London, 17 February 2005
Product name: **INDUCTOS**
Procedure No. **EMEA/H/C/408/II/07**

SCIENTIFIC DISCUSSION

TABLE OF CONTENTS

1. INTRODUCTION

This type II variation application aims to extend the therapeutic indications for InductOs (dibotermin alfa). The proposed additional new indication is:
"InductOs is indicated for single-level (L4 - S1) anterior lumbar spine fusion as a substitute for autogenous bone graft in adults with degenerative disc disease who have had at least 6 months of non-operative treatment for this condition."
For this indication, InductOs must be used with the LT-CAGE® Lumbar Tapered Fusion Device.

The currently approved therapeutic indication reads as follows:

"InductOs is indicated for the treatment of acute tibia fractures in adults, as an adjunct to standard care using open fracture reduction and intramedullary nail fixation."

The MAH claims significant medical benefits of InductOs in spine fusion surgery as a direct replacement for autogenous bone graft. These include relief from the symptoms of degenerative disc disease, achieved without the pain and morbidity associated with a second surgical site to harvest autogenous bone graft, less blood loss during surgery and shorter operative times.
Outside of the EU, dibotermin alfa/ACS (Absorbable Collagen Sponge) is currently approved for marketing, under the name 'INFUSE Bone Graft' in the USA, Canada and Mexico. In the USA, it is approved as a medical device for both anterior lumbar spine fusion procedures and acute tibia fractures, whereas in Canada and Mexico, it is approved for anterior lumbar spine fusion procedures only.

2. QUALITY REGARDING THE MEDICAL DEVICE

Following validation of the application, the MAH has provided information regarding the LT-CAGE.

The proprietor is Medtronic Sofamor Danek.

The LT-CAGE Lumbar Tapered Fusion Device consists of a hollow, perforated, machined cylinder with opposite flats. The cage has a tapered design with an angle of 8.8^{o} and is available in diameters ranging from 14 mm to 18 mm end of taper, 17 to 22 mm at the wide end of the taper, and in lengths ranging from 20 mm to 26 mm. There are two holes on each of the two flat sides. On each of the two rounded aspects, there is a single rounded slot. The implants have a helical screw thread on the outer surface. One end of the device is closed and is used to engage the drive instrument for insertion of the device.

The LT-CAGE Device is made from implant grade titanium alloy (Ti-6A1-4V) described by such standards as ASTM F136 or its ISO equivalent.

Technical drawings of the device and the Package Insert have been provided. The Package Insert is in compliance with the EU Medical Devices Directive (93/42/EEC), and is subject to an annual review by the designated EU Notified Body.

The CHMP noted that the indications for use of the LT-CAGE Lumbar Tapered Fusion Device are in line with the proposed therapeutic use of this device with InductOs i.e. *for spinal fusion procedures in skeletally mature patients with degenerative disk disease (DDD) at one level from L2-S1. Patients should have had at least six months of nonoperative treatment prior to treatment with LT-CAGE*. According to the Package Insert, the device is indicated for *use with autogenous bone graft.*
Therefore, the CHMP concluded that the therapeutic indication for InductOs should also specify that patients should have a history of at least six months of nonoperative treatment. The MAH agreed with the CHMP's proposal and amended the initial proposed indication to insert that patients should have a history of at least six months of nonoperative treatment.

Additionally, the CHMP proposed to delete the sentence "that InductOs must be used with the specific LT-CAGE Lumbar Tapered Fusion Device" from the initially proposed indication since it blocks the use of other devices. Since so far experience is limited to the LT-CAGE, this must be mentioned in section 4.2 "Posology and method of administration" in the SPC. The MAH agreed on the CHMP's proposal.

3. NON-CLINICAL ASPECTS

InductOs is a bone inductive agent consisting of recombinant human Bone Morphogenetic Protein-2 (rhBMP-2) and Absorbable Collagen Sponge (ACS). rhBMP-2 is a glycosylated, disulfide-bonded, dimeric protein produced by mammalian cell culture methods. Local administration of rhBMP-2 results in the induction of new bone tissue at the site of implantation. To facilitate surgical application, rhBMP-2 is combined with a matrix, the ACS, resulting in a moldable cohesive implant. As bone is formed, the matrix is degraded as is the rhBMP-2 component.

The ACS matrix is the Helistat Absorbable Collagen Hemostatic Sponge manufactured from bovine type I collagen derived from tendons. It is CE-marked in Europe, and sold commercially in the US, Europe, Japan, and Canada as an intra-operative hemostatic agent which can be left in the surgical site. Helistat has a long (>20 years) commercial history of safe use in medical applications.

At the time of surgical implantation, the ACS is wetted with a solution of rhBMP-2 to form the product (rhBMP-2/ACS). While application of rhBMP-2 alone is sufficient for osteoinduction, ACS as a carrier for rhBMP-2 provides a couple of functions. ACS localizes rhBMP-2 to the surgical site, and increases the retention of rhBMP-2 at the desired site compared to rhBMP-2 in buffer alone. This is important for optimal and localised bone formation. The pharmacological studies previously submitted have demonstrated that rhBMP-2/ACS induces bone formation, heals bony defects, and augments fracture repair. These studies suggested that bone formation initiated by rhBMP-2/ACS is a self-limiting process, ie, only a defined volume of bone is created. This self-limitation is due to eventual loss of rhBMP-2 from the implant site, as well as the presence of BMP inhibitors in the surrounding tissues. In addition, several studies indicate that there is a negative feedback mechanism at the molecular biology level that limits bone induction by BMPs.

The product used in the interbody spine fusion application with the LT-Cage is identical to that described in the InductOs MAA in terms of protein formulation, carrier matrix and concentration. Therefore, previously reported toxicology and pharmacokinetic data are applicable to the indication described in this submission. With general safety of rhBMP-2 and rhBMP-2/ACS established, the focus of the nonclinical studies is on spinal fusion efficacy and safety. This submission contains the nonclinical information to demonstrate that rhBMP-2/ACS is effective for use in an interbody spinal fusion application and safe for use in a spinal application in proximity to the spinal canal and nerve roots.

The pharmacology studies, with the exception of the 1 spinal safety study, were not performed in accordance with Good Laboratory Practice (GLP) regulations.

The six non-clinical studies include lumbar fusion studies in nonhuman primates and sheep and a cervical fusion study in goats. Two of the studies most relevant to the proposed indication had treatment groups that allowed for direct comparison of rhBMP-2/ACS to autograft for promoting spinal fusion in titanium interbody cages.

Study report RPT-52965: Graft Materials for a Titanium Threaded Interbody Fusion Device for Anterior Interbody Fusion in a Sheep Lumbar Spine Model

The primary purpose of this study was to compare the effectiveness of rhBMP-2/ACS to that of autograft in promoting interbody spinal fusions using a titanium fusion cage. Twelve skeletally mature sheep underwent L4-L5 interbody spinal fusion using the titanium cages. Animals were randomised

into one of two treatment groups specifying the material to be used inside the fusion cage (autogenous iliac crest bone or 0.43 mg/mL rhBMP-2/ACS). Animals were sacrificed at 24 weeks. Both study groups resulted in 100% fusion rates as assessed via manual palpation. Biomechanical stiffness results were reported in all autograft and five of six rhBMP-2/ACS treated animals and there was no statistically significant difference between the two groups. A trend toward greater stiffness to flexion with rhBMP-2/ACS was demonstrated. However, both the rhBMP-2/ACS and autograft treatment groups were found to be statistically significantly stiffer than untreated normal disc spaces from unoperated spinal segments. Changes in interbody height were also analysed and no differences were found between rhBMP-2/ACS treated animals and autograft controls. Histologic analyses showed a 37% fusion rate with autograft filled cages, as opposed to 100% fusion for the rhBMP-2/ACS group. The rhBMP-2/ACS treated animals had dense remodeled bone growing through the holes in the cage walls and trabeculae bridging adjacent vertebral bodies.

Study Report RPT-52963: Cervical Interbody Fusion Cages: An Animal Model With and Without BMP

Although this nonclinical study was performed in a cervical model as opposed to a lumbar spine model, it is considered relevant to the proposed application of InductOs because it compares rhBMP-2/ACS to iliac crest autograft inside a titanium fusion cage in an interbody fusion model.

The primary purpose of this study was to compare the effectiveness of rhBMP-2/ACS to that of autograft in promoting interbody spinal fusions using a titanium fusion cage. Fourteen skeletally mature goats underwent 3 contiguous cervical interbody spinal fusions using threaded interbody fusion cages. Animals were randomised into one of 2 treatment groups specifying the bone graft material to be used inside the fusion cage (iliac crest autograft or 0.40 mg/mL rhBMP-2/ACS). The same bone graft material was used in all 3 cages within each animal.

Animals were sacrificed at 12 weeks. Levels were graded as having a successful fusion, a failed fusion, or an intermediate result based on analysis of microradiographs and histologic sections. Ninety-five percent (95%) of the rhBMP-2/ACS-treated levels had a successful fusion as opposed to only 48% for the autograft treated levels. The remaining 5% of the rhBMP-2/ACS filled cages had an "intermediate" result (presence of some fibrous tissue) in comparison to 38% of the autograft filled cage group. The failed fusion rate was 14% for the autograft versus 0% for rhBMP-2/ACS. Biomechanical stiffness results did not reveal any statistical differences in the 2 treatment groups. In addition, there was no statistically significant difference in stiffness in any loading mode by fusion result. The lack of statistically significant differences may have been due to the stability provided by the cage itself. Histologic analysis revealed that the use of rhBMP-2/ACS increased the rate of bone formation within and around the cage and accelerated the time to bone revascularization compared to autograft.

Study Report RPT-52962: Laproscopic Anterior Spinal Arthrodesis with rhBMP-2/Helistat® in a Titanium Interbody Threaded Fusion Cage in the Non-Human Primate

The purpose of this study was to compare the effectiveness of various doses of rhBMP-2/ACS in promoting interbody spinal fusion using titanium interbody cages. Eight adult Macaca mulatta (rhesus) monkeys underwent L7-S1 interbody spinal fusion using a titanium cage. Animals were randomised into 1 of 3 treatment groups according to the concentration of rhBMP-2 to be used inside the fusion cage (0.0, 0.75, or 1.50 mg/mL rhBMP-2/ACS). One animal at 0.75 mg/mL died on postoperative day 3 due to a complication of the surgical procedure which was unrelated to rhBMP-2. The remaining 7 animals were sacrificed at 4 weeks.

All animals treated with rhBMP-2/ACS had solid fusions at 24 weeks as assessed by palpation, CT analysis, and histologic analysis. Animals in the 0.0 mg/mL rBMP 2/ACS group did not have solid fusions as assessed by the same 3 methods. CT scans of the 0.75 and 1.50 mg/mL rhBMP-2/ACS-treated animals showed continuous bone through the cage in all animals, while the CT scans of the 0.0 mg/mL rhBMP-2/ACS animals showed some bone growth at the vertebral bodies that was not continuous across the disc space. The bone formed using the higher dose (1.50 mg/mL) of rhBMP-2

appeared to be denser than that formed using the lower dose (0.75 mg/mL) of rhBMP-2. Histologic analysis confirmed the results of the
CT analysis. The cages filled with 0.0 mg/mL rhBMP-2/ACS were filled primarily with fibrous tissue while the cages filled with 0.75 and 1.50 mg/mL rhBMP-2/ACS had normal trabecular bone throughout. No animal had neurologic compression inside the spinal canal from newly forming bone or extension of bone formation to an unintended area.

Study Report RPT-52966: Evaluation of rhBMP-2/ACS in a Non-Human Primate Anterior Interbody Fusion Model Utilizing a Freeze-Dried Allograft Cylinder

The purpose of this study was to assess the safety and effectiveness of rhBMP-2/ACS in an allograft bone dowel in promoting an interbody spinal fusion in a non-human primate. This study is considered to be relevant to the proposed application of InductOs since in compares iliac crest autograft to rhBMP-2/ACS in a higher order animal interbody fusion model. Six skeletally mature rhesus monkeys underwent an anterior L7-S1 interbody lumbar fusion. The animals were randomised into 1 of 2 treatment groups according to the concentration of rhBMP-2 to be used inside the allograft bone dowel (iliac crest autograft or 1.5 mg/mL rhBMP-2/ACS). One animal from each group was sacrificed at 3 months and the remaining 4 at 6 months.

At 3 months, the rhBMP-2/ACS treated animal was manually, radiographically, and histologically fused while the autograft control was not fused. The use of rhBMP-2/ACS also significantly increased the rate of incorporation of the allograft bone dowel. The dense cortical bone dowel which was visible radiographically immediately postoperative could not be detected in any of the three rhBMP-2/ACS animals at 3 months. This observation was confirmed histologically. The allograft had undergone almost complete incorporation. Evidence of creeping substitution was observed on a small piece of allograft remaining at 3 months. No inflammatory or immune response was observed. In addition, no ectopic or overgrowth of bone was observed around critical neural structures. In contrast, the appearance of the allograft dowels filled with autograft on the 3 month CTs was the same as the appearance immediately postoperative. The autograft controls had some osteoclastic resorption occurring and new bone deposited on the allograft surfaces, but not to the extent seen with rhBMP-2/ACS.

At 6 months, both of the remaining 2 animals treated with rhBMP-2/ACS were fused along with one of the 2 autograft controls. The authors concluded that this study demonstrated the efficacy of rhBMP-2/ACS and a cortical allograft dowel in promoting anterior interbody fusion in a nonhuman primate model. The rate of new bone formation and fusion with the use of rhBMP-2/ACS and the cortical allograft dowel was superior to that of autogenous cancellous iliac crest graft with the cortical allograft dowel.

Study Report RPT-52964: Safety of Recombinant Human Bone Morphogenetic Protein-2 After Spinal Laminectomy in the Dog

The purpose of this study was to assess the effects of rhBMP-2/ACS on exposed dura and neural tissue after standard decompressive lumbar laminectomy using a canine model. This study was conducted in compliance with GLP regulations. Twenty skeletally mature beagles underwent a spinal laminectomy at the L5 spinal level. One-half of the animals also received a “dural nick” made with a 22 gauge needle in the posterior midline of the spinal cord until cerebro-spinal fluid was noted to egress from the nick. Then, either autogenous bone graft or rhBMP-2/ACS was implanted directly on the exposed spinal cord in the laminectomy defect. Animals were randomised into one of four treatment groups (Rib autograft with or without dural nick (N=5), rhBMP-2/ACS (0.10 mg/mL) with or without dural nick (N=5). This concentration of rhBMP-2 was previously shown to be effective in promoting spinal fusion in a canine model. Animals were sacrificed at 12 weeks. Evaluation consisted of clinical, neurological and radiographic examination and histological analysis. The clinical exam involved weekly body weights, monthly blood tests and cerebrospinal fluid analysis at necropsy. Neurology consisted of weekly gait observations and placing reflex, patellar reflex and the pain withdrawal of both hind limbs. Radiographic analyses were done on a monthly basis assessing changes in the spinal

cord, surrounding spinal canal and graft material using pre-established measurement parameters. Histology was used to study the effect of rhBMP-2/ACS in direct contact with neurological tissue.

Neither rhBMP-2/ACS nor the dural nick presented deleterious consequences to the animals. The implants resulted in a physical depression of the dural membrane which was radiographically apparent, suggesting that the implant came to rest adjacent to the thecal sac. The rhBMP-2/ACS stimulated transient bone growth around the margin of the spinal canal. This suggests that the rhBMP-2/ACS came in direct contact with the dural membrane. It may even have leaked into the neuroforamina since there was a bony reaction there. There was no radiographic evidence of mineralization within the thecal sac. There was no evidence clinically of any neurological abnormalities in these animals. There was no evidence of any clinical abnormalities in these animals based on blood and cerebrospinal fluid analyses.

Study Report RPT-52961: Binding Properties of rhBMP-2 to Absorbable Collagen Sponge After Various Fluid Expression Amounts

Since ACS is compressible, it is possible that during intraoperative handling fluid will be expressed from the rhBMP-2/ACS. This fluid may contain rhBMP-2. The purpose of this study was to determine the amount of rhBMP-2 in fluid expressed from rhBMP-2/ACS under different handling conditions. For this study, 2.5 x 5 cm rhBMP-2/ACS strips were prepared by evenly distributing 1.4 mL of 1.5 mg/mL rhBMP-2 solution onto each of 30 ACS strips. The rhBMP-2/ACS were allowed to soak for 15 or 120 minutes and then rolled and compressed using forceps to intentionally express fluid. Strips were subjected to 1 of 3 handling conditions based on the volume of expressed fluid (X): Group 1: 100 µl < X < 250 µl, Group 2: 300 µl <X <650 µl, Group 3: 750 µl < X. The amount of rhBMP-2 in the expressed fluid from each group (n=5) was determined by RP-HPLC.

It was determined that fluid expressed from rhBMP-2/ACS did contain rhBMP-2; however, only a small amount of rhBMP-2 was released from ACS with compression, and this decreased with soaking time. The rhBMP-2 concentration of the fluid expressed from ACS under different handling conditions was consistent when compared at specific soak time. The mean concentration in the expressed fluid was 35% of the applied concentration for the 15 minute soak time and 20% of the applied concentration for the 120 minute soak time. Since the concentration of the expressate was consistent the amount of rhBMP-2 lost from the ACS increased with increased fluid expression in a linear fashion. With the most mild compression tested in this study (Group 1), the amount of rhBMP-2 retained was 95% for the 15 minute soak time and 97% for the 120 minute soak time.

In an attempt to gain clinical perspective on these study results, the amount of fluid loss was recorded during rolling and placement of hydrated ACS into an LT-cage. For this part of the experiment, a 2.5 cm x 5 cm ACS was placed into a 14x20 LT-cage. The fluid volume lost ranged from 13 to 27 µL. This study verifies the effectiveness of ACS in incorporating and retaining rhBMP-2 for surgical implantation. Using compression and handling conditions that seem to be extreme relative to what would occur in normal intraoperative handling and placement in the LT-cage, the ACS still retained at least 95% of the applied rhBMP-2 dose.

3.1 Discussion on non-clinical aspects

The non-clinical safety of rhBMP-2/ACS has been established based on information submitted in the original Marketing Authorisation Application previously. The MAH has submitted additional non-clinical data to support the use of rhBMP-2/ACS in the proposed new therapeutic indication. The use of InductOs for spinal fusion naturally entails new risks, especially the risk of rhBMP-2 leakage from the implant and LT-cage and potential excessive bone formation or bone formation close to sensitive neural structures. Furthermore, there is a risk of local inflammation and oedema potentially leading to neural and/or vascular complications.

The pharmacology studies, with the exception of the spinal safety study in dogs (RPT-52964), were not performed in accordance with Good Laboratory Practice (GLP) regulations. This is a clear drawback and reflects the device-oriented development of the product. However, since the studies are adequately reported, the CHMP concluded that this does not preclude approval of the variation.

The six non-clinical studies include lumbar fusion studies in nonhuman primates and sheep and a cervical fusion study in goats. Two of the studies most relevant to the proposed indication had treatment groups that allowed for direct comparison of rhBMP-2/ACS to autograft for promoting spinal fusion in titanium interbody cages.

Except for RPT-52962 and RPT-52966, the preclinical pharmacodynamic/safety studies used a lower concentration of dibotermin than that proposed for clinical use (1.5 mg/ml). Although the studies are relevant in terms of showing the primary pharmacological action (bone formation and spinal fusion), their relevance for safety assessment is less obvious. Furthermore, in study RPT-52966, InductOs was used together with cortical allograft.

Non-clinical data underline the importance of following the instructions given in the SPC on the appropriate preparation and handling of the implant to avoid leakage of rhBMP-2. The company should commit to produce suitable educational material for surgeons and other medical staff.

Since the non-clinical data relevant for the proposed indication do not provide a strong justification to use the 1.5 mg/ml concentration of dibotermin alfa, the CHMP during its September 2004 plenary meeting requested the MAH to discuss the possibility that a lower concentration could have a more favourable benefit/risk profile.

Following the provision of supplementary information from the MAH, the CHMP noted that the company argued that the results of the nonhuman primate interbody fusion study support the choice of the higher 1.50 mg/ml concentration for clinical use. It is correct that while the nonhuman primate interbody fusion study (RPT-52962) showed that both 0.75 and 1.50 mg/mL concentrations resulted in 100% fusion rates, increased bone density was observed by the investigators with the higher concentration and the rate of bone formation appeared to be slower with the 0.75 mg/ml concentration. It is agreed that more important information for the choice of the dose come from other approved and experimental clinical applications of Inductos, suggesting increased rate of healing with the 1.5 mg/ml compared to lower concentrations. However, the MAH's conclusion that there are no safety concerns with Inductos in the applied indication is not correct. It is not known if the 1.5 mg/ml concentration is optimal in terms of safety in this clinical application as it is possible that complications, e.g. inflammation and excessive bone formation are concentration-related. Nevertheless, from the efficacy perspective the CHMP agreed that the issue is resolved and the safety concern can be dealt with by giving appropriate information in the SPC and educational material.

During its plenary meeting in September 2004 the CHMP commented that although the spinal safety study had a relevant design to examine the potential undesirable effects of application of InductOs near dural membrane, it is was unfortunate that the concentration of rhBMP-2/ACS used was very low (7% of the concentration intended for clinical use) limiting the relevance of the study significantly. The CHMP requested the MAH to comment on a major drawback that was the lack of evaluation of direct neurotoxicity or rhBMP-2/ACS.

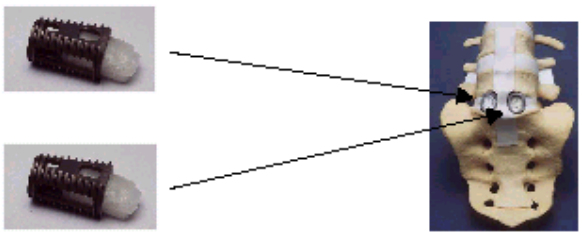
Following the provision of supplementary information by the MAH, the CHMP noted that the company argued that use of low rhBMP-2 concentration in the canine laminectomy safety study was justified in view of the higher sensitivity of the species to the pharmacological effects of rhBMP-2 compared to man. This is accurate in view of the previously submitted non-clinical studies in rodents, dogs and non-human primates. The MAH believes that use of a higher concentration would have led to excessive bone formation in dogs and would not have been relevant for safety assessment. This may well be the case. The canine laminectomy study was designed to model a "worst case" scenario in which rhBMP-2/ACS is implanted inside the spinal canal in direct contact with exposed dura. The actual implantation of rhBMP-2/ACS in this location would not be anticipated under any conditions in a clinical setting.
With these considerations, the CHMP noted that the MAH's approach is reasonable and concluded that the issue was resolved.

4. CLINICAL ASPECTS

Degenerative disc disease (DDD) is a leading cause of low back pain and one of the most prevalent health problems in the world. Non-operative treatments for DDD, including medication, exercise, and manipulation, are the first-course standard of care. Many patients respond to non-operative treatment. However, others continue to experience chronic back pain that can be debilitating. When non-operative forms of treatment have failed to provide sufficient relief from pain and disability for these patients, lumbar spine fusion is considered a viable operative treatment option.

A standard care in Europe for surgical treatment of DDD is fusion of the involved spinal segments, and anterior lumbar interbody spine fusion (ALIF), using autogenous bone with interbody fusion cages, represents about 20-25% of these cases. One such interbody fusion cage is the LT-CAGE Lumbar Tapered Fusion Device, which is CE-marked and has been commercially available in Europe since 1997. The cage may be inserted using either an open or a laparoscopic surgical approach after the removal of the painful, degenerated disc (Figure 1). The function of the cage is to re-establish the proper spinal curvature, realign and decompress the facet joints, relieve stress on the musculature, re-tension the disc annulus, enlarge the foraminal space (thus relieving nerve root pressure), and provide stability to the spinal segment – all with the aim to provide relief of the symptoms of DDD. The autogenous bone graft then facilitates the fusion process in the stable environment provided by the cage, and the fusion makes the treatment permanent. Due to the volume of autogenous bone required by the procedure, the standard practice is to harvest the autogenous bone graft from the iliac crest. This harvest is not infrequently associated with significant morbidity, including complications and pain that may last for several weeks, months, or even years at the harvest site.

Figure 1. LT-CAGE with InductOs.



Because of rhBMP-2's osteoinductive properties, it was believed that rhBMP-2 had the potential to provide significant medical benefit in spine fusion surgery as a direct replacement for autogenous bone

graft harvested from the iliac crest. The potential benefit for the patient is relief from the symptoms of DDD, achieved without the additional pain and morbidity associated with autograft harvesting.

Since rhBMP-2/ACS had not been used in a human spine fusion application previously, the initial human exposure was planned for a small-scale pilot clinical study. It was anticipated that the results of this study would help confirm the appropriateness of the dosage in producing fusion and expose possible safety issues that needed to be addressed in larger clinical studies. In the pilot study, patients received a single-level anterior lumbar interbody fusion procedure using either 1.50 mg/mL rhBMP-2/ACS or autogenous bone harvested from the iliac crest delivered in 2 LT-CAGE˜ Lumbar Tapered Fusion Devices. Two large-scale, prospective clinical studies were planned. Together, these studies focused on determining the effectiveness of the product to fuse the treated spinal level and to relieve pain and on assessing the product's safety. In order to reflect a clinical benefit, a primary endpoint was developed that incorporated both efficacy and safety features into a single variable termed "overall success." Safety and efficacy of the investigational treatment would be proclaimed if the overall success rate for the investigational treatment patients was statistically non-inferior to that for a standard of care control group. In the pivotal Phase III study, rhBMP-2/ACS was implanted with the LT-CAGE Device using an open surgical approach. This study had a prospective, randomized, controlled design. An open surgical approach was chosen due to its popularity among surgeons. A second large-scale study was planned to support the safe use of the same product using a laparoscopic surgical approach, a method that is also popular among surgeons but is used to a much lesser degree. The second study had the same design except that it did not have a randomized control group. It was thought that the results from this laparoscopic surgical approach study would be complementary to the open surgical approach data and that the data would support a label claim for single-level (L 4 -S 1) anterior lumbar spine fusion in adults with degenerative disc disease, irrespective of surgical approach.

The clinical studies that are the basis for this application were performed in the United States and were conducted in accordance with applicable US FDA regulations for devices. The FDA regulations were written in the spirit of the Declaration of Helsinki and good clinical practice.

4.1 Clinical Pharmacology

No new clinical pharmacology data have been provided. The clinical pharmacology comments provided in the Clinical Overview at the time of the first submission for the Marketing Authorisation in Europe are applicable to this application since this variation covers the same formulation for InductOs. However, the pilot study evaluating the feasibility of InductOs when used together with the LT-Cage device has been reviewed.

CSR-52093 (Study 3100N3-117-US): A Prospective, Randomised Feasibility Investigation of Recombinant Human Bone Morphogenetic Protein-2 (rhBMP-2) and Absorbable Collagen Sponge with the Tapered Interbody Fusion Device for Anterior Lumbar Interbody Fusion in Patients with Degenerative Disc Disease

Efficacy Results
Based on either CT or x-ray assessments, the fusion success rate at 12 and 24 months for the investigational treatment group was 100.0% (7/7 subjects treated by open surgical technique and 4/4 subjects treated by laparoscopic approach). All three control subjects were treated using an open approach and were evaluated as fused after 12 months, but one subject had an additional surgical procedure at 18 months postoperative, which caused the subject to be considered a treatment failure at 24 months postoperative.

Safety Results
The study determined that there were no safety issues to hinder implantation of the rhBMP- 2/ACS in larger pivotal clinical trials. There were no additional surgical procedures required in the investigational treatment group. No investigational subject had an antibody response to rhBMP-2. Three of the 11 investigational subjects had antibody responses to bovine collagen. Subjects who had antibody responses to bovine collagen were not found to have positive antibody responses to human

Type I collagen. In addition, there were no medically important differences in the complete blood count or serum chemistry screening results between the investigational and control groups.

Two subjects (18.2%) in the investigational group and one subject (33.3%) in the control group had surgical procedure changes (endcaps not used due to difficulties). One subject (9.1%) in the investigational group and one subject (33.3%) in the control group had hardware failures relating to the endcaps to the LT-CAGE Device (ie, would not engage properly or dislodged after surgery). No complications were noted from these events. The snap-on endcaps, which had been used for this pilot study, were not used in any other rhBMP-2/ACS studies.

4.2 Clinical Efficacy

To support the proposed indication the MAH submitted 3 clinical studies:

- A pilot study (3100N3-117) was performed to assess the feasibility of executing larger clinical trials with rhBMP- 2/ACS as a replacement for autogenous bone harvested from the iliac crest, when used with the LT- CAGE Device;
- An open surgical approach study (3100N3-303) which was considered as the pivotal trial;
- A laparoscopic study (3100N3-304), which was considered as supportive to the pivotal trial.

Study 3100N3-117 (Pilot study):

This was a prospective, multicentre, randomised (3:1) clinical study in 14 patients receiving either two rhBMP-2/ACS-filled LT-CAGE Devices in an anterior (7 subjects) or laparoscopic (4 subjects) surgical approach or two autogenous bone filled (control) LT-CAGE Devices in an open anterior surgical approach (3 subjects). The devices were implanted at 1 level from L2-S1.
Successful fusions occurred in all 14 (100%) subjects receiving the investigational treatment at 24 months postoperative, compared with 2 (66.7%) of the 3 of subjects who received the standard of care control treatment. No significant safety issues were noted during the study. One-year follow-up data from the pilot study were deemed necessary to characterize the outcomes before larger pivotal studies could commence. Based on these data the open surgical approach study and the laparoscopic approach study were designed.

Study 3100N3-303 (open surgical approach study, pivotal trial)

Study Design:

In this study, the patients had at least 6 months of nonoperative treatment for the pain associated with DDD, still had documented pain from the condition, were seeking additional treatment, and were recommended for spine fusion by their physician. A nonsurgical treatment option was not practical or ethical for this subject population because nonsurgical treatments had already failed to provide needed relief; instead, fusion was recommended to alleviate the pain. Thus, the subject population for this open surgical approach study was a subset of subjects with DDD—those subjects with back pain who had not responded to 6 months of nonoperative treatment and for whom spine fusion had been recommended.

The open surgical approach study was open-label with respect to subjects and surgeons.
Subjects were randomised (1:1) either to the investigational treatment group (rhBMP-2/ACS) or to the control group (autogenous bone harvested from the iliac crest). Subject and surgeon blinding was not possible after treatment group assignment because it is necessary for the surgeon to obtain autogenous bone from the iliac crest as part of the control treatment. However, the independent radiographic reviewers who evaluated the radiographs and CT scans were blinded to treatment group. This was included in the study design to eliminate bias in determining radiographic outcomes between the 2 treatment groups. Subjects had only 1 investigational surgery in the study and received rhBMP-2 at a concentration of 1.50 mg/mL during the surgery.

The length of subject follow-up (24 months) was sufficient to evaluate the safety and efficacy of rhBMP-2/ACS, including the osteoinductive properties and beneficial effects of using rhBMP-2/ACS instead of harvesting autogenous bone. The 24-month follow-up time also allowed sufficient time to observe fusion induced by rhBMP-2/ACS, which was expected to occur by 12 months following surgery.
A non-inferiority trial design was used on the premise that the control treatment was recognized as a very effective treatment from earlier clinical studies with fusion rates of at least 89.4% at 24 months. Non-inferiority was considered to be reasonable based on the standard that the control had established and on the fact that the investigational treatment would offer the additional benefit of eliminating the second surgery to harvest bone.

Inclusion and exclusion criteria:
Male and female subjects, age ≥18 years, with DDD as noted by back pain of discogenic origin, with or without leg pain, with degeneration of the disc confirmed by subject history and radiographic studies with one or more of the following: a) instability, b) osteophyte formation, c) decreased disc height, d) thickening of ligamentous tissue, e) disc degeneration or herniation, and/or f) facet joint degeneration. Subjects were required to have a preoperative Oswestry score ≥35, no greater than Grade 1 spondylolisthesis (utilizing Meyerding's Classification), and single-level symptomatic degenerative involvement from L4 to S1. Subjects should not have responded to 6 months of non-operative treatment (eg, bed rest, physical therapy, medications, spinal injections, manipulation, and/or transcutaneous electrical nerve stimulation (TENS)).

Main exclusion criteria:
A subject meeting any of the following criteria was excluded from the study:
- Previous anterior spine fusion surgical procedure at the involved level.
- Posterior spinal instrumentation (which will not be removed) stabilising the involved level or a previous posterior lumbar interbody fusion procedure at the involved level.
- Presence of active malignancy.
- History of autoimmune disease.
- History of exposure to injectable collagen implants.
- History of hypersensitivity to protein pharmaceuticals (monoclonal antibodies or gamma globulins) or collagen.
- Any previous exposure to any/all BMPs of either human or animal extraction.
- History of allergy to bovine products or a history of anaphylaxis.
- Osteopenia, osteoporosis, or osteomalacia to a degree that spinal instrumentation would be contraindicated; history of endocrine or metabolic disorder known to affect osteogenesis (eg, Paget's disease, renal osteodystrophy, Ehlers-Danlos syndrome, or osteogenesis imperfecta)
- Presence of active malignancy or infection (local or systemic)
- Obesity (ie, weight >40% over ideal for their age and height)
- Medications that could affect fusion (e.g. corticosteroids)

Efficacy variables:
The primary efficacy variables for Studies 3100N3-303 and 3100N3-304 were:
1) fusion—measured by independent radiographic reviewers using methods recommended by FDA;
2) pain/disability status—measured by the subject in response to the Oswestry Low Back Pain Disability Questionnaire.

The Oswestry questionnaire records a subject's response to 10 questions, which focus on pain, personal care, lifting, walking, sitting, standing, sleeping, sex life, social life, and ability to travel. Oswestry scores can range from 0% to 100%, with a lower percentage indicating less pain and disability. The Oswestry Questionnaire was administered preoperatively as well as at each postoperative visit.

Primary efficacy endpoints:

The primary efficacy endpoints were the fusion success status at 24 months and the Oswestry (pain/disability) success status at 24 months.

Overall success was the primary endpoint of the study comprising the following safety and efficacy variables:

1) radiographically demonstrated fusion,
2) Oswestry pain/disability improvement,
3) maintenance or improvement in neurological status,
4) no Grade 3 or 4 adverse event classified as implant-associated or implant-/surgical procedure-associated, and
5) no additional surgical procedure performed that was classified as a "failure."

Fusion success was defined as:

- Evidence of bridging trabeculae, based on the presence of a continuous bony connection from the superior vertebral body to the inferior vertebral body in at least 1 of the following areas: lateral, medial, anterior, posterior, and/or through either one or both of the implants. The primary method of assessment was radiographs. If evidence of bridging trabeculae could not be observed with radiographs, CT scans were permitted as a secondary method only. The study design included scheduled radiographs and CT scans for all subjects.
- No evidence of motion, as defined by:
    - No more than 3 mm difference in translation on the lateral flexion/extension radiographs, as determined by superimposing the 2 views one upon the other, and
    - Less than 5° difference in angular motion between flexion and extension, as seen on lateral flexion/extension radiographs.
- No evidence of radiolucency surrounding greater than 50% of either LT-CAGE Device. This determination was made with radiographs.

Statistical methods:

The study was designed as a non-inferiority trial. A frequentist method was utilised to assess the study hypotheses.

The study hypotheses defined in the statistical plan were one-sided equivalence (non-inferiority) hypotheses. A non-inferiority margin (d) of 0.10 was defined for all of the variables except for Oswestry success, where a margin of 0.15 was specified. Justification of the delta choices was based on an FDA point-to-consider document.

The primary outcome variables were analysed using Blackwelder's one-sided equivalence procedure. Pooling data from all the study sites was planned for final statistical analyses for assessing the study hypotheses. The Breslow-Day test procedure would be used for assessing homogeneity of treatment outcomes across study sites (i.e. interaction between study site and treatment) to justify the pooling.

Two (2) interim analyses and one final analysis were defined in the statistical plan using the Fleming, Harrington, and O'Brien procedure.

A non-inferiority trial design was used on the premise that the control treatment was recognised as a very effective treatment from earlier clinical studies with fusion rates of at least 90%. Non- inferiority was considered to be reasonable based on the standard that the control had established efficacy and on the fact that the investigational treatment would offer the additional benefit of no second surgical site to harvest bone.

Three (3) primary efficacy variables and 3 primary safety variables were considered in the determination of sample size in the original statistical considerations for the study. The resulting sample size hinged on the variable "Oswestry pain/disability success," which required the largest sample size of all of the variables. The basic assumptions were as follows: significance (one-sided alpha) level of 0.05, power of 0.80, non-inferiority margin of 0.15, and success rate of 68.5% in both the investigational and control treatment groups. The final sample size was estimated to be a total of

270 subjects, with 135 in each treatment group, after adjusting for approximately 10-15% lost-to-follow-ups.

During the conduct of the study, the statistical plan and protocol were amended to allow Bayesian analyses in order to assess results prior to completion of the 24-month follow-up and to define the composite variable overall success as the sole primary endpoint of the study. In preliminary consultations with Regulatory Authorities, frequentist statistics were requested as the primary analysis.

No interim analyses using frequentist statistical methods, as defined in the original protocol, were ever performed because of subsequent protocol changes. Therefore, there is no need for alpha adjustments.

The original protocol defined 3 primary efficacy variables (fusion success, Oswestry success, and neurological success) and 3 primary safety variables (Grade 3 or 4, product-associated, adverse events; additional surgical procedures classified as failures; and Grade 3 or 4, permanent adverse events). The variable overall success was defined but not indicated as either a primary or a secondary endpoint in the original protocol and statistical plan. In the amendments to these documents, overall success was defined as the sole primary endpoint to measure efficacy and safety of the investigational product. The main reason for the change was to avoid the statistical multiplicity issues.

Finally, for the study report, a "per protocol" analysis dataset, which was the primary analysis dataset minus the 9 subjects with protocol deviations, was defined and also analyzed for the primary study endpoint overall success.

- **Clinical results:**

In total, 143 subjects completed the investigational treatment, and 136 subjects completed the control treatment in the clinical study. Subject disposition for the clinical study through 24 months postoperative is presented in the table below:

Subject Status	Investigational	Control	TOTAL
Enrolled and Randomized	152	147	299
Went to Surgery	145	137	282
Completed Surgery as Randomized	143	136	279
Deaths	0[a]	1[b,c]	1
Evaluated – 12 Months Postoperative	96.5% (138/143)	96.3% (131/136)	96.5% (269/279)
Evaluated – 24 Months Postoperative	93.7% (134/143)	90.4% (123/136)	92.1% (257/279)

a: Does not include the death of 1 subject in the investigational treatment group that occurred after the 24-month evaluation time period. This death is included in the discussions of deaths in Section 10.4.1.1.
b: The death occurred after the 6-month evaluation (see Section 10.4.1.1), so information was not available on the subject at 12 or 24 months postoperative.
c: Does not include the death of 1 subject that occurred after the 24-month evaluation. (see Section 10.4.1.1)

Results on the fusion success rates for the investigational and control treatment groups at 12 and 24 months after surgery for the primary analysis dataset are shown in the table below:

Fusion success rates at 12 and 24 months – primary analysis dataset:

Time Point	Investigational	Control	p-value (d =10%)
12 Months Postoperative[a]	96.9% (127/131)	92.6% (112/121)	<0.0001
24 Months Postoperative[b]	94.6% (123/130)	89.1% (106/119)	<0.0001

a: At 12 months postoperative, fusion data were unavailable for 12 subjects in the investigational treatment group and 15 subjects in the control group.
b: At 24 months postoperative, fusion data were unavailable for 13 subjects in the investigational treatment group and 17 subjects in the control group.

A "missing-equals-failure" analysis dataset was constructed for analysis of the primary study endpoint overall success. In this dataset, all missing observations from all the study subjects (143 investigational and 136 control subjects), including subjects missing observations, deaths, and additional surgery "failures," were included in the denominators of the calculated rates (ie, assumed as "failures"). A missing-equals-failure analysis is also presented for both primary efficacy parameters, fusion and pain/disability, and for the safety parameter, neurological success.
The "per-protocol" dataset was constructed in the exactly same way as the primary analysis dataset, except that 9 subjects with the protocol deviations were excluded. This was a simple subset of the primary analysis dataset, also just for analysis of the primary study endpoint overall success.

Fusion success rates at 12 and 24 months – "missing equals failure" dataset:

Time Point	Investigational	Control	p-value (d =10%)
12 Months Postoperative	88.8% (127/143)	82.4% (112/136)	<0.0001
24 Months Postoperative	86.0% (123/143)	77.9% (106/136)	<0.0001

By considering missing data as treatment failures, the outcome rates in the "missing-equals-failure" analysis were lowered in both groups at 24 months postoperative. The fusion success rate was numerically higher in the investigational treatment group than that in the control group at 24 months. The non-inferiority of the investigational treatment to the control treatment is clearly established in fusion success at 24 months, with a non-inferiority margin of 0.10.

For both treatment groups at all postoperative time periods, mean overall Oswestry scores significantly improved ($p<0.001$), as compared to the preoperative scores. The mean improvement in Oswestry scores was also similar for both treatment groups at the various clinical time periods. Oswestry scores for the investigational treatment group improved by an average of 29.2 points from surgery to 24 months, as compared to an average of 29.9 for the control group.

The primary endpoint of the study was overall success at 24 months, consisting of 2 efficacy and 3 safety components. The overall success rate at 24 months for the investigational treatment group was found to be statistically non-inferior ($p=0.0029$) to the control group rate, with the predefined non-inferiority margin of 0.15 (Table below).

Overall Success Rates at 12 and 24 Months – Primary Analysis Dataset

Time Point	Investigational	Control	p-value[a] (d =15%)
12 Months Postoperative[b]	59.7% (80/134)	60.8% (76/125)	0.0112
24 Months Postoperative[c]	58.6% (78/133)	56.6% (69/122)	0.0029

a: p-values were also calculated for d=10%. At 12 months postoperative, the p-value was 0.0717. At 24 months postoperative, the p-value was 0.0255.
b: At 12 months postoperative, overall success data were unavailable for 9 subjects in the investigational treatment group and 11 subjects in the control group.
c: At 24 months postoperative, overall success data were unavailable for 10 subjects in the investigational treatment group and 14 subjects in the control group.

The overall success rates for "missing-equals-failure" subjects at 12 and 24 months postoperative are shown below.

Overall Success Rates at 12 and 24 Months – "Missing-Equals-Failure" Dataset

Time Point	Investigational	Control	p-value[a] (d =15%)
12 Months Postoperative	55.9% (80/143)	55.9% (76/136)	0.0057
24 Months Postoperative	54.5% (78/143)	50.7% (69/136)	0.0008

a: p-values were also calculated for d=10%. At 12 months postoperative, the p-value was 0.0453. At 24 months postoperative, the p-value was 0.0104.

By considering missing data as treatment failures, the outcome rates in the "missing-equals-failure" analysis were lowered in both groups at 24 months postoperative. The overall success rate was higher for "missing-equals-failure" subjects in the investigational treatment group than for "missing-equals-failure" subjects in the control group at 24 months. The non-inferiority of the investigational treatment to the control treatment is shown.

The overall success rates for "per protocol" subjects, or subjects who did not have a major protocol deviation are shown in the following table:

Time Point	Investigational	Control	p-value[a] (d =15%)
12 Months Postoperative	58.3% (74/127)	60.5% (75/124)	0.0196
24 Months Postoperative	57.5% (73/127)	55.8% (67/120)	0.0042

a: p-values were also calculated for d=10%. At 12 months postoperative, the p-value was 0.1046. At 24 months postoperative, the p-value was 0.0324.

At 24 months postoperative, the overall success rate for the "per protocol" subjects was similar between the groups, and the criterion for declaring non-inferiority was met, not only with a non-inferiority margin of 0.15 but also with a margin of 0.10.

The secondary efficacy variable (graft site pain status, disc height measurement, general health status and pain status) results support the primary efficacy and combined overall treatment success endpoint results and suggest similar efficacy in terms of Quality of Life, global perceived effect by patient and physician, back and leg pain. The absence of pain related to bone graft harvesting is naturally a substantial benefit of rhBMP-2/ACS LT-CAGE treatment

Study 3100N3-304 (laparoscopic surgical approach study, supportive trial)

This Study used a laparoscopic surgical approach instead of an open surgical approach for the implantation of rhBMP-2/ACS in ALIF procedures. Except for the change in the surgical approach, the purpose, primary objectives, and procedures of the laparoscopic surgical approach study were the same as those for the open surgical approach study.
The secondary efficacy variables for this study were

- Disc Height Measurement
- General Health Status
- Pain Status (back pain, leg pain)

Neurological status was assessed preoperatively and postoperatively by the investigational team using a comprehensive neurological status scale. Neurological status is based on 4 types of measurements (sections): motor, sensory, reflexes, and straight leg raise. The motor and sensory sections of the scale were developed and validated by the American Spinal Injury Association (ASIA), Chicago, Illinois.

Serum samples were taken from each subject preoperatively, to establish their baseline condition, and at 3 months following surgery. The samples were analyzed by enzyme-linked immunosorbent assay (ELISA) for the presence of antibodies specific for BMP-2 and bovine Type I collagen. If a subject had a positive response to bovine Type I collagen, the serum was also tested for antibodies to human Type I collagen.
The design for the laparoscopic approach study included using a concurrent, non-randomised control. Because using the control group from the open surgical approach study would not address all potential biases, only nonstatistical comparisons were planned and conducted between the investigational treatment group of study 3100N3-304 and the control group of study 3100N3-303. The intention was to nonstatistically compare results from study 3100N3-304 with those from the control group of the open surgical approach study, because all other methods and endpoints of the 2 studies were essentially identical and both studies investigated the safety and efficacy of rhBMP-2/ACS.

Study Design:
As described above, the Study Design was similar to Study 3100N3-303 with the above-mentioned exceptions. The original statistical plan for the laparoscopic approach study used the control group from study 3100N3-303 (in which subjects were implanted with a combination of autogenous bone graft and the LT-CAGE Device via an open surgical procedure, which is considered to be the standard of care) as the control group for study 3100N3-304. However, as statistical differences were noted between subjects of both studies for some important demographic characteristics, the MAH decided that it was not appropriate to statistically compare the two groups from these studies.
The concentration of reconstituted rhBMP-2 administered to subjects was constant at 1.50 mg/mL, with the total dose of rhBMP-2 varying according to the quantity of rhBMP- 2/ACS required. The quantity of rhBMP-2/ACS required was determined by the size of cage used. Based on the cages in the clinical study, the quantity of rhBMP-2/ACS that was placed into the cages was either 2.8 or 5.6 mL (for 2 cages). This equated to a total dose of 4.2 or 8.4 mg rhBMP-2.

Clinical results:

In total, 134 subjects completed this study (see table below).

TABLE 8.1A. OVERALL SUBJECT DISPOSITION
THROUGH 24 MONTHS POSTOPERATIVE

Subject Status	Study 3100N3-304	Study 3100N3-303 Control group
Enrolled	142	147
Went to Surgery	136	137
Completed Surgery	134	136
Deaths	0	1[a,b]
Evaluated – 12 Months Postoperative	94.0% (126/134)	96.3% (131/136)
Evaluated – 24 Months Postoperative	91.0% (122/134)	90.4% (123/136)

a: The death occurred after the 6-month evaluation, so information was not available on the subject at 12 or 24 months postoperative.
b: Does not include the death of 1 subject that occurred after the 24-month evaluation.

Of the rhBMP-2/ACS treated subjects, 57.5% were female, their mean age was 42 years and 24.6% had had previous back surgery. Preoperatively, instability was present in 8.2%, osteophytes in 26.9%, decreased disk height in 88.8%, thickened ligaments in 20.1%, disk herniation in 34.3% and facet joint degeneration in 40.3% of subjects.

The majority of patients received treatment for L5-S1 DDD (84.3%).

Efficacy:

The primary analysis dataset included all 134 subjects in this study who received study implants and completed surgical procedures. Primary statistical analyses were based on the observed data, and missing data due to lost-to-follow-up or invalid radiographic assessments were not imputed. According to the protocol, subjects who had additional surgical interventions were deemed as failures for overall success, if the additional surgical procedures were classified as failures according to the protocol definition. In addition, fusion status was also considered as a failure if these additional surgical procedures were due to purported failed fusion as reported by the investigator, regardless of what radiographic evidence showed.

A ”missing-equals-failure” analysis dataset was constructed for analysis of the primary study endpoint overall success. In this dataset, all missing observations from all 134 subjects in this study, including subjects missing observations, deaths, and additional surgery failures, were included in the denominators of the calculated rates.

The fusion success rates for this study were over 90% at both the 12- and 24-month time points (94.1% and 92.9%, respectively). In the ”missing equals failure” dataset, the corresponding figures were 70.9% and 68.7%.

The Oswestry success rates for this study were 79.8% and 85.6% at 12 months and 24 months, respectively. The corresponding figures in the ”missing equals failure” analysis were 67.9% and 66.4%.

The secondary efficacy variable success rates are shown in the table below:

Secondary efficacy variable success rates (primary analysis dataset)

Variable	Time Point	Study 3100N3-304
Disc Height	12 Months Postoperative[a]	99.0% (95/96)
	24 Months Postoperative[b]	95.6% (86/90)
SF-36 – PCS	12 Months Postoperative[c]	89.4% (101/113)
	24 Months Postoperative[d]	91.3% (95/104)
SF-36 – MCS	12 Months Postoperative[e]	69.9% (79/113)
	24 Months Postoperative[f]	72.1% (75/104)
Back Pain	12 Months Postoperative[g]	81.6% (93/114)
	24 Months Postoperative[h]	81.7% (85/104)
Leg Pain	12 Months Postoperative[i]	81.6% (93/114)
	24 Months Postoperative[j]	81.7% (85/104)

Throughout this study, subjects were asked about their overall satisfaction with the study treatment. At 24 months postoperative, 81.7% (85/104) of the subject group responded that it was ”definitely true” or ”mostly true” that they were satisfied with the results of the surgery. Over seventy-five percent (75.7%, 78/103) of the subjects at 24 months postoperative responded that it was ”definitely true” or ”mostly true” that they were helped as much as they thought they would be by the surgery. At 24 months postoperative, 83.5% (86/103) of the subject group responded that it was ”definitely true” or ”mostly true” that, all things considered, they would have the surgery again for the same condition.

At 12 and 24 months following surgery, 72.8% (83/114) and 77.9% (81/104), respectively, of subjects in this study indicated that they had either ”completely recovered” or were ”much improved”.

At 12 months following surgery, the investigators´ global evaluation was that 84.8% (95/112) of the subjects from this study were in excellent or good condition. At 24 months, the corresponding figure was 86.4%.

The primary endpoint of this study was overall success at 24 months, consisting of 2 efficacy and 3 safety components. According to the primary analysis dataset, overall success was reported in 69.2% of patients at 12 monts and in 68.3% of patients at 24 months. The corresponding figures in the ”missing-equals-failure” analysis were 55.2% and 53.0%. In the primary analysis dataset, neurological success rates at 12 months and 24 months were 93.8% and 90.3%, respectively.

4.3 Clinical Safety

Patient exposure:

A total of 455 subjects were enrolled in the 3 studies, and 427 were treated and provided safety data. A total of 288 subjects received a single implantation of rhBMP-2 at a concentration of 1.50 mg/mL on an ACS.

Synopses of additional 11 studies are provided in the dossier. These additional studies supplement the safety from the 3 main studies to support the use of rhBMP-2/ACS in anterior lumbar spine fusion, when used in combination with the LT-CAGE device. some of these studies use a concentration or quantity of rhBMP-2/ACS or a matrix that differs from that which is the subject of this variation (i.e.a concentration of 1.5 mg/mL, a total dose of up to 12 mg, and absorbable collagen sponge/ACS matrix). In each case, dibotermin alfa is used in combination with a medical device other than the LT-CAGE device.

Altogether 612 patients have received rhBMP-2/ACS in these additional 11 clinical trials, several of which are ongoing.

Safety information in support of the use of rhBMP-2/ACS in combination with the LT-CAGE Device in ALIF procedures comes mainly from the same 3 studies that support efficacy. In these studies a total of 455 subjects were enrolled, and 427 were treated and provided safety data. A total of 288 subjects received a single implantation of rhBMP-2 at a concentration of 1.50 mg/mL on an ACS.
Although not directly relevant to the use of rhBMP-2/ACS in combination with the LT-CAGE Device in anterior lumbar spine fusion procedures, supporting safety information also comes from additional safety information collected in 13 other clinical studies, 6 of which are ongoing. Six hundred and four (604) subjects have received treatment with rhBMP-2 in these additional studies, compared with 716 subjects who were treated with another device for comparison. These figures are based on the final report or last annual report for the various studies. Some of these trials use a different concentration or quantity of rhBMP-2/ACS or a matrix that differs from the one proposed in this variation (ie, a concentration of 1.50 mg/mL, a total dose of up to 12 mg, and absorbable collagen sponge matrix). In addition, in each case, rhBMP-2 is used in combination with a device other than the LT-CAGE Device. The safety information from these studies has been reviewed and is considered not to influence the safety profile observed in the 3 main studies.

Adverse events
The table below summarises the number of subjects of the three submitted studies who have adverse events by organ system according to COSTART code, through the 24-month evaluations:

Body System	Study 3100N3-117		Study 3100N3-303		Study 3100N3-304
	Control N=3	rhBMP-2/ACS N=11	Control N=136	rhBMP-2/ACS N=143	rhBMP-2/ACS N=134
Body as a whole	66.7% (2/3)	63.6% (7/11)	55.9% (76/136)	53.8% (77/143)	50.7% (68/134)
Cardiovascular	0.0% (0/3)	0.0% (0/11)	7.4% (10/136)	3.5% (5/143)	6.7% (9/134)
Digestive System	33.3% (1/3)	18.2% (2/11)	19.1% (26/136)	19.6% (28/143)	15.7% (21/134)
Endocrine System	0.0% (0/3)	0.0% (0/11)	1.5% (2/136)	0.7% (1/143)	0.7% (1/134)
Hemic and Lymphatic System	0.0% (0/3)	0.0% (0/11)	0.7% (1/136)	0.0% (0/143)	0.0% (0/134)
Metabolic and Nutritional Disorders	0.0% (0/3)	0.0% (0/11)	1.5% (2/136)	0.7% (1/143)	0.7% (1/134)
Musculo-Skeletal	66.7% (2/3)	18.2% (2/11)	28.7% (39/136)	31.5% (45/143)	17.9% (24/134)
Nervous System	66.7% (2/3)	27.3% (3/11)	25.0% (34/136)	32.9% (47/143)	25.4% (34/134)
Respiratory System	0.0% (0/3)	9.1% (1/11)	5.1% (7/136)	3.5% (5/143)	2.2% (3/134).
Skin and Appendages	0.0% (0/3)	0.0% (0/11)	2.9% (4/136)	2.8% (4/143)	2.2% (3/134)
Urogenital System	0.0% (0/3)	0.0% (0/11)	11.0% (15/136)	14.0% (20/143)	12.7% (17/134)

This review does not suggest that subjects reporting adverse events for any of these body systems were in larger proportions after rhBMP-2/ACS exposure. More patients in the active treated group had adverse events in the nervous system (32.9%) versus 25.0% in the control group. This was mainly due to neuropathy and urinary retention. One report of neuralgia in the investigational group was considered to be possibly related to the implant.
Four types of adverse events were observed in ≥10% of all subjects: "Accidental Injury," "Back Pain," "Bone Disorder," and "Neuralgia." These events were equally observed in investigational and control subjects, suggesting that they were related to subjects' condition rather than to rhBMP-2/ACS.

Study 3100N3-303 (open surgical approach study, pivotal trial)

Safety
Safety criteria were analyses of adverse events, additional surgical procedures, neurological status, laboratory analyses of antibodies to rhBMP-2 and bovine collagen, and histological analysis of any explanted/removed implants.

Neurological status was assessed preoperatively and postoperatively by the investigational team using a comprehensive neurological status scale. Neurological status is based on 4 types of measurements (sections): motor, sensory, reflexes, and straight leg raise. The motor and sensory sections of the scale were developed and validated by the American Spinal Injury Association (ASIA), Chicago, Illinois.

Due to the proteinaceous nature of both rhBMP-2 and ACS, the development of antibodies was assessed as part of the study protocol. Subjects were considered to have an authentic antibody response if their preoperative sample was negative (titer <50) and the postoperative sample was positive (titer ≥50) or if the preoperative sample was positive and the postoperative sample titer was 3-fold higher than the preoperative titer. Serum samples were taken from each subject preoperatively, to establish their baseline condition, and at 3 months following surgery. The samples were analysed by enzyme-linked immunosorbent assay (ELISA) for the presence of antibodies specific for rhBMP-2 and bovine Type I collagen. If a subject had a positive response to bovine Type I collagen, the serum was also tested for antibodies to human Type I collagen.

Overall: The primary endpoint for the study was "overall success." This variable was comprised of the following efficacy and safety criteria:
1. Radiographically demonstrated fusion
2. Oswestry pain/disability improvement
3. Maintenance or improvement in neurological status
4. No Grade 3 or 4 adverse event classified as implant-associated or implant-/surgical procedure-associated
5. No additional surgical procedure classified as a "failure"

Each subject was followed for 24 months after surgical treatment, with study evaluations occurring preoperatively and at 6 postoperative time points (surgery/discharge, 6 weeks, 3 months, 6 months, 12 months, and 24 months). Evaluations included the following:
- Radiographic assessment by independent radiographic reviewers of the spinal level that was treated surgically
- Neurological assessment by the investigational staff
- Treatment outcomes as perceived by the subject and the investigator
- Documentation of adverse events (AEs)
- Documentation of subsequent treatments classified as additional surgical procedures
- Documentation of classes of concomitant medications
- Collection of serum samples to measure antibody formation to rhBMP-2, bovine Type I collagen (from which the ACS is made), and human Type I collagen

- **Safety results:**

Because this study was designed and performed as a device study, clinical laboratory analyses, vital signs and other physical findings were not recorded.
The total number of subjects who received rhBMP-2/ACS during surgery was 143 (78 male and 65 female patients). There were no large differences between treatment groups in type of adverse events. Patients in the investigational group experienced more ileus (7.0%), arthralgia (8.4%), neuropathy (7.7%), urinary retention (7.7%) and abnormal ejaculation (3.5%) compared to control patients (4.4%, 5.1%, 4.4%, 1.5%, 0.7% respectively). Patients in the control group had more abdominal pain than patients from the investigational group (3.7% versus 0.0% respectively).
A total of 11 subjects had adverse events related to oedema. Six (6) of these events involved investigational subjects. Five subjects experienced lower extremity swelling, and 1 subject experienced laryngeal oedema shortly after surgery. The latter subject tested negative postoperatively for both rhBMP-2 and bovine Type I collagen antibodies. The oedema events occurring in the 5 control subjects were due to lower extremity swelling (4 subjects) and scrotal swelling (1 subject). None of these events were believed to be implant-related.

An overview of the commonly reported adverse events in study 3100N3-303 is shown in the table below:

Body System Adverse Event	Investigational	Control	Total
Body as a Whole			
Abdominal Pain	0.0% (0/143)	3.7% (5/136)	1.8% (5/279)
Allergic Reaction	2.1% (3/143)	2.2% (3/136)	2.2% (6/279)
Cyst	0.7% (1/143)	2.2% (3/143)	1.4% (4/279)
Chest Pain	1.4% (2/143)	0.0% (0/136)	0.7% (2/279)
Edema	3.5% (5/143)	2.9% (4/136)	3.2% (9/279)
Granuloma	0.0% (0/143)	1.5% (2/136)	0.7% (2/279)
Headache	2.1% (3/143)	1.5% (2/136)	1.8% (5/279)
Hernia	4.9% (7/143)	0.0% (0/136)	2.5% (7/279)
Infection	7.7% (11/143)	9.6% (13/136)	8.6% (24/279)
Neck Pain	3.5% (5/143)	2.2% (3/136)	2.9% (8/279)
Pain	7.0% (10/143)	5.9% (8/136)	6.5% (18/279)
Surgical Procedure Change[a]	1.4% (2/143)	1.5% (2/136)	1.4% (4/279)
Cardiovascular System			
Syncope	0.7% (1/143)	1.5% (2/136)	1.1% (3/279)
Thrombosis	0.7% (1/143)	2.2% (3/136)	1.4% (4/279)
Digestive System			
Cholelithiasis	1.4% (2/143)	0.0% (0/136)	0.7% (2/279)
Constipation	1.4% (2/143)	3.7% (5/136)	2.5% (7/279)
Diarrhea	1.4% (2/143)	0.7% (1/136)	1.1% (3/279)
Fecal Incontinence	0.0% (0/143)	1.5% (2/136)	0.7% (2/279)
Ileus	7.0% (10/143)	4.4% (6/136)	5.7% (16/279)
Intestinal Obstruction	0.7% (1/143)	1.5% (2/136)	1.1% (3/279)
Nausea	4.9% (7/143)	4.4% (6/136)	4.7% (13/279)
Nausea and Vomiting	2.1% (3/143)	2.2% (3/136)	2.2% (6/279)
Musculo-Skeletal System			
Arthralgia	8.4% (12/143)	5.1% (7/136)	6.8% (19/279)
Arthritis	2.1% (3/143)	0.0% (0/136)	1.1% (3/279)
Bone Fracture Spontaneous	1.4% (2/143)	2.2% (3/136)	1.8% (5/279)
Tenosynovitis	2.1% (3/143)	2.9% (4/136)	2.5% (7/279)
Nervous System			
Depression	1.4% (2/143)	2.2% (3/136)	1.8% (5/279)
Hypesthesia	2.1% (3/143)	0.7% (1/136)	1.4% (4/279)
Neuropathy	7.7% (11/143)	4.4%(6/136)	6.1% (17/279)
Paresthesia	3.5% (5/143)	5.1% (7/136)	4.3% (12/279)
Urinary Retention	7.7% (11/143)	1.5% (2/136)	4.7% (13/279)
Respiratory System			
Dyspnea	0.0% (0/143)	2.9% (4/136)	1.4% (4/279)
Pneumonia	0.0% (0/143)	1.5% (2/136)	0.7% (2/279)
Skin and Appendages			
Rash	1.4% (2/143)	0.7% (1/136)	1.1% (3/279)
Urogenital System			

Body System Adverse Event	Investigational	Control	Total
Abnormal Ejaculation	3.5% (5/143)	0.7% (1/136)	2.2% (6/279)
Cystitis	1.4% (2/143)	1.5% (2/136)	1.4% (4/279)
Hematuria	1.4% (2/143)	0.0% (0/136)	0.7% (2/279)
Impotence	1.4% (2/143)	0.7% (1/136)	1.1% (3/279)
Kidney Calculus	2.1% (3/143)	0.7% (1/136)	1.4% (4/279)
Urinary Tract Infection	3.5% (5/143)	2.2% (3/136)	2.9% (8/279)

a: Category does not belong to the COSTART dictionary of terms. The category was generated to account for adverse events that occurred when changes were made during the surgical procedure (ie, due to abnormal subject anatomy).

A total of 53 subjects in the investigational group (37.1%) had at least one Grade 3 or 4 adverse event. However, only 11 of those subjects (7.7%) were reported to have had a Grade 3 or 4 adverse event classified as possibly related to the implant by the MSD clinical staff. It is important to stress that, for complications classified as possibly related to the implant, causality assessments did not separate whether the complications were caused by the cage or by rhBMP-2/ACS. Hence, related events were reported in both treatment groups. For the control group, of 41.9% subjects with Grade 3 or 4 adverse events, 8.8% were deemed related.

Serious adverse events and deaths:
One subject who received rhBMP-2/ACS and two subjects who received autogenous bone graft died within 48 months of receiving treatment. In the opinions of the study investigators, none of the deaths were related to the investigational treatment.

Antibody development:
The presented data on antibodies do not indicate difficulties in that area. However, as a result of follow-up measures 025 and 026 the applicant has developed and validated a new antibody ELISA for antibodies to rhBMP-2 that has the potential to detect all antibody isotypes. In addition a neutralisation assay for antibodies to rhBMP-2 has been developed and validated. Since it is assumed that the data presented have been collected using the old method, the applicant is requested to submit data collected with the new assays from retrospective or prospective studies.

Study 3100N3-304 (laparoscopic surgical approach study, supportive trial)

Safety results:

Through the 24-month postoperative evaluations, 1 or more adverse events were reported by 98/134 (73.1%) subjects who received the rhBMP-2/ACS treatment.

The most commonly reported adverse event was accidental injury (20.9% of subjects). The other common (1-10%) adverse events are listed in the table below:

Body System Adverse Event	Investigational	Study 3100N3-303 Control
Body as a Whole		
Accidental Injury, Surgical[a]	6.7% (9/134)	11.0% (15/136)
Back Pain	6.7% (9/134)	13.2% (18/136)
Chest Pain	1.5% (2/134)	0.0% (0/136)
Chills and Fever	1.5% (2/134)	0.0% (0/136)
Edema	1.5% (2/134)	2.9% (4/136)
Hernia	1.5% (2/134)	0.0% (0/136)
Implant Malpositioning/ Displacement[b]	1.5% (2/134)	0.0% (0/136)
Infection	6.7% (9/134)	9.6% (13/136)
Neck Pain	2.2% (3/134)	2.2% (3/136)
Pain	9.0% (12/134)	5.9% (8/136)
Surgical Procedure Change[c]	9.0% (12/134)	1.5% (2/136)
Cardiovascular System		
Tachycardia	1.5% (2/134)	0.0% (0/136)
Thrombosis	1.5% (2/134)	2.2% (3/136)
Digestive System		
Constipation	5.2% (7/134)	3.7% (5/136)
Gastritis	2.2% (3/134)	0.0% (0/136)
Ileus	6.0% (8/134)	4.4% (6/136)
Nausea	1.5% (2/134)	4.4% (6/136)
Nausea and Vomiting	1.5% (2/134)	2.2% (3/136)
Rectal Disorder	2.2% (3/134)	0.0% (0/136)
Musculo-Skeletal System		
Arthralgia	3.0% (4/134)	5.1% (7/136)
Bone Disorder[d]	6.0% (8/134)	14.7% (20/136)
Bursitis	1.5% (2/134)	0.7% (1/136)
Joint Disorder	5.2% (7/134)	7.4% (10/136)
Nervous System		
Anxiety	1.5% (2/134)	0.7% (1/136)
Depression	1.5% (2/134)	2.2% (3/136)
Hypesthesia	3.0% (4/134)	0.7% (1/136)
Neuralgia	7.5% (10/134)	12.5% (17/136)
Neuropathy	8.2% (11/134)	4.4% (6/136)
Urinary Retention	5.2% (7/134)	1.5% (2/136)
Respiratory System		
Pneumonia	1.5% (2/134)	1.5% (2/136)
Urogenital System		
Abnormal Ejaculation	4.5% (6/134)	0.7% (1/136)
Abortion	1.5% (2/134)	0.0% (0/136)
Urinary Tract Infection	3.0% (4/134)	2.2% (3/136)

a: Category reflects adverse events that were reported during the laparoscopic surgical procedure.
b: Category does not belong to the COSTART dictionary of terms. The category was generated to account for adverse events recorded in the original study related to implant loosening or migration that were not hardware failures.
c: Category does not belong to the COSTART dictionary of terms. The category was generated to account for adverse events that occurred when changes were made during the surgical procedure (ie, conversion from laparoscopic approach to open approach due to abnormal subject anatomy).
d: Category reflects adverse events such as delayed union, pseudarthrosis, stenosis, etc.

No subjects died within 24 months of receiving this study treatment.

One or more Grade 3 or 4 adverse events were reported by 48 subjects (35.8%) through the 24-month postoperative time period. Adverse events of severity Grade 3 or 4 considered to be at least possibly related to the implant are summarised in the table below, grouped according to specific categories according to COSTART codes:

Body System Adverse Event	Investigational	Study 3100N3-303 Control
Body as a Whole		
Back Pain	0.0% (0/134)	2.2% (3/136)
Implant Malpositioning/ Displacement	0.7% (1/134)	0.0% (0/136)
Surgical Procedure Change	0.7% (1/134)	0.0% (0/136)
Musculo-Skeletal System		
Bone Disorder[a]	3.0% (4/134)	6.6% (9/136)

a: Category reflects adverse events such as delayed union, pseudarthrosis, stenosis, etc.

Two implant removal procedures occurred in this study. Both of these removals occurred early in the postoperative phase of this study and are described below.

- Subject # 31: This removal occurred as a result of issues associated with cage placement and migration. At 8 weeks postoperative, this subject underwent a secondary surgery including laparoscopic lysis of adhesions, exploration of the L5- S1 fusion site, removal of a displaced right cage, and the placement of posterior instrumentation at the L5-S1 level. The retrieved investigational cage underwent histological and metallurgical analyses. In these analyses, vigorous osteogenesis by the intramembranous pathway was observed, and the site of the cage appeared to be healing well. There were no cytological findings to suggest any inflammatory response other than that seen with normal wound healing.
- Subject # 426: This removal occurred at 1 day postoperative as the result of a malpositioned cage. Due to the close proximity in time to surgery, a histological analysis was not performed.

Supplemental fixations occurred at a rate of 5.2% in this study (7/134 subjects). Three supplemental fixations were due to an investigator diagnosis of a possible pseudarthrosis. Two other subjects had supplemental fixations due to cage removals. Another subject had a supplemental fixation due to adjacent disc degeneration at the level above the initial surgery. One subject underwent a laminectomy and supplemental fixation at 7 months postoperative due to spinal stenosis.

One patient had a postoperative sample that was positive for antibodies to rhBMP-2 three months following surgery. The preoperative sample was not available. The determination was conservatively designated as an authentic response. To determine if the antibody response to rhBMP-2 persisted, a serum sample was collected from the subject 12 months after surgery and tested for antibodies to rhBMP-2. This follow-up sample was negative, and the subject was conservatively considered to have had a transient antibody response to rhBMP-2. The subject had 2 AEs. There was no evidence that these adverse events were related to the implant. The incident was used to calculate the anti-rhBMP-2 antibody formation rate for this study, which was 0.8% (1/129).

Antibodies to bovine Type I collagen were detected in the postoperative serum samples of 56 subjects in this study. Of these 56 subjects, 32 subjects were considered to have an authentic antibody response. The remaining 24 subjects had a positive preoperative result without a substantial increase in postoperative titer and thus did not qualify as authentic antibody responses. Three subjects from this study with positive preoperative samples had no postoperative samples for testing.

Sixteen of the 32 subjects in this study who had an authentic positive antibody response to bovine Type I collagen were classified as an overall success at 24 months. Two additional subjects were classified as an overall success at 12 months (ie, 24-month data for overall success determination was incomplete). One subject was a failure in the pain component of overall success at 12 months (ie, 24 month data were not available for this subject). Nine subjects were failures in other areas at 24 months in pain status, 4 in neurological status, and 2 in pain and neurological status. Two subjects were overall success failures due to an additional surgical procedure that was classified as a failure in the protocol. The final 2 subjects who had authentic positive antibody responses did not return for 12- and 24-month evaluations, so no overall success information was available.

There were 27 subjects in this study with evaluable data who had positive baseline titers of bovine Type I collagen antibodies. Only 3 (11.1%) of these subjects developed an authentic response following their surgeries. This finding also indicates that a pre-existing antibody response to bovine collagen is not stimulated by surgery or treatment with rhBMP-2/ACS.

None of these subjects had a positive response to human Type I collagen.

Routine clinical chemistry, haematology and vital sign listings and analysis is not included in the study report. These data were not collected.

One patient (0.8%) had a transient antibody response to rhBMP-2 administration. The adverse events reported by this patient are not considered to be associated with the antibody response and the patient achieved overall treatment response at 24 months.

Antibody response to bovine type I collagen was very commonly reported in this study (authentic antibody response in 32 patients, i.e. in patients who were not antibody positive at baseline). The possibility that these antibody responses could adversely impact treatment outcome (efficacy) cannot be excluded, since overall response was reported in only 50% of these patients. However, there is no clear evidence of stimulation of immune reaction in the majority of patients with existing bovine type I collagen antibodies.

Other clinical studies supporting the safety of the medicinal product in the proposed therapeutic indication

Synopses of additional 11 studies are provided in the dossier. These additional studies supplement the safety from the 3 main studies to support the use of rhBMP-2/ACS in anterior lumbar spine fusion, when used in combination with the LT-CAGE device. Some of these studies use a concentration or quantity of rhBMP-2/ACS or a matrix that differs from that which is the subject of this variation (i.e.a concentration of 1.5 mg/mL, a total dose of up to 12 mg, and absorbable collagen sponge/ACS matrix). In each case, dibotermin alfa is used in combination with a medical device other than the LT-CAGE device.

Further details are given here of Study Number C9806: A Prospective, Randomized, Clinical Investigation of Recombinant Human Bone Morphogenetic Protein-2 and Absorbable Collagen Sponge with the INTER FIX ™ Device for Posterior Lumbar Interbody Fusion in Patients with Degenerative Disc Disease. One issue of note in this clinical study was the appearance of new bone formation posterior to the placement of interbody fusion cages implanted from the posterior surgical approach. The posterior bone formation was not observed in all patients, but was present in both the investigational and control groups, although more so in the investigational group. This finding is believed to be related to the posterior surgical technique and did not appear to be correlated with clinical outcome. The patients receiving rhBMP-2/ACS in this study had similar, or better, outcomes than the patients receiving autograft bone.

Based on the safety assessments, the MAH considers rhBMP-2/ACS at 1.50mg/mL a safe alternative for autogenous bone graft, but the particular methods for implanting the INTER FIX™ Device, which contains the rhBMP-2/ACS, should be carefully considered and further investigated when using a posterior surgical approach. Heterotopic ossification (includes abnormal or excessive bone formation) was reported in two patients in the rhBMP-2/ACS group.

Postmarketing information

In the PSUR covering the period 09 September 2003 to 08 March 2004, two topics are discussed in detail with cumulative summaries of the available data. Seven reports (covering 16 patients) of localised edema wherein dibotermin alfa/ACS was used off label in the cervical spine have been reviewed. Though causality has not been established, an association between dibotermin alfa/ACS and localized edema is possible and Wyeth is amending the reference safety information (RSI) to reflect this information. An all time review of the cases of exuberant bone growth did not identify a new safety signal.

During this reporting period, the MAH received nine spontaneous reports involving 12 different suspected serious and unlisted ADRs; all were from the US in the setting of spine surgery. There were no reports of death, lack of efficacy, drug interactions, drug abuse/misuse, pregnancy exposure, malignancy, bone necrosis, or intestinal obstruction.

Fourteen clinical trials, performed in North America under device regulations by Wyeth's business partner, MSD, have been identified for inclusion in the variation application. Wyeth reviewed the information from these 14 MSD clinical trials and identified several possible suspected serious adverse drug reactions that meet the criteria for expedited reporting for medicinal products.

In the previous PSUR, four reports of localized edema coincident with the use of rhBMP-2/ACS in the cervical spine were discussed. During the current reporting period, the MAH received follow-up information on three of the reports, one of which noted that this AE occurred in 10 patients at the site. In addition, three new reports have been received. Consequently, a full review of this topic is included in the PSUR.

In general, post-operative soft tissue complications following anterior cervical discectomy (ACD) include airway complications, dysphagia, and hoarseness. Airway compromise can occur secondary to hematoma, allergic reactions, and pharyngeal edema and most reviews that discuss localised edema in the setting of cervical spine surgery describe it in the context of airway complications.

The MAH database was searched all-time through 08 March 2004 for reports of swelling, inflammation, and edema in patients treated with rhBMP-2. A total of nine reports were identified. The reports contained the preferred terms Swelling (n=7), Inflammation (n=2), Oedema (n=1), and Inflammation localised (n=1). The number of events exceeds the number of reports since two reports contained two of these terms. One report described a patient who received rhBMP-2/ACS in the lumbar spine and experienced localised inflammation associated with a large hematoma.
One report described several patients who experienced swelling in the setting of an "immune-like" response to rhBMP-2/ ACS. The remaining seven reports describe localised cervical edema following rhBMP-2/ACS implantation.

In all of the cases the product was used off-label in the cervical spine. In general, the patients had an uneventful post-operative course and presented 1.5-7 days after surgery with neck swelling. Six of the patients recovered, with many receiving corticosteroids. In one report, the outcome is unknown. At least two of the patients had evidence of airway compromise; both had complicated spine surgery. One of these patients required an emergent cricothyrotomy for airway protection and eventually recovered with some residual swallowing problems. The other patient recovered with conservative measures including steroids. Another patient required surgical decompression three days after surgery; the surgeon noted that the rhBMP-2 had been hyperconcentrated on the sponge.

Localised edema has been noted in nonclinical and some clinical studies evaluating rhBMP-2/ACS, though a clear causal association has not been established. Similarly localized edema has been reported after routine ACD, though the actual incidence is difficult to ascertain. Pharyngeal edema is typically discussed in the context of airway complications, which have been noted in up to 6% of patients undergoing ACD, generally in the early post-operative period.

Though causality has not been established, overall the data suggests that rhBMP-2/ACS may be associated with, or contribute to, the development of localised edema. Such edema is more likely to be symptomatic and visually discernable in the neck area. Given the potential clinical importance of the observed events Wyeth is planning to add wording to the SmPC to caution physicians about the potential of localised edema coincident with the use of rhBMP-2/ACS, and to warn against use in the cervical spine.

Four spontaneous reports of ectopic, heterotopic, or exuberant bone growth were reviewed in the PSUR. In three of the cases a posterior surgical approach was employed; the surgical technique was not specified in the fourth case. In addition, three of the patients had symptoms including sciatica, leg weakness with back pain and foot drop, though it is not clear if the symptoms were related to the bone growth. The RSI describes the potential of these AEs as follows: *"Use of InductOs may cause heterotopic ossification in the surrounding tissues, which can result in complication*s." Hence, based on this review, no new safety signals for rhBMP-2 are identified.

5. OVERALL DISCUSSION AND BENEFIT/ RISK ASSESSMENT

5.1 Non-clinical data

Non-clinical data were submitted previously by the MAH in the context of FUM 024 and assessed at that time (Final AR dated 19-05-2004). No new non-clinical data were submitted.
According to the MAH both in vitro and in vivo studies performed by the MAH as part of a FUM did not demonstrate a tumour growth promoting effect. Published studies gave conflicting results and were not reproduced. The MAH concluded that the non-clinical data showed no evidence for tumour induction and the potential for tumour growth promotion is low.
Although the CHMP initially agreed with the conclusions of the MAH, in view of the clinical findings of malignancies, the CHMP endorsed some additional comments:

- The MAH studied a range of tumour cell lines amongst which 3 pancreas tumour cell lines for the presence of BPM-2 receptor mRNA. The MAH concluded that 10 tumour cell lines were positive, but none of the pancreas cell lines. However the CHMP commented that the limits were set arbitrarily and that in fact all, but two (amongst which one pancreas tumour cell line) were in fact positive (i.e. had higher levels of BMP-2 mRNA than the negative control).
- The MAH tested only those cell lines in an in vitro system that were judged positive for BMP-2. Consequently no pancreas tumour cell lines were investigated any further.
- In an in vivo model, using xenografts in nude mice, 6 cell types were tested. None of these tumour types showed enhanced growth following rhBMP-2 treatment. But again although the choice of the cell types was logical, the study did not investigate pancreas tumour cell types.

In view of the malignancies seen in the clinical studies, the CHMP suggested that the MAH further investigates the growth-promoting properties of other tumour cell types that have not been investigated so far. For instance a study with pancreas tumor xenografts (e.g BXPC3 or Capan2) in nude mice.

5.2 Clinical efficacy

The CHMP had raised concerns that non-inferiority with respect to standard therapy has not been demonstrated.

The CHMP noted that the statistical method used to evaluate non-inferiority of the investigational treatment in the main clinical study is not in compliance with CPMP/ICH guidance. The recommended method to show non-inferiority is to use two-sided 95% CI for the difference between treatment arms and to compare this with the predefined non-inferiority delta.
Therefore, the CHMP requested the MAH to discuss on this issue.
Further to the discussion by the MAH, the CHMP noted that the predefined margins were 15% for overall success and Oswestry, and 10% for fusion and neurological success.
It is agreed that in all of the datasets (per protocol, primary dataset and missing-equals-failure), non-inferiority of Inductos+LT-CAGE treatment to autograft+LT-CAGE was shown with regards to the primary efficacy variable “Overall success” by comparing the lower bound of two-sided 95% Confidence Interval to the chosen 15% non-inferiority margin both at 12 and at 24 months. The results are hence robust and consistent. With regards to the fusion success rates, non-inferiority was also consistently shown in all datasets. The Oswestry Pain score success and neurological success rates were similar in the treatment groups, but formal non-inferiority was consistently shown only for the Oswestry scores.

Since the definition of fusion criteria of the FDA was used, the CHMP requested the MAH to indicate what the sensitivity/accuracy of this assay was. Additionally, the MAH should justify the choice of the non-inferiority margins.
For studies 3100N3-303 and -304 fusion was determined from radiographic evidence of bridging trabeculae. If such evidence could not be seen in radiographs, CT scans could then be used. CT scans

have increased ability for detecting bridging bone. According to the company's response, both radiographs and CT scans were reviewed to determine fusion. Additional criteria had to be fulfilled before fusion could be declared: no radiographic evidence of motion (using accepted criteria to assess motion, taking into consideration the inherent measurement errors) and no evidence of radiolucency surrounding greater than 50% of either of the implanted LT-CAGE devices. The fact that both plain radiographs and CT scans were used for detecting fusion makes the results more solid. The methods used in the clinical trials, albeit representing surrogate evidence of fusion, have been used in other published clinical trials and can be considered reliable, sensitive and accurate. Use of invasive methods would not have been possible. It is unlikely that use of these methods has introduced any bias in favour of Inductos+LT-CAGE treatment arm. On the contrary, the non-inferiority analysis is likely to be conservative due to the presence of mineralised bone inside the LT-CAGE in the bone autograft+LT-CAGE treatment arm.
The company has reviewed available published data on efficacy of anterior lumbar interbody fusion procedures. The CHMP agreed that the results of the clinical trials with LT-CAGE with autograft or Inductos are in line with published data from other studies, showing generally fusion rates of 90% or higher. Fusion rate is expected to be negligible without surgical intervention and, therefore, the company has a strong argument in favour of using the 10% non-inferiority margin for fusion success. The 15% non-inferiority margin used for Oswestry Pain score and overall success is more difficult to justify. However, based on review of published literature on clinical trials that have used other surgical methods and have included Oswestry scores among their endpoints the choice of "delta" can be defended.

The CHMP noted that high response rates have been reported for autograft-induced spinal fusion. However, the MAH was requested to specifically review the results of autograft treatment (radiological and functional endpoints, i.e., all components of the primary endpoint) in published trials using the same device and surgical approach relevant to the current application to further justify the chosen noninferiority margin.
The MAH noted that there are no published studies directly comparing the efficacy of fusion procedures with fusion cages with non-surgical treatment. However, the study by Fritzell et al. (Spine 2001; 26(23):2521-2534) is helpful in establishing that patients with severe chronic low back pain and lumbar spine disc degeneration are unlikely to experience any significant relief of pain without surgical intervention as judged by changes in Oswestry score over 2 years vs. posterolateral fusion procures. As concluded in the review of MAH's response, the CHMP considered that the 15% non-inferiority margin for Oswestry Pain score success is reasonable. A remarkable improvement in Oswestry score was observed in both treatment groups in the main study -303. Taking into consideration the reported minimal or no improvement in patients treated conservatively, the non-inferiority delta of 15% can be considered justifiable and conservative for Oswestry success and overall success (Oswestry was part of overall success evaluation).

It was noted that in a non-inferiority trial, the main focus is on the per protocol analysis. Only the results of per protocol dataset analysis of the primary combined efficacy/safety endpoint have been provided. To be able to further assess the validity of noninferiority conclusion, the MAH should provide the per protocol dataset analysis results for the two primary efficacy endpoints in the main clinical study, and a new non-inferiority analysis for the combined endpoint and efficacy endpoints using the recommended method and all protocol defined datasets.
The results of the per protocol dataset analysis for the two primary efficacy endpoints (Oswestry and fusion) and for the combined endpoint of overall success have been provided. This analysis utilizes two sided 95% confidence intervals for the difference between treatment arms.
For the per protocol dataset analysis, the absolute value of the lower limits of the 95% two-sided confidence intervals are all smaller than the non-inferiority margins that were pre-defined in the protocol at both 12 and 24 months. The predefined margins were 15% for overall success and Oswestry, and 10% for fusion. For the per protocol analyses at 24 months, the absolute value of the lower limit of the two-sided 95% confidence interval was 11.20% for Oswestry, 1.53% for fusion, and 10.72% for overall success.

Thus, non-inferiority with respect to the standard therapy has been demonstrated with the per protocol analysis, as well as with the primary data set and missing-equals-failure dataset. This issue have been considered resolved.

The CHMP noted that non-clinical and clinical data underline the importance of following instructions given in the SPC on the appropriate preparation and handling of the implant to avoid leakage of dibotermin alfa. Therefore the CHMP concluded that MAH should commit to produce suitable educational material for surgeons and other medical staff. This material should be submitted to the CHMP for review.
The draft brochure is considered a helpful start. However, the MAH should consider producing a video outlining the correct preparation of InducsctOs for use in spine infusion procedure, handling and use of Inductos with LT-CAGE device. This educational material should be available in a reasonable deadline for its submission for review.

The CHMP raised a concern since the MAH states that it is a minor omission that no donor-site pain data have been collected for the investigational subjects. Donor-site pain is the reason why rhBMP-2 is used instead of autogenous bone graft. The CHMP concluded that if donor-site pain is included in the total pain score the MAH should have conducted a superiority trial and not a non-inferiority trial for the endpoint pain.
Pain from donor site played a role in the first 6 weeks to 3 months after surgery, but was minimal at 12 and 24 months. With adjustment of the Oswestry score by donor-site pain, the lower limit of the confidence interval for Oswestry pain and Overall success at 24 months shifted slightly to more negative values, but was still within the predefined limit of -15%. The CHMP concluded that this issue is resolved.

The CHMP noted that in the LT-CAGE study lower success percentages were reached with the LT-CAGE filled with autologous bone as in study 3100N3-303. The CHMP requested the MAH to give an explanation for this.
The additional data provided by the MAH show that fusion rates are similar in both studies (data are from the primary analysis set), but Oswestry Pain/Disability Improvement and therefore Overall Success are still lower in the IDE G9 50165 study. The MAH argued that surgeons have become more familiar with the fusion technology with the LT-CAGE Device at the time of the main study. This should be kept in mind when comparing the results of both studies.
Although there is no proof, the CHMP considered this issue to be answered sufficiently and therefore resolved.

The CHMP raised a concern on the maximal total dose used in the clinical study 3100N3-303-US). In this study maximal total dose was 8.4 mg of rhBMP-2 for the 2 cages (size 18 mm x 26 mm) which is different from the dose as applied for given in the table of the SPC sect. 4.2 which amounts to 6 mg per cage (size 18 mm x 26 mm) resp. 12 mg of rhBMP-2. This dose has not been tested. The MAH is asked to explain this discrepancy with respect to any dose effects.
The MAH has proposed to resolve the issue by changing the number of large LT-CAGE in section 4.2 in the SPC from 3 to 2 to reflect the number of pieces of InductOs used in the clinical studies.

5.3 Clinical safety

The safety profile of rhBMP-2/ACS when used with the LT-CAGE for anterior single-level lumbar spine fusion appears acceptable and favourable compared to LT-CAGE + bone autograft. This conclusion is based on the pivotal clinical trial where an open surgical approach was used. In general, the profile of adverse events was expected in the clinical context. However, certain adverse events that are not uncommon after spinal fusion procedures (joint disorder, neuralgia, neuropathy, urinary retention and abnormal ejaluation) were more frequently reported in the rhBMP-2/ACS group

compared to autograft group. Therefore the CHMP requested the MAH to discuss on these adverse events.
The CHMP concluded that all of the adverse events reviewed ("joint disorder", "neuralgia", "neuropathy", "urinary retention" and "abnormal ejaculation") may well be related to the surgical procedure as such or to the progression of degenerative disc disorder at other levels of the spine. The concern was related to the fact that the individual adverse events appear to be more frequently reported in the Inductos+LT-CAGE group than in the control group. When the neurological success and overall success rates are compared, there is no sign that the higher frequency of adverse events might be related to inferior efficacy of the investigational treatment. Neurological success rates were similar in both treatment arms. Urinary retention and abnormal ejaculation are not infrequent adverse events following spinal fusion procedures. Furthermore, none of the differences between the treatment arms were statistically significant. Finally, the aggregate analysis of neurological adverse events does not suggest a clear difference between the treatment arms.
The CHMP concluded that the MAH should closely monitor neurological events in clinical use.

The CHMP raised a concern on a case of spinal stenosis reported in the laparoscopic study and requested the MAH to discuss in more detail.
Further to the discussion by the MAH, the CHMP concluded that the review of the detailed information provided on the reported case of spinal stenosis does not allow drawing any firm conclusion as to the role of Inductos+LT-CAGE treatment. However, the patient's history and clinical findings suggest that the condition may be secondary to degenerative disc disease rather than to the investigational treatment. This issue was considered resolved.

The presented data on antibodies do not indicate difficulties in that area. However, as a result of follow-up measures 025 and 026 the MAH has developed and validated a new antibody ELISA for antibodies to rhBMP-2 that has the potential to detect all antibody isotypes. In addition a neutralization assay for antibodies to rhBMP-2 has been developed and validated. Since it is assumed that the data presented have been collected using the old method, the CHMP requested the to submit data collected with the new assays from retrospective or prospective studies.
The preliminary analysis of samples from clinical trials using the "old" and newly developed ELISA assays suggests that a higher frequency of rhBMP-2 antibodies is detected with the new assay. The new data should be included in the SPC after the MAH has submitted the data and assay details for review by the CHMP. It is unfortunate that the samples have not yet been tested in the neutralisation assay. The company should keep the CHMP up to date with regards to the evaluation of the assay details by the FDA.
If neutralising antibodies are detected, the MAH should also consider and examine potential cross-reactivity of neutralising antibodies with other members of the TGF-ß family, and to provide a detailed discussion on clinical relevance. The possibility of developing neutralising antibodies is also important to consider in the context of safety in pregnancy.

The CHMP agreed with the MAH's view to maintain the contraindication for pregnancy. Although the CHMP does not believe that the non-clinical data indicate serious risks for pregnancy, the CHMP agreed that the lack of information on the potential effects of antidibotermin neutralising antibodies on pregnancy is an important reason to maintain pregnancy as contraindication. Indeed, The CHMP does not know whether neutralising antibodies are formed. Also the effects of such antibodies have not been studied. Therefore the answer cannot be given at this time. If neutralising antibodies are formed it is conceivable that such antibodies have an effect on foetal development. Yet if neutralising antibodies are formed and they would adversely affect foetal development, a contraindication alone might not be enough. In fact in that case pregnancy ought to be prevented as long as immunological memory for dibotermin is present. This should be further discussed when data on neutralising properties of antibodies found in clinical studies have been made available.
The CHMP concluded that this issue is unresolved and therefore the MAH should commit on the provision of these data.
The CHMP raised concern on malignancy and during its plenary meeting in December 2004 the CHMP adopted a follow-on request of supplementary information to be addressed by the MAH. With

reference to the summarisation on malignancy cases reported in the clinical trials sponsored by Medtronic Sofamor Danek (MSD) the MAH was requested to submit more detailed information on the cases of malignancy.
The CHMP concluded that the MAH has presented detailed information on the cases of malignancy. With respect to the cases of pancreatic cancer Wyeth and MSD conducted site visits and detailed trip reports were provided. The MAH has made efforts to retrieve all relevant information. Though one cannot say for certain, it appears unlikely that if rhBMP-2 induced malignant transformation of cells, the patients would present within a year with symptomatic/metastatic disease. The available information does not allow to comment on what role rhBMP-2 might play in stimulating pre-existing neoplasms. This may be particularly relevant for those cancers (e.g. pancreatic and liver cancer) found in the proximity to the site of implantation, as the overall systemic exposure to rhBMP-2 is brief.

The CHMP noted that the data from MSD shows an imbalance in the proportion of patients with reports of SEER (Surveillance, Epidemiology and End Result) malignancies in the active and in the control arms. Therefore the MAH was requested to discuss on the difference of the malignancy cases between the active group and the control group. Further to the provision of responses to this issue, the CHMP concluded that it could be doubted that one-year difference in mean age will have contributed significantly to the observed imbalance in malignancies. Post study surveillance in a single arm indeed may introduce a reporting bias. However, incidence rates were determined according to protocol-mandated follow-up time. Therefore, the CHMP concluded that it is unlikely that these factors may confound the interpretation of the data.

The CHMP noted that the data from MSD shows an imbalance in the proportion of patients with reports of SEER (Surveillance, Epidemiology and End Result) malignancies in the active and in the control arms. Therefore the MAH was requested to compare the observed rates of these malignancies to those expected for age and gender matched controls.
The CHMP noted that observed rates of malignancies were compared to the frequency of cancer in the general US population. It should be remarked that not all studies were conducted in the US. The tibia-fracture study (450 patients), for instance, was conducted in South Africa, Australia and Europe. However, the approach can be accepted.
The overall frequency of malignancies was comparable to the expected rate, but there were more pancreatic cancers. The MAH may be right that one cannot conclude that rhBMP-2 increases the risk of pancreatic cancer based on this evaluation, but it cannot be refuted either. The MAH has submitted a detailed description of the three patients. One cannot conclude with certainty that there is no relationship. It is appreciated that the MAH plans to obtain expert review of the data and pursue the feasibility of a formal epidemiological study to evaluate any association between rhBMP-2 and pancreatic cancer.

The CHMP requested the MAH to compare the data from Wyeth studies and MSD studies and discuss the differences.
In its responses, the MAH mentioned a number of factors that can contribute to the differences in data between Wyeth and MSD studies. The CHMP noted that treatment indication, comorbidity, pre-existing risk factors and age are factors that might explain the difference. The CHMP concluded that a concern is the fact that this higher ”background incidence” of malignancies could be the target for an effect of dibotermin alfa.

There is an imbalance in the total (or total SEER) number of malignancies in rhBMP-2 treated patients compared to control patients. However, when the rates are adjusted for the differences in duration of follow-up time between the two groups, they are not statistically significant. Also, when compared to the frequency of cancer in the general US population, the overall frequency of malignancy was comparable to that expected, but there were more pancreatic cancers.
In the light of three reports of pancreatic cancer in the rhBMP-2 treated patients, further causality evaluations were performed. For the time being, causal relationship with the observed cases of malignant tumours in patients who have received InductOs cannot be concluded. Therefore the MAH should submit a proposal for pro-active monitoring of malignancies.

Although it appears unlikely that locally administered dibotermin alfa could affect tumour cells at distant sites, due to its low systemic availability and short duration of action, the occurrence of a higher than expected number of pancreatic cancers does raise some concern, as this site is relatively close to the site of implantation in lumbar spine fusion. Another cause of concern is the fact that the target population for the proposed indication is generally older than tibia fracture patients, resulting in a higher "background incidence" of malignancies that could be the target for an effect of dibotermin alfa.

The CHMP endorsed the MAH's plan to obtain expert review of the data and pursue the feasibility of a formal epidemiological study to evaluate any association between rhBMP-2 and pancreatic cancer. The MAH has provided a summary of the expert panel meeting, which was held on 31 January 2005. The conclusions of this meeting give no cause for further comments.

The PSUR cycle should be kept at one year for the moment.

5.4 Benefit/Risk assessment

Based on the review of the data provided, the CHMP considered that the variation application for InductOs, for the proposed new indication of spine fusion is approvable, provided that the MAH commits to further investigate the growth-promoting properties of other tumour cell types that have not been investigated so far, to submit a proposal for pro-active monitoring of malignancies and to explore further the possibility of a formal epidemiological study.

6. CHANGES TO THE PRODUCT INFORMATION

Further to the assessment of the different proposals of the Marketing Authorisation Holder to amend the Product Information and in the light of the assessment of the submitted data, the CHMP requested the following additional amendments of the SPC:

Section 4.1 "Therapeutic indication"

The therapeutic indication has to be in line with that of the LT-CAGE device and clinical trial study population: therefore it was added that patients should have at least six months of nonsurgical treatment. The sentence "For this indication, InductOs must be used with the LT-CAGE® Lumbar Tapered Fusion Device" has been deleted and it has been moved to section 4.2.

Section 4.2 "Posology and method of administration"

The following sentence has been inserted immediately below the heading "Instructions for use in anterior lumbar spine fusion surgery": InductOs should not be used alone for this indication, but must be used with the LT-CAGE Lumbar Tapered Fusion Device.
Following the CHMP's concern on the maximal total dose used in the clinical study, the number of large LT-CAGE has been changed from 3 to 2 to reflect the number of pieces of InductOs used in the clinical studies.

4.3 Contraindications

"Pregnancy" is maintained as contraindication.

4.4 Special warnings and special precautions for use

The MAH has committed to update this section after the submission of data from the newly developed ELISA assays.

4.6 Pregnancy and lactation

The following sentence has been inserted: "*Animal studies have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. Due to the unknown risks to the fetus associated with the potential development of neutralising antibodies to dibotermin alfa, InductOs is contraindicated in pregnancy (see sections 4.3 and 4.4).*"
When new data on neutralising antibodies become available, the wording in this section has to be reconsidered.

4.8 Undesirable effects

Further to the provision of supplementary information by the MAH on some adverse events ("joint disorder", "neuralgia", "neuropathy", "urinary retention" and "abnormal ejaculation") the CHMP concluded that none of the differences between the treatment arms were statistically significant and that the aggregate analysis of neurological adverse events did not suggest a clear difference between the treatment arms. Therefore the proposed text from the MAH does not need any further revision.

5.1 Pharmacodynamic properties

The sentence on donor-site pain has been deleted ("As expected, patients who received autogenous bone graft reported pain at the site of graft harvest, with 31% of them still experiencing some graft-site pain at 24 months") and the overall success rates have been included.

5.3 Preclinical safety data

This paragraph has been updated in line with the revision proposed by the CHMP (i.e. *"Preclinical data reveal no special hazard for humans on conventional studies of pharmacology, acute and repeat exposure toxicity. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, maternal toxicity, embryolethality, or fetotoxicity. However, in reproductive toxicity studies in rats, where dibotermin alfa was administered intravenously to maximize systemic exposure, increased fetal weight and increased fetal ossification was observed and a treatment related effect could not be ruled out. The potential effects of anti-dibotermin antibodies have not been investigated. InductOs has not been tested for in vivo carcinogenicity. Dibotermin alfa has demonstrated variable effects on human tumour cell lines in vitro. Although the available in vitro data suggest a low potential for promotion of tumour growth, the use of InductOs is contraindicated in patients with an active malignancy or in patients undergoing treatment for a malignancy (see also section 4.3 Contraindications). InductOs has been studied in a canine spinal implantation model. InductOs was implanted directly onto the exposed dura following a laminectomy. Although narrowing of the neuroforamen and stenosis was observed, no mineralization of the dura, no spinal cord stenosis, and no neurological deficits subsequent to the application of InductOs were observed. The significance of these data for humans is not known.").*

Where relevant changes are also reflected in the Package Leaflet.
Additionally, the CHMP requested the following additional amendments in the Package Leaflet.

2. BEFORE YOU RECEIVE InductOs

In the paragraph "The following are precautions for use of InductOs to be discussed with your doctor" the following sentence has been inserted "You should inform your doctor if you have any bone disease".

7. CONCLUSION

The CHMP considered this Type II variation to be acceptable and agreed on the proposed wording to be introduced into the Summary of Product Characteristics and Package Leaflet based on the observations and the appropriate conclusions, subject to the additional follow-up measures undertaken by the Marketing Authorisation Holder (see Annex 9 of this Assessment report).

The CHMP adopted on 17 February 2005 an Opinion on a Type II variation to be made to the terms of the Community Marketing Authorisation, as amended.