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.