active comparator group), largely due to a higher proportion of patients dropping out due to AEs. In this context it should be noted that patients in the active control arm already were known to tolerate their treatment since the inclusion criteria stated that they should have been treated with maximum doses for at least 6 months.

Baseline characteristics including baseline medical history were balanced between groups. Few patients over the age of 65 were included. The majority of patients were Caucasians. Most of the patients were on previous treatment with octreotide LAR at inclusion.

The study met its primary endpoint and the outcome was confirmed by the sensitivity analyses performed, thus the finding appears robust. Thus with pasireotide treatment additional previously inadequately controlled patients achieved response. Furthermore, a dose-response effect was observed with more patients responding on pasireotide 60 mg (23 %) than on pasireotide 40 mg (17 %), although not formally tested. No responders were observed in the active control group.

In study C2402, the proportion of uncontrolled patients who achieved a response at week 24 with the new and stricter criteria of acromegalic treatments' response (GH<1 µg/L and IGF-1 normalisation, Giustina 2010) was calculated. Statistically significant difference was obtained only with the dose of 60 mg pasireotide LAR versus

comparator (OR [CI (2.06, infinity)] (p = 0.0059) but not with the dose of 40 mg LAR pasireotide (p = 0.0556, OR [95% CI (0.95, infinity)]). Thus a trend to a better efficacy of pasireotide LAR in uncontrolled patients is revealed from these results.

No meaningful conclusions can be drawn from the analysis of the outcome by randomisation strata due to the low number of patients in the lanreotide strata, The outcome of the primary endpoint was mainly driven by the patients on octreotide. Also in the second randomisation stratum (GH > or < 10 µg/L), the number of patients with very high GH was too low for any conclusions to be drawn.

The proportion of patients with normalised IGF-1 was significantly higher in the pasireotide treated groups with a less pronounced difference between the two doses (26 % vs 25 % for the 40 mg and 60 mg dose groups respectively). No responders were observed in the control group. The key secondary endpoint thus supports the outcome of the primary endpoint.

The proportion of patients responding with regards to GH was significantly higher for both doses of pasireotide (35 % vs 43 % for the 40 mg and 60 mg dose groups respectively) compared to active control (13 %). A dose response effect was observed with a higher response rate in the pasireotide 60 mg group.

The change from baseline in GH at 24 weeks and over time in the active control arm was strongly affected by one patient with very high GH levels which makes comparison with the pasireotide treated groups difficult. However, in the pasireotide treated groups a slight decrease in GH levels was observed across the study period with a similar decrease in both dose groups.

A more pronounced effect on standardised IGF-1 levels was observed in the pasireotide treated groups compared to the octreotide treated group, with no apparent difference between the two doses.

The analysis of response categories based on randomisation strata is hampered by the small size of the study, precluding any firm conclusion. Numerically, a somewhat weaker response was observed in patients previously treated with lanreotide and in patients with high GH levels at inclusion.

A reduction in tumour volume was observed in all treatment groups with no apparent difference between the two doses of pasireotide. Notably, a number of patients in each group showed an increase in tumour volume emphasising the need for continuous monitoring of tumour status.

No significant changes in acromegaly symptoms or QoL were observed in this short-term study.

Interim data from the extension of study C2402 were provided with the responses to the Day 120 LoQ. These data support maintenance of effect of pasireotide up to one year in patients not responding to other SSAs. The rate of new responders recruited in the "cross-over to pasireotide" group was in line with that observed in the core phase of the study.

The outcome in patients that crossed-over from octreotide to pasireotide and vice versa in study C2305 was also provided. This dataset provides supportive data in patients inadequately controlled with octreotide LAR or pasireotide LAR. Notably, a larger proportion of patients responded in the group that crossed-over from octreotide to pasireotide (17 %) than in the group that crossed over from pasireotide, where no responders were observed at Month 12.

The analysis of the different response categories showed that the rate of FR increased with pasireotide after cross-over, whereas the rate of PR remained constant. In the octreotide treated group, the rate of FR decreased and the rate of PR increased, however, numbers were very low. Over-response was reported in about 10 % of patients treated with pasireotide.

In line with the composite endpoint, the proportion of patients reaching the GH target was higher in the pasireotide treated group. Notably, 24 % of patients in the octreotide treated group reached the GH target whereas no patients reached FR at 12 months. In patients treated with pasireotide after cross-over, GH continued to decrease, whereas GH slightly increased in the octreotide treated group. A higher proportion of patients who were treated with pasireotide after cross-over shifted to a lower GH category than in the octreotide group.

An improvement in GH nadir values after OGTT was observed with both treatments. Although the improvement was numerically greater with pasireotide, comparisons between treatments are not meaningful due to the low numbers.

A higher proportion of patients on pasireotide showed a response with regards to IGF-1 compared to octreotide. Notably more patients in the pasireotide group also showed an over-response. In line with the observations on GH over time, IGF-1 decreased over time in the group crossed-over to pasireotide whereas IGF-1 remained stable in the octreotide treated group.

A higher proportion of the patients treated with pasireotide after cross-over showed a decrease or no change in tumour volume; however absolute change in tumour volume did not differ between treatment groups.

PRL levels decreased in the patients treated with pasireotide after cross-over, whereas no change in PRL levels was observed in the octreotide treated group at Month 12.

Acromegaly symptoms improved slightly in the pasireotide treated group after cross-over. Improvements in ring size were observed but did not differ between groups. QoL scores remained stable and did not differ between groups.

Due to the underlying difference in study design between studies C2305 and C2402, no pooling of data was performed for sub-group analysis. Sub-group analyses by race, ethnicity or age were performed in both study C2305 and C2402, however these analyses were hampered by the sizes of the studies. No clinically relevant differences in treatment effect were observed due to race, ethnicity or age.

No studies in special populations were conducted. Considering that acromegaly is a rare condition, this is acceptable.

Study C2110 was an open-label, randomized study assessing PK, safety, and tolerability profiles of 20, 40, and 60 mg doses of pasireotide LAR in patients with acromegaly or carcinoid disease. Following the completion of the core study patients were eligible to enter the extension Study C2110E1. In this small short-term study, three doses of pasireotide LAR were compared. A rapid decrease in GH, with a somewhat slower decrease in IGF-1 was observed for all doses. A dose response relationship was observed, although not statistically significant.

Study B2201 was an open-label, randomized, crossover study in patients with acromegaly receiving multiple doses of pasireotide sc and octreotide sc to assess efficacy, safety, and PK/PD relationship. After completion of the 16-week core treatment period, patients were allowed to enroll into the extension. This study investigated the subcutaneous pasireotide formulation at different doses. The highest response rate was observed with the 600 µg bid dose.

The proof-of-concept study B2103 was a double-blind, randomized, crossover study in patients with acromegaly to assess efficacy of single-dose pasireotide sc vs. octreotide sc. A suppression of GH comparable to that achieved with octreotide 100 µg was observed with the pasireotide 250 µg dose.

2.5.4. Conclusions on the clinical efficacy

The application was supported by two well-designed and well-conducted studies of considerable size; taking into account that acromegaly is a rare disease.

The primary endpoint (percentage of responders defined as a reduction of GH level to < 2.5 µg/L and normalized IGF-1) was met in study C2305 and study C2402.

Further long term data will be provided as extension studies in both categories of patients are ongoing. Data up to 26 months of treatment in medically naïve and 12 month data in patients inadequately controlled have been provided showing that the efficacy of pasireotide appears to be maintained over time.

2.6. Clinical safety

Data describing the safety profile of pasireotide comes mainly from the two pivotal studies C2305 and C2402, which both are of considerable size considering that acromegaly is a rare disease. Supportive data is available from studies C2110/C2110E1 (with the LAR formulation), studies B2201/B2201E and B2103 (with the subcutaneous formulation) as well as from studies in healthy volunteers.

Patient exposure

Table 29 Clinical studies providing safety data in acromegaly with pasireotide LAR

Study	Study objective, population	Patients enrolled to pasireotide LAR	Patients exposed to pasireotide LAR/ Mean duration (days)	Patients with long-term safety data (>12 months exposure)	Dosage of pasireotide LAR	LPLV/ Data cut-off
Active-controlled studies						
C2305 (core completed extension ongoing)	Phase 3, blinded, active-controlled, randomized study of pasireotide LAR vs. octreotide LAR patients with acromegaly to assess efficacy, safety, QoL, PK, and PK/PD relationship	Core and extension up to crossover: N=176 (FAS)	Core and extension up to crossover: N=178 Mean= 527.2 days	N= 86 (>365 days)	Pasireotide LAR q28d: 40 mg Dose adjustment permitted (dose increase after Month 3, dose decrease any time for tolerability)	29-Dec-2011
		Extension after crossover: N=81 (CAS)	Extension after crossover: N=81 Mean (after crossover only)= 449.8 days	N=56 (>365 days)		
C2402 (core completed extension ongoing)	Phase 3, double-blind 40 mg or 60 mg pasireotide LAR vs. open-label octreotide LAR or lanreotide ATG in patients with acromegaly to assess efficacy and safety.	N=130 (Full analysis set)	N=125 Mean=164.3 days	0	Pasireotide LAR q28d: 40 mg Pasireotide LAR q28d: 60 mg	22-Jan-2013
Open-label study						
C2110	Phase 1, open-label, randomized study assessing PK, safety, and tolerability profiles of 3 doses of pasireotide LAR in patients with acromegaly or carcinoid disease	N=40 (all acromegaly patients who were randomized to the study)	N=35 (acromegaly) Mean=84.3 days	0	Pasireotide LAR q28d: 20 mg, 40 mg, or 60 mg	11-Sep-2007
C2110E	Open-label extension of Study C2110 to assess long-term safety and PK/PD profiles	N=29 (all acromegaly patients who entered the extension)	N=29 (acromegaly) Mean =1138.9 days (core+extension)	N=24 (>365 days)	Pasireotide LAR q28d: 20 mg, 40 mg, or 60 mg; dose adjustment permitted	14-Jan-2011

LPLV= last patient last visit; PK=pharmacokinetics; PD=pharmacodynamics, QoL=quality of life; q28d=every 28 days

Exposure in medically naïve patients

The mean duration of exposure to study drug in the core phase (i.e. up to Month 12) was similar between pasireotide LAR (300.8 days) and octreotide LAR (315.7 days). The median number of injections was 12 in both

groups, and over 80% of patients had received more than 9 injections. Two patients in the pasireotide group and 6 patients in the octreotide group mistakenly received a 13th injection in the core phase and did not enter the extension study.

The mean duration of exposure across the core and extension for patients who continued the same treatment in the extension was longer in the pasireotide LAR group (527.2 days) than in the octreotide LAR group (414.6 days) (Table 30). This imbalance is at least partly due to the fact that patients on octreotide who reached Month 12 prior to Amendment 4 could not continue with octreotide in the extension (15 patients in pasireotide LAR and 19 in octreotide LAR, completed the core phase prior to Amendment 4). Additionally the lower response rate in octreotide could have an impact, reducing the number of patients continuing with octreotide in the extension as per protocol. Furthermore, patients receiving octreotide in the extension (allowed post-Amendment 4) were not followed after Month 26. This imbalance can also be seen in the proportion of patients with more than 26 injections (pasireotide LAR: 30.9%, octreotide LAR: 2.8%).

Table 30 Duration of exposure to study drug in medically naive patients – Study C2305 up to crossover (SAS)

	Pasireotide LAR N=178	**Octreotide LAR** N=180
Duration of exposure (days)		
Mean (SD)	527.2 (334.34)	414.6 (190.01)
Median (range)	365.0 (28.0-1340.0)	364.0 (28.0-995.0)
Number of injections		
Median (min-max)	13.0 (1.0-48.0)	13.0 (1.0-34.0)
1 injection	9 (5.1%)	6 (3.3%)
>1 - ≤ 3 injections	4 (2.2%)	2 (1.1%)
>3 - ≤ 6 injections	7 (3.9%)	4 (2.2%)
>6 - ≤ 9 injections	12 (6.7%)	7 (3.9%)
>9 - ≤ 12 injections	33 (18.5%)	48 (26.7%)
>12 - ≤ 15 injections	42 (23.6%)	74 (41.1%)
>15 - ≤ 18 injections	4 (2.2%)	0
>18 - ≤ 21 injections	1 (0.6%)	1 (0.6%)
>21 - ≤ 24 injections	0	0
>24 - ≤ 26 injections	11 (6.2%)	33 (18.3%)
>26 injections	55 (30.9%)	5 (2.8%)

Per protocol, injections were planned every 28 days

Exposure in inadequately controlled patients

In Study C2402 the mean duration of exposure to study drug in the core phase (up to 24 weeks of treatment) was similar between pasireotide LAR 40 mg, pasireotide LAR 60 mg and the active control (octreotide LAR or lanreotide LAR) (Table 31). The median number of injections was 6 in all groups.

Table 31 Duration of exposure to study drug in inadequately controlled patients – Study C2402 (SAS)

Exposure variable	Pasireotide LAR 40 mg N=63	Pasireotide LAR 60 mg N=62	Active control N=66
Duration of exposure (weeks)			
Mean (SD)	23.67 (2.461)	23.28 (3.471)	24.45 (2.581)
Median (min-max)	24.00 (11.9-28.0)	24.00 (4.0-26.0)	24.00 (8.1-29.9)
Number of injections[1]			
Median (min-max)	6 (3-6)	6 (1-6)	6 (2-8)
1	0	1 (1.6%)	0
2	0	0	1 (1.5%)
3	2 (3.2%)	2 (3.2%)	0
4	1 (1.6%)	1 (1.6%)	0
5	2 (3.2%)	1(1.6%)	1 (1.5%)
6	58 (92.1%)	57 (91.9%)	51 (77.3%)
>6	0	0	13 (19.7%)[1]

1: Number of injections received during the core phase (24 weeks of treatment) 13 patients in the control arm were incorrectly reported as having >6 injections.

In Study C2305 after crossover, the mean duration of exposure was longer for pasireotide LAR (449.8 days) than for octreotide LAR (341.7 days) (Table 32). Patients who crossed over to octreotide LAR were not followed after Month 26.

Table 32 Duration of exposure to study drug in inadequately controlled patients – Study C2305 after crossover (CAS)

	Crossed over to Pasireotide LAR N=81	Crossed over to Octreotide LAR N=38
Duration of exposure (days)		
Mean (SD)	449.8 (246.90)	341.7 (71.56)
Median (min-max)	420.0 (28.0-1003.0)	364.0 (85.0-421.0)
Number of injections		
Median (min-max)	15.0 (1.0-36.0)	13.0 (3.0-14.0)
1 injection	3 (3.7%)	0
>1 - ≤ 3 injections	5 (6.2%)	1 (2.6%)
>3 - ≤ 6 injections	6 (7.4%)	2 (5.3%)
>6 - ≤ 9 injections	5 (6.2%)	1 (2.6%)
>9 - ≤ 13 injections	11 (13.6%)	30 (78.9%)
>13 injections	51 (63.0%)	4 (10.5%)

Per protocol, the injections were planned every 28 days

Exposure in supportive studies with LAR formulation

In Study C2110 patients were randomized to receive pasireotide LAR 20 mg, 40 mg or 60 mg for 3 months (i.e. 3 injections, q28d). All 35 patients who started pasireotide LAR treatment completed the planned 3 months of pasireotide LAR treatment. The mean duration of exposure was approximately 84 days for each of the respective dose groups.

After completing Study C2110 patients could continue the same treatment in the optional extension C2110E. In the extension, the dose could be increased or decreased by 20 mg at any time (smallest allowed dose: 20 mg; maximum dose: 60 mg). For the 29 patients that continued in the extension phase, the mean duration of exposure to pasireotide LAR across the core and extension was 1138.9 days.

Exposure in supportive studies with sc formulation

Study B2201/E

In Study B2201 (core phase), all patients received first octreotide 100 µg sc tid for 28 days. Each patient was randomized to one of six treatment sequence groups to receive successively either pasireotide 200 µg, 400 µg, or 600 µg sc bid, over three consecutive periods of 28 days. For the 60 patients who were treated in the core phase, the overall mean duration of exposure was 84.3 days. For the 30 patients who continued in the extension phase, the mean duration of exposure (calculated across core and extension) was 29.2 months.

Study B2103

In Study B2103, twelve patients received a single sc dose of pasireotide 100 µg, pasireotide 250 µg, and octreotide 100 µg in a crossover design with a minimum of 6 days washout between each treatment.

Exposure in healthy volunteer studies

Healthy volunteer studies with pasireotide LAR formulation

Subjects in Study B2116, Study C2112, and Study C2101 were administered pasireotide sc formulation (300 µg in C2101, dose range 300 to 900 µg in B2116 and C2112) prior to administration of a single dose of pasireotide LAR (range 10 to 60 mg).

Subjects in Study G1101 and C2111 were only administered pasireotide LAR. Subjects in Study G1101 received a single dose of pasireotide LAR (10, 20, 40 or 60 mg). Subjects in Study C2111 were administered pasireotide LAR 60 mg from 2 different manufacturing plants in a 2-way crossover design, thus the majority of these subjects received 2 doses of pasireotide LAR (1 from each plant).

A total of 311 subjects received pasireotide LAR in these healthy volunteer studies (42 subjects in Study B2116, 45 subjects in Study C2112, 78 subjects in Study C2101, 114 subjects in Study C2111, and 32 subjects in Study G1101).

Special safety studies (pasireotide sc)

A total of 448 subjects received pasireotide sc in these studies.

Adverse events

Due to the similarities in the pasireotide safety profile between medically naïve patients and patients inadequately controlled a pooled analysis of all safety data for studies 2305 and 2402 was performed and

presented with the responses to the Day 120 LoQ. These tables are given below (Table 33 and Table 34) followed by descriptions of the safety findings in the separate studies.

Common adverse events in the pooled data set

Table 33 Adverse events (>5% in the All grades column) regardless of study drug relationship – pooled data (Safety analysis set)

	Pasireotide LAR N=384		Active control N=284	
	All grade n (%)	Grade 3/4 n (%)	All grade n (%)	Grade 3/4 n (%)
Total	**360 (93.8)**	**109 (28.4)**	**248 (87.3)**	**59 (20.8)**
Diarrhoea	113 (29.4)	1 (0.3)	91 (32.0)	7 (2.5)
Cholelithiasis	91 (23.7)	5 (1.3)	86 (30.3)	4 (1.4)
Hyperglycaemia	120 (31.3)	22 (5.7)	32 (11.3)	1 (0.4)
Headache	69 (18.0)	2 (0.5)	57 (20.1)	5 (1.8)
Diabetes mellitus	83 (21.6)	13 (3.4)	16 (5.6)	0
Abdominal pain	46 (12.0)	4 (1.0)	47 (16.5)	1 (0.4)
Nausea	41 (10.7)	2 (0.5)	46 (16.2)	0
Nasopharyngitis	56 (14.6)	0	38 (13.4)	0
Alopecia	42 (10.9)	0	37 (13.0)	0
Arthralgia	35 (9.1)	3 (0.8)	29 (10.2)	1 (0.4)
Back pain	34 (8.9)	1 (0.3)	26 (9.2)	3 (1.1)
Dizziness	34 (8.9)	0	27 (9.5)	0
Blood creatine phosphokinase increased	33 (8.6)	6 (1.6)	30 (10.6)	4 (1.4)
Fatigue	30 (7.8)	2 (0.5)	26 (9.2)	0
Hypertension	26 (6.8)	4 (1.0)	22 (7.7)	5 (1.8)
Abdominal distension	22 (5.7)	1 (0.3)	25 (8.8)	1 (0.4)
Vomiting	24 (6.3)	1 (0.3)	18 (6.3)	1 (0.4)
Hypoglycaemia	24 (6.3)	3 (0.8)	16 (5.6)	1 (0.4)
Abdominal pain upper	20 (5.2)	0	19 (6.7)	3 (1.1)
Blood glucose increased	32 (8.3)	0	6 (2.1)	0
Constipation	19 (4.9)	1 (0.3)	21 (7.4)	0
Anaemia	26 (6.8)	0	13 (4.6)	1 (0.4)
Hepatic steatosis	17 (4.4)	1 (0.3)	15 (5.3)	0
Influenza	21 (5.5)	1 (0.3)	14 (4.9)	0
Urinary tract infection	18 (4.7)	1 (0.3)	15 (5.3)	0
Cough	13 (3.4)	0	18 (6.3)	0
Upper respiratory tract infection	20 (5.2)	0	9 (3.2)	0
Oropharyngeal pain	11 (2.9)	0	16 (5.6)	0
Lipase increased	14 (3.6)	0	15 (5.3)	3 (1.1)
Glycosylated haemoglobin increased	20 (5.2)	1 (0.3)	5 (1.8)	1 (0.4)

Source: [Appendix 1-Table pool_q108_1_1]

Common adverse events in medically naïve patients

AEs profile up to crossover (i.e. up to data cut-off for patients who continued the same treatment in the extension, and up to crossover for those who did not) was in keeping with known profile of patients on pasireotide.

Most patients (94.1%) experienced at least one AE. Gastrointestinal disorders were the most frequent SOC in both treatment groups, 64.0% for pasireotide LAR vs. 72.8% for octreotide LAR. The largest difference between the treatment groups was observed for the SOC metabolism and nutrition disorders, 64.0% for pasireotide LAR vs. 33.3% for octreotide LAR.

AEs that were more frequent (at least 5% difference) in the pasireotide LAR group were mostly related to glucose metabolism: hyperglycaemia, diabetes mellitus, blood glucose increased, and type 2 diabetes mellitus. AEs that were less frequent in the pasireotide LAR than octreotide LAR were mostly related to GI disorders: diarrhoea (39.9% vs. 45.0%), cholelithiasis (32.6% vs. 39.4%), abdominal pain (18.5% vs. 24.4%), nausea (15.2% vs. 22.8%) and constipation (5.6% vs. 10.6%).

SSAs are known to cause alopecia. The difference in AEs of alopecia between Study C2305 (19.1% in pasireotide and 20% in octreotide) and Study C2402 (1.6% and 6.5% for pasireotide 40 mg and 60 mg and none in the active control) is likely due to all patients in Study C2402 having prior exposure to SSA and would therefore have developed alopecia prior to study entry.

The most common grades 3-4 AEs for pasireotide LAR group were diabetes mellitus (5.1%) and hyperglycaemia and blood creatine phosphokinase increased (3.4% each). In the octreotide LAR group most common grade 3-4 AEs were diarrhoea (2.8%) and headache (2.8%).

Common AEs in inadequately controlled patients

In Study C2402 most patients in all 3 treatment groups experienced at least one AE during the study. Metabolism and nutrition disorders was the most frequent SOC in all 3 treatment groups. The three most common AEs in the pasireotide LAR 40 mg and 60 mg groups were hyperglycaemia (33.3% and 30.6%) and diabetes mellitus (20.6% and 25.8%), followed by diarrhoea (15.9% and 19.4%). In the active control group they were hyperglycaemia and cholelithiasis (13.6% each) and diabetes mellitus (7.6%). The type of AEs is similar to what was reported for medically naïve patients in Study C2305. The patients treated with pasireotide LAR (40 mg and 60 mg) had a higher incidence of grades 3-4 AEs than the patients treated with the active control (17.5% and 19.4% vs. 7.6%).

In the Study C2305 after crossover results were similar to Study C2402 and pooled inadequately controlled analysis (patient from Studies C2402 and C2305 after crossover). The most frequent AEs were hyperglycaemia (30.9%) and diarrhoea (24.7%) in the pasireotide LAR group and diarrhoea (18.4%) and nasopharyngitis (18.4%) in the octreotide LAR group. The patients treated with pasireotide LAR had more high grades AEs (28.4% vs. 21.1% in octreotide LAR). The difference was mainly due to a higher frequency of grade 3-4 hyperglycaemia (4.9% vs. none) and diabetes mellitus (2.5% vs. none).

Common adverse events in supportive studies

Common adverse event with pasireotide LAR and sc formulations in supportive studies in the acromegaly population and healthy volunteers are consistent with those observed in Study C2305, with GI disturbances and hyperglycaemia (mostly grade 1 or 2) being the most commonly observed events.

Events suspected to be drug-related in the pooled data set

Table 34 Adverse events (>5% in the All grades column) suspected to be drug related – pooled data (Safety analysis set)

	Pasireotide LAR N=384		Active control N=284	
	All grade n (%)	Grade 3/4 n (%)	All grade n (%)	Grade 3/4 n (%)
Total	**307 (79.9)**	**59 (15.4)**	**193 (68.0)**	**22 (7.7)**
Diarrhoea	92 (24.0)	1 (0.3)	77 (27.1)	6 (2.1)
Cholelithiasis	87 (22.7)	5 (1.3)	80 (28.2)	4 (1.4)
Hyperglycaemia	111 (28.9)	19 (4.9)	21 (7.4)	1 (0.4)
Diabetes mellitus	77 (20.1)	12 (3.1)	13 (4.6)	0
Abdominal pain	32 (8.3)	2 (0.5)	33 (11.6)	1 (0.4)
Alopecia	35 (9.1)	0	27 (9.5)	0
Nausea	23 (6.0)	1 (0.3)	28 (9.9)	0
Abdominal distension	18 (4.7)	1 (0.3)	20 (7.0)	0
Blood creatine phosphokinase increased	22 (5.7)	3 (0.8)	21 (7.4)	2 (0.7)
Blood glucose increased	28 (7.3)	0	6 (2.1)	0
Dizziness	20 (5.2)	0	13 (4.6)	0

Source: [Appendix 1-Table pool_q108_2_1]

Events suspected to be drug-related in medically naïve patients

In Study C2305 up to cross over AEs that were suspected to be related to study drug by the investigator showed similar profiles to the known safety profile of pasireotide and octreotide. The most frequent AEs overall were diarrhoea and cholelithiasis, and these were more frequent in the octreotide LAR group than in the pasireotide LAR group. In addition nausea was also more frequent in the octreotide LAR group. Study drug-related AEs that were more frequent in the pasireotide LAR group (by at least 5%) were all related to glucose metabolism (hyperglycaemia, diabetes mellitus, blood glucose increased, and type 2 diabetes mellitus). In the octreotide arm the AEs that were more frequent than in pasireotide arm (by at least 5%) were diarrhoea, cholelithiasis, and nausea. Grade 3 or 4 AEs related to glucose metabolism (hyperglycaemia, diabetes mellitus, type 2 diabetes mellitus) were more frequent in the pasireotide LAR group, whereas grade 3-4 diarrhoea was more frequent in the octreotide LAR group.

Events suspected to be drug-related in inadequately controlled patients

In Study C2402 and for the pooled analysis on inadequately controlled patients, AEs suspected to be related to study drug showed similar profiles to the known safety profiles of pasireotide LAR and the active control (octreotide LAR and lanreotide ATG). The most frequent AEs overall were hyperglycaemia, diabetes mellitus, diarrhoea, and cholelithiasis. In Study C2402 AEs suspected to be related to study drugs that were more frequent (at least 5% difference) in the pasireotide LAR groups than in the active control group were hyperglycaemia, diabetes mellitus, blood glucose increase and diarrhoea. Grade 3-4 events reported in the pasireotide groups were generally related to hyperglycaemia. No grade 3 or grade 4 AEs were reported in the active control group.

In Study C2305 after crossover AEs suspected to be drug related that were more frequent (>5% difference) in patients treated with pasireotide LAR compared to octreotide LAR were similar to those in Study C2402 (hyperglycaemia-related AEs and diarrhoea). In addition the incidences of cholelithiasis and headache were also higher (>5%) in patients who crossed over to pasireotide while the incidence of blood creatine phosphokinase

increased and abdominal distension were higher in the octreotide group. Most study drug-related AEs were grade 1-2.

Serious adverse event/deaths/other significant events

An overview of SAEs and other clinically significant events for medically naïve patients (Study C2305) is provided in Table 35 and for inadequately controlled patients (Study C2402 and C2305 after crossover) in Table 36. These events are discussed in the sections below.

Table 35 Clinically significant events in medically naïve patients (Study C2305, Safety set)

	Pasireotide LAR N=178 n (%)	Octreotide LAR N=180 n (%)
Deaths	**1 (0.6)**	**2 (1.1)**
SAEs	**35 (19.7)**	**27 (15.0)**
SAEs related to study drug	13 (7.3)	11 (6.1)
SAEs leading to discontinuation	9 (5.1)	0
AEs leading to discontinuation	**16 (9.0)**	**9 (5.0)**
AEs leading to dose interruption/adjustment	**17 (9.6)**	**9 (5.0)**
Grade 3 or 4 AEs	**63 (35.4)**	**46 (25.6)**
Grade 3	52 (29.2)	40 (22.2)
Grade 4	11 (6.2)	6 (3.3)
AEs of special interest related to:		
Hyperglycaemia	113 (63.5)	45 (25.0)
Diarrhoea	71 (39.9)	81 (45.0)
Gallbladder and biliary	71 (39.9)	77 (42.8)
Nausea	34 (19.1)	46 (25.6)
Pancreatitis	30 (16.9)	32 (17.8)
Bradycardia	28 (15.7)	27 (15.0)
Rhabdomyolysis	25 (14.0)	24 (13.3)
Low blood cell	21 (11.8)	15 (8.3)
Liver safety	19 (10.7)	20 (11.1)
QT-prolongation	16 (9.0)	13 (7.2)
Injection site reaction	15 (8.4)	15 (8.3)
Hypothyroidism	13 (7.3)	11 (6.1)
Constipation	10 (5.6)	19 (10.6)
Hypocortisolism	6 (3.4)	5 (2.8)
Coagulation	3 (1.7)	3 (1.7)
GI bleeding	3 (1.7)	0
Hypocalcemia	2 (1.1)	3 (1.7)
Growth hormone deficiency	1 (0.6)	0
Hypotension	0	2 (1.1)

Table 36 Clinically significant events in inadequately controlled patients (Studies C2402, Safety set and C2305 after crossover, CAS)

	Study C2402			Study C2305, after crossover	
	Pasireotide LAR, 40 mg	**Pasireotide LAR, 60 mg**	**Active control**	**Pasireotide LAR**	**Octreotide LAR**
	N=63	**N=62**	**N=66**	**N=81**	**N=38**
	n (%)	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Deaths	**0**	**0**	**0**	**1 (1.2)**	**0**
SAEs	**6 (9.5)**	**2 (3.2)**	**3 (4.5)**	**8 (9.9)**	**6 (15.8)**
SAEs related to study drug	2 (3.2)	1 (1.6)	0	3 (3.7)	1 (2.6)
SAEs leading to discontinuation	1 (1.6)	0	0	2 (2.5)	0
AEs leading to discontinuation	**3 (4.8)**	**4 (6.5)**	**0**	**13 (16.0)**	**0**
AEs leading to dose interruption/adjustment	**1 (1.6)**	**0**	**0**	**4 (4.9)**	**2 (5.3)**
Grade 3 or 4 AEs	**11 (17.5)**	**12 (19.4)**	**5 (7.6)**	**23 (28.4)**	**8 (21.1)**
Grade 3	10 (15.9)	12 (19.4)	5 (7.6)	20 (20.4)	5 (13.2)
Grade 4	1 (1.6)	0	0	3 (3.7)	3 (7.9)
AEs of special interest related to:					
Hyperglycaemia	42 (66.7)	38 (61.3)	20 (30.3)	55 (67.9)	8 (21.1)
Diarrhoea	10 (15.9)	12 (19.4)	3 (4.5)	20 (24.7)	7 (18.4)
Gallbladder and biliary	8 (12.7)	9 (14.5)	11 (16.7)	24 (29.6)	8 (21.1)
Nausea	4 (6.3)	4 (6.5)	2 (3.0)	9 (11.1)	3 (7.9)
Pancreatitis	2 (3.2)	0	1 (1.5)	3 (3.7)	4 (10.5)
Bradycardia	5 (7.9)	2 (3.2)	0	5 (6.2)	3 (7.9)
Rhabdomyolysis	0	1 (1.6)	0	7 (8.6)	6 (15.8)
Low blood cell	4 (6.3)	2 (3.2)	2 (3.0)	10 (12.3)	1 (2.6)
Liver safety	2 (3.2)	1 (1.6)	1 (1.5)	5 (6.2)	0
QT-prolongation	0	0	0	4 (4.9)	0
Injection site reaction	0	1 (1.6)	2 (3.0)	0	1 (2.6)
Hypothyroidism	0	0	0	3 (3.7)	3 (7.9)
Constipation	3 (4.8)	1 (1.6)	1 (1.5)	5 (6.2)	1 (2.6)
Hypocortisolism	1 (1.6)	0	0	1 (1.2)	0
GI bleeding	0	0	0	0	1 (2.6)
Growth hormone deficiency	0	0	0	0	1 (2.6)
Hypotension	0	1 (1.6)	0	0	0

Serious adverse events

In ***medically naïve patients*** in Study C2305, SAEs were experienced by 19.7% of patients on pasireotide LAR and 15.0% of patients on octreotide LAR (Table 35). The most frequent SAEs overall were those related to the gallbladder (6 vs. 5 patients on pasireotide LAR vs. octreotide LAR). Most of these events resolved following cholecystectomy and/or medical therapy, and none led to discontinuation. These were also the most frequent SAEs overall with suspected relationship to study drug.

SAEs related to glucose metabolism occurred in 5 patients on pasireotide LAR (all related to increased blood glucose) and one patient on octreotide LAR (hypoglycemia in a patient treated with insulin); these patients were all either pre-diabetic or diabetic at baseline. Three of the 5 patients in the pasireotide LAR group discontinued study drug.

Although the SAE profile by individual preferred terms was generally comparable between the treatments, SAEs led to discontinuation only in the pasireotide LAR group (9 patients). Four of these cases were due to study drug-related events: 3 patients had hyperglycaemia-related events and a fourth patient discontinued due to worsened fatigue.

In ***inadequately controlled patients*** in Study C2402, SAEs occurred in 9.5%, 3.2% and 4.5% of patients in the pasireotide LAR 40 mg, 60 mg and active control groups, respectively (Table 36). SAEs considered related to study drug were reported for 3 patients on pasireotide LAR: 2 patients in the 40 mg group (one patient with anemia and hyperglycaemia, and one patient with blood glucose increased) and one patient in the 60 mg group (hyperglycaemia). None of these events led to discontinuation. In Study C2305, SAEs occurred in 9.9% and 15.8% of patients who crossed over to pasireotide LAR and octreotide LAR, respectively. SAEs considered related to study drug were cholelithiasis (2 patients who crossed to pasireotide LAR and 1 patient who crossed to octreotide LAR, and type 2 diabetes in a patient who crossed to pasireotide LAR). The type 2 diabetes led to discontinuation, whereas the 3 cases of cholelithiasis resolved after the patients underwent cholecystectomy.

SAEs in the supportive acromegaly studies and healthy volunteers were in line with those seen in Study C2305.

Deaths

Four deaths (1 in the core and 3 in the extension) were reported on treatment in Study C2305. Two deaths occurred on pasireotide LAR treatment and the other 2 deaths occurred on octreotide LAR treatment. None of the deaths were considered related to the study treatment by the investigator. Close examination of the 4 deaths (myocardial infarction, septic shock, suicide, and aortic aneurysm rupture, respectively) revealed no consistent pattern in the nature or timing of the events or suspected causality to study treatment deaths.

Adverse events of special interest

A comprehensive analysis using grouped AE terms was performed to characterize AEs that are considered to be of special interest in connection with pasireotide treatment. A total of 20 groups of AEs of special interest were defined.

This analysis was performed using data from studies C2305, C2402 and C2110/E in patients with acromegaly.

The overall incidence of AEs of special interest is shown in Table 35 (Study C2305) and Table 36 (Study C2402 and Study C2305 after crossover). Those AEs of special interest that represent the most important clinical concerns with pasireotide LAR treatment are discussed below (Special safety topics). These are: hyperglycaemia, QT prolongation, bradycardia, liver safety, gallbladder and related events and pituitary hormones. Other safety topics which were considered to warrant commentary are gastrointestinal events, pancreatitis-related events, and injection-site reactions; these are briefly discussed below.

Gastrointestinal events

GI-related events are a known class effect of SSAs and were the most commonly observed events with pasireotide treatment across the development program. In medically naïve patients, diarrhoea-related and nausea-related events were reported in 39.9% and 19.1% of patients on pasireotide LAR, and 45.0% and

25.6% of patients on octreotide LAR (Table 35). Diarrhoea and nausea were approximately twice more frequent in the first 3 months of pasireotide LAR treatment than in the following time intervals.

Diarrhoea and nausea events were also common in inadequately controlled patients, however the incidences were generally lower than for medically naïve patients (Table 35, Table 36), most likely because patients' tolerance to treatment improves over time. This is further supported by the low incidence of diarrhoea-related events (4.5%) among patients who continued their previous treatment in the control group of Study C2402.

Pancreatitis-related events

Pancreatitis is a potential adverse reaction associated with the use of SSAs. Adverse events potentially linked to pancreatitis (e.g. abdominal distension, lipase increased) were observed at comparable rates with pasireotide LAR and active control in the Phase 3 studies; the overall incidences were higher in medically naïve patients (16.9% and 17.8% for pasireotide LAR and octreotide LAR) than on pasireotide LAR in inadequately controlled patients (<4%; Table 35, Table 36). One patient discontinued due to such an event (a patient on pasireotide LAR with acute pancreatitis not suspected to be related to study medication by the investigator).

In supportive acromegaly studies C2110/E, B2201/E or B2103, no patient discontinued due to a pancreatitis-related event.

Elevations in lipase values were observed on both pasireotide LAR and active control. In Study C2305, elevations (mostly grade 1-2) were seen in around 25% of patients in each group. Similar results were seen after crossover to pasireotide LAR, with slightly lower rates (around 10 % of patients had grade 1-2 lipase) after crossover to octreotide LAR. In Study C2402, lipase elevations were rare.

Injection site reactions

Injection site reaction-related AEs (e.g. injection site pain, injection site discomfort) were all grade 1 or 2 in severity, and seen in ~8% of medically naïve patients. The incidence of such events was highest in the first 3 months of treatment. Injection site reaction-related AEs were less frequent in inadequately controlled patients (≤ 3% in any treatment group) (Table 35, Table 36).

Laboratory findings
Haematology

Haematology findings with pasireotide were consistent with known SSA effects, and in line with preclinical findings of decreased erythropoiesis due to IGF-1 suppression and binding of pasireotide to SSTRs on hematopoietic precursor cells. Slight decreases in hemoglobin levels (typically grade 1) were the most frequent observation in clinical studies with pasireotide.

Coagulation parameters

Overall, in studies C2305 and C2402, there were no changes from baseline to last value in PT and PTT parameters, and no clinically relevant shifts from baseline were observed.

Clinical chemistry

The results for other biochemistry parameters were consistent with the expected safety profile of SSAs. In the Phase 3 studies C2305 and C2402, newly occurring or worsened abnormalities in electrolytes, blood lipids, and renal parameters were mostly grade 1-2, and comparable on pasireotide LAR and active control. Findings in supportive acromegaly studies C2110/E and B2201/E were consistent with those in the Phase 3 studies.

Urinalysis

Urinalysis results did not reveal any findings of clinical concern.

Vital signs, physical findings, and other observations related to safety

A common abnormality in Study C2305 up to crossover was low pulse rate (16.9% vs. 12.2% for pasireotide LAR vs. octreotide LAR), which is expected considering the known bradycardic effect of SSAs. Weight decrease of ≥ 10% was seen for 22.5% vs. 8.9% of patients in the respective groups up to crossover. This finding may be related to decreases in IGF-1 levels. After crossover, weight decrease ≥ 10% was reported for 12.3% vs. 2.6% of patients, and an increase in weight for 4.9% vs. 5.3% of patients, respectively. Findings in supportive studies C2110/E and B2201/E were consistent with these results.

Special safety topics

Special safety topics were defined based on knowledge of SSA class effects, and emerging clinical experience with pasireotide using the sc and LAR formulations. The evaluation of these topics in the sections below is based on analysis of AEs of special interests, as well as laboratory investigations, ECG and gallbladder ultrasound as relevant.

Glucose Metabolism

Hyperglycaemia-related events in patients with acromegaly

In medically naïve patients, the incidence of hyperglycaemia-related events (e.g. diabetes mellitus, hyperglycaemia, blood glucose increased) was higher on pasireotide LAR (63.5%) than octreotide LAR (25.0%), and more patients had events that were grade 3 or 4 on pasireotide LAR (9.0% vs. 1.7% on octreotide LAR). The results were similar for inadequately controlled patients, where 60-80% of patients on pasireotide LAR experienced such events, compared to 20-40% of those on active control; grade 3-4 events were reported only for those on pasireotide LAR (10-15%). Hyperglycaemia-related AE led to study drug discontinuation more often from pasireotide LAR (3.4% in medically naïve patients, 1.6% to 6.5% in inadequately controlled patients in Study C2402) than from active control (<2% overall). Hyperglycaemia-related events were also observed AEs in studies C2110/E and B2201.

Time-interval analysis of hyperglycaemia-related AEs in studies C2305 and C2110E indicated that the incidence of these events was higher in the first 3 months of treatment than subsequent time intervals analyzed, but increased again with longer treatment.

Two cases of hyperglycaemia-related emergencies requiring hospitalization were reported in Study C2305 (one case of diabetic ketoacidosis, and one case of hyperglycaemic coma). Both events occurred after pasireotide LAR dose was increased from 40 mg to 60 mg. Both patients had elevated FPG levels prior to the dose increase, and neither patient was receiving any anti-hyperglycaemic agents at the time. Both patients recovered; study drug was discontinued for one patient and the other patient continued in the study. No such events were reported in Study C2402.

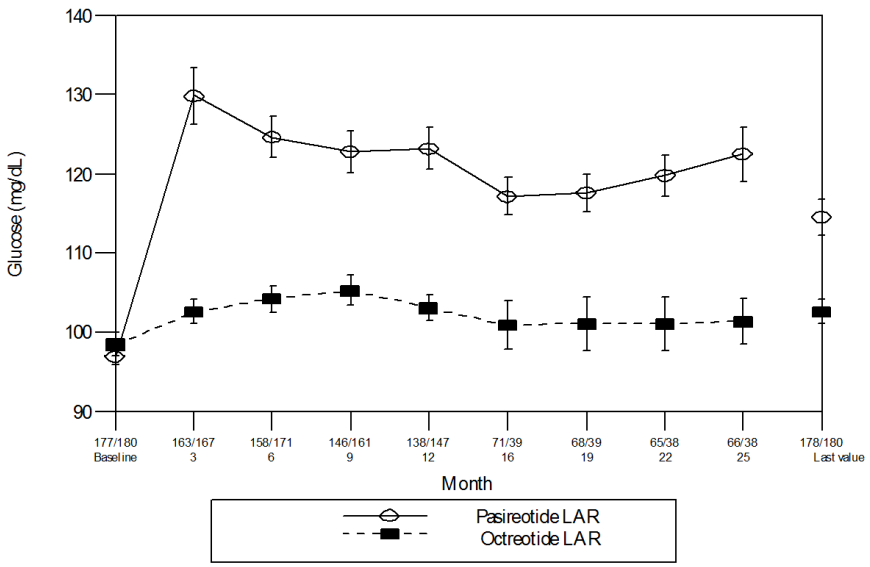
Patients with impaired glucose metabolism at baseline are at a higher risk of developing hyperglycaemia-related AEs that are severe or serious, and to require discontinuation of treatment. Among medically naïve patients the incidence of grade 3-4 AEs on pasireotide LAR was higher in diabetic patients (18.9%) than those who were pre-diabetic (5.9%) or had normal glucose tolerance (3.5%). Hyperglycaemia-related SAEs were more frequent in diabetic patients (5.7%) than pre-diabetic patients (2.9%); none were reported in those with normal glucose

tolerance. The rate of discontinuation was also higher among diabetics (9.4%) than pre-diabetics (0%) or those with normal glucose tolerance (1.8%). The results for inadequately controlled patients were consistent with those in medically naïve patients, with hyperglycaemia-related grade 3 AEs reported in 15-25% of diabetic patients vs. <3% of pre-diabetics, and none in those with normal glucose tolerance receiving pasireotide LAR. Hyperglycaemia-related SAEs, or AEs leading to discontinuation, were only reported in patients who were diabetic at baseline.

FPG and HbA1c in patients with acromegaly

In medically naïve patients, a more pronounced increase in FPG and HbA1c levels was observed with pasireotide LAR than octreotide LAR. Mean FPG and HbA1c levels peaked within the first 3 months of treatment with pasireotide LAR (mean increase from baseline to Month 3: FPG +33.3 mg/dL, HbA1c +0.90%), followed by a slight decrease and stabilization (mean increase from baseline to Month 12: FPG +27.1 mg/dL, HbA1c +0.78%; Figure 11). For octreotide LAR, a much smaller and slower increase was seen for mean FPG and HbA1c, with highest levels attained after 9-12 months of treatment (mean increase from baseline to Month 12: FPG +5.1 mg/dL, HbA1c +0.17%). In inadequately controlled patients, FPG and HbA1c levels increased in patients treated with pasireotide LAR. Similar to medically naïve patients, the levels peaked initially and then remained stable. At the end of the 6-month core phase in Study C2402, the mean increase in FPG was +22.9 mg/dL and +40.5 mg/dL for pasireotide LAR 40 mg and 60 mg, respectively; the respective values for HbA1c were +0.77% and +1.08%.

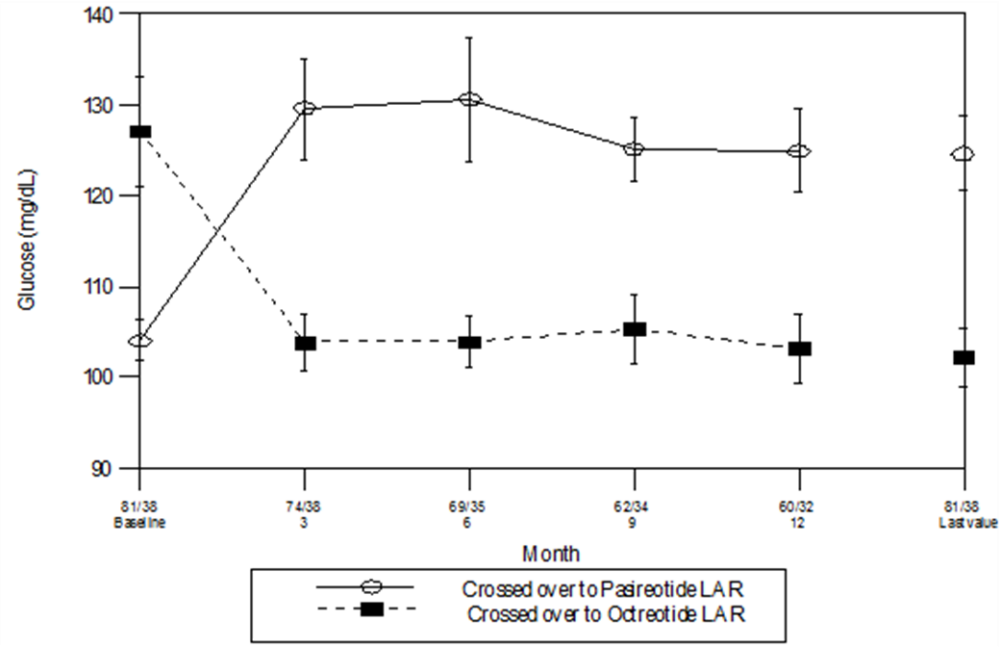
Figure 11 Mean (SE) FPG by visit in medically naïve patients – Study C2305 up to crossover (SAS)



The numbers xx/xx at the bottom are the numbers of patients in pasireotide/octreotide treatment group at the respective time points.

The pasireotide-induced hyperglycaemia is reversible upon discontinuation of treatment. This is demonstrated by the rapid decrease in FPG and HbA1c levels in patients who crossed from pasireotide LAR to octreotide LAR in Study C2305, with FPG and HbA1c stabilizing at levels comparable to those of medically naive patients treated with octreotide LAR (Figure 12). Furthermore, for patients who discontinued pasireotide LAR treatment, FPG levels were lower at the follow-up safety assessment, however the duration of the safety follow-up was not sufficiently long (<60 days) to allow FPG levels to return to baseline levels.

Figure 12 Mean (SE) FPG over time by treatment - Study C2305 after crossover (CAS)



The numbers xx/xx at the bottom are the numbers of patients in pasireotide/octreotide treatment group.

Shifts in FPG and HbA1c were analyzed based on American Diabetes Association categories (ADA 2010). In Study C2305, around 60% of patients on pasireotide LAR had shifted to a higher FPG and HbA1c category by their last assessment, compared to around 30% for octreotide LAR, and the shifts tended to be to higher categories than for octreotide LAR. Similar results were seen for inadequately controlled patients, where around 60% of patients shifted to a worse category on pasireotide LAR, compared to 20% on active control. In Study C2402, more shifts to the highest categories occurred on the 60 mg than the 40 mg pasireotide LAR dose. It should be noted that for both pasireotide LAR and active control there were also shifts from a higher baseline category to a lower category at the last assessment, indicating that there was substantial inter-patient variability in the hyperglycaemic effect for both pasireotide LAR and active control.

Consistent with the observation of a peak in FPG levels at Month 3, analyses of shifts to most extreme value on treatment showed a higher proportion of patients shifting to a worse category compared to analysis of shifts to last available value for both medically naïve and inadequately controlled patients. These results indicate that many patients who initially shifted to a higher category shifted to a lower category by the last assessment. These results were consistent with those observed in C2110E, where time-interval analysis showed that the majority of shifts occurred within the first 6 months of treatment, and that some patients shifted to a lower ADA category with continued treatment.

Analyses of hyperglycaemia by ***patient's baseline diabetic status*** (diabetic, pre-diabetic, normal glucose tolerance) in medically naïve patients show that the peak increase seen after 3 months of treatment in FPG and HbA1c were substantially higher in diabetic patients than in pre-diabetics or those with normal glucose tolerance, but decreased in diabetic patients over time and stabilized at a lower level. The incremental increase in mean FPG and HbA1c from baseline to last value on treatment was similar in all diabetic status subgroups (FPG: mean increase 15 to 20 mg/dL, HbA1c: mean increase 0.6 to 0.9%). This suggests that the level of hyperglycaemia induced by pasireotide can be predicted based on a patient's baseline diabetic status; however it should be kept in mind that the responses in individual patients may vary. Data from inadequately controlled

patients in Study C2305 after crossover are consistent, showing that the absolute increase in FPG and HbA1c with pasireotide LAR is largely independent of a patient's diabetic status. However, this was not the case in Study C2402, where the increase was proportionally higher in diabetic patients than in the normal and pre-diabetic patients. This may be because the duration of the core study was shorter (24 weeks), therefore the full effect of the anti-diabetic intervention on FPG and HbA1c may not have been seen by the time of data cut-off.

Analyses of ***anti-diabetic medication*** use in Study C2305 for patients with a FPG and/or HbA1c abnormality indicates that pasireotide-induced hyperglycaemia responds to medication. Mean FPG levels decreased in patients who developed, or had a worsening of hyperglycaemia, and who were treated with anti-diabetic medication.

The improvement in mean FPG and HbA1c levels observed after the initial peak at Month 3 is most likely due to a combination of several factors, such as dose adjustment, anti-diabetic intervention, improvement in GH and IGF-1 levels with pasireotide LAR treatment, and attenuation of the hyperglycaemic effect of pasireotide over time. It should be noted that the study was not designed to address the contribution of different factors on the progression of hyperglycaemia.

Analyses of ***hyperglycaemia in relation to efficacy response*** revealed that patients who achieved biochemical control on pasireotide LAR developed, on average, less hyperglycaemia than those who did not achieve biochemical control. The effect was clearer in medically naïve than in inadequately controlled patients. A similar trend of a lower degree of hyperglycaemia in responders was seen for octreotide LAR in Study C2305, suggesting that this phenomenon is common among SSAs. The underlying mechanism is not fully understood, but may be related to the known insulin resistance caused by GH excess.

Analyses of ***response rate by baseline diabetes status*** in medically naïve patients showed that response rates at Month 12 for both pasireotide LAR vs. octreotide LAR were higher for patients with normal glucose tolerance at baseline (42.1% vs. 22.0%), intermediate for pre-diabetics (30.9% vs. 21.9%), and lowest in diabetics (20.8% vs. 13.6%). These results also show that pasireotide LAR is superior to octreotide LAR regardless of a patient's diabetic status at baseline. In inadequately controlled patients, response rates were higher in patients with normal glucose tolerance than those who were pre-diabetic or diabetic at baseline.

QT prolongation in patients with acromegaly

The proportion of patients with notable ECG cardiac conduction intervals was comparable on pasireotide LAR and active control both in medically naïve and in inadequately controlled patients. Around 10-20% of patients had a QTcF >450 ms, less than 2% had QTcF >480 ms, and none had QTcF >500 ms. No trend towards prolongation of mean QTcF values over time was seen for either pasireotide LAR or active control. It should be noted that ECG monitoring in Study C2305 and C2402 included an ECG assessment 20 days after pasireotide LAR injection (i.e. time of maximum plasma concentration of pasireotide) to ensure that the maximal potential effect of pasireotide on cardiac conduction intervals was captured.

In Study C2305, QT-prolongation-related AEs were reported in 9.0% vs. 7.2% of patients on pasireotide LAR vs. octreotide LAR (Table 35). In Study C2402, no such events were reported, whereas in Study C2305 after crossover the incidence was 4.9% after crossover to pasireotide LAR and 0% after crossover to octreotide LAR (Table 36). Most of the events were grade 1-2, and led to discontinuation for one patient (a medically naïve patient with a grade 3 event on octreotide LAR in Study C2305).

There was no indication of an increased incidence in QT prolongation-related events with longer treatment (>1 year), either in Study C2305 or C2110/E.

Bradycardia

Bradycardia has been observed in human studies with pasireotide as well as octreotide and lanreotide, and is a recognized class effect of SSAs in humans. In medically naïve patients in Study C2305, a decrease in mean heart rate was seen based on ECG recordings within the first month of treatment, with mean values subsequently stabilizing at a rate approximately 10 bpm lower than at baseline on both pasireotide LAR and octreotide LAR. No such trend for heart rate was seen in Study C2402.

In Study C2305, the incidence of bradycardia (including the preferred terms bradycardia and sinus bradycardia) was 10.7% vs. 7.2% on pasireotide LAR vs. octreotide LAR; 9.0% vs. 5.6% of patients had events that were considered study drug related. In Study C2402, 1.6% of patients in each pasireotide LAR arm had such an event (none on active control), with no events considered related to study drug.

There was no indication of an increased incidence in bradycardia-related events with longer treatment (>1 year), either in Study C2305 or C2110/E. All events were grade 1-2.

Liver safety

Elevations in transaminases and cholelithiasis are known to occur with SSA treatment. A comprehensive analysis of liver safety was conducted across the pasireotide development program for studies in which the sc formulation was used. This included more than 650 healthy volunteers and more than 300 patients (acromegaly, Cushing's disease and carcinoid disease) in clinical studies and compassionate use programs. The analyses included laboratory results, AE reporting in clinical studies and in the Novartis ARGUS safety database, a literature review, and Modeling and Simulation analyses.

In the pasireotide development program 4 cases were identified with biochemical findings consistent with "Hy's Law", i.e. ALT/AST >3xULN, TB ≥ 2xULN, and ALP <2xULN, however, the temporal relationship (moderate, almost synchronous elevation of ALT/AST and TB with rapid normalization post discontinuation) is not consistent with the typical pattern (very high ALT/AST, followed by persistent TB elevations) of severe drug induced liver injury. Three of these cases occurred in healthy volunteers, none of which was symptomatic, and all resolved. The fourth case, a patient in a compassionate use program, was more consistent with hepatitis than obstruction.

No cases meeting the biochemical criteria for Hy's law have been observed with pasireotide LAR.

Liver safety in patients with acromegaly

In Study C2305 and C2402, liver safety-related AEs (predominantly increases in AST and/or ALT) were seen in around 10% of medically naive patients and in <6.2% of inadequately controlled patients, with comparable incidences on pasireotide LAR and active controls. The majority of events were grade 1-2 and resolved without intervention; 2 patients discontinued (both from Study C2305) due to elevation in transaminases. The elevations resolved for both patients after pasireotide LAR was discontinued.

No liver safety-related AEs were reported in Study C2110/E.

In medically naïve patients the incidence of abnormal serum transaminase values (ALT or AST >3xULN) was comparable on pasireotide LAR (5.1%) and octreotide LAR (3.3%). Among inadequately controlled patients one single patient in Study C2402 (a patient on pasireotide LAR 40 mg) had ALT >5xULN; this resolved after temporarily interrupting study drug. No such abnormalities were reported in Study C2305 after crossover. In Study C2110 no cases were reported in the core phase with pasireotide LAR treatment; one case during the extension resolved without intervention. There were no patients with biochemical findings compatible with Hy's law in Studies C2305, C2402 or C2110/E.

Gallbladder and related events

Somatostatin is known to decrease bile secretion and bile flow as a result of inhibition of biliary flow. Preclinical studies with pasireotide did not show any evidence of cholelithiasis in monkeys or mice, and no signs of cholestasis in rats. However, cholelithiasis is commonly reported in human studies with pasireotide as well as octreotide with long-term treatment. In the pasireotide development program, regular gallbladder ultrasound assessments are implemented to closely monitor the occurrence of gallbladder abnormalities.

Gallstones or sludge were frequently observed by gallbladder ultrasonography both on pasireotide LAR and active control. In Study C2305, a new or worsened abnormality was seen in approximately a third of patients on both pasireotide LAR and octreotide LAR. Similarly, in Study C2110E, approximately one-third of patients had a gallbladder result that was new or worsened from baseline. The proportion of patients with such abnormalities was lower in Study C2402 (15%-20% on all treatments), which may be expected due to the shorter follow-up in this study (6 months, compared to 12 or more months in studies C2305 and C2110E).

Data from studies C2305, C2402 and C2110E show that the frequency of cholelithiasis is comparable on pasireotide LAR and active control, and that the incidence increases over time. In Study C2305 cholelithiasis was seen in 30-40% of medically naïve patients; in Study C2402 the incidence was lower at 10%-14%, as expected due to the shorter follow-up. While cholelithiasis was asymptomatic in most patients, an increase in the number of patients who underwent cholecystectomy after a year of treatment was seen in Study C2305. The emerging long-term data indicates that as for other SSAs, the incidence of cholelithiasis, and the number of patients who require surgery, increases over time.

Pituitary hormone function

As somatostatin suppresses the secretion of pituitary hormones, patients with acromegaly that are treated with SSAs may experience deficiencies in one or more pituitary hormones. Furthermore, patients may have impaired pituitary function at baseline due to prior pituitary surgery or radiation therapy.

ACTH and hypocortisolism

There was no relevant difference in ACTH or cortisol levels between pasireotide LAR and active controls in Studies C2305 and C2402, and no clinically relevant reductions in ACTH or cortisol were seen in these studies or in Study C2110E.

Few patients had hypocortisolism-related AEs. In medically naïve patients in Study C2305, such AEs were reported (pasireotide LAR vs. octreotide LAR) in 3.4% vs. 2.8% of patients. In addition, hypocortisolism was reported as an AE in 2 inadequately controlled patients receiving pasireotide LAR (one in Study C2402 and one in Study C2305 after crossover). Most events were grade 1-2, however 2 medically naïve patients had grade 3-4 events (one on pasireotide LAR and one on octreotide LAR). Some of these patients had abnormal ACTH or cortisol values at baseline (including one patient with Cushing's syndrome and elevated ACTH at baseline). All cases resolved, some of them in response to concomitant therapy. No hypocortisolism-related AEs were seen in Study C2110 or Study B2201.

Hypothyroidism

There was no relevant difference in TSH and free T4 levels between pasireotide LAR and active controls in Studies C2305 and C2402, and no clinically relevant changes in hormone levels were seen in these studies. Hypothyroidism-related AEs were reported in <10% of patients in Study C2305, with similar incidences for pasireotide LAR and octreotide LAR (<10% of patients); none of the AEs were grade 3-4. No AEs related to

abnormal thyroid function were reported in Study C2402 or Study C2110/E; in Study B2201/E one case of hypothyroidism and one case of hyperthyroidism was reported.

Safety in special populations
Special populations

The inclusion criteria in all studies in the pasireotide clinical development program specify a minimum age of at least 18 years. Patients with acromegaly due to other causes than a pituitary adenoma were also excluded, and these criteria are in line with the proposed label. To ensure patient safety, patients with certain co-morbidities were excluded from clinical studies, and these are appropriately reflected in the proposed label.

Patients with renal impairment

Clinical studies have not been performed in patients with impaired renal function. Renal clearance of pasireotide represents a small fraction (~14%) of its total elimination from the body; this was verified by results from pasireotide sc (Study B2112) and supported by similar findings from animal studies. A common dose for the different subgroups of renally impaired patients is suggested.

No specific safety analysis with respect to renal function was presented.

Patients with hepatic impairment

Pasireotide is eliminated mainly via hepatic clearance. The results from the hepatic impairment study (Study B2114) with pasireotide sc were used for bridging to the LAR formulation. These results indicate that no dose adjustment is needed for patients with mild hepatic impairment. The maximum dose for patients with moderate hepatic impairment is 40 mg every 28 days with a starting dose of 20 mg.

Elevations of liver enzymes and TB were observed in pasireotide sc studies. As a precautionary measure, patients with acromegaly and severe hepatic impairment should not be treated with pasireotide LAR.

Sub-groups of the study population

In Study C2305 AEs and shifts in FPG/HbA1c ADA categories were evaluated according to demographic subgroups of gender, race (Caucasian, Asian, other), and age group (<65 years and ≥ 65 years).

An overview of AEs by demographic subgroups is presented in Table 37. No marked differences were seen between subgroups in terms of overall severity of AEs, or discontinuations due to AEs, in these analyses. Evaluation of shifts in FPG/HbA1c or incidences in individual preferred terms revealed no major differences for race or age group.

Based on population mixed-effect modelling, gender was found to be a significant covariate for steady-state trough concentrations of pasireotide LAR, with female patients having approximately 30% higher pasireotide concentrations than male patients after adjusting for bodyweight and GGT level. Whether this translates into a higher safety risk for females than males is uncertain, as the 30% difference in concentrations lies within inter- and intra-patient PK variability. Evaluating gender differences for special safety risks could not lead to a firm conclusion because the studies were not powered to demonstrate such gender differences; however females may be at a slightly higher risk of developing hyperglycaemia than males, as highlighted from the PK-pop further analysis.

Table 37 AEs by grade and by subgroup for gender, age and race up to crossover in medically naïve patients - Study C2305 up to crossover (SAS)

	Pasireotide LAR N=178 n (%)			Octreotide LAR N=180 n (%)		
All patients	**172 (96.6)**			**165 (91.7)**		
Gender	Male	Female		Male	Female	
Any grade	85/86 (98.8)	87/92 (94.6)		79/86 (91.9)	86/94 (91.5)	
Grade 1	19 (22.1)	13 (14.1)		28 (32.6)	20 (21.3)	
Grade 2	35 (40.7)	42 (45.7)		38 (44.2)	33 (35.1)	
Grade 3	25 (29.1)	27 (29.3)		11 (12.8)	29 (30.9)	
Grade 4	6 (7.0)	5 (5.4)		2 (2.3)	4 (4.3)	
AE leading to discontinuation	8 (9.3)	8 (8.7)		5 (5.8)	4 (4.3)	
Age	<65 years	≥65 years		<65 years	≥65 years	
Any grade	164/170 (96.5)	8/8 (100.0)		151/165 (91.5)	14/15 (93.3)	
Grade 1	31 (18.2)	1 (12.5)		42 (25.5)	6 (40.0)	
Grade 2	75 (44.1)	2 (25.0)		67 (40.6)	4 (26.7)	
Grade 3	50 (29.4)	2 (25.0)		36 (21.8)	4 (26.7)	
Grade 4	8 (4.7)	3 (37.5)		6 (3.6)	0	
AE leading to discontinuation	13 (7.6)	3 (37.5)		9 (5.5)	0	
Race	Caucasian	Asian	Other	Caucasian	Asian	Other
Any grade	103/107 (96.3)	38/39 (97.4)	31/32 (96.9)	98/109 (89.9)	39/43 (90.7)	28/28 (100.0)
Grade 1	25 (23.4)	4 (10.3)	3 (9.4)	28 (25.7)	18 (41.9)	2 (7.1)
Grade 2	42 (39.3)	20 (51.3)	15 (46.9)	42 (38.5)	16 (37.2)	13 (46.4)
Grade 3	30 (28.0)	13 (33.3)	9 (28.1)	25 (22.9)	4 (9.3)	11 (39.3)
Grade 4	6 (5.6)	1 (2.6)	4 (12.5)	3 (2.8)	1 (2.3)	2 (7.1)
AE leading to discontinuation	9 (8.4)	3 (7.7)	4 (12.5)	5 (4.6)	3 (7.0)	1 (3.6)

Immunological events

Anti-pasireotide antibodies were detected in rat studies. However, based on the sustained pharmacologic effects observed, these antibodies do not appear to have a neutralizing effect on pasireotide.

No clinical samples have been collected to evaluate immunogenicity of pasireotide.

Safety related to drug-drug interactions and other interactions

Pasireotide has moderate protein binding and is metabolically highly stable.

The potential for drug to drug interaction (DDI) of pasireotide and P-gp inhibitors has been tested in healthy male subjects in Study B2127. The purpose of the study was to investigate the potential drug-drug interaction

when pasireotide sc is used in combination with oral verapamil, a known P-gp inhibitor. There was no change in the rate or extent of pasireotide availability with co-administration of verapamil. No new safety concerns were identified during the study when pasireotide sc was administered alone or in combination with verapamil sustained release.

In addition, based on in vitro studies at therapeutic dose levels, pasireotide is not expected to be:

- a substrate, inhibitor or inducer of CYP450 (cytochrome P450);
- a substrate of the efflux transporter BCRP (breast cancer resistance protein) nor of the influx transporters OCT1 (organic cation transporter 1) and OATP (organic anion-transporting polypeptide) 1B1, 1B3 or 2B1;
- an inhibitor of UGT1A1 (uridine diphosphate glucuronosyltransferase 1A1), influx transporter OATP 1B1 or 1B3, OAT1 or OAT3 (organic anion transporter), OCT1 or OCT2, efflux transporter P-gp, BCRP, MRP2 (multi-drug resistance protein 2) or BSEP (bile salt export pump).

Based on all these in vitro data, the potential for protein binding, metabolism and/or transporter mediated DDI is low between pasireotide and co-medications in vivo.

Caution is required when co-administering pasireotide LAR with anti-arrhythmic medicines and other drugs that may prolong the QT interval.

Discontinuation due to adverse events

The discontinuation rate in medically naïve patients was slightly higher in the pasireotide LAR group (9.0%) than the octreotide LAR group (5.0%: Table 35). The difference is primarily due to hyperglycaemia-related events (6 patients [3.4%] on pasireotide LAR (5 with grade 3-4 AE) and 3 patients [1.7%] on octreotide LAR (1 with a grade 3-4 AE)), and AEs related to liver safety (2 patients [1.1%] on pasireotide LAR (both grade 1-2 AEs), none on octreotide LAR. Two of the patients who discontinued due to a hyperglycaemia-related event had a grade 4 event; these were also SAEs.

In inadequately controlled patients, AEs leading to discontinuation only occurred on pasireotide LAR treatment (Table 36). In Study C2402, 6 of the 7 patients who discontinued did so due to a hyperglycaemia-related event. None of these events were serious, and all were grade 2 or 3. The seventh patient discontinued due to an unrelated event of colon cancer. In Study C2305, 16.0% of patients who crossed to pasireotide LAR discontinued treatment; all except one case was due to hyperglycaemia-related AEs.. None of the patients who crossed to octreotide LAR discontinued due to AE.

AEs leading to discontinuation in the supportive acromegaly studies were rare and consistent with those seen in the Phase 3 studies, and included discontinuations due to hyperglycaemia-related events.

2.6.1. Discussion on clinical safety

The safety profile is mainly based on two studies including a total of 556 patients of which 241 have been treated with pasireotide LAR. Data for up to 2 years of treatment has been provided for 55 patients. Considering that acromegaly is a rare disease, the safety population is considered sufficient both with regards to the number of subjects exposed and the duration of exposure.

The safety profile of pasireotide appears comparable to that of octreotide. However, hyperglycaemia related events occurred with higher frequency in the pasireotide treated group. In addition, more high-grade events were observed with pasireotide, again mainly hyperglycaemia related events.

Apart from hyperglycaemia AEs, no gross differences were observed in the pasireotide safety profile between medically naïve patients and patients inadequately controlled with regards to common adverse events. High-grade hyperglycaemia related events were more common in the pasireotide treated groups also in this population. Some AEs occurred at a lower frequency in the population experienced with somatostatin analogue treatment, i.e. alopecia. However, although frequencies may differ somewhat between experienced and medically naïve populations there appears to be no qualitative differences between groups.

All AEs reported in the pasireotide sc studies and HV studies were as expected. No new safety concerns arise from this reporting.

With the exception of hyperglycaemia related events which were much more common in the medically naïve pasireotide treated group and a slightly lower reporting of gastrointestinal and hepatobiliary events in the pasireotide treated group; the reporting of drug-related AEs was very similar in the two groups. As in medically naïve patients, hyperglycaemia related events were more common in the inadequately controlled patients on pasireotide. In contrast to the observation in the medically naïve patients, an increased reporting of GI events was observed in these patients indicating a somewhat different effect of pasireotide in patients already shown tolerant to other somatostatin analogues.

Considering that there appear to be no qualitative differences between the AEs reported by experienced or medically naïve patients, a pooled analysis of all common adverse events and drug related events for studies C2305 and C2402 was provided. This analysis is the basis for the presentation of the AEs in the SmPC.

SAEs were rather few also in the long-term study. The predominant SAEs in both groups (medically naïve and inadequately controlled) were related to gallbladder function and hyperglycaemia. No new safety concerns arise. None of the four deaths were assessed as related to study medication. This is endorsed.

With regards to adverse events of special interest, no gross differences were observed between pasireotide and octreotide treatments, except for hyperglycaemia and diabetes. The frequencies differed slightly between medically naïve patients and those experienced with somatostatin analogue treatment. This may reflect a selection of patients in the experienced population as well as the fact that some AEs become less common with prolonged treatment.

Concerning laboratory findings, slight decreases in hemoglobin and WBC were observed in the studies. This is in line with the known pharmacodynamic effects of somatostatin and its analogues. Most of the events were of grade 1-2. No changes in coagulation parameters were observed; however, patients with known coagulation abnormalities were excluded from the studies due to a weak signal in the non-clinical studies. A warning regarding this lack of information has been included in section 4.4 of the SmPC taking into account that pasireotide LAR is administered as a deep intramuscular injection.

The most prominent findings with regards to clinical chemistry were hyperglycaemia and increases in transaminases. High grade hyperglycaemia events were frequently observed and more common than with octreotide. Increases in liver tests were usually grade 1-2 and no cases fulfilling Hy's law were observed. As expected, no clinically relevant observations were made with regards to urinary analyses.

With regards to vital signs, Bradycardia was commonly observed in both pasireotide and octreotide treated patients in line with the known effect of somatostatin analogues. Weight decrease was more common in the

pasireotide treated groups. The Applicant proposes that this may be due to the decrease in IGF-1 levels but an effect of gastrointestinal adverse events cannot be excluded.

An analysis of adverse events of special interest was provided. Hyperglycaemia related AEs were clearly more common and more severe in patients treated with pasireotide compared to active comparators. The frequency and severity was related to the degree of metabolic impairment at baseline. Most of the events occurred within 3 months after initiation of therapy. When FPG and HbA1c was analysed over time there was a rather steep increase in both parameters over the first three months after which values slowly decreased although stayed well above the baseline level. The decrease is assumed to reflect the response to anti-diabetic treatment. This was confirmed by further analyses of patients in whom anti-diabetic treatment was started. The proportion of patients without anti diabetic treatment at baseline and who started such treatment during the study was 36% with pasireotide LAR and 4.4% with octreotide LAR.

With the responses to the Day 120 LoQ, the Applicant has provided an analysis of the different types of anti-diabetic treatments used at baseline and during the study. Although the data presented should be interpreted with caution due to the low numbers it shows that standard oral anti-diabetic treatment was sufficient to control the pasireotide-induced hyperglycaemia and rather few patients were in need of insulin treatment. The recommendations given in the SmPC are supported by the data provided.

Cross-over data from the extension show that the hyperglycaemia is reversible. Hyperglycaemia was less prominent in responders. This may be explained by the fact that lowering of GH levels may decrease insulin resistance. When results were analysed by diabetic status, a somewhat lower response was observed in patients with diabetes compared to patients with normal glucose tolerance at baseline, however this effect did not differ between treatment groups. The risk of hyperglycaemia and recommendations on monitoring and treatment are included in the SmPC. Further to this, as recommended during the assessment of the MAA for the sc formulation, a study with the aim of investigating the treatment of pasireotide-induced hyperglycaemia in patients with Cushing's disease or acromegaly is planned. The final results are expected to be available in Q2 of 2018. Considering that study C2305 and C2402 has provided reassuring data showing that pasireotide-induced hyperglycaemia may be adequately handled applying standard diabetes treatment algorithms, this is acceptable. The study has been included in the RMP.

Of note, even in diabetic patients on anti-diabetic treatments, long-term microvascular complications, such as diabetic nephropathy, neuropathy and retinopathy and macrovascular complications cannot be excluded. These complications represent major causes of morbidity and mortality for patients.

A slight trend towards a higher reporting of QT-prolongation-related AEs in the pasireotide treated groups was observed. No arrhythmia events reported. The risk of QT-prolongation is reflected in the SmPC. A slightly higher reporting of bradycardia was also observed in pasireotide treated patients. The risk of bradycardia is reflected in the SmPC. This risk is included as an identified risk in the RMP.

Concerning liver safety, cases fulfilling Hy's law have been reported in the pasireotide development program; however no cases have been reported for pasireotide LAR. In studies 2305 and 2402 elevations of liver enzymes were reported in < 10 % of patients and most events were of grade 1-2; however 2 patients discontinued due to elevation of transaminases. The risk of elevated liver tests is reflected in the SmPC.

Formation of gallstones or sludge is a well-known AE occurring with somatostatin analogue treatment. Gallbladder related events occurred at comparable frequencies for both pasireotide and octreotide. The SmPC contains recommendations on monitoring of gallbladder related events.

Although no relevant ACTH or cortisol suppression was noted in the pasireotide LAR program, hypocortisolism related events were reported. Both grade 1-2 and grade 3-4 events were reported. In some of the cases specific therapy was needed. Warnings regarding the risk of hypocortisolism and recommendations on monitoring are included in the SmPC.

Although no clinically relevant changes in TSH and free T4 levels were observed in the studies, hypothyroidism related events were reported in < 10 % of patients in both treatment groups. Warnings and recommendations on monitoring are included in the SmPC.

No studies have been conducted in special populations; instead treatment recommendations are based on PK data. Considering that acromegaly is a rare disease, this is acceptable.

Regarding hepatic impairment, elevations of liver enzymes and TB were observed in pasireotide sc studies. As a precautionary measure, patients with acromegaly and severe hepatic impairment should not be treated with pasireotide LAR. Based on pharmacokinetic data from the hepatic impairment study (Study B2114) with pasireotide sc, doses for mild and moderate hepatic impairment was established. No dose adjustment is needed for patients with mild hepatic impairment and the maximum dose for patients with moderate hepatic impairment is 40 mg every 28 days, with a starting dose of 20 mg. The applicant´s bridging of PK data from pasireotide sc to the LAR formulation is acceptable.

Given the elevations of liver enzymes associated with pasireotide and as efficacy and safety data in patients with moderate hepatic impairment treated with 20 mg of pasireotide LAR are lacking, it is recommended that the use of the proposed dose (20 mg pasireotide LAR) in patients with hepatic impairment is included as part of the missing information "Patients with liver disease" in the RMP and consequently monitored within future PSURs.

A clinical study in subjects with impaired renal function is ongoing. As renal clearance of pasireotide represents a small fraction (~14%) of its total elimination from the body, mild and moderate renal impairment is not expected to significantly impact the circulating levels of pasireotide. It cannot be excluded that systemic exposure is increased in severe renal impairment. A dedicated study (B2126) in patients with renal impairment (mild, moderate, severe and end stage renal disease) is ongoing.

Subgroup analysis of the AE pattern due to gender, age or ethnicity did not reveal any relevant differences. Grade 4 AEs were more common in patients above the age of 65, however the number of patients was very low and therefore no firm conclusions can be drawn. Exposure is higher in females than males and this is highlighted in SmPC section 5.2 *Pharmacokinetic properties*, sub section *Special population*.

No analysis on immunological events or research on antigenicity has been conducted in humans. However, no hypersensitivity reactions were reported in the studies and injection site reactions were reported in about 8 % of medically naïve subjects and in < 3 % of experienced patients. This reporting rate is lower than for the sc formulation. Allergic reactions/immunogenicity is included as an important potential risk in the RMP.

No new safety concerns regarding drug-interactions arise from the newly submitted data. The potential drug-drug interactions are adequately reflected in the SmPC.

Discontinuations due to AEs were higher in the pasireotide treated groups and the predominant AE leading to discontinuation was hyperglycaemia.

The safety data submitted with the PSURs for Signifor in the Cushing disease (sc administration schema) has not revealed any new safety concerns. As pointed out, post-marketing experience is still very limited.

In the clinical studies, long-acting pasireotide as well as long-acting octreotide was introduced in medically naïve patients without testing the patient's tolerance to somatostatin analogues. Considering the low drop-out rates

this strategy appeared feasible. Data presented from studies with both short-acting pasireotide and short-acting octreotide support that starting with a short-acting agent can neither alleviate gastrointestinal nor hyperglycaemic adverse events

2.6.2. Conclusions on the clinical safety

With the exception of hyperglycaemia which was more common in the pasireotide LAR treated groups and occurred with higher severity, but can be managed with glucose-lowering therapy, the safety profile is comparable to that of octreotide and lanreotide. The overall safety profile was therefore found to be acceptable by CHMP. .

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

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

2.8. Risk Management Plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 4.1 is acceptable. In addition, minor revisions were recommended to be taken into account with the next RMP update. The PRAC endorsed PRAC Rapporteur assessment report is attached.

The CHMP endorsed this advice with one minor change:

It is recommended that the use of the proposed dose (20 mg pasireotide LAR) in patients with hepatic impairment is included as part of the missing information "Patients with liver disease" in the RMP and consequently monitored within future PSURs. Such revision can be submitted with the next update of the RMP.

Safety concerns

Table 1: Summary of the 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
	Elderly patients
	Patients with cardiac diseases (such as unstable angina, congestive heart failure, recent myocardial infarction or clinically significant bradycardia)
	Children and adolescents (patients < 18 years)
	Patients with liver diseases
	Long-term safety in patients
*only applicable for Cushing's disease	

Pharmacovigilance plan

Table 2: on-going and planned studies in the Post-authorisation Pharmacovigilance Development 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)
CSOM230B2410 (non-interventional, 3)	Non-interventional study for the generation of long term safety and efficacy data of pasireotide sc 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.
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	Planned start Q2 2014	Study report planned to be submitted by Q2 2018.

Risk minimisation measures

Table 4: Proposal from MAH for risk minimisation measures (copy from V.3 of RMP)

Safety concern	Routine risk minimization measures	Additional risk minimization measures
Identified Risks		
Hypocortisolism/ Cortisol withdrawal syndrome	This item is appropriately communicated through current labeling: Cushing's and Acromegaly SPC Section 4.4 Special warnings and precautions for use. Relevant preferred terms are included as ADRs in Cushing's SPC Section 4.8 Undesirable effects.	None
Hyperglycemia	This item is appropriately communicated through current labeling: Cushing's and Acromegaly SPC Section 4.4 Special warnings and precautions for use. Cushing's and Acromegaly SPC section 4.5 Interaction with other medicinal products and other forms of interaction. Relevant preferred terms are included as ADRs in Cushing's SPC Section 4.8 Undesirable effects.	None
Bradycardia	This item is appropriately communicated through current labeling: Cushing's and Acromegaly SPC Section 4.4 Special warnings and precautions for use, section 4.5 Interaction with other medicinal products and other forms of interaction. Relevant preferred terms are included as ADRs in	None

Safety concern	Routine risk minimization measures	Additional risk minimization measures
	Cushing's and Acromegaly SPC Section 4.8 Undesirable effects.	
QTc interval prolongation	This item is appropriately communicated through current labeling: Cushing's and Acromegaly SPC Section 4.4 Special warnings and precautions for use, Section 4.5 Interaction with other medicinal products and other forms of interaction. Relevant preferred terms are included as ADRs in Cushing's and Acromegaly SPC Section 4.8 Undesirable effects.	None
Cholelithiasis	This item is appropriately communicated through current labeling: Cushing's and Acromegaly SPC Section 4.4 Special warnings and precautions for use. Relevant preferred terms are included as ADRs in Cushing's and Acromegaly SPC Section 4.8 Undesirable effects.	None
Hematological abnormalities	This item is appropriately communicated through current labeling: Relevant preferred terms are included as ADRs in Cushing's and Acromegaly SPC Section 4.8 Undesirable effects.	None
Liver enzymes increased	This item is appropriately communicated through current labeling: Cushing's and Acromegaly SPC Section 4.4 Special warnings and precautions for use. Relevant preferred terms are included as ADRs in SPC Section 4.8 Undesirable effects.	None
Injection site reactions	This item is appropriately communicated through current labeling: Cushing's and Acromegaly SPC Section 4.2 Posology and method of administration Relevant preferred terms are included as ADRs in Cushing's and Acromegaly SPC Section 4.8 Undesirable effects.	None
Gastrointestinal disorders	This item is appropriately communicated through current labeling: Relevant preferred terms are included as ADRs in Cushing's and Acromegaly SPC Section 4.8 Undesirable effects.	None
Potential risks		
Clinically significant GH/IGF-I Decrease*	This item is communicated through current labeling: Cushing's SPC Section 4.4 Special warnings and precautions for use.	None
Hypothyroidism	This item is appropriately communicated through current	None

Safety concern	Routine risk minimization measures	Additional risk minimization measures
	labeling: Cushing's and Acromegaly SPC Section 4.4 Special warnings and precautions for use.	
Pancreatitis	This item is appropriately communicated through current labeling: Relevant preferred terms are included as ADRs in Cushing's and Acromegaly SPC Section 4.8 Undesirable effects.	None
Coagulation abnormalities	This item is appropriately communicated through current labeling: **Cushing's disease:** SPC Relevant preferred terms are included as ADRs in SPC Section 4.8 Undesirable effects. **Acromegaly:** Currently available data do not support the need for risk minimization.	None
Hypotension	This item is appropriately communicated through current labeling: **Cushing's disease:** SPC Relevant preferred terms are included as ADRs in SPC Section 4.8 Undesirable effects. **Acromegaly:** Currently available data do not support the need for risk minimization.	None
Hypocalcemia	Risk minimization is not needed. 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	Risk minimization is not needed. 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	This item is appropriately communicated through current labeling: Relevant preferred terms are included as ADRs in Cushing's and Acromegaly SPC Section 4.5 Interaction with other medicinal products and other forms of interaction.	None

Safety concern	Routine risk minimization measures	Additional risk minimization measures
Off-label use in children and other indications	This item is appropriately communicated through current labeling: Cushing's and Acromegaly SPC section 4.2 Posology and method of administration, 5.2 Pharmacokinetic properties	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 for risk minimization.	None
Missing Information		
Pregnancy and Breast-feeding	This item is appropriately communicated through current labeling: Cushing's and Acromegaly SPC Section 4.6 Fertility, pregnancy and lactation, and 5.3 Preclinical safety data.	None
Elderly patients	This item is appropriately communicated through current labeling: Cushing's and Acromegaly SPC Section 4.2 Posology and method of administration, and 5.2 Pharmacokinetic properties.	None
Patients with cardiac diseases	This item is appropriately communicated through current labeling: Cushing's and Acromegaly SPC Section 4.4 Special Warnings and precautions for use, 4.8 Undesirable effects, and 4.5 Interaction with other medicinal products and other forms of interaction.	None
Children and adolescents (patients < 18 years)	This item is appropriately communicated through current labeling: Cushing's and Acromegaly SPC section 4.2 Posology and method of administration. Section 5.2 Pharmacokinetic properties	None
Patients with liver disease	This item is appropriately communicated through current labeling: Cushing's and Acromegaly SPC Section 4.2 Posology and method of administration, 4.3 Contraindications and 5.2 Pharmacokinetic properties	None
Long-term safety in patients	Currently available data do not support the need for risk minimization.	None
* only applicable for Cushing's disease		

2.9. Product information

2.9.1. User consultation

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

3. Benefit-Risk Balance

Benefits

This application concerns a long-acting formulation of pasireotide (Signifor) intended for the treatment of patients with acromegaly. The treatment is to be administered as monthly intramuscular injections. A short-acting formulation of pasireotide (Signifor) for the treatment of patients with Cushing's disease was approved in April 2012.

Beneficial effects

The effect of pasireotide has been evaluated in two large and well-conducted clinical trials. The studies investigated two different populations. In the largest study (2305), which included 358 patients, the effect of pasireotide LAR was compared to the effect of octreotide LAR in medically naïve patients. Both patients who had undergone surgery (42 %) and de novo patients were included. Data up to 2 years of treatment has been provided. The smaller study (2402) included 198 patients inadequately controlled on maximal doses of either octreotide LAR or lanreotide ATG. This study investigated two different doses of pasireotide LAR, 40 mg and 60 mg once monthly.

In medically naïve patients, superiority of pasireotide LAR to octreotide LAR was investigated. The primary endpoint was response to therapy with responders having to achieve lowering of both GH and IGF-1. The study met its primary endpoint showing that the number of responders with pasireotide LAR (31 %) was significantly higher than for octreotide LAR (19 %; OR 1.94 (1.19, 3.17)). The primary analysis was consistently supported by the sensitivity analyses performed, thus the data appear robust. Response rates in patients that had undergone surgery were higher for both treatments and the overall outcome was mainly driven by this group. A slightly higher proportion in the pasireotide treated group "over-responded", i.e. GH decreased to <2.5 µg/L and IGF-1 <LLN.

The proportion of patients with GH response did not differ between treatment groups at Month 12 (48 % vs 52 % for pasireotide and octreotide respectively). The difference in GH response was less prominent between post surgery and de novo patients. As shown by the separate analyses for GH and IGF-1 response, the outcome of the primary endpoint was mainly driven by a higher response with regards to IGF-1 with pasireotide LAR (39 %) compared to octreotide LAR (24 %). The difference in IGF-1 response was more prominent between post surgery and de novo patients.

Data from the extension phase show that the rate of responders decreased somewhat over time, however, responder rates were consistently higher in the pasireotide treated group (24 % vs 14 % at Month 25 for pasireotide and octreotide respectively; OR 2.1 (1.14, 3.7)).

Symptoms of acromegaly improved in both treatment groups with no significant differences observed. Improvements with regards to Quality of Life were observed in both groups.

In patients inadequately controlled on other somatostatin analogues, 6 months treatment with pasireotide LAR resulted in 15.4 % and 20 % responders with the 40 mg and 60 mg dose respectively, whereas no responders were observed in the active control group. Thus the study met its primary endpoint and the outcome was confirmed by the sensitivity analyses.

The proportion of patients with normalised IGF-1 was significantly higher in the pasireotide treated groups with a less pronounced difference between the two doses (26 % vs 25 % for the 40 mg and 60 mg dose groups respectively). No responders were observed in the control group.

The proportion of patients responding with regards to GH was significantly higher for both doses of pasireotide (35 % vs 43 % for the 40 mg and 60 mg dose groups respectively) compared to active control (13 %). A dose response effect was observed with a higher response rate in the pasireotide 60 mg group.

The outcome in patients that crossed-over from octreotide to pasireotide and vice versa in study 2305 was also provided. This dataset provides supportive data in patients inadequately controlled with octreotide LAR or pasireotide LAR. Notably, a larger proportion of patients responded in the group that crossed-over from octreotide to pasireotide (17 %) than in the group that crossed over from pasireotide, where no responders were observed after 12 months of treatment.

Both studies investigated the effect of pasireotide LAR on tumour size as part of the secondary endpoints. In medically naïve patients, both treatments showed comparable effects on tumour volume with a mean percent reduction of 38-39.7 %. The proportion of patients that achieved at least 20 % reduction was also comparable between treatments (75 % for pasireotide LAR vs. 72 % for octreotide LAR). In patients inadequately controlled, a reduction in tumour volume was observed in all treatment groups with no apparent difference between the two doses of pasireotide. A difference between pasireotide group and control group was however observed.

Uncertainty in the knowledge about the beneficial effects

A new cut-off limit of GH to assess the efficacy of a treatment in acromegaly has been defined in a recent consensus paper (Giustina 2010) after the pivotal studies with pasireotide were initiated. Based on this new definition, a response was associated with "*reduction of GH levels < 1 µg/L and normalization of IGF-1 levels",* instead of "*reduction of GH levels < 2.5 ug/L and normalisation of IGF-1*". Further to the day 120 LoQ, the Applicant provided post-hoc analysis regarding proportion of responders taking into account this "new" cut-off level. Results have to be interpreted with caution (post-hoc approach). A trend to a better efficacy of pasireotide LAR in uncontrolled patients was revealed from these results.

The long-term effect of treatment in patients inadequately controlled on other somatostatin analogues is still lacking. This far, only interim 12 month data from extension phase of study C2402 has been provided. These results, however, indicate that the effect of pasireotide is maintained over time also in this population.

Although not formally investigated in the pivotal studies, relevant and sufficient data have been presented to support the use of the 20 mg dose in patients over-responding to the 40 mg dose, as well as temporarily for tolerability reasons. Adequate recommendations on the use of the 20 mg dose are given in section 4.2 of the SmPC.

Risks

Unfavourable effects

The safety profile is mainly based on two studies including a total of 556 patients of which 241 have been treated with pasireotide LAR. Data for up to 2 years of treatment has been provided for 55 patients. Considering that

acromegaly is a rare disease, the safety population is considered sufficient with regards to the number of subjects exposed. Furthermore, there is long experience with other somatostatin analogues. With this submission, comparative data has become available and the safety profile of pasireotide was compared to alternative treatments (octreotide and lanreotide). More high-grade events were observed with pasireotide, mainly hyperglycaemia related events.

No gross differences were observed in the pasireotide safety profile between medically naïve patients and patients inadequately controlled with regards to common adverse events. The only relevant difference between medically naïve patients and patients experienced with treatment was a lower reporting of drug-related gastrointestinal events in the medically naïve patients compared to octreotide LAR whereas an increased reporting of GI events was observed in treatment experienced patients when switching to pasireotide, indicating a somewhat different effect of pasireotide in patients already shown tolerant to other somatostatin analogues.

SAEs were rather few also in the long-term study (20 % in the pasireotide treated group and 15 % in the octreotide treated group, medically naïve patients). The predominant SAEs in both groups (medically naïve and inadequately controlled) were related to gallbladder function and hyperglycaemia. None of the four deaths reported from the clinical trials were assessed as related to study medication. This is endorsed.

Concerning laboratory findings, slight decreases in haemoglobin and WBC were observed in the studies. Most of the events were of grade 1-2. The most prominent findings with regards to clinical chemistry were hyperglycaemia and increases in transaminases. High grade hyperglycaemia events were frequently observed and more common with pasireotide LAR than with octreotide LAR. Increases in liver tests were usually grade 1-2 and no cases fulfilling Hy's law were observed. As expected, no clinically relevant observations were made with regards to urinary analyses.

With regards to vital signs, bradycardia was commonly observed in both pasireotide (11 %) and octreotide (7 %) treated patients in line with the known effect of somatostatin analogues. Weight decrease was more common in the pasireotide treated groups.

The following adverse events of special interest were analysed – hyperglycaemia, QT-prolongation, liver safety including the formation of gallstones, effects on other pituitary hormones (i.e. ACTH, TSH). Except for hyperglycaemia, the reporting rates for these events with pasireotide LAR did not show any meaningful difference compared to octreotide LAR. Warnings and recommendations on monitoring of these events have been included in relevant sections in the SmPC. These recommendations are acceptable.

With the new comparative data provided with this application it is clear that pasireotide has a higher potential for inducing hyperglycaemia than octreotide. Hyperglycaemia related AEs were clearly more common and more severe in patients treated with pasireotide (64 %) compared to octreotide (25 %). The frequency and severity was related to the degree of metabolic impairment at baseline. Most of the events occurred within 3 months after initiation of therapy. When FPG and HbA1c was analysed over time there was a rather steep increase in both parameters over the first three months after which values slowly decreased although they stayed well above the baseline level. Analyses of patients in whom anti-diabetic treatment was started showed that these patients adequately responded to the anti-diabetic therapy.

Importantly, the proportion of patients without anti-diabetic treatment at baseline and who started such treatment during the study was 36% with pasireotide LAR and 4.4% with octreotide LAR.

No analysis on immunological events or research on antigenicity has been conducted in humans. However, no hypersensitivity reactions were reported in the studies and injection site reactions were reported in about 8 %

of medically naïve subjects and in < 3 % of experienced patients. This reporting rate is lower than for the sc formulation.

All important safety issues identified are addressed in relevant sections of the SmPC, and these issues are also already included in the pasireotide RMP.

Uncertainty in the knowledge about the unfavourable effects

Hyperglycaemia: AEs related to hyperglycaemia tended to occur in particular during the first 3 months of treatment with pasireotide, with attenuation or stabilization of the effect over time. However, it is not clear whether this attenuation is related to the use/adjustment of anti-diabetic medication or to the attenuation of the pasireotide effect on glucose metabolism. Of note the management of patients for hypoglycaemia in the clinical studies was not harmonised across all the sites/countries.

Also, the incidence of SAE related to hyperglycaemia was limited in the clinical studies with pasireotide. This can be related to the relatively small population size of patients in the phase 3 clinical studies. Taking into account that patients with acromegaly are likely to have comorbidities, in particular glucose metabolic disorders then worsening of their glycaemic parameters with pasireotide is expected. Therefore, the occurrence of serious events such as ketoacidosis or diabetic hyperglycaemic coma cannot be excluded.

There is still insufficient data on how to best treat pasireotide-induced hyperglycaemia. Data presented shows that standard oral anti-diabetic treatment was sufficient to control the pasireotide-induced hyperglycaemia and rather few patients were in need of insulin treatment. The recommendations given in the SmPC are supported by the data provided. Considering that study 2305 and 2402 has provided reassuring data showing that pasireotide-induced hyperglycaemia may be adequately handled applying standard diabetes treatment algorithms, this is acceptable. The planned study to investigate this issue has been included in the RMP.

Of note, even in diabetic patients on anti-diabetic treatments, long-term microvascular complications, such as diabetic nephropathy, neuropathy and retinopathy and macrovascular complications cannot be excluded. These complications represent major causes of morbidity and mortality for patients.

Liver safety: Elevations of liver enzymes were associated with SSA treatments and such elevations were observed with pasireotide. As a precautionary measure, pasireotide is therefore contraindicated in patients with severe hepatic impairment.

Based on pharmacokinetic data from the hepatic impairment study (Study B2114) with pasireotide sc, doses for mild and moderate hepatic impairment was established. No dose adjustment is needed for patients with mild hepatic impairment and the maximum dose for patients with moderate hepatic impairment is 40 mg every 28 days, with a starting dose of 20 mg.

Given the elevations of liver enzymes associated with pasireotide and as efficacy and safety data in patients with moderate hepatic impairment treated with 20 mg of pasireotide LAR are lacking, it is recommended that the use of the proposed dose (20 mg pasireotide LAR) in patients with hepatic impairment is included as part of the missing information "Patients with liver disease" in the RMP and consequently monitored within future PSURs.

Renal impairment: Clinical studies have not been performed in patients with impaired renal function. As renal clearance of pasireotide represents a small fraction (~14%) of its total elimination from the body, mild and moderate renal impairment is not expected to significantly impact the circulating levels of pasireotide. It cannot be excluded that systemic exposure is increased in severe renal impairment. A dedicated study (B2126) in patients with renal impairment (mild, moderate, severe and end stage renal disease) is ongoing.

In the clinical studies, long-acting pasireotide as well as long-acting octreotide was introduced in medically naïve patients without testing the patient's tolerance to somatostatin analogues. Considering the low discontinuation rates due to AEs (9 % vs 5 % in pasireotide LAR and octreotide LAR treated subjects respectively), this strategy appears feasible.

Balance

Importance of favourable and unfavourable effects

Although transphenoidal surgery is the most frequently recommended treatment in acromegaly, there is a need for medical treatment in patients where surgery has failed or when surgery is not an option.

The primary endpoint (percentage of responders defined as a reduction of GH level to < 2.5 µg/L and normalized IGF-1) was met in study C2305 and study C2402, thus pasireotide has been shown to be superior compared to octreotide. However, this superiority was obtained with the "old" cut-off of GH<2.5µg/l and this cut-off was revised by the Acromegaly Consensus Group to GH<1µg/l after the pivotal studies were initiated.

In medically naïve patients, no difference between treatments was observed with regards to the effect on tumour size reduction whereas a difference was observed in uncontrolled patients. However, the finding that a proportion of patients experienced an increase in tumour size (with all treatments) emphasizes the need for continuous monitoring.

The safety profile of pasireotide is generally comparable to that known for other somatostatin analogues with the exception of a greater risk for hyperglycaemia. Although manageable with appropriate treatments and reversible after treatment discontinuation, the extent of changes in glycaemic parameters was clearly higher with pasireotide LAR compared with octreotide LAR. Also, even in diabetic patients on anti-diabetic treatments, long-term microvascular complications, such as diabetic nephropathy, neuropathy and retinopathy and macrovascular complications cannot be excluded. These complications represent major causes of morbidity and mortality for patients. More knowledge is needed on the best treatment for pasireotide-induced hyperglycaemia; in the meantime the treatment recommendations included in the SmPC are acceptable.

Benefit-risk balance

Discussion on the benefit-risk assessment

The application is supported by two well-designed and well-conducted studies of considerable size (taking into account that acromegaly is a rare disease). Data provided support the use of pasireotide as an alternative in patients with acromegaly, especially in patients who have failed on other somatostatin analogue treatment (uncontrolled patients).

The risk of hyperglycaemia is clearly higher with pasireotide than with octreotide, but this risk is possible to monitor and data show that if hyperglycaemia occurs it can be managed with standard anti-diabetic treatment in the majority of cases.

However, inducing hyperglycaemia/diabetes in medically naïve patients is not acceptable. Indeed efficacy with regard to GH and IGF-1 might be obtained in these patients with alternative treatments associated to a moderate risk of hyperglycaemia/diabetes. Thus, the benefit-risk balance of pasireotide LAR was found to be not

favourable in the group of medically naïve patients. The approved indication was therefore restricted to patients inadequately controlled with other treatments.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Pasireotide 20mg, 40mg, 60 mg, powder and solvent for suspension for injection in the treatment of Acromegaly is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and 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.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.