SCIENTIFIC DISCUSSION

This module reflects the initial scientific discussion for the approval of SOMAVERT. For information on changes after approval please refer to module 8.

1. Introduction

Pegvisomant, the active substance in Somavert, is a pegylated recombinant analogue of the human growth hormone (GH) which has been genetically engineered to function as a GH receptor antagonist.

Somavert is indicated for the treatment of patients with acromegaly who have had an inadequate response to surgery and/or radiation therapy and in whom an appropriate medical treatment with somatostatin analogues did not normalize IGF-I concentrations or was not tolerated.

The disease

Acromegaly is a rare debilitating endocrine disease characterised by hypersecretion of growth hormone (GH), occurring almost exclusively as a result of a benign pituitary adenoma. Most pituitary tumours arise spontaneously and are not genetically inherited, occurring from a genetic alteration in a single pituitary cell which leads to increased cell division and tumour formation. This mutation is not present at birth but is acquired during life. The mutation occurs in a gene that regulates the transmission of chemical signals with pituitary cells, permanently switching on the signal that tells the cells to divide and secrete GH.

Acromegaly most commonly affects middle-aged adults and can result in serious illness and premature death. Once recognised, acromegaly is treatable in most patients, but because of its slow and often insidious onset, it frequently is not diagnosed correctly.

Patients with acromegaly have significantly increased morbidity and mortality. The most frequent causes of death are cardiovascular, cerebrovascular and respiratory diseases, but significant increases in the death rate of acromegalic patients, due to both lung infections and malignancies, have been reported.

Studies have shown that acromegalic patients have a 2.45 –fold increased rate of malignant tumours over non-acromegalic patients. Up to 46% of acromegalic patients have been found to have colonic polyps which are frequently precursors of colon carcinoma. Other complications of acromegaly include acral enlargement, disfigurement, arthropathy, nerve entrapment, hypertension and cardiac disease. Cardiovascular complications of acromegaly, including hypertension, premature coronary artery disease, congestive heart failure and cardiac arrhythmia are major causes of morbidity and mortality in acromegaly. Left ventricular hypertrophy has adverse effects on cardiac function and also contributes to the mortality associated with the disease.

It is generally accepted that the clinical manifestations of acromegaly are mediated through elevations in serum IGF-I concentrations. The increased incidence of diabetes and glucose intolerance may be a direct effect of GH. The IGF-I peptide is formed through intracellular transduction when GH bridges GH-specific cell membrane receptors (receptor dimerization), and circulating IGF-I levels correlate with GH concentration.

In over 90 percent of acromegaly patients, the overproduction of GH is caused by a benign tumour of the pituitary gland, generally adenoma that produces excess GH and, as expands, compresses surrounding brain tissues, such as the optic nerves. This expansion causes the headaches and visual disturbances that are often symptoms of acromegaly.

In addition, compression of the surrounding normal pituitary tissue can alter production of other hormones, leading to changes in menstruation and breast discharge in women and impotence in men.

Current treatment

The treatment of first intention in acromegaly remains surgical tumor excision by transphenoïdial route. Radiotherapy can be given either as primary treatment or as an adjunct to surgery. Medical treatment is intended for patients with acromegaly not adequately treated by surgery, in patients in whom surgery is contraindicated or poses a high-risk, or for those patients waiting for radiotherapy to become effective. The currently available medical therapy is somatostatin analogues (i.e. octreotide, lanreotide, vapreotide) and dopamine agonists. Somatostatin analogues bind to somatostatin receptors

present on the tumour leading to inhibition of GH secretion and IGF-1 levels reduction. Dopamine agonists (e.g. bromocriptine and pergolide) bind to pituitary dopamine type2 (D2) receptors and suppress GH secretion in some patients with acromegaly.

Pegvisomant action

Treatment with Somavert is a new approach in medical therapy of acromegaly. Due to its molecular design, pegvisomant binds to growth hormone receptors on cell surfaces, where it blocks growth hormone binding, and thus interferes with intracellular growth hormone signal transduction.

The therapeutic objective of pegvisomant is to normalise IGF-1 serum concentrations (IGF-I levels correlate with disease activity and with GH levels) and to improve the systemic manifestation as well as metabolic disorder (diabetes and glucose intolerance) observed in acromegalic patients. All known GH effects, including any direct effects, are mediated via the GH receptor, which is blocked by pegvisomant. The action of a GH receptor antagonist is independent of the characteristics of the pituitary tumour. This is because it blocks the effect of excess GH at a cellular level, reducing the action of GH rather than inhibiting its secretion. The selectivity of pegvisomant for the GH receptor should reduce the risk of adverse effects mediated by stimulation or inhibition of other endocrine systems. Pegvisomant is highly selective for the GH receptor, and does not significantly bind to the prolactin receptor, despite the sequence homogeneity between GH and prolactin.

2. Part II: Chemical, pharmaceutical and biological aspects

Composition

The finished product is presented as a powder and solvent for solution for subcutaneous injection. It is supplied in three strengths: 10, 15, and 20 mg pegvisomant per vial. The lyophilised powder, presented in a glass vial, contains the following excipients: glycine, mannitol (E421), sodium phosphate dibasic anhydrous, and sodium phosphate monobasic monohydrate. Before use, each vial is to be reconstituted with 1 ml water for injections supplied in an 8 ml glass vial. The product does not contain ingredients of animal or human origin.

Active substance

Pegvisomant is a 40-50 kDa molecular variant of the human growth hormone (hGH) consisting of recombinant protein component and polyethylene glycol (PEG). The protein molecule (B2036) consists of 191 amino acids with two internal disulphide bonds obtained by expression in *E. coli* cells from which it is extracted and purified. The molecule is then further modified by covalent addition of polyethylene glycol (PEG) molecules resulting in a pegylated protein (B2036-PEG) with 4 and 5 PEG groups per B2036-PEG molecule. The purpose of pegylation of the protein component is to increase the half-life of the molecules. Pegvisomant has been designed to function as an antagonist of the hGH receptor (HGHR) by substitution of certain amino acids in the backbone of the protein hGH.

Development genetics and cell bank system

The production process of pegvisomant uses a transformed *E. coli* 33B6 host strain, comprehensively described in the application, containing an expression cassette coding for the human growth hormone analogue. After selection, one subclone was used to establish the Master Cell Bank (MCB). The methods used to establish the MCB have been well described and involved standard techniques used in DNA recombinant technology.

Characterisation studies of the various cell banks were carried out using classical tests. Cell banks were found to be free of microbial contamination and their viral safety has been adequately documented and is not a matter of concern.

The genetic stability has been demonstrated to be adequate for the consistent production of the active substance.

Production process

The unpegylated protein (B2036) is produced by fermentation, which has been adequately described in the application. The equipment and dedicated facilities as well as cleaning in place and sterilisation

procedures are satisfactorily documented. The composition of the various culture media (including the origin of the various components) used in the fermentation process have been adequately documented. The various relevant parameters recorded during each phase of the bioreactor cell culture process have been documented in detail. In-process controls assure appropriate cell growth and the absence of microbial contamination. The In-process specifications have defined acceptance criteria.

Cell harvest and the downstream purification process, consisting of a sequence of validated chromatography and ultrafiltration steps leading to the protein bulk solution, has been described in detail. The various in-process monitoring and control parameters have been presented in detail for each purification step.
Once the identity and purity of the purified protein have been verified by different chromatography methods, the protein is chemically modified by pegylation (i.e.covalent attachment of PEG molecules), which results in a heterogeneous product. The heterogeneity is reduced as far as possible by an appropriate downstream purification process.

The production process of the active substance, which complies with Good Manufacturing Practice (GMP) requirements takes place at Diosynth RTP, Inc. (USA). The manufacturing process of the active substance has been validated. The various critical steps of the production process, from the cell culture to purification and subsequent pegylation have been identified. Based on the results obtained regarding the upstream (cell culture) as well as the downstream (purification and pegylation) processes, the capacity, robustness and consistency of the production process are satisfactory and lead to an active substance bulk solution with a reproducible good quality.

Characterisation, routine tests and specifications of the active substance
The characterisation of pegvisomant has been performed to highlight the heterogeneity of the pegylated protein and to study the effect of the pegylation on the protein structure. A number of analytical tests have been used.

Routine tests are performed on both the pegvisomant intermediate bulk (unpegylated protein) and the pegvisomant formulated bulk (pegylated protein) for which specifications have been set. Results for several lots of the intermediate and formulated bulks have been presented.

The analytical methods and specifications for the release of the pegvisomant intermediate bulk and of the pegvisomant formulated bulk ensure consistent quality of pegvisomant with respect to identity, purity, potency, and safety. The tests selected to be performed on a routine basis are satisfactory; their proposed limits are also considered to be acceptable. The various methods used for quality control of pegvisomant have been described, justified, and validated for their analytical performances, and particularly in terms of accuracy, precision, limit of quantification, limit of detection, specificity, linearity/range and robustness. The proposed routine quality control test methods and specifications were selected in order to assess, on a routine basis, the identified key features of the active substance such as the biological activity

Based on the physico-chemical and biological characterisation data provided, it can be concluded that sensitive and quantitative tests have been developed and validated for identity, purity, and potency of the active substance.

Stability of active substance
Based on stability data for 5 batches, an acceptable shelf life for the active substance could be established.

Other ingredients
The active substance is formulated together with the following excipients: glycine, mannitol (E421), sodium phosphate dibasic anhydrous, and sodium phosphate monobasic monohydrate. The finished product is presented in glass vials in which nitrogen is used as a head-fill and is supplied with Water for Injections (Ph.Eur.) presented in glass vials to be used for administration. All excipients are commonly used in parenteral formulations and comply with specifications as described in European (Ph.Eur.) or USA (USP) pharmacopoeia. Adequate descriptions, specifications and batch analysis for

all packaging materials used for the bulk active substance or the finished product were provided in the application.

Product development and finished product
The finished product is formulated as a sterile lyophilised powder in the mannitol/glycine/phosphate system. Overall the formulation of the product is justified and its development has been adequately documented. As the product does not contain preservatives, the reconstituted solution should be used immediately.

Method of preparation
The manufacturing process, which complies with Good Manufacturing Practice (GMP), takes place in a dedicated facility at Abbott Laboratories Inc. (USA). The manufacturing process has been adequately validated with results on batches of the finished product manufactured at the intended commercial scale. The data showed that the finished product consistently met the proposed specifications and demonstrated that the manufacturing process is consistently reproducible. A summary of the microbiological aspects of the formulation and filling process has been provided and is adequate. In-process controls to control the manufacturing process are appropriate.

The manufacturing process of the water for injections, provided in vials, is classical and has been described in detail. The manufacturing process, which complies with GMP, takes place in dedicated facilities at Pharmacia N.V./S.A (Belgium).

Specifications of the finished product
All test methods used for routine testing, except those from the European and Unites States Pharmacopoeias, have been validated. Control tests on the finished product will sufficiently guarantee the consistency of the manufacturing process of the finished product.

Stability of the finished product
Stability of the finished product has been studied for 8 batches of finished product. The stability protocol was designed to provide information on the stability of the finished product at the recommended storage temperature (i.e. ≤25°C) as well as under accelerated conditions. Based on available results for three months under the recommended storage conditions, a shelf life of ≤9 months at ≤25°C, protected from light, for the finished product is acceptable. After reconstitution, the product should be used immediately.

Viral safety
No adventitious viruses or retroviruses were detected in all the tests performed on the cell lines and therefore the established cell banks exhibit a satisfactory level of viral safety.

The manufacturing process is documented to be free from viral contamination. Overall, the viral safety of Somavert has been adequately demonstrated.

Discussion on the chemical, pharmaceutical and biological aspects
In general, the different aspects of the chemical, pharmaceutical and biological documentation comply with existing guidelines. The information provided in the application demonstrated consistent production of pegvisomant achieving a well-defined quality for the active substance and the finished product. The fermentation, down-stream processes, including pegylation, and purification of the active substance are adequately controlled. Pegvisomant has been well-characterised using state-of the-art methods with regard to its physicochemical characteristics. The manufacturing process of the finished product, which complies with Good Manufacturing Practice (GMP), has been described in sufficient detail and product specifications are adequate. In general, methods to control the quality of the product are adequate. The submitted documentation assured viral safety of the finished product. Stability data support a shelf life of 9 months for the finished product.

The quality of Somavert is considered to be acceptable when used in accordance with the conditions defined in the SPC, with the exception of a limited number of points to be addressed as post-approval commitments. Physicochemical and biological aspects relevant to the uniform clinical performance of

the product have been investigated and are controlled in a satisfactory way. Viral safety and batch-to-batch consistency has been documented and the relevant test will be performed according to the agreed specifications.

3. Part III: Toxico-pharmacological aspects

Pegvisomant is a molecular variant of the human growth hormone in which a total of nine mutations have been introduced to alter the binding characteristics of the molecule with human growth hormone receptor (HGHR) sites 1 and 2. The protein component of pegvisomant (B2036) has been further modified by covalent addition of polyethylene glycol (PEG) molecules resulting in a pegylated protein (B2036-PEG). B2036-PEG has been studied in mice, rabbits and monkeys for its pharmacological effects. The binding of B2036-PEG to hepatic GH receptors and to other receptors has been assessed in various species.

Pharmacodynamics

GH normally binds to two specific sites on its receptor. Binding to site 2 activates the cellular signalling mechanism. Pegvisomant binds to HGHR site 1 and blocks site 2, and is able to displace native GH. As a result, signal transduction is blocked and circulating concentration of insulin-like growth factor 1 (IGF-I), the principal mediator of GH action, is decreased.
The ability of pegvisomant to displace radio-labelled growth hormone [^{125}I]-hGH was studied in an *in vitro* binding assay using microsomal liver cell membranes of human, rat, mouse, dog, rabbit and rhesus monkey origin. The specific receptor binding in rhesus monkey and rabbit was similar to man. The binding of pegvisomant blocked the physiological cascade that follows the GH receptor activation. The release of IGF-I was prevented from occurring in the rhesus monkey. Other species are not relevant for assessing this pharmacological effect.
Despite the enhancement of binding of hGH analogues at site 2, there was no change in the somatotropin dependent proliferation of indicator cells, or the degree of activation of the specific Janus kinase 2 (Jak2) activated by GH.

The purpose of direct pegylation of the protein was used to prolong half-life of B2036 and to reduce a potential immunogenicity. B2036-PEG showed decreased binding at the site 2 of the HGHR compared with B2036. Despite the reduced affinity for the receptor, work on the protein had shown increased potency of the pegylated form due to the prolonged circulating half-life [1].

The most important effect of GH is the synthesis and the release of IGF-I, which is responsible for many of the physiological effects that follow the release of hGH from the pituitary gland. In transgenic mice expressing the gene for the mutated form of GH, the suppression of this mechanism early in life leads to dwarfism. Two single-dose studies in rhesus monkeys with up to 1 mg/kg pegvisomant administered through the intravenous (IV) or subcutaneous (SC) routes, and one study in rabbits showed a dose related decrease in serum IGF-I. The GH level did not show any major change. These studies showed that pegvisomant was a potent competitive antagonist of the binding of hGH. The pharmacological effect was a decrease in circulating IGF-I levels, accompanied by an increase in GH and IGFBP-3 levels.

In vitro studies showed that B2036-PEG did not bind to or activate the human rPRL receptor, nor was it an antagonist at that receptor. B2036-PEG had no specific activity at any of a wide range of autocoid, neurokinin and opioid receptors of human origin.

Safety pharmacology
No specific safety pharmacology studies have been conducted. Effects on the major physiological systems have been investigated in high dose acute toxicity tests of pegvisomant in the mouse, in repeat dose tests in the mouse, rat and rhesus monkey, and in a single-dose IV study in the responsive cynomolgus monkey. Acute toxicity studies did not reveal toxicity on the cardiovascular, respiratory, central nervous or gastro-intestinal systems after IV bolus injection of high doses of pegvisomant. In a single-dose IV study in cynomolgus monkeys, no clinical signs and no treatment related changes were

noted at ECG examinations. Renal function was not affected. Prolonged studies in rat and monkey also showed no toxicity to the main functions of the physiological systems. The lack of toxicity was confirmed by clinical studies, after acute and repeated administration of doses up to 1 mg/kg /day.

Pharmacokinetics

Several pharmacokinetic studies were performed with pegvisomant in the mouse, rat, rabbit and monkey. Pegvisomant was assayed by a radioimmunoassay specifically developed and validated for this product, or by radioactivity after [^{125}I] labelling.
Pegvisomant was administered IV only in mouse and monkey, showing a clearance and a volume of distribution higher in the female mouse, 19.3 ml/h/kg and 442 ml/kg respectively, and 2.74 ml/h/kg and 82.2 ml/kg in the male mouse and monkey respectively. Bioavailability of the SC route was 0.45-0.81 in these species. In rat, tissues containing the highest percentage of administered radioactivity were muscle (3.47%), brown fat (injection site) (2.64%), liver (2.15%) and bone (1.24%). All other tissues each contained less than 1% of the administered dose. Whole body autoradiography confirmed these findings and also demonstrated that radioactivity did not cross the blood-brain barrier.
Elimination half-life was 16.7-31.1 h (mouse, rat, monkey). In rat, radioactivity was primarily excreted by the renal route with more than 85% of the total radioactivity found in the urine 48 hours after the administration.

Distribution
[^{125}I]-pegvisomant was administered to Sprague-Dawley rats (3 male, 3 female) by SC injection as a single 3 mg/kg dose. Cmax values for total radioactivity in the serum and blood cellular fraction were reached at 24 hours and then declined slowly. The ratio of radioactivity in the blood cell fraction to serum was 0.898 at 0.5 hours after dose administration and 0.333 at 24 hours. The ratio was relatively constant for the remainder of the study.

The apparent maximum mean tissue concentration of radioactivity was reached in all tissues at 24 hours with the exception of brown fat (injection site), stomach, and thyroid/parathyroid gland where the maximum was reached at 8, 8 and 72 hours, respectively. The highest radioactivity concentrations were found in brown fat (injection site) > thyroid/parathyroid > ovaries, lungs and kidneys. After 24 hours, the radioactivity concentrations in all tissues except thyroid/parathyroid declined. Mean tissue to serum concentration ratios for all tissues except adrenal gland (0.5 hours), brown fat (0 to 24 hours) and thyroid/parathyroid gland (72 and 168 hours) were less than 1 at all time points, which indicates minimal distribution of pegvisomant-associated radioactivity into the tissues. Male rat tissue concentrations were somewhat lower than female tissue concentrations at comparable time points.

Tissues containing the highest percentage of administered dose were muscle (3.47%), brown fat (injection site) (2.64%), liver (2.15%) and bone (1.24%). All other tissues each contained less than 1% of the administered dose.
Whole body autoradiography confirmed the above findings and also demonstrated that radioactivity did not cross the blood-brain barrier.

Metabolism and Excretion
Specific metabolism studies with pegvisomant have not been performed. In rat, radioactivity was primarily excreted by renal route with more than 85% of total radioactivity found in the urine 48 hours after administration. Faeces accounted for less than 2% of administered radioactivity. On the whole, recovery of administered radioactivity was 88.3% and 92.2% for males and females, respectively. Available information did not allow to distinguish the clearance by excretion and metabolism in the kidney. However, there was almost no unchanged pegvisomant in the urine in studies in humans and consequently the radioactive material noted in animal studies consisted of degradation products. The renal clearance of pegvisomant was almost *nil*. The location of the metabolism is still unknown.

Interactions with other medicinal products or other substances
No interaction studies were performed. GH is known to be a major determinant of hepatic cytochrome P450 activity in rats. One study conducted in a small series of GH deficient subjects, has indicated that GH modulates hepatic CYP450 activity[2]. *In vitro* data showed that GH may exert this action through

upregulation of a specific CYP 3A4, a major drug metabolising CYP in humans[3]. The possibility that pegvisomant may alter the clearance of compounds known to be metabolised by CP450 liver enzymes (e.g., corticosteroids, anticonvulsants, cyclosporin) was addressed. Interactions with cytochrome P450 caused by increased levels of GH are not expected because the goal with pegvisomant therapy is to normalise the disturbed GH/IGF-I system.

Toxicology

Compliance to GLP was satisfactory.

Acute and subacute toxicity
Acute toxicity studies in mice using SC or IV administration at doses up to 10 mg/kg did not induce any functional or other toxic effects. In single-dose toxicity studies, the most important findings were scabs at injection site in several animals from each treated group. Alkaline phosphatase reduction was the unique effect in males and females, together with increased basophilia of centrilobular hepatocytes, and of signs of trauma at injection sites.
Repeated dose toxicity studies consisted of two 2-week studies in mouse (SC and IV) and one 4-week study in monkey (SC, 0, 0.1, 0.3, 1, 3 mg/kg every other day). Alkaline phosphatase dose related reduction and an increase in total protein and calcium were found in one study in mice. No changes in necropsy or in the histological examination were observed. In monkeys, a slight decrease in alkaline phosphatase in all animals in the two higher dose groups and minimal trauma at the injection sites were observed.

The Company has presented a comparison of exposure across species. Exposure ratios have been calculated from data of the toxicokinetic analysis conducted in the 26 week SC study in the rat and in the 26 week SC toxicity study in the rhesus monkey. The exposure ratios included the maximum clinical dose in patients. Exposure ratios indicated that adequate exposure had been accomplished in the rat. Preclinical data revealed no special hazard for humans based on studies of repeated dose toxicity in rat and monkey. However, exposure in monkey was not higher than in patients at therapeutic dose, and this is reflected in the SPC (see section 5.3., *Preclinical safety data*).

Chronic Toxicity
Two 6-month chronic toxicity studies were performed using the SC route. In one study in rats, toxicokinetic analysis showed that serum levels at all times were dose-related, indicating a lack of pegvisomant antibodies, since the specific assay was shown not to be reliable in presence of the compound. The main findings were chronic inflammation at the injection sites, significant decrease in alkaline phosphatase in all treated males and top dose females, and vacuolated macrophages in different lymph nodes or spleen. The NOAEL after 26 weeks was 10 mg/kg/d SC.

In a second study conducted in monkeys using 0, 0.3, 1, 3 mg/kg (once weekly), the pharmacological activity of pegvisomant was demonstrated in the 1 and 3 mg/kg/week animals, in terms of reduction of IGF-I, reduction of insulin in males treated at the top dose, and unaffected prolactin levels. IGF-I and insulin returned to normal during the recovery period. Decrease in alkaline phosphatase in higher dose males and females, reduction in trabecular bone were observed in mid-dose males and top-dose animals. No vacuolated macrophages were recorded. The overall NOAEL was 0.3 mg/kg/week and the NOAEL was 1 mg/kg/week SC. In this study, pegvisomant was administered weekly for 6 months whereas it is injected daily in humans. Thus, exposure in monkey was not higher than in patients at therapeutic dose. This information is reflected in the SPC (section 5.3).

Reproduction studies
An experiment was conducted in the rabbit with dose levels of 0, 1, 3 or 10 mg/kg/d SC. No significant effect was observed on dams and foetuses. Maternal GH has been known to influence the foetal growth in rats. A published study describing a small series of cases with acromegaly (including patients that had octreotide administered during only a part of their pregnancy, with most having therapy discontinued in the first or second trimester) observed no major side-effects, and birth weights were within the normal range despite discontinuation of therapy[4]. Nevertheless, the SPC warns against administration of pegvisomant to women who are pregnant or are likely to become pregnant.

Genotoxicity
The genotoxicity data presented comprised an AMES test and a chromosome aberration test in human lymphocytes. Both tests were negative and did not raise any genotoxicity concern.

Carcinogenicity
Formal carcinogenicity studies have not been conducted by the Company. The results of 4 non-GLP *in vitro* studies were submitted.

GH is known to produce anabolic and mitogenic effects *in vitro* and *in vivo* at *supra* physiological levels. A possible direct growth stimulant effect of GH itself on neoplastic cells has been suggested from *in vitro* or *in vivo* studies. These studies have not always distinguished between the actions of GH itself and induced release of IGF-I [5,6]. Controversy remains about this action of GH. In the available product information for authorised products, GH is contraindicated in patients with active neoplasm. Growth hormone therapy should be discontinued if evidence of tumour growth develops. Also, in patients with previous malignant disease, special attention should be given to signs and symptoms of relapse [7].
Results of studies using human cell lines suggested that the structure of pegvisomant itself lacks tumorigenic potential. IGF-I is a strong tumour mitogen. There is limited experimental evidence that enhanced IGF-I concentrations may increase the tumour incidence at certain sites. The goal of B2036-PEG therapy is to normalise the GH/IGF-I system. The administration of this GH antagonist produces a reduction in serum concentrations of IGF-I. This is expected to reduce the risk of tumour development in acromegaly patients.
An additional safety concern was related to tumour promoting potential. In the clinical studies 3613, 3613A, 3614 and 3615, there was a rise of GH level in association with a fall of IGF-I level. The negative feedback mechanism in relation to the decrement in plasma IGF-I level can give rise to tumour growth by directly activating growth-stimulatory GH receptors on tumour cells. The CPMP had indicated that if the clinical data showed normalisation of the GH/IGF-I system, further carcinogenicity studies would not be required. The clinical experience did not show any expansion of the pituitary neoplasms underlying the acromegalic state. However, clinical studies were of limited duration and it could not be ruled out that long-term treatment might cause an increase in GH levels resulting from a feedback mechanism. Such potential increase could be accompanied by growth of the pituitary tumour. The SPC of Somavert adequately reflects this information (see section 4.4, *Special warnings and special precautions for use*). All patients with growth hormone-secreting tumours should be carefully monitored in order to avoid any progression in tumour size under treatment.

Local tolerance
A test was performed employing a conventional protocol in the rabbit SC, 6 times over 8 days. A minimal local reaction attributed to the trauma of the injection procedure was observed. The local tolerability of pegvisomant was considered acceptable.

Immunogenicity
Pegvisomant is a polypeptide differing from human GH by the substitution of 9 amino acids. Even after the pegylation, B2036-PEG remains potentially immunogenic. Several attempts were made during the development of pegvisomant to develop a technique to detect antibodies during repeated dosing. The technical difficulty was the presence of relatively high concentrations of GH and pegvisomant molecules in the samples of animal sera, that interfered with the assay for anti-pegvisomant antibodies. These inconclusive data suggested that a low titre of probable antibody was detected in 1 out of 2monkeys, two weeks after the cessation of the treatment. Although the immunogenic potential of Somavert is not a matter of particular concern at present, the Company will keep this issue under review, particularly in view of the fact that Somavert is intended for long-term administration.

Discussion on toxico-pharmacological aspects

The pharmacodynamic studies presented showed that pegvisomant is a potent competitive and specific antagonist of hGH binding *in vitro* and *in vivo*.

Studies performed in rhesus monkey have shown that the blockage of GH receptor produced a decrease in IGF-I levels and an increase in GH levels in blood. The interest of the pharmacodynamic studies in animals was limited because of the specificity of B2036-PEG for human growth hormone receptor.

Pre-clinical data revealed no special hazard for humans based on studies of repeated dose toxicity in rat and monkey. However, exposure in monkey was not higher then in patients at therapeutic dose. This has been adequately reflected in the SPC (see section 5.3, *Preclinical safety data*).

No animal studies on reproduction toxicity were conducted, except for one experiment in the rabbit. The SPC includes appropriate warnings against administration of pegvisomant to women who are pregnant or are likely to become pregnant
No data on carcinogenic potential have been submitted. The lack of carcinogenicity study was acceptable as there is sufficient evidence of reduction of IGF-I levels in patients treated with pegvisomant.
The potential for carcinogenic risk cannot be fully excluded; however, *in* vitro studies in a number of tumour cell lines identified an inhibitory effect on their growth.

The chronic active inflammation in association with vacuolated macrophages at the injection site, in association with vacuolated macrophages in lymph nodes and in spleen, may well be a non-specific response to repeated injections. Nevertheless, it was not possible to rule out immunogenicity. Although the immunogenic potential of Somavert is not a matter of particular concern at present, the Company will keep this issue under review, particularly in view of the fact that Somavert is intended for long-term administration.

4. Part IV: Clinical aspects

The clinical development of B2036-PEG was undertaken in the U. S. A. and Europe. The clinical documentation presented include a total of three clinical pharmacology studies and two main clinical trials.

The two main clinical efficacy studies consisted of a phase III and a phase II study. The first was a double-blind, placebo controlled randomised study (SEN-3614) together with its long-term safety extension (SEN-3615). This trial studied three dose levels of pegvisomant administered once daily for 12 weeks. One double-blind, placebo-controlled, randomised phase II study (SEN-3611) together with its long-term safety extension (SEN-3613) evaluated pegvisomant at two dose levels, once weekly for 6 weeks.

Clinical Pharmacology

Three Phase I studies were conducted: two in healthy volunteers (SEN-3601 and 3623) and one in patients with acromegaly (SEN-3602).

SEN-3601 was a double-blind study that evaluated the safety and pharmacology of pegvisomant in healthy volunteers after single SC administration at 4 rising dose levels. Patients were randomly assigned to one of the four possible dose groups, and to pegvisomant (6 per dose group) or placebo (3 per dose group).

SEN-3623 was a single-dose crossover study in healthy volunteers to assess the bioavailability of a single SC dose of pegvisomant. Twelve subjects were randomly assigned to receive single doses of pegvisomant 20 mg (≅ 0.3 mg/kg) SC or 10 mg IV infusion, followed by a cross-over after a 4-week washout period and crossover to receive the opposite treatment.

SEN-3602, was a small study designed to assess the pharmacokinetics of pegvisomant administered as a single SC administration of two dose levels (0.3 or 1.0 mg/kg) in a total of 6 patients with acromegaly.

The method employed for quantitative determination of B2036-PEG in serum/plasma was a radioimmunoassay developed and validated at Phoenix International Life Sciences (St Laurent, Quebec, Canada). The lower limit of quantification (LLOQ) of the method was 4.675 ng/ml with an intra-assay precision and accuracy of 9.5 % and 102.1% and an inter-assay precision and accuracy of 7.9 % and 102 %, respectively. Cross-reactivity with endogenous compounds (GH) accounted for the apparent baseline concentrations of pegvisomant prior administration. The baseline concentrations were higher in acromegaly patients than in healthy individuals.

Pharmacokinetics
Pharmacokinetic data for pegvisomant were available for 48 healthy volunteers, and 151 patients with acromegaly (6 had been included in the pharmacokinetics study SEN-3602 and 145 in the clinical studies).

Single-dose study (SEN–3623)

Following SC administration, pegvisomant was absorbed slowly with Tmax at 49.0 hr (32.5 %) (arithmetic mean) and a Cmax of 1390 ng / ml (45.3 %) (geometric mean). The fraction absorbed after SC injection (bioavailability) was 56.7 % (48.7% - 64.7 %). The total volume of distribution (VD) was 23.3 L (77.3 %) (SC) and 12.4 L (43.5 %) (IV).

Only a small fraction of unchanged pegvisomant was excreted in the urines (0.0015 after SC dosing versus 0.0041 after IV dosing). Only a small amount of the active substance is recovered in the urine over 96 hours (<0.6%).

Elimination half-lives (study SEN-3623) for IV and SC administration were similar and were approximately 138 hours for all subjects included in the analysis, with a ratio of SC to IV of 1.0028.

The total clearance was very low (study SEN-3623): 1.80 ml/min (29.4 %) for SC administration and 1.03 ml/min (33.0 %) for IV administration. There appeared to be a difference between male and female subjects in the mean Cmax and AUC values of pegvisomant after SC administration. The large variability observed and the limited number of subjects precludes any conclusions based on these differences. A population pharmacokinetic model presented based on clearance only showed that clearance of pegvisomant did not differ between male and female patients. Mean systemic clearance was estimated to be 28 ml/h for pegvisomant doses of 10 to 20 mg administered SC (study SEN - 3614). The clearance was closely related to body weight. Clearance increased by 0.6 ml/h for each kilogram of body weight greater than the average body weight of 94 kg.

Dose ranging studies (SEN-3601, SEN-3602)

Study SEN-3601, recruited 36 male healthy volunteers receiving pegvisomant (6 subjects per dose group) or placebo (3 subjects per dose group) and SEN-3602 included 6 patients with acromegaly (3 patients per group). Complete serum concentrations *versus* time profile of pegvisomant were generated up to day 10 after administration in study SEN-3601 and up to Day 21 in study SEN-3602. In SEN-3601 pegvisomant was slowly absorbed with maximum serum concentration (Cmax) being achieved between 12 and 60 hours post dose (0.03, 0.1, 0.3 and 1.0 mg/kg). The terminal half-life was 74-99 hours.

Similar pharmacokinetic parameters were observed in healthy volunteers and in acromegaly patients with single SC administration of 0.3 mg/kg and 1.0 mg/kg doses. The half-lives were slightly but not significantly longer in the SEN-3602 study (80-109 hours). Some evidence of non-linearity for Cmax and AUC was suggested by the data on rising doses of pegvisomant.

Pharmacokinetics at steady state
Steady-state concentrations were obtained in 143 patients in the long-term extension studies (SEN-3613A and SEN - 3615) after daily SC administration of various pegvisomant doses (5 to 40 mg). In total, 1440 pegvisomant concentration observations were measured with a mean of 9.9 observations per patient (range: 1-29). Since pegvisomant concentrations were similar in the two studies for the most commonly used doses (10, 15 and 20 mg), data from the two studies were pooled into a single data set for analysis. Dose escalations were made not more frequently than every 2 weeks in both studies. Pegvisomant exhibited dose linear population pharmacokinetics for daily doses of 5 mg to at least 35 mg (9.3 ± 6.3 μg/mL, 14.3 ± 7.5 μg/mL and 18.1 ± 10.1 μg/mL after the 10 mg, 15 mg and 20 mg dose). Conclusions about pharmacokinetic linearity for doses above 35 mg may be compromised by the small number of patients treated with 40 mg.

The Company performed a population pharmacokinetics analysis at steady state in acromegalic patients (SEN-3614). The results of this analysis were considered more relevant than those from the single-dose studies in healthy volunteers. There was a tendency for clearance to change with dose but the effect of a covariate accounting for dose-dependent clearance was not statistically significant. In univariate screening, the largest effect was observed for a covariate accounting for clearance changing linearly with body weight. No covariate to account for non-linear clearance entered the final population pharmacokinetic model. Pegvisomant clearance was not associated with age or gender. As the two multiple-dose studies (SEN-3613A and SEN-3615) were also consistent with dose linear disposition of pegvisomant the Company concluded that pegvisomant exhibited approximately dose linear pharmacokinetics following administration of clinically relevant doses.

Interaction studies

No interaction studies were performed.

Pharmacokinetic studies in special populations

No pharmacokinetic study was performed in specific populations such as children, elderly people or subjects with impaired renal function and this has been adequately reflected in the SPC. The Company will provide access to physicians wishing to use Somavert in paediatric patients, access to the post-marketing database and submit to the CPMP results on those patients captured in the programme.

Pharmacodynamics
The primary pharmacodynamic objective in the clinical development of B2036-PEG was to document the suppression of IGF-I production as a function of the dose and B2036-PEG plasma concentration. Secondary objectives targeted plasma levels of GH, IGF-BP-3, insulin, TSH, PRL as well as GH and B2036-PEG antibodies determination. The pharmacodynamic characteristics of B2036-PEG were mainly evaluated in studies SEN-3601 (healthy volunteers) and SEN-3602 (subjects with acromegaly) and as secondary end points in SEN-3623 study (healthy volunteers).

IGF-I was analysed using two radioimmunoassay, which had been developed and validated by Pharma Bio-Research Laboratories (study SEN-3601) and by Endocrine Sciences (studies SEN - 3602 and SEN - 3623, SEN - 3614). According to the data provided by the Company a sensitivity of 4.50 ng/ml was observed for Pharma Bio-Research Laboratories method and of 10 ng/ml for Endocrine Sciences method.

From the data provided (study SEN–3601) the effective dose level causing a 49.24% suppression of IGF-I was 1.0 mg/kg obtained at 120 hours after dosing and the maximum effect was not reached. No decrease in serum IGF-I concentrations was observed for doses of 0.03 and 0.1 mg/kg. For the doses 0.3 mg/kg, a maximum decrease was reached at 72 hours after dosing (27.7% decrease from baseline). Acromegalic patients (study SEN–3602) showed a similar IGF-I reduction for the doses 0.3 and 1.0 mg/kg to that observed in healthy volunteers. In the 1.0 mg/kg group, a decrease from baseline of 61.3%, 54.0% and 38.6% was observed on day 3, 7 and 21, respectively.

In study SEN–3623 (healthy volunteers), a slight increase above baseline was observed initially after either IV or SC administration. This increase reached a maximum at 100 hours, in females (+10.7% and +29.9% after SC and IV administration, respectively) and males (+19.4% and +8.6% after SC and IV administration, respectively). Concentrations decreased to below pre-treatment values by day 8. IGF-1 concentrations had returned to baseline values) at day 16 for both routes of administration.

A population based pharmacodynamic analysis was undertaken in SEN-3614 study. The mean steady-state serum IGF-I concentration was 648.15 ng/ml. The serum pegvisomant concentration that produced 50% of the maximal IGF-I suppression (C50) was 15,500 ng/ml. The value of C50 was independent of patient demographics such as sex, race, body weight and baseline GH concentrations.

A significant effect of opioid treatment on pegvisomant C50 was demonstrated such that C50 was approximately twice in the population on opioids therapy (11% of the study population) than in the other individuals (27 400 ng/ml v. 14 000 ng/ml).

Concerning other pharmacodynamic effects studied, the AUCs of GH showed large intra-individual fluctuations. For IGF-I/BP-3, insulin, prolactin and TSH concentrations no consistent changes from baseline were observed.

The Cmax of pegvisomant achieved in the 20 mg SC dose group was approximately 50% less than the Cmax achieved in the 10 mg IV dose group (1387 ng / ml vs 4271 ng / ml). This difference did not lead to any distinguishable effect on IGF-I reduction (SEN–3623). Indeed, in the pharmacokinetic population study (SEN-3614), the mean serum trough concentration of pegvisomant that produced 50% of the maximum IGF-I suppression (IC50) was estimated to be 15,500 ng/ml. This was well above the Cmax levels of ~4,270 ng/ml observed after the 10 mg IV dose in study SEN-3623.

B2036-PEG antibodies

Human GH as well as the B2036-PEG antibodies were evaluated in the SEN 3626 study. Human GH antibodies were detected at B2036-PEG concentrations of 2000 ng/ml and more and at human GH concentrations of 80 ng/ml or more. GH antibodies were analysed at baseline and on day 16. No positive antibody was found for any subject at either of these time points.

Cholesterol metabolism

Exogenous administration of GH has been shown to increase the expression of the LDL receptor, which is manifested as better cholesterol catabolism [8]. The observed effects of GH on LDL, total cholesterol and apo B, the apolipoprotein component of LDL, are generally thought to result from increased LDL and apo B clearance. A possible impact of Somavert on cholesterol metabolism has been explored. In studies SEN-3613 and SEN-3613A, total LDL, and HDL cholesterol levels were obtained in 36 patients treated with pegvisomant for a mean duration of 22.5 months. Total cholesterol, and LDL cholesterol increased by 9 and 7 % compared to baseline, respectively, and HDL cholesterol increased by 18.4 %. In another study in 20 patients with active acromegaly treated with pegvisomant for a mean of 10 months, normalisation of serum IGF-I resulted in an increase in total cholesterol (5.0 to 5.7 mmol/L), increase in LDL cholesterol (3.0 to 3.7 mmol/L), and increase in apo B (110 to 127 mg/L), restoring the distribution of values to that of the general population. Triglycerides and HDL cholesterol were unaffected by treatment, but apoA1, the major apolipoprotein component of HDL, was increased (153 to 166 mg/L). Lipoprotein (a) was reduced (342 to 235 mg/L). A decrease in serum insulin, glucose / insulin ratio and, in some cases, fasting glucose has been demonstrated in other studies with pegvisomant (SEN-3613A, 3615, SEN-3614).

Discussion on Clinical Pharmacology

The pharmacokinetic profile of SC administration of Somavert is characterised by:

- slow absorption (Tmax: 49.02 h ± 32.4%) and slow distribution (half-life: 138 hours);
- an absolute bioavailability of 56.7%;
- a clearance influenced by weight and concomitant administration of opiates

- a similar pharmacokinetic profile after single SC Somavert administration in healthy volunteers and in patients with acromegaly;
- a non-linearity for Cmax and AUC (increase more than dose proportional) observed after a single administration study in pharmacokinetic studies with a dose linear increase observed at steady state (population pharmacokinetic).

Although the analysis of covariance showed no statistically significant effects for baseline GH, pharmacodynamic data suggested that higher baseline GH levels could be related to lower efficacy or to require higher doses of pegvisomant. To evaluate the effect of baseline GH levels on pegvisomant response, a retrospective analysis was conducted for patients in the SEN-3615 study (N=109). Patients were stratified into two groups: low baseline GH level (<5 ng/ml) and high baseline GH level (>5 ng/ml). The endpoints for this analysis were percentage of patients with a normal serum IGF-I concentration at final visit and percent change in serum IGF-I concentration from baseline to final visit. These two endpoints showed comparable results, regardless of baseline GH level (46.0% vs. 50.0% and 95.0% vs. 89.6% for the low and high GH baseline groups, respectively). The mean daily dose required to achieve these responses, however, was slightly higher in the high baseline GH group compared to the low baseline GH group (15.5 mg vs. 12.4 mg, respectively). These results indicated that the IGF-I response to pegvisomant dosing is not altered by baseline GH status, but a slightly higher dose is required to achieve optimal therapy in patients with higher baseline GH levels.

The proposed treatment regimen is an 80 mg loading dose followed by daily administration of 10 mg and has been adequately justified.
The use of the 80 mg loading dose aims at reaching therapeutic pegvisomant concentrations faster, and to elicit a relatively rapid reduction in IGF-I concentrations.

Pegvisomant metabolism is expected to involve normal protein catabolism through peptide cleavage in the liver and other organs. It is generally recognized that proteins are not substrates of CYP450. Although a slight modification in the structure of the molecule (Lys pegylation modifies and removes two peptides from the tryptic map), it is expected that this should not result in a significant alteration from the natural metabolic pathways for human growth hormone. The fate and disposition of PEG moieties is well described in the literature. Lastly, acromegaly is not associated with specific hepatic and renal complications, and therefore, the disease is not expected to impact on pegvisomant metabolism. Indeed, pegvisomant clearance was observed to be similar in healthy subjects and acromegaly patients. As sufficient understanding on the metabolism of proteins can be gathered from the literature the absence of data from studies performed by the Company is acceptable and is in line with the current regulations.

A population PK-PD analysis was conducted on study SEN-3614. Although dose was included after the initial screen for possible covariates, it was found unnecessary to include any parameters, such as dose, in the final population PK model to account for non-linear clearance. Only one covariate, body weight, resulted in a statistically significant effect on systemic clearance and was retained in the final pharmacokinetic model where the typical clearance value increased by 0.6 ml/h for each kilogram of body weight greater than the average body weight of 94 kg. The additional pharmacokinetic data from multiple dose studies (SEN-3613 and SEN-3615) confirmed the linear disposition of pegvisomant. Thus, it was concluded that linearity is observed at steady-state following administration of clinically relevant doses (10, 15 and 20 mg).

Justifications were provided to support the higher dose treatment recommendation. In the original MAA data, a total of 29 patients were exposed to doses of $\geq$ 25 mg/day with 15 of these patients receiving $\geq$ 30 mg/day. Within this subset, 10 patients required greater than 20 mg Somavert per day to normalize their IGF-I during Study SEN-3615. Normalization of the IGF-I was achieved in 8 of 108 evaluable patients at a maximum dose of 30 mg/day. None of these patients experienced significant adverse events and these did not differ by dose. Based on these data, a maximum daily dose of 30 mg/day was recommended.

Clinical Efficacy

From the available pharmacokinetic, once weekly dosing schedule was chosen for clinical trials. The selected doses were 0.3 mg/kg and 1 mg/kg as those which were effective for IGF-I levels reduction. In clinical trials, these doses were simplified trial to 30 mg and 80 mg and were administered in 2 trials: SEN-3611, a double-blind, placebo-controlled and SEN-3613 an open extension of SEN-3611.

Main clinical studies
The primary efficacy endpoint for all studies was percent suppression in IGF-I concentrations from baseline. Secondary efficacy endpoints varied across studies, and included the proportion of patients with normalized IGF-I concentrations and other measures of the GH-IGF axis, such as free IGF-I, IGF BP-3, acid labile submit (ALS). The severity of individual signs and symptoms was evaluated on a scale from 0 to 14. Other secondary endpoints were ring size (standard European jeweller's rings), and quality of life.

Selection criteria
The selection criteria used in the clinical trials were designed so as to recruit male and postmenopausal or surgically sterile females aged 18 years or more with diagnosis of acromegaly and presenting IGF-I value as ≥ 30 % above the upper limit of normal range for the SEN-3614 study and as ≥ 50 % for the SEN- 3611 study. The main exclusion criteria were prior treatment with any long-acting somatostatin analogue within 3 months, with any somatostatin analogue within 2 weeks and with any dopamine agonists within 5 weeks of screening visit. Patients with presence of other conditions that could result in elevated GH and/or IGF-I concentrations (e.g., severe hepatic or renal disease, anorexia nervosa, Laron's syndrome, treatment with levodopa, narcotic analgesic, or heroin abuse) were also not eligible.

SEN-3611 and follow-up (3613 and 3613A)
Study SEN-3611 was a 6-week double-blind, placebo-controlled, phase II dose ranging study. Patients were allocated to 3 different treatment groups (placebo, pegvisomant 30 mg, and pegvisomant 80 mg). The treatment was administered once weekly during 6 weeks. The primary efficacy endpoint was percent suppression of IGF-I concentrations compared to baseline values (at randomisation). The secondary endpoints were acromegaly severity score, and ring size.

Subjects that completed SEN-3611 successfully were offered to continue in an open-label extension study (SEN-3613). The dose regimen in SEN-3613 was once weekly, SC injection of 30 mg of pegvisomant at the beginning of the study with every two weeks dose adjustment by 10 mg increments up to 80 mg during 12 weeks and then every two months. The dose level adjustment depended on investigator's assessment taking into account multiple variables such as: study medication tolerability, IGF-I concentration, sign and symptom of acromegaly, ring size. Descriptive statistics were produced for IGF-I concentrations, IGF-I normalisation, GH and IGFBP-3, signs and symptoms of acromegaly, and ring size. The extension study was later amended, with dosing changed from weekly to daily (SEN-3613A).

In SEN-3613A, pegvisomant was administered in all subjects as 80 mg bolus loading dose at the beginning of the study followed by a daily SC administration of 10 mg of pegvisomant. Then, dose adjustment was performed in 5 mg increments, up to 40 mg occurred every two weeks and was again based on the investigator's assessment. Descriptive statistics were produced for IGF-I concentrations, signs and symptoms of acromegaly, and ring size.

SEN-3614 and follow-up (SEN-3615)
SEN-3614 study was a double-blind placebo-controlled, phase III study. Patients were randomised to 4 treatment groups (placebo, pegvisomant 10, 15, or 20 mg). Patients were stratified at randomisation according to IGF-I level (1.3-2.0 vs. >2.0 × age-adjusted UNL). A sample size of 25 patients/group was calculated to detect a 20% difference in IGF-I levels, with 80% power and a two-sided alpha of 0.05. The study duration was 12 weeks. At the first visit each patient received the bolus loading dose of either 80 mg of pegvisomant or placebo, followed by a daily self administration of randomly attributed treatment. The main study objective was to demonstrate the efficacy and safety of the 10

and 20 mg/day doses and to test an intermediary dose of 15 mg/day. The primary efficacy endpoint was percent suppression in IGF-I concentrations at week 12, compared to baseline. Secondary endpoints included incidence of normalisation of IGF-I, reduction in acid labile subunits and free IGF-I, IGFBP-3, GH, acromegaly signs and symptoms (9-point scales for soft-tissue swelling, arthralgia, headache, perspiration and fatigue), ring size of the non-dominant hand ring finger (standard European jeweller's rings), and quality of life. Antibody development was also assessed. The study has been completed.

SEN-3615 was an open-label follow-up of SEN-3614 study, including also new patients. At the first study visit all subjects received in a blinded manner a bolus loading dose either of placebo (those who were treated with active substance in SEN 3614) or of 80 mg of active substance (those who previously received placebo). The loading dose was followed in an open-label manner by a self administration of 10 mg/day of active substance. A dose adjustment was possible after the first 8 weeks of treatment and was made by 5 mg/day increments up (max to 30 mg/day) or down (min to 5 mg/day). Doses of up to 20 mg were to be administered in a single injection and greater than 20 mg via two injections. The dose adjustment was based on the normalisation of IGF-I concentration (within the normal range for age-adjusted controls). The main study objective was to evaluate the long-term safety and efficacy. The primary efficacy endpoint was percent suppression in IGF-I concentrations from baseline of study SEN 3614. Secondary endpoints included normalisation of IGF-I, reduction in acid labile subunits, IGFBP-3, and free IGF-I, acromegaly severity score, and ring size. The study is still ongoing, and interim results have been provided for a 6-months study period (cut-off date 31 May 2000).

Analysis
Main efficacy analyses included only randomised patients with at least one post-treatment assessment. Efficacy analyses were performed using an analysis of variance model (ANOVA) with step-down hierarchical procedure testing to account multiple comparisons. Primary comparisons were performed between each of the 3 pegvisomant treatments groups (10, 15 and 20 mg) and placebo after 12 weeks of therapy. Additionally the covariates such as baseline IGF-I concentration, IGF-I study entry strata, baseline GH concentration, gender and baseline body weight were added in the statistical analyses for efficacy. Furthermore for the subjects taking somatostatin analogue or dopamine agonist therapy prior to participating in the study, comparative analyses were conducted between treatment groups.

Results

SEN-3611 and follow-up (3613, 3613A)
Forty-six patients were included in study 3611, and allocated to 3 groups. 15 patients were assigned to the placebo group. Sixteen and 15 patients were assigned to the 30 and 80 mg of pegvisomant, respectively. In total, 31 patients started pegvisomant treatment, and duration of exposure to pegvisomant between 0.14 to 34.3 weeks with a mean of duration 23 weeks.

All 46 subjects were included in the main efficacy analysis; 44 patients completed protocol treatment whereas 2 dropped from the study (protocol violation and voluntary patient decision). IGF-I values at baseline were comparable between groups. After 6 weeks of treatment, the mean percent change from baseline in IGF-I concentrations observed for the 30 mg group was −15.7±4.8. The change observed for the 80 mg group was −31.3%±6.7. No significant change was observed in the placebo group (–0.4%±4.8%). The observed difference between two doses was not statistically significant. The differences observed between placebo and either of the two doses were statistically significant (ANOVA p=0.0426 for 30 mg group and p=0.0008 for 80 mg group). Of 46 analysed patients, only 7 normalized their IGF-I levels: one in the placebo group, two (12.5%) in the 30 mg group and 4 (26.7%) in the 80 mg group. In the treated patients the effect was obtained after 2-3 weeks of treatment. For secondary endpoints, at 6 weeks, the mean percent changes observed for placebo for free IGF-I and IGF-I/BP-3 were lower than those observed for the 80 mg group (p=0.068 and p= 0.050, respectively). No statistically significant differences were observed for signs and symptoms of acromegaly.

In total, 36 patients were enrolled into the study SEN-3613. This included 34/44 patients that had completed SEN-3611. Of the remaining 10/44 patients, 4 did not enrol, due to voluntary decision, whilst 6 delayed participation (one for incurring haematuria, 5 because of lack of supply of medicinal product). The patient that had voluntarily dropped out before completion of SEN-3611 and one patient that had not previously been enrolled onto SEN-3611 were also included (in violation of the protocol). After inclusion into SEN-3613, 4 patients dropped out from the study, 2 of whom because of lack of efficacy (headache, and lack of response for IGF-I, respectively). No formal efficacy analyses were performed, although promising results were noted in terms of mean IGF-I concentrations over time.

Results from SEN-3611 and SEN-3613 had shown only a small proportion of patients with normalized IGF-I levels. A new dose regimen was proposed to be tested in SEN-3613A study a daily dose of 10 mg/day allowing for dose increase up to 40 mg and following an 80 mg loading dose. In total 38 patients were included in study SEN-3613A. The 32/36 patients that completed SEN-3613 continued onto the amended SEN-3613A, together with the 6 patients that had delayed participation following completion of SEN-3611. Treatment was still ongoing for 7/38 patients, at the cut-off date for the study report submitted (31 May 2000). No formal efficacy analyses were performed. Mean IGF-I levels for the 32 patients who continued directly from SEN-3613 decreased from 900 prior to pegvisomant treatment to 445, and 275 ng/ml, at the end of SEN-3613, and after switching to daily dosing in SEN-3613A, respectively. Normalisation of IGF-I concentrations had been observed in 37/38 subjects in the course of study SEN-3613A, and 35 (92%) patients had normal IGF-I concentrations at the time of data cut off. The effect was more frequently observed with the 10 mg/day dose. The weighted average dose at which IGF-I first normalized was 14.4 mg/day. No improvement was observed with the new regimen for secondary efficacy end points such as mean score for total signs and symptoms of acromegaly, and ring size, for patients who had participated in both studies (SEN-3613 and SEN-3613 A)

SEN-3614 and follow-up (SEN-3615)
A total of 112 patients were entered into study SEN-3614 and 108 completed protocol treatment. The study was conducted in 16 centres in the EU and U. S. A. Four subjects withdrew prematurely, two in the placebo arm (protocol violation and lack of efficacy, respectively), and two in the 15 mg/day group (lack of efficacy, and transaminase increase, respectively). One patient was withdrawn 5 days after treatment start, and before the first efficacy assessment, because review of baseline MRI revealed a large pituitary adenoma requiring prompt surgical referral. This patient was excluded from the main efficacy analysis. The number of patients included in efficacy analyses was 111 (with 31, 26, 26, and 28 patients entered into the placebo, 10, 15, or 20 mg/d pegvisomant arm, respectively).

Patient characteristics were comparable across treatment arms in terms of age, gender, duration of acromegaly, and previous treatments. Baseline IGF-I levels were also similar, *i.e.*, 670±52, 627±49, 649±58, and 732±39 ng/ml for placebo, and 10, 15, and 20 mg/day groups, respectively. In the main efficacy analysis of the primary endpoint, IGF-I values for all pegvisomant groups were statistically significantly different from placebo at all post-baseline visits, and was dose-related (Table 3). The reduction in IGF-I was significantly greater with pegvisomant 20 mg than 10 mg at all visits, and the 15 mg dose was significantly better than 10 mg from week 8 onward. Pegvisomant 20 mg was significantly better than the 15 mg dose at weeks 4 and 12.

A subgroup analysis of 49 subjects receiving somatostatin analogues prior to study entry compared IGF-I values at 12 weeks with those measured during patient selection, when patients remained on their prior therapy. A decrease at 12 weeks of 39% and 32 % in IGF-I was observed in the 15 mg/day and 20mg/day groups, respectively.

Table 3. Summary of the main efficacy analysis for the primary endpoint in the main clinical study SEN-3614 (N=111).

IGF- (ng/ml)	Placebo (N=31)	Somavert 10mg/d (N= 26)	Somavert 15mg/d (N= 26)	Somavert 20mg/d (N= 28)
Mean	639.7	449.1	320.9	278
Range	148-1291	89-894	70-878	78-720
Mean % change from baseline	-4.0	-26.7	-50.1	-62.5
p-value (vs placebo)		0.0001	0.0001	0.0001
p-value (vs 10 mg/d)			0.0048	0.0001
p-value (vs 15 mg/d)				0.0155

The proportion of patients whose IGF-I concentrations became normal was significantly higher in all pegvisomant groups as compared to placebo at each visit. A summary of week-12 results is presented in Table 4.

Table 4. Normalisation of IGF-I levels at week 12 in SEN-3614 (N=111)

Normalized IGF-I	Placebo (N=31)	Somavert 10mg/d (N= 26)	Somavert 15mg/d (N= 26)	Somavert 20mg/d (N= 28)
N(%)	3 (9.7)	10 (38.5)	18 (75.0)	23 (82.1)
p-value (vs placebo)		0.0157	0.0001	0.0001
p-value (vs 10 mg/d)			0.0072	0.001
p-value (vs 15 mg/d)				0.4681

At week 12 a decrease from baseline was observed for the severity score of all individual signs and symptoms of acromegaly in all three Somavert groups, with the largest decrease in the 20 mg/d group, compared to baseline. Conversely, an increase was observed in the placebo group. All three Somavert groups had statistically significant improvements in total signs and symptoms score compared with the placebo group. A dose - response was observed in the change in ring size (Table 5).

Table 5. Change in ring size (standard European jeweller's rings) for SEN-3614 (N=111)

Ring size	Placebo (N=31)	Somavert 10mg/d (N= 26)	Somavert 15mg/d (N= 26)	Somavert 20mg/d (N= 28)
Baseline mean (range)	46.8 (30-63)	46.7 (31-63)	48.3 (30-63)	45.1 (27-63)
Week 12 mean (range)	46.7 (31-63)	47.3 (31-63)	46.2 (31-63)	42.6 (25-63)
Mean change from baseline	-0.1	-0.8	-1.9	-2.5
p-value (vs placebo)		0.16	0.001	<0.001
p-value (vs 10 mg/d)			0.023	0.003
p-value (vs 15 mg/d)				0.46

Dose-dependent, statistically significant reductions in concentrations of free IGF-I, IGFBP-3 and ALS (the acid-labile subunit of the free IGF) were observed at all post-baseline evaluations in patients treated with pegvisomant. The mean serum concentrations for each of these measures at baseline and the change from baseline at week 12 are summarised in table 6.

About 50% of the patients recruited had received radiotherapy prior to entry into the study. A retrospective analysis of SEN-3614 study was conducted to study the impact of prior

radiotherapy on IGF-I response. Results showed that IGF-I response was generally comparable regardless of history of previous radiotherapy, or duration of radiotherapy.

Table 6. Measures of GH-IGF axis for SEN-3614 (N=111)

GH-IGF axis		Placebo (N=31)	Somavert 10mg/d (N= 26)	Somavert 15mg/d (N= 26)	Somavert 20mg/d (N= 28)
ALS	baseline mean (mg/ml)	21.5	22.0	23.1	23.3
	Mean change from baseline	-0.5	-3.1	-6.4	-9.5
	p-value (vs placebo)		<0.05	<0.001	<0.001
Free IGF-I	baseline mean (ng/ml)	7.0	6.4	6.2	6.2
	Mean change from baseline	-0.2	-2.5	-3.6	-3.9
	p-value (vs placebo)		<0.05	<0.001	<0.001
IGFBP-3	baseline mean (mg/l)	5.1	5.2	5.5	5.3
	Mean change from baseline	-0.1	-0.7	-1.6	-1.6
	p-value (vs placebo)		<0.05	<0.001	<0.001

Patient follow-up

SEN-3615 followed SEN 3614 and included a total of 109 patients at the cut-off date (31 May 2000). These included 102/108 patients that had completed SEN-3614, whilst 6 patients did not continue onto the follow-up study (due to either inconvenience or delay in IRB approval). Additionally, one patient that had dropped-out from SEN-3614 entered the follow-up study, together with 6 new patients (these were admitted by protocol, at the discretion of the sponsor). At the cut-off date, the mean exposure for daily dosing was 41.6 weeks (range 1 day - 80 weeks).

Mean IGF-I levels decreased from 567 ng/ml (SEM ± 37) at the start of SEN-3615 to 349 ng/ml (± 18) at the cut-off date, having been 718 ng/ml (± 31) at the start of SEN-3614. This represents a reduction of 47.8% from the start of SEN-3614. IGF-I levels became normal in 92.6 % of the patients. This percentage was slightly lower than reported in SEN-3613A, possibly because some patients were still in the dose-titration phase at the time of clinical data cut-off. One subject developed a transient GH antibody titre of 1:1024, which fell to 1:128, despite an increase in the dose of pegvisomant from 15 to 25 mg/day. His IGF-I level became normal on the 25 mg dose and remained normal throughout the remainder of the trial. GH increased from 9.7 ng/ml (± 1.65) at baseline to 19.0 ng/ml (± 2.72) at the cut-off date. As was observed in other studies, there were no clinically significant changes in pituitary remnant volume as measured by MRI with the exception of one patient

Comparison with somatostatin analogues

The Company presented a comparison between study SEN-3614 and published results for somatostatin analogues. The literature review presented pooled results from 27 published studies that reported percent IGF-I normalization using somatostatin analogues. The severity of acromegaly of the published series was similar to that of patients in the clinical studies with Somavert. Normalisation of IGF-I ranged from 22-74%. These values were compared with the results from the pegvisomant studies (97%-SEN3613A and 92.6 %-SEN 3615). The differences were claimed by the Company to be due to the different mechanisms of action of these two classes of active substances (dependency of somatostatin analogues upon the presence of somatostatin receptors in the tumour tissue and the GH receptor in normal tissues, e.g. liver as a target receptor for Somavert). Cardiovascular (bradycardia, arrhythmia), gastrointestinal (diarrhoea, abdominal pain, flatulence) and endocrinological (hypothyroidism and hyperglycaemia) adverse events were frequently observed with somatostatin analogues and less commonly in the clinical trials with Somavert. Elevation in serum aminotransferases was more frequently observed with Somavert and elevations in liver function tests were observed for both types of agents.

The Company also presented a subgroup analysis of 49 patients previously treated by somatostatin analogues in SEN-3614. In this subgroup, a total of 19 patients had normalised IGF-I levels at the time

of selection while still undergoing previous treatment. After 12-week treatment by pegvisomant 15, and 20 mg/day, 9/11 (81.8%), and 12/14 (85.7%) had normalized IGF-I levels, against percentages with somatostatin analogues observed at screening of 3/12 (25%), and 7/14 (50%), for the two doses, respectively. In the 10 mg/day group, 4/9 (44.4%) had normalised IGF-I levels at the time of selection, but only 2/9 (22.2%) had normalized their IGF-I levels after the 12-week treatment by pegvisomant 10 mg/day.

Clinical studies in special populations

No specific studies have been performed in special populations, such as children, patients with renal or hepatic impairment**.**

Discussion on Clinical Efficacy

The proposed dosing schedule of 10 to 30 mg once daily is based on data from SEN-3614, SEN-3613A, and SEN-3615. In the double-blind, placebo-controlled study SEN-3614, daily doses of 10 to 20 mg resulted in significant reductions of mean serum IGF-I concentration and significant percentages of patients whose IGF-I concentrations were normalized. The 80 mg loading dose is based on results from study SEN-3614, which included this loading dose regimen and demonstrated reductions of serum IGF-I concentrations within 2 weeks of treatment initiation.

The efficacy of a daily pegvisomant therapy of 10-30 mg, following a 80 mg bolus dose was demonstrated compared to placebo in the phase III SEN-3614 study. The proportion of subjects with normalized IGF-I concentrations was significantly greater for each of pegvisomant doses at each time point compared to placebo.

No comparative clinical trial was carried out versus a reference medicinal product and the submitted documentation did not allow to conclude on the respective efficacy of Somavert versus somatostatin analogues. This is reflected in the approved indication. From a pharmacodynamic point of view, the mechanisms of action of somatostatin analogues and pegvisomant appear complementary (decrease of secretion + blocking the binding to receptors) and on this basis the Company has committed to explore the benefit of combination treatment using somatostatin analogues with pegvisomant by conducting a post-authorisation clinical study. Combination therapy is at present not recommended and this is appropriately reflected in the approved indication.

Clinical Safety

Patient exposure

In total 260 different patients were enrolled into one or more of the clinical trials with pegvisomant. These were 48 healthy volunteers, 167 acromegalic patients, and 45 diabetic subjects. The primary population considered in the analysis of clinical safety consisted of the 167 individual acromegalic patients recruited into one or more of the clinical trials (6, 43, 1, 111, and 6 new patients recruited into SEN3602, 3611, 3613, 3614, and 3615, respectively). Of the 167 patients, 7 received placebo only, 40 received placebo initially and started pegvisomant at some later point, and 120 received pegvisomant initially. Thus, for the primary analysis of safety, two groups were considered: cases having received pegvisomant at any time (n=160), and cases having received placebo at any time (n=47), with 40 patients being considered in both groups, depending on the different treatment considered.

The main demographic characteristics of these two groups are shown in Table 7. There were no pregnant, lactating, postmenopausal, or surgically sterile female patients. All the patients were 18 years of age or older with a diagnosis of acromegaly and an IGF-I value 30% (or 50%) or greater above the upper limit of normal at screening.

Table 7. Summary of patient characteristics in acromegalic population

	Pegvisomant n (%)	Placebo n (%)
No. of patients	160	47
- Male	94 (59)	24 (51)
- Female	66 (41)	23 (49)
- Age: mean	46.2	
- Age: range	20-82	

Exposure to pegvisomant is summarised in Table 8. Of the 260 different subjects enrolled in all Somavert trials, 241 received active substance. Among them, 52 received 30 and 40 mg per week and 152 received 5 to 40. One patient treated with 80 mg per day took an accidental overdose of 80 mg per day, and is discussed separately.

Table 8. Summary of exposure to daily injections of pegvisomant (studies SEN-3613A, 3614, 3615)

Total Weeks Exposed	5mg od	10mg od	15mg od	20mg od	25mg od	30mg od	35mg od	40mg od	Total any dose
≤13 wks	2	72	63	76	18	4	2	0	9
>13-≤26 wks	2	39	24	18	4	6	3	1	14
>26-≤52 wks	1	21	15	12	7	4	0	2	45
>52 wks	1	16	8	14	0	1	0	0	84
Total for each dose	6	148	110	120	29	15	5	3	152*

Abbreviations: OD, once daily.
*Patients given more than one dose are counted with each dose, but only once in the "Total any dose" column.

Adverse events
Adverse event (AE) occurrence was determined by non-specific questioning at the assessments visits. Treatment Emergent Signs and Symptoms (TESS) were defined as any AE that occurred on or after the start of study treatment administration or a pre-existing AE that changed in severity or relationship while on therapy.

The overall incidence of TESS reported by at least 5% of all subjects (48 healthy volunteers, 167 acromegalic patients, and 45 patients with diabetes) was similar in the pegvisomant (78%) and in the placebo (68%) groups with a maximum treatment duration for each group of 34.6 and 3 months respectively.

There were 23 AEs that occurred ≥ 5% more commonly in patients on pegvisomant compared with placebo. The most likely explanation for the difference between the groups is the longer duration of observation in the pegvisomant group (up to 34.6 months versus 3 months).

The majority of AEs were mild in severity. Fifty out of the 167 acromegalic patients were reported to have a total of 73 SAEs with an overall incidence of TESS of 85% for pegvisomant and 70% for placebo. The only AE that was graded severe in ≥ 5% of patients was headache, which is a common symptom of acromegaly. Severe headache was reported in 7% of patients on pegvisomant but also 4% on placebo.

The majority of AEs were judged as not related, or remotely related to study treatment with either pegvisomant or placebo.

Common AEs considered more often related (possibly, probably, or definitely) were injection site reaction (10% related versus 1% not related in the pegvisomant group and 4% related versus 0% not related in the placebo group); dizziness (2% related versus 8% not related in the pegvisomant group and 4% related versus 0% not related in the placebo group) and sweating (2% related versus 5% not related in the pegvisomant group and 9% related versus 0% not related in placebo).

Differences between groups were observed in the body as a whole (65% pegvisomant group vs 39% placebo group). Within this term, Individual symptoms included infection (23% vs 3%), flu syndrome (15% vs 2%), accidental injury (16% vs 3%), injection site reaction (12% vs 3%), nervous, metabolic and nutritional disorders systems.

Most of the reported TESS were considered mild in severity in both groups and not or remotely related to study medication (42.3% in the pegvisomant group against 74.6% in the placebo group). Among those considered as more often related to study medication were injection site reaction, dizziness and sweating.

Within the most commonly used doses of 10 mg/day, 15 mg/day and 20 mg/day, there was evidence of a dose-related increase in the incidence of diarrhoea, nausea, flatulence, and somnolence. The number of subjects treated with 5 mg, 35 mg, and 40 mg was considered too small for a meaningful comparison with other doses. The most frequently reported AEs were infection (reported by 17%, 13%, and 13% of subjects receiving 10, 15, and 20 mg pegvisomant daily, respectively) and headache (reported by 18% of subjects receiving 20 mg of pegvisomant daily).

Deaths and serious adverse events (SAEs)

Six deaths were reported during the pegvisomant clinical program. None was attributed to pegvisomant.

A total of 81 SAEs were reported by 55 subjects including 41 pegvisomant subjects (who experienced 59 events), 3 placebo subjects and 11 subjects who were not receiving any study medication. Of the 59 SAEs reported by pegvisomant treated subjects, 50 were considered not related or remotely related to treatment while 9 events in 6 subjects were considered as possibly or probably related to pegvisomant therapy. Among SAEs considered as possibly related to pegvisomant therapy there were : acute vertigo (Meniere's syndrome) and overdose with active substance (administration of 80 mg/day dose during 7 days leading to fatigue and dry mouth) both occurred with a regimen of 80 mg/ week of active substance. The remaining seven SAEs which occurred with 20 mg/day dose regimen were: hospitalisation for panic attacks, chest pain and blocked artery, artery occlusion, hypoglycaemia, intermittent angina with exertion, myocardial infarction.

Three cases of cancer were discovered during trials. One case of prostate carcinoma was observed in the placebo group in SEN-3614. Two cases (pancreatic carcinoma and colon carcinoma) were observed in the group treated with pegvisomant 10 mg/day in SEN-3613A study. One further case of gastric carcinoma was observed after the data cut off.

Withdrawals

Eleven out acromegalic patients were withdrawn prematurely primarily due to AEs or death. The events that led to premature discontinuation in acromegaly patients were: death attributed to myocardial infarction, elevated liver function tests, lipohypertrophy, severe headache, limbs oedema, cerebrovascular accident, pancreatic cancer, weight gain and the case of gastric carcinoma reported after the data cut-off date.

Laboratory examinations

Liver function tests

Elevations of ALT and AST ≥1.9 times the upper limit of normal (Table 11) and minimal changes in lipids metabolism (Table 12) were observed for a small percentage of the 235 and the 59 subjects treated with pegvisomant or placebo, respectively, for whom laboratory data were available. ALT elevations greater than three times the upper limit of normal were observed in 5 patients. Two patients were withdrawn due to significantly increased AST and ALT levels (compared to normal). One was withdrawn from SEN 3614 study, after 8 weeks of 15 mg/day pegvisomant treatment and the other from SEN-3613A, after 4 weeks of 10 mg/day pegvisomant treatment. Regarding ALT, no difference in the incidence of abnormal value in subjects treated with weekly (5.8%) and daily (6.4%) doses of pegvisomant was observed. Regarding AST, one subject (2%) had abnormal value at weekly regimen compared to 6 subjects (3.3%) on daily dosing. There was no relationship between medication dose and change in mean ALT and AST concentrations. Time to first ALT and AST elevation was observed from 4 to 21 weeks of pegvisomant intake, mostly between 4 and 8 weeks.

Table 11. Subjects with abnormal liver functions test values during the course of the studies.

Test	Value (×UNL)	Somavert No. (%) (N=235)	Placebo No. (%) (N=59)
ALT	1.9-3.0	7 (2.9)	2 (1.4)
	>3.0-10	3 (1.2)	3 (2.1)
	>10	2 (0.8)	0 (0.0)
AST	1.9-3.0	2 (0.9)	2 (3.4)
	>3.0-10	2 (0.9)	0 (0.0)
	>10	2 (0.9)	0 (0.0)
AP	1.9-3.0	0 (0.0)	0 (0.0)
Total bilirubin	1.9-3.0	0 (0.0)	0 (0.0)

Lipid profile

Exogenous administration of GH is known to upregulate LDL receptors and lead to increased LDL clearance, and an improved lipid profile with a better cholesterol catabolism [8]. GH also has diabetogenic effects, inducing insulin resistance with lowering of HDL and increases of triglycerides. As expected, pegvisomant tended to increase both LDL and HDL cholesterol. Total cholesterol values (normal limit0-5.14 mmol/l) increased slightly in all treated patients from 5.1 mol/l to 5.3 mmol/l at 12 weeks. Triglicerides remained stable at a mean value of 1.8 mmol/l. No increase was observed for the placebo-treated patients. In the SEN-3614 study, a slight dose-relation is observed with cholesterol (Table 12). Lipid analysis results including all subjects treated with pegvisomant (healthy volunteers, acromegaly patients and diabetic patients) were also provided. Overall, a slight increase at 12 weeks compared to baseline was observed for total cholesterol (5.11 against 5.18 mmol/l), for HDL-Cholesterol (1.10 against 1.17 mmol/l). A slight decrease was observed for LDL Cholesterol (3.21 against 3.16 mmol/l) and triglicerides (1.74 against 1.7 mmol/l). In all treated acromegalic patients, an increase of triglycerides was observed (1.59 at baseline against 1.78 mmol/l at end-point). A decrease of total triglycerides was observed in the diabetic population (2.59 at baseline against 1.92 mmol/l at 12 weeks). This might be due to possibly decreased insulin resistance associated with GH antagonism.

Table 12. Dose-response relationship for total cholesterol levels in study SEN-3614 (N=111)

Somavert dose	Baseline (mom/l)	12-weeks	Min.	Max.
10 mg/day	5.34	5.38	5.1	5.9
15 mg/day	5.24	5.44	5.12	5.78
20 mg/day	5.11	5.45	5.10	5.86
Placebo	5.08	4.99	4.8	5.4

Neutralising antibodies

It was not technically feasible to measure anti-pegvisomant antibodies from the serum of pegvisomant treated patients.

Among 154 patients tested for the presence of anti-GH antibodies, 27 (16.9%) had at least one positive sample with elevated titre. No relationship was found between the development of these isolated low-titre anti-GH antibodies and treatment duration or study dose medication. No antibodies were detected in any subjects taking placebo. Currently there is no evidence of a relationship between anti-GH antibodies and a decrease in efficacy or an increase in adverse events frequency. As with any recombinant protein, the clinical significance of developed antibodies is unknown and therefore should be monitored.

Pituitary Tumour Size/MRI Results

In order to assess whether pegvisomant had any effects on tumour size, MRIs were analysed at baseline, every 6 months and at the final visit in 5 studies (SEN-3611, 3613, 3613A, 3614 and 3615). Results for changes in tumour volume by prior tumour therapy were presented (prior treatment included surgery alone, radiation alone, and the combination of surgery and radiation). Overall, subjects who received pegvisomant had no significant change in tumour volume from baseline to endpoint (mean of 11.5 months between baseline and final MRI) compared with a slight decrease of 0.22 cc in the placebo group (mean of 2.5 months between MRIs). However, in the subgroup of patients with surgery alone as prior treatment an increase of 0.10 cc was observed in the pegvisomant group, whereas a decrease of 30 cc was observed in the placebo group.This was probably due to two patients in the pegvisomant group who required treatment due to progression in tumour size (from 2.93 cm^3 to 5.41 cm^3 in one case and from 5.53 cm^3 to 8.71 cm^3 in the second one). Both had large, globular tumours with impingement on the optic chiasm at baseline. A single patient experienced growth from 5.53 cm^3 to 8.71 cm^3 during intermittent pegvisomant treatment, and was treated with radiotherapy. The second (3613A-401) had an increase in tumour volume from 2.93 cm^3 to 5.41 cm^3 over a period of 31 months on intermittent pegvisomant and octreotide treatment.

Elevations in Serum GH Concentrations

SEN-3614 results showed that serum GH concentrations increased in a dose-dependent manner in patients treated by pegvisomant. Serum GH concentrations were also observed to increase in the follow-up studies (SEN 3613 and SEN 3613-A). The mean serum GH concentrations stabilised once serum IGF-I concentrations became normal. The rise occurred after 2 weeks of treatment. Thereafter GH levels remained stable.

Insulin sensitivity

Data from SEN -3611 and SEN -3613A studies in patients with acromegaly showed a decrease in fasting insulin from 22.62±3.40 at the beginning of SEN –3611 study to 13.08±2.01 at data cut off, without any changes in glucose levels, suggesting a significant improvement in insulin sensitivity.

In the SEN-3631 study, pegvisomant was assessed in 13 subjects with type 1 diabetes and in 12 subjects with type 2 diabetes. Mean fasting plasma glucose decreased from 11.6 mmol/L at baseline to 9.2 mmol/L at Week 12 (21% decrease); mean HbA1c decreased from 8.54% at baseline to 7.82% at

Week 12 for the composite group (decrease of 0.72). Four non-serious adverse events of hypoglycaemia were reported.

A warning regarding the hypoglycaemic risk in diabetic patients treated either by insulin or by oral hypoglycaemic agents is mentioned in the SPC (see sections 4.2, 4.4, and 4.5).

Vital signs

No meaningful changes were noted in vital signs or anthropometrical parameters. Pegvisomant had no clinically significant effect on these safety parameters. No meaningful changes were produced in ECG.

Discussion on Clinical Safety

Given the short follow-up, there is presently no evidence that treatment with pegvisomant results in pituitary tumour growth or regression. Tumour size, should, however, be monitored periodically during treatment with Somavert. Long-term follow-up on tumour size will be provided by the planned post-market database. Taking into account that somatostatin analogues reduce tumour size in a substantial proportion of patients, Somavert was considered inferior to somatostatin analogues in terms of tumour control. In order to clarify the precise impact of Somavert on tumour growth, the Company have committed to conduct a long-term study of tumour volume in patients treated with Somavert as part of their post-authoriation obligations.Serum concentrations of alanine aminotransferase and aspartate transaminase should be monitored at four to six week intervals for the first six months of treatment with Somavert, or at the occurrence of any signs suggestive of hepatitis. A warning and recommendations on monitoring of liver enzymes has been included in the SPC (see section 4.4, *Special warnings and special precautions for use*). A warning regarding the hypoglycaemic risk in diabetic patients treated either by insulin or by oral hypoglycaemic agents is mentioned in the SPC (see sections 4.2, 4.4, and 4.5). The clinical significance of the detected serum anti-GH antibodies is unknown. Given that Somavert is intended for long-term administration, correct assessment of the immunogenicity of pegvisomant remains important and will be further explored by the Company.

5. Overall conclusions, benefit/risk assessment and recommendation

Quality

Except for a limited number of points, which can be addressed as part of post-authorisation commitments, the quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Viral safety and batch-to-batch consistency has been documented and the relevant test will be performed according to the agreed specifications.

Preclinical pharmacology and toxicology

The pharmacodynamic studies presented showed that pegvisomant is a potent competitive and specific antagonist of hGH binding *in vitro* and *in vivo*.
Preclinical data revealed no special hazard for humans based on studies of repeated dose toxicity in rat and monkey. However, due to the marked pharmacological response in monkey, systemic exposures higher than those achieved in patients at therapeutic doses have not been studied.

Clinical efficacy

The effectiveness of a daily Somavert therapy of 10-30 mg, following a 80 mg bolus dose was demonstrated as compared to placebo in the phase III SEN-3614 study. The percentage of subjects

with normalized IGF-I concentrations was significantly greater for each of Somavert doses at each time point compared to placebo.

There was evidence of a relationship between the dose of Somavert and the percentage of subjects with normalized IGF-I concentrations. The 20 mg dose was statistically superior to the 10 mg dose from week 4 onward. The 15 mg dose is statistically superior to the 10 mg dose from 8 week onward. However, there was no difference between 15 and 20 mg.

The analysis of covariance showed no statistically significant effects for baseline IGF-I, entry strata, baseline GH or gender. Baseline body weight was a statistically significant covariate in the pairwise treatment comparisons.

No comparative clinical trial was carried out versus a reference medicinal product and the submitted documentation did not allow to conclude on the respective efficacy of Somavert versus somatostatin analogues. This is reflected in the approved indication. From a pharmacodynamic point of view, the mechanisms of action of somatostatin analogues and pegvisomant appear complementary (decrease of secretion + blocking the binding to receptors) and on this basis the Company has committed to explore the benefit of combination treatment using somatostatin analogues with pegvisomant by conducting a post-authorisation clinical study. Combination therapy is at present not recommended and this is appropriately reflected in the approved indication.

Clinical safety

The safety concerns are specifically related to pituitary tumour size and the presented data do not indicate that treatment with Somavert reduces tumour size. Appropriate text regarding the need to monitor tumour growth has been included in the SPC (see section 4.4, Special warnings and special precautions for use). Furthermore, the Company has committed to a long-term post marketing surveillance on pituitary tumour growth.

Benefit/risk assessment

No comparative trial was conducted with a reference medicinal product, i.e somatostatin analogues. Due to the lack of prospective clinical efficacy data comparing pegvisomant to somatostatin analogues, it was not possible to conclude on the respective efficacy of Somavert versus somatostatin analogues. The safety concerns are specifically related to pituitary tumour size and based on presented data, treatment by Somavert does not reduce tumour size. Therefore, the use of Somavert is limited to the treatment of patients with acromegaly who have had an inadequate response to surgery and/or radiation therapy and in whom an appropriate medical treatment with Somatostatin analogues did not normalize IGF-I concentrations or was not tolerated.
The benefit/risk of Somavert is considered positive and in order to address remaining issues, which are not at present a matter of concern, the Company has committed to quality, safety and efficacy follow-up measure agreed with the CPMP.

Recommendation

Based on the CPMP review of data on quality, safety and efficacy, the CPMP considered by consensus that the benefit/risk profile of Somavert in the *treatment of patients with acromegaly who have had an inadequate response to surgery and/or radiation therapy and in whom an appropriate medical treatment with somatostatin analogues did not normalize IGF-I concentrations or was not tolerated* was favourable and therefore recommended the granting of the marketing authorisation.

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