European Medicines Agency
*Evaluation of Medicines for Human Use*

Doc.Ref.: EMEA/CHMP/545666/2008



**CHMP ASSESSMENT REPORT**
**FOR**
**Opgenra**

International Nonproprietary Name:
Eptotermin alfa

**Procedure No. EMEA/H/C/000819**

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

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 75 23 70 51
E-mail: mail@emea.europa.eu http://www.emea.europa.eu

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# 1. BACKGROUND INFORMATION ON THE PROCEDURE

## 1.1 Submission of the dossier

The applicant Howmedica International S. de R. L. submitted on 20 December 2006 an application for Marketing Authorisation to the European Medicines Agency (EMEA) for Opgenra, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC, as amended

The applicant applied for the following indication:
**"**Opgenra is indicated for posterolateral lumbar spinal fusion in adult patients with spondylolisthesis who have failed at least six months of conservative non-surgical treatment."

**Scientific Advice:**
The applicant received Scientific Advice from the CHMP on 27 January 2003. The Scientific Advice pertained to clinical aspects of the dossier.

**Licensing status:**
Opgenra, under the name OP-1 Putty, was approved as a Humanitarian Use Device in the USA on April 2004. A PMA (pre-market approval) was submitted under the name OP-1 Putty, in June 2006.

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

Rapporteur: Pirjo Laitinen-Parkkonen (FIN) Co-Rapporteur: Patrick Salmon (IRL)



## 1.2 Steps taken for the assessment of the product

- The application was received by the EMEA on 20 December 2006.
- The procedure started on 21 February 2007.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 14 May 2007 . The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 14 May 2007.
- During the meeting on 18 – 21 June 2007, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 21 June 2007.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 16 December 2007.
- The summary report of the inspection carried out at the following site (Sterix Corporation Isomedix Services, 435 Whitney Street, Northborough, MA 01532, USA) between 15-16 August 2007 was issued on 14 November 2007.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 5 February 2008 .
- During the CHMP meeting on 18 – 21 February 2008, the CHMP agreed on a list of outstanding issues to be addressed in writing and in an oral explanation by the applicant. The final list of outstanding issues was sent to the applicant on 21 February 2008.
- The applicant submitted the responses to the list of outstanding issues on 25 April 2008.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the list of outstanding issues to all CHMP members on 15 May 2008.
- The Rapporteurs circulated an updated Joint Assessment Report Overview and Risk Management Plan to all CHMP members on 26 May 2008.

- During the CHMP meeting on 27 – 30 May 2008, outstanding issues were addressed by the applicant during an oral explanation before the CHMP.
- During the meeting on 23 – 26 June 2008, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a negative opinion for granting a Marketing Authorisation to Opgenra on 26 June 2008.

## 1.3 Steps taken for the re-examination procedure

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

Rapporteur: Tomas Salmonson (SE) Co-Rapporteur: Robert Hemmings (UK)

- The Applicant submitted a letter to the EMEA dated 8 July 2008 requesting the re-examination of Opgenra CHMP Opinion of 26 June 2008.
- During its meeting on 21-24 July 2008, the CHMP appointed Tomas Salmonson as Rapporteur and Robert Hemmings as Co-Rapporteur for the re-examination procedure.
- The detailed grounds for the re-examination request were submitted by the applicant on 27 August 2008 (Appendix 5.1). The re-examination procedure started on 28 August 2008.
- The Rapporteur's Assessment Report on the detailed grounds for the re-examination was circulated on 2 October 2008 . The Co-Rapporteur's Assessment Report was circulated on 1 October 2008.
- An Ad-hoc expert meeting was convened at the EMEA on 9 October 2008 to consider the grounds for re-examination.
- The Rapporteurs' Joint Assessment Report on the detailed grounds for the re-examination was circulated on 16 October 2008.
- During the CHMP meeting on 20 October 2008, the grounds for refusal were addressed by the applicant during an oral explanation before the CHMP.
- During the meeting on 20-23 October 2008, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a final positive Opinion by majority decision for granting a Marketing Authorisation for Opgenra. The applicant provided the letter of undertaking on the specific obligations to be fulfilled post-authorisation on 22 October 2008.

# 2. SCIENTIFIC DISCUSSION

## 2.1 Introduction

Spondylolisthesis, a condition characterised by the slippage of one vertebral segment on the one below, is often a result of a degenerative disc disease process. If pain, neurological deficits, and instability do not respond to conservative management, decompression and lumbar spinal fusion are the most common surgical options for progressive degenerative spondylolisthesis with spinal stenosis.

Autologous bone is the standard treatment for the spinal fusion. The limitations of obtaining autograft bone are obvious: the amount is limited and the harvesting of autograft bone causes secondary morbidity at the harvesting site. Allograft bone is widely used, but it has not solved all the problems in bone grafting: the amount of allograft is also limited and autogenous graft has been shown to be superior to allograft, as remodelling and bone healing takes place more slowly in allografts compared to autografts. Allografting carries a risk of transmissible diseases, such as hepatitis and HIV. Xenografts are even more problematic.

Various synthetic materials have been developed as bone substitutes and as alternatives to bone materials. The synthetic materials are not osteoinductive, i.e. they do not induce the formation of new bone. The development of appropriate osteoconductive carriers has not progressed as rapidly as the isolation and synthesis of growth factors. This has significantly slowed down the development of clinically successful biosynthetic composite implants.

Opgenra is composed of two separate units (2 vials):

- Eptotermin alfa (OP-1) and bovine collagen matrix as a single unit
  This combination is also known as Osigraft which was granted a MA in the EU through a centralised procedure on 17 May 2001 for the indication). The current EU therapeutic indication of Osigraft is "*treatment of non-union of the tibia of at least 9-month duration, secondary to trauma, in skeletally mature patients, in cases where previous treatment with autograft has failed or use of autograft is unfeasible.* "
- Carboxymethylcellulose (CMC) in a separate vial

In the United States and Canada Osigraft (OP-1 Implant) and Opgenra (OP-1 Putty) have been classified as medical devices.

The active substance of Opgenra is eptotermin alfa that is a recombinant human osteogenic protein (also known as bone morphogenetic protein 7, BMP-7, or OP-1 protein). Eptotermin alfa is a growth factor belonging to the BMP family.
The BMP family of proteins is the largest subgroup of the transforming growth factor-β (TGF-β) superfamily. BMPs are growth and differentiation factors, causing pluripotent mesenchymal cells to terminally differentiate (mature) into a number of specialised cell types including osteoblasts, chondrocytes, myoblasts, fibroblasts, and adipocytes.
Human BMP-7 is a member of the TGF-beta superfamily of growth and differentiation factors and is a glycosylated, disulfide-bonded, dimeric protein with two major subunit species of amino acids. Eptotermin alfa is expressed and secreted in a Chinese hamster ovary (CHO) cell culture
process."

Eptotermin alfa and collagen matrix, on one hand, and CMC, on the other hand, are manufactured and primary packaged separately. Once released, they are packaged together as Opgenra. The CMC imparts the putty-like consistency for ease of moulding between the transverse processes of the spine. The active substance in the product is still eptotermin alfa, which acts as an osteoinductive agent at the treatment site. The contents of the 2 vials must be aseptically combined and mixed with 2.5 ml sterile saline just before use at the time of surgery to produce a product with a putty-like consistency. The product is implanted into each side of the spine bridging the dorsal surfaces of the transverse processes.

Opgenra is proposed for use as an alternative to autograft in patients requiring posterolateral lumbar spinal fusion. The initially proposed indication was *"Opgenra is indicated for posterolateral lumbar spinal fusion in adult patients with spondylolisthesis who have failed at least six months of conservative non-surgical treatment."*

At the time of the oral explanation the applicant proposed a more limited indication: *"Opgenra is indicated for posterolateral lumbar spinal fusion in adult patients with spondylolisthesis where autograft has failed, is not feasible or is unlikely to be efficacious."*

The approved indication is Opgenra is indicated for posterolateral lumbar spinal fusion in adult patients with spondylolisthesis where autograft has failed or is contra-indicated.

## 2.2 Quality aspects

**Introduction**

Opgenra is composed of two separate vials: a vial with Eptotermin alfa (OP-1) and bovine collagen matrix and a vial with Carboxymethylcellulose (CMC).

Eptotermin alfa and collagen matrix, on one hand, and CMC, on the other hand, are manufactured and primary packaged separately. Once released, they are packaged together as Opgenra. The CMC imparts the putty-like consistency for ease of moulding between the transverse processes of the spine. The active substance in the product is still eptotermin alfa, which acts as an osteoinductive agent at the treatment site.

Currently eptotermin alfa is marketed in the EU under the invented name of Osigraft, which is practically the same recombinant human osteogenic protein 1 (OP-1) in a type I bovine collagen matrix as with Opgenra but without the putty CMC. Osigraft was granted an MA in the EU through a centralised procedure on 17-May-2001.



**Active Substance**

Eptotermin alfa Drug Substance is a recombinant human protein (eptotermin alfa) produced from a genetically altered recombinant Chinese Hamster Ovary (CHO) cell line.

The cDNA for the eptotermin alfa gene was cloned from human c-DNA libraries using a probe based on peptide sequences of bovine osteogenic proteins. The host cell line used for the construction of the production cell line is a Chinese Hamster Ovary cell line. Details on the preparation, testing and storage of the cell banks were provided.

- Manufacture

Bulk eptotermin alfa is manufactured using a standardized mammalian cell culture process. All manufacturing steps of Eptotermin alfa have been validated. The preparation of the MCB and WCB is well described. MCB, WCB and End of production cells underwent extensive microbial/viral testing.

During fermentation of eptotermin alfa, raw materials from animal origin are used. Assurance has been given that these raw materials do not present a risk of BSE/TSE. Appropriate in-process controls have been implemented. Mycoplasma and *in vitro* adventitious virus testing is performed.

The purification process consists of ultrafiltration, viral filtration and column chromatography steps. Appropriate in-process controls have been implemented. Viral clearance has been validated with reference to the appropriate CHMP guidelines.

The active substance may be stored up to 24 months at the approved storage temperature.

- Specification

The active substance release specifications have been suitably justified and are supported by consistent data from multiple lots.

- Stability

The data confirm that the active substance may be stored up to 24 months at the recommended storage temperature.

**Medicinal Product / Vial with eptotermin alfa and collagen**

The drug product vial contains one gram of sterile powder containing 3.5 mg eptotermin alfa protein and bovine collagen (Type I, derived from bone) in a 2 ounce vial for reconstitution. This formulation is identical to the one approved for Osigraft. The Drug Product is presented as a sterile powder for reconstitution in 2 ounceType1 borosilicate glass vial (USP/PhEur). The vial is sealed with a 43 mm grey butyl pre-siliconized lyophilization stopper and crimped with a gamma stable plastic/aluminium seal.

- Manufacture of the Product

Bovine collagen, or collagen matrix, is an osteoconductive excipient of the Drug Product. The starting material for the production of collagen matrix is bone powder derived from the midshaft of femurs and tibias that are sourced from animals of USA origin. The collagen is manufactured by chemical extraction of crushed bone. The collagen is particulate and is sieved to ensure a specific particle size range. The production process has been validated to ensure viral clearance using appropriate viral models. The collagen matrix has been characterised by protein chemistry, biological and immunological techniques.

The manufacture of Drug Product consists of rehydration of the collagen matrix and reconstitution of eptotermin alfa. Glass vials are filled with defined amounts of both components and the vials are vacuum-dried. The powder is mixed and separate vials are filled to yield units containing 1 g powder with 3.5 mg eptotermin alfa. The Drug Product is terminally sterilised by gamma irradiation. All steps of the manufacturing process have been validated.

- Product Specification

The experience of the Applicant in production of Osigraft is extensive. The release specifications of the Osigraft and all analytical methods have been used for more than 6 years. Appropriate release specifications have been set for the finished product.

- Stability of the Product

The data confirm that the drug product may be stored up to 24 months at the recommended storage temperature of 2 to 8°C.

**Medicinal Product / Opgenra**

- Manufacture of the Product

Opgenra Drug Product is composed of separately primary packed Drug product vial containing eptotermin alfa and collagen and Carboxymethylcellulose (CMC) vial.

The CMC component consists of 230 mg of sterile CMC in a 10 ml vial. Both vials are maintained sterile within individual blister packs comprised of plastic trays and lids. At the time of surgery, the contents of each vial are transferred to a sterile mixing bowl, reconstituted with normal saline, and mixed with a spatula to produce a product with a putty-like consistency.

The company purchases the CMC from a commercial vendor and it is refilled into more suitable containers and quality tested before final filling. Filled CMC vials are sterilised by gamma irradiation by Sterix Isomedix. The company has clarified the source and vendor for the CMC and the quality of this excipient has been demonstrated to comply with Ph.Eur. requirements. Also the release test methods have been evaluated and are accepted for release of CMC.

- Product Specification

Appropriate release specifications have been set for the finished product.

Compatibility of the Osigraft Drug Product with the new excipient has been studied and the company has provided adequate justification not to include further release tests for the Opgenra Drug Product.

- Stability of the Product

The proposed shelf life for CMC is 24 months under ambient storage conditions.

## 2.3 Non-clinical aspects

**Pharmacology**

The pharmacological basis for the development of Opgenra is based on the experience gained with Osigraft.

- Primary pharmacodynamics

The relevance of animal models was evaluated by comparing OP-1 binding to the BMP receptor extracellular domains (ECD) from human, rat and rabbit in a Biacore assay. Comparative binding affinities (Kd) between human, rat and rabbit BMPR ECDs were demonstrated. However, the receptor binding of OP-1 in large animal models, dog and sheep, was not addressed.

Athymic rats were used to compare the efficacy of Opgenra with Grafton Putty® (DBM, demineralised bone matrix). A significantly higher fusion rate was observed for Opgenra than for Grafton Putty®. However these results have been obtained using a Grafton Putty® dose lower than that used in the studies where the efficacy was shown
.

Dogs were used to evaluate and compare treatments of Opgenra alone, Opgenra in conjunction with autograft, and autograft alone in terms of their respective abilities to promote a successful posterolateral spinal arthrodesis. Overall, these data showed that spinal fusion rate with Opgenra is comparative to autograft, and that the fusion rate can be accelerated with Opgenra without compromising the structural integrity of the bone.

Rabbit pseudarthrosis repair model was used to evaluate the ability of Opgenra to induce fusion under challenging conditions. Nicotine exposure is known to impair bone healing and is used here to induce pseudarthrosis. These data showed that in conditions where spinal fusion is compromised, Opgenra appeared to produce efficient healing where autograft did not.

Opgenra was shown to produce comparative healing results in another challenging condition where multi-level spinal fusion was attempted, namely the sheep model. Opgenra was compared with autograft, collagen+CMC carrier and with no-graft treatment. Depending on the method of assessment, a 56% fusion rate at best was noted. While no fusion was detected in the no-graft and carrier groups, Opgenra and autograft treatments produced significantly higher and comparable fusion rates when assessed by manual palpation, radiographic analysis and biomechanical testing. No difference was seen between Opgenra and autograft treatments.

Efficacy of Opgenra was compared with Osigraft and autograft (control) in the dog laminectomy and spinal fusion model. The fusion rate success appeared to vary depending on the method of assessment. Manual palpation revealed 91% fusion rate for Opgenra and 80% for Osigraft, while 25% of the animals in the control group fused. However, when more strict fusion criteria of CT evaluation were used the fusion rates were 63% for Opgenra, 40% for Osigraft and 25% for the control.

A study was performed in dogs to evaluate the effects of the osteogenic protein device on neurological tissue in a canine laminectomy and posterolateral spinal fusion model. The primary objective of this study was to discover potential neurotoxic effects of OP-1 formulations (Osigraft and Opgenra) on the spinal cord in a clinically relevant model of spine fusion. The safety assessment included clinical monitoring for neurological deficit, computed tomography imaging (CT) and gross observation at necropsy of spinal canal stenosis and neuropathological evaluation of the spinal cord for neurotoxicity. The dura was opened and small amounts of Osigraft and Opgenra were placed in the subarachnoid space. Although pathological features of neurotoxicity were not detected, there were certain findings, such as spinal cord compression, oedema, and demyelination that were observed in majority of the animals of the OP-1 treatment groups but not in the control animals. Furthermore, all Osigraft and Opgenra treated animals showed clear signs of inflammation

These studies provide evidence that Opgenra is effective in large animal posterolateral lumbar fusion models. With regard to size, sheep would be the best large animal model to support clinical use. However, there is a significant caveat in the sheep studies. No information on randomisation and/or normalisation of data according to the weight has been provided. As sheep can substantially vary in weight, either randomisation of animals into treatment groups according to the weight, or normalisation of data according to weight may be necessary. Furthermore, these studies have been performed in animals that are skeletally mature but relatively young in their adulthood. Therefore, it can be assumed that the new bone formation and bone healing properties of these animals are optimal. The same properties within human patients may be compromised in special populations.

- Secondary pharmacodynamics

Secondary pharmacodynamic studies have not been performed. The absence of pharmacodynamic drug interaction studies are justified by the fact that Opgenra will remain at the site of administration, and by the experience from clinical use of Osigraft.

- Safety pharmacology programme

The submitted safety pharmacology studies have been evaluated during the marketing authorisation process of Osigraft and were not re-evaluated. Those studies were performed in rat, and effects on the cardiovascular function were observed. The observed effects included transient increase in blood pressure, tachycardia, bradycardia and elevated temperature. To further evaluate the cardiovascular effects of OP-1, an additional safety pharmacology study in dog was submitted in response to the D120 List of Questions. The observations in rats were assumed to be due to intravascular precipitation and embolisation, and to minimise such effects OP-1 was administered as a slow bolus injection into the dogs. Intravenous slow bolus injection of OP-1 was not associated with changes in cardiovascular or respiratory function.

- Pharmacodynamic drug interactions

The absence of pharmacodynamic drug interaction studies has been justified by the fact that Opgenra will remain at the site of administration, and by the experience from clinical use of Osigraft.

**Pharmacokinetics**

$^{125}$I-Opgenra pharmacokinectis and distribution have been studied in the rats and monkeys following single intravenous administration of the OP-1 protein in the fusion site.

A dose proportional exposure (AUC) and a rapid clearance were observed in **monkeys** dosed with a single i.v. bolus of eptotermin alfa. Rapid biphasic elimination was observed at the high-dose level. Elimination half lives were dependent on dose. Clearance data indicated that renal clearance may have been predominant. The apparent volume of distribution was low indicating that eptotermin alfa was not distributed into a deep compartment in tissues.

In **rat**, similar PK characteristics were observed for all measured parameters at the doses used. Rats were dosed with a single i.v. bolus of eptotermin alfa at 0.025, 0.25, 2.5, and 3.5 mg/kg. Exposure was dose proportional and clearance was rapid with a biphasic elimination profile observed for all dose levels. Elimination half lives were dependent on dose. Clearance was similar to the glomerular filtration rate in the rat. Volume of distribution was low and comparable to total body water of the rat.

Another study in rat was conducted using radio-labelled $^{125}$I-eptotermin alfa to determine the rate of clearance from the systemic circulation. $^{125}$I-eptotermin alfa was administered intravenously. Elimination of radioactivity from the blood stream exhibited first order kinetics. The terminal half-lives of total and TCA-precipitable protein-bound radioactivity were independent of dose over the dose range in both male and female rats. The mean $t_{1/2}$ of total radioactivity was 8.0 and 5.9 hours in male and female rats, respectively, and for the protein-bound radioactivity the $t_{1/2}$ was estimated to be 15.1 and 9.6 hours, respectively.

Disposition kinetics of radiolabelled eptotermin alfa was determined in male **rabbits** following surgical implantation of $^{125}$I-Opgenra into lumbar spine. The radioactivity concentrations in blood were low. Maximum blood levels were achieved at 24 hours. These data show that radioactivity is continuously released from the implant. However, it is not known whether it is native protein-bound (eptotermin alfa) or free $^{125}$I or $^{125}$I bound to degradation products.
Tissue distribution of $^{125}$I-eptotermin alfa was evaluated in **rat** following an i.v. administration. Peak concentrations in the blood, liver, lungs, spleen, and thyroid were much higher than those in other tissues regardless of the gender.

The tissue distribution of $^{125}$I-eptotermin alfa was also evaluated in **rabbit** following the surgical implantation of $^{125}$I-Opgenra. The highest tissue radioactivity concentration and AUC values were obtained from the surgical sites, urinary bladder wall, urinary bladder contents, and thyroid gland. The thyroid levels were suggested to be attributed to free $^{125}$I. The high concentrations in urinary bladder wall and urinary bladder contents are somewhat expected since Opgenra is predominantly excreted into urine. Besides the surgical site, thyroid gland and urinary bladder wall, radioactivity was noted up to 72h in several organs and tissues. Apart from the implant site, thyroid gland and urinary bladder wall, relatively high $AUC_{0\text{-tlast}}$ values were determined for seminal vesicle, myocardium and prostate gland. No exposure was observed in the adipose tissue (white and brown fat), brain, eye, pituitary gland, skeletal muscle (dorsal), and spinal cord where the mean radioactivity concentrations were below the limit of quantification (LOQ) for all time points. Toxicokinetic evaluation in a new toxicity study submitted in response to D120 questions confirmed that OP-1 is continuously released at low level from the implant site.
Excretion of radioactivity was evaluated in the rabbit following the surgical implantation of $^{125}$I-Opgenra. Excretion occurred mainly via urine.
Placental transfer was evaluated in pregnant rats using $^{125}$I-eptotermin alfa. Considering that no more that 2 to 3% of the dose is found in the bloodstream after implantation, the expected potential transfer of eptotermin alfa may be negligible.



**Toxicology**

Opgenra toxicology studies include a pivotal single-dose toxicology study with subcutaneous implantation of Opgenra in rat, a genotoxicity study (Ames test) with Opgenra, a cytotoxicity study in L292 cells, and an epicutaneous sensitisation study in guinea pig. All toxicology studies were conducted in compliance with the GLP regulations, except where stated. Those exceptions are considered not to have had an impact on the outcome of the toxicology program.

- Single dose toxicity

Single-dose toxicity studies with intravenous injection of eptotermin alfa were performed in mouse and in rats. No acute toxicity was observed in these studies.

Single-dose toxicity studies with subcutaneous implantation of Osigraft (2studies) with doses up to 1.740mg/kg eptotermin alfa, were performed in rats. Evidence of systemic toxicity was not noted in the short-term (14 or 21 days) studies.
In the 52-week study (a subgroup of animals from the 104-weeks carcinogenicity study) neoplastic changes were observed after a single subcutaneous administration of Osigraft. These consisted of pleiomorphic sarcomas at the site of implantation of Osigraft. The sarcomas showed a trend of increased incidence with dose of Osigraft

In the 14-day subcutaneous implantation study with Opgenra a statistically significant decrease in haemoglobin, packed cell volume levels and red blood cell count was noted in the high-dose group female, as well as females in the low and mid-dose groups had statistically significant decrease in haemoglobin level. These findings are unrelated to the treatment because all individual values fell within the recorded background values. Significant increase of adrenals and liver weights was noted in high-dose females.

Local foci of ossification were found in short-term and long-term studies after subcutaneous implantation with Osigraft and Opgenra at all dose levels. Inflammation was the most notable finding common to all studies. Signs of chronic inflammation were observed in majority of the animals at all dose levels, and were associated with fibroplasia and fibrosis. There may be several mechanisms for these inflammatory reactions. They may represent a stimulated regeneration or foreign body reactions. However, an immune reaction cannot be excluded.

- Repeat dose toxicity (with toxicokinetics)

Repeat-dose toxicity studies with intravenous injection of eptotermin alfa were performed in rats and in monkey. Body weight decrease was observed in both rats and monkeys.
Changes in haematology were observed in the 4-week rat study; decreased haemoglobin, haematocrit, packed cell volume, as well as elevated levels of platelets, neutrophils and leukocytes in high-dose males and females. Also, a decrease in serum albumin, and increase in serum globulin, potassium and cholesterol was noted in high-dose males and females. Changes in the organ weights were also noted; reduced ovary weight in females and increased testis weight in males. Thymus weight was decreased in both females and males. Hyperplastic and ossified cartilage was noted locally at all doses. This was considered as a pharmacological effect of eptotermin alfa.

In the 4-week monkey study, local unresolved (8 weeks recovery) responses were observed at all dose levels. These included damage of blood vessels at injection site, local vasculopathy, thrombi, and fibrosis. These were also noted in control group but to a less extent. A small focus of osseous differentiation at the injection site was seen in the high-dose animals. In monkeys, clinical observations were done on a twice a day basis throughout the study and there no observations other than the injection sites described above. A complete list of tissues and organs were microscopically examined for histopathological findings. There were no findings other than those at the injection site.

Toxicokinetics could not be adequately assessed since most of the serum sample eptotermin alfa concentration results were at or below the level of detection of the ELISA used to detect eptotermin alfa concentrations in serum.

- Genotoxicity

Genotoxicity of Osigraft and Opgenra was tested in *in vitro* studies. A gene mutation test in bacteria (Ames test) proved to be negative for both Osigraft and Opgenra, as was the chromosomal aberration test in Chinese hamster ovary cells for Osigraft eluates. Mutagenic potential is not anticipated for Opgenra.

- Carcinogenicity

The applicant conducted a 104-week carcinogenicity study in rats using subcutaneous administration of Osigraft. There was a problem with the design of the study, however, in that the control group did not receive a positive control for solid-state carcinogenicity (see below). It is therefore not possible to extract with any certainty the effect of Osigraft from the effect of implantation per se. In the 104-week carcinogenicity study, neoplastic changes were observed after a single subcutaneous administration of Osigraft. These consisted of pleiomorphic sarcomas at the site of implantation of Osigraft. The sarcomas showed a trend of increased incidence with dose of Osigraft.

To clarify the clinical relevance of this finding, the applicant conducted a review of the available literature, an additional analysis of the data from the 104-week carcinogenicity study, and a review of the clinical use of Osigraft. Taking into account the short-lived bioavailability of OP-1, the reported effects of bone morphogenetic proteins on malignant cell lines *in vitro,* the lack of genotoxicity and histology observations from several other studies, the known sensitivity of the rat to the development of tumors at the site of subcutaneous implants, and the finding that sarcomas were observed at the site of the implant and ectopic ossification, it is concluded that it is unlikely that OP-1 initiates or promotes tumorigenesis. Nevertheless, Osigraft must not be applied in the vicinity of any tumours. It is likely that the bone formation resulting from subcutaneous Osigraft was treated as a foreign body having the characteristics which are known to induce solid state carcinogenesis or 'Oppenheimer effect' in reactive animal species.

- Reproduction Toxicity

Reproduction and developmental toxicity was evaluated in rats and rabbits with intravenous injection of eptotermin alfa and subcutaneous administration of eptotermin alfa + Freund's adjuvant. There was no indication of maternal toxicity. There was no indication of any effects on the embryo-foetal development in the offspring of the rabbits. However, although not statistically significant, more skeletal malformations were observed in the offspring of the high-dose group. Dose-dependency could not be determined since malformations were not evaluated in the low or the medium-dose groups. Prenatal and postnatal function was evaluated in rabbits that were repeatedly dosed with subcutaneous injections of eptotermin alfa and adjuvant during gestation. There was no evidence of any effects on parturition or on the postnatal development of the kits raised to Day 28 of lactation. However, a statistically significant increase in skeletal malformations (misaligned sternabrae) was noted in the offspring compared to controls within the study, although these malformations were within the levels observed in historical controls.
Placental transfer was evaluated in a rat PK study. Rats were given 3.8 mg/kg of $^{125}$I-eptotermin alfa i.v. (38 times the human dose). It was determined that less than 1% of the dose was transferred to the foetus. Most of the radioactivity was located in the thyroids and stomach, the expected locations for free iodine. Considering that no more than 2 to 3% of the dose is found in the bloodstream after surgical implantation the expected potential placental transfer of eptotermin alfa is negligible.

- Local tolerance

*In vitro* studies with rabbit blood and cultured cell lines were used to evaluate haemolytic potential and cytotoxicity of Osigraft. Opgenra was also tested for cytotoxicity in cultured cells. Overall, the results were mainly inconclusive; cytotoxicity could not be reliably excluded. Dermal irritation was evaluated in guinea pig, and minimal erythema was observed at dose level 0.35mg eptotermin alfa.

Dermal and epicutaneous sensitisation assays with Osigraft or Opgenra revealed no evidence of delayed hypersensitivity.

- Other toxicity studies

Tumour promotion assays were performed with Osigraft. The effect of eptotermin alfa on malignant human cell lines has been mainly differentiating, not proliferative. It is unlikely that the tumour promotion potential of Opgenra would be different from what has been observed for Osigraft.

However, the theoretical possibility of stimulation of tumour growth has not been excluded. This possibility has to be dealt with by observing occurrence of malignancies in the post-marketing surveillance data.

Immunogenicity of Opgenra was not assessed in non-clinical models. Osigraft has proved to be highly immunogenic in animal studies, and the OP-1 antibodies seem to have neutralising capacity. It would have been of interest to compare immunogenicity of Osigraft and Opgenra. There is a possibility that the CMC component would increase immunogenicity of the product. Nevertheless, there are human data on the immunogenicity of Opgenra. These data demonstrate that a relatively weak immune reaction against both OP-1 and collagen is induced after first administration. These data have led to a recommendation to avoid re-administration in order to avoid a secondary immune response.

**Ecotoxicity/environmental risk assessment**

The assessment of the risk to the environment from the use of Opgenra has been prepared in accordance with EMEA/CHMP/SWP/4447/00 issued 1 June 2006. The drug substance, eptotermin alfa, and the matrix, Type 1 bovine bone collagen, are both proteins and, as such, are exempt from the requirement for an Environmental Risk Assessment. Apart from saline, the only other significant component of the product is sodium carboxymethylcellulose, which is a widely used approved excipient in pharmaceutical products and is unlikely to result in any significant risk to the environment.

## 2.4 Clinical aspects

**Introduction**

The clinical dossier is very limited. Only one pivotal study and one pilot study have been submitted. This reflects the fact that the product has been initially developed and approved in the USA as a medical device according to the Humanitarian Device Exemption for which demonstration of efficacy is not required.

**GCP**

The pivotal Clinical trial was performed in accordance with GCP.

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

**Pharmacokinetics**

- Absorption
- Distribution
- Elimination
- Dose proportionality and time dependencies

No pharmacokinetic studies have been carried out in man. The distribution, metabolism and excretion of Opgenra in man are not known but are expected to be similar to OP-1 from Osigraft. Opgenra is administered locally and the pharmacokinetic studies in the non-clinical section of the dossier suggest that OP-1 is largely confined to the implantation site.

- Special populations

Studies in subjects with organ impairment have not been conducted, and this was accepted by CHMP for the same reason: Opgenra is administered locally and the pharmacokinetic studies in the non-clinical section of the dossier suggest that OP-1 is largely confined to the implantation site.

- Pharmacokinetic interaction studies

Neither *in vivo* nor *in vitro* pharmacokinetic or pharmacodynamic data on the possible interactions have been provided by the applicant. Obviously, conventional drug-drug interactions are unlikely. However, drug-device interaction cannot be ruled out. For example, it is known that the product Calstrux (beta calcium triphosphate), an absorbable bone void filler, used in combination with other BMP-containing products has resulted in localised induration, swelling, inflammation, wound drainage, infection and device migration. This possible interaction has been appropriately specified in the SPC. Moreover, there is evidence that prostaglandin E1, for example, promotes the osteogenic activity of rhBMP (Ono *et al.* 1996).

**Pharmacodynamics**

- Mechanism of action

The pre-clinical studies performed suggest that Opgenra acts locally and generates new bone that is similar to normal bone.

- Primary and Secondary pharmacology

No pharmacodynamic studies have been carried out in man. Given the biological actions of OP-1 and the specific characteristics of the product (an implant), this has been considered acceptable.

**Clinical efficacy**

- Dose response studies

No dose response studies have been performed in man. The amount of OP-l/g collagen matrix and CMC in the product used in the pivotal study was chosen on the basis of dose-ranging studies in rabbits, dogs and primates. The absence of dose-ranging studies in man is acceptable provided that the product is proved to be safe and effective, with reference to the Note for Guidance on Dose Response Information to Support Drug Registration (CPMP/ICH/378/95). It is acknowledged that considering the proposed indication, it would not be possible to search for the lowest effective dose.

Possible off label use can entail the use of doses different to (namely larger) than those of the current posology and can also entail use in other patient groups, namely children. Furthermore, there is a possibility of putative repeated off-label use.

- Main studies

The applicant has submitted two clinical studies: the pilot study S99-01S (a feasibility study) and the pivotal study S01-01US in support of the efficacy and safety of Opgenra.
The pilot study does not add to the overall assessment of efficacy but provides some safety data.

Pivotal Study S01-01US

METHODS

*Study Participants*
This randomised open label multicentre study population comprised patients with a diagnosis of degenerative lumbar spondylolisthesis of grade I and II demonstrated by medical history, physical examination and radiographic imaging, deemed eligible for decompression and spinal fusion with the use of autograft. Each patient was required to have undergone 6 months of pre-trial non-operative treatment. Patients with non-degenerative spondylolisthesis of any grade at the affected level and patients with degenerative spondylolisthesis of grade III or IV were excluded.

*Treatments*

Patients were randomized to treatment in a 2:1 ratio to either Opgenra or a control arm, in which autogenous bone graft from the iliac crest (autograft) was used. This was considered appropriate as autograft was considered the current standard-of-care for spinal fusion.

*Objectives*
The objective of the study is to demonstrate that Opgenra treatment is non- inferior to autograft treatment.

*Outcomes/endpoints*
Efficacy was measured by calculating the 12-, 24-, and 36- month overall success rates.
The primary efficacy variable was the overall success rate at 24 months in the Opgenra and the autograft groups.

A patient was considered an "overall success" if he or she met all 6 of the following criteria:
1. Radiographic demonstration of spinal fusion (radiographic success) defined as meeting all three of the following conditions: Presence of bridging bone (on AP or lateral radiographs) between transverse processes of 2 vertebral bodies, and angulation of ≤5°, and translational movement of <2 mm on flexion/extension radiographs of the affected level.
2. ODI (Oswestry Disability Index) improvement of at least 20% from the pre-treatment visit.
3. No revisions, removals, or supplemental fixations (criteria based on the Guidance Document for Preparation of IDEs for Spinal Systems, January 13, 2000)
4. The absence of serious device-related AEs during the course of the study.
5. No unresolved neurological deficits at the final examination that were not present prior to study treatment, unless the deficit was due to a concurrent medical condition.
6. No decreases in neurological status at the final examination from the preoperative evaluation, unless the decrease is due to a concurrent medical condition.

The following additional information was also collected for each patient:
- Visual Analogue Scale Results for Pain Assessment
- Donor Site Pain (autograft patients only)
- Medication Use
- Hospitalisation Data
- General Health Survey (SF-36)

The criteria for treatment success are in line with the recommendations of the FDA guidance on spinal systems, although they are not very stringent (for example the amount of bridging is not defined).

*Sample size*
The estimated overall success rates were 53% for the Opgenra group as compared to 47% for the autograft group. The non inferiority margin was set to 10% .
*The predefined non inferiority criterion of 10% was post hoc amended to 14%.*

*Randomisation*
The randomisation scheme was stratified by investigational site.
Randomising within the numerous sites can be expected to lead to some treatment imbalance and loss of power. In an open-label trial stratified by investigational site, treatment allocation becomes predictable towards the end of a block, which can influence the investigators` decision about the subjects' entry into the trial. The withdrawal of 41 patients (21 Opgenra patients versus 20 autograph), on knowing the treatment allocation might have introduced a bias related to the intervention.

*Blinding (masking)*
The lack of blinding is, as such, acceptable because of the need to harvest bone from the iliac crest in the autograph group. To minimize bias, the radiographic outcomes were evaluated by two separate reviewers who were blinded to patient identification, clinical history and treatment.

*Statistical methods*

Two populations were defined for efficacy analyses: Per Protocol Population and (modified) Intent to Treat Population**.**

Later, prior to datalock, the following data sets were defined for the SAP (statistical analysis plan):

**Table 1 – Study Populations for SAP Analysis**

| Parameter | Number (%) of Patients | | |
|---|---|---|---|
| | Overall | OP-1 Putty | Autograft |
| Safety Population | 295 (100.0) | 208 (100.0) | 87 (100.0) |
| Modified ITT Population | 293 (99.3) | 207 (99.5) | 86 (98.9) |
| Per Protocol Population | 289 (98.0) | 204 (98.1) | 85 (97.7) |

Source: Table 14.1-Table .1.1, A1.1
Note: Percentages are based on total number of safety patients for each treatment group or overall as appropriate.

For the mITT population, the SAP analysis used a logistic regression model to take into account the effects on success rate of baseline characteristics that were statistically significant at the 0.10 significance level. The model yielded adjusted success rates. The characteristics considered in this analysis were: Age: <45 years old, 45-65 years old, >65 years old; Clinical site; Gender: male, female; Level fused: L3-L4, L4-L5, L5-S1; Grade of spondylolisthesis: Grade 1 or Grade 2; Prior treatment: surgical (laminectomy, facetectomy, foraminotomy, discectomy), not surgical (includes no previous treatment); Concurrent medical condition: metabolic bone disease and/or osteoporosis (yes/no); Concurrent medical condition: diabetes (yes/no); Workers' compensation status: no or yes (includes current, pending, litigation, and other); BMI; ODI.
The characteristics found to be statistically significant and included in the analysis were the following: Level fused; Diabetes; Workers' compensation status and ODI.



RESULTS

*Participant flow and recruitment*
A total of 312 patients were planned. A total of 336 patients were actually enrolled and randomized and 295 were treated: 208 received OP-1 and 87 received autograft. The remaining 41 patients withdrew prior to study treatment.

*Conduct of the study*
The numerous protocol violations, post hoc amendments of the study endpoints, (including the post hoc amendment of the primary endpoint) are of concern. These concerns include the following main points in the initial study report:
Overall success
1. The radiographic demonstration of effectiveness was modified. As a consequence the radiographs were re-read by the radiologists who performed the initial evaluations.
2. Addition of 'absence of serious treatment related AE' and 'absence of re-treatment' and inclusion of the 'neurological outcome' as a new post hoc efficacy endpoints
3. Post hoc amendments to the neurological success
4. Post hoc changes to fixed non inferiority margins (from 10% to 14%)
5. Post hoc changes to the definition of efficacy population (to so called modified intention to treat population, mITT
6. Post hoc imputations were changed from LOCF to multiple imputations.

*Baseline data*
Baseline data were comparable between the two treatment groups. The mean age was 68/69 years, approximately two thirds being women.

Numbers analysed

*Outcomes and estimation*
Table 12 presents the Overall Success rate at 24 months in the mITT population using the SAP analyses. Opgenra (OP-1 Putty) treatment was not demonstrated to be non- inferior to autograft (*P*=0.331). The estimated success rates were 38.7% for Opgenra and 49.4% for autograft.

**Table 2 – Overall Success Rate at 24 Months (mITT Population)**

| OP-1 Putty | | Autograft | | 95% Upper Confidence Bound[2] (%) | *P* Value for Non-Inferiority[3] |
|---|---|---|---|---|---|
| Number of Patients | Success Rate (%)[1] | Number of Patients | Success Rate (%)[1] | | |
| 207 | 38.7% | 86 | 49.4% | 22.8% | 0.331 |

Source: Statistical Table 3.2 in Section 14.
Note: Missing values were imputed.
(1) The percentage of successes and its standard error are based on estimates of the treatment effect adjusted for covariates in logistic regression and on variance estimates obtained from multiple imputation.
(2) The 95% upper confidence bound is for the difference between the angular-scale values corresponding to the success rates in the two treatment groups.
(3) *P Value* is based on one-sided two-sample test for non-inferiority in the angular scale with a non-inferiority margin of 0.14 (radians); estimates and standard errors are based on logistic regression and multiple imputation.

Results were similar for the analysis defined by the original protocol (31.7% for the OP-1 Putty group and 47.6% the autograft using the ITT population, *P*= 0.824, Statistical Table A1.2 in Section 14).

*According to the footnote the 95% upper confidence bound is for the difference between the angular scale values (in radians), so it should be 0.228. Because this value is greater than the stated non-inferiority margin 0.14, the non-inferiority of OP-1 treatment to autograft treatment was not shown. The observed p-value (p=0.33) indicates that OP-1 treatment is not non- inferior to autograft treatment.*

The individual components of the overall success score (pre-defined) were as follows:

ODI (Oswestry Disability Index): the treatment groups were similar (80.4% for Opgenra, and 85.5% for autograft). Statistical testing of non- inferiority did not show that Opgenra was non- inferior to autograft with respect to ODI (*P*=0.178),
Absence of retreatment: Opgenra was statistically non- inferior to autograft at 24 months (92.3% for OP-1 Putty and 88.6% for autograft, *P*=0.001).
Absence of serious treatment-related AEs: Opgenra was statistically non-inferior to autograft (88.7% for Opgenra and 91.4% for autograft, *P*=0.038).
Neurological success: Opgenra was statistically non- inferior to autograft (100% for OP-1 Putty, and 93.9% for autograft, *P*<0.001).
Radiographic success: Opgenra patients had statistically significantly lower rate of overall radiographic success than autograft patients (52.4% for OP-1 Putty and 74.6% for autograft, *P*=0.003).

*Post hoc* analyses showed the following:
Presence of bone on plain film: presence of bone on plain film was statistically significantly lower in the Opgenra patients compared to autograft (61.7% for Opgenra and 83.1% for autograft, *P*<0.001)
Translational movement success: Opgenra was non- inferior to autograft (93.6% for Opgenra and 96.3% for autograft, *P*=0.004).
Angulation success: Opgenra was similar to autograft (76.6% for Opgenra and 79.3% for autograft). While statistical testing of non-inferiority did not show that Opgenra was non- inferior to autograft with respect to angulation success (*P*=0.087), neither did statistical testing of superiority indicate that autograft was superior to Opgenra (*P*=0.629).

Presence of bone on CT at 9 months: Opgenra was clinically similar to autograft (84.9% for OP-1 Putty and 98.6% for autograft). Statistical testing of non- inferiority did not show that Opgenra was non- inferior to autograft with respect to presence of bone by CT (*P*=0.929).

Additional patient outcome measures of SF-36 and VAS pain scales suggest early and durable improvements for patients in both groups. In addition, the avoidance of a second surgical procedure resulted in decreased operative time, decreased blood loss, and absence of donor site pain, all of which are clinical benefits of Opgenra versus autograft.

In a *post hoc* analysis, Opgenra was statistically non- inferior to autograft with regard to overall clinical success, a composite parameter consisting of ODI success, absence of retreatment, absence of serious treatment-related AEs, and neurological success (71.2% in the OP-1 Putty group, and 69.0% in the autograft group, *P*=0.029).

*The pivotal study failed to show that Opgenra treatment is non-inferior to autograft treatment with respect to overall success. When evaluating the results of secondary endpoints some multiplicity adjustment should be done. Using p<0.01 as cut off point, non-inferiority of Opgenra treatment was shown only for success rate based on the absence of re-treatment and for overall neurological success at 12 and 24 months.*

*The rates of bridging bone, one of the protocol endpoints, were significantly different, 31.3% for Opgenra and 53% for autograft. Analysis on non inferiority is not provided. This endpoint was subsequently amended to bone formation. The post hoc overall clinical success composite excludes any radiographic criterion.*

Data presented at the Time of the Oral Explanation

**Table 3 - Overall Success Requires "Success" on all 7 Endpoints:**

| Endpoint | "Success" Criterion |
|---|---|
| Clinical Success | |
| 1) Oswestry Disability Index | • ≥ 20% improvement |
| 2) Neurological | • No clinically relevant neurological deterioration (original any neurologic deficit) |
| 3) Device-related SAEs | • No serious adverse events related to device |
| 4) Retreatments | • No retreatments intended to induce fusion |
| Radiological Success: | Assessed by plain films: |
| 5) Presence of bone | • Presence of bone (original bridging bone) |
| 6) Angulation success | • ≤ 5° of angular movement |
| 7) Translation success | • ≤ 3 mm of translational movement (original <2 mm) |

Key Additional Endpoints

- Individual components of overall success
- SF-36 validated measure of quality of life
- Visual Analog Scale (VAS) pain assessment
- Operative time, blood loss
- Donor site pain (autograft only)

**Table 4 - Subcomponents of Overall Success at 24 Months, mITT**

| Outcome | Opgenra | Autograft | p-value for difference 1 |
|---|---|---|---|
| Components of Overall Radiographic Success | | | |
| -Presence of bone by plain film2 | 61.7% | 83.1% | <0.001 |
| -Angulation ≤ 5 degrees on flexion/extension[2] | 73.3% | 75.6% | 0.684 |
| -Translation ≤ 3 mm on flexion/extension[2, 3] | 87.7% | 87.8% | 0.978 |
| ODI Success | 74.5% | 75.7% | 0.839 |
| Absence of Retreatment | 92.3% | 88.6% | 0.347 |
| Absence of Serious Treatment-related Adverse Events | 85.6% | 84.7% | 0.863 |
| Neurological Success | 92.1% | 84.1% | 0.057 |

[1] p-value is based on chi-square or Fisher's exact test, as appropriate, to test the difference between treatment groups; [2] Calculated with missing data imputed by Last Observation Carried Forward; [3] Translation ≤ 2 mm on flexion/extension: Opgenra (85.1%), autograft (84.1%) p-value=0.831

**Figure 1 - Post Hoc Modified Overall Success with Imputation (using 36+ Month Radiographic Success)**

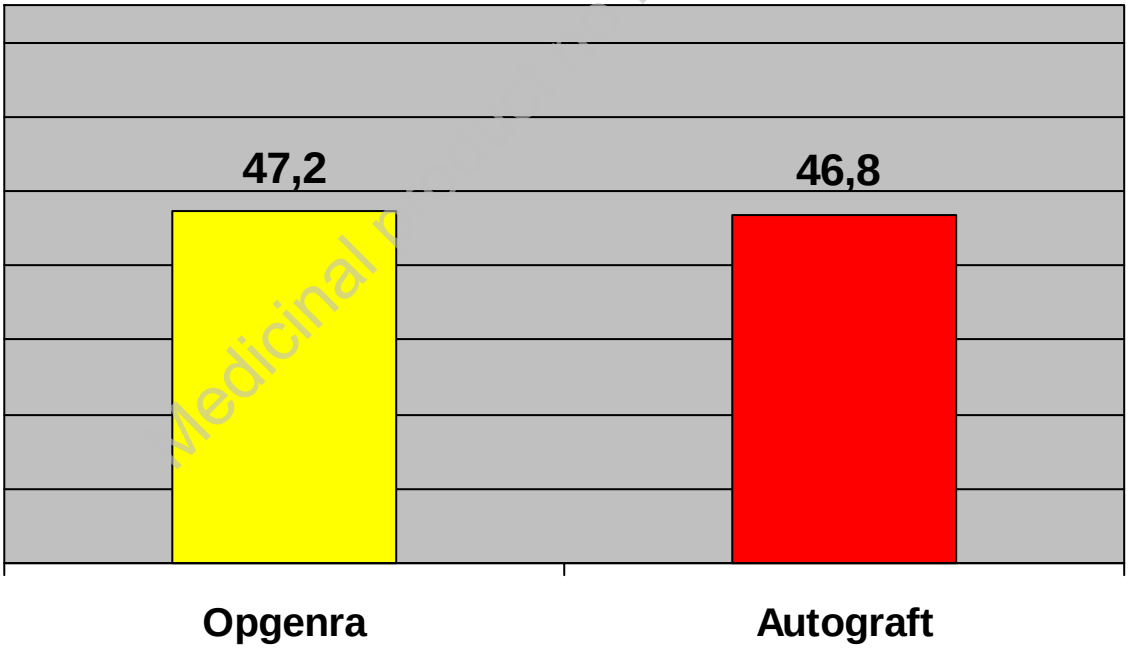

**Table 5 - Post Hoc Subcomponents of Modified Overall Success, mITT**

| Outcome | Opgenra | Autograft | p-value Superiority [1] |
|---|---|---|---|
| Components of Overall Radiographic Success at 36+ Months | | | |
| ▪ Presence of Bone by 36+ month CT Scan 2 | 74.8% | 77.4% | 0.852 |
| ▪ Angular motion ≤5○ at 36+ Months 2 | 69.3% | 68.4% | 1.000 |
| ▪ Translational movement ≤ 3 mm at 36+ Months [2, 3] | 75.7% | 75.4% | 1.000 |
| ODI Success (24 Months) | 74.5% | 75.7% | 0.839 |
| Absence of Retreatment (36+ Months) | 87.7% | 83.3% | 0.529 |
| Absence of Serious Treatment-related AEs (24 Months) | 85.6% | 84.7% | 0.863 |
| Neurological Success (24 Months) | 92.1% | 84.1% | 0.057 |

[1]p-value is based on Fisher's exact test; [2]Missing or non-evaluable data are excluded; [3]Translation ≤ 2 mm on flexion/extension: Opgenra (61.0%), autograft (60.7%) p-value=1.000

Based on the data presented in the OE, the efficacy was not considered to be demonstrated in the initial and newly proposed indications.

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

Not applicable

- Clinical studies in special populations

No studies in special groups were performed. It should however be noted that, although the age range of the study population in the pivotal study was wide (from 36 years to 84 years), the mean age of the study population was 68 years.

- Supportive studies

**Pilot study S99-01US** was designed and performed as a safety and feasibility study to the phase three pivotal clinical study. It is stated in the statistical plan that this study was designed to only produce descriptive data. The sample size was chosen on this basis and no efficacy sample size calculations were performed.

*Objectives:*
The objectives of this study were to demonstrate the feasibility of OP-1 Putty alone or as an autograft adjunct as measured by:

- Safety: comparison of complications and neurological status within the OP-1 Putty treatment groups and control group (autograft alone)
- Efficacy: comparison of overall fusion success and time to fusion, and pain/function outcome within the OP-1 treatment groups (Op-1 alone and OP-1 in combination with autograft), and in the control group (autograft alone).

*Methodology:*
This was a controlled, randomized, open-label (radiographs were reviewed by 2 independent radiologists who were blinded to treatment group), multicentre, pilot clinical study to evaluate the safety and efficacy of OP-1 Putty for lumbar spinal fusion, both alone and as an adjunct to autogenous bone graft (autograft) in patients with single level (L3-S1) degenerative lumbar spondylolisthesis (Grade 1 or 2) with spinal stenosis. The initial protocol specified 2 treatment groups: an investigational

arm of OP-1 Putty and autograft, and a control arm of autograft alone. A protocol revision added a new investigational arm of treatment with OP-1 Putty alone, and eliminated enrolment in the OP-1 Putty and autograft arm. At all times patients were randomized in a 2:1 manner to the OP-1 Putty-containing treatment arm versus the autograft treatment arm.
Patients underwent standard surgical procedures for lumbar spinal posterior decompression with concomitant posterolateral intertransverse process arthrodesis using OP-1 Putty alone, OP-1 Putty with autograft, or with autograft alone, as specified by randomization. Patients were evaluated postoperatively at 6 weeks, and 3, 6, 9, 12, and 24 months, and annually thereafter until the last patient in the Pivotal study (S01-01US) achieved 2-year follow-up.

*Number of Patients (planned and analyzed):*
The study planned 48 patients: 24 in the OP-1 Putty alone group, 12 in the OP-1 Putty and autograft group, and 12 in the autograft alone group. Fifty-seven patients were enrolled. Forty-eight patients were randomized to 1 of 3 treatment groups and were distributed across treatment groups as planned. Both analysis datasets (the intent-to-treat [ITT] dataset and the safety dataset) used all 48 treated patients. Of the 9 patients enrolled but not included in analyses, 8 patients were withdrawn prior to treatment, and 1 patient did not receive the protocol-specified treatment, so was not included in analyses.

*Diagnosis and Main Criteria for Inclusion*: Patients with single level (L3-S1) degenerative lumbar spondylolisthesis (Grade 1 or 2) with spinal stenosis.

*Criteria for Evaluation*:
**Efficacy:** The clinical protocol did not categorically define outcome variables as primary or secondary endpoints. For the purposes of analysis and reporting, outcome variables have been identified as either a primary endpoint or ancillary clinical outcome.
The primary efficacy variable was overall success, a composite measure consisting of radiographic demonstration of spinal fusion (presence of bridging bone and ≤5° angular motion and ≤ 2 mm translational motion), improvement of at least 20% on the Oswestry Disability Index (ODI), and absence of retreatment. Ancillary clinical outcomes included SF-36 Health Outcomes Survey scores, leg/buttock pain and donor site pain as measured by a visual analogue scale, disc height by radiographic assessment, and degree of angular motion and translational movement by radiographic assessment.
**Safety:** Safety outcomes were adverse events and immunogenicity.

*Statistical Methods:*
Descriptive statistics were used for data analysis. Analysis of the overall success rate was calculated both with and without a 'last observation carried forward' (LOCF) approach.

*Changes to the Protocol*
Several revisions were made to the protocol during the course of the pilot study.
The original version of the Pilot Study protocol, Revision 1.0, was filed with the IDE on 29 January 1999. The first version under which patients were studied was Revision 2.0. Revisions 3.0 and 4.0 to the protocol were minor and/or editorial in nature. Subsequent revisions to the protocol are described briefly.

- Protocol Revision 5.0: eliminated the OP-1 Putty and autograft arm of the study, and added an OP-1 Putty alone arm. After this Revision, further enrolment to the OP-1 Putty and autograft arm was terminated with a total of 12 patients treated.
- Protocol Revision 5.1: increased the number of patients in the OP-1 Putty arm from 12 to 24, and set maximum enrolment at 48 patients.
- Protocol Revision 5.2: eliminated the 10-day follow-up visit because of low patient compliance and lack of potential safety and efficacy data resulting from this visit.
- Protocol Revision 5.3: allowed for inclusion of a third independent radiologist in cases where the primary radiographic reviewers disagreed on the evaluation of radiographic success.
- Protocol Revision 5.4: included an expansion of the 1-year follow-up visit window from ± 1 month to ± 2 months per the FDA Guidance Document for the Preparation of IDEs for Spinal Systems (13 January 2000).

- Protocol Revision 5.5: increased the follow-up to include an additional annual evaluation until the last patient in the Pivotal Spine Study achieved 2-year follow up.

*Changes to the Planned Analysis*
The protocol objectives included assessment of time to fusion. As this variable was not defined prospectively, it will not be discussed further.

RESULTS
**Demographics and Baseline Characteristics**: The groups were similar in age (mean age was 65 years, with the range among groups of 43 to 80 years), weight, height distribution. Females accounted for more than half of the patients in each treatment group, and comprised 54.2% of the Opgenra alone group, 58.3% of the autograft alone group, and 75% of the Opgenra and autograft combination group.

**Efficacy:**
- Overall Success: treatment groups appear to be comparable at 24 months
- Greater Radiographic Success is noted in both Opgenra groups versus autograft, but small sample sizes preclude the ability to assess differences between treatment groups.
- Angular motion: The proportion of patients who achieved success in angular motion is higher in the Opgenra alone treatment group versus other treatment groups at both 12 and 24 months.
- ODI percent success for both Opgenra treatment groups suggests an advantage for Opgenra over autograft.
- Patient 105 (Opgenra and autograft) underwent re-treatment for pseudarthrosis (supplemental fixation) at 7.6 months post-operatively. Two additional patients (Patients 153 and 455 in the Opgenra alone group) underwent re-treatment after 24 months.
- Treatment groups were similar for disc height, leg/buttock pain, donor site pain, and SF-36 scores.

The following table is a summary of results for the primary endpoint, Overall Success, and for the 3 components of Overall Success: Radiographic Success, ODI, and re-treatment at 24 months.

**Table 6 - Overall Success Rates and Success for Components of Overall Success at 24 Months**

**(Adapted from Clinical Study Report: S99-01US)**

| Outcome | Opgenra Treatment Alone | | Opgenra + Autograft | | Autograft Alone | |
|---|---|---|---|---|---|---|
| | **Number of Patients** | **Number (%) Successes** | **Number of Patients** | **Number (%) Successes** | **Number of Patients** | **Number (%) Successes** |
| **Overall success with LOCF** | 24 | 11 (45.8) | 12 | 5 (41.7) | 12 | 4 (33.3) |
| **Overall success without LOCF** | 18 | 10 (55.6) | 9 | 4 (44.4) | 9 | 3 (33.3) |
| **Radiographic success** | 19 | 11 (57.9) | 10 | 5 (50.0) | 10 | 4 (40.0) |
| Bridging Bone | 19 | 15 (78.9) | 10 | 7 (70.0) | 10 | 9 (90.0) |
| Angulation Success | 18 | 14 (77.8) | 10 | 5 (50.0) | 10 | 5 (50.0) |
| Translational Movement | 18 | 16 (88.9) | 10 | 6 (60.0) | 10 | 7 (70.0) |
| **ODI** | 18 | 17 (94.4) | 9 | 8 (88.9) | 10 | 6 (60.0) |
| **No Re-treatment** | 24 | 24 (100.0) | 12 | 11(91.7) | 12 | 12 (100.0) |

- Discussion on clinical efficacy

The statistical planning or analyses of the pilot study are not adequate enough to allow any firm conclusions on the efficacy. Considering concurrently the results of the pivotal study, it would appear, in hindsight, that the pilot study did have value as a feasibility study. In a setting where the autograft control arm has an overall success rate of only 33%, the clinical relevance of which cannot be considered convincing, it would have been appropriate to question the feasibility of a pivotal study of this design.
The conclusion of the applicant, drawn from the results of this pilot study, that OP-1 Putty compares favourably with autograft in posterolateral spinal fusion is unfounded.

The pivotal study S01-01US was a randomised controlled open label study comparing Opgenra to autograft in posterolateral lumbar spinal fusion in adult patients with spondylolisthesis who have failed at least six months of conservative non-surgical treatment. Although this study (the aim of which was to demonstrate non-inferiority of Opgenra to autograft) was a large study considering the area of orthopaedics, it had major flaws including overoptimistic sample size calculations, its analysis included substantial post hoc changes and the study could not demonstrate non-inferiority as compared to the autograft.

The applicant made available, the results of a follow up study of the pivotal study using new post hoc determined clinical endpoints. In spite of two rounds of questions and responses, the non-inferiority of Opgenra to autograft remained doubtful.

*The pivotal study failed to show that OP-1 treatment is non-inferior to autograft treatment with respect to overall success. Using p<0.01 as cut off point, non-inferiority of OP-1 treatment was shown only for success rate based on the absence of re-treatment and for overall neurological success at 12 and 24 months.*
*In reviewing the outcome, it should be kept in mind that both the outcome criteria and the non inferiority margins were amended post hoc. Even so, this trial did not demonstrate non inferiority of OP-1Putty over autograft on the primary endpoint of overall success at 24 months (P=0.331).*
*The only significant success outcomes were on variables that were not determined a priori. Bearing this in mind the results must be viewed with caution.*
*The rates of bridging bone, one of the protocol endpoints, were significantly different, 31.3% for OP-1 Putty and 53% for autograft (analysis on non inferiority not provided). This endpoint was subsequently amended to bone formation. The post hoc overall clinical success composite excludes any radiographic criterion.*

Major concerns remained about the robustness of the single pivotal study:
1. the applicant has not provided in the written responses the requested ITT analyses based on the original analysis plan i.e. on the a priori determined endpoints of the pivotal study, as requested also by scientific advice and gave no reason for not presenting them.
2. the applicant has not provided adequate or sufficient evidence to justify the post hoc changes made to the original analysis plan;
3. the applicant`s response to the question on the compliance of the pivotal study to guidance (Guideline on 'Points to Consider on Application with 1. Meta-Analysis; 2. One Pivotal Study'. CPMP/EWP 23) is inadequate as it excludes major issues, such as the reason for not presenting the results on ITT analysis on the original analysis plan and the post hoc nature of the presented data
4. the presentation and discussion of the handling and the impact of missing data is inadequate and insufficient and not according to scientific advice;

At the time of the oral explanation the applicant addressed the above concerns as follows:
The original protocol indicated that the analysis was to be completed on treated patients only (ITT in protocol). The applicant explained that the major change to the primary endpoint (presence of bone instead of originally bridging bone) was done because of insensitivity of plain films at assessing bridging bone Translational movement of ≤ 3mm instead of originally ≤2 mm was based on FDA guidance. The original neurologic endpoint was not specifically defined and would have resulted in failure in overall success in all patients (both groups).

Imputation was conducted in 4 ways. However, careful discussion of the impact of the large number of missing data was not presented.
Furthermore, to explain the apparent discrepancy between presence of bone and clinical and radiographic measures of stability (angulation and translation), the applicant presented the hypothesis that medial bone formation led to underestimation of presence of bone at 24 months since plain X-rays provide poor visualisation medially.

Also at the time of the oral explanation, the applicant proposed a more restricted target population:

- patients with co-morbidities or characteristics that make autograft not feasible or unlikely to be efficacious, including: osteoporosis or other conditions affecting bone quality; significant underlying medical conditions in which minimising operative time is critical; steroid or other medications that impair bone formation; smokers
- patients who have failed prior autograft attempts.

To support the new indication, a summary of a prospective cohort study of 30 patients was presented (Fehling Study)

The explanations and proposals provided by the applicant did not fully resolve the CHMP concerns. Furthermore, no data from the pivotal study (subgroup analysis) specifically support the efficacy and safety of the medicinal product in the newly proposed restricted target population; and extrapolation of efficacy to the newly proposed population based on the failed pivotal study is difficult.

An issue already presented in the Day150 Joint rapporteurs` assessment report and discussed again during the oral explanation, concerned the fact that the optimal surgical methodology has changed since the time the study was carried out, and that the technique used in the pivotal study (non-instrumental) is not anymore considered to be state-of-the art.

In conclusion, non-inferiority of Opgenra to bone autograft, in the proposed therapeutic indication, has not been demonstrated. The validity, robustness and the clinical relevance of the presented results of the single pivotal trial to support the safety and efficacy of Opgenra are questionable.

**Clinical safety**

- Patient exposure

In the pivotal study all 208 patients in the Opgenra group were treated once with 2 units (7.0 mg) of Opgenra and followed for up to 36 months. All 87 patients in the autograft group were treated with autologous iliac crest bone graft and followed for up to 36 months.

In the pilot study S99-01US 48 patients received treatment, 36 of which included Opgenra.

Opgenra formulation has been on the market already for several years in the USA and the estimated patient exposure to Opgenra is reported to be over 16000 patients solely in the USA.

Adverse events

The following table shows the treatment emergent AEs in the **pivotal study**:

**Table 7 – Treatment-Emergent Adverse Events (Safety Population)**

| Parameter | OP-1 Putty (N=208) | | Autograft (N=87) | |
|---|---|---|---|---|
| | Number (%) of Patients with Events | 95% CI | Number (%) of Patients with Events | 95% CI |
| Any Adverse Event | 201 (96.6) | (93.2, 98.6) | 82 (94.3) | (87.1, 98.1) |
| Severe Adverse Event | 43 (20.7) | (15.4, 26.8) | 17 (19.5) | (11.8, 29.4) |
| Treatment-related Adverse Event | 54 (26.0) | (20.1, 32.5) | 23 (26.4) | (17.6, 37.0) |
| Unanticipated Adverse Event | 6 (2.9) | (1.1, 6.2) | 0 (0.0) | (0.0, 4.2) |
| Serious Adverse Event | 104 (50.0) | (43.0, 57.0) | 43 (49.4) | (38.5, 60.4) |
| Serious and Unanticipated Adverse Event | 5 (2.4) | (0.8, 5.5) | 0 (0.0) | (0.0, 4.2) |
| Treatment-related Serious Adverse Event | 25 (12.0) | (7.9, 17.2) | 6 (6.9) | (2.6, 14.4) |
| Neoplasms Benign, Malignant And Unspecified (incl Cysts And Polyps) | 12 (5.8) | (3.0, 9.9) | 8 (9.2) | (4.1, 17.3) |
| Death | 7 (3.4) | (1.4, 6.8) | 4 (4.6) | (1.3, 11.4) |

Note: Percentages are based on total number of enrolled subjects.
Note2: The 95% confidence interval for the proportion of patients with AEs is based on the exact (Clopper-Pearson) method. Note: The 95% confidence interval for the proportion of patients with AEs is based on the exact (Clopper – Pearson) method.

**Table 8 – Incidence of Treatment-Emergent Adverse Events by MedDRA System Organ Class (Safety Population)**

| System Organ Class/Preferred Term | Number (%) of Patients | | *P* Value(a) | Number (%) of Events | |
|---|---|---|---|---|---|
| | OP-1 Putty (N=208) | Autograft (N=87) | | OP-1 Putty | Autograft |
| **Total** | **201 (96.6)** | **82 (94.3)** | 0.345 | **919 (100.0)** | **392 (100.0)** |
| Blood and Lymphatic System Disorders | 12 (5.8) | 13 (14.9) | 0.019 | 12 (1.3) | 14 (3.6) |
| Cardiac Disorders | 27 (13.0) | 5 (5.7) | 0.098 | 30 (3.3) | 5 (1.3) |
| Ear And Labyrinth Disorders | 4 (1.9) | 1 (1.1) | 1.000 | 5 (0.5) | 1 (0.3) |
| Endocrine Disorders | 2 (1.0)) | 0 (0 ) | 1.000 | 2 (0.2) | 0 (0.0) |
| Eye Disorders | 7 (3.4) | 3 (3.4) | 1.000 | 8 (0.9) | 3 (0.8) |
| Gastrointestinal Disorders | 45 (21.6) | 12 (13.8) | 0.145 | 66 (7.2) | 15 (3.8) |
| General Disorders and Administration Site Conditions | 29 (13.9) | 17 (19.5) | 0.224 | 32 (3.5) | 19 (4.8) |
| General System Disorders Nec | 2 (1.0) | 0 (0) | 1.000 | 2 (0.2) | 0 (0) |
| Hepatobiliary Disorders | 1 (0.5) | 1 (1.1) | 0.503 | 1 (0.1) | 1 (0.3) |
| Immune System Disorders | 3 (1.4) | 2 (2.3) | 0.633 | 3 (0.3) | 2 (0.5) |
| Infections And Infestations | 49 (23.6) | 13 (14.9) | 0.117 | 61 (6.6) | 18 (4.6) |
| Injury, Poisoning and Procedural Complications | 70 (33.7) | 41 (47.1) | 0.035 | 93 (10.1) | 51 (13.0) |
| Investigations | 20 (9.6) | 13 (14.9) | 0.223 | 24 (2.6) | 15 (3.8) |
| Metabolism and Nutritional Disorders | 12 (5.8) | 6 (6.9) | 0.790 | 13 (1.4) | 6 (1.5) |
| Musculoskeletal and Connective Tissue Disorders | 156 (75.0) | 60 (69.0) | 0.313 | 322 (35.0) | 135 (34.4) |
| Neoplasms Benign, Malignant And Unspecified (incl Cysts And Polyps) | 12 (5.8) | 8 (9.2) | 0.313 | 12 (1.3) | 9 (2.3) |
| Nervous System Disorders | 65 (31.3) | 33 (37.9) | 0.280 | 95 (10.3) | 52 (13.3) |
| Psychiatric Disorders | 17 (8.2) | 7 (8.0) | 1.000 | 17 (1.8) | 7 (1.8) |
| Renal and Urinary Disorders | 24 (11.5) | 10 (11.5) | 1.000 | 28 (3.0) | 11 (2.8) |
| Reproductive System and Breast Disorders | 2 (1.0) | 2 (2.3) | 0.584 | 4 (0.4) | 2 (0.5) |
| Respiratory, Thoracic and Mediastinal Disorders | 33 (15.9) | 6 (6.9) | 0.039 | 38 (4.1) | 10 (2.6) |
| Skin And Subcutaneous Tissue Disorders | 16 (7.7) | 4 (4.6) | 0.449 | 18 (2.0) | 4 (1.0) |
| Surgical and Medical Procedures | 4 (1.9) | 0 (0.0) | 0.323 | 4 (0.4) | 0 (0.0) |
| Vascular Disorders | 25 (12.0) | 12 (13.8) | 0.701 | 29 (3.2) | 12 (3.1) |

Note: Number of patients refers to patients with at least one adverse event of the indicated type. Number of events refers to all events of the indicated type. Percentages are based on the total number of patients or the total number of adverse events, as appropriate.
Patients experiencing multiple events under the same system organ class/preferred term are counted only once for that system organ class/preferred term.
(a) *P* values are calculated for all SOC terms and PT terms that happened to >= 5% patients in at least one treatment group, using Fisher's exact test.



Post-operative anaemia was reported more frequently in the autograft group (13.8% of patients) versus the Opgenra group (4.8% of patients, *P*=0.013). This is presumed to be related to the additional surgical procedure (i.e., autograft harvest) and is corroborated by findings of increased operative time and estimated blood loss in this treatment group.

A conservative statistical cut-off (*P*=0.2) was imposed to identify potential differences in AEs between treatment groups. While the safety profiles of the 2 treatment groups were generally comparable, there were 4 System Organ Class (SOC) categories in which the OP-1 Putty group showed an overall higher incidence of AEs than did the autograft group based on this statistical cut-off. The categories were:

- Cardiac Disorders: 13% in Opgenra patients, 5.7% in Autograft (*P*=0.098)
- Infections and Infestations: 23.6% in Opgenra patients, 14.9% in Autograft patients (*P*= 0.117)
- Respiratory, Thoracic And Mediastinal Disorders: 15.9% in Opgenra patients, 6.9% in autograft patients (*P*=0.039)
- Gastrointestinal Disorders: 21.6% in Opgenra patients, 13.8% in autograft patients (*P*=0.145).

There were 2 SOCs that had AEs reported more frequently in the autograft group than in the Opgenra group:

- Blood And Lymphatic System Disorders: 5.8% in Opgenra patients, 14.9% in autograft patients (P=0.019)
- Injury, Poisoning and Procedural Complications : 33.7% in Opgenra patients, 47.1% Autograft patients (P=0.035)

**Cardiac AEs**: The following AEs were reported only by patients randomised to the Opgenra treatment group: acute coronary syndrome (1.0%), atrial fibrillation (2.4%), cardiac failure (0.5%), cardiac failure congestive (1.4%), chest discomfort (0.5%), coronary artery disease (1.0%), myocardial ischaemia (0.5%), and tachycardia (1.4%). Of note, myocardial infarction was reported more frequently in Opgenra patients as opposed to autograft patients (2.4% and 1.1% respectively). Supraventricular tachycardia was reported once by a patient who received autograft. Most of the events in the Opgenra group, and all in the autograft group, were classified as "mild" or "moderate" in severity. Patients in the Opgenra group who experienced "severe" events reported myocardial infarction (1.4%), coronary artery disease (1.0%), chest pain (0.5%), and cardiac failure (0.5%).

*The patient population studied in this trial was generally elderly, with a mean age of 68 years, and many patients had pre-existing cardiac risk factors such as cardiovascular disease, hypertension, hypercholesterolemia, and diabetes reported pre-operatively.*

In the **Infections and Infestations** category, 23.6% of Opgenra patients experienced AEs, representing 6.6% of the events, while 14.9% of the autograft group patients experienced AEs, representing 4.6% of the events (*P*=0.117),. None of the events reported were determined to be 'suspected related' to the autograft. The following AEs were reported only by patients randomized to the Opgenra treatment group : clostridium colitis (1.9%), cystitis (0.5%), ear infection (1.0%), gastroenteritis viral (0.5%), herpes virus infection (0.5%), meningitis (0.5%), nasopharyngitis (0.5%), oral infection (0.5%), parotitis (0.5%), post-polio syndrome (0.5%), sepsis (0.5%), upper respiratory tract infection (0.5%), urosepsis (0.5%), and wound infection staphylococcal (0.5%). Bone infection, laryrinthitis, and stitch abscess were only reported by one patient each who received autograft (1.1%). Of the Infections and Infestations AEs, there were 4 preferred terms that appeared to show a preponderance of events in the Opgenra treatment group over the autograft group: *Clostridium* colitis (1.9% vs. 0%), herpes zoster (2.9% vs. 1.1%), pneumonia (2.9% vs. 1.1%), and urinary tract infection (5.3% vs. 3.4%). Infections are commonly observed in the post-operative setting. There is no known basis for suspecting that Opgenra contributed to these events, whether from mechanism of action, preclinical studies of pharmacology or toxicology, or post- market surveillance.

In the SOC **Respiratory, Thoracic and Mediastinal Disorders**
Although the 2 treatment groups were statistically identified as potentially different based on conservative criteria SOC P=0.2 level (15.9% in the Opgenra group and 6.9% in the autograft group) (*P*=0.039), no concerning pattern of clinical events emerged in the Opgenra treatment group.



**<u>Pilot study S99-01US</u>**.

- Adverse events (AE) occurred in 100% of patients across all treatment groups: 149 in the 36 patients in the Opgenra treatment groups (with or without autograft), and 51 in the 12 patients treat who received autograft.
- Thirty-six serious AEs (SAEs) were reported in 18 patients across all treatment groups, and none were attributed to the use of Opgenra.
- Four patients across treatment groups reported 8 malignancies, none of which were attributed to the use of Opgenra.
- One death, due to carcinomatosis, occurred in this study.
- Pseudarthrosis was reported predominantly between 6 and 12 months postoperatively and in 13 (36%) patients who received an Opgenra-containing regimen (10 patients, 28% in the Opgenra alone arm). Only 2 of these 13 patients required a surgical retreatment due to pseudarthrosis. There were no reports of pseudarthrosis in the autograft alone treatment group.

- Post-operative wound infections occurred in 4 patients who received Opgenra alone, and did not occur in patients who received an autograft.
- There was no evidence of neurological deterioration post-operatively in any treatment group.
- Seven patients in the Opgenra alone group had neutralizing antibodies at either 6 weeks or 6 months post-procedure, however no pattern of immunologically mediated AEs has emerged. The Overall Success rates of Opgenra patients with or without neutralizing antibodies appeared comparable, 42.3% vs. 44.8%.

Although the applicant concluded that safety in S99-01S was comparable for the two study groups, several AEs, including pseudarthrosis and wound infection were overrepresented in the Opgenra treatment group.

- Serious adverse event/deaths/other significant events

As seen in the Table below, there was no difference between the numbers of deaths between the treatment groups (taken the 2:1 randomisation into account)

**Table 9 - Deaths**

| Treatment Group | Patient ID | Cause of Death | Days From Surgery | Relationship to Treatment |
|---|---|---|---|---|
| OP-1 Putty | 1305 | Bone and liver cancer secondary to renal cell carcinoma | 1016 days* | Not related |
| | 1326 | Pulmonary embolism | 18 days | Not related |
| | 1706 | Cerebral haemorrhage | 200 days | Not related |
| | 2506 | Myocardial infarction | 192 days | Not related |
| | 4120 | Small cell lung carcinoma | 758 days | Not related |
| | 4207 | Cardiac failure | 730 days | Not related |
| | 5010 | Multiple myeloma | 241 days | Not related |
| Autograft | 2519 | Lung neoplasm malignant | 757 days | Not related |
| | 3010 | Endometrial cancer metastatic | 257 days | Not related |
| | 4401 | Small cell lung cancer | 1020 days* | Not related |
| | 5012 | Refractory anemia with excess blasts | 584 days | Not related |

* Death occurred >24 months post-procedure



- Laboratory findings

No clinically meaningful differences were found between treatment groups.

- Immunological events

Immunogenicity evaluation was carried out as part of studies S99-01US and S01-01US using patient serum samples collected preoperatively (baseline), post-operatively, and at the 6 week, 3, 6, 12 and 24 month follow up visits. Enzyme-linked immunosorbent assays (ELISA) were performed to detect the presence of anti-OP-1 antibodies in all samples. ELISA methods were validated to detect human antihuman OP-1 antibodies with IgG, IgM, and IgE isotypes. The ELISA cut point for this study was statistically based and reflects a false positive rate of 5 %, as recommended in Mire-Sluis, et al., 2004. Positive samples in the screening ELISA were evaluated in a titer ELISA to quantitate the level of anti-OP-1 antibodies in the sample. The results of this assay are reported as a log titer, which corresponds to the lowest dilution of the sample that yields a positive result. The measurable log titer range in this assay extends from 1.90 to 6.11.

Samples found to be positive in the titer ELISA were further analyzed to determine whether antibodies to OP-1 had the ability to neutralize its activity in vitro. Initially, ELISA positive samples were tested in an alkaline phosphatase-based neutralizing antibody assay). In this assay, anti-OP-1 neutralizing antibodies are detected based on their ability to reduce the OP-1-induced alkaline phosphatase activity

measured 48 hours post treatment. The cut point for this Neutralising Antibody (Nab) assay was determined statistically, based on the variability of the response of preoperative (N=245) serum samples from this study. As described above for the ELISA, this Nab assay cut point was set to reflect a 5% false positive rate.

*The assessment of the used methodology, and consequently the results, is limited without any method validation data. No validation data for the described ELISA 'screening assay', the ELISA 'titer method', the Nab assay, the PCR method were provided. A method for the quantitative determination of OP-1 antibodies was presented, but no quantitative data based on these analyses were presented or discussed.*

The following Table 10 is a short summary of the results of the immunological status of the patients:

**Table 10 – Patients with Positive Screening Test and Anti-OP-1 Neutralizing Antibody at Any Visit (Safety Population)**

| Parameter | Any Visit | Pre-Operative | Operative (1) | 6 Weeks | 3 Months | 6 Months | 12 Months | 24 Months |
|---|---|---|---|---|---|---|---|---|
| **OP-1 Putty** | | | | | | | | |
| Total Number of Patients | 207 | 185 | 134 | 180 | 184 | 185 | 181 | 173 |
| Number (%) of ELISA Positive | 194 (93.7) | 5 (8.1) | 8 (6.0) | 164 (91.1) | 176 (95.7) | 159 (85.9) | 133 (73.5) | 71 (41.0) |
| Number (%) of Neutralizing | 53 (25.6) | 1 (0.5) | 1 (0.7) | 31 (17.2) | 36 (19.6) | 13 (7.0) | 2 (1.1) | 0 (0.0) |
| **Autograft** | | | | | | | | |
| Total Number of Patients | 86 | 75 | 62 | 70 | 73 | 72 | 68 | 56 |
| Number (%) of ELISA Positive | 18 (20.9) | 10 (13.3) | 3 (4.8) | 9 (12.9) | 7 (9.6) | 7 (9.7) | 6 (8.8) | 4 (7.1) |
| Number (%) of Neutralizing | 1 (1.2) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (1.5) | 0 (0.0) |

Note: Neutralizing is Anti-OP-1 positive.
(1) Operative includes hospitalization (surgical procedure) and within 72 hours of postoperative.



No significant patterns emerge from these profiles except that the peak presence of antibody titers was observed between 6 weeks and 3 months and declined thereafter.

There was no evidence of an increase in the number of patients with the following AEs at any time point in the neutralising antibody-positive patients' versus the neutralising antibody-negative patients.

For the follow up study the applicant presented a final study report, the validation reports of the immunological methods and has included a summary and also raw data of the immunological analyses of the follow-up study of the single pivotal study of this MAA. The methodology used in the follow-up study differs from that used in the pivotal study.

The results of the immunological testing of this follow up study support the results and conclusions of the pivotal study: Opgenra is immunogenic, the main conclusion being that repeated use cannot be recommended due to risks associated with an enhanced (secondary) immune response, which has been adequately reflected in the SPC of Opgenra.

Safety in special populations

No clinical studies in special populations have been performed.

- Safety related to drug-drug interactions and other interactions

Drug-drug interactions are unlikely but drug-device interactions have been reported with BMP-2-containing bone implants

- Discontinuation due to adverse events

The nature of the treatment means that patients could not be discontinued as such.

- Post marketing experience

OP-1 Putty formulation has been on the market already for several years in the USA and elsewhere and the estimated patient exposure to OP-1 Putty is reported to be over 16 000 patients solely in the USA. A completed and thoroughly checked update of the US post-marketing data should be made available. There is a substantial amount of post-marketing data available provided their quality is acceptable.



## 2.5 Pharmacovigilance

**Detailed description of the Pharmacovigilance system**

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

**Risk Management Plan**

The MAA submitted a risk management plan, which, upon request of CHMP included a risk minimisation plan.

However, the CHMP, having considered the data submitted in the application was of the opinion that it was not appropriate to consider risk minimisation activities at this time.

## 2.6 Overall conclusions, risk/benefit assessment and recommendation

Opgenra is a product that is composed of two separate units:

- Eptotermin alfa (OP-1) and bovine collagen matrix excipient as a single unit
- Carboxymethylcellulose (CMC) in a separate vial

Thus, Opgenra has the same drug substance and excipient (OP-1 and collagen) as Osigraft, a product that has been approved in the centralised procedure since more than five years.

Opgenra is proposed for use as an alternative to autograft in patients requiring posterolateral lumbar spinal fusion. The initially proposed indication was *"Opgenra is indicated for posterolateral lumbar spinal fusion in adult patients with spondylolisthesis who have failed at least six months of conservative non-surgical treatment."*

At the time of the oral explanation (May 2008) the applicant proposed a more limited indication: *"Opgenra is indicated for posterolateral lumbar spinal fusion in adult patients with spondylolisthesis where autograft has failed, is not feasible or is unlikely to be efficacious."*

**Quality**

From the quality point of view, the major objections were resolved, as well as most of the other concerns. The issues which remained to be resolved were listed as follow up measures.

**Non-clinical pharmacology and toxicology**

The non-clinical data submitted were adequate and no unresolved issues remain. Animal experiments have provided the proof of concept for the use of Opgenra in spinal fusion and showed that Opgenra can promote new bone formation.

**Efficacy**

Opgenra contains both an osteoconductive component (collagen) and an osteoinductive component (BMP-7, OP-1). The CMC component of Opgenra increases the plasticity of the product and facilitates its moulding between the transverse processes of the spine.

The applicant presented one pivotal clinical trial, study S01-01US, to support the non-inferiority of Opgenra as compared to autograft. This randomised controlled open label study compared Opgenra to autograft in posterolateral lumbar spinal fusion in adult patients with spondylolisthesis who have failed at least six months of conservative non-surgical treatment.

The non-inferiority of Opgenra to autograft has not been unequivocally demonstrated. The pivotal study failed to show that OP-1 treatment is non-inferior to autograft treatment with respect to overall success. Both the outcome criteria and the non inferiority margins were amended post hoc. The only significant success outcomes were on variables that were not determined a priori.

To address the CHMP concerns the applicant held an oral explanation and at that time also proposed a more restricted target population. To support the new indication, a summary of a prospective cohort study of 30 patients was presented (Fehlings Study).

The explanations provided by the applicant did not fully resolve the CHMP concerns. Furthermore, no clinical study data (subgroup analysis) demonstrated the efficacy of the medicinal product in the newly proposed restricted target population; and extrapolation of efficacy to the newly proposed population based on the failed pivotal study is difficult.

Furthermore the optimal surgical methodology has changed since the time the study was carried out, and the technique used in the pivotal study (non-instrumental) is not anymore considered to be state-of-the art.

In conclusion, non-inferiority of Opgenra to bone autograft in the proposed therapeutic indication has not been demonstrated. The validity, robustness and the clinical relevance of the presented results of the single pivotal trial to support efficacy and safety of Opgenra are questionable.

**Safety**

The overall safety profile of Opgenra appears to be comparable to that of autograft. However, unexplained inflammation at the application site has been reported. The product triggers an immune response to the BMP-7 and bovine collagen. This immune response seems to have little clinical consequences after single application. Off-label use, for example, for spinal fusion at multiple levels in children and repeated use, may take place in clinical practice. This scenario is of concern as the safety and efficacy has not been demonstrated in these situations. Furthermore, only limited safety data was made available. For example, very few safety data from the post marketing exposure (which was stated at the oral explanation to be >16 000 patients), was presented, although some of it was referred to in the proposed Risk Management Plan.

**Risk-benefit assessment**

Benefits

Autologous bone is the standard treatment for spinal fusion, but has its limitations. The amount is limited, harvesting of autograft bone causes secondary morbidity, is inconvenient and is not always possible. Thus, omission of autografting would be an advantage.
Synthetic materials have been developed as bone substitutes and as alternatives to bone materials. However, the synthetic materials are osteoconductive but not osteoinductive. A synthetic bone implant has been approved for single-level anterior lumbar spinal fusion.

Animal studies showed that Opgenra can promote new bone formation. However, efficacy of Opgenra (non-inferiority versus autograft) has not been demonstrated in the clinical pivotal study, and this study had major flaws. Finally, efficacy was not demonstrated at all for the restricted indication.

Risks

No safety data on the newly proposed target population is available
Although no clear safety signal was detected in the originally presented limited safety database for the previous indication, there were concerns with regard to the use of the product:

- Unexplained inflammation at the application site has been reported.
- Off-label use (for example, for spinal fusion at multiple levels in children and repeated use) may take place in clinical practice.

In addition, only limited post-marketing safety data is available.

Risk-benefit

CHMP considers that the benefits to be expected from the demonstration of clinical efficacy do not outweigh the risks discussed above and thus the benefit/risk balance is considered negative.

**Recommendation**

Based on the CHMP review of data on quality, safety and efficacy, the CHMP at the time of their meeting in June 2008 considered by consensus that the risk-benefit balance of Opgenra, *for posterolateral lumbar spinal fusion in adult patients with spondylolisthesis where autograft has failed, is not feasible or is unlikely to be efficacious,* was unfavourable and therefore did not recommend the granting of the marketing authorisation.



**GROUNDS FOR REFUSAL**

EFFICACY

- Efficacy (non-inferiority of Opgenra to bone autograft) in the proposed restricted therapeutic indication *"Opgenra is indicated for posterolateral lumbar spinal fusion in adult patients with spondylolisthesis where autograft has failed, is not feasible or is unlikely to be efficacious."* has not been demonstrated. No efficacy data has been submitted to support the efficacy of the product in the target population; and the extrapolation of efficacy to the newly proposed indication cannot be done based on the pivotal study performed for the wider indication; the pivotal study had major flaws (including poorly documented post hoc changes to the analysis) and failed to show non-inferiority of Opgenra to bone autograft.

SAFETY

- No safety data on the newly proposed target population is available.

- Unexplained inflammation at the application site has been reported in the database for the initially proposed indication.

- Only limited post-marketing safety data is available.

In view of the above the CHMP has recommended the refusal of the granting of the Marketing Authorisation for Opgenra.

## 2.7 Re-examination of the CHMP opinion of June 2008

Following the CHMP Opinion concluding that the benefit risk of Opgenra administered for posterolateral lumbar spinal fusion in adult patients with spondylolisthesis where autograft has failed, is not feasible or is unlikely to be efficacious was not considered favourable, the applicant submitted detailed grounds for the re-examination of the grounds for refusal.

**Detailed grounds for re-examination submitted by the applicant**

EFFICACY

The Applicant acknowledges that the pivotal study failed to meet the strict, predefined study success endpoint for demonstrating non-inferiority of Opgenra to autograft for use in the general population undergoing posterolateral lumbar spinal fusion. However, the applicant argued that the body of evidence, comprised of the pivotal clinical study, pilot clinical study, series of pre-clinical studies, published clinical data on target population, post-market surveillance, and surgeon experience, demonstrates a positive risk/benefit profile for use of Opgenra as an alternative to autograft in the specific population described in the proposed restricted indication and that the assessment should take into account the unmet medical need.



Applicant`s description of the restricted indication

Lumbar spinal fusion is the surgical treatment of choice for many diseases of the lower spine in order to provide stability and prevent further displacement of the spine for conditions such as spondylolisthesis. For patients with persistent pain despite medical therapy, surgery should be considered. Surgical treatment involves decompression of the nerve roots by removing bone (laminectomy) followed by spinal fusion to stabilize the affected vertebrae. Spinal fusion is accomplished with the aid of a bone graft material (usually iliac crest autograft) placed either between the vertebral bodies (interbody fusion) and/or between the transverse processes (intertransverse fusion, also called posterolateral fusion) of adjacent vertebrae. Posterolateral fusion is typically indicated where the objective of the surgery is to restore alignment or provide stability to prevent further deterioration in the alignment of the spine.

Iliac crest autograft is a very effective bone graft for use in creating a fusion in most patients. Nevertheless, it does have some associated complications and is not efficacious in all patients. The inherent risks associated with iliac crest donor site surgery include ongoing post-operative pain at the graft site and a series of additional rare but potentially catastrophic complications that are well-documented in the spinal surgical literature. Complications are more likely in the elderly, the obese, and those with underlying medical conditions. In addition, the surgical harvest of the autograft material adds approximately 20 minutes to the fusion surgery, also adding additional risk to patients with significant underlying medical conditions.

Primary attempts at spinal fusion of the lumbar spine are not always successful, and may fail due to infection, poor vascularisation (associated with smoking, diabetes or other factors causing small vessel disease), or poor autograft bone quantity or quality. When spinal fusion attempts using autograft fail, the efficacy of autograft to promote bone fusion during subsequent fusion attempts is markedly reduced. When a repeated autograft is necessary, the limited supply of autograft becomes a factor in the feasibility of repeat procedures. Other factors that can put patients at risk also need to be considered. Soft tissue risks such as nerve and vascular injury may increase because of the residual

soft tissue damage and scarring at the donor site (from previous surgeries) which complicates future dissections. Pain at either the original or second donor site can be severe and chronic, such that it affects ambulation and may result in increased use of pain medication including narcotics. Further, the general health of the patient may be compromised secondary to infection at the donor site from the first autograft attempt, making further autograft attempts too high risk. Finally, the risk of repeat autograft harvest procedures may increase complications with other concurrent medical illnesses. In addition, the quality of autograft bone available may compromise the viability of the autograft for either primary cases or revisions. Patients with skeletal diseases such as osteoporosis/osteomalacia, Paget's disease are often not candidates for autograft because removing autograft from the donor site could further weaken the graft area. Also, underlying bone diseases are associated with poor-quality bone graft, which is compromised in its capacity to form new bone and often fails to promote spine fusion. If primary fusion fails in these patients then a revision procedure re-using the same compromised iliac crest autograft is also very unlikely to be successful.

Data supporting efficacy for use of Opgenra in the target population

Preclinical tests support the utility of Opgenra in the restricted indication. A preclinical study in a primate model of posterolateral fusion demonstrated the safety and efficacy of the Opgenra/collagen matrix combination in promoting spine fusion over a broad dose range. Fusion in the clinical equivalent dose group was better than the autograft group at 3 months. BMP-7 has also been tested in animal models that are compromised in their capacity for bone formation. In models of chronic infection, diabetes and osteoporosis, BMP-7 was able to overcome these compromising factors and induce the formation of new bone. Further, when the activities of BMP-7 and autograft were compared directly in a model of nicotine exposure, BMP-7 was shown to be superior to autograft in revising posterolateral spinal pseudoarthroses.

The pivotal clinical trial demonstrated the clinically relevant efficacy of Opgenra in all of the prospectively defined as well as post-hoc analyses:

The MAH acknowledges that Opgenra failed to demonstrate non-inferiority to autograft according to the initially defined composite overall success endpoint at 24 months. Failure to demonstrate non-inferiority of Opgenra compared with autograft was primarily attributable to one component of one parameter, the presence of bone as assessed by plain films. Nevertheless, the Opgenra group achieved clinically comparable improvements in all other key clinical outcomes at 24 months post surgery including Oswestry Disability Index (ODI), absence of retreatment, absence of treatment-related serious adverse effects and absence of decrease in neurological status. Comparable success in the other radiographic parameters measuring stability of the fused level (angulation and translation) at 24 months was also observed. In addition, Opgenra subjects had statistically shorter operative times and less blood loss during surgery on average than autograft subjects.

Opgenra also demonstrated non-inferiority to autograft according to the modified composite overall success endpoint at 24 months, with clinical assessments performed at 24 months and radiographic and retreatment components at 36+ months. Opgenra was clinically comparable to autograft on all pre-specified 24 month clinical, functional radiographic and post hoc subcomponents of overall success, which was further supported by the post hoc radiographic assessment for presence of bone at 36+ months.

Unlike autograft, Opgenra eliminates the pain and morbidity associated with surgical harvesting of autograft bone from the iliac crest. The use of Opgenra also reduced the time of the operation by 20 minutes ($p=0.006$) and significantly reduced blood loss ($p=0.004$) compared to autograft use.

Extrapolation of efficacy data from the pivotal study to the restricted indication use. Multiple subpopulations (spinal level fused, grade of spondylolisthesis, presence of metabolic bone disease or osteoporosis, presence of diabetes, existence of prior surgical treatment) evaluated had similar efficacy in both treatment groups as the total population in the trial.

The pilot trial (including its extension study) results were consistent across multiple clinical and radiographic efficacy endpoints.

With respect to pain and disability scores; avoidance of reoperation and serious treatment-related complications; maintenance or improvement of neurologic function; radiographic evidence of new bone formation (using CT scan data to assess presence of bone); functional stability (measured by angulation and translation); and long-term durability of success in patients followed for a mean of 4.4 years, Opgenra achieved uniformly successful and clinically meaningful results.

Research indicates that patients who undergo decompression with arthrodesis for degenerative spondylolisthesis may exhibit satisfactory clinical improvements at early time points (through 2 years post-operatively) regardless of whether they have achieved fusion or not; while at longer-term follow-up intervals, patients who have not achieved fusion exhibit worse clinical outcomes than patients who achieved fusion. The durability of the good clinical results seen in the Opgenra pivotal study group at a mean 4.4 years follow-up therefore further demonstrate Opgenra's effectiveness in achieving posterolateral spinal fusion and providing the attendant long-term clinical benefits of fusion.

The applicant concludes that efficacy for the restricted indication has been supported by clinical trial data and post-market data from the US where the product is authorized for a similar indication. The post-market data consists of surveillance/pharmacovigilance reporting as well as clinical experience documented in both published reports and expert statements. The applicant concludes that these support the clinical utility of Opgenra for promoting spinal fusion in patients where autograft has failed, is not feasible, or is unlikely to be efficacious.



SAFETY

1. <u>No safety data on the newly proposed target population is available</u>

The MAH has presented safety information for the newly proposed target population, which are derived from post-marketing data in approximately 16,000 patients treated in the US under a US HDE approval. The HDE status in the US places on the user and manufacturer a responsibility to record any adverse events associated with the clinical use of the product. In addition, HDE approved products require annual IRB approval and oversight of the use of the product. Every effort was made by the manufacturer to ensure the capture of all adverse events associated with the use of the product in compliance with the local requirements for safety monitoring of implantable medical devices. The nature of adverse events reported was generally similar to that seen during clinical development.

Since the launch of Opgenra in the USA as a medical device in 2004, spontaneously reported adverse events and those identified through medical and scientific literature review have been entered into a Pharmacovigilance database. There has been an average of 0.28 adverse events reported per 100 units of Opgenra sold in the US. Most of the adverse events received were found to be undesirable effects of surgery and were considered by the attending surgeons to be causally unrelated to Opgenra. A tabulated summary of these events was submitted in the RMP at Day 180 of the procedure.

When requested by the CHMP, specified information was provided on:

- Myocardial infarction:
  There were two events in patients with significant past medical histories of cardiovascular disease.
- Infections
  No clinically significant pattern of infections or infection related adverse events was detected.
- Inflammation
  There were 14 events related to inflammation; average time from implantation to onset of the AE was 8 days (range 2-15 days). All events were determined to be possibly related to Opgenra or Opgenra in combination with varying quantities of a bone void filler, Calstrux (tricalcium phosphate, carboxymethylcellulose) or other substances (blood or locally harvested bone chips). Of the 14 adverse events identified, 7 were procedures whereby the surgeon combined Opgenra with varying amounts of Calstrux and inflammation occurred within the context of product migration. Product migration has been reported when Opgenra products are used in combination with Calstrux or other bone void fillers. A specific warning against such concomitant use has

been written in the proposed SmPC and will be added to the physician training module to ensure such use is understood by the user.
Only two events appeared to have an allergic component to them, and the timing of exposure-to-onset (11 days and 7 days post-op) may be suggestive of a possible product-related allergic response. It is important to note however, that one patient had a prior exposure to BMP-2 which is contraindicated in the labelling instructions and the length of time preceding exposure to BMP-7 is unknown. The second patient had a 6-level fusion done and the amount of Opgenra used is not known. The surgeon thought the event may have been an allergic reaction to the bovine collagen carrier.

2. Unexplained inflammation at the application site has been reported in the database for the initially proposed indication.

All adverse event reports related to signs or symptoms of inflammation or of fluid collection have been reviewed.
There were only 19 adverse events out of a total of approximately 16,000 treated patients related to signs or symptoms of inflammation from all sources (pivotal study and post-market adverse event reporting).

- Five (5) adverse events reported through the pivotal study were of mild severity and none of the events appears to be product related.
- Fourteen (14) adverse events were reported through post-market surveillance, and seven of those were associated with mixing Opgenra with the bone void filler Calstrux. A specific warning against such concomitant use has been written in the proposed SmPC. Some of the adverse events were reported to have had wound infections with positive identification of the infecting organism, a common complication associated with surgery. Two of the events may have had an allergic component (see response to Ground 2).

Consideration of the various types of events represented by these 19 reports does not suggest that Opgenra is associated with any concerning pattern of inflammation-related adverse events.
There were 5 events of fluid collection from all sources (pivotal study and post-market adverse event reporting) out of approximately 16,000 treated patients.

- Two events reported through the pivotal study were of mild severity requiring no treatment and were reported as not related to the product.
- Three events reported through post-market surveillance were reported as severity unknown and causal relation to product unknown. Two of these three events were associated with concomitant use of the bone void filler Calstrux. A specific warning against such concomitant use was written in the proposed SmPC. The third event was reported as "seroma" and further detail on the severity or treatment was not provided to Stryker Biotech.

Consideration of these five events from all sources does not suggest that fluid collection is a safety concern for Opgenra when Opgenra is used according to the proposed SmPC.

Despite the fact that patients in the pivotal trial in the Opgenra group had a higher incidence of neutralizing anti-OP-1 antibody formation than autograft patients, analyses demonstrated that the patients who had neutralizing antibodies did not experience a higher incidence of adverse events than patients who did not, and that patients who had neutralizing antibodies experienced clinical outcomes comparable to the patients who did not. In addition, neutralizing antibodies were present in only 2 patients (1.1%) by 12 months, and in no patients at 24 months or at 36+ months follow up period.

**Report from the Ad-hoc Expert meeting on Opgenra re-examination**

Following the request from the applicant, as agreed by the CHMP, an Ad-hoc Expert meeting has been convened on 9 October 2008 to provide comments on the grounds for negative opinion and advice on the list of questions raised by the CHMP and adopted at the September 2008 CHMP meeting.

The experts considered the CHMP grounds for refusal and agreed that, although they have no reasons to doubt the principal pharmacological action of Opgenra, compelling clinical data on efficacy have not been presented for the broader nor for the restricted indication. The primary efficacy endpoint in the pivotal trial was not met.
The experts were not convinced that the applicant`s argument of "lack of sensitivity of the initial radiologic endpoint" is an appropriate justification to explain the change in endpoint, or to explain the failure of demonstrating non-inferiority of Opgenra to autograft in the pivotal trial. It is acknowledged that CT-scans are more sensitive than X-ray, but CT imaging is impaired by artefacts in case of instrumented surgery (although it was pointed out that this could be overcome by use of special material). The experts felt, that the timing of the CT scans in the pivotal trial was also a weakness of the study. However, in any case demonstration of bridging bone was thought to be the most important endpoint whether demonstrated by X-ray or CT-scan. In this regard, non-inferiority of Opgenra versus autograft had not been demonstrated either by X-ray, or by CT scan at +9 months and +36 months for this critical endpoint.

The experts considered that showing bridging bone on CT was necessary for the establishment of non-inferiority of Opgenra compared to autograft and that clinical endpoints only were not sufficient. They also had doubts concerning the sensitivity of the clinical parameters. The expert group felt that the clinical outcomes were more difficult to interpret since all patients had received surgical decompression and laminectomy, which would be expected to improve symptoms.

The experts acknowledged the case series presented on situations where autograft has failed. However, it was noted that the case studies presented described a very heterogeneous population (e.g. the Fehling study included also cervical spine fusions), and the product had been used in combination with other strategies to promote fusion such as instrumentation and heterogeneous use of autografting. In view of this it was felt that the results could not easily be extrapolated to the requested indication and the numbers were considered to be very small.

The experts agreed that although there is a need for a second-line alternative to autograft, the data currently available do not establish efficacy in the proposed restricted indication. A prospective trial in the high risk population (autograft failure or not feasible) would be valuable; such a trial would not necessarily have to be very large, but it would be important to be well designed and control well for variability. The trial population and methodology would need to be well defined in the study protocol

Subgroup analysis data presented for the pivotal trial were not compelling. Results presented suggested Opgenra to be less efficacious in osteoporotic versus non-osteoporotic patients (and idem for diabetes). However, a comparison of Opgenra versus autograft in these subgroups of patients would, based on the small numbers of individuals, have too limited power to yield definitive results. It was felt, that a prospective trial would be needed to demonstrate efficacy. For example, autograft versus Opgenra, or standard care with Opgenra versus standard care alone in a high risk population.
It was not possible to look in cohorts of patients according to concomitant treatment (e.g. biphosphonates), as baseline concomitant medication was not recorded. This was felt to be desirable if a future study was being planned.

From the experts` discussion on instrumented versus uninstrumented surgery, it transpired that the current standard of care in Europe tends to be instrumented fusion (with orthopaedic rods, screws or disc replacement), and would involve 360° fusion or/and interbody fusion rather than - or in addition to - posterolateral fusion. In most of the surgeon statements provided by the applicant, the surgical method used involved some way of instrumentation.
The expert group did not feel that instrumentation was likely to impair the biological effects of Opgenra. However the results of the pivotal trial could not easily be extrapolated to the situation of instrumented fusion, where it would be expected that the effects of both autograft and Opgenra in promoting fusion might be enhanced. There was a divergent view on whether uninstrumented or instrumented fusions represented a universal standard of care. One expert expressed the view that there exist methodological advantages of doing uninstrumented fusion, for example that this allows an RSA (roentgen stereophotogrammetric analysis) study, which would be impossible in case of instrumented fusion.

The expert group did not conclude on the role of instrumentation in a future study as this was out with the remit of the meeting.

The experts acknowledged that there is no major safety concern on the target population from the pivotal trial; the experts noted the availability of some post-marketing data, which was considered to be reassuring. In their opinion, inflammation is not a major issue. Antibodies to OP-1, malignancy and potential off-label use would need to be followed closely.

**Overall conclusion on grounds for re-examination and updated benefit/risk assessment**

The active substance of Opgenra is eptotermin alfa that is a recombinant human osteogenic protein (also known as bone morphogenetic protein 7, BMP-7, or OP-1 protein). Eptotermin alfa is a growth factor belonging to the BMP family. Currently eptotermin alfa is marketed in the EU under the invented name of Osigraft for the treatment of nonunion of tibia. Osigraft is, practically the same recombinant human osteogenic protein 1 (OP-1) in a type I bovine collagen matrix as with Opgenra but without the putty CMC.

The preclinical data support the concept of induction of new bone formation. These findings have previously been assessed and accepted by the CHMP and the proposed pharmacological action of Opgenra was also acknowledged by the ad hoc expert meeting that took place 9 Oct 2008. Thus, there is a substantial body of data supporting positive effects of Opgenra on new bone formation.

In the pivotal trial, treatment with Opgenra resulted in clinical outcomes that were non-inferior to treatment with autograft. Radiographic success in terms of new bone formation was, however, not consistently shown. Since it was the opinion of the ad hoc expert group that radiographic success was necessary to show efficacy, it is concluded that non-inferiority for Opgenra was not shown for the wider indication.

Autograft is currently the standard of care in first line posterolateral spinal fusion for patients with no risk factors for non-union. However, when it fails, there is an important decrease in the success rate of subsequent revision(s) with autograft alone. Therefore, an alternative therapy is needed in these patients, a view that was shared by the ad-hoc expert meeting.

Autograft is a weak source of BMP and with limited quantity and/or quality of the graft material, there is often an inadequate amount of BMP present to ensure proper stem cell signalling to allow bone formation. A significant increase in the BMP with the use of Opgenra can allow bone to form in this setting or in other hostile environment such as scarring from previous surgery. Therefore, there is a strong rationale for using Opgenra in patients who have failed prior autograft surgery or where autograft is not feasible. However, it was the opinion of the ad hoc expert group that the data currently available do not establish efficacy in the proposed restricted indication.

The two trials performed by the Applicant have provided evidence that Opgenra alone has substantial efficacy as first line therapy in a general population at low risk for non-union. In the pilot trial 11 of 16 patients in the Opgenra group showed radiographic success as compared to 3 of 6 in the autograft group after 4 years (7). In the pivotal trial, Opgenra appeared not to be as effective as autograft, as indicated by the failure in the radiographic demonstration of new bone formation. These results are comparable to the results of Johnsson et al, where bridging bone was seen in 6 of 10 patients in the Opgenra group and 8 of 10 in the autograft group (3).

Such a slightly less effective treatment would be acceptable in the situations mentioned above where there is no alternative available but actual evidence is lacking since these patients were excluded from the trials. However, in the US, Opgenra is used in these patients; there is some published evidence of its efficacy although current practice combines it with autologous local bone and often with instrumentation, which minimizes the motion between adjacent vertebrae (Fehling series (1)).

Having re-examined the data submitted and having considered the conclusions of the Ad-hoc expert group meeting, it is the CHMP' view that the data support a very restricted indication in patients who have failed prior autograft surgery or where autograft is contra-indicated.

In contrast, situations where autograft is unlikely to be efficacious cover a too broad range of conditions; moreover, superiority over autograft would have to be shown in this setting. No such evidence is currently available in the absence of a detailed analysis of this subpopulation in the trials performed by the Applicant. Experience from the US again shows that Opgenra is usually combined with autologous bone and instrumentation.

**Efficacy**

Although no such patient has been studied in the clinical trials, efficacy data for the target population can reasonably be derived from these trials and the US published experience to support a very limited indication as an alternative to autograft when it has already failed or when it is contra-indicated.

- Results from various animal models of pseudarthrosis suggest that Opgenra may be superior to autograft in conditions with high risk of non fusion.

- There is evidence of efficacy on both clinical and radiological endpoints in the clinical trials where Opgenra was compared to the gold standard. These trials enrolled a number of patients at high risk of pseudarthrosis. Furthermore, comparative long-term data (up to 4 years) from the small pilot trial suggest maintenance of the effects of Opgenra similar to autograft.

- Limited data on patients with prior autograft failure (i.e. the proposed indication), who have been treated in the US, are available from the literature.

- Current practice in the proposed indication, as reflected by the US data, usually combines the use of Opgenra with local bone autograft and/or supplemental instrumentation; these options are left at the discretion of the surgeon.

- Additional advantages of the use of Opgenra rather than revision(s) with autograft are shorter operative time, less blood loss, and much less post-operative pain due to eliminating the harvesting procedure from the iliac crest.

- However, due to the limited amount of data available in the proposed indication, there is a need for a long-term post-marketing observational study (see Section 2.7).

**Safety**

- The risks of Opgenra have been reasonably well characterised in the clinical trials.

- Post-marketing experience in the US is large.

- In addition, the experience gained with Osigraft, the same product without CMC, is extensive and there is no suggestion that the safety profile of Osigraft in its restricted indication (in the EU) differs from its safety profile in other countries where its indication is much broader.

- The proposed SPC adequately covers all known safety issues.

- The RMP for Opgenra should be updated with regard to its indication and to the post-marketing data from the US, which should be thoroughly checked by the Applicant. It should also include a long-term post-marketing observational study. A UK and European registry that is focused on the application of BMP-7/OP-1 already exists with a database administered at the University of Leeds (bmpusergroup.co.uk). The website provides the following preamble: *"Pre-clinical and clinical safety assessments have revealed little evidence of toxic effects and there have been few reports of adverse events related to their use. A small rate of immunological reaction following administration, resulting in antibody formation, has been*

**Risk Management Plan**

The MAA submitted a risk management plan, which, upon request of CHMP included a risk minimisation plan.

Opgenra has the same drug substance as Osigraft that is used for another therapeutic indication, tibial non-union fractures. Opgenra differs from Osigraft by its methylcellulose component that makes the product easier to shape. The marketing authorisation of Osigraft has been renewed.

Patients with non-degenerative spondylolisthesis of any grade at the affected level and patients with degenerative spondylolisthesis of Grade 3 or 4 have not been investigated. Furthermore pregnant women and patients with risk factors of impaired healing, such as tobacco, nicotine or corticosteroids have not been studied.

There have been no observable trends or safety-related concerns identified regarding the approved use of Opgenra that would impact the current safety profile of the products. Information regarding post-marketing exposure is submitted annually to all relevant regulatory agencies, as required by law.

Pharmacovigilance plan

The Applicant was of the opinion that there are no special activities required beyond routine pharmacovigilance, that no pattern of clinically relevant laboratory changes has been associated with Opgenra treatment, and that there does not appear to be any association of neutralising antibodies and the development of potentially immunologically-related AEs or SAEs of any kind.

In the pivotal study, there was an increase of cardiac disorders, infections and infestations, respiratory, thoracic and mediastinal disorders, and gastrointestinal disorders in the Opgenra group as compared to the autograft group. These have been adequately taken into account in the SPC and PL texts.

Because of the potential off label use in vulnerable groups or application sites and the potential risk with local inflammation, including inflammation and device/drug migration with bone void filler use (Calstrux), routine pharmacovigilance is not sufficient.

The Applicant presented a new RMP which fulfils EU criteria and addresses issues raised during the review process. A detailed description of the educational program would need to be agreed with CHMP and the Member States before launch. It is suggested that the MAH presents (with regard to the EudraVigilance interface) a set of relevant MedDRA terms with special focus on inflammation and related terms. A review on hair loss and cessation of nail growth has been requested as a post-marketing follow-up measure, based on a possible signal in the latest Osigraft PSUR (possibly indicating a systemic adverse reaction). (see Section 2.7)

Table Summary of the risk management plan

| **Safety Concern** | **Proposed Pharmacovigilance Activities** | **Proposed Risk Minimisation activities** |
|---|---|---|
| 1. Hypersensitivity and antibody formation | Routine pharmacovigilance monitoring | Warning in section 4.3 regarding patients with hypersensitivity to active |

| Safety Concern | Proposed Pharmacovigilance Activities | Proposed Risk Minimisation activities |
|---|---|---|
| | | substance or excipients<br><br>Warning in section 4.4 of the SPC regarding the formation of antibodies and the unknown clinical significance of this.<br><br>Warning in section 4.4 of the SPC: "Repeated use of Opgenra cannot be recommended. Studies with anti-OP-1 antibodies demonstrated some cross-reactivity with closely related BMP proteins BMP-5 and BMP-6. Anti-OP-1 antibodies have the ability to neutralise the *in vitro* biological activity of at least BMP-6. Therefore, upon re-administration of Opgenra, a risk of developing autoimmunity towards the endogenous BMP proteins may exist."<br><br>Educational material |
| 2. Embryo-foetotoxicity | Routine pharmacovigilance monitoring and follow-up on pregnancy reports | Warning in section 4.6 of the SPC that effects of anti-OP-1 antibodies on embryofoetal development cannot be ruled out<br><br>Advice in section 4.6 that women of childbearing potential should use effective contraception for 2 years<br><br>Information in section 5.3 of the SPC on animal foetal malformations<br><br>Educational material |
| 3. Ectopic bone formation | Routine pharmacovigilance monitoring<br><br>Post marketing surveillance study : Observational Study in all subjects treated with Opgenra at selected academic sites in the European Union. | Warning in section 4.4 of the SPC that material dislodged from the fusion site may cause ectopic ossification<br><br>Educational material |

| Safety Concern | Proposed Pharmacovigilance Activities | Proposed Risk Minimisation activities |
|---|---|---|
| | Post marketing surveillance study : Prospective Cohort Study of Opgenra in subjects undergoing posterolateral fusion where autograft has failed or is contraindicated | |
| 4. Pseudarthrosis | Routine Pharmacovigilance monitoring<br><br>Post marketing surveillance study : Observational Study in all subjects treated with Opgenra at selected academic sites in the European Union.<br><br>Post marketing surveillance study : Prospective Cohort Study of Opgenra in subjects undergoing posterolateral fusion where autograft has failed or is contraindicated | Labelled in section 4.8 of the SPC |
| 5. Interaction with bone void fillers | Routine pharmacovigilance monitoring<br><br>Post marketing surveillance study : Observational Study in all subjects treated with Opgenra at selected academic sites in the European Union. | Warnings in sections 4.4 and 4.5 of the SPC that concomitant use with bone void fillers is not recommended.<br><br>Educational material |
| 6. Repeat Use | Routine pharmacovigilance monitoring<br><br>Post marketing surveillance study : Observational Study in all subjects treated with Opgenra at selected academic sites in the European Union. | Statement in section 4.2 of the SPC that Opgenra intended for single use.<br><br>Warning in section 4.4 of the SPC that repeat use is not recommended (see also warning on hypersensitivity and antibody formation.)<br><br>The Opgenra product information will be modified to incorporate a patient exposure label to be placed in their medical records which will specify that the patient has been implanted with a medicinal product containing |

| Safety Concern | Proposed Pharmacovigilance Activities | Proposed Risk Minimisation activities |
|---|---|---|
| | | eptotermin alfa and that repeat use must not occur.<br><br>Educational material |
| 7. Long term safety data | 2 years follow up data from the following Post marketing surveillance study :<br><br>Observational Study in all subjects treated with Opgenra at selected academic sites in the European Union.<br><br>Prospective Cohort Study of Opgenra in subjects undergoing posterolateral fusion where autograft has failed or is contraindicated | Educational material |
| 8. Off-label use | Post marketing surveillance study : Observational Study in all subjects treated with Opgenra at selected academic sites in the European Union. | Educational material |



The proposed SPC adequately covers all known safety issues.

The CHMP, having considered the data submitted, was of the opinion that:

- pharmacovigilance activities in addition to the use of routine pharmacovigilance were needed to investigate further some safety concerns.
- the following additional risk minimisation activities were required: see as detailed in section 2.3

The MAH shall agree the details of an education programme for surgeons with the National Competent Authorities and must implement such programme nationally to ensure that:

Prior to use of the product, surgeons should be provided with educational material containing:
- a copy of the SPC
- a detailed description of:

- Risk of hypersensitivity and antibody formation
- Potential embryo-foetotoxicity and need for contraception for 2 years
- the recommended methods for reconstitution of the product prior to implantation
- the preparation of the selected paraspinal site where the intended implantation will occur
- the recommended manner of placement of the material together with some comments on the importance of local haemostasis
- the methods for soft tissue closure around the implant. These descriptive texts are included in the product information.

- Information about:
  - Hypersensitivity and antibody formation

    - Embryo-foetotoxicity and the need for women with childbearing potential to use effective contraception for 2 years following implant
    - the risks of ectopic bone formation
    - interaction with bone void fillers
    - that the product should only be used once
- details of the post marketing surveillance studies including information on how to enroll patients

In addition, prior to use, surgeons intending to use Opgenra should receive a Training DVD containing images recorded during the course of an operation on a live patient and including the following information:

- Product description
- Placement in sterile field
- Wound opening (soft and hard tissues)
- Reconstitution of product
- Implant field preparation (haemostasis)
- Administration (implantation)
- Containment of implanted materials (soft tissues)
- Instrumentation
- Wound closure (drainage)
- Follow-up measures

In addition, protocols for a study or studies to investigate the long term safety and efficacy of patients treated with Opgenra and also actual drug utilisation in real life will be submitted by the MAH and agreed with the CHMP before product launch and before the study is started.

**User consultation**

The user testing performed on the PL, which differs from the proposed PL of this MAA, is acceptable and it is considered to comply with the requirements in Articles 59(3) and 61(1) of the Directive 2001/83/EC, as amended. However, bridging justification for the discrepancies with the proposed PL is to be performed and provided post-authorisation.

**Risk/Benefit Assessment**

The population represented by the more restricted population (adult patients with spondylolisthesis where autograft has failed or is contra-indicated) has not been evaluated in a clinical trial. However, efficacy data can reasonably be derived from these trials and the US published experience to support a very restricted indication in these patients where autograft has failed or is contra-indicated.

There are no outstanding safety concerns identified in the pivotal study or post marketing experience that could not be adequately taken care of in the SPC and RMP.

In conclusion, the CHMP are of the opinion that the benefit/risk balance of Opgenra in the very restricted indication "*where autograft has failed or is contra-indicated"* is positive.

**Recommendation following re-examination**

Based on the CHMP review of data on quality, safety and efficacy, the CHMP revised its opinion by majority decision and concluded that the risk-benefit balance of Opgenra administered for posterolateral lumbar spinal fusion in adult patients with spondylolisthesis where autograft has failed or is contra-indicated satisfied the criteria for authorisation and therefore recommended the granting of the marketing authorisation.

Divergent opinions were based on the following considerations:

- Compelling efficacy data was lacking, since the pivotal study failed to demonstrate non-inferiority to autograft with regard to the primary endpoint and also with regard to the primary radiographic endpoint (presence of bridging bone) in the broader indication, the population for the restricted indication was actively excluded from the pivotal study, and the other efficacy data available (case studies) described small numbers of a very heterogeneous population where Opgenra was used in combination with other strategies.

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