European Medicines Agency

EMEA/H/C/0408

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE
EUROPEAN PUBLIC ASSESSMENT REPORT (EPAR)

INDUCTOS

International Nonproprietary Name (INN): **Dibotermin alfa**

Abstract

Active substance:	Dibotermin alfa
Pharmaco-therapeutic group (ATC Code):	Bone morphogenetic protein M05BC01
Currently approved therapeutic indication:	Single-level (L_4 - S_1) 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. Treatment of acute tibia fractures in adults, as an adjunct to standard care using open fracture reduction and intramedullary nail fixation.
Authorised presentations:	See the Module "All authorised presentations"
Marketing Authorisation Holder:	Wyeth Europa Ltd Huntercombe Lane South Taplow, Maidenhead Berkshire SL6 0PH United Kingdom
Date of issue of Marketing Authorisation valid throughout the European Union:	9 September 2002
Orphan medicinal product designation date:	Not applicable

The active substance of InductOs is dibotermin alfa, a bone morphogenetic protein, which is an osteoinductive protein that results in the induction of new bone tissue at the site of implantation by binding to receptors on the surface of mesenchymal cells and causing cells to differentiate into cartilage-and bone-forming cells.

Inductos is approved for the treatment of acute tibia fractures in adults, as an adjunct to standard care using open fracture reduction and intramedullary nail fixation. The effect of dibotermin alfa in patients was demonstrated in a multinational, randomized, controlled, single-blind study of patients with open tibial shaft fractures requiring surgical management. Patients with all fracture severity levels were included, excluding only patients at high risk of amputation. Patients received standard care (control group) consisting of intramedullary (IM) nail fixation and routine soft tissue management or standard care plus InductOs. This study showed that InductOs increased the probability of fracture healing; patients treated with InductOs had a reduced risk of treatment failure (where secondary intervention to

7 Westferry Circus, Canary Wharf, London E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 86 68
E-mail: mail@emea.eu.int http://www.emea.eu.int

promote fracture healing was required) compared with patients in the standard-care group. In the subgroup of patients who received reamed IM nail fixation, InductOs was not observed to reduce the rate of secondary intervention.

The efficacy and safety of InductOs were subsequently demonstrated in a randomised, controlled, multicenter, non-inferiority study in patients undergoing an open anterior lumbar interbody fusion procedure. These patients had received at least six months of non-operative treatment prior to treatment with InductOs for anterior lumbar spine fusion. Therefore on 29 March 2005 the European Commission amended the Marketing Authorisation to include that InductOs is indicated for single-level (L_4 - S_1) 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 new indication InductOs should not be used alone, but must be used with the LT-CAGE Lumbar Tapered Fusion Device.

The most common adverse events observed during treatment for acute tibia fractures were generally representative of the morbidity associated with either orthopaedic trauma or the surgical procedure. However, increased amylasaemia, headache, tachycardia and hypomagnesaemia were observed more frequently in the InductOs treatment group.

The undesirable effects observed in anterior lumbar spine fusion patients were generally representative of the morbidity associated with spine fusion using autogenous bone graft taken from the iliac crest. Very common undesirable effects were accidental injury, neuralgia, back pain and bone disorder: these undesirable effects were similar in both control and InductOs treatment groups.

The CHMP, on the basis of efficacy and safety data submitted, considered that InductOs showed adequate evidence of efficacy for the approved indication, as well as a satisfactory risk/benefit profile and therefore recommended that the Marketing Authorisation should be granted.

For detailed conditions for the use of this product, scientific information or procedural aspects please refer to the relevant modules.

SCIENTIFIC DISCUSSION

This module reflects the initial scientific discussion for the approval of Inductos. This scientific discussion has been updated until 1 January 2004. For information on changes after 1 January 2004 please refer to module 8B.

Introduction

InductOs (dibotermin alfa/ACS) is a surgically implantable medicinal product, consisting of a solution of recombinant human Bone Morphogenetic Protein-2 (rhBMP-2 or dibotermin alfa) applied to a matrix, an Absorbable Collagen Sponge (ACS). When administered locally, dibotermin alfa /ACS results in the induction of new bone at the site of implantation.
Human BMP-2 is a member of the TGF-beta superfamily of growth and differentiation factors and is a glycosylated, disulfide-bonded, dimeric protein with two major subunit species of 114 and 131 amino acids. dibotermin alfa is expressed and secreted in a Chinese hamster ovary (CHO) cell culture process.
Recombinant hBMP-2 binds to receptors on the surface of mesenchymal cells and causes cells to differentiate into cartilage- and bone-forming cells. dibotermin alfa is combined with a matrix to facilitate surgical implantation and dibotermin alfa retention at the treatment site.
The indication sought for InductOs is the treatment of acute tibia fractures in adults, as an adjunct to standard care using open fracture reduction and intramedullary nail fixation.

1. Part II: Chemical, pharmaceutical and biological aspects

Composition
InductOs 12 mg kit for implant comprises a 20 ml vial containing 12 mg of dibotermin alfa (rhBMP-2), a 10 ml vial with solvent (water for injection), a 7.5 x 10 cm matrix (Absorbable Collagen Sponge), two 10 ml syringes, and two 20G needles. After reconstitution the solution is applied to the matrix.

Active substance
The active substance, dibotermin alfa, is recombinant human Bone Morphogenetic Protein-2 (rhBMP-2) produced in a CHO cell culture. It is a dimeric glycosylated protein with an apparent molecular weight of approx. 30 kDA.

Development genetics and cell banks
The cDNA for dibotermin alfa was cloned from a human osteosarcoma cell line using as a probe a bovine genomic BMP-2 fragment. Through multiple subcloning procedures, the human BMP-2 cDNA was ligated into a mammalian expression vector. The resulting expression construct was used to transfect the CHO cells. The strain was adapted for growth in serum-free, antibiotic free suspension culture to prepare the MCB and WCB.

The stability of the expression system during inoculum preparation and full scale fermentation has been extensively verified. The preparation of the MCB and WCB is well described. MCB, WCB and End of production cells underwent extensive microbial/viral testing.

Fermentation
The cell culture process is a suspension culture in which cells replicate constantly and constitutively secrete dibotermin alfa. Appropriate in-process controls have been implemented. Mycoplasma and *in vitro* adventitious virus testing is performed.

Purification
The purification process consists of validated chromatographic and ultrafiltration steps and viral filtration. Appropriate in-process controls have been implemented.

Column resin cleaning and regeneration procedures and storage conditions of the columns are well described. Maximum lifetimes for the columns have been set. The storage time and temperature of the different intermediate products have been extensively validated. Viral validation studies of the purification process demonstrated that the process effectively removes enveloped and some non-enveloped viruses. The purification process, together with the viral testing after fermentation assure the viral safety of the product.

Characterisation of dibotermin alfa
The active substance has been characterized using a combination of traditional and state-of-the-art techniques. dibotermin alfa has also been characterized in combination with the matrix (ACS).

Analytical methods used during dibotermin alfa development and current test methods for release of active substance and the dibotermin alfa vialed protein have been qualified or validated in concordance with guidelines in force.

Specifications and routine tests
The active substance is adequately controlled by a combination of physico-chemical, biological and immunological methods. All analytical methods have been appropriately validated. Batch analysis demonstrates consistent manufacture of active substance. All tests for release of the active substance and the dibotermin alfa vialed protein have been extensively described and thoroughly validated.

Other ingredients
Excipients
All excipients (sucrose, glycine, polysorbate 80, sodium chloride, L-glutamic acid, water for injections) comply with the European Pharmacopoeia.

Matrix: Absorbable collagen sponge (ACS).
Genetics Institute uses an Absorbable Collagen Sponge, manufactured by Integra LifeSciences Corporation, as a matrix for dibotermin alfa . ACS consists of purified bovine type I collagen cross-linked and sterilised by chemical means.

The specifications of the ACS have been statistically justified. The preparation of the type I collagen for ACS involves an alkaline treatment step. A virus validation study was performed to assess the ability of this step to inactivate relevant and model viruses. It can be concluded that this alkaline step has a sufficient capacity to inactive a broad range of viruses.
A TSE Certificate of Suitability of the European Pharmacopoeia for the ACS has been granted by the EDQM. The ACS matrix showed stability for 36 months at room temperature.

Packaging material
The protein vial and the solvent vial are made of type I glass, closed by bromobutyl stoppers and flip-off plastic caps. The ACS sponge is packaged in 20 ml trays formed from polyvinyl chloride (PVC) and sealed with Tyvek lids. The packages are double blisters.

Product development and finished product
The manufacturing of the vialed protein takes place at Abbott Laboratories, Kansas, USA. Labelling and packaging of dibotermin alfa /ACS is performed at Wyeth Laboratories, New Lane, Havant, UK. This site is also responsible for EU batch release.

The specifications and test methods for the vialed protein were selected to ensure identity, purity, potency, quality and safety. Specifications and release criteria have also been set for dibotermin alfa in combination with the ACS matrix.

Stability of the Product
The vialed protein is stable for 24 months at 2-30°C. The reconstituted protein is stable for 3 hours at room temperature.
Based on the stability data provided for storage of the kit (vialed protein, solvent and matrix) at room temperature, a shelf life as indicated in the SPC is acceptable.

2. Part III: Toxico-pharmacological aspects

Considering the nature (biotechnology product) and intended use of the product, the applicant has carried out a fairly extensive preclinical pharmacology and safety study programme. Appropriate statements regarding GLP compliance have been attached to the study reports.

Pharmacodynamics

The proposed concentration of dibotermin alfa /ACS to be used in clinical practice is 1.5 mg/ml.

- *In vitro* studies

The submitted in vitro data describe several bone forming related effects of dibotermin alfa. It has been demonstrated that the effect of dibotermin alfa is local and that no systemic effects have been found. The local effect of dibotermin alfa is likely to be due to a combination of its specificity and its rapid systemic clearance. A comparison of the affinity of dibotermin alfa and natural BMP-2 for the receptor(s) was not feasible due to the difficulty in obtaining individual purified BMP proteins. The signal transduction role of the type I and type II serine/threonine kinase receptor subunits of dibotermin alfa receptors has been closely examined and a comparison of iodinated dibotermin alfa with "native" dibotermin alfa showed no differences. It has also been shown that dibotermin alfa does not bind to any other receptor component of the TGF-β superfamily.

- *In vivo* studies

A number of preclinical studies support the ability of dibotermin alfa /ACS to induce the formation of new bone at the site of implantation in diaphyseal defect models (critical size bone defects), metaphyseal defects, augmentation of fracture repair, and extraosseous sites. Altogether, these studies suggest that the relationship between dose and osteogenic response is complex and remarkably different depending on the animal model and species.

Numerous pharmacodynamic studies in several models in rats, dogs, rabbits, sheeps, goats and nonhuman primates were conducted to show the safe and efficacious use of dibotermin alfa /ACS.

Healing of critical size diaphyseal defects was demonstrated with dibotermin alfa /ACS in the rat femoral defect model, canine radial defect model and nonhuman primate radial and ulnar defect models.

The best results in the canine radius defect model were obtained at a very low concentration compared to that proposed for clinical use (0.05 vs. 1.5 mg/ml). At concentrations clearly below those intended for clinical use, formation of voids in the bone, heterotopic bone formation and potentially inferior biomechanical strength and radiographic density of the defect area were observed compared to autologous bone graft. It has been observed in each of the studied species, that the bone formation in response to dibotermin alfa , both in quantitative and qualitative terms, depends on the concentration of dibotermin alfa . At the low end of the concentration range, inadequate bone formation is observed. At the high end, excessive bone formation and/or generation of fluid-filled voids within the induced bone are observed. The applicant claims that fluid-filled voids in the newly formed bone seen in this animal model have not been observed in man. Nevertheless it is reassuring that the newly formed bone with voids was not biomechanically inferior to bone autograft group.

However, it must be noted that in the set of similar experiments using the canine radial defect model, results were not quite uniform from one experiment to another. Equal or event trendwise superior biomechanical strength compared to autograft were observed in some experiments.

The nonhuman primate critical size radial defect model has a lower sensitivity compared to the canine radial defect model. In the monkey, concentrations of dibotermin alfa /ACS approximately equal to, or even double those intended for clinical use did not lead to significant bone formation. The lack of consistent efficacy to bridge critical-sized defects in primates does not appear to be related to impaired bone formation at increasing concentrations of dibotermin alfa or changes in the dibotermin alfa manufacturing process. Rather, it is more likely that the dibotermin alfa /ACS implant was unable to resist soft tissue compression during bone induction, resulting in insufficient bone to repair the defect.

Soft tissue compression has a more pronounced effect in nonhuman primate models than in models of lower animal species due to a slower rate of dibotermin alfa -induced bone formation. This conclusion is supported by the random distribution of successful bridging in individual animals in the radius defect studies, and the histologic observation of soft tissue compression into the defect observed in the accompanying time series studies. Additionally, successful bridging was demonstrated in the positive control animals implanted with dibotermin alfa added to autogenous bone graft; a material much more resistant to soft tissue compression than ACS.
Two studies in sheep evaluated the ability of dibotermin alfa /ACS to induce bone formation when implants were placed into trabecular bone in the metaphyseal region (femoral head core defect). These two studies reveal an important property of dibotermin alfa /ACS: when used to fill trabecular bone defects, resorption of surrounding trabecular bone is observed in the initial phase of healing. This appears to have taken place mostly during the first two weeks. Histology revealed the presence of multinucleated giant cells degrading the peripheral region of the implant. This phenomenon has been described in the the SPC and for the time being use in metaphyseal fractures and endoprosthetic applications are discouraged.

Several studies have evaluated the ability of dibotermin alfa /ACS to facilitate fracture repair (acceleration of repair and/or assurance of healing) in rabbits and goats when used as an onlay. These models are relevant in view of the proposed therapeutic indication. However, this effect has not been investigated in monkeys, where the osteoinductive capacity was shown to be relatively poor.

The rabbit ulnar diaphysis fracture onlay model provides evidence of a significant acceleration of healing in response to dibotermin alfa /ACS. The variable and modest effect of ACS alone (with buffer) in this model suggests that dibotermin alfa has more than an ancillary role in the efficacy of the product that resembles the intended clinical use. However, no dose response relationship could be observed with regard to concentration of dibotermin alfa .

As regards the goat tibial fracture model, a decreased consolidation and internal callus in dibotermin alfa /ACS treated fractures compared to untreated controls has been observed. The rapid rate of healing with extensive periosteal new bone formation highlights one of the major weaknesses of using closed tibia fracture in goats as a model for closed fractures in human. Periosteal stripping was not found to be effective in slowing down the healing response of closed fractures in this model. Due to these limitations, the goat model was not studied further.

- Pharmacodynamic drug interactions

No traditional *in vitro* product interaction studies have been conducted which is considered acceptable for biopharmaceutical agents. In *in vivo* studies glucocorticoids reduced dibotermin alfa /ACS-induced bone formation in rats and rabbits.

- General and safety pharmacology programme

In rabbits, healing of osteotomies in bone previously induced by dibotermin alfa /ACS was comparable in nature and kinetics to that of native bone.

Repair of rabbit distal radial defects by dibotermin alfa /ACS and evaluation of the potential effects on the radiocarpal joint has been studied. When dibotermin alfa /ACS was placed in a bone defect communicating with a joint, no pathological changes in the joints or its capsules were observed. However trabecular bone resorption, periarticular bone formation and joint damage remain potential risks despite the results of this study. For the time being, the product should not be used in the treatment of fractures that involve joint space.

Treatment of ulnar osteotomies with dibotermin alfa /ACS was studied in juvenile rabbits. The purpose of this study was to evaluate the effect of treating unilateral mid-diaphyseal ulna osteotomies with the product in growing juvenile rabbits with open growth plates. In growing juvenile dibotermin alfa /ACS accelerated osteotomy bridging and healing were observed without clinically relevant effects (< 1.5 %) on total limb length. Although the difference in total length between dibotermin alfa /ACS treated and control limbs was small and the effect of treatment of growth plate

thickness was not statistically significant, the differences were of such magnitude that a true effect is likely and biologically plausible. The product must not be used in skeletally immature patients.

A series of conventional safety pharmacology studies were conducted in accordance with GLP regulations to examine the potential extraneous pharmacological effects of dibotermin alfa . These experiments showed that dibotermin alfa had no effects on locomotion, the central nervous system, locomotor activity, respiration and cardiovascular systems, gastrointestinal systems, urinary system and blood coagulation at the doses tested. Therefore, it is concluded that the potential of dibotermin alfa exerting extraneous pharmacological effects - if there were to be inadvertent systemic exposure, is minimal.

Pharmacokinetics

- *Pharmacokinetics after a single dose/repeated administration*

The pharmacokinetic data are limited. Pharmacokinetic single dose IV studies were perfomed in rats and monkeys and showed minimal systemic exposure of dibotermin alfa . However, only plasma levels (C_{Max}) are available of these studies. AUC data were not present in the dossier. A single dose IV injection in rats (juvenile) of 3mg/kg resulted in a C_{Max} of 21 µg/ml, 5.3 mg/kg in a C_{Max} of 30µg/ml and a dose of 0.86 mg/kg in a C_{Max} of 18µg/ml.

The PK of dibotermin alfa following bolus IV administration was examined also in the rat and in cynomolgus monkeys. The clearance of dibotermin alfa from the circulation is high. Although the uptake of dibotermin alfa by highly perfused tissues and organs is rapid, residence of the protein in these tissues is short. As a result of these pharmacokinetic characteristics, systemic presence of dibotermin alfa in the circulation is minimal after IV dosing. The C_{Max} and AUC values are shown below in the table.

Table Blood C_{max} and AUC of dibotermin alfa After Intravenous Administration in Rats and Monkeys (Mean±SD)

Species	Report No.	Dose (mg/kg)	C_{max}[a] (ng/ml)	AUC (ng•min/ml)
Rat	PB-034-91	0.00043	4.0[b]	4.0
		0.0043	122±16	66.2±21.4
		0.043	892±110	955.6±424.7
		0.86	7811±492	39,091±5331
	PS-010-94	5.3	28,662±2916	172,391±43,339
Monkey	PB-024-92	0.0049	161.09±74.51	136.1±71.8

a: Determined at the first sampling time (0.5 min post doing).
b: n=2

The pharmacokinetic studies in rats show that the clearance of ^{125}I dibotermin alfa from blood was biexponential with mean half-lives of 0.8 and 15.3 minutes (increase with dose). Rapid metabolism of ^{125}I dibotermin alfa was suggested by the increase in trichloroacetic acid (TCA) soluble counts in the blood as early as 5 min after dosing. It is considered to be likely that the early increase in TCA-precipitable radioactivity reflects the rapid metabolism of dibotermin alfa , but it is also bourne in mind that the systemic exposure to dibotermin alfa may be overestimated by measuring TCA-precipitable radioactivity.

The pharmacokinetics of IV bolus dose of dibotermin alfa in the cynomolgus monkey are in line with those obtained in rats.

Following implantation of dibotermin alfa /ACS, ^{125}I-dibotermin alfa was slowly released from the implant site with a mean residence time of approximately 8 days. The peak amount of radiolabeled dibotermin alfa detected in the blood was small; 0.1% of the implanted dose, and consistent with the rapid systemic clearance described above. Studies evaluating retention of dibotermin alfa when implanted SC in rats showed an initial recovery at the site of implantation of 70–75% of the dibotermin alfa , and a mean residence time of 4.6 to 5.6 days. The pharmacokinetic data obtained in the implant studies correlate with a bi-exponential model in which the initial half live is very short

(0.1 to 0.04 days) and the second half life is 3 to 4 days. After 2 weeks 1.2 to 4 % of the implanted radioactivity is still present in the implant. Systemic exposure appears to be low and to decline rapidly. Cmax values were generally less than 10 ng/ml and, hence, reliable AUC values for dibotermin alfa could not be calculated.

Release of dibotermin alfa *in vitro* and *in vivo* from ACS was studied in the rabbit ulna osteotomy model. The results of this study show that the incorporation of dibotermin alfa in ACS, when the sponge is soaked with dibotermin alfa at the concentration intended for clinical use, varies substantially from as low as 54% to virtually complete incorporation. Although the % incorporation in the sponge did not affect the pharmacokinetic behaviour of the dibotermin alfa /ACS device, the possibility of the total dose and the efficacy being affected has been examined since it has been argued that the ACS has the capacity to absorb more fluid than what is administered in the soaking process. The worst possible case scenario has been examined (where up to 70% of the fluid administered would be lost from the ACS) and it is agreed that a loss of this magnitude is unlikely to affect the efficacy of the product.

Different buffers have been used in the dibotermin alfa formulations during development of the product. The pharmacokinetic parameters following intravenous administration of dibotermin alfa in Arg/His or MFR 00842 are similar after adjusting for the doses administered in each study. The original formulation of dibotermin alfa used with ACS was MFR 00842. Very minor modifications to the MFR 00842 buffer were made to minimize the potential for precipitation of the protein in the presence of ACS. These modifications have had no impact on the efficacy of the dibotermin alfa /ACS product.

- *Distribution in normal and pregnant animals used in reproduction studies*

The distribution of rhBMP-s is restricted to the blood volume in monkeys and to the extracellular volume in rats. dibotermin alfa is transiently observed in the liver kidney and spleen in rats. Preclinical studies evaluating the PK of dibotermin alfa during pregnancy, placental transfer and milk excretions have not been performed.

- *Biotransformation & Excretion*

Dibotermin alfa is an endogenous protein that is rapidly degraded in the liver and excreted via the kidneys. The renal excretion was found to consist mainly of trichloroacetic acid (TCA)-soluble radioactivity, reflecting dibotermin alfa metabolism.

Toxicology

The toxicity studies that were performed conform to GLP.

Dose extrapolation

Dose extrapolation is complex for this product, it has been difficult to identify an effective dose. Species variances for this local implant application are unknown, which makes dose extrapolation complex. Based on the highest single IV dose (5.3 mg/kg), the C_{Max} values in the toxicity studies are a multiple (10 to 10^3) of the anticipated human C_{Max} (2.3 µg/ml- 2.3 ng/ml). In rats the highest IV dose used in the repeated toxicity studies was 0.16 mg/kg.

- *Single dose toxicity*

In Sprague-Dawley rats the intravenous no-toxic-effect level was 0.533 mg/kg, the highest dose tested. A second single-dose intravenous toxicity study of dibotermin alfa using doses up to 5.33 mg/kg in Sprague-Dawley rats showed no toxicity. Single-dose i.v. administration in beagle dogs resulted in a no-toxic-effect dose of 5.33 mg/kg, the highest dose tested.

- *Repeated dose toxicity*

In rats and dogs receiving i.v. injections of dibotermin alfa for 28 days, there were no treatment-related haematology, clinical chemistry, urinalysis, or organ weight findings. In rats discoloration was noted at the injection site of some rats. Treatment and dose-related histopathology findings at the injection site included soft tissue thickening and cartilage and bone formation. In dogs histologically, dose-related perivascular fibroplasia was observed at the injection site in all dibotermin alfa -treated

groups. Slight-to-severe osseous metaplasia of the fibrous tissue surrounding the injection site was observed in some dogs from the mid- and high-dose groups after 28 days and in all of the high-dose dogs after the 28-day recovery period. All injection-site-related changes were a result of the expected pharmacologic activity of dibotermin alfa and were not considered toxicologically significant. The no-toxic-effect level was 0.16 mg/kg/day in rats and dogs, the highest dose tested. No remote site effects on bony tissues were observed macroscopically or microscopically.

The safety of implanted dibotermin alfa /ACS was evaluated in a mandibular/maxillofacial inlay study in beagle dogs and a femoral onlay study in Sprague-Dawley rats.

In both studies there were no treatment-related adverse systemic effects and dose-related increases in the incidence of post-surgical swelling was observed. In dogs, histologic examinations of the implant sites demonstrated dose-related fibrocellular tissue and/or new bone formation within and around the implant sites in the dibotermin alfa -treated groups. There were also fluid-filled tissue cysts and occasional strands of residual ACS material at some implant sites with apparent regression/remodeling, but not complete resolution of these changes between 3 and 6 months. The implant site tissue responses were the expected pharmacologic response to dibotermin alfa /ACS and were not toxicologically adverse. There was no systemic toxicity at any dose level, and the no-toxic-effect dose was 0.78 mg/kg.

In rats hard, raised areas or masses at the implant sites of dibotermin alfa -treated animals were observed in a dose related fashion. Microscopically, the implant sites were characterized by dose-related periosteal new bone formation with occasional fibrocellular tissue proliferation within the center of the newly formed bone. The presence and persistence of slight to moderate new bone formation along the lateral aspect of the femur resulted in remodeling over time with cancellation (increased porosity) of the pre-existing cortex and integration of the new bone into the cortex. These changes were considered to result from normal remodeling due to altered biomechanical forces on the cortex as a result of the new bone formation.

The administration of dibotermin alfa /ACS as a femoral orthotopic implant in the rat at doses up to 1.6 mg/kg did not result in toxicity during the 12-month duration of this study. There was an expected pharmacologic response of dose-related increased incidence and/or severity of post-surgical soft tissue swelling, which was associated with the expected bone formation at the implant site. The no-toxic-effect dose observed was 1.6 mg/kg (4.0 mg/ml).

Antibodies to rh-BMP-2 were only detected in the dog implant study.

- *Reproduction studies*

In all the studies animals received the dibotermin alfa via intravenous injection. In fertility and early embryonic development studies dibotermin alfa treatment at dosages up to 0.16 mg/kg/day had no effect on reproduction and fertility in male and female rats.

Embryo-fetal development studies in gravid rabbits treated with dibotermin alfa did not result in systemic maternal toxicity, embryo lethality or gross fetal abnormalities at dosages up to 1.6 mg/kg/day. Measurement of dibotermin alfa transfer across the placenta at doses comparable to those used clinically cannot be performed because the ELISA (sensitivity limit of 0.9 ng/ml in rat serum) will not detect the dibotermin alfa in the serum of the dam or the fetus.

Treatment of rats with high intravenous doses of rhBMP (1.6 or 0.5 mg/kg/day) during organogenesis resulted in increased foetal weight in 2/3 experiments. Additionally, some skeletal variations were observed indicating a more advanced foetal development. These differences were attributed to the variance in time to cesarean section. An effect of BMP-2 can not be ruled out. The product should therefore not be used in pregnant women and is contraindicated as such in the SPC.

The route, level and frequency of exposure of the effects can be considered to be of limited relevance for the clinical situation.

- *Mutagenic potential*

The mutagenic potential was not investigated. This is acceptable according to the (ICH) guidance on Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals.

- *Oncogenic/carcinogenic potential*

In vitro studies to assess the potential effects of dibotermin alfa on tumor cell growth using various tumor cell lines and primary tumor isolates have shown minimal evidence of growth potentiation, including studies of osteosarcoma cell lines.

Additionally, the literature review of the role of BMP-2 on growth regulation and tumor biology provided indicates that BMP-2 and its role in growth regulation and tumor biology does not warrant cause for concern about the carcinogenic potential of dibotermin alfa /ACS in relation to its surgical application. The product is intended for single local use and there is almost no systemic exposure; the local exposure is transient.
A panel of human tumor cell lines were assayed for their ability to respond to dibotermin alfa. The tumor cell types were chosen for their relationship to bone (osteosarcomas) and by the increased incidence of certain tumor types to metastasize to bone (prostate, breast, lung). dibotermin alfa had no statistically significant effect on thymidine uptake in the presence or absence of serum in TE-85, SaOS-2 or U-2 OS osteosarcoma cell lines**.** MG-63 osteosarcoma cells were slightly inhibited (not significantly).

The applicant proposes that further studies be carried out to investigate the effects of dibotermin alfa on tumor cell growth. BMP-2 receptor expression will be assessed. Post-authorisation studies have been proposed and the tumor types/cell lines outlined by the applicant are considered to be sufficient.

dibotermin alfa did not change basal alkaline phosphatase activity in MG-63, U2 OS or TE-85 cells, but slight to moderate increases were observed in the SaOS-2 cells. This suggests inhibition of proliferation and increased differentiation of this osteosarcoma cell line. However the changes in alkaline phosphatase are also quite modest relative to the response to dibotermin alfa in other cell lines and it has been concluded that dibotermin alfa has minimal effects on SaOS-2 cells. A more careful evaluation of the effects of dibotermin alfa on tumor cell growth is warranted, and a series of in vitro and in vivo experiments are underway as mentioned above.

Standard in vivo carcinogenicity testing has not been carried out with dibotermin alfa /ACS. Considering the product profile, the arguments against requiring standard carcinogenicity testing are:

- The product is intended for single dose administration and biologically active dibotermin alfa is expected to be present locally for a limited period of time. dibotermin alfa released into blood circulation is rapidly eliminated in all studied animal species.
- The availability of a relevant animal model is questionable.
- Considering experience with other products containing recombinant bone morphogenetic factor and collagen matrix, the finding that no neoplasia was induced by dibotermin alfa /ACS in the long-term observation studies is reassuring.

- *Local tolerance*

Due to the nature of the product, local tolerance assessment was part of the general toxicity studies. In the 6-month toxicity study of dibotermin alfa /ACS in dogs using the mandibular/maxillofacial inlay model, gum lesions adjacent to implant were observed. The histologic findings observed in the gingival (gum) lesions adjacent to the implant site did not correlate with the induction of detectable anti-dibotermin alfa antibodies. Furthermore, soft tissue cyst formation was noted in the same study. Two types of cystic lesions were observed: reversible soft tissue cysts and less readily reversible bony cysts. The development of these lesions is likely to be a reflection of the pharmacodynamic activity of the product. Histological analysis and immunohistochemistry did not suggest that the lesions were inflammatory or of vascular (endothelial) origin.

- *Immunogenicity*

The immunogenicity of dibotermin alfa and bovine collagen was not assessed in most of the preclinical studies nor were the antibodies detected evaluated for neutralising activity. This is not ideal

because the potential impact of immune responses either on the presence or absence of toxicological findings or variability in efficacy in the animal models cannot be assessed. Immunogenicity in the rat cannot be excluded due to very sparse sampling. Dibotermin alfa was clearly immunogenic in dogs and rhesus monkeys. Anti-dibotermin alfa antibody responses were more frequent than anti-bovine type I antibody responses. Indeed, the possibility of neutralising antibodies cannot be excluded based on the available preclinical data. However, at least the limited available data do not suggest that antibody response to dibotermin alfa was associated with lack of osteogenic efficacy.

- *Special toxicity studies*

This section contains studies for medical devices. The studies were performed according to International Standard ISO-10993 "Biological Evaluation of Medical Devices Part 1: Evaluation and Testing". They revealed no adverse effects.

- *Ecotoxicity/Environmental risk assessment*

The applicant's evaluation of environmental risk was reviewed. The manufacture and use of the medicinal product is not expected to lead to any adverse environmental consequences.

3. Part IV: Clinical aspects

Appropriate statements regarding GCP compliance have been attached to the clinical study reports.

Clinical pharmacology

Pharmacodynamics

The osteoinductive effect of dibotermin alfa /ACS has been evaluated in three dental-craniofacial studies where the product was used for alveolar ridge preservation/augmentation (study C9514-11) and maxillary sinus floor augmentation (studies C9409/10-11 and C9531-11). Bone formation was assessed by measurement of the change in alveolar ridge height and width and bone density using quantitative computed tomography (QTC) and histology.

Three concentrations of dibotermin alfa /ACS applied to the matrix have been studied in these trials: 0.43, 0.75, and 1.5 mg/ml. Osteoinduction was demonstrated at all 3 concentrations in a majority of patients (80% to 100%). The lowest concentration was found to be suboptimal (C9409/10-11) and the highest was the most effective for bone induction (C9531-11 and C9514-11). A concentration-dependent response was observed between 0.75 and 1.5 mg/ml in 2 dental-craniofacial studies (C9514-11 and C9531-11).

In a study in which a matrix-only control was feasible to use, dibotermin alfa /ACS was more effective than the matrix alone; both the matrix alone and no treatment were not significantly osteoinductive (C9514-11). Comparisons made to ACS alone, clearly demonstrate that dibotermin alfa has a more than ancillary role in the product.

Pharmacokinetics

- General:

The applicant has not performed formal pharmacokinetic trials in healthy subjects since such trials were not feasible in view of the nature and intended use of the product.

The applicant has collected a limited set of blood samples in two exploratory clinical trials (C9414-11 and C9109-11). Dibotermin alfa was measured using ELISA method (limit of detection 10 ng/ml). Dibotermin alfa (max. dose 12 mg) implanted in patients with bone fractures, revealed no concrete data with regard to the pharmacokinetics, as only predose and 1 day post-dose samples were analysed. In the 1 day post-dose samples no dibotermin alfa could be detected (detection limit 10 ng/ml and 4 ng/ml).

According to preclinical pharmacokinetic data in rats and monkeys, rapid elimination of dibotermin alfa from blood is expected. However, this cannot be verified in man with the currently available methods.

In preclinical studies, the mean local residence time of dibotermin alfa when implanted with ACS was approximately 5 to 8 days (using radiolabeled dibotermin alfa). Similar studies are not feasible in man.

Altogether, the pharmacokinetic characteristics of dibotermin alfa in man are unknown. However, preclinical data suggest that any dibotermin alfa escaping the implant to circulation would be rapidly eliminated.

The influence of renal function on the pharmacokinetics of dibotermin alfa is not studied. This is agreed, as renal elimination of dibotermin alfa is considered to be a minor pathway for dibotermin alfa clearance.
The influence of hepatic function on the pharmacokinetics of dibotermin alfa is not studied. As it is expected that the metabolic pathway of dibotermin alfa will follow the pathways of other proteins (peptide hydrolysis), an impaired liver function is not expected to affect the pharmacokinetics of dibotermin alfa in a clinically significant way.

In this particular case, considering the nature and intended clinical use of the product, the lack of human pharmacokinetic data is not considered an obstacle for marketing authorisation.

- Interaction studies:

In vitro interaction studies have not been carried out and no specific in vivo clinical drug interaction studies have been performed. It is argued that s dibotermin alfa is a protein, it is: 1) not expected to bind to proteins, 2) expected that metabolic degradation will follow the pathways of other proteins, i.e. peptide hydrolysis, and therefore unlikely to be a candidate for pharmacokinetic drug-drug interactions.

Clinical efficacy

Clinical documentation of the efficacy and safety of dibotermin alfa /ACS consists of one pivotal trial in open tibial shaft fractures requiring surgical management (Study report **C9530-11**) and a dose-finding study in open tibial shaft fractures (**C9612-11**). In addition to these two studies, the applicant has conducted two small-scale pilot studies (C9414-11 and C9320-11) where the emphasis is on safety of the product. Several small-scale studies have evaluated the rationale for methodology, endpoints and choice of patient population for the pivotal trial.

The maximum feasible concentration of dibotermin alfa is noted to be 1.5 mg/ml. Higher concentrations have been found to lead to precipitation when the active substance is added to the collagen sponge. This is important, since the clinical trial results cannot conclude that 1.5 mg/ml is the optimal concentration, although it has shown to be superior to the 0.75 mg/ml concentration.

Dose response study

Study report C9612-11: A dose finding study of dibotermin alfa /ACS in open tibial shaft fractures requiring surgical management and intramedullary (IM) nailing. This was a multicentre (n=10) randomised, single-masked, dose-finding, stratified controlled study. The objectives were to evaluate the safety of dibotermin alfa /ACS, to identify the optimal dibotermin alfa dose that will prevent a delayed union of open tibial shaft fractures, to assess the time to radiographic fracture union, and to evaluate the potential economic benefit of treatment. Patients were randomised to standard surgical treatment or standard treatment plus one of two dibotermin alfa doses (0.75 mg/ml or 1.5 mg/ml) at the time of definitive wound closure. Patients were followed for 12 months after definitive wound closure.
Sixty patients were planned, 59 were assessed for efficacy and 60 were evaluated for safety. There were 19 patients evaluable for efficacy in the control group, 20 in the 0.75 mg/ml group and 20 in the 1.5 mg/ml group.

Based on current knowledge, it appears that the assumptions behind sample size determination for this dose-finding study were unrealistic and the study was underpowered to detect differences between the standard and standard plus dibotermin alfa /ACS treatment groups.

Main study **C9530-11**

1. Description of the study

This is a multinational, multicentre, prospective, single-blind, stratified, randomised, controlled Phase III study of the efficacy and safety of dibotermin alfa /ACS in open tibial shaft fractures requiring surgical management (treatment with intramedullary nailing - IM - nailing).

An appropriate statement regarding GCP compliance has been attached to the final study report.

The primary objectives of the study were to demonstrate that in at least one of the two treatment groups in which dibotermin alfa /ACS (0.75 mg/ml or 1.5 mg/ml) was added to the standard of care (SOC) at the time of Definitive Wound Closure (DWC):

- An increased assurance of fracture healing in patients treated with dibotermin alfa /ACS
- The safety of dibotermin alfa /ACS

The secondary objectives were as follows:

- To demonstrate that the rate of fracture healing at 6 months is higher among patients who receive dibotermin alfa /ACS as compared to SOC
- To demonstrate that the independent radiographic assessment of fracture union is observed earlier among patients who receive dibotermin alfa /ACS as compared to SOC
- To evaluate the potential economic benefit compared to SOC

- The primary efficacy variable was the proportion of patients who require a secondary intervention to promote fracture healing within 12 months of DWC. All surgical procedures performed to promote fracture healing after DWC were considered secondary interventions (such procedures included augmentation bone grafting with autograft or allograft, or bone graft substitutes, IM nail dynamisation, exchange nailing, or exchange to external fixation). In addition, noninvasive treatments (ultrasound, magnetic field or electrical stimulation) were considered secondary interventions. Patients with hardware failure resulting in dynamisation were counted as treatment failures

To check for potential bias in the assessment of fracture union, the investigator's assessment was to be compared with the independent radiographic assessment. A combined clinical and radiographic endpoint (CCRE) analysis was performed, incorporating both the investigator's and the independent radiology panel's assessments. This endpoint combines 2 independent sets of outcomes:

1. Investigator's assessment:
- no secondary intervention recommended and/or performed (success)
- secondary intervention recommended and/or performed (failure)

2. Independent radiographic assessment:
- fracture united (success)
- not united (failure)

The secondary efficacy variables were as follows:

- Clinical - rate of fracture healing at 6 months: The proportion of patients healed without secondary intervention. This variable was based on investigator's clinical and radiological assessment: radiographic fracture union as assessed by investigator, full weight bearing, no tenderness at the fracture site upon palpation.
- Independent radiographic assessment - time to fracture union: Three radiologists blinded to treatment assignment.
- Pharmacoeconomic

Patient treatment assignments were stratified by Gustilo fracture classification at the time of randomisation. Stratum A consisted of Gustilo Grade I, II and IIIA. Stratum B consisted of Gustilo Grade IIIB fractures. This prospective stratification was justified on the basis of study C9402-11 where the rate of secondary interventions was substantially higher in Gustilo IIIB fractures compared

to less severe grades. Only patients with high risk of amputation (Gustilo IIIC) were excluded. Patients were followed up for 12 months after DWC.

IM nails are used more frequently and were the standard treatment for patients in this study. Use of a larger diameter nail requires enlargement of the intramedullary canal (IM reaming). The effect of reaming is uncertain, but benefit in terms of fracture healing has been described. As there is no clear consensus about the use of reaming in open tibial shaft fractures, both reamed and unreamed nail insertion techniques were included in the study.
The total dose of dibotermin alfa was 6 mg or 12 mg. In line with the experience from the pilot studies, the use of dibotermin alfa /ACS in the treatment of open tibial shaft fractures is limited to one unit. The choice of control group (standard of care) is acceptable. Since ACS alone has not been found to possess osteoinductive properties in preclinical experiments, the omission of a "placebo" (ACS matrix plus buffer) is acceptable. Had a "placebo" group been included, the SOC control group would still have been necessary, effectively preventing the conduct of the study under double-blind conditions.

The method of implantation, the amount of ACS used, the location of ACS relative to tibia and bone circumference covered by ACS were well balanced in the 0.75 mg/ml and 1.5 mg/ml dibotermin alfa /ACS treatment groups.

The study evaluations occurred at 7 postoperative time points at 6, 10, 14, 20, 26, 39, and 50 weeks. Treatment was administered within 24 hours of randomisation.

2. Statistical analysis

For the purpose of sample size estimation, a conservative rate of recommendation for secondary interventions (35%) was projected for the SOC group (based on study C9402-11). Under these conditions, a sample of 120 patients per treatment group would give >80% power to detect an 18% difference in the rate of recommendation for secondary interventions using a two-sided Fisher's exact test. The primary analysis was based on the ITT population. A second analysis was performed on the evaluable patient population (patients who underwent the assigned treatment within 14 days of the initial injury, had no major protocol violations, and had a verifiable study outcome).

Two analyses of the CCRE endpoint were performed. In the first analysis, patients with no secondary intervention and united (category 1) and patients with no secondary intervention and not united (category 2) were considered successes. In the second, more conservative analysis, only category 1 patients was considered a success.

3. Study populations/accountability of patients

Altogether 49 investigators from 11 countries participated in the study, and 450 patients were randomised. Of the 450 patients, 150 were randomized to the standard of care (SOC) group, 151 were randomized to the 0.75 mg/ml dibotermin alfa /ACS group, and 149 were randomized to the 1.50 dibotermin alfa /ACS group. A total of 421 of the 450 randomized patients (94%) completed the final study visit. Nineteen of the 29 patients (66%) who did not complete the study were lost to follow-up. Seven patients withdrew at the patient's or investigator's request and 3 patients died during the study. A total of 437 (97%) patients received their randomized treatment: 149 patients in the SOC group, 147 patients in the 0.75 mg/ml dibotermin alfa /ACS group, and 141 patients in the 1.50 dibotermin alfa /ACS group. At the time of randomisation, 85% of the patients were in Stratum A and 15% in Stratum B. The ITT population consisted of 437 patients, and the evaluable population of 404 patients.

Although there was a statistically significant difference among treatment groups for patient age, with younger patients in the 1.50 mg/ml dibotermin alfa /ACS group as compared with the SOC and 0.75 mg/ml dibotermin alfa /ACS groups (P = 0.0243 and P = 0.0202, respectively), the difference was not clinically meaningful. It appears likely that 1) there were very few postmenopausal female patients and 2) there were few elderly patients, male or female (actually only 14 patients were at least 65 years of age). A great majority (>70%) of the patients were Caucasian. There was a slightly higher proportion of patients with smoking history in the dibotermin alfa /ACS groups compared to controls,

but this is unlikely to be of clinical significance. Less than 3% of the patient population had diabetes. Approximately 58% of the population had isolated tibia fractures. Most injuries were caused by a high energy trauma and 61% were motor-vehicle accidents. Most fractures (85%) were classified as Gustilo Grade I, II, or IIIA (stratum A). There were more Gustilo IIIB fractures in the dibotermin alfa /ACS groups, but the difference among groups was not statistically significant. The distribution of fractures by AO classification also was similar among treatment groups. Most fractures in all 3 treatment groups were between the middle and distal third of the tibia and the fracture location was similarly distributed across treatment groups.

4. Efficacy results

Primary efficacy endpoint: Rate of secondary interventions within 12 months after Definitive Wound Closure: The primary efficacy endpoint was evaluated for the ITT and evaluable patient populations. Patients in the SOC group had a higher rate of secondary intervention (46%) than patients in the dibotermin alfa /ACS treatment groups (37% and 26% for the 0.75 and 1.50 mg/ml groups, respectively); the difference among treatment groups reflects a dose-dependent effect and was statistically significant *(P* = 0.0017, chi-square test). Pairwise comparison of the difference between the SOC and 1.50 mg/ml dibotermin alfa /ACS groups was highly significant *(P* = 0.0005, Fisher's exact test). The rate of secondary interventions in the 0.75 mg/ml dibotermin alfa /ACS group was lower than that in the SOC group; however, the difference between groups was not statistically significant *(P* = 0.1162, Fisher's exact test). Patients treated with 1.50 mg/ml dibotermin alfa /ACS had a 44% reduced risk for secondary intervention to promote fracture healing compared with patients in the SOC group (RR = 0.56; 95% CI = 0.40 to 0.78).

Results for the primary efficacy endpoint analysis in the evaluable patient population were similar to those for the ITT population.

The rate of secondary interventions in the standard of care control group is somewhat higher than the expected 35%. Although dose-dependence of clinical effect cannot be deduced from two points, the results do suggest a trend of increasing efficacy towards the higher 1.5 mg/ml concentration. According to the applicant, 1.5 mg/ml is the highest feasible concentration since precipitation has been found to occur above this.

Examination of subgroups for primary endpoint: Demographic and baseline comorbidity: To establish whether demographic characteristics influenced treatment outcomes, the rate of secondary interventions by age, sex, race and smoking history were examined. Within each of these subgroups, the results of the primary efficacy analysis were similar to the entire ITT population.

The nails were inserted using a reaming procedure in 33% of all patients. The percentage of patients with reamed nails was lowest in the SOC group (27%) and highest in the 1.50 mg/ml dibotermin alfa /ACS group (41%); the difference between these 2 groups was statistically significant (*P* = 0.0131). This imbalance appears to be attributable to an imbalance at some centers in patients randomized to the SOC, 0.75 mg/ml dibotermin alfa / ACS, and 1.50 mg/ml dibotermin alfa /ACS groups, which coincided with those centers' preferred use of reamed nails in a majority of their patients, independent of treatment group. More patients randomized to 1.50 mg/ml dibotermin alfa /ACS were entered in centers using primarily reamed nails. In contrast, an evaluation of the distribution by center of SOC patients reveals that more were recruited at centers using unreamed nails. This baseline imbalance seen in the ITT population was not statistically significant for the randomized and evaluable patient populations. In each of the 3 treatment groups, the median IM nail diameter was 9 mm. Over all treatment groups, 88% of the IM nails were statically locked; this proportion was consistent across treatment groups.

Primary efficacy variable: analysis according to nail type (reamed vs unreamed)
As noted previously, the proportion of subjects receiving reamed IM nails was higher in the 1.50 mg/ml dibotermin alfa /ACS group compared to control group (standard of care). According to the pivotal study report, dibotermin alfa /ACS was more effective than SOC only in the subgroup of patients who received an unreamed IM nail. Overall, the results were better in the subgroup of patients

who received reamed nails, but dibotermin alfa /ACS did not provide improvement over SOC in this subgroup.
The applicant confirms in the response that dibotermin alfa /ACS was not better than SOC in the subgroup of patients who received reamed IM nail. The rate of secondary intervention (primary efficacy endpoint) was the same in the SOC and dibotermin alfa groups (24%). Furthermore, although not statistically significant, there was a trend (p=0.08) in the post hoc logistic regression analysis suggesting nail type and dibotermin alfa /ACS treatment interaction with respect to the primary efficacy endpoint. The odds ratio of secondary intervention for delayed union was significantly lower in patients who received reamed IM nails compared to unreamed nails (0.55, 95% CI 0.35-0.86).

Both the protocol defined and post hoc analyses (requested by the CPMP) suggest that the clinical benefit is mainly observed in patients who receive unreamed IM nail. However, it is recognised that the study was not powered for subgroup analyses. Furthermore, although the primary efficacy endpoint analysis does not confirm efficacy in the important subgroup of patients who received reamed IM nails, several secondary efficacy variables (acceleration of fracture healing, reduction in the rate of hardware failure, acceleration of soft tissue healing) are favourable. In conclusion, the data do not suggest that the indication should be limited to tibia fractures treated with unreamed IM nails. The SPC states that the rate of secondary intervention was not reduced by dibotermin alfa /ACS compared to standard of care in patients who received reamed IM nail.

Secondary efficacy endpoint: Clinical - rate of fracture healing at 6 months: Fracture healing status at 6 months (Visit 7) for each patient was determined based on clinical and radiographic assessments performed by the investigator. There was a dose-dependent increase in the rate of fracture healing. The higher rate of fracture healing observed in the 1.50 mg/ml dibotermin alfa /ACS group (58.2%) compared with the other 2 treatment groups (0.75 mg/ml 41.9%, SOC 37.6% healed) was statistically significant *(P* = 0.0013). Pairwise comparisons revealed statistically significant differences between the 1.50 mg/ml dibotermin alfa /ACS group compared with the SOC *(P* = 0.0008) and 0.75 mg/ml dibotermin alfa /ACS groups *(P* = 0.0082). For the purpose of this analysis, patients who were not yet healed at 6 months comprised those who already required a secondary intervention and those who were recommended follow-up care with no intervention.

Combined clinical and radiographic endpoint (CCRE): This secondary endpoint was developed to assess outcomes by taking into consideration both the investigators' and independent radiology panel's assessments. The CCRE analysis was performed in an expanded patient data set comprising the ITT population and the non-ITT patients who were treated. The four different outcome categories analysed are shown in Table 11.4.1.5.2-1.

Two analyses of the CCRE were performed, comparing successes with failures. In the first analysis, patients in the first and second categories (no secondary intervention and united, no secondary intervention and not united) were scored as treatment successes and all other patients as treatment failures. In this analysis, the difference in success rates among treatment groups was statistically significant *(P* = 0.0027, chi-square test). Pairwise comparison of the difference between the 73% success rate for the 1.50 mg/ml dibotermin alfa /ACS group and the 54% success rate for the SOC group was statistically significant *(P* = 0.0009, Fisher's exact test).

In the second, more conservative analysis only patients in the first category (no secondary intervention and united) were scored as treatment successes and all other patients were scored as treatment failures. In this analysis, the difference in success rates among treatment groups also was statistically significant *(P* = 0.0114, chi-square test), as was the pairwise comparison between the 1.50 mg/ml dibotermin alfa /ACS and SOC groups (success rates of 64% and 47%, respectively; *P* = 0.0042, Fisher's exact test).

Table 11.4.1.5.2-1 Combined Clinical and Radiographic Endpoint Summary – ITT Population Plus Non-ITT Patients Who Were Treated

	Number (%) of Patients		
Patients with:	**SOC n = 143[a]**	**0.75 mg/mL rhBMP-2/ACS n = 143[a]**	**1.50 mg/mL rhBMP-2/ACS n = 143[a]**
1) No secondary intervention within 12 months and fracture united within 12 months	67 (46.9)	77 (53.8)	92 (64.3)
2) No secondary intervention within 12 months and fracture not united within 12 months	10 (7.0)	13 (9.1)	13 (9.1)
3) Secondary intervention within 12 months and fracture united at the time of secondary intervention	2[b] (1.4)	0	0
4) Secondary intervention within 12 months and fracture not united at the time of secondary intervention	64 (44.8)	53 (37.1)	38 (26.6)

Source: *Analysis of Combined Clinical and Radiographic Endpoints (*E3.06), Section 14.2.

a In this population analysis, 5 patients in the SOC group, 7 patients in the 0.75 mg/mL rhBMP-2/ACS group, and 3 patients in the 1.50 mg/mL rhBMP-2/ACS groups were missing either a clinical outcome or independent radiology panel assessments are therefore were not included in this analysis.

b Patient 48 was considered united at the visit when a secondary intervention was recommended. Patient 396 was found to have self-dynamized at the same visit when he was determined both united by the independent radiology panel and healed by the investigator.

Internal validity of the study has also been examined to address the issue of presence or absence of bias in the study and the evidence points to consistent results supporting the conclusion that study conduct and primary outcome determination were not biased. The most important findings are as follows:

- A centralised, automated block randomisation procedure was used
- An independent radiology panel, blinded to treatment assignment reviewed the radiographs. High concordance was found between clinical diagnosis and blinded independent radiology review. Patients without recommendations for secondary intervention were consistently considered united by the radiology panel. Similarly, patients with recommendations for secondary intervention were consistently considered not united by the radiology panel at the time the recommendation was made. Atlhough these analyses were secondary, they support the primary efficacy variable analysis.
- The imbalance observed in the rate of outpatient rehabilitation (clearly more frequently prescribed in the 1.50 mg/ml dibotermin alfa /ACS group compared to control group) could be a chance finding. Although the latter cannot be verified, it is important to note that no significant interaction was found between the prescription of outpatient rehabilitation and efficacy of the product with respect to the primary efficacy endpoint (Breslow-Day test) and the overall treatment effect was confirmed in the Cochran-Mantel-Haenszel test identifying patients with and without outpatient rehabilitation.

- The imbalance observed in the distribution of reaming procedure (reamed vs. non-reamed intramedullary nailing) in the treatment groups (more frequent in the dibotermin alfa /ACS 1.50 mg/ml group than in the control group) appears to be the result of the central randomisation system. Centres that enrolled a higher proportion of patients in the 1.50 mg/ml group were also centres that primarily used reamed IM nails. However, within those centres which used predominantly reamed IM nails, there was no noticeable imbalance between the treatment groups, suggesting that the choice of fixation method was not affected by treatment group allocation. Hence, the likelihood of bias caused by knowledge of treatment allocation appears small. The possible impact of this imbalance as a confounding factor on efficacy results is discussed below.
- The fact that the time to recommendation for secondary intervention was similar across treatment group and that there was good concordance between prescription and performance of secondary interventions suggest absence of meaningful bias.
- The treatment effect was dose-dependent and consistent across a number of subgroup analyses, including analysis by geographical region and risk factors (smoking and Gustilo-Andersen type).

Secondary efficacy endpoint: Independent radiographic assessment - time from definitive fracture fixation to fracture union: There were no statistically significant differences between the treatment groups in the time to independent radiographic assessment of fracture union. The median time to fracture union was 275, 271, and 271 days for the SOC, 0.75 mg/ml and 1.5 mg/ml groups.

Secondary efficacy endpoints: Pharmacoeconomic: Initial hospitalisations were evaluated to establish comparability between treatment groups. The incidence and duration was similar across the groups. The proportion of patients with inpatient rehabilitation prescribed after the initial hospitalisation was similar across groups. However, a statistically significant number of patients in 1.5 mg/ml group (37%) had outpatient rehabilitation prescribed as compared with the SOC group (22%). This imbalance appears to be driven by differences in prescribed rehabilitation at specific centres, but could bias the results in favour of dibotermin alfa /ACS.

Rate of secondary and subsequent interventions to promote healing: This measure of health resource consumption was expected to closely relate to the primary efficacy measure. It differs, however, in two respects: it captures only interventions actually performed and considers overall procedures. In the ITT population, there was a dose-dependent trend towards a decrease in the overall number of procedures that was caused by a decrease in the number of most invasive interventions (Table 11.4.1.4.2-1). Some of the procedures required hospitalisation. This resulted in 317 hospital days for patients in the SOC group compared to 185 days in the 1.5 mg/ml group.

Table 11.4.1.4.2-1 Summary of Number of Secondary and Subsequent Interventions to Promote Fracture Healing by Invasiveness–Evaluable Population

	Number (%) of Procedures				
Invasiveness	SOC n = 139	0.75 mg/mL rhBMP-2/ACS n = 130	1.50 mg/mL rhBMP-2/ACS n = 135	Total n = 404	*P* Value[a]
Most invasive[b]	29 (43.3)	26 (38.8)	12 (17.9)	67 (100)	0.0264*
Less invasive[c]	29 (42.6)	21 (30.9)	18 (26.5)	68 (100)	0.3074
Non invasive[d]	0	0	2 (100)	2 (100)	
Total	58 (42.3)	47 (34.3)	32 (23.4)	137 (100)	0.0326*

Source: *Analysis of Number of Procedures as Secondary and Subsequent Interventions for Delayed Union or Non-Union – Evaluable (B1.15b)*, Section 14.2

a *P* value from chi-square test for goodness of fit.

b Most invasive includes bone graft, exchange nailing, plate fixation, fibula osteotomy, and bone transport.

c Less invasive includes dynamization of IM nail and exchange from internal fixation to functional brace.

d Non invasive includes ultrasound, electrical stimulation, and magnetic field stimulation.

*Statistically significant difference among groups.

These data are important in showing that 1) the rate of both invasive and less invasive procedures was lower in the dibotermin alfa /ACS groups compared to SOC, although the difference was not statistically significant with regard to less invasive procedures, and 2) the division of interventions into invasive and less invasive within the threatment groups is similar.

Secondary endpoint: Time from definitive fracture fixation to fracture healing: There were statistically significant, and clinically meaningful, differences between treatment groups in the time to fracture healing, with earlier healing in the 1.50 mg/ml dibotermin alfa /ACS group compared with the SOC group *(P* = 0.0022 [Wilcoxon]; *P* = 0.0595 [log rank]) and 0.75 mg/ml dibotermin alfa /ACS group *(P* = 0.0127 [Wilcoxon]; *P* = 0.0407 [log rank]). A 50% probability of fracture healing was observed at 184, 187, and 145 days in SOC, 0.75 mg/ml dibotermin alfa /ACS, and 1.50 mg/ml dibotermin alfa /ACS groups, respectively. However, the median time to clinical decision of healing was 138 days in the 1.5 mg/ml group, 157 days in the 0.75 mg/ml group, and 155 days in the SOC group. Here the clinical relevance of the difference is less obvious.

It is agreed that there is medical need to improve treatment results in long bone fractures requiring open surgical reduction and IM nail fixation and also that tibia fractures are the most demanding model for new treatments. However, tibia fractures tend to heal more slowly and delayed union or non-union are more frequent in fractures of the tibia compared to other long bone fracture. Therefore, the question is left open whether use of this medicinal product would offer any clinically relevant advantage over standard of care in fractures which heal more rapidly. The claim for a broader indication would have to be substantiated with data. The indication is therefore restricted to the following:
"InductOs is indicated in the treatment of acute tibia fractures in adults, as an adjunct to standard care using open fracture reduction and IM nail fixation."

Clinical studies in special populations
There is very limited experience with the use of dibotermin alfa /ACS in children and elderly patients. Sections 4.2 (Posology) and 4.3 (Contraindications; for children) of the SPC have been revised to reflect this.

Experience with the use of dibotermin alfa /ACS in diabetic patients is limited. Results up to now do not indicate an increased risk for retinopathy in diabetic patients.

The use of dibotermin alfa /ACS in patients with osteoporosis or age-related osteopenia should be safe because dibotermin alfa /ACS, when applied to long-bone diaphyseal fractures, does not increase the risk of bone resorption. However a statement in the warning section of the SPC that the product should

not be used for direct applications to trabecular when bone resorption may create a risk of bone fragility has been added.

Subgroup analyses and exploratory analysis performed across trials

Fracture and wound characteristics: Subgroup analyses of the primary endpoint were also done by Gustilo strata and AO classification, and the presence of gap following fracture reduction. In the analysis of patients in stratum A (Gustilo I-IIIA), the rate of secondary intervention was statistically significantly lower in the 1.50 mg/ml dibotermin alfa /ACS group (23%) compared with the SOC (41%) and 0.75 mg/ml dibotermin alfa /ACS (35%) groups *(P* = 0.0026 and 0.0438, respectively; Fisher's exact test). For patients with more severe fractures (stratum B; Gustilo IIIB), the rates of secondary intervention were also statistically significantly lower in the 1.50 mg/ml dibotermin alfa /ACS group (42%) and the 0.75 mg/ml dibotermin alfa /ACS group (45%) compared with the SOC group (88%) *(P* = 0.0074 and *P* = 0.0157, respectively; Fisher's exact test). AO classification did not appear to be a strong predictor of outcome. The failure rate in SOC patients with type A, B or C fractures did not show a progression from less to more severe. Overall, the presence of a post fracture reduction gap was associated with an increased risk of secondary intervention. In the SOC group, patients who were left after fracture reduction with a gap >2mm had twice as many secondary interventions to promote fracture healing as compared with SOC patients with no gap *(P* = 0.0129). However, dibotermin alfa /ACS appears to affect healing and decrease the rate of secondary interventions irrespective of the presence of a post reduction gap.

The results of primary efficacy variable analysis according to nail type (reamed, nonreamed) has already been discussed above.

Time from definitive fracture fixation to clinical decision of secondary intervention was similar in the three treatment groups (105 to 107 days). This is suggested to show that no bias was introduced in assessment of patient status and recommending secondary interventions.

The number of secondary interventions that were recommended but not performed was low and similarly distributed among the groups. There were no patients with a clinical outcome of secondary intervention who met the criteria of a healed patient at the time of the decision.

An analysis of investigator treatment interaction has been subsequently presented and. the results do not suggest that the treatment effect was different across countries/centres.

A total of 11 patients had diabetes, 10 of these had a clinical outcome. The rate of outcomes was 75% in the SOC group and 50% in the 1.5 mg/ml group.

The rate of secondary interventions has been analysed according to NSAID and corticosteroid use. Only 16 patients used corticosteroids and the results do not allow a clear conclusion (20-33% rate of secondary interventions, no dose-related trend). Altogether 151 patients used NSAIDs. The rate of secondary interventions in these patients decreased with increasing dibotermin alfa /ACS dose: 60% (SOC), 45% (0.75 mg/ml), and 39% (1.5 mg/ml). The relatively high rate of secondary interventions in patients who used NSAIDs regardless of treatment group is noteworthy. NSAIDs may impair fracture healing.

Clinical safety

The safety of dibotermin alfa /ACS has been evaluated in altogether 13 studies. For the Integrated Summary of Safety (ISS), two separate data sets were generated. The first includes the orthopaedic trauma studies (long-bone fracture data set). The second includes all GI sponsored studies (all-studies data set). The five studies included in the long-bone data set are C9320-11, C9414-11, C9530-11 (pivotal phase III trial), C9612-11, and C9828-11, all evaluating the safety of the medicinal product in patients with open tibial shaft fractures.

Patient exposure

The long-bone fracture data set comprises 588 patients. A total of 202 patients were treated with standard of care (SOC), 12 with 0.43 mg/ml dibotermin alfa /ACS, 172 with 0.75 mg/ml and 202 with 1.50 mg/ml.

The all-studies data set comprises 1000 patients, and includes 348 patients who received 1.50 mg/ml dibotermin alfa /ACS, 239 patients treated with 0.75 mg/ml, and 48 patients treated with 0.43 mg/ml. The proposed dibotermin alfa /ACS concentration for clinical use is 1.50 mg/ml.

Long-bone fracture data set

No patients were withdrawn from studies due to dibotermin alfa /ACS complications. The average follow-up was 45 weeks. The patients were predominantly under 65 years of age (97%), male (81%) and Caucasian (67%).

The most frequently reported adverse events (reported by at least 10%) are representative of the morbidity observed in the trauma setting (pain, oedema, anaemia) (Table 4.3.1-1). The frequency of these AEs was similar across treatment groups with the exception of pain (more frequent in the SOC group compared to dibotermin alfa /ACS groups).

Table 4.3.1-1 Adverse Events Reported in ≥10% of Long-Bone Fracture Patients

	Number (%) of Patients			
COSTART Term	SOC (n=202)	All rhBMP-2/ACS Patients (n=386)	Total (n=588)	p-Value[a]
Pain	153 (76)	243 (63)	396 (67)	0.0016*
Edema	99 (49)	168 (44)	267 (45)	0.2224
Anemia	93 (46)	167 (43)	260 (44)	0.5412
Hyperglycemia	71 (35)	147 (38)	218 (37)	0.5294
Bone disorder[b]	72 (36)	118 (31)	190 (32)	0.2278
Hypocalcemia	58 (29)	129 (33)	187 (32)	0.2639
Fever	56 (28)	117 (30)	173 (29)	0.5677
Infection	67 (33)	102 (26)	169 (29)	0.1027
Healing abnormal[c]	50 (25)	113 (29)	163 (28)	0.2859
SGOT increased	47 (23)	95 (25)	142 (24)	0.7613
Arthralgia	35 (17)	85 (22)	120 (20)	0.1969
Insomnia	47 (23)	70 (18)	117 (20)	0.1574
Hypophosphatemia	34 (17)	66 (17)	100 (17)	1.000
Lactic dehydrogenase increased	34 (17)	65 (17)	99 (17)	1.000
Constipation	27 (13)	71 (18)	98 (17)	0.1308
Hardware failure[d]	38 (19)	50 (13)	88 (15)	0.0678
Nausea	26 (13)	53 (14)	79 (13)	0.8005
SGPT increased	27 (13)	48 (12)	75 (13)	0.7949
Hypesthesia	18 (9)	51 (13)	69 (12)	0.1387
Rash[e]	23 (11)	36 (9)	59 (10)	0.4705

a p-values are based on two-sided Fisher's exact test ($p<0.05$).
b Delayed union, nonunion or pseudarthrosis; hypertrophic callus and/or heterotopic ossification; other bone disorders.
c Events related to the healing of injured soft tissues, other than infections.
d Inadvertent, spontaneous events of either nail breakage or locking screw breakage or bending.
e Primarily erythema of superficial tissue.
*=Marks statistically significant difference

Adverse events reported in <10%, but more than 10 patients (>1.7%) also were consistent with the morbidity associated with trauma setting. The frequency of AEs in this category was similar across groups with two exceptions: tachycardia and increased serum amylase occurred more frequently in the dibotermin alfa /ACS compared to controls. A total of 4, 11, and 11 patients in the SOC, 0.75 mg/ml, and 1.50 mg/ml groups, respectively, reported tachycardia (overall in 2% of patients in the SOC group and 6% in the combined dibotermin alfa /ACS groups). The events were graded mild to moderate and resolved without sequelae. The tachycardia was correlated to concurrent anaemia and/or fever

secondary to trauma. Patients who experienced increased amylasaemia did not show overt signs of pancreatitis. A total of 6, 21, and 10 patients in the SOC, 0.75 mg/ml, and 1.50 mg/ml groups, respectively, experienced increased amylasaemia. Two additional patients (1 in the SOC and 1 in 0.75 mg/ml group) were identified in the all-studies data set. This finding has been attributed to the trauma setting. The overall frequency of increased amylasaemia was 3% in the SOC group and 8% in the combined dibotermin alfa /ACS groups. No dose- response effect was observed. This issue, as well as cases of pancreatitis, will remain under close surveillance.

The updated data with regard to cardiovascular reactions, including tachycardia, do not suggest that these reactions are related to the use of dibotermin alfa /ACS.

Twenty-eight Grade 4 (life-threatening) adverse events were reported. The most frequent Grade 4 AE was anaemia.

The frequency of serious AEs was similar in the SOC (42%) and dibotermin alfa /ACS groups (38%). Five deaths were reported in this data set, one patient randomised to SOC and 4 patients randomised to dibotermin alfa /ACS. All cases were considered unrelated to administration of dibotermin alfa /ACS.

Six patients underwent amputation of the limb under study. Three of these patients received dibotermin alfa /ACS before amputation. Five of the cases were considered unrelated to treatment. In one case, the relationship to dibotermin alfa /ACS was reported as unknown.

Overall, the patients treated with dibotermin alfa /ACS had fewer instances of hardware failure when compared to SOC, and fewer patients experienced delayed union or nonunion. Hypertrophic callus or soft tissue calcification was reported in 3% of patients. The ISS data set does not suggest an increased risk of hypertrophic callus or soft tissue calcification compared to SOC.

In contrast, the pivotal efficacy and safety study showed, quite expectedly, that hypertrophic callus or local heterotopic ossification was more frequent following dibotermin alfa /ACS implantation. The frequency in the SOC group was 2.7% and in the 1.50 mg/ml group it was 5.5%. Furthermore, it should be noted that patients with a history of heterotopic ossification were excluded from clinical studies.

Twenty-five percent of patients evaluated in this data set for the region under study developed infections. Of these, 20% required administration of antibiotics and 8% required surgery. There was no difference in the frequency of infection across treatment groups.

Soft tissue healing complications (e.g. delayed wound healing, discharge, erythema, necrosis, inflammation) were equally distributed in the SOC and dibotermin alfa /ACS treatment groups.

In the long bone fracture studies dataset, the frequency of soft tissue healing complications (e.g. delayed healing, discharge, erythema, necrosis, inflammation) were equally distributed in the treatment groups. The higher incidence of ”healing abnormal”, wound draining and oozing in one of the studies is a cause of some concern. However, this could be related to pharmacological activity of dibotermin alfa with resulting oedema and extravasation of fluid.

Compartment syndrome was not reported, but one patient treated with dibotermin alfa /ACS underwent fasciotomy after definitive wound closure.

The updated integrated summary of safety shows that the frequency of hypesthesia is not significantly higher in dibotermin alfa /ACS treated patients compared to controls. However, the frequency remains slightly higher (10.7% vs. 7.1%). The severity of trauma (and differences in the severity between treatment groups) and resulting oedema/compression is thought to be the most likely explanation. No clear association was found between hypesthesia and inflammation, heterotopic ossification or antibody response.

All-studies data set

The average follow-up was 54 weeks. The majority of patients were under 65 years of age (94%), male (69%) and Caucasian (72%).

The most frequently reported AEs (at least 10% of patients) were pain, oedema, anaemia, and hyperglycaemia. With the exception of pain, oedema, and rash (erythema) which were observed more frequently in SOC patients, the frequency of AEs was similar across treatment groups.

The incidence of tachycardia and increased amylasaemia was not significantly different across treatment groups in this larger data set. The increased amylasaemia is thought to reflect the patients' trauma status. The high incidence of hyperglycemia is largely a result of postoperative fluid replacement.

With regard to AEs reported in <10% of patients, but in more than 10 patients (>1%), headache was reported by a statistically significant higher percentage of patients treated with dibotermin alfa /ACS when compared to SOC. By treatment group, 7% of SOC patients, 12% of 0.75 mg/ml patients and 10% of 1.50 mg/ml dibotermin alfa /ACS treated patients reported headache.

All deaths and Grade 4 AEs were reported in the long-bone fracture data set. Serious adverse events were evenly distributed cross treatment groups.

Malignancies

An updated review of all reported cases of cancer or other malignancies in all patients enrolled in dibotermin alfa /ACS studies sponsored by Genetics Institute up to 15 September 2001.
This evaluation includes 1250 patients, with a cumulative follow-up of 1744 years. A total of 517 patients were enrolled in control groups, 28 received only the ACS matrix, and 705 patients were enrolled in dibotermin alfa treatment groups.

Of the 517 patients enrolled in control groups, 6 patients (1%) reported 6 cases of malignancy. Of 705 patients enrolled in dibotermin alfa -treatment groups, 7 patients (1%) reported 9 cases of malignancy. No case was reported in any of the 28 patients who received the ACS alone. Of the 9 cases reported by dibotermin alfa -treated patients, 3 occurred either before treatment or at short intervals after exposure to dibotermin alfa (<52 weeks). This makes drug-related carcinogenicity unlikely. No reports of malignancy have been received for patients in the pivotal study, C9530-11.

Thirteen (13) of 15 cases reported were found in patients enrolled in dental craniofacial or in orthopedic nontrauma studies. This observation is consistent with the older patient population enrolled in these studies and the longer follow-up required by these studies. There are various types of malignancies reported, which are generally representative of those observed in this older patient population: 6 skin cancers (including 1 melanoma), 4 breast cancers, 2 prostate cancers, 1 cancer of abdominal lining cells, 1 multiple myeloma, and 1 brain tumor. None of the cancers appeared at the site of product implantation, and there is no indication that their development was unusual. The low number of cases observed does not allow for an accurate calculation of the incidence index for any one of them.

Data on the occurrence of malignancies seem to be reassuring, with no indication of an increased risk of cancer in patients exposed to dibotermin alfa /ACS. However, total follow-up is still relatively short for most patients. Therefore postmarketing periodic safety updates will specially address this issue of the occurrence malignancies.

Due to the pharmacodynamic properties of dibotermin alfa , use of the product must be contraindicated in the vicinity of any tumor or metastasis. The limited data available so far (including tumor incidence in control and dibotermin alfa /ACS groups and tumor types) does not suggest an increased incidence relative to general population. However, the available database is too small to be conclusive. The concerns with regard to oncogenic potential of dibotermin alfa have been outlined in the preclinical assessment report.

Quality of bone

Bone biopsies were obtained systematically only in patients enrolled in the oral surgery studies, and occasionally in a subset of patients treated for long-bone fractures. These samples indicated that osteoinduction was observed without signs of excessive inflammation or excepssive or abnormal bone formation. No residual ACS was found 16 weeks following implantation. Unfortunately, in the pivotal efficacy and safety trial, only a limited number of bone biopsies were performed and only at the time of secondary intervention. Therefore, it is not unexpected that the findings were consistent with fibrous nonunion.

The "radiolucent voids" that were reported in dental-craniofacial studies were actually hypodense areas of nonmineralized bone rather than radiolucent voids. The findings of hypodense areas were reported as "radiolucent void" in the clinical studies because the reporting form did not include other options such as "hypodense area." Furthermore this radiographic finding is quite different from the radiographic findings observed in the preclinical program where, unlike in the human radiograph, a distinct shell of bone is present at the dibotermin alfa /ACS implantation site.

The occurrence of adjacent bone resorption (trabecular or cortical) clearly appears to exceed the expected resorption taking place during remodelling. This finding has been observed in both preclinical and clinical trials (c.f. C9524-11) and has been reflected in the SPC: it has been mentioned that dibotermin alfa /ACS should not be used in the treatment of metaphyseal fractures and should not be used to facilitate attachment of endoprosthetic devices.

Safety in special populations

Safety of dibotermin alfa /ACS was also analysed in subsets of the population (age, gender, and race). No conclusion could be drawn for patients over 65 years of age due to low numbers. In addition, no conclusion could be drawn when examining the data by gender since women were more numerous in the oral surgery studies and males were more numerous in the long-bone fracture studies. The Black population was found to have no increased risks. Administration of dibotermin alfa /ACS in pregnant or nursing women and in children has not been systematically studied. Three patients in the clinical trials became pregnant 10-582 days after administration of dibotermin alfa /ACS. In one case the pregnancy was diagnosed 10 days after administration. The patient delivered a full-term healthy baby. One of the patients had an elective abortion and the third had 2 uncomplicated pregnancies carried to term.

The very limited experience in elderly patients has been stated in the SPC. The use of the medicinal product has been contraindicated during pregnancy.

Interactions

The concomitant use of glucocorticoids or non-steroidal anti-inflammatory drugs (NSAIDs) was not found to increase overall safety risks. However, patients taking NSAIDs for more than 14 days and who received dibotermin alfa /ACS concomitantly, experienced an increased frequency of mild to moderate healing abnormal AEs when compared with patients receiving dibotermin alfa /ACS without concomitant NSAIDs.

NSAIDs may impair normal healing process. An interaction between NSAIDs and dibotermin alfa /ACS leading to impaired efficacy/safety of the medicinal product cannot be excluded. The above data are consistent with the efficacy results of the pivotal long-bone fracture trial. In the pivotal trial, a relatively high rate of secondary interventions (to promote fracture healing) in patients who used NSAIDs is noted regardless of the treatment group.

Immunogenicity

In all studies combined, 3% of patients had an immune response to dibotermin alfa . Almost all patients presenting with an immune response were exposed to dibotermin alfa /ACS. Twenty-three of 582 (4%) patients who received dibotermin alfa /ACS developed antibodies to dibotermin alfa compared with 2/296 (0.7%) patients in the SOC group. This difference was significant (p=0.0045). The incidence in the group receiving 1.50 mg/ml dibotermin alfa was 6%.

In the pivotal phase III trial, a dose-dependent immune response to dibotermin alfa was observed. The number of patients who developed antibodies against dibotermin alfa in the SOC, 0.75 mg/ml dibotermin alfa /ACS, and 1.50 mg/ml dibotermin alfa /ACS groups, respectively, were 1 (1%), 3 (2%), and 9 (6%). The immune response was characterized by low titers mostly present 6 weeks after definitive fracture fixation and of a transient nature (titers were negative in 10/10 patients with samples available for follow-up). However, based on the small data set, there appears to be no relationship between antibody responses and secondary interventions (efficacy) or incidence of specific adverse events. However, a larger database would be needed to rule out an impact.

Anti-bovine Type I collagen antibody responses: For all protocols combined, 14% of patients had antibody responses to bovine Type I collagen. Increased levels of circulating antibodies were observed in 11% of patients in the SOC group, 7% of the patients treated with buffer/ACS alone, and 15% of all patients in the BMP-2/ACS group. The difference in the incidence of anti-bovine Type I collagen antibodies in patients receiving dibotermin alfa /ACS compared with SOC approached significance ($p=0.0610$). To evaluate this trend, 2 analyses were performed: 1) comparing the incidence of anti-bovine Type I collagen antibodies in SOC and dibotermin alfa /ACS-treated patients in the long-bone and other orthopaedic studies and 2) comparing the incidence of anti-bovine Type I collagen antibodies in SOC and dibotermin alfa /ACS-treated patients in the oral surgery studies. The difference between SOC and dibotermin alfa /ACS-treated patients in the long-bone and other orthopaedic studies was significant ($p=0.0010$), the result of this analysis for the oral surgery studies was not ($p=0.5132$).

A review of the immune response to dibotermin alfa and to bovine Type I collagen in a subset of patients enrolled in 6 dental craniofacial studies was also carried out. A separate evaluation of this dental craniofacial subgroup of patients was thought to be relevant because they were enrolled in studies designed to have a longer follow-up (up to 5 years). There was no time-dependent emergence of manifestations associated with the presence of autobodies to dibotermin alfa /ACS or to bovine Type I collagen.

It is not clear why patients in the SOC group developed antibodies to bovine collagen. A review of the medical history for these patients indicated they were not exposed to other medical products containing bovine collagen. Overall, patients receiving 1.50 mg/ml dibotermin alfa /ACS experienced a 19% incidence of anti-bovine Type I collagen antibodies.

No association between the presence of circulating anti-bovine type I collagen antibodies and clinical symptoms of an immune/allergy response was noted. Since the bovine type I collagen in the product is clearly immunogenic, the occurrence of hypersensitivity reactions cannot be ruled out.

All of the patients with positive titers to bovine type I collagen were tested for the presence of an immune response to human type I collagen. Cross-reacting antibodies were not found.

Thus far there is no evidence of an association of antibody response to dibotermin alfa and loss of efficacy or undesirable effects. However, the current database is too limited to be conclusive. The applicant will continue to address this issue in ongoing studies and post-marketing surveillance. The immunogenicity of the product is reflected in the SPC.

Based on the current database, both the local safety of the product, in terms of adverse events affecting the anatomical region of interest, and general safety appears favourable. The fact that an increased incidence of inflammation, infections and wound/soft tissue healing abnormalities was not reported compared to control group in the target population is reassuring. No deleterious effect on wound healing was observed, but actually a potentially favourable outcome in the high dose group despite. The favourable wound healing profile altogether is also a reflection of the patient population selected for the pivotal trial (e.g. the number of diabetic patients was small). Furthermore, hardware failures were clearly less frequent in the dibotermin alfa /ACS 1.5 mg/ml group compared to SOC group.

4. Overall conclusions and benefit/risk assessment

Quality

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Viral Safety and Batch to batch consistency has been documented and the relevant test will be performed according to the agreed specifications. Appropriate post-approval commitments related to the ACS matrix and the stability testing of the vialed protein have been agreed.

Preclinical pharmacology and toxicology

Locally administered dibotermin alfa /ACS results in the induction of new bone at the site of implantation. Pharmacodynamic studies in rats, dogs, rabbits, sheep, goats and nonhuman primates were conducted to show the safe and efficacious use of dibotermin alfa /ACS. The submitted *in vitro* data describe several bone forming related effects of dibotermin alfa . From the *in vivo* studies it can be concluded that depending on the dose of dibotermin alfa used, new formed bone by dibotermin alfa /ACS was as strong as native bone. A clear dose-dependent effect, however, was not always observed. Furthermore, in long-bone critical-sized defect studies, especially in nonhuman primates, the bone formation effect of dibotermin alfa /ACS was variable and not always reproducible.

Dibotermin alfa is an endogenous protein which distribution is restricted to the blood volume/extracellular volume and dibotermin alfa is rapidly degraded in the liver and excreted via the kidneys. After implantation 0.1 % of the implanted dose is released systemically. The half life of dibotermin alfa is approximately 15 minutes.

The toxicity of rhBMP was studied in rats and dogs either by i.v. injection or by a dibotermin alfa /ACS implants. The only effects observed were related to the pharmacodynamic action of dibotermin alfa , i.e. bone formation. Antibodies to dibotermin alfa were monitored in the toxicity studies, the reporting of these studies was not complete therefore a final conclusion can not be reached. Reproduction and fertility in male and female rats was not affected by dibotermin alfa .

Embryo-fetal development studies in gravid rabbits treated with dibotermin alfa did not result in systemic maternal toxicity, embryo lethality or gross fetal abnormalities at dosages up to 1.6 mg/kg/day.

Treatment of rats with high intravenous doses of rhBMP (1.6 or 0.5 mg/kg/day) during organogenesis resulted in increased foetal weight in 2/3 experiments. Additionally, some skeletal variations were observed indicating a more advanced foetal development.

From preclinical studies no clear optimal dose can be extrapolated for the clinical use of this product due to efficacy differences between used models and species. With the exception of bone formation, local inflammatory changes, possible effects on skeletal variants in teratology studies and antibody formation, no significant effects were observed in the preclinical toxicology studies. The fact that all of the studied species were sensitive to the primary pharmacologic action is naturally reassuring and the main reason for the differences in sensitivity between species may well be the species-specific differences in bone formation kinetics. The absence of a sufficiently sensitive method to quantify dibotermin alfa in human plasma following implantation of the product makes it impossible to compare systemic exposure between experimental animals and man.

Efficacy

Clinical efficacy of dibotermin alfa /ACS is mainly based on one pivotal trial in 450 patients (C9530-11). This was a multinational, multicenter, single blind, stratified, randomised, controlled study in 450 patients with open tibial shaft fractures that required surgical management with IM nailing. Patients with all fracture severity levels were included, excluding only patients at high risk of amputation (Gustilo classification IIIC). Furthermore, patients were required to undergo immediate wound treatment (to reduce the infection risk), fracture reduction and stabilisation with IM nailing, which represents the standard of care for tibial shaft fractures at the participating sites. Patient treatment assignments were stratified by Gustilo classification. Patients were randomised to 1 of 3 treatment

groups: standard of care (SOC), 0.75 mg/ml dibotermin alfa /ACS, or 1.50 mg/ml dibotermin alfa /ACS. In each of the 3 treatment groups, patients received standard surgical management of the fractured tibia (including IM nailing) and soft tissue. In the dibotermin alfa /ACS treatment groups, patients received standard surgical management plus 0.75 or 1.50 mg/ml dibotermin alfa /ACS implanted at the time of definitive wound closure (DWC).

Primary efficacy endpoint was the proportion of patients who required a secondary intervention to promote fracture healing within 12 months of DWC. Secondary endpoints were healing rate at 6 months, acceleration of fracture union. Additional endpoints were the combined clinical and radiographic endpoint, time to prescription of secondary intervention, and number and invasiveness of interventions actually performed.

Treatment with 1.5 mg/ml dibotermin alfa /ACS produced a significant reduction in the rate of secondary interventions prescribed to promote fracture healing, and in the invasiveness of the second and subsequent interventions actually performed. The treatment was associated with a significantly increased rate of clinical fracture healing at 6 months after definitive wound closure, with significant improvement in fracture healing rates seen as soon as 10 weeks after DWC, and further confirmed through 12 months after DWC.

As regards the acceptability of the single pivotal trial for marketing authorisation, it is concluded that with the exception of external validation (suitability for extrapolation) and consistency of effect across subgroups, the criteria for acceptance have been fulfilled. These two deficiencies have been resolved through restriction of the therapeutic indications and appropriate description of study results in the SPC.

Safety

With respect to safety, data presented up to date has not revealed any concerns. In particular, there was no difference in the occurrence of infections across treatment groups, dibotermin alfa /ACS does not appear to increase the incidence of bone disorders, such as local soft tissue or heterotopic ossification. Furthermore, findings from histologic analysis were unremarkable. Antibody formation was not a cause for a significant safety concern. Until now, 15 malignancies (most skin cancers) were reported in 13 patients. However, safety data are limited to 1000 patients with a mean follow up of 54 weeks. This time period is considered to be too short for the development and diagnosis of malignancies, and for the formation of antibodies. The applicant will continue to monitor this issue in ongoing studies and post-marketing surveillance.

Benefit/risk assessment

From a quality and pre-clinical point of view, appropriate post-marketing commitments have been made. The product information reflects the pre-clinical findings.

It is concluded that efficacy and safety of dibotermin alfa /ACS are acceptable for the patient population studied, that is: for patients with an open tibial shaft fracture requiring surgical management with intramedullary nailing. The use of more than one kit should be avoided.

dibotermin alfa /ACS is not recommended for use in

- in children and in elderly patients,
- in large segmental defect repair of long bones, in which significant soft tissue compression can occur,
- in patients with any malignancy.

Efficacy and safety have not been demonstrated in patients with other long-bone fractures that require open surgical management. Although one might suppose that dibotermin alfa /ACS will be osteoinductive in these fractures, the benefit for the patient in reduction of secondary intervention and time to fracture healing in patients with other long-bone fractures is not clear.

The Applicant has made the following commitments:

- to conduct a controlled, randomised clinical trial of InductOs (plus standard care) versus standard care in patients treated with reamed IM nails.
- studying long-term risks of dibotermin alfa /ACS, especially for the development of malignancies and antibodies.

Based on the CPMP review of data on quality, safety and efficacy, the CPMP considered by consensus that the benefit/risk profile of InductOs was favourable in the treatment of acute tibia fractures in adults, as an adjunct to standard care using open fracture reduction and intramedullary nail fixation.

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.

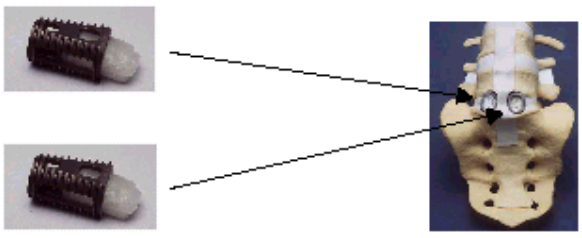
Following the provision of supplementary information by the MAH, the CHMP noted that the company argued that use of low rhBMP-2 concentration in the canine laminectomy safety study was justified in view of the higher sensitivity of the species to the pharmacological effects of rhBMP-2 compared to man. 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.