20 November 2014
EMA/CHMP/649027/2014
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

InductOs

Procedure no. EMEA/H/C/000408/II/0071

Marketing authorisation holder (MAH): Medtronic BioPharma B.V.

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

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List of abbreviations

ACS	Absorbable Collagen Sponge
ALIF	Anterior Lumbar Interbody Fusion
AE	Adverse Event
ASTM	American Society for Testing and Materials
CE	Conformité Européenne
CI	Confidence Interval
CSR	Clinical Study Report
CT	Computed Tomography
CTRL	Control
DDD	Degenerative Disc Disease
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
ICBG	Iliac Crest Bone Graft
INV	Investigational
MAH	Marketing Authorisation Holder
MCID	Minimally Clinically Important Differences
MD	Mean Difference
n	Number of patients in study/treatment group
NRS	Non-randomised controlled study
ODI	Oswestry Disability Index
OR	Odds Ratio
PEEK	Polyetheretherketone
PLIF	Posterior Lumbar Interbody Fusion
RCT	Randomised Clinical Trial
RD	Risk Difference
rhBMP-2	recombinant human Bone Morphogenetic Protein 2 (INN: dibotermin alfa)
SAE	Serious Adverse Event
SD	Standard Deviation
SEM	Standard Error of the Mean
SmPC	Summary of Product Characteristics
TLIF	Transforaminal Lumbar Interbody Fusion
USA	United States of America

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Medtronic BioPharma B.V submitted to the European Medicines Agency on 04 April 2014 an application for a variation including an extension of indication.

This application concerns the following medicinal product:

Medicinal product:	**International non-proprietary name:**	**Presentations:**
InductOs	Dibotermin alfa	See Annex A

The following variation was requested:

Variation requested		**Type**
C.1.6 a)	*Addition of a new therapeutic indication or modification of an approved one*	II

The MAH applied for an extension of the indication to broaden the use of InductOs in lumbar interbody spine fusion. Consequently, the MAH proposed the update of sections 4.1, 4.2, 4.8, 4.9 and 5.1 of the SmPC. Further, the MAH proposed to update the SmPC section 4.4 with warnings related to type of surgery, device and spinal level, and to update sections 4.4, 4.5, 4.6, 5.1 and 5.3 of the SmPC based on newly available non-clinical and clinical data relating to immunogenicity, tumorigenicity or fusion success. The Package Leaflet was proposed to be updated accordingly. Furthermore, the MAH proposed to update the standard term from "kit for implant" to "powder, solvent and matrix for implantation matrix", and to change the expression of the strength from 12mg to 1.5 mg/ml throughout the SmPC, labelling and Package Leaflet. In addition, the MAH proposed to take the opportunity to implement the latest QRD template (version 9.0) and to make editorial changes throughout the annexes. A revised RMP version 2 was provided as part of the application.

The variation proposed amendments to the SmPC, Annex II, Labelling and Package Leaflet as well as the Risk Management Plan.

Information on paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The applicant did not seek scientific advice at the CHMP.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Pieter de Graeff Co-Rapporteur: Janne Komi

Submission date:	04 April 2014
Start of procedure:	25 April 2014
Rapporteur's preliminary assessment report circulated on:	18 June 2014
Request for supplementary information and extension of timetable adopted by the CHMP on:	24 July 2014
MAH's responses submitted to the CHMP on:	18 September 2014
Rapporteur's preliminary assessment report on the MAH's responses circulated on:	16 October 2014
PRAC RMP advice and assessment overview adopted by PRAC :	06 November 2014
CHMP opinion:	20 November 2014

2. Scientific discussion

2.1. Introduction

InductOs, containing dibotermin alfa (recombinant human Bone Morphogenetic Protein-2 (rhBMP-2)), is an osteoinductive protein for inducing bone formation when used as an implant with a suitable matrix. InductOs (EMEA/H/C/408) is a single-use medicinal product presented as a powder, solvent and matrix for implantation. It includes 12 mg of dibotermin alfa, a solvent (Water for Injection) and an absorbable collagen sponge (ACS), a matrix made from bovine Type I collagen. InductOs is prepared for use by reconstituting the lyophilised dibotermin alfa in Water for Injection to form a 1.5 mg/mL solution, which is then applied to the ACS for implantation.

Currently InductOs is indicated:

- for single-level (L4-S1) anterior lumbar spine fusion as a substitute for autogenous bone graft in adults with degenerative disc disease (DDD) who have at least 6 months of non-operative treatment for this condition.
- for the treatment of acute tibia fractures in adults, as an adjunct to standard care using open fracture reduction and intramedullary unreamed nail fixation.

The initial indication was treatment of acute tibia fractures (approved in 2002). It was limited to *unreamed* nail fixation in 2008, because of an increased infection rate in subjects treated with *reamed* nail fixation. The second indication – anterior lumbar spine fusion – was approved in 2005.

With this variation the MAH aims to:

1) demonstrate the clinical safety and efficacy of InductOs when used in conjunction with CE-marked interbody fusion devices made of titanium (in addition to LT-CAGE Device), or polyetheretherketone (PEEK) and allograft bone spacers for lumbar interbody spine fusion;

2) support the responsible implantation of InductOs using surgical approaches other than anterior, or anterior laparoscopic for lumbar interbody fusion;

3) support the use of InductOs for spine fusion at all lumbar levels.

The proposed new indication is as follows:

*'InductOs is indicated for single-level ~~(L4-S1) anterior~~ lumbar **interbody** spine fusion as a substitute for autogenous bone graft in adults with degenerative disc disease who have at least 6 months of non-operative treatment for this condition.'*

2.2. Non-clinical aspects

2.2.1. Introduction

The aim of the present Type II variation is to (1) demonstrate the (non-)clinical efficacy and safety of rhBMP-2/ACS when used in conjunction with CE-marked interbody fusion devices/spacers, other than the LT CAGE device and which are made of titanium, polyetheretherketone (PEEK) and allograft bone for lumbar interbody spine fusion; (2) support the safe use of InductOs in surgical approaches other than anterior approaches; and (3) support spine fusion at all lumbar levels.

2.2.2. Pharmacology

Primary pharmacodynamic studies

To support this application, the MAH analysed seven (7) animal pharmacology studies; five (5) sheep and two (2) nonhuman primate spine fusion model studies (Table 1).

The ideal model for lumbar spine fusion includes a spine with anatomy and loading similar to that of humans as well as bone formation comparable to that of humans. The model that most closely matches these criteria is the nonhuman primate model.

The sheep spine model has also been used to reduce the number of primate studies and, because of the biomechanical similarities between the sheep and human spines, it is able to serve as a relevant animal model for the human spine (Wilke, 1997).

Table 1: Overview of primary pharmacodynamics studies

Study report	Type of study	Species and groups (n=animals/group)	Observations[k]
PC-9503	titanium interbody fusion device[a]: ALIF fusion at L4-L5	Sheep A: rhBMP-2/ACS (n=6) B: ICBG (n=6)	Fusion (at 6 months) rhBMP: 6/6 ICBG: 2/6 Stiffness: No difference
PC-9905	titanium interbody fusion device[b]: PLIF fusion at L4-L5	Sheep A: ICBG (n=6) B: rhBMP-2/ACS (n=6) C: rhBMP-2+CRM (n=8) - sham[h] (n=7)	Fusion: rhBMP: complete 5/6, partial: 1/6 ICBG: complete 3/6, partial: 2/6 Stiffness and tensile loading rhBMP-2/ACS> ICBG
PC-0009	PEEK interbody	Sheep	Fusion:

	fusion device[c]: ALIF fusion at L4-L5	A: ICBG (n=7) B: rhBMP-2/ACS (n=6) - sham[h]	No difference Stiffness: B increased stiffness in flexion and left lateral bending only.
PC-0510	PEEK interbody fusion device[d]: DLIF fusion at L2-L3 and L4-L5	Sheep[i] A: rhBMP-2/ACS normal dose B: rhBMP-2/ACS high dose (7x normal)	High dose: resorption at early time point At 20 weeks: complete fusion (both doses)
PC-0103	PEEK interbody fusion device[e] Fusion at C2-C3 and C4-C5	Sheep[i,j] - ICBG - rhBMP-2/ACS - sham[h]	Fusion slightly higher for rhBMP-2/ACS treated animals Stiffness: No difference
PC-9602	titanium interbody fusion device[a], ALIF Fusion at L7-S1	rhesus monkeys - 0 mg/ml rhBMP-2/ACS (n=2) - 0.75 mg/ml rhBMP-2/ACS (n=3) - 1.5 mg/ml rhBMP-2/ACS (n=3)	Fusion: 0.75, 1.5 solid fusion, 0: no fusion
PC-9605	custom-machined cortical dowel allograft cylinder, ALIF Fusion at L7-S1	rhesus monkeys - ICBG (n=3) - rhBMP-2/ACS (n=3)	Fusion: rhBMP-2/ACS: 100% solid fusion ICBG: partial fusion Stiffness: rhBMP-2/ACS>ICBG * ICBG group showed pseudoarthrosis (2) or minimal fusion (1)

*ALIF: Anterior Lumbar Interbody Fusion, PLIF: Posterior Lumbar Interbody Fusion, ICBG: iliac crest bone graft, CRM: Compression Resistant Matrix, DLIF: Direct Lateral Interbody Fusion;*a: cylindrical fenestrated titanium (Ti-6Al-4V) interbody fusion device (INTER FIX™, Medtronic Sofamor Danek);b: posterior instrumentation and titanium (CP Grade 2) mesh device (Pyramesh, Medtronic Sofamor Danek);c: a threaded cylindrical PEEK interbody fusion device (PEEK-Optima, 14 mm x 20 mm;d: a PEEK interbody spacer specifically designed for the sheep interbody space;e: PEEK Impacted Device and INFUSE Bone Graft;h: Sham treatment: cadaver spines implanted with the device alone;i: 2 treatments per animal;j: 3 sheep were euthanized at 1, 2, 3, 4, 8, 12 and 20 weeks post-operation;k: effect of treatment was evaluated through radiographic, biomechanic, and histologic analyses
l: histological analysis at 6 month

Study PC-9503: The data showed that there was no significant difference between ICBG and rhBMP-2 groups in biomechanical stiffness, in any direction. The rhBMP-2/ACS-treated animals had dense remodelled bone growing through the holes in the cage walls and trabecular bone bridging adjacent vertebral bodies. In contrast, the cages from the autograft treated animals were variably filled with new bone, remnants of autograft, fibrous tissue, and fibrocartilage.

Study PC-9905: Compared with a sham control group, A and B showed increased stiffness in all rotational directions and in tensile loading. Group B showed the most complete fusion with numerous trabeculae through the disc space connecting the L4 and L5 vertebral bodies; implant osseointegration was observed in 50% of animals. In Group A, most of the fusion was in the form of an anterior callus that bridged the vertebral bodies.

Study PC-0009: The difference between Groups A and B was not significant. There was no significant difference between histological fusion rates in Group A (71%) versus Group B (100%). Compared with Group A (ICBG), Group B (rhBMP-2/ACS) showed a significant increase in stiffness in the loading directions of flexion and left lateral bending ($P<0.01$). Increases in all other loading directions were not statistically significant. For all 6 loading directions: Groups A and B showed significantly greater

stiffness than the sham Group (P<0.05). Biomechanical data correlated well with radiographic and histological data for Groups A and B.

Study PC-0510: In the high dose fusion, a moderate to marked endplate and peri-implant resorption was observed by 3-weeks and continuing to 4-weeks. In comparison, the normal dose levels demonstrated minimal endplate and vertebral body resorption. By 20 weeks, bone resorption effects were not observed in either group and bone formation occurred demonstrating the transient nature of this response.

Study PC-0103: This study was presented to provide additional evidence on the biocompatibility of rhBMP-2/ACS with interbody fusion devices made from PEEK. The variation did not intend to seek an additional indication for cervical spine fusion. There were 2 treatments per animal, per group. Compared with the sham Group (cadaver sheep spines), animals treated with rhBMP-2/ACS or ICBG for 12 months showed significant increases in stiffness in all 6 loading directions.

Study PC-9602: The 3 animals in the rhBMP-2/ACS high-dose Group (1.5 mg/mL) showed continuous bone growth through the device to the adjacent vertebra at 12 weeks. The low-dose Group (0.75 mg/mL) showed slightly less bone density of the formed bone at 12 weeks. By 24 weeks, both rhBMP-2/ACS Groups showed similar continuous bone growth through the device. The CT scans of the control animals (0 mg/mL rhBMP-2/ACS) only showed some bone growth at the vertebral bodies that was not continuous across the disc space.

Safety pharmacology programme

The main risks identified with the use of rhBMP-2/ACS in spine fusion were associated with the pharmacological properties of BMPs and the role they play in the process of bone regeneration and healing which includes an initial acute inflammatory response, a resorptive phase, subperiosteal and endosteal proliferation, bone formation, consolidation and finally remodelling by osteoclast and osteoblast activity. Collectively there are 3 main concerns:

- Formation of fluid collections (possibly leading to pseudocysts , localised oedema & implant site effusion),
- Bone resorption (possibly leading to osteolysis, device dislocation & subsidence of the disc space), and
- Heterotopic ossification (possibly leading to nerve compression).

The results from four (4) studies are presented in table 4.

Table 4: Overview of additional safety studies

Study number	Study type	Species (groups)	Observations
PC-0615	encapsulated fluid collection	Sheep (fusion at L2/L3 and L4/L5, n=8/group) A: rhBMP-2/ACS in PEEK B: rhBMP-2/ACS in PEEK, overfill C: rhBMP-3/ACS in PEEK + 0.2cc anterior D: rhBMP-3/ACS in PEEK + anterior and posterior	At 4 weeks: Small intra-osseous fluid pockets in ~20%, most commonly in group B. Pockets were filled with blood or newly deposited bone. No pockets at 8 weeks. No histological evidence of pseudocysts
PC-0523	localised oedema	Rat implantation in muscle A: rhBMP-2/ACS with 0, 30, 129, 450 µg rhBMP-2, B: 0, 10, 150 ug rhBMP-2 in ACS or fluid	rhBMP-2/ACS gave soft tissue edema at day 2 and Day7, More edema when – ACS was present, - rhBMP-2 dose was higher, - at day 2(vs day 7) At day 7: periimplant chondroplasia/ossification, mineralization and fibroplasia
PC-0443	bone resorption	Sheep Implantation in cancellous bone defect, rhBMP-2/ACS at: A: 1x (normal fill, normal concentration B: 3.5x (normal fill, hyper-concentrated C: 2x (double fill, normal concentration) D: 7x (double fill, hyper-concentrated) E: 0x	At week 1: little resorption in 1x, moderate to marked resorption at higher rhBMP-2 dose (dose-dependent) At week 4 onset of defect healing, shift from osteoclastic to osteoblastic activity At 8 weeks: majority of defects healed. Control (0x) defects showed no osteoclastic activity with little to no bony healing
PC-9502	contact of rhBMP-2/ACS with nerve tissue	Dog bilateral laminectomy at L5 (implanted directly onto exposed dura) A: rhBMP-2/ACS (n=10) B:autologous bone graft (n=10) Half of the animals/group received additional dural nick	Evaluation up to 12 weeks. no clinical, radiographic, or histologic evidence of neurologic abnormalities rhBMP-2/ACS stimulated bone growth which came in direct contact with the dural membrane no evidence of abnormal mineralization within the thecal sac or in the spinal cord

Study PC-0615: This study was performed following limited reports of encapsulated fluid collections (pseudocysts) observed following off-label use of InductOs in transforaminal lumbar interbody fusion (TLIF) or posterior lumber interbody fusion (PLIF) procedures. The normal fill group (A) and other groups where rhBMP-2/ACS was placed outside of the interbody device (C and D) did not consistently demonstrate resorption or fluid pockets. This suggested that transient bone resorption and possibly fluid formation may not only be influenced by the total rhBMP-2 dose supplied, but by the total dose supplied per volume of space to be grafted.

Study PC-0523: The results from this rat ectopic model and cancellous bone environment showed that higher concentrations of rhBMP-2 lead to exaggerated pharmacological effects of rhBMP-2 leading to fluid collection and an imbalance between osteoblastic and osteoclastic activity in bone remodelling.

Study PC-0443: The results showed that as the local concentration of rhBMP-2 increases, either by increasing the solution concentration or by overfilling the defect with rhBMP-2/ACS the peri-implant

effects of osteoclastic activity increases. This increased osteoclastic activity caused peri-implant transient resorption in the overfilled and or hyper-concentrated groups.

Study PC-9502: The results showed that there was an increased incidence of narrowing of the neuroforamina and stenosis in the rhBMP-2/ACS-treated groups, however, without clinical or neurological consequences.

2.2.3. Pharmacokinetics

The MAH sought to remove the limitation of using a single, titanium interbody fusion device (LT-CAGE device), and permit the use of rhBMP-2/ACS with other interbody fusion devices/spacers made from plastic/polymer materials such as PEEK or allograft bone. Compatibility with rhBMP-2/ACS in terms of the binding and release of rhBMP-2 with these materials was evaluated in two (2) *in vitro* [^{125}I]-rhBMP-2 binding and release studies.

Two (2) other in vitro pharmacokinetic studies were also included in the application.

Table 2: Overview of submitted pharmacokinetic studies

Study number	Type of study	Groups	Results
PC-0634	Binding of [^{125}I]-rhBMP-2 to PEEK	rhBMP-2 bound to ACS rhBMP-2 in solution	≤ 2% binding of rhBMP-2 to PEEK
PC-0339	Binding and release of [^{125}I]-rhBMP-2 to cortical and cancellous bone	Cortical bone was untreated, or surface demineralized, or biocleansed, machined with straight pits or undercut pits	cortical bone treatment options increase binding of rhBMP2 but binding levels remain low (<10% binding), release of bound rhBMP is very slow.
1064-028	release of [^{125}I] rhBMP-2 from the ACS matrix placed in PEEK device and exposed to different immersion media	Immersion media were: - FBS - PBS, - DMEM+10%FBS - SBF	Amount of [^{125}I] rhBMP-2 on ACS at day 14 was: 50% FBS, 55% PBS, 44% SBF, and 47% DMEM (value at day 7; dissolved at day 14). For all immersion fluids <10% bound to PEEK device at day 7 and/or 14.
1064-029	incorporation of [^{125}I] rhBMP-2 in hemostatic agents	hemostatic agents - FloSeal - Fibrin - Tisseel - Gelfoam - Duraseal	**Hemostatic Agents Mean % Recovery** Time Point Hemostatic Agent / Day 1 / Day 3 / Day 7 / Day 10 / Day 14 FloSeal® / NA / NA / NA / NA / NA Fibrin Blood Clot / 11.19 / 2.31 / 4.34 / 4.84 / 5.65 Tisseel / 3.45 / 6.52 / 11.87 / 14.58 / 17.42 Gelfoam® / 1.82 / 3.56 / NA / 5.79 / NA DuraSeal® / 1.27 / 1.50 / 2.63 / 2.20 / 2.60

FBS: Foetal Bovine Serum, PBS: Phosphate Buffered Saline, DMEM: Dulbecco's Modified Eagle's Medium, SBF: Simulated Body Fluid

Study PC-0634 and PC-0339: These studies were performed to permit the use of rhBMP-2/ACS with interbody fusion devices/spacers made from plastic/polymer materials such as PEEK or allograft bone.

When compared with the Drug Product specification for rhBMP-2 content (11.6-14.8 mg/vial), the results indicated that the amount of [^{125}I]-rhBMP-2 which binds to PEEK and allograft bone is a very small amount relative to vial content.

Study PC1064-028 and PC1064-029: These studies were conducted to investigate *in vitro* the impact of different immersion media or hemostatic agents that are frequently used during spine fusion surgery on rhBMP-2 release from the ACS matrix. Across the various immersion media used about 60% or more of the radioactivity was retained on Day 1, and >45% is retained on day 7-14. rhBMP-2 radioactivity became associated with the fibrin clot and Tisseel a fibrin based sealant. There was minimal association of rhBMP-2 radioactivity with DuraSeal a hydrogel based sealant, while the gelatin based haemostatic agents, Gelform and Floseal dissolved in the media. Both studies show limited binding of rhBMP-2 to PEEK.

2.2.4. Toxicology

Carcinogenicity

BMPs are known to regulate cell differentiation and growth in some tissues (Reddi, 1998). In addition, several tumours express BMP or BMP receptors, including cancers of the bone, breast, lung, prostate and pancreas (Thawani, 2010). As a consequence of this potential risk, the use of rhBMP-2/ACS is contraindicated in patients with any active malignancy or a patient undergoing treatment for a malignancy.

The MAH has performed several studies to address this safety concern (see table 3).

Table 3: Overview of submitted studies on tumorigenic potential of Inductos/rhBMP2

Study number	Study type	Conclusions
V0023-211	Ames test (DMSO extract of rhBMP-2/ACS)	negative
V0002-130	Chromosome aberration test (DMSO extract of rhBMP-2/ACS on CHO-WBL cells)	negative
T0566-500	Micronucleus study (saline/sesame oil extract of rhBMP-2/ACS)	negative
RPT-50783	The Effects of rhBMP-2 on the Growth of Human Tumor Xenografts in Nude Mice	rhBMP-2/ACS does not promote in vivo growth of xenograft expressing receptors for BMP-2
RPT-57510	BMP-2 Receptor Protein Expression in 7 Human Tumor Cell Lines	All 7 cell lines used in study RPT-50783 express BMP receptor -IA, -IB and -II although at varying levels
RPT-62433	The Effects of rhBMP-2 on the Growth of Human (pancreatic) Tumor Xenografts in Nude Mice	rhBMP-2/ACS does not promote in vivo tumor growth or the infiltrative growth or metastasis of pancreatic xenograft
RPT-44654	PCR screening of BMP-2 receptors in human tumor cells	10 of 21 human tumor cell lines express functionally relevant levels of BMP receptor II
RPT-45118	The effect of rhBMP-2 on the in vitro proliferation of human cancer cells	rhBMP-2 did not enhance in vitro growth of 11 tumor cell lines

Reproduction toxicity

In the initial MAA, the results from a rat teratology study of rhBMP-2 (Study 95477) showed statistically significant reductions in the percentage of foetuses with sternebral variants 5 and xiphisternum in parallel with increased foetal weights in the treated groups leading to the following wording in the product information: "In reproductive toxicity studies in rats, where dibotermin alfa was administered intravenously to maximise systemic exposure, increased fetal weight and increased fetal ossification was observed and a treatment-related effect could not be ruled out. The clinical relevance of these effects is unknown".

In Study 95477 animals had been selected for caesarean in a staggered rather than a random fashion and this may have been responsible for the apparent trends in foetal maturity. The results from a partial repeat of the same study design (Study 96086), with only the high-dose (1.6 mg/kg/day) and vehicle controls groups and with random selection for time of caesarean section confirm that there is no evidence of special hazard for humans based on conventional studies of safety pharmacology, acute and repeated exposure toxicity and genotoxicity.

In clinical studies low levels of transient antibodies to rhBMP-2 have been detected in patients treated with InductOs, which raises concerns regarding the potential effects of anti-BMP-2 antibodies on foetal development in women of childbearing potential. To assess these concerns antibodies to rhBMP-2 have been investigated in pregnant rabbits following immunisation with rhBMP-2 (Study RPT-56475). Results from this study showed a greater incidence in reduced ossification of frontal and parietal bones than that observed historically which was considered reversible. The current product information already contains wording reflecting the outcome of this study (procedure II/020 approved in 2006).

2.2.5. Ecotoxicity / environmental risk assessment

No environmental risk assessment has been provided in accordance with the CHMP guidance EMEA/CHMP/SWP/4447/00 (01 June 2006) as proteins are exempted from testing because of their chemical structure.

2.2.6. Discussion on non-clinical aspects

A total of ten (10) nonclinical studies were included evaluating the efficacy/biocompatibility, safety and compatibility of rhBMP-2 with interbody fusion devices/spacers.

Titanium devices

A total of three (3) preclinical studies have used titanium interbody devices, two (2) in the sheep lumbar interbody fusion model; one using ALIF (Sandhu, 2002), and one using PLIF. The third study was in a nonhuman primate model of ALIF (Boden, 1998). All three studies used a 6-month endpoint.

The use of an rhBMP-2 concentration of 0.43 mg/mL (which is lower than the non-human primate and human concentration of 1.5 mg/mL) in the sheep model has been agreed by the CHMP in view of the higher sensitivity of sheep to the pharmacological effects of rhBMP-2 compared to man.

The titanium devices varied between the three studies, and were all Medtronic. Of the two sheep studies, one used a horizontal cylindrical threaded device (INTERFIX) made of a titanium alloy (Ti-6A1-4V) (Sandhu, 2002), and the other used a horizontal cylindrical non-threaded device the (PYRAMESH) made of grade-2 titanium. The primate study used a horizontal cylindrical threaded device made of titanium alloy (Ti-6Al-4V) (Boden, 1998).

Fusion was the main efficacy outcome in all four studies. For rhBMP-2, the rate of histological fusion at 6 months was 100%, with evidence of fusion as early as 8 weeks (Sandhu, 2002). In contrast, the rate of fusion was 33–83% at 6 months for ICBG (Sandhu, 2002), not evident until 6 months (Sandhu, 2002).

Ex vivo tests of biomechanical stiffness suggested some benefit for rhBMP-2 over autograft.

Only one (sheep) study documented safety outcomes, recording an apparently unrelated acute inflammatory response.

PEEK devices

A total of five preclinical studies have used PEEK devices, with three of these relevant to the efficacy of rhBMP-2 in lumbar interbody fusion. Two were in the sheep lumbar interbody fusion model (Toth, 2006). The other was in the sheep endplate-sparing interbody fusion model (Bae, 2012), using transpsoas interbody fusion.

The PEEK devices in the three lumbar-relevant studies were a threaded cylindrical PEEK interbody fusion device (PEEK-OPTIMA, InVibio, Greenville, SC) (Toth, 2006), an impacted PEEK interbody device, and a specially designed endplate-sparing impacted PEEK spacer (Bae, 2012).

In one study, there was no significant difference in fusion rates for autograft (71%) versus rhBMP-2 (100%, P>0.05) at 6 months. The other relevant studies reported 100% fusion at 20 weeks (Bae, 2012), and fusion starting at 4 weeks.

Ex vivo tests of biomechanical stiffness suggested some benefit for rhBMP-2 over autograft.

Safety outcomes were reported by two of the three lumbar-relevant studies. At 6 months, only a mild chronic inflammatory response was present (ASTM F981-93 rating of 0 to 1.0 for all inflammatory cells for all implants), with a mean overall host response score of 0.54±0.14 (a score of 1.0 is interpreted as mild) (Toth, 2006). The other study found that overdosing with rhBMP-2 may be associated with resorption, but that this was only transient.

The other two studies are not directly relevant to the topic of efficacy of rhBMP-2 in lumbar interbody fusion: one was in the sheep cervical spine model, the other was an *in vitro* binding study using radiolabelled rhBMP-2 and a PEEK spacer.

Allograft spacer

One preclinical study used a cortical allograft bone dowel (Hecht, 1999) in a nonhuman primate model of ALIF. The data are reported descriptively with no 'fusion' not clearly defined, but at 6 months 100% of the rhBMP-2 group had achieved fusion (based on histology, radiography and CT scan descriptions) versus approximately 33–66% of the autograft group. Inflammation was noted in the autograft group, whereas in the rhBMP-2 group, no inflammatory or immune response was observed.

Another study, not directly relevant to the efficacy of rhBMP-2 in lumbar interbody fusion, was an *in vitro* binding study using cortical and cancellous bone constructs and radiolabelled rhBMP-2.

Overview of results from nonclinical studies

These nonclinical studies report excellent rates of histological fusion for rhBMP-2 used with various interbody fusion devices/spacers. The safety findings were either unremarkable, or a generally mild-to-moderate chronic inflammatory response that was observed in both rhBMP-2 and autograft groups, and with a variety of interbody fusion devices.

Four in vitro pharmacokinetic studies were presented by the MAH. The data indicate that binding of rhBMP-2 to PEEK or bone is relatively limited. Furthermore, immersion studies indicate that approximately half of rhBMP-2 is retained on ACS in the first week.

Studies on the effects of haemostatic agents on rhBMP-2 release from the ACS matrix indicate that a relatively large amount of rhBMP-2 becomes associated with Tisseel fibrin sealant. This was less for the other tested haemostatics. This suggested that a physical barrier might be preferable over Tisseel. However, this preference does not extend to other haemostatic agents.

Three genotoxicity studies were submitted. These were all negative.

In addition, five other studies (in vitro, and in vivo) addressing the potential role of rhBMP2 and its receptors on tumour formation or outgrowth were provided. Even though all these studies do not indicate a concern, there are also studies in the public domain which do suggest a role for rhBMP2 in tumour formation. This apparent dual behaviour of BMP-2 is adequately reflected in the currently approved product information. The submitted studies have already been reviewed at the time of initial MAA or during the lifecycle of the product. No new data have become available, nor new insights been obtained.

Four studies have been submitted which have been performed to address clinical concerns on the formation of fluid collections (possibly leading to pseudocysts), bone resorption and heterotopic ossification. No new safety concerns have been identified in these animal studies.

Considering the above data, Dibotermin alfa is not expected to pose a risk to the environment.

2.2.7. Conclusion on the non-clinical aspects

The aim of the nonclinical testing strategy was to evaluate the efficacy/biocompatibility, safety and compatibility of rhBMP-2 when implanted with interbody fusion devices/spacers made from materials widely used in humans for such devices/spacers. The materials used consisted of titanium and polyetheretherketone (PEEK), of a medical grade consistent with materials for CE-marked interbody fusion devices used in humans. This applied to the allograft bone spacers.

To support the current Type II variation, there were seven (7) animal pharmacology studies (five (5) sheep and two (2) nonhuman primate spine fusion model studies). Most studies were reviewed at the time of the initial application for the spine indication.

The limitations of studies in animal models, specifically due to anatomical differences are recognised. Within these limitations, the MAH has provided an adequate package of non-clinical studies to support the proposed change in indication. The data indicate that the use of rhBMP-2/ACS or bone graft in combination with a titanium or PEEK device enhances spine fusion and stiffness when compared to device alone. In these studies the effect of rhBMP-2/ACS appears similar or slightly better than when a bone graft was used. An extensive evaluation of the effect of the device, the spinal location or the site of application (anterior/posterior) on bone fusion has not been performed. However the data do not indicate a major effect of any of these variables on bone formation.

The available *in vivo* data on human tumour cell lines do not suggest a potential for promotion of tumour growth or metastasis. As a single use product, InductOs has not been tested for *in vivo* carcinogenicity.

The other studies submitted by the MAH do not provide any new cause for concern and do not impact on the benefit risk evaluation.

In conclusion, the requested change in indication is acceptable from a non-clinical point of view.

2.3. Clinical aspects

2.3.1. Introduction

In support of this application, the MAH has also presented data from eight Medtronic-sponsored studies, data from additional analyses, and clinical synopsis from selected publications covering 19 trials.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

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

- Tabular overview of clinical studies

Table 1: Overall Summary of Clinical Trials: Medtronic-sponsored

Study Approach / Device	Phase	Design (Lumbar levels)	N (INV/CRTL)
3100N3-117 ALIF/LT-CAGE/Titanium	I Pilot	Multicentre, randomised, controlled, 24 month follow-up (L2-S1)	14 (11/3)
3100N3-303 ALIF/LT-CAGE/Titanium	III Pivotal	Multicentre, randomised, controlled, 24 month follow-up, (L4-S1)	279 (143/136)
3100N3-304 ALIF/LT-CAGE/Titanium	II Supportive	Multicentre, uncontrolled*, 24 month follow-up (L4-S1)	134 (134/NA)
C-9703 ALIF/Bone Dowel	I Pilot	Multicentre, randomised, controlled 24 month follow-up (L4-S1)	46 (24/22)
P00-01 ALIF/Bone Dowel	II Supportive	Multicentre, randomised, controlled 24 month follow-up (L4-S1) – **Terminated** planned 180	85 (55/30)
C-9804 ALIF/INTER FIX/Titanium	I Pilot	Multicentre, randomised, controlled 24 month follow-up (L2-S1)	45 (25/20)
C-9806 PLIF/INTER FIX/Titanium	II Supportive	Multicentre, randomised, controlled 24 month follow-up (L2-S1) – **Terminated** planned 220	67 (34/33)
P01-07 PLIF/TELAMON/PEEK	I Pilot	Multicentre, non-randomised, uncontrolled, 24 month follow-up (L1-S1)	30 (30/NA)
Total			**700** (456/244)

CTRL=control (ICBG); INV=investigational (InductOs) N=total number of patients

* In the CSR, the control arm from Study 3100N3-303 is used as concurrent control; the study is considered as uncontrolled in this summary

Four 'pilot' studies are included (**Table 1**). No formal statistical analyses were carried out for the comparison of efficacy endpoints between treatments in the three controlled pilot studies.

Two studies were prematurely terminated. The sample size for each study was smaller than expected; the planned statistical analyses were not carried out and the studies are best described as 'supportive' rather than 'pivotal,' as stated in their protocols.

In addition to the studies shown in Table 1, two studies were presented but not further described by the MAH (Table 2). Study P01-08 is a large study, including 577 subjects. The study is completed, but only a synopsis was presented initially.

The other study, P05-06, is still ongoing. Total number of subjects to be randomized was 534. The first patient was enrolled in November 2011; as of 1 September 2013, 15 subjects were enrolled and underwent surgery.

Table 2: two additional studies

P01-08 (53772)	To demonstrate that the surgical treatment of DDD with the MAVERICK Total Disc Replacement is at least as safe and effective as the control treatment; INFUSE Bone Graft with the LT-CAGE Lumbar Tapered Fusion Device*.	Prospective, randomized, controlled, open, multicentre. Phase II MAVERICK Total Disc Replacement*	•rhBMP-2/ACS •4.2, 8.4 or 12 mg dibotermin alfa (1.5 mg/mL) •Surgical implantation	LT-CAGE	577 (172 rhBMP-2 arm , 405 MAVERICK arm)
P05-06	To demonstrate non-inferiority of the INFUSE Bone Graft with the CAPSTONE Spinal System and Posterior Supplemental Fixation as compared to the control treatment of Autologous Bone Graft with the CAPSTONE Spinal System and Posterior Supplemental Fixation.	Prospective, multicentre, open, randomized, controlled. Phase III ICBG/CAPSTONE Spinal System + Posterior Supplemental Fixation	•rhBMP-2/ACS •4.2 mg dibotermin alfa (1.5 mg/mL) •Surgical implantation - TLIF	CAPSTONE® Spinal System and Posterior Supplemental Fixation	15 (11 INV, 4 CTRL)

* Note: In this study, the investigational arm was the Maverick arm, while the control arm was the rhBMP-2 arm

2.3.2. Discussion and conclusion on clinical pharmacology

This submission covers the same formulation of InductOs that was previously approved in the EU in 2002. Therefore, the clinical pharmacology program of the original MAA is applicable to this variation.

In addition, the pharmacodynamic results from animal model studies in sheep and nonhuman primates provided histological evidence of fusion with dibotermin alfa at the site of implantation; moreover, the bone formed is of a higher quality (e.g., less fibrosis, greater proportion of trabecular bone) when compared with ICBG. This observation was irrespective of the interbody device/spacer material implanted with dibotermin alfa/ACS. These results provide a mechanistic rationale to explain the lower rate of pseudarthrosis observed in the InductOs treated patients in the pooled safety data analysis when compared with the ICBG-treated patients.

Furthermore, the following results from in vitro studies presented provide relevant information regarding potential interaction:

• Uptake of dibotermin alfa at the site of implantation into fibrin (Study 1064- 029)

• Use of allograft or local bone to re-create a physical barrier between the matrix and any neurological tissue, if leakage into the spinal canal and the nerve root is possible, is supported by the minimal uptake of dibotermin alfa by allograft or local bone (Study PC-0339)

Therefore the absence of PK data in this population is considered acceptable by the CHMP.

2.4. Clinical efficacy

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

The aim of the meta-analysis was to evaluate the clinical efficacy and effectiveness of recombinant human bone morphogenetic protein-2/absorbable collagen sponge (rhBMP-2/ACS) versus autogenous bone graft (ABG) in lumbar interbody fusion in patients with degenerative disc disease (DDD), spondylolisthesis or chronic low back pain. The main hypothesis was that the efficacy of rhBMP-2/ACS relative to the use of ABG remains unchanged regardless of the interbody fusion device or surgical approach used. The primary comparison was to be the proportion of patients with radiological fusion

success at 24 months post-operation across the Medtronic-sponsored controlled clinical trials. The hypothesis would also be tested in combination with published data from both randomized controlled trials (RCTs) and non-randomized controlled studies (NRS).

Relevant studies were identified by searching Medtronic clinical study reports, bibliographic databases (MEDLINE, EMBASE, Web of Science, Cochrane Library), trial registries (WHO ICTRP) and references of retrieved articles.

Inclusion criteria were controlled trials of rhBMP-2/ACS versus ABG with minimum 6-month follow up in adults with degenerative disc disease, spondylolisthesis or chronic low back pain who were undergoing lumbar interbody fusion via any approach and with any interbody fusion device.

The meta-analysis was conducted in two parts:

i) Medtronic-sponsored RCTs of InductOs in lumbar interbody fusion compared with ICBG (3100N3-117, 3100N3-303, C-9703, P00-01, C-9804, and C9806). Two Medtronic-sponsored trials were not eligible for the meta-analysis. Study 3100N3-304 was not included because the comparator was a concurrent control taken from another study, and Study P01-07 was not included because there was no comparator.

ii) All controlled clinical trials (Medtronic-sponsored or not, published or unpublished, randomized or not) of InductOs in lumbar interbody fusion compared with ICBG.

2.4.1. Results

Six Medtronic-sponsored trials and seven other published studies were identified. The six Medtronic-sponsored trials were RCTs. Only one of the seven published studies was an RCT; the other six were NRS. The studies included a total of 585 patients treated with rhBMP-2/ACS (292 in Medtronic trials and 293 in non-Medtronic studies) and 422 patients treated with ABG (244 in Medtronic trials and 178 in non-Medtronic studies). The data provided by non-Medtronic published studies were somewhat limited. After combining data from Medtronic trials and non-Medtronic published studies, meta-analysis was possible for fusion success, ODI score improvement and secondary procedures. The duration of follow-up varied, being 24 months for Medtronic studies and 9–34 months for published studies.

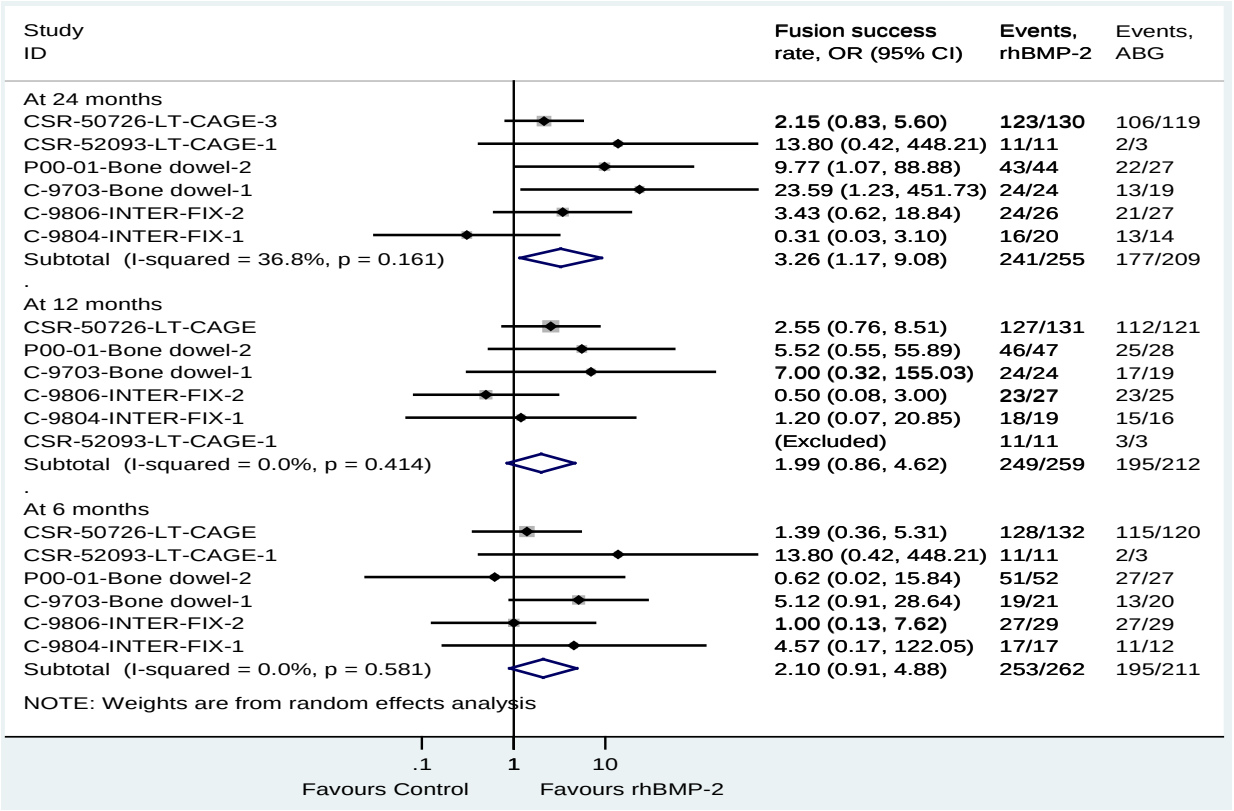
2.4.1.1. Fusion success rate for primary analysis set

Figure **1** shows the forest plot results of meta-analysis for the primary analysis dataset from the six Medtronic-sponsored RCTs of InductOs compared with ICBG (3100N3-117, 3100N3-303, C-9703, P00-01, C-9804 and C9806). At 24 months post-surgery, the use of InductOs was associated with a higher fusion success rate (94.5%, 241/255) compared with ICBG (84.6%, 177/209). The difference between the two groups was statistically significant (OR 3.262, P=0.024). The heterogenecity across studies was moderate (I^2 =36.8%, P=0.161). The estimated absolute difference in fusion success rate between the InductOs and ICBG groups was 11.7% (P=0.035); however, the heterogeneity across studies was moderate and statistically significant (I^2 =56.2%; P=0.044). The addition of non-Medtronic RCT (one study) and NRS data (six studies) to the Medtronic CSRs did not affect the finding of a significantly increased fusion success rate for rhBMP-2/ACS versus ABG.

For the primary analysis dataset at 6 and 12 months, the fusion success rate was 96.6% (253/262) and 96.1% (249/259) respectively, for InductOs and 92.4% (195/211) and 91.2% (195/212) respectively, for ICBG, with no significant difference between the groups at either time point. This does not support a claim for accelerated fusion.

For the missing-equals-failure dataset, the estimated absolute difference in fusion success rate between the InductOs and ICBG groups was 13.2% (p=0.034). Based on odds ratios, there was no significant difference in fusion success rate at any time point (p>0.05 for OR at 6 months, 12 months, and 24 months).

Figure 1: Meta-Analysis for Fusion Success, Odds Ratio (OR) (Primary analysis dataset, Medtronic trials)



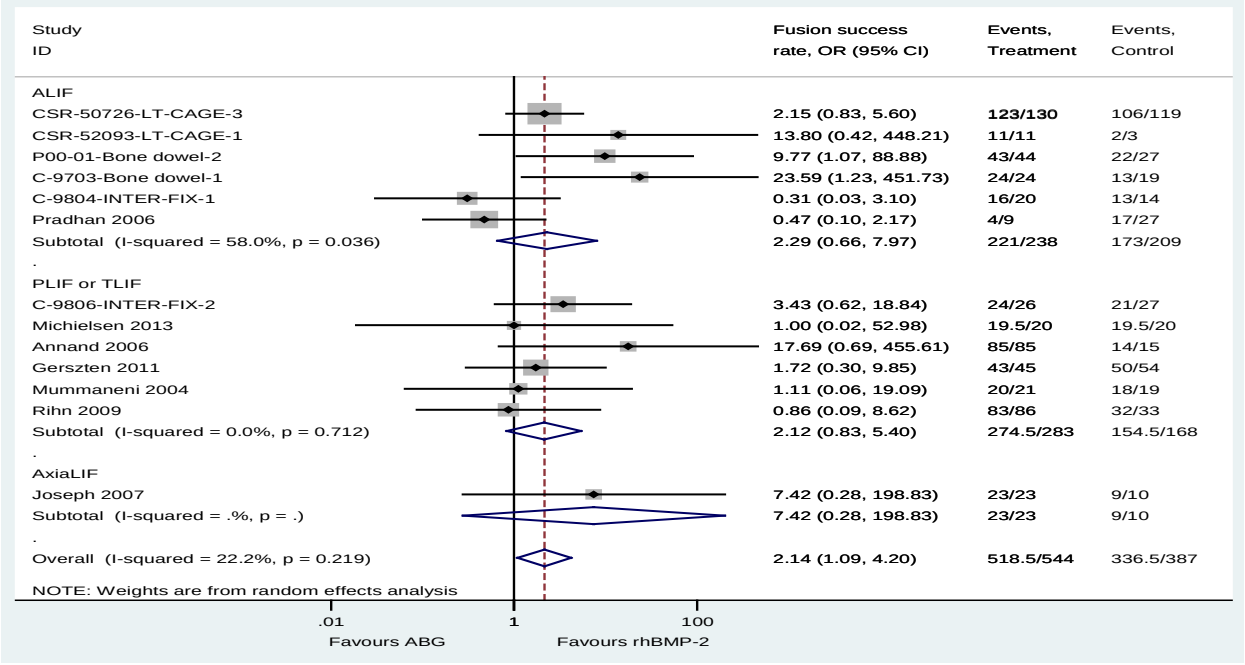
CSR-50726-LT-CAGE-3 = 3100N3-303 (ALIF/LT-CAGE/Open); CSR-52093-LT-CAGE-1 = 3100N3-117 (ALIF/LT-CAGE/Pilot); P00-01-Bone dowel-2 = P00-01 (ALIF/Bone Dowel/Pivotal); C-9703-Bone dowel-1 = C-9703 (ALIF/Bone Dowel/Pilot); C-9806-INTER-FIX-2 = C-9806 (PLIF/INTER FIX); C-9804-INTER-FIX-1 = C-9804 (ALIF/INTER FIX); ABG = autogenous bone graft; iliac crest bone graft in all studies. Events = Number of patients with fusion success/total number of evaluable patients

Effect of surgical approach

Fusion success rate

In a subgroup analyses for fusion success by surgical approach (Figure 2) for all six anterior lumbar interbody fusion studies, fusion success was 92.8% (221/238) for InductOs compared with 82.8% (173/209) for ICBG (OR 2.29). This compares with 96.8% (274/283) and 91.7% (154/168) for InductOs and ICBG, respectively, in all seven posterior studies (OR 2.12). A formal meta-regression analysis found no statistically significant difference in the effect of InductOs on fusion success between ALIF and other surgical approaches (ratio of odds ratios ROR=0.863, p=0.847).

Figure 2: Fusion Success Rate by Surgical Approach, Odds Ratio (OR) – Medtronic trials plus non-Medtronic published studies

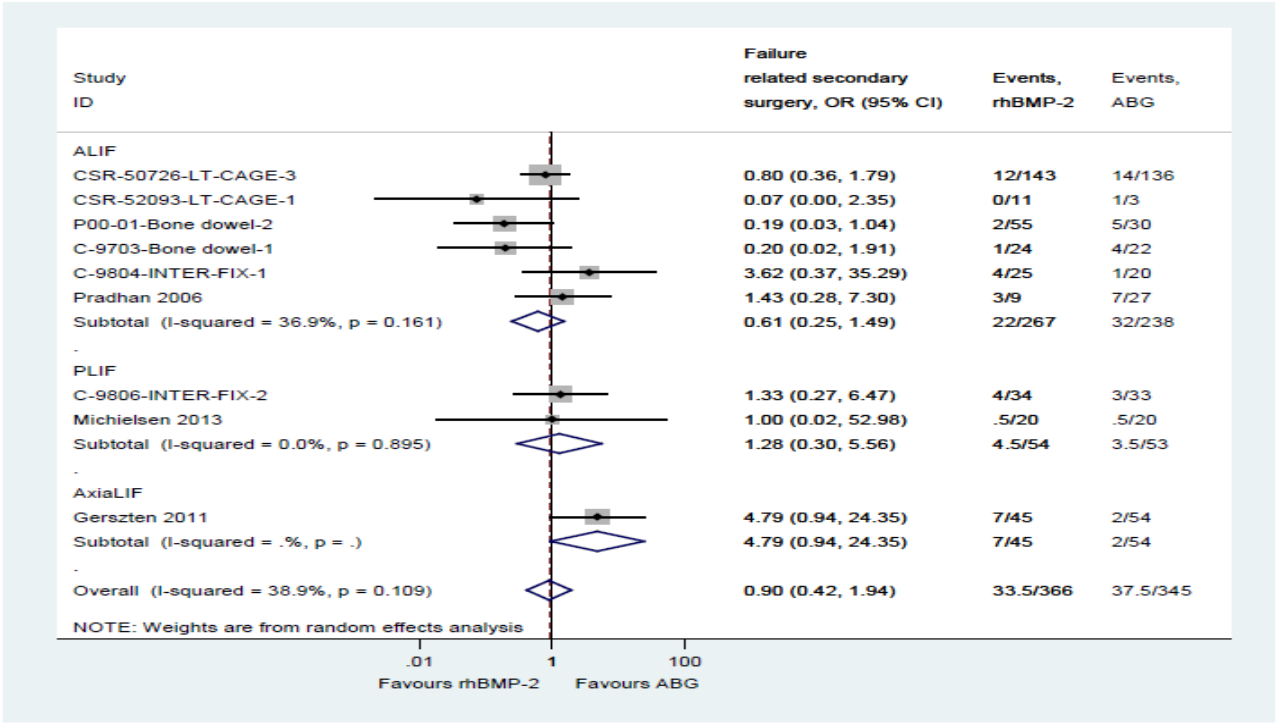


CSR-50726-LT-CAGE-3 = 3100N3-303 (ALIF/LT-CAGE/Open); CSR-52093-LT-CAGE-1 = 3100N3-117 (ALIF/LT-CAGE/Pilot); P00-01-Bone dowel-2 = P00-01 (ALIF/Bone Dowel/Pivotal); C-9703-Bone dowel-1 = C-9703 (ALIF/Bone Dowel/Pilot); C-9806-INTER-FIX-2 = C-9806 (PLIF/INTER FIX); C-9804-INTER-FIX-1 = C-9804 (ALIF/INTER FIX); ABG = autogenous bone graft; iliac crest bone graft in all studies. Events = Number of patients with fusion success/total number of evaluable patients

Failure-related secondary surgery

Results of subgroup analyses by surgical approach for failure-related secondary surgery are shown in Figure 3. There was no significant difference in the effect of rhBMP-2/ACS on failure-related secondary surgery between different subgroups by surgical approach ($\chi 2=4.84$, df=2, p=0.09).

Figure 3: Failure-related secondary surgery by surgical approach, odds ratio (OR) – Medtronic trials plus non-Medtronic published studies

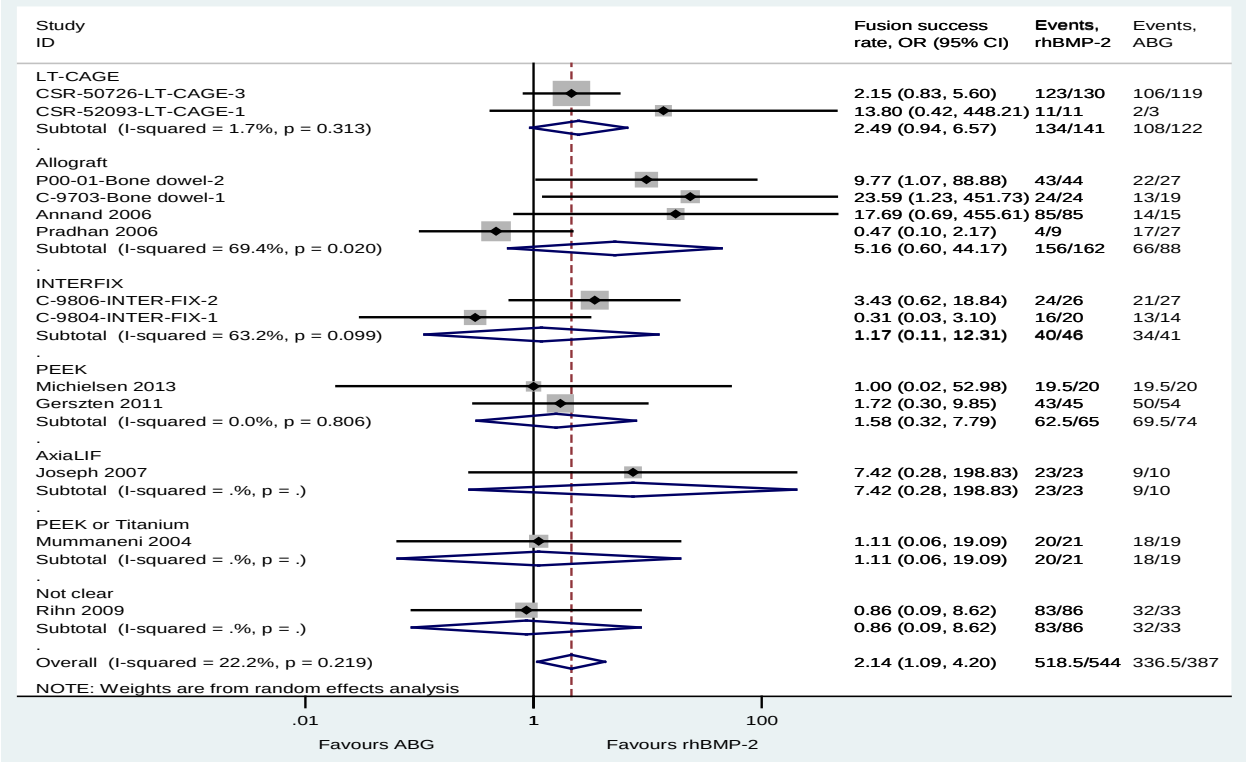


Effect of interbody fusion device

Fusion success rate

Results for the effect of types of interbody devices are shown in Figure 4. The relative effect of InductOs was not significantly associated with the types of interbody device used (χ^2=2.48, df=6, p=0.870). For titanium devices (LT-CAGE or INTER FIX devices, four studies), the InductOs fusion rate was 93.0% (174/187) and 87.1% (142/163) for ICBG. For allograft spacers (four studies), the InductOs fusion rate was 96.3% (156/162), compared with 75.0% (66/88) for ICBG. For PEEK devices, the fusion rate was 95.4% (62/65) for InductOs and 94.6% (70/74) for ICBG. The difference in the effect of InductOs on fusion success was statistically non-significant between being administered with an allograft device and other devices (ROR 1.948, p=0.442).

Figure 4: Fusion Success Rate by Type of Interbody Device, Odds Ratio (OR) – Medtronic trials plus non-Medtronic published studies

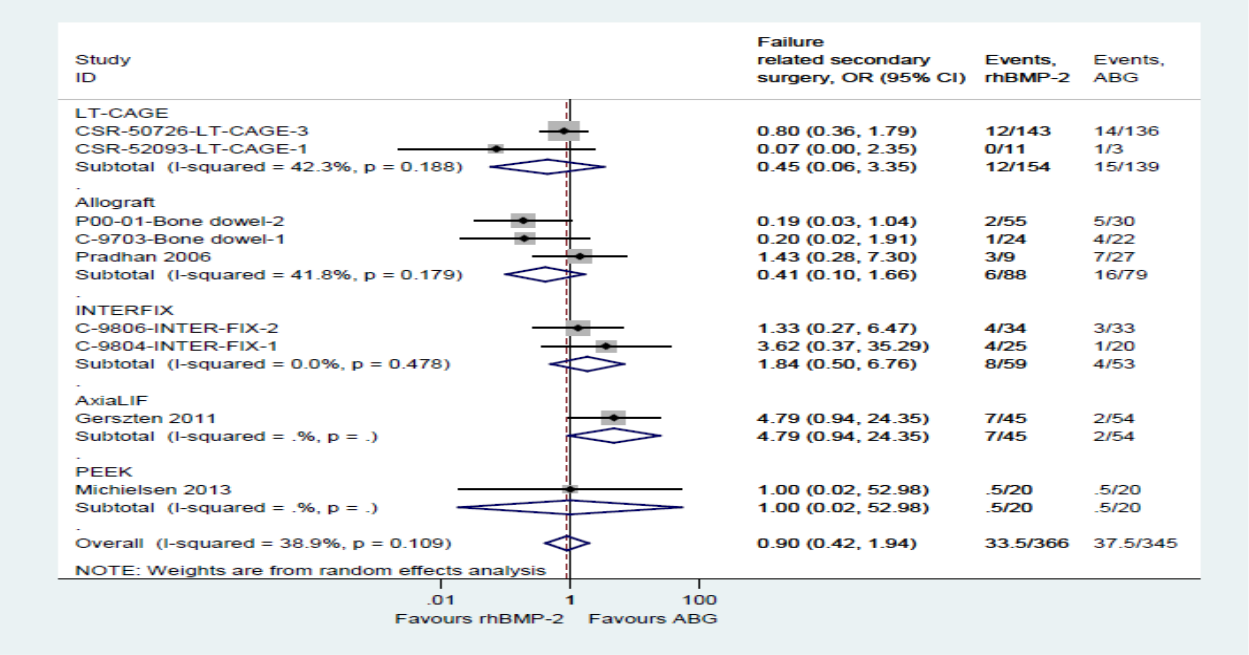


CSR-50726-LT-CAGE-3 = 3100N3-303 (ALIF/LT-CAGE/Open); CSR-52093-LT-CAGE-1 = 3100N3-117 (ALIF/LT-CAGE/Pilot); P00-01-Bone dowel-2 = P00-01 (ALIF/Bone Dowel/Pivotal); C-9703-Bone dowel-1 = C-9703 (ALIF/Bone Dowel/Pilot); C-9806-INTER-FIX-2 = C-9806 (PLIF/INTER FIX); C-9804-INTER-FIX-1 = C-9804 (ALIF/INTER FIX); ABG = autogenous bone graft; iliac crest bone graft in all studies. Events = Number of patients with fusion success/total number of evaluable patients

Failure-related secondary surgery

Results of subgroup analyses by devices used for failure-related secondary surgery are shown in Figure 5. There was no significant difference in the effect of rhBMP-2/ACS on failure-related secondary surgery between subgroups by type of interbody device ($\chi 2=5.86$, df=4, P=0.210).

Figure 5: Failure-related secondary surgery by type of interbody device, odds ratio (OR) – Medtronic trials plus non-Medtronic published studies



Literature

The MAH selected 20 publications, including 1730 patients treated with dibotermin alfa and 251 patients receiving other treatments. According to the MAH this literature provides evidence supporting the administration of InductOs in approaches other than ALIF (e.g. PLIF or TLIF – 75.6%, 1497/1981), with interbody devices other than the LT-CAGE Device (e.g. polymer interbody fusion devices – 53.4%, 1058/1981), and at levels other than L4-S1. Fusion success rates appear to be consistent with those found in Medtronic-sponsored trials and independent of surgical approach, administration with interbody devices other than LT-CAGE Device and lumbar level fused.

Supportive studies

In addition to the studies presented in
Table 1, the efficacy of InductOs administered with interbody fusion devices other than the LT-CAGE Device, in surgical techniques other than anterior lumbar interbody fusion and implanted at lumbar levels other than L4-S1 was supported by the following cumulative sets of clinical evidence:

- A post-hoc meta-analysis of six Medtronic-sponsored RCTs, including Study 3100N3-303, comparing InductOs (N=292) and ICBG (N=244) was conducted in accordance with Points to Consider on Application with Meta-analysis (CPMP/EWP/2330/99). This permitted an evaluation of efficacy and effectiveness across trials that individually failed to reach the necessary statistical power.

- A sub-group and meta-regression analysis exploring the potential for differences in fusion success rates between InductOs (N=544) and ICBG (N=387) due to surgical approach (anterior *versus* posterior) or by type of interbody fusion device. The data set included seven RCTs (including six Medtronic-sponsored RCTs) and six non-randomised controlled studies (NRS).

- Clinical synopses from 20 selected publications covering 19 clinical studies and 1981 subjects (overview provided in Table 3). The publications included non-Medtronic RCTs and NRS including non-Medtronic publications that did not meet the inclusion criteria for the meta-analysis.

Table 3: Overall Summary of Clinical Trials – Published non-Medtronic: Sample Size by Interbody Fusion Device Material and Surgical Approach

	Titanium		Polymer		Allograft		Not reported	
Surgical Approach**	**INV**	**CTRL**	**INV**	**CTRL**	**INV**	**CTRL**	**INV**	**CTRL**
ALIF	-	-	-	-	54	57	-	-
PLIF/TLIF	9	0	954	29	85	15	107*	52*
Other	45	54	60	15	-	-	-	-
ALIF, PLIF/TLIF	-	-	-	-	25	29	-	-
ALIF, Other PLIF/TLIF	-	-	-	-	-	-	391	0
TOTALS	**54**	**54**	**1014**	**44**	**164**	**101**	**498**	**52**

* Including Titanium or PEEK; ** Other' includes lateral lumbar interbody fusion (LLIF); CTRL=control (ICBG); INV=investigational (InductOs)

2.4.2. Discussion on clinical efficacy

Design and conduct of clinical studies

In support of the application, the MAH has presented data from eight Medtronic-sponsored studies, data from additional analyses, and clinical synopsis from selected publications covering 19 trials. Four of these studies are pilot studies, three are supportive studies, leaving one of the studies as pivotal (3100N3-303). Studies 3100N3-117, 303 and 304 were already presented with the initial marketing authorisation application for the spinal fusion indication. Important for this application are studies performed with other devices than the LT-CAGE, with other surgical techniques than ALIF (Anterior Lumbar Interbody Fusion) and in other lumbar levels than L4-S1. All these were only investigated in pilot trials or in the supportive trials.

In addition to these studies, the MAH performed a post-hoc meta-analysis of six Medtronic-sponsored trials, permitting an evaluation of efficacy across trials that individually failed to reach the necessary statistical power.

Furthermore, a sub-group and meta-regression analysis was performed exploring the potential for differences in fusion success rates between InductOs and ICBG (Iliac Crest Bone Graft) due to surgical approach (anterior vs. posterior) or by type of interbody fusion device. The data set included seven RCTs, of which six were Medtronic-sponsored RCTs, and six NRS.

Results of independent meta-analyses were presented by the MAH in 2012 (post-authorisation measure 063.1). During this procedure, two meta-analyses were discussed, one by York University and the other by Oregon Health & Science University (OHSU). These analyses also included the Medtronic sponsored studies. The York analysis showed an increased rate of fusion with rhBMP-2 compared to ICBG. There was also a moderate improvement in pain that did not seem to be the result of the increase in fusion. The OHSU meta-analysis concluded that in spinal fusion rhBMP-2 and ICBG appear to be similarly effective when used in ALIF and PLF. The CHMP's overall conclusion at that time was that efficacy of InductOs was non-inferior or superior compared to standard of care.

As this application concerns an extension of the indication to all types of surgery for anterior interbody fusion, all types of CE-marked devices made of titanium PEEK or allograft, and all lumbar levels, the accent of the assessment is on the subgroup analysis where the type of device and surgical approach were analysed. Efficacy and safety in general were already presented with the two former meta-analyses and in the original variation application for spinal surgery.

The primary comparison in the meta-analysis was the proportion of patients with radiological fusion success at 24 months post-operation across the Medtronic-sponsored controlled clinical trials. Fusion success rate and failure-related secondary surgery were analysed by surgical approach and by type of interbody device. Other parameters, such as Oswestry Disability Index (ODI), Short Form (SF)-36 score, back pain and leg pain score, neurological success rate, disc height success rate were presented by the MAH, but these parameters were not analysed by surgery approach or type of interbody device. Therefore, the CHMP considered that these data do not contribute to the discussion on benefit/risk of surgical approach, type of device and lumbar level, and are not discussed further.

Two additional studies were submitted by the MAH. Study P01-08 is a large study, including 577 subjects. During this procedure the MAH has submitted the Final study report of study P01-08 (MAVERICK study). In this study the MAVERICK Total Disc Replacement System was compared to Spinal Fusion (rhBMP-2/ACS in LT-Cage) in subjects with degenerative disc disease. Although MAVERICK was superior compared to InductOs for several key outcomes, there were also some adverse events. Therefore, the CHMP considered that the comparison is not valid for this application.

The other study, P05-06, is still ongoing. Total number of subjects to be randomized was 534. The first patient was enrolled on 28 November 2011. Enrolment was suspended on 19 October 2012, due to one subject experiencing an expected AE (fluid collection (wound seroma)) that triggered a pre-defined enrolment suspension criteria and subsequent Data Monitoring Committee review. As of 1 September 2013, 15 subjects had been enrolled and undergone surgery (11 subjects in the investigational Treatment group and 4 subjects in the Control group).The main enrolment difficulties were linked to the Body Mass Index (BMI) criteria, as well as the challenge of enrolling to the control group given it was not considered standard of care. The main screen failures were due to patient being osteoporotic, having low ODI scores at screening or having too mild leg pain scores. The reasons for “slow enrolment” were acknowledged by the CHMP.

The MAH performed a literature review to support the clinical trials and meta-analysis described above. Twenty publications, representing 19 trials, were selected. Seven studies were also included in the meta-analysis, reducing the supportive value of this literature review.

Efficacy data and additional analyses

The CHMP was of the view that data presented for Fusion Success Rate were in line with the data from the previous submitted meta-analyses, as can be expected.

In the six Medtronic-sponsored trials, at 24 months post-surgery, the use of InductOs was associated with a higher fusion success rate (94.5%, 241/255) compared with ICBG (84.6%, 177/209). The difference between the two groups was statistically significant (OR 3.262, p=0.024). For the primary analysis dataset at 6 and 12 months, the fusion success rate was 96.6% (253/262) and 96.1% (249/259) respectively, for InductOs and 92.4% (195/211) and 91.2% (195/212) respectively, for ICBG, with no significant difference between the groups at either time point. This did not support a claim for accelerated fusion.

The addition of non-Medtronic RCT (one study) and NRS data (six studies) to the Medtronic CSRs did not affect the finding of a significantly increased fusion success rate for rhBMP-2/ACS versus ABG.

In a subgroup analysis for fusion success by surgical approach (for all six anterior lumbar interbody fusion studies), fusion success was 92.8% (221/238) for InductOs compared with 82.8% (173/209) for ICBG (OR 2.29). This compares with 96.8% (274/283) and 91.7% (154/168) for InductOs and ICBG,

respectively, in all seven posterior studies (OR 2.12). A formal meta-regression analysis found no statistically significant difference in the effect of InductOs on fusion success between ALIF and other surgical approaches (ratio of odds ratios ROR=0.863, P=0.847). In this analysis, two studies have been changed by mistake (Joseph et al (2007) and Gerszten et al (2011)). The MAH acknowledge that the Joseph (Joseph et al. 2007) and Gerszten (Gerszten et al. 2011) studies were indeed incorrectly listed in the Meta-analysis report and corrected it. In addition, the MAH re-ran the original search (cut-off 20 June 2013) to capture eligible studies published up to 2 July 2014. One new non-randomised study was identified (Adams et al. 2014) that reported on patients undergoing TLIF or PLIF with rhBMP-2 administered using PEEK interbody devices. The CHMP considered that the correction of the error in the listing of the Joseph and the Gerszten studies, and the addition of the new Adams study, did not change the results in a relevant way. The difference in fusion success rates was unchanged for the anterior approach studies (92.8% for InductOs vs 82.8% for ICBG) and was slightly increased for PLIF/TLIF (97.1% for InductOs vs 91.6 % for ICBG; previously it was 96.8 % vs 91.7%).

When analysing the effect of the device, similar results were obtained. The relative effect of InductOs was not significantly associated with the types of interbody device used ($\chi 2=2.48$, df=6, P=0.870). For titanium devices (LT-CAGE or INTER FIX devices, four studies), the InductOs fusion rate was 93.0% (174/187) and 87.1% (142/163) for ICBG. For allograft spacers (four studies), the InductOs fusion rate was 96.3% (156/162), compared with 75.0% (66/88) for ICBG. For PEEK devices, the fusion rate was 95.4% (62/65) for InductOs and 94.6% (70/74) for ICBG. The difference in the effect of InductOs on fusion success was statistically non-significant between being administered with an allograft device and other devices (ROR 1.948, p=0.442). It is remarkable in these studies that the InductOs fusion rate is not dependent on the type of device (93-96%), but the ICBG fusion rate varies from 75-95%. The CHMP considered that here too, numbers were small, and it was not possible to draw a firm conclusion.

The CHMP also considered that the results for Failure-related secondary surgery were in line with data for fusion success rate.

In order to increase the number of studies suitable for meta-analysis the MAH, during the procedure, widened the inclusion criteria. An additional 30 studies were identified by literature search. Overall, the studies available for the supplementary meta-analysis included data from seven randomised controlled trials (with ABG (autogenous bone graft) control), seven non-randomised controlled studies (with ABG control), and 29 other studies (with no ABG control arm). Together, these 43 studies contributed to 59 treatment arms (45 rhBMP-2/ACS and 14 ABG arms), with a total of 2586 patients treated with rhBMP-2/ACS and 405 patients treated with ABG.

The statistical methods used for this supplementary meta-analysis were similar to those used in the original meta-analysis, and are acceptable. This broader range of studies, including uncontrolled studies and studies with a small proportion of patients undergoing lumbar interbody fusion for adult spinal degenerative deformity, led to considerable heterogeneity. Even though the same amount of heterogeneity was found earlier in a similar study, suggesting this heterogeneity reflects the real use of the product, the results of this supplementary meta-analysis have to be interpreted with caution. Furthermore, a potential problem in meta-analyses is publication bias. By widening the inclusion criteria for the supplementary meta-analysis, the risk of publication bias has likely become higher. It is therefore possible that the supplementary meta-analysis exaggerates the outcome. Most newly added studies were retrospective and uncontrolled. In addition, the definition of radiological fusion varied widely in the 30 new studies. These are also limitations of the supplementary meta-analysis.

For all studies, fusion success rate for rhBMP-2/ACS was 94.0% (95% CI: 91.3-96.3) compared to 84.5% (95% CI: 80.7-91.4) for autogenous bone graft.

Subgroup analysis according to surgical procedure revealed no significant differences in fusion success rates for the rhBMP-2/ACS group: ALIF 91.6%, PLIF/TLIF 95.0%, Other 95.0%. In the ABG group differences approached statistical significance, with ALIF performing least: ALIF 78.5%, PLIF/TLIF 91.1%, Other 91.8%. The MAH reasons that this may be due to the use of transpedicular screws in TLIF/PLIF procedures for achieving segmental fixation and as a consequence high fusion rates. This seemed plausible to CHMP, as a stable fixation is important for successful fusion. However, the added value of rhBMP-2/ACS in procedures other than ALIF can be questioned. The difference in fusion success rates in PLIF/TLIF procedures between rhBMP-2/ACS and ABG is only 4.9%. In the corrected meta-analysis, using only controlled studies, the difference in fusion success rates in PLIF/TLIF procedures between rhBMP-2/ACS and ABG was 5.5%. The majority of lumbar interbody fusion procedures performed in Europe are performed via posterior approaches (PLIF + TLIF) and they represented more than 80% of all procedures performed in 2011 compared with ALIF representing less than 15% of all procedures. Thus, for Europe, using rhBMP-2/ACS is approved for the ALIF-procedure, but this is hardly employed; for the mostly used PLIF-procedure the difference in fusing rate between rhBMP-2/ACS and ABG is about 5%. On the other hand, results for rhBMP-2/ACS with PLIF are numerically better than the approved rhBMP-2/ACS with ALIF, which supports the PLIF procedure.

Fusion success rates with rhBMP-2/ACS were not significantly different for interbody device types composed of titanium, PEEK, allograft, or other materials ($p=0.975$), while the difference in fusion success between interbody devices in ABG patients was statistically significant ($p=0.025$).

In the 30 new studies, there were 17 studies reporting use at L1-L4. However, number of patients treated at other levels is not known and outcome data were not stratified for lumbar level. Thus, no additional data are available for other levels. For fusion, biological and mechanical environment are important. These do not differ much between L1, L2 and L4-S1. For mechanical stability it is required that the osseous component of the end-plate remains intact. Difficulties may arise in patients with osteoporosis, for whom there may be a loss of bone density in subchondral trabeculae. Overall, factors such as osteoporosis, age, and disease severity may influence the nature of the vertebral endplate in contact with rhBMP-2/ACS, but these factors are common to all levels of the lumbar spine, with the exception that the frequency of disease severity increases caudally. Other anatomical features of the endplate vary more within a single disc level than they do at different lumbar levels.

The CHMP therefore considered that the extension of the indication to: “single-level lumbar interbody spine fusion as a substitute for autogenous bone graft in adults with degenerative disc disease who have had at least 6 months of non-operative treatment for this condition” is acceptable.

2.4.3. Conclusions on the clinical efficacy

In support of the variation, the MAH has presented data from 8 Medtronic-sponsored studies and data from literature. Important for this variation is the post-hoc meta-analysis of 6 Medtronic studies and literature, and a subgroup and meta-regression analysis exploring the potential for differences in fusion success rates between InductOs and ICBG due to surgical approach (anterior vs posterior) or by type of interbody fusion device. The data set included seven RCTs (including six Medtronic RCTs) and six non-randomised controlled studies (NRS).

The post-hoc meta-analysis of 6 controlled clinical trials with data from patients treated with InductOs or autogenous bone graft administered using CE-marked interbody fusion devices or allograft bone spacers and various surgical approaches showed that, at 24 months post-surgery, InductOs was associated with a higher fusion success rate (95 %, 241 out of 255 patients) compared with autogenous bone graft (85 %, 177 out of 209 patients), with an odds ratio of 3.26 (95 % CI: 1.172,

9.075; P = 0.024). The estimated absolute difference in fusion success rate between InductOs and autogenous bone graft was 11.7 % (95 % CI: 8.0 %, 22.5 %; P = 0.035).

Although the results of this supplementary meta-analysis have to be interpreted with caution, due to considerable heterogeneity, the CHMP considered that in the EU, using rhBMP-2/ACS is approved for the ALIF-procedure, but this is hardly employed; for the mostly used PLIF-procedure the difference in fusing rate between rhBMP-2/ACS and ABG is about 5%. The fusion success rates with rhBMP-2/ACS were not significantly different for interbody device types composed of titanium, PEEK, allograft, or other materials (p=0.975).

The CHMP agreed to extend the indication to single-level lumbar interbody spine fusion.

The CHMP also agreed that InductOs should be used with an approved (CE-marked) lumbar interbody fusion device(s) and that compatibility has been demonstrated with titanium, polyetheretherketone (PEEK), and allograft bone.

2.5. Clinical safety

2.5.1. Introduction

Patient exposure

Safety analysis included trials presented in

Table 1. Thus a total of 700 patients were involved, 456 on InductOs and 244 ICBG. The MAVERICK study was also not included in the safety analysis.

Adverse events

The overall frequency of AEs in patients at 24 months was 80.9% in the pooled InductOs data, compared with 85.7% in the pooled control data (Table 4). The overall frequency of patients reporting (S)AEs, related (S)AEs and donor site complications were approximately 4-5% lower in the pooled InductOs group compared with the pooled control group.

The overall frequencies of (S)AEs and related (S)AEs in patients between selected individual studies representing different surgical approaches, different interbody device designs and materials, do not raise concerns for InductOs compared with ICBG.

The overall frequency of AEs by SOC in pooled data is shown in Table 5. The most frequently affected SOC was Musculoskeletal and Connective Tissue Disorders for both investigational and control groups.

In the pooled study data, Back Pain, Pain in Extremity and Fall were the most frequently occurring AEs in patients at 24 months. The most notable finding is the frequency of Pseudarthrosis; the rate of the event in the InductOs group (6.1%), compared with the control (13.1%). Although Musculoskeletal Pain has a frequency of 8.1% in the investigational group and just 4.9% in the control, Muscle Spasm has a frequency of 3.5% in the investigational group and 6.6% in control. An imbalance in the rates of Retrograde Ejaculation has been noted previously and is unique to the ALIF surgical procedure.

Treatment-related AEs

Pseudarthrosis was the most frequently occurring individual treatment-related AE in patients at 24 months, followed by Device Dislocation in both treatment groups. Frequencies in patients of treatment-

related Pseudarthrosis AEs were 4.8% in the pooled investigational study data compared with 12.7% in pooled control study data, representing the effectiveness of dibotermin alfa.
The frequency of an AE of Device Dislocation in pooled study data was 3.5% in investigational patients and 2.5% in control patients at 24 months.

Serious adverse event / deaths / other significant events

The frequency of each SAE by MedDRA preferred term was generally low and differences unremarkable. Some categories such as Musculoskeletal Pain (2.0% INV *versus* 0.4 % CTRL) and Surgical and Medical Procedures (2.4% INV *versus* 1.2% CTRL) were numerically higher in the INV group, but others such as Road Traffic Accident (1.1% INV *versus* 2.5% CTRL) and Respiratory, Thoracic and Mediastinal Disorders (1.3% INV *versus* 2.5 % CTRL) were numerically lower in the INV group. These differences are most likely due to chance. Of note, Pseudarthrosis was 2 times lower in the InductOs group compared with autograft control (4.6% *versus* 8.6%, respectively).

There were few deaths in all 8 studies throughout the 24-month study duration: 0.2% (1/456) in the InductOs groups, compared with 1.6% (4/244) for control. None of the 5 deaths in either treatment group was considered to be related to the treatment or the surgical procedure.

Table 4: Overall Frequency of All Adverse Events in Patients in Individual Studies and Pooled Studies up to 24 Months

Study	3100N3-117 ALIF/LT/PIL		3100N3-303 ALIF/LT/OPEN		3100N3-304 ALIF/LT/LAP	C-9703 ALIF/BD/PIL		P00-01 ALIF/BD/PIV		C-9804 ALIF/IFIX		C-9806 PLIF/IFIX		P01-07 PLIF/TEL	Pooled Studies	
Event	**INV N=11 % (n)**	**CTRL N=3 % (n)**	**INV N=143 % (n)**	**CTRL N=136 % (n)**	**INV N=134 % (n)**	**INV N=24 % (n)**	**CTRL N=22 % (n)**	**INV N=55 % (n)**	**CTRL N=30 % (n)**	**INV N=25 % (n)**	**CTRL N=20 % (n)**	**INV N=34 % (n)**	**CTRL N=33 % (n)**	**INV N=30 % (n)**	**INV N=456 % (n)**	**CTRL N=244 % (n)**
Any AE	72.7 (8)	100.0 (3)	83.2 (119)	83.8 (114)	75.4 (101)	79.2 (19)	81.8 (18)	78.2 (43)	76.7 (23)	68.0 (17)	90.0 (18)	97.1 (33)	100.0 (33)	96.7 (29)	80.9 (369)	85.7 (209)
Any Implant or Implant/Surgical Procedure AE	36.4 (4)	66.7 (2)	11.9 (17)	12.5 (17)	11.9 (16)	8.3 (2)	36.4 (8)	5.5 (3)	23.3 (7)	16.0 (4)	5.0 (1)	14.7 (5)	15.2 (5)	6.7 (2)	11.6 (53)	16.4 (40)
Any SAE	18.2 (2)	33.3 (1)	37.8 (54)	41.9 (57)	42.5 (57)	58.3 (14)	36.4 (8)	21.8 (12)	40.0 (12)	44.0 (11)	30.0 (6)	35.3 (12)	54.5 (18)	36.7 (11)	37.9 (173)	41.8 (102)
Any Implant or Implant/Surgical Procedure SAE	0.0 (0)	33.3 (1)	7.7 (11)	8.8 (12)	4.5 (6)	4.2 (1)	18.2 (4)	3.6 (2)	13.3 (4)	12.0 (3)	5.0 (1)	11.8 (4)	9.1 (3)	3.3 (1)	6.1 (28)	10.2 (25)

Table 5: Overall Frequency of Patients with AEs by SOC (AEs in ≥ 1% of Patients in Pooled Studies)

System Organ Class At 24 months	**Pooled INV** **N = 456** **P (%)**	**Pooled CTRL** **N = 244** **P (%)**
Patients with Any AE	**369 (80.9)**	**209 (85.7)**
Gastrointestinal Disorders	51 (11.2)	32 (13.1)
General Disorders and Administrative Conditions	83 (18.2)	49 (20.1)
Immune System Disorders	2 (0.4)	3 (1.2)
Infections and Infestations	43 (9.4)	19 (7.8)
Injury, Poisoning and Procedural Complications	195 (42.8)	120 (49.2)
Investigations	15 (3.3)	13 (5.3)
Musculoskeletal and Connective Tissue Disorders	259 (56.8)	145 (59.4)
Nervous System Disorders	114 (25.0)	64 (26.2)
Psychiatric Disorders	23 (5.0)	14 (5.7)
Renal and Urinary Disorders	26 (5.7)	12 (4.9)
Reproductive System and Breast Disorders	29 (6.4)	11 (4.5)
Respiratory, Thoracic and Mediastinal Disorders	17 (3.7)	12 (4.9)
Skin and Subcutaneous Tissue Disorders	19 (4.2)	10 (4.1)
Surgical and Medical Procedures	12 (2.6)	3 (1.2)

Evaluation of undesirable effects in the currently approved SmPC

Neuralgia

The currently approved product information states that the most common adverse reaction related to the use of InductOs in spine surgery was neuralgia. This event was introduced in the product information based on studies coded in COSTART in which 27 patients (18.9%) in the InductOs group and 17 patients (12.5%) in the control group had an adverse reaction of Neuralgia. Due to the lack of granularity in COSTART, several neurological events were coded to Neuralgia. The MAH has recently recoded the data to MedDRA and pooled the data from 8 relevant studies for the analysis of adverse reactions. This allowed a more precise analysis of the observed events. The frequency of neuralgia with InductOs appeared to be similar to that with control: InductOs 0.4% (2 events, 2 patients) vs. Control 1.6% (4 events, 4 patients).

Nerve compression/nerve root disorders

Radiculitis is described in the currently approved product information based on post-market reports. In the current pooled analysis, the frequency of radiculitis and radiculopathic events is similar – 6.6% for both InductOs and the control group. Table 6 presents the occurrence of radiculitis/radiculopathy in the pooled study data by surgical approach.

Table 6: Overall Frequency of Patients with Treatment-Related Adverse Events Associated with Radiculitis/Radiculopathy at 24 Months by Surgical Approach (Pooled Data)

Surgical Approach	**ALIF**		**PLIF**	
	Pooled INV N = 392	**Pooled CTRL N = 211**	**Pooled INV N = 64**	**Pooled CTRL N = 33**
Preferred Term (MedDRA)	**AEs Events | Patients* (%)**		**AEs Events | Patients* (%)**	
Lumbar Radiculopathy	9 | 9 (2.3%)	0 | 0 (0.0%)	2 | 2 (3.1%)	1 | 1 (3.0%)
Radicular Pain	4 | 4 (1.0%)	3 | 3 (1.4%)	3 | 3 (4.7%)	3 | 3 (9.1%)
Radiculitis Lumbosacral	1 | 1 (0.3%)	1 | 1 (0.5%)	0 | 0 (0.0%)	0 | 0 (0.0%)
Radiculopathy	7 | 7 (1.8%)	5 | 5 (2.4%)	0 | 0 (0.0%)	0 | 0 (0.0%)
Sciatica	4 | 4 (1.0%)	3 | 3 (1.4%)	1 | 1 (1.6%)	0 | 0 (0.0%)
Radiculitis	0 | 0 (0.0%)	0 | 0 (0.0%)	0 | 0 (0.0%)	0 | 0 (0.0%)
Total	**25 | 24 (6.1%)**	**12 | 12 (5.7%)**	**6 | 6 (9.4%)**	**4 | 4 (12.1%)**

Back pain

The adverse event Back Pain was very common in both groups (24-28%). This is anticipated, even after treatment, and both groups report this event. Only a few of the cases were considered treatment-related.

Device migration

The currently approved product information states that device migration is commonly observed during use in anterior lumbar spine surgery.

In the pooled data there is slightly more device migration (Device Dislocation and Device Extrusion) reported in the investigational group than in the control group (3.7% vs 2.5%). These issues with the medical device used may be due to the device itself or the techniques used by the surgeon.

Resorption Bone Increased

Bone resorption is normal part of the bone remodelling process and osteoclastic activity is a component of the mode of action of dibotermin alfa to form new bone.
In a higher-dose prospective observational study of the PLIF surgical approach, InductOs (12 mg) was associated with transient, asymptomatic vertebral endplate resorption in 17/17 patients.
Table 7 provides the overall frequency for bone resorption increased and pseudarthrosis from pooled study data.

Table 7: Overall Frequency of Patients with Treatment-Related Adverse Events Associated with Bone Resorption Increased and Pseudarthrosis (Pooled Data)

Preferred Term (MedDRA) At 24 months	**Pooled INV N = 456**	**Pooled CTRL N = 244**	**Pooled INV N = 456**	**Pooled CTRL N = 244**
	AEs Events | Patients (%)		**Treatment-Related AEs Events | Patients (%)**	
Osteolysis	1 | 1 (0.2%)	0 | 0 (0.0%)	0 | 0 (0.0%)	0 | 0 (0.0%)
Pseudarthrosis	28 | 28 (6.1%)	32 | 32 (13.1%)	22 | 22 (4.8%)	31 | 31 (12.7%)
Resorption Bone Increased	1 | 1 (0.2%)	0 | 0 (0.0%)	1 | 1 (0.2%)	0 | 0 (0.0%)
Total (excl Pseudarthrosis)	**2 | 2 (0.4%)**	**0 | 0 (0.0%)**	**1 | 1 (0.2%)**	**0 | 0 (0.0%)**
Total	**30 | 30 (6.6%)**	**32 | 32 (13.1%)**	**23 | 23 (5.0%)**	**31 | 31 (12.7%)**

Heterotopic ossification

The frequency of heterotopic ossification in relation to surgical approach is shown in Table 8. For subjects who underwent an ALIF procedure, similar frequencies are found in the investigational group (2.0%; 8/392) and the control group (1.9%; 4/211). However, for subjects who underwent a PLIF procedure, there is a difference. In the investigational group a frequency of 7.8% (5/64 subjects) was found compared with 0% (0/33 subjects) in the control group.

Table 8: Overall Frequency of Patients with AEs Associated with Heterotopic Ossification by Surgical Approach at 24 Months (Pooled Data)

Surgical Approach	**ALIF**		**PLIF**	
	INV N = 392	**CTRL N = 211**	**Pooled INV N = 64**	**Pooled CTRL N = 33**

Preferred Term (MedDRA)	AEs Patients (%)		AEs Patients (%)	
Exostosis	8 (2.0%)	4 (1.9%)	4 (6.3%)	0 (0.0%)
Implant Site Calcification	0 (0.0%)	0 (0.0%)	1 (1.6%)	0 (0.0%)
Total	**8 (2.0%)**	**4 (1.9%)**	**5 (7.8%)**	**0 (0.0%)**

Fluid Collection

The event of fluid collection and cyst/pseudocyst was previously added to the product information based on post-market reports and a potential causal link between effusion/oedema and administration of the product. Animal studies suggested it to be a possible dose-related response linked with the initial pro-inflammatory or angiogenic activity of dibotermin alfa.
When reviewing the events describing fluid collection and cyst/pseudocyst in the pooled study data, a higher frequency was found for the control group compared to the investigational group (1.2%*versus* 0.7%, respectively). In a recently published systematic review (Brown et al., 2013), two papers were examined for the relative risk of inflammatory cyst formation for InductOs compared with control. Only one paper was found with sufficient evidence to draw a conclusion. The study was a retrospective analysis of medical records (Williams et al., 2011). There were 43 inflammatory cyst formation events out of a total of 18 267 events. There was no evidence of a difference in inflammatory cyst formation (RR 1.05; 95% CI 0.59; 1.89) between treatment with and without InductOs in this study (Brown et al., 2013).

Pseudarthrosis

The frequency of Pseudarthrosis in the pooled study data was approximately 2-fold lower in the InductOs group compared with control patients at 24 months for both anterior and posterior surgical approaches (Table 9).

Table 9: Overall Frequency of Patients with the Adverse Event Pseudarthrosis

Event at 24 months	Surgical Approach	InductOs % Patients	Control % Patients
AE Pseudarthrosis	All	6.1%	13.1%
Related AE Pseudarthrosis	All	4.8%	12.7%
SAE Pseudarthrosis	All	4.6%	8.6%
Related SAE Pseudarthrosis	All	3.5%	8.2%
AE Pseudarthrosis	Anterior	6.6%	12.8%
Related AE Pseudarthrosis	Anterior	5.1%	12.3%
AE Pseudarthrosis	Posterior	3.1%	15.1%
Related AE Pseudarthrosis	Posterior	3.1%	15.2 %

Immunological events

The currently approved product information contains a warning in Section 4.4 that both dibotermin alfa and bovine type I collagen have been found to elicit immune responses in patients. The MAH has conducted an extensive review of the information on the immune response to dibotermin alfa and bovine type I collagen from both Medtronic-sponsored and Pfizer-sponsored clinical trials.
Of the 17 dibotermin alfa spinal studies with antibody testing conducted by Medtronic, three out of the 40 patients with positive dibotermin alfa antibody titres were judged to be fusion failures, and two of these were control patients who did not receive dibotermin alfa. Within these spine fusion studies, 32

out of the 33 investigational patients (97%) fused successfully in the presence of antibodies to dibotermin alfa.

2.5.2. Discussion on clinical safety

Adverse events for InductOs (n=456) and control groups (n=244) in all 8 studies were pooled to improve the accuracy of the estimation of AE frequencies at the MedDRA preferred term level. A range of doses of dibotermin alfa was used (3.9 to 16.8 mg at 1.5 mg/mL), extending beyond the maximum recommended dose of 8 mg for this indication; both anterior and posterior surgical approaches were employed; different interbody devices were used.
No statistical analyses were performed comparing the frequency of AEs in the pooled InductOs and control group data. Several AEs with numerically higher or lower frequencies in the pooled InductOs group were highlighted. No new or unexpected safety issues were identified.

In the pooled safety data analysis of 8 clinical trials at 24 months post-surgery, the frequency of patients with pseudarthrosis was approximately 2-fold lower following treatment with InductOs (4.8 %, 22 out of 456 patients) compared with autogenous bone graft (12.7 %, 31 out of 244 patients).

The currently approved product information states that the most common adverse reaction related to the use of InductOs in spine surgery was neuralgia. This event was introduced in the product information based on studies coded in COSTART in which 27 patients (18.9%) in the InductOs group and 17 patients (12.5%) in the control group had an adverse reaction of Neuralgia. Due to the lack of granularity in COSTART, several neurological events were coded to Neuralgia. The MAH has recently recoded the data to MedDRA and pooled the data from 8 relevant studies for the analysis of adverse reactions. This allowed a more precise analysis of the observed events. The frequency of neuralgia with InductOs appeared to be similar to that with control: InductOs 0.4% (2 events, 2 patients) vs. Control 1.6% (4 events, 4 patients). The MAH therefore proposed to delete 'Neuralgia' as an adverse reaction from section 4.8. This was agreed by the CHMP.

Radiculitis is described in the currently approved product information based on post-market reports. In the current pooled analysis, the frequency of radiculitis and radiculopathic events is similar – 6.6% for both InductOs and the control group. The frequency of radiculitis/radiculopathy seemed slightly higher when the posterior surgical approach was used (PLIF), based on the pooled study data. The frequency is consistent with the literature. The use of threaded dowels and cages for PLIF has been reported in the literature to be associated with postoperative radiculopathy in up to 13% of cases. The MAH considered there is a potential causal link between radiculitis/radiculopathy and the use of InductOs. The MAH proposed to add the following terms to radiculitis in the table in Section 4.8 of the SmPC: Lumbar Radiculopathy, Radicular Pain, Radiculitis Lumbosacral, Radiculopathy and Sciatica. This group of terms occurs commonly with a frequency of 6.6%. This was agreed by the CHMP.

The adverse event Back Pain was very common in both groups (24-28%). This is anticipated, even after treatment, and both groups report this event. Only a few of the cases were considered treatment-related. The MAH was the opinion that this event is a common condition in the target population and not causally related to the use of InductOs. Given the lack of causality and the similar incidence in both the InductOs and the control group, the MAH proposed to remove this event from the table in Section 4.8 of the SmPC. This was agreed by the CHMP.

In the pooled data there is slightly more device migration (Device Dislocation and Device Extrusion) reported in the investigational group than in the control group (3.7% vs 2.5%). These issues with the medical device used may be due to the device itself or the techniques used by the surgeon. However, a contributory factor from use of InductOs cannot be excluded. Post-market reports have suggested a

link between bone resorption (radiolucency) and device dislocation. The frequency in the approved product information correctly reflects the frequency observed in the pooled study data; hence no change was proposed by the MAH. However, the MAH has updated the wording to the up-to-date Preferred Term "Device Dislocation". This was agreed by the CHMP.

In the pooled study data, the number of Osteolysis and Resorption Bone Increased events was very low and a comparison between the investigational and the control group is difficult to make. Overall, publications report a range of frequencies for osteolysis from 0% to 100% associated with the use of InductOs in lumbar interbody fusion administered using either an anterior or posterior surgical approach (and may not necessarily have any adverse clinical consequences). Given the wide range of frequencies observed the MAH proposed to keep both 'Osteolysis' and 'Bone Resorption Increased' terms in the SmPC and the frequency as 'unknown'. This was agreed by the CHMP.

A detailed post-hoc radiological assessment of the rate of heterotopic ossification was conducted for Study P01-07 and Study C-9806. In both studies the majority of patients showed radiographic evidence of heterotopic ossification. This may indicate that a causal relationship between exposure to InductOs and heterotopic ossification is made more likely by the posterior surgical approach. The currently approved product information states that when DDD was treated by a posterior lumbar interbody fusion procedure with cylindrical threaded cages and dibotermin alfa, posterior bone formation was observed in some instances. The proposed product information keeps the warning but removes the reference to a specific interbody fusion device and states:" In clinical trials when degenerative disc disease was treated by a posterior lumbar interbody fusion procedure with dibotermin alfa, posterior bone formation was observed". This was agreed by the CHMP.

The event of fluid collection and cyst/pseudocyst was previously added to the product information based on post-market reports and a potential causal link between effusion/oedema and administration of the product. Animal studies suggest it to be a possible dose-related response linked with the initial pro-inflammatory or angiogenic activity of dibotermin alfa. When reviewing the events describing fluid collection and cyst/pseudocyst in the pooled study data, a higher frequency was found for the control group compared to the investigational group (1.2%*versus* 0.7%, respectively). In a recently published systematic review (Brown et al., 2013), two papers were examined for the relative risk of inflammatory cyst formation for InductOs compared with control. Only one paper was found with sufficient evidence to draw a conclusion. The study was a retrospective analysis of medical records (Williams et al., 2011). There were 43 inflammatory cyst formation events out of a total of 18 267 events. There was no evidence of a difference in inflammatory cyst formation (RR 1.05; 95% CI 0.59; 1.89) between treatment with and without InductOs in this study (Brown et al., 2013).

The MAH took the view that a causal link between fluid collection and the known pharmacology of dibotermin alfa is possible. The frequency of these events may be estimated as 'common'. Therefore, the MAH proposed to change the table in Section 4.8 accordingly. This was agreed by the CHMP.

To better characterise the safety profile, the Medtronic Clinical trial safety database was pooled by surgical approach, i.e. ALIF and PLIF. In general, more patients in the PLIF group experienced AEs as compared to the ALIF group. However, there were no differences between rhBMP-2/ACS treated subjects and ABG subjects.

The System Organ Class (SOC) with the most reported adverse events was Musculoskeletal and Connective Tissue Disorders in both groups, with 441 events in 208 subjects for ALIF and 158 events in 51 subjects for PLIF. The SOC Nervous System Disorders ranked second with regards to number of reported events (ALIF: 115 events in 85 subjects; PLIF: 46 events in 29 subjects). There were no important differences between rhBMP-2/ACS treated patients and ABG treated patients.

Comparison of the other events from the ALIF and PLIF trials showed that the differences predominantly reflect the known potential risks of the two specific surgical approaches and that these surgical risks are independent of the use of rhBMP-2/ACS.

An exception is pseudoarthrosis, occurring less frequently in rhBMP-2/ACS subjects as compared to controls in both ALIF and PLIF.
Furthermore, the risk for heterotopic ossification is an acknowledged risk with spinal surgery in general and PLIF in particular. With respect to the occurrence after lumbar interbody fusion with rhBMP-2/ACS three sources of evidence were discussed by the MAH: 1) Medtronic clinical trials, 2) Published literature reports, and 3) Post-marketing adverse drug reaction reports. Medtronic clinical trial data showed that, as a whole, even with increased rates of radiographic evidence of heterotopic ossification, reoperation rates were not increased and overall clinical outcomes were not worse for rhBMP-2-treated patients than control patients. Following surgery with rhBMP-2 in posterior approaches, the risk of symptomatic heterotopic ossification (mostly requiring surgery) varies from 0.59% to 6.7% (Rihn et al. 2009, Crandall et al. 2013, Pimenta et al. 2013, Singh et al. 2013, Adams et al. 2014, Nandyala et al. 2014).
The MAH proposed an update of the product information with more detailed instructions regarding administration/handling of the product. This was agreed by the CHMP.
The indication anterior lumbar spine fusion was approved in the EU in 2005. During the procedure, there were spontaneous reports from the US of localised oedema following unlicensed use in cervical spine fusion procedures. The SmPC has therefore been updated with warnings on type of surgery, device and spinal level. The MAH also analysed the spontaneous cases possibly linked to cervical spine surgery (all originating from US) and no new safety finding was observed. It is agreed with the MAH that the number of cervical off-label use cases is low at the moment, in the context of 1.3 million patients exposed, however this might also be due to underreporting and the real rates might be higher. The MAH will therefore continue monitoring the off-label use of InductOs and report it in PSURs, which is accepted by the CHMP.

In general, more patients in the PLIF group experienced AEs as compared to the ALIF group. However, there were no differences between rhBMP-2/ACS treated subjects and ABG subjects. The risk of heterotopic ossification can be adequately minimised by informing the HCPs on how to correctly use this product, by taking care not to overfill, prevent leakage and create a physical barrier between the device and neurological tissue. The update of the SmPC and MAH's proposals for risk minimisation are considered adequate by the CHMP.

2.5.3. Conclusions on clinical safety

No new or unexpected safety issues were identified. The overall frequency of AEs in patients at 24 months was 80.9% in the pooled InductOs data, compared with 85.7% in the pooled control data. In the pooled study data, back pain, pain in extremity and fall were the most frequently occurring AEs in patients at 24 months. The most notable finding is the frequency of pseudarthrosis; the rate of the event in the InductOs group (6.1%), compared with the control (13.1%). Although musculoskeletal pain has a frequency of 8.1% in the investigational group and just 4.9% in the control, muscle spasm has a frequency of 3.5% in the investigational group and 6.6% in control. An imbalance in the rates of retrograde ejaculation has been noted previously and is unique to the ALIF surgical procedure.

The Medtronic Clinical trial safety database was pooled by surgical approach, i.e. ALIF and PLIF. In general, more patients in the PLIF group experienced AEs as compared to the ALIF group. However, there were no differences between rhBMP-2/ACS treated subjects and ABG subjects.

The System Organ Class (SOC) with the most reported adverse events was Musculoskeletal and Connective Tissue Disorders in both groups, with 441 events in 208 subjects for ALIF and 158 events in 51 subjects for PLIF. The SOC Nervous System Disorders ranked second with regards to number of reported events (ALIF: 115 events in 85 subjects; PLIF: 46 events in 29 subjects). There were no important differences between rhBMP-2/ACS treated patients and ABG treated patients.

Data from Medtronic trials showed that, even with increased rates of radiographic evidence of heterotopic ossification, clinical outcomes were not different for rhBMP-2/ACS treated subjects. The MAH proposed an update of the product information with more detailed instructions regarding administration/handling of the device. In addition, other risk minimisation measures have been proposed (see RMP and PRAC report), which are considered sufficient.

Comparison of the other events from the ALIF and PLIF trials shows that the differences predominantly reflect the known potential risks of the two specific surgical approaches and that these surgical risks are independent of the use of rhBMP-2/ACS.

An exception is pseudarthrosis, occurring less frequently in rhBMP-2/ACS subjects as compared to controls in both ALIF and PLIF.

2.5.4. PSUR cycle

The PSUR cycle remains unchanged.

2.6. Risk management plan

2.6.1. PRAC advice

The CHMP received the following PRAC advice on the submitted Risk Management Plan.

PRAC Advice

Based on the PRAC review of the Risk Management Plan version 2.0 the PRAC considers by consensus that the risk management system for Dibotermin alfa (InductOs) for:

- single level lumbar interbody spine fusion as a substitute for autogenous bone graft in adults with degenerative disc disease who have had at least 6 months of non-operative treatment for this condition

could be acceptable provided an updated risk management plan and satisfactory responses to the List of Questions as outlined in the attached PRAC Rapporteur's RMP AR are submitted.

The applicant implemented the changes in the RMP as requested by PRAC.

The Advice is based on the following elements of the RMP.

Safety concerns

The applicant identified the following safety concerns in the RMP:

Table 10: Summary of the Safety Concerns

Summary of safety concerns	
Important identified risks	Heterotopic ossification Osteolysis/resorption bone increased

Summary of safety concerns	
	Fluid collection
Important potential risks	Malignancies Antibody formation Medication errors and incorrect use
Missing information	None

The PRAC agreed.

Pharmacovigilance plan

The PRAC, having considered the data submitted, was of the opinion that routine pharmacovigilance is sufficient to identify and characterise the risks of the product.

Risk minimisation measures

Table 11: Summary table of Risk Minimisation Measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Heterotopic ossification	Text in section 4.2 of the SmPC describing the proper administration, warning and precaution in section 4.4, listed as known adverse reaction in section 4.8 and other routine risk minimisation measures	Educational materials (video and preparation guide) describing the proper preparation and administration of InductOs from the SmPC
	Text in SmPC: **Posology and method of administration in section 4.2:** **"**Care should be taken not to compress the product or overfill the volume intended for new bone formation." (…) InductOs must not be implanted posterior to the lumbar interbody fusion device where direct access to the spinal canal and/or nerve root(s) is possible. If leakage into the spinal canal and the nerve root is possible, a physical barrier between the matrix and any neurological tissue must be re-created by using, for example, local bone or allograft (see section 4.5). (…) Outside the intervertebral disc space, the surgical field should be irrigated as needed, and any fluid loss from the wetted matrix should be washed away." **Warning in section 4.4:** "Use of InductOs may cause heterotopic ossification at the site of implantation and/or the surrounding tissues, which may result in complications. (…) To avoid exaggerated pharmacological effects of InductOs, care and caution should be used to prevent overfilling the	

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	lumbar interbody fusion device and/or the anterior portion of the intervertebral disc space. *Heterotopic ossification* Bone formation outside the intervertebral disc space is not desirable as it may have a deleterious impact on local neurovascular structures. In clinical trials when degenerative disc disease was treated by a posterior lumbar interbody fusion procedure with dibotermin alfa, posterior bone formation was observed in CT scans. In some cases it may lead to nerve compression potentially requiring surgical intervention (see section 4.8). As a precaution, a physical barrier between the matrix and any neurological tissue must be re-created (see section 4.2)." **Listed (frequency common) and described in section 4.8:** "Heterotopic ossification includes exostosis, extraskeletal ossification, postoperative heterotopic calcification, bone formation increased and implant site calcification. (...) *New bone formation and bone remodelling* As part of the pharmacological mechanism of action of dibotermin alfa, bone remodelling occurs (see section 5.1). In this process, both bone resorption and formation occur. In some circumstances an exaggeration of these processes can lead to complications such as nerve compression (due to heterotopic ossification). (...) During two years follow-up in clinical trials for lumbar interbody fusion using a posterior approach, heterotopic ossification seen on radiographs occurred more often in patients treated with InductOs compared with autograft (see section 4.4). This radiographic finding may be asymptomatic or symptomatic" **Special precaution for handling in 6.6: "**InductOs must not be used in concentrations higher than 1.5 mg/ml."	
Osteolysis/ resorption bone increased	Text in section 4.2 of the SmPC describing the proper administration, warning and precaution in section 4.4, listed as known adverse reaction in section 4.8 and other routine risk minimisation measures	None
	<u>Text in SmPC</u>: **Posology and method of administration in section 4.2:** **"**Care must be taken not to compress the product or overfill the volume intended for new bone formation." (...) Outside the intervertebral disc space, the surgical field should be irrigated as needed and any fluid loss from the wetted matrix should be washed away.." **Warning in section 4.4 to:** "Bone resorption increased InductOs can cause initial resorption of surrounding	

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	trabecular bone as evidenced by radiolucency. Therefore, in the absence of clinical data, the product should not be used for direct applications to trabecular bone where transient bone resorption may create a risk of bone fragility (see section 4.8)." **<u>Listed (frequency unknown) and described in section 4.8</u>:** "*New bone formation and bone remodelling* As part of the pharmacological mechanism of action of dibotermin alfa, bone remodelling occurs (see section 5.1). In this process, both bone resorption and formation occur. In some circumstances an exaggeration of these processes can lead to complications such as (…) device dislocation (associated with bone resorption or osteolysis)." **Special precaution for handling in 6.6: "**InductOs must not be used in concentrations higher than 1.5 mg/ml." **Other routine risk minimisation measures:** Routine risk minimization, information in sections 4.2, 4.4, 4.8 and 6.6 of the SmPC. InductOs is a medicinal product subject to restricted medical prescription to be used by an appropriately trained healthcare professional in an operating room of a hospital or clinic which routinely conducts surgeries.	
Fluid collection	Text in section 4.2 of the SmPC describing the proper administration, warning and precaution in section 4.4, listed as known adverse reaction in section 4.8 and other routine risk minimisation measures	None
	<u>Text in SmPC</u>: **Posology and method of administration in section 4.2: "**Care must be taken not to compress the product or overfill the volume intended for new bone formation." (…) Outside the intervertebral disc space, the surgical field should be irrigated as needed and any fluid loss from the wetted matrix should be washed away." **Warning in section 4.4 to:** "Formation of a fluid collection (pseudocyst, localised oedema, implant site effusion), sometimes encapsulated and in some cases resulting in nerve compression and pain, has been reported associated with the use of InductOs. Clinical intervention (aspiration and/or surgical removal) may be required if symptoms persist (see section 4.8)." **Listed (frequency common) and described in section 4.8:** "Fluid collection includes localised oedema, pseudocyst and implant site effusion. (…) *Fluid collection* Due to the angiogenic activity of InductOs, fluid collection (pseudocyst, localised oedema, implant site effusion) can	

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	occur, sometimes encapsulated, sometimes resulting in nerve compression and/or pain. Localised oedema was common when InductOs was used for cervical spine fusion. The oedema was delayed in onset and, in some cases, severe enough to result in airway compromise (see section 4.4)." **Special precaution for handling in 6.6: "**InductOs must not be used in concentrations higher than 1.5 mg/ml." **Other routine risk minimisation measures:** Routine risk minimization, information in sections 4.2, 4.4, 4.8 and 6.6 of the SmPC. InductOs is a medicinal product subject to restricted medical prescription to be used by an appropriately trained healthcare professional in an operating room of a hospital or clinic that routinely conducts surgeries.	
Malignancies	A contraindication for patients with an active malignancy or undergoing treatment for a malignancy in section 4.3 of the SmPC and a precaution in section 4.4 and other routine risk minimisation measures	None
	Text in SmPC: **Contraindication in section 4.3:** "InductOs is contraindicated for patients with any active malignancy or patient undergoing treatment for a malignancy" **Precaution in section 4.4:** "InductOs should not be used in patients with history or clinical suspicion of malignancy at the site of application (see section 4.3)." **Preclinical safety data in 5.3:** "Dibotermin alfa has demonstrated variable effects on human tumour cell lines *in vitro*. The available *in vivo* data on human tumour cell lines do not suggest a potential for promotion of tumour growth or metastasis. As a single use product, InductOs has not been tested for *in vivo* carcinogenicity (see also section 4.3)." **Other routine risk minimisation measures:** Routine risk minimization, information in the contraindications, precautions and non-clinical safety sections of the SmPC. InductOs is a medicinal product subject to restricted medical prescription to be used by an appropriately trained healthcare professional in an operating room of a hospital or clinic that routinely conducts surgeries.	
Antibody formation	A warning and precaution in section 4.4 of the SmPC and other routine risk minimisation measures	None
	Text in SmPC: **Warning in section 4.4 to:** "Immune response Both dibotermin alfa and bovine Type I collagen have been found to elicit immune responses in patients. *Anti-dibotermin alfa antibodies*: In spine fusion studies,	

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	1.3% of patients receiving InductOs developed antibodies to dibotermin alfa versus 0.8% of patients receiving autogenous bone graft. In long-bone fracture studies, 6.3 % of patients receiving dibotermin alfa with bovine Type I collagen matrix developed antibodies to dibotermin alfa versus 1.3 % in the control group. All patients who were tested for neutralizing antibodies to bone morphogenetic protein-2 were negative. *Anti-bovine Type I collagen antibodies*: In spine fusion studies, 13.5 % of patients receiving InductOs developed antibodies to bovine Type I collagen versus 14.3 % of patients receiving autogenous bone graft. In long-bone fracture studies, 13.0 % of patients receiving dibotermin alfa with bovine Type I collagen matrix developed antibodies to bovine Type I collagen versus 5.3 % of control patients. None of the patients with positive titers to bovine type I collagen had cross-reacting antibodies to human type I collagen. Although no association with clinical outcome or undesirable effects could be observed in clinical studies, the possibility of developing neutralising antibodies or hypersensitivity-type reactions cannot be excluded. The possibility of an immune response to the product should be considered in cases where an undesirable effect with immunological background is suspected. Special consideration of risks and benefits should be given for patients who have previously received injectable collagen (see section 4.3). In the absence of any experience, the repeat use of InductOs is not recommended." **Other routine risk minimisation measures** Routine risk minimization, information in the warnings section of the SmPC. InductOs is a medicinal product subject to restricted medical prescription to be used by an appropriately trained healthcare professional in an operating room of a hospital or clinic which routinely conducts surgeries.	
Medication errors and incorrect use	Text describing the proper indications and administration of the product in section 4.1 and 4.2 of the SmPC, a warning in section 4.4, instructions and information for proper administration in section 6.2 – 6.6, and other routine risk minimisation measures	Educational materials (video and preparation guide) describing the proper preparation and administration of InductOs from the SmPC
	(Given the extent of the SmPC text relevant to this minimisation measure, at some instances "full text" is stated. For the complete SmPC wording, please refer to Annex 2) **Text in SmPC:** **Indication in section 4.1:** Full text	-

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	Posology and method of administration in section 4.2: Full text; selected paragraphs of special importance: "InductOs should be used by an appropriately qualified surgeon." <u>Posology</u> "InductOs must be prepared exactly in accordance with the directions for preparation (see section 6.6). (...) The appropriate dose is determined by the volume of wetted matrix required for the intended indication." *Lumbar interbody fusion surgery* "Care must be taken not to compress the product or overfill the volume intended for new bone formation. (...) The maximum dosage is limited to 8 mg (5.3 cm^3, 2/3 of the matrix) in the intervertebral disc space." *Acute tibia fracture surgery* "The volume of InductOs to be implanted is determined by the fracture anatomy and the ability to close the wound without overly packing or compressing the product. Generally, each fracture site is treated with the contents of one pack. The maximum dosage is limited to 24 mg (2 entire matrices)." <u>Method of administration</u> "The medicinal product is administered by implantation. For instructions on reconstitution of the medicinal product before administration, see section 6.6. Failure to follow the method of administration of InductOs may compromise its safety and efficacy. Forceps should be used to handle InductOs. During handling and implantation, minimize fluid loss from the matrix. Do not squeeze." <u>*Lumbar interbody spine fusion surgery*</u> "InductOs must not be used alone for this indication, but should be used with an approved (CE-marked) lumbar interbody fusion device(s). (...) Care and caution must be used to prevent overfilling the lumbar interbody fusion device and/or the intervertebral disc space (see section 4.4)." **Warning in section 4.4:** "Failure to follow the product preparation instructions in section 6.6 and the method of administration in section 4.2 may compromise the safety and efficacy of InductOs." (...)	

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	Special warnings and precautions for use specific to lumbar interbody fusion "To avoid exaggerated pharmacological effects of InductOs, care and caution should be used to prevent overfilling the lumbar interbody fusion device and/or the anterior portion of the intervertebral disc space." (...) Special warnings and precautions for use specific to acute tibia fracture (...) "The implant may only be administered to the fracture site under adequate vision and with utmost care (see section 4.2)." (...) "InductOs does not provide mechanical stability and should not be used to fill a void in the presence of compressive forces. Long bone fracture and soft tissue management procedures should be based on standard practice, including control of infection." **Instructions in 6.2:** "This medicinal product must not be mixed with other medicinal products, except those mentioned in section 6.6." **Shelf life in 6.3:** "3 years" **Storage information in 6.4:** "Do not store above 30°C. Do not freeze. Store in the original package in order to protect from light." **Content in 6.5:** "Each pack of InductOs is provided with: • Powder in a vial (Type I glass) with a stopper (bromobutyl rubber). • Solvent in a vial (Type I glass) with a stopper (bromobutyl rubber). • One matrix in a blister package (polyvinyl chloride - PVC). • Two syringes (polypropylene). • Two needles (stainless steel)." **Reconstitution instructions in 6.6:** Full text	

The PRAC, having considered the data submitted, was of the opinion that the proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication.

The CHMP endorsed this advice without changes.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.8, 4.9 and 5.1 of the SmPC have been updated (**addition,** ~~deletion~~). The Package Leaflet has been updated accordingly.

4.1 Therapeutic indications

InductOs is indicated for single-level ~~(L4 – S1) anterior~~ lumbar **interbody** spine fusion as a substitute for autogenous bone graft in adults with degenerative disc disease who have had at least 6 months of non-operative treatment for this condition.

4.2 Posology and method of administration

Posology

~~Firstly, the entire~~ **InductOs** ~~product should~~ **must be prepared exactly in accordance with** ~~T~~**t**he directions for preparation ~~for each kit should be followed exactly~~**(see section 6.6).**, ~~using the appropriate amount of InductOs~~

The appropriate dose is determined by the volume of wetted matrix required for the intended indication.

If the surgical setting requires that only a portion of the product is needed, the wetted matrix should be cut to the desired size, and the unused portion ~~should~~ **must be discarded**.~~In the absence of any experience, the repeated use of the medicinal product is not recommended.~~

Dosing table for InductOs wetted matrix

Portion of InductOs wetted matrix	Dimensions of wetted matrix	Volume of wetted matrix	Concentration of wetted matrix	Dibotermin alfa dose
1/6 of the matrix	2.5 cm x 5 cm	1.3 cm^3	1.5 mg/cm^3	2 mg
1/3 of the matrix	2.5 cm x 10 cm	2.7 cm^3	1.5 mg/cm^3	4 mg
2/3 of the matrix	5 cm x 10 cm	5.3 cm^3	1.5 mg/cm^3	8 mg
Entire matrix	7.5 cm x 10 cm	8 cm^3	1.5 mg/cm^3	12 mg

~~Anterior l~~Lumbar ~~spine~~ interbody fusion surgery

The **required volume** ~~number of pieces~~ of InductOs ~~required~~ is determined by the ~~size of the LT-CAGE Lumbar Tapered Fusion Device~~ **intervertebral disc space and the size, shape, and internal volume of the lumbar interbody fusion device(s)** being used. ~~Using the table below, identify the number of 2.5 x 5 cm pieces of InductOs required for the size of LT-CAGE Lumbar Tapered Fusion Device.~~**Care ~~should~~ must be taken not to compress the product or overfill the volume intended for new bone formation (see section 4.4).**

Typically, 4 mg (2.7 cm^3, 1/3 of the matrix) of InductOs is used in the intervertebral disc space and placed within the lumbar interbody fusion device(s) or in the anterior portion of the intervertebral disc space.

The maximum dosage is limited to 8 mg (5.3 cm^3, 2/3 of the matrix) in the intervertebral disc space.

~~LT-CAGE Lumbar Tapered Fusion Device Size (lead diameter x length)~~	~~Number of 2.5 x 5 cm pieces of InductOs per LT-CAGE Lumbar Tapered Fusion Device~~
~~14 mm x 20 mm~~	~~1~~

~~14 mm x 23 mm~~	~~1~~
~~16 mm x 20 mm~~	~~1~~
~~16 mm x 23 mm~~	~~2~~
~~16 mm x 26 mm~~	~~2~~
~~18 mm x 23 mm~~	~~2~~
~~18 mm x 26 mm~~	~~2~~

Acute tibia fractures~~ surgery~~

The ~~number of InductOs kits to use and the~~ volume of InductOs to be implanted ~~are~~ **is** determined by the fracture anatomy and the ability to close the wound without overly packing or compressing the product. Generally, each fracture site is treated with the contents of one ~~kit~~ **pack**. The maximum dosage ~~of InductOs~~ is limited to 2**4 mg (2 entire matrices)** ~~kits.~~

Paediatric population

The safety and efficacy of InductOs in children below 18 years ~~old~~ **of age** have not been established. No data are available.

Method of administration

The medicinal product is administered by implantation.

For instructions on reconstitution of the medicinal product before administration, see section 6.6. Failure to follow the method of administration of InductOs may compromise its safety and efficacy.

~~The reconstituted product is administred by implantation.~~
Forceps should be used to handle InductOs. During ~~product preparation~~, handling and implantation, ~~avoid excessive~~ **minimize** fluid loss from ~~InductOs~~ **the matrix**. Do not squeeze.
~~For instructions on reconstitution of the medicinal product before administration, see section 6.6.~~

~~Anterior l~~ Lumbar interbody ~~spine~~ fusion surgery

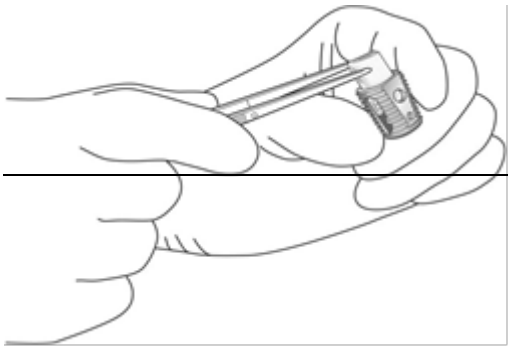
InductOs must not be used alone for this indication, but should be used with ~~the LT-CAGE Lumbar Tapered Fusion Device~~. **an approved (CE-marked) lumbar interbody fusion device(s). Compatibility has been demonstrated with titanium, polyetheretherketone (PEEK), and allograft bone.**
~~Failure to follow the product preparation instructions for InductOs may compromise its safety and effectiveness.~~ Care and caution **must** ~~should~~ be used to prevent overfilling ~~of~~ the **lumbar interbody fusion device** ~~construct~~ and/or **the anterior portion of the** intervertebral **disc** space (see section 4.4).

Pre-implantation

~~Cut t~~**T**he wetted matrix ~~of InductOs~~ **should be cut** into 6 equal **pieces** (approximately 2.5 x 5 cm) ~~pieces~~ **as an aid for dose selection**~~. During cutting and handling, avoid excessive fluid loss from InductOs. Do not squeeze~~**.The selected pieces can be further cut as required.**

The hollow geometry of the lumbar interbody fusion device must~~should~~ **be carefully and loosely filled with the volume** ~~Using forceps to avoid excessive squeezing, carefully roll the required number~~ of InductOs **corresponding to the internal volume of the device**.

~~pieces for each LT-CAGE device and insert each roll into the matching LT-CAGE Lumbar Tapered Fusion Device, as shown in the figure .~~



Implantation

As per standard practice, ~~D~~**d**isc material and the cartilaginous portions of the vertebral endplates should be removed, preserving the cortical portions of the endplates, **and haemostasis should be achieved (see section 4.5)**as per standard practice.

For instructions ~~of~~ **to** implant~~ation~~ **the lumbar interbody fusion device** ~~of the LT-CAGE Lumbar Tapered Fusion Device~~, please refer to the **manufacturer's instructions for use** ~~package leaflet for the LT-CAGE device~~.

InductOs must not be implanted posterior to the lumbar interbody fusion device, where direct access to the spinal canal and/or nerve root(s) is possible. If leakage into the spinal canal and the nerve root is possible, a physical barrier between the matrix and any neurological tissue must be re-created by using, for example, local bone or allograft (see section 4.5).

Post-implantation

Once InductOs and the **lumbar interbody fusion** ~~LT-CAGE~~ device**(s)** are implanted, ~~do not irrigate~~ the **inside of the** intervertebral **disc** space ~~should~~ **must not be irrigated. Outside the intervertebral disc space, the surgical field should be irrigated as needed, and any fluid loss from the wetted matrix should be washed away.**

If a surgical drain is required, ~~place~~ the drain **should be placed** remotely from the implantation site or, preferably, one layer superficial~~ly~~ to the implantation site.

Acute tibia fracture surgery ~~Instructions for use in acute tibia fractures~~

Pre-implantation

~~Achieve d~~**D**efinitive fracture reduction, fixation, and h**a**emostasis **should be achieved** prior to InductOs implantation.

~~InductOs does not provide mechanical stability and should not be used to fill spaces in the presence of compressive forces.~~
~~Fold or cut~~ InductOs **should be folded or cut** as needed prior to implantation. ~~If the surgical setting requires that only a portion of the product is needed, first prepare the entire InductOs product (see section 6.6), cut the product to the desired size, and discard the unused portion.~~

Implantation

InductOs is implanted after the completion of standard fracture and wound management~~,~~ **(**i.e. at the time of soft-tissue closure**)**.

To the extent possible, the accessible surface area of the fracture (fracture lines and defects) should be covered with InductOs. ~~Place~~ InductOs **should be placed** ~~so that it~~ bridg**ing**~~es~~ the fracture region and

mak**ing**~~es~~ good contact with the major proximal and distal fragments. ~~It is not necessary to overlay the contents of multiple kits to achieve the desired effect.~~

InductOs may be placed into a void (loosely packed), folded, rolled~~,~~ or wrapped, as the geometry of the fracture requires. **InductOs does not provide mechanical stability and should not be used to fill a void in the presence of compressive forces.**

Post-implantation

Once InductOs is implanted, do not irrigate the wound.

If a surgical drain is required, ~~place~~ the drain **should be placed** remotely from the implantation site or, preferably, one layer superficially to the implantation site.

~~In order t~~**T**o achieve maximum potential efficacy, it is important to ~~achieve~~ **attain** complete soft-tissue coverage of InductOs following its implantation.

4.4 Special warnings and precautions for use

Failure to follow the **product preparation instructions in section 6.6 and the method of administration in section 4.2** ~~product preparation instructions for InductOs~~ may compromise **the** ~~its~~ safety and eff**icacy of**~~ectiveness~~ **InductOs**. ~~Care and caution should be used to prevent overfilling of the construct and/or intervertebral space.~~

Cervical spine surgery
The safety and efficacy of InductOs in cervical spine surgery have not been established, and InductOs should not be used in this condition. Localised oedema associated with the use of InductOs has been reported in patients undergoing cervical spine surgery. The oedema was delayed in onset and usually occurred in the first week post-operation. In some cases, the oedema was severe enough to result in airway compromise. ~~The safety and efficacy of InductOs in cervical spine surgery have not been established, and InductOs should not be used in this condition.~~

Malignanc**y**~~ies~~
InductOs should not be used in patients with history or clinical suspicion of malignancy at the site of application (see section 4.3).

~~Formation of fluid collections~~
~~Formation of fluid collections (pseudocysts, localised oedema, implant site effusion), sometimes encapsulated, in some cases resulting in nerve compression and pain, has been reported in patients undergoing spine surgery associated with the use of InductOs. Many of these reports have occurred when InductOs was used in unapproved approaches/devices or in a manner inconsistent with the instructions for use. Clinical intervention (aspiration and/or surgical removal) may be required if symptoms persist (see section 4.8).~~

Heterotopic ossification
Use of InductOs may cause heterotopic ossification at the site of implantation and/or the surrounding tissues, which may result in complications.

Bone resorption **increased**
InductOs can cause initial resorption of surrounding trabecular bone **as evidenced by radiolucency**. Therefore, in the absence of clinical data, the product should not be used for direct applications to trabecular bone whe**re**~~n~~ transient bone resorption may create a risk of bone fragility **(see section 4.8)**. ~~When InductOs was used with the LT-CAGE device (section 4.2) in clinical trials for anterior lumbar spine fusion, the frequency and severity of resorption of bone as evidenced by radiolucencies and/or device migration was similar to that observed for patients treated with autogenous bone graft.~~

Fluid collections
Formation of a fluid collection (pseudocyst, localised oedema, implant site effusion), sometimes encapsulated and in some cases resulting in nerve compression and pain, has been reported associated with the use of InductOs. Clinical intervention (aspiration and/or surgical removal) may be required if symptoms persist (see section 4.8).

~~Heterotopic ossification~~
~~Use of InductOs may cause heterotopic ossification in the surrounding tissues, which can result in complications. Exuberant bone formation at the site of implantation and ectopic bone formation have been observed.~~

~~Nerve compression~~
~~Nerve compression associated with ectopic bone formation and InductOs use has been reported (see section 4.8). Additional surgical intervention may be required.~~

~~Device migration~~
~~Device migration can occur after the use of InductOs in spinal fusion surgery, which may necessitate surgical revision (see section 4.8).~~

Immune response
Both dibotermin alfa and bovine Type I collagen have been found to elicit immune responses in patients.

Anti-dibotermin alfa antibodies: In ~~anterior lumbar~~ spine fusion studies~~, 0.7~~**1.3**% of patients receiving InductOs developed antibodies **to dibotermin alfa** *versus* 0.8% of patients receiving autogenous bone graft. In **long-bone**~~acute tibia~~ fracture studies, ~~4.4~~**6.3** % of patients receiving ~~InductOs~~ **dibotermin alfa with bovine Type I** ~~bovine~~ **collagen matrix** developed antibodies **to dibotermin alfa** *versus* ~~0.6~~**1.3** % in the control group. **All patients who were tested for neutralizing antibodies to bone morphogenetic protein-2 were negative.**

Anti-bovine Type I collagen antibodies: In ~~anterior lumbar~~ spine fusion studies, ~~19~~**13.5** % of patients receiving InductOs developed antibodies to bovine Type I collagen *versus* ~~13~~**14.3** % of patients receiving autogenous bone graft. In **long-bone**~~acute tibia~~ fracture studies, ~~15.7~~**13.0** % of patients receiving ~~InductOs~~ **dibotermin alfa with bovine Type I** ~~bovine~~ **collagen matrix** developed antibodies to bovine Type I collagen *versus* ~~11.8~~**5.3** % of control patients. **None of the patients with positive titers to bovine Type I collagen had cross-reacting antibodies to human type I collagen**.~~In either of the two indications, no patients who tested positive for anti-bovine Type I collagen antibodies developed antibodies to human Type I collagen.~~

Although no ~~clear~~ association with clinical outcome or undesirable effects could be observed in clinical studies, the possibility of developing neutralising antibodies or hypersensitivity-type reactions cannot be excluded. **The possibility of an immune response to the product should be considered in cases where an undesirable effect with immunological background is suspected**. Special consideration of risks and benefits should be given for patients who have previously received injectable collagen (see section 4.3). **In the absence of any experience, the repeat use of InductOs is not recommended**.~~The possibility of an immune response to the product should be evaluated in cases where an undesirable effect with immunological background is suspected.~~

Special populations
The safety and efficacy of the use of InductOs in patients with known autoimmune disease have not been established. These autoimmune diseases include rheumatoid arthritis, systemic lupus erythematosus, scleroderma, Sjögren's syndrome and dermatomyositis/polymyositis.

The safety and efficacy of InductOs have not been demonstrated in patients with metabolic bone diseases.

No studies have been performed in patients with hepatic, ~~or~~ renal **or cardiac** impairment.

For ~~all~~ these ~~patient groups~~**special populations**, the physician is advised to give a careful~~l~~-consideration to the benefits and risks for the specific patient before using InductOs. A close monitoring of the patient for any adverse reactions and the success of the treatment is recommended.

Excipients
This medicinal product contains less than 1 mmol (23 mg) sodium per maximum dose (2 ~~kits~~**packs**), i.e. it is essentially 'sodium-free'.

Special warnings and precautions for use specific to ~~anterior~~ lumbar ~~spine~~ **interbody** fusion

The safety and efficacy of InductOs have not been established in the following conditions:

- used with ~~spinal implants~~ **interbody fusion devices made from material** other than **titanium, PEEK or bone** ~~the LT-CAGE device~~
- implanted at locations other than ~~L4 – S1 in the lower~~ lumbar spine
- used in surgical techniques other than ~~anterior open or anterior laparoscopic approaches~~**lumbar interbody fusion**

~~When degenerative disc disease was treated by a posterior lumbar interbody fusion procedure with cylindrical threaded cages and dibotermin alfa, posterior bone formation was observed in some instances.~~

To avoid exaggerated pharmacological effects of InductOs, care and caution should be used to prevent overfilling the lumbar interbody fusion device and/or the anterior portion of the intervertebral disc space.

Heterotopic ossification

Bone formation outside the intervertebral disc space is not desirable as it may have a deleterious impact on local neurovascular structures.

In clinical trials when degenerative disc disease was treated by a posterior lumbar interbody fusion procedure with dibotermin alfa, posterior bone formation was observed in CT scans. In some cases it may lead to nerve compression potentially requiring surgical intervention (see section 4.8). As a precaution, a physical barrier between the matrix and any neurological tissue must~~should~~ **be re-created (see section 4.2)**.

Device dislocation

Device dislocation can occur after the use of InductOs in spinal fusion surgery that may necessitate surgical revision (see section 4.8).

4.5 Interaction with other medicinal products and other forms of interaction

In acute tibia fracture clinical trials, more InductOs patients receiving concomitant NSAIDs for 14 consecutive days experienced mild or moderate adverse events related to wound healing (e.g., wound drainage) than InductOs patients not taking NSAIDs. Although patient outcome was not affected, an interaction between NSAIDs and InductOs cannot be excluded.

Information from clinical studies in acute tibia fractures indicated that the use of InductOs in patients receiving glucocorticoids was not associated with any apparent adverse reactions. In ~~pre~~non-clinical studies, concurrent administration of glucocorticoids depressed bone repair (measured as a % change from control), but the effects of InductOs were not altered.

In an *in vitro* study, dibotermin alfa was shown to bind to fibrin-based haemostatic agents or sealants. The use of these products in close proximity to InductOs is not recommended as this may lead to bone formation at the site of implant of the fibrin-based haemostatic agent or sealant (see section 4.2).~~In acute tibia fracture clinical trials, more InductOs patients receiving concomitant NSAIDs for 14 consecutive days experienced mild or moderate adverse events related to wound healing (e.g. wound drainage) than InductOs patients not taking NSAIDs. Although patient outcome was not affected, an interaction between NSAIDs and InductOs cannot be excluded.~~

4.6 Fertility, pregnancy and lactation

Pregnancy ~~and women of childbearing potential~~

There is no ~~adequate~~ **or limited amount of** data from the use of dibotermin alfa in pregnant women. ~~Studies in a~~Animal~~s~~ **studies** ~~are insufficient with respect to~~ have shown reproductive toxicity (see section 5.3). ~~The potential risk for humans is unknown.~~

~~Animal studies have been conducted that cannot rule out effects of anti-dibotermin alfa antibodies on embryo-foetal development (see section 5.3).~~

Due to the unknown risks to the foetus associated with the potential development of neutralising antibodies to dibotermin alfa, **InductOs is not recommended during pregnancy and in women of childbearing potential not using contraception (see section 4.4)** ~~InductOs should not be used during pregnancy unless clearly necessary (see section 4.4). Women of childbearing potential should be advised to use effective contraception up to at least 12 months after treatment.~~

4.8 Undesirable effects

Summary of the safety profile

The most common adverse reactions ~~related to the use of~~**for** InductOs **in lumbar interbody fusion surgery** were ~~neuralgia~~ **radiculopathic events**, ~~in spine surgery~~ and **in acute tibia fracture surgery it was** localised infection~~ in tibia fracture repair~~. The most severe adverse reaction is localised oedema in cervical spine surgery. The incidence of adverse reactions with InductOs was not affected by gender, age or race.

Tabulated list of adverse reactions

Over 1~~6~~**7**00 patients have received InductOs in clinical studies. In the long-bone fracture studies, over **500**~~485~~ patients received InductOs. In ~~spine~~ **lumbar interbody fusion** studies, ~~almost 900~~ **over 600** patients received InductOs. ~~The last group of~~**The remaining** patients participated in studies using InductOs for indications not currently approved in the EU. These data are supplemented with information from use of InductOs in the general population.

The frequency of adverse reactions in patients exposed to treatment with InductOs is presented in the table below. Frequencies are defined as very common (≥1/10) or common (≥1/100 to <1/10). No reactions are observed with the frequency uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000) or very rare (<1/10,000).

The frequencies of adverse reactions identified during post-marketing use of InductOs are not known as these reactions were reported from a population of uncertain size.

System organ class	**Frequencies**		
	Very common	**Common**	**Unknown**
General disorders and administration site conditions		Device **dislocation[1]*** **Fluid collection[2]***	~~Localised oedema*~~ ~~Pseudocyst*~~ ~~Implant site effusion*~~
Musculoskeletal and connective tissue disorders		~~Extraskeletal ossification,~~ ~~Postoperative heterotopic calcification,~~ ~~Bone formation increased~~ ~~(Ectopic bone formation)~~ **Heterotopic ossification[1, 3]*** ~~Back pain1~~ ~~Bone disorder1~~	Osteolysis* Resorption bone increased*
Nervous system disorders	~~Neuralgia[1]~~	**Radiculopathic events[1, 4]**	~~Radiculitis[1]~~
Infections and infestations	Localised infection[2~~5~~]*		

[1] Observed during use in ~~anterior~~ lumbar **interbody** ~~spine~~ fusion

[2] Fluid collection includes localised oedema, pseudocyst and implant site effusion.

[3] Heterotopic ossification includes exostosis, extraskeletal ossification, postoperative heterotopic calcification, bone formation increased and implant site calcification.
[4] Radiculopathic events includes radiculitis, lumbar radiculopathy, radicular pain, radiculitis lumbosacral, radiculopathy and sciatica.
~~[2]~~ Observed during use in acute tibia fractures
* Additional information provided below

Description of selected adverse reactions

New bone formation and bone remodelling ~~*Bone remodeling*~~
As part of the pharmacological mechanism of action of ~~InductOs~~ **dibotermin alfa**, bone remodelling occurs (see section 5.1). In this process, both bone resorption and formation occur. In some circumstances **an exaggeration of** these processes can lead to complications such as nerve compression (due to ~~bone formation or~~ heterotopic ~~calcification~~**ossification**) or device ~~migration~~ **dislocation** (associated with bone resorption or osteolysis).

During two years follow-up in clinical trials for lumbar interbody fusion using a posterior approach, heterotopic ossification seen on radiographs occurred more often in patients treated with InductOs compared with autograft (see section 4.4). This radiographic finding may be asymptomatic or symptomatic.

~~*Localised infection*~~
~~Localised infection specific to the fractured limb occurred very common (≥1/10) in patients in a clinical study in which the intramedullary canal was reamed to cortical chatter. An increased rate of infection was observed in the InductOs-treated group versus the standard of care control group (19% versus 9%, respectively; see section 4.4). For use with unreamed nails, estimated rates of infection were similar between treatment groups in a study (21% versus 23%, respectively).~~

Fluid collection ~~*(localised oedema, pseudocyst, implant site effusion)*~~
Due to the angiogenic activity of InductOs, ~~formation of~~ fluid collection~~s~~ (pseudocyst, localised oedema, implant site effusion) can occur, sometimes encapsulated, sometimes resulting in nerve compression and/or pain.

Localised oedema ~~is~~ **was** ~~observed very~~ common when InductOs ~~is~~ **was** used for ~~spinal~~ **cervical spine** fusion ~~in the cervical spine~~. The oedema was delayed in onset and, in some cases, severe enough to result in airway compromise (see section 4.4).

Localised infection
Localised infection specific to the fractured limb was very common (≥1/10) in patients in a clinical study in which the intramedullary canal was reamed to cortical chatter. An increased rate of infection was observed in the InductOs-treated group *versus* the standard of care control group (19 % *versus* 9 %, respectively; see section 4.4). For use with unreamed nails, estimated rates of infection were similar between treatment and control groups in a study (21 % *versus* 23 %, respectively).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

In case of overdose (i.e. a patient receives a concentration or amount of dibotermin alfa greater than recommended), treatment should be supportive.

Use of InductOs in patients undergoing cervical spine surgery in ~~concentrations or~~ amounts **lower than or similar to**~~greater than~~ those ~~recommended in~~ ~~section 4.2~~for ~~the approved indications~~ **lumbar interbody fusion** has been associated with reports of localised oedema **severe enough to result in airway compromise** (see section 4.4).

~~In the case of patients receiving concentrations or amounts greater than those recommended, treatment should be supportive.~~

5.1 Pharmacodynamic properties

~~Remodeling of the surrounding trabecular bone occurs in a manner that is consistent with the biomechanical forces placed on it.~~ Placement of InductOs into trabecular bone resulted in transient resorption of the bone surrounding the implant, followed by replacement with new, more dense bone. **Remodeling of the surrounding bone occurs in a manner that is consistent with the biomechanical forces placed on it.** The ability of InductOs to support bone remodeling may be responsible for the biological and biomechanical integration of the new bone induced by InductOs with that of the surrounding bone. Radiographic, biomechanical and histologic evaluation of the induced bone indicates that it functions biologically and biomechanically as native bone. Furthermore, ~~preclinical~~ **non-clinical** studies have indicated that the bone induced by InductOs, if fractured, can repair itself in a manner indistinguishable from native bone.

Histological evidence from animal studies of lumbar interbody fusion using anterior or posterior surgical approaches showed dibotermin alfa administered with titanium, PEEK or allograft interbody devices was biocompatible and produced consistently high rates of fusion independent of surgical approach or device material with less fibrous tissue evident compared with autograft.

Pharmacodynamic information specific to ~~anterior~~ lumbar ~~spine~~ interbody fusion studies

The efficacy and safety of InductOs were demonstrated in a randomised, controlled, multicenter, non-inferiority study of 279 patients aged 19–78 years undergoing an open anterior lumbar interbody fusion procedure. Patients had received at least six months of non-operative treatment prior to treatment with InductOs for anterior lumbar spine fusion. Patients were randomised to receive ~~the LT-CAGE Lumbar Tapered Fusion Device~~**a titanium interbody fusion device** filled with either InductOs or autogenous bone graft taken from the iliac crest.

At 24 months post-operation, InductOs was demonstrated to be statistically non-inferior to autogenous bone graft **with a** ~~The~~ success rate for radiologically determined fusion ~~was~~**of** 94.4 % for InductOs *versus* 88.9 % **for autogenous bone graft** (95 % two-sided CI of the difference: -1.53, 12.46) ~~for autogenous bone graft~~. For pain and disability (Oswestry score), the success rate was 72.9 % **in the group using InductOs** *versus* 72.5% **in the group using autogenous bone graft** (95 % two-sided CI of the difference: -11.2, 12.0). ~~A single, multi-component endpoint, known as overall success was the primary variable of the study. Overall success consists of the following primary efficacy and safety considerations:~~

- ~~Radiographically demonstrated fusion~~
- ~~Oswestry pain/disability improvement~~
- ~~Maintenance or improvement in neurological status~~
- ~~No Grade 3 or 4 adverse event classified as implant-associated or implant/surgical procedure-associated~~
- ~~No additional surgical procedure performed that was classified as a "failure"~~

~~At 24 months post-operation, the overall success rate was 57.5% for InductOs versus 55.8% (95% two-sided CI of the difference: -10.72, 14.01) for autogenous bone graft.~~

~~An additional, non-comparative study of 134 patients who received anterior lumbar interbody fusion procedures via a laparoscopic surgical technique yielded similar success rates of 92.9% for fusion, 85.6% for pain and disability, and 90.3% for neurological status. The study confirmed the applicability of anterior lumbar spine fusion using InductOs via laparoscopic surgical implantation techniques.~~

A post-hoc meta-analysis of 6 controlled clinical trials with data from patients treated with InductOs or autogenous bone graft administered using CE-marked interbody fusion devices or allograft bone spacers and various surgical approaches showed that, at 24 months post-surgery, InductOs was associated with a higher fusion success rate (95 %, 241 out of 255 patients) compared with autogenous bone graft (85 %, 177 out of 209 patients), with an odds ratio of 3.26 (95 % CI: 1.172, 9.075; P = 0.024). The estimated absolute difference in

fusion success rate between InductOs and autogenous bone graft was 11.7 % (95 % CI: 8.0 %, 22.5 %; P = 0.035).

In a pooled safety data analysis of 8 clinical trials at 24 months post-surgery, the frequency of patients with pseudarthrosis ~~requiring a secondary intervention~~ **was approximately 2-fold lower following treatment with InductOs (4.8 %, 22 out of 456 patients) compared with autogenous bone graft (12.7 %, 31 out of 244 patients).**

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans **based** on conventional studies of **safety** pharmacology, acute and repeat**ed** exposure toxicity **and genotoxicity**, ~~toxicity to reproduction and development.~~

In reproductive toxicity studies in rats, where dibotermin alfa was administered intravenously to maximize systemic exposure, increased foetal weight and increased fo~~e~~etal ossification was observed and a treatment-related effect could not be ruled out. The clinical relevance of these effects is unknown.

Anti-dibotermin antibodies have been investigated in pregnant rabbits following hyper**-**immunisation with dibotermin alfa to experimentally induce anti-~~BMP-2~~**dibotermin alfa** antibodies. In some foetuses with decreased body weights, there were decreases in ossification of frontal and parietal bones (4 out of 151 foetuses), which is generally considered to be reversible, and antibody related effects could not be ruled out. There were no other alterations in foetal external, visceral, or skeletal morphology. ~~Other animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, maternal toxicity, embryolethality, or fetotoxicity.~~

~~InductOs has not been tested for *in vivo* carcinogenicity~~. Dibotermin alfa has demonstrated variable effects on human tumour cell lines *in vitro*. ~~Although t~~**T**he available *in vi**vo**~~tro~~* data **on human tumour cell lines do not** suggest a ~~low~~ potential for promotion of tumour growth **or metastasis. As a single use product, InductOs has not been tested for *in vivo* carcinogenicity**, ~~the use of InductOs is contraindicated in patients with an active malignancy or in patients undergoing treatment for a malignancy~~ (see also section 4.3).

InductOs has been studied in a canine spinal implantation model. InductOs was implanted directly onto the exposed dura following a laminectomy. Although narrowing of the neuroforamen and stenosis was observed, no mineralization of the dura, no spinal cord stenosis, and no neurological deficits subsequent to the application of InductOs were observed. ~~The significance of these data for humans is not known.~~

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8, 4.9, 5.1 and 5.3 of the SmPC have been updated.

Annex II and the Package Leaflet have been updated accordingly.

The MAH also took the opportunity to:

- Update the standard term: Replacement of the term "kit for implant" (rejected on 23 May 2012) by the approved standard term "powder, solvent and matrix" (approved on 24 October 2012). This was requested by the CHMP during the renewal procedure and the standard term is officially approved.
- Change in the expression of the strength from 12mg to 1.5 mg/ml. In the "QRD recommendations on the expression of strength in the name of centrally authorised human medicinal products", for single use reconstituted 'partial use' products the strength should be expressed as the concentration after reconstitution.

Changes were also made to the PI to bring it in line with the current Agency/QRD template, SmPC guideline and other relevant guideline(s) [e.g. Excipients guideline, storage conditions, Braille, etc…], which were reviewed and accepted by the CHMP.

These changes were agreed by the CHMP.

No full user consultation with target patient groups on the package leaflet has been performed as the impact of the proposed modifications in the Package Information Leaflet readability is considered negligible. This was agreed by the CHMP.

3. Benefit-Risk Balance

Benefits

Beneficial effects

In support of the variation, the MAH has presented data from 8 Medtronic-sponsored studies and data from literature. Important for this variation is the post-hoc meta-analysis of 6 Medtronic studies and literature and a subgroup and meta-regression analysis exploring the potential for differences in fusion success rates between InductOs and ICBG due to surgical approach (anterior vs posterior) or by type of interbody fusion device. The data set included seven RCTs (including six Medtronic RCTs) and six non-randomised controlled studies.

In the 6 Medtronic-sponsored trials, at 24 months post-surgery, the use of InductOs was associated with a higher fusion success rate (94.5%, 241/255) compared with ICBG (84.6%, 177/209). The difference between the two groups was statistically significant (OR 3.262, p=0.024). For the primary analysis dataset at 6 and 12 months, the fusion success rate was 96.6% (253/262) and 96.1% (249/259) respectively, for InductOs and 92.4% (195/211) and 91.2% (195/212) respectively, for ICBG, with no significant difference between the groups at either time point. This does not support a claim for accelerated fusion.

The addition of non-Medtronic RCT (one study) and NRS data (six studies) to the Medtronic CSRs did not affect the finding of a significantly increased fusion success rate for rhBMP-2/ACS versus ABG.

In a subgroup analysis for fusion success by surgical approach for all 6 anterior lumbar interbody fusion studies, fusion success was 92.8% (221/238) for InductOs compared with 82.8% (173/209) for ICBG (OR 2.29). This compares with 96.8% (274/283) and 91.7% (154/168) for InductOs and ICBG, respectively, in all seven posterior studies (OR 2.12). A formal meta-regression analysis found no statistically significant difference in the effect of InductOs on fusion success between ALIF and other surgical approaches (ratio of odds ratios ROR=0.863, P=0.847).

In order to increase the number of studies suitable for meta-analysis the MAH widened the inclusion criteria. An additional 30 studies were identified by literature search. Most newly added studies were retrospective and uncontrolled. In addition the definition of radiological fusion varied widely in the 30 new studies. For all studies, fusion success rate for rhBMP-2/ACS was 94.0% (95% CI: 91.3-96.3) compared to 84.5% (95% CI: 80.7-91.4) for autogenous bone graft.

Subgroup analysis according to surgical procedure revealed no significant differences in fusion success rates for the rhBMP-2/ACS group: ALIF 91.6%, PLIF/TLIF 95.0%, Other 95.0%. In the ABG group differences approached statistical significance, with ALIF performing least: ALIF 78.5%, PLIF/TLIF 91.1%, Other 91.8%.

Fusion success rates with rhBMP-2/ACS were not significantly different for interbody device types composed of titanium, PEEK, allograft, or other materials (p=0.975), while the difference in fusion success between interbody devices in ABG patients was statistically significant (p=0.025).

Uncertainty in the knowledge about the beneficial effects

Initially, the number of studies for subgroup analysis (exploring the potential for differences in fusion success rates between InductOs and ICBG due to surgical approach (anterior vs posterior) or by type of interbody fusion device) was small, and the statistical power to detect differences between subgroups was rather low. In the supplementary meta-analysis provided by the MAH the number of studies was increased. This broader range of studies, including uncontrolled studies and studies with a small proportion of patients undergoing lumbar interbody fusion, led to considerable heterogeneity. Even though the same amount of heterogeneity was found earlier in a similar study, suggesting this heterogeneity reflects the real use of the product, the results of this supplementary meta-analysis were interpreted with caution by the CHMP.

Risks

Unfavourable effects

No new or unexpected safety issues were identified. The overall frequency of AEs in patients at 24 months was 80.9% in the pooled InductOs data, compared with 85.7% in the pooled control data. In the pooled study data, Back Pain, Pain in Extremity and Fall were the most frequently occurring AEs in patients at 24 months. The most notable finding is the frequency of Pseudarthrosis; the rate of the event in the InductOs group (6.1%), compared with the control (13.1%). Although Musculoskeletal Pain has a frequency of 8.1% in the investigational group and just 4.9% in the control, Muscle Spasm has a frequency of 3.5% in the investigational group and 6.6% in control. An imbalance in the rates of Retrograde Ejaculation has been noted previously and is unique to the ALIF surgical procedure.

The Medtronic Clinical trial safety database was pooled by surgical approach, i.e. ALIF and PLIF. In general, more patients in the PLIF group experienced AEs as compared to the ALIF group. However, there were no differences between rhBMP-2/ACS treated subjects and ABG subjects.

The System Organ Class (SOC) with the most reported adverse events was Musculoskeletal and Connective Tissue Disorders in both groups, with 441 events in 208 subjects for ALIF and 158 events in 51 subjects for PLIF. The SOC Nervous System Disorders ranked second with regards to number of reported events (ALIF: 115 events in 85 subjects; PLIF: 46 events in 29 subjects). There were no important differences between rhBMP-2/ACS treated patients and ABG treated patients.

Comparison of the other events from the ALIF and PLIF trials shows that the differences predominantly reflect the known potential risks of the two specific surgical approaches and that these surgical risks are independent of the use of rhBMP-2/ACS. An exception is pseudarthrosis, occurring less frequently in rhBMP-2/ACS subjects as compared to controls in both ALIF and PLIF.

Uncertainty in the knowledge about the unfavourable effects

The risk for heterotopic ossification is an acknowledged risk with spinal surgery in general and PLIF in particular (as described in the RMP). Medtronic clinical trial data show that, as a whole, even with increased rates of radiographic evidence of heterotopic ossification, reoperation rates were not increased and overall clinical outcomes were not worse for rhBMP-2-treated patients than control

patients. In literature, following surgery with rhBMP-2 in posterior approaches, the risk of symptomatic heterotopic ossification (mostly requiring surgery) varies from 0.59% to 6.7%.

Benefit-Risk Balance

Importance of favourable and unfavourable effects

Fusion success rate is an important favourable effect. In the eight Medtronic-sponsored studies, only 11 subjects were treated at a higher **lumbar level** than L4-S1. The vertebral endplates at L1-L3 and L4-S1 are anatomically and histologically similar, and the fusion process is fundamentally the same within the intervertebral spaces of the lumbar spine. Therefore, it is reasonable to remove the restriction L4-S1 because it seems implausible that the lumbar level alone would affect the osteoinductive action of InductOs.

In most controlled studies overall success was used as primary endpoint, a composite of fusion success rate and pain. For the meta-analysis fusion success rate was used, as overall success contains elements that are more likely to be affected by aspects of the surgical intervention than the pharmacological action of dibotermin alfa. This might be true, but in spinal fusion surgery, the pharmacological action of dibotermin alfa cannot be seen separated from the surgical procedure.

Heterotopic ossification is a significant risk, especially with the posterior approach. This risk is described in the RMP. When the spinal canal is involved, spinal stenosis can occur.

Pseudarthrosis is a risk of spinal surgery. InductOs treated subjects experienced less pseudarthrosis, which can be seen as a positive result.

Benefit-risk balance

Discussion on the Benefit-Risk Balance

For successful spinal surgery, a number of factors are important, among which the biological environment, patient characteristics, type of surgery. The MAH has submitted a number of studies, but most of these are too small to draw conclusions. Therefore, a meta-analysis and subgroup analyses were performed.

As the number of studies was still limited, the MAH widened the inclusion criteria for meta-analysis and conducted a supplementary meta-analysis on a total of 43 studies. This broader range of studies, including uncontrolled studies and studies with a small proportion of patients undergoing lumbar interbody fusion, led to considerable heterogeneity. Therefore, results of this supplementary meta-analysis have to be interpreted with caution, also taking into account the issue of publication bias.

The figures indicated that for the rhBMP-2/ACS group surgical approach does not affect fusion success rate. In the ABG group differences approached statistical significance, with ALIF performing least: ALIF 78.5%, PLIF/TLIF 91.1%, Other 91.8%. The MAH reasons that this may be due to the use of transpedicular screws in TLIF/PLIF procedures for achieving segmental fixation and as a consequence high fusion rates. This seems plausible to the CHMP, as a stable fixation is important for successful fusion. However, the added value of rhBMP-2/ACS in procedures other than ALIF can be questioned. The difference in fusion success rates in PLIF/TLIF procedures between rhBMP-2/ACS and ABG is only 4.9%. In the corrected meta-analysis, using only controlled studies, the difference in fusion success rates in PLIF/TLIF procedures between rhBMP-2/ACS and ABG was 5.5%. The majority of lumbar interbody fusion procedures performed in Europe are performed via posterior approaches (PLIF + TLIF)

and they represented more than 80% of all procedures performed in 2011 compared with ALIF representing less than 15% of all procedures. Thus, for Europe, using rhBMP-2/ACS is approved for the ALIF-procedure, but this is hardly employed; for the mostly used PLIF-procedure the difference in fusing rate between rhBMP-2/ACS and ABG is about 5%.

The relative effect of InductOs was not significantly associated with the types of interbody device used. The effect of surgery and device was analysed for two parameters (fusion success rate and secondary surgery). Other parameters were not analysed, and thus influence of surgery and device on these parameters is not known.

Only 11 patients underwent surgery at higher levels than in L4-S1 in the original meta-analysis. In the supplementary analysis, 17 studies were included that reported surgery at higher levels. However, the number of patients treated at other levels is not known and outcome data were not stratified for lumbar level. Thus, no additional data are available for other levels. For fusion biological and mechanical environment are important. These do not differ much between L1, L2 and L4-S1. For mechanical stability it is required that the osseous component of the end-plate remains intact. Difficulties may arise in patients with osteoporosis, for whom there may be a loss of bone density in subchondral trabeculae. Overall, factors such as osteoporosis, age, and disease severity may influence the nature of the vertebral endplate in contact with rhBMP-2/ACS, but these actors are common to all levels of the lumbar spine, with the exception that the frequency of disease severity increases caudally. Other anatomical features of the endplate vary more within a single disc level than they do at different lumbar levels. Therefore, extension of the indication to levels L1-S1 can be accepted.

In this application, the safety issues related to surgery, device and spinal level (L1-S1 only) were removed from the product information. This was agreed by the CHMP. In general, more patients in the PLIF group experienced AEs as compared to the ALIF group. However, there were no differences between rhBMP-2/ACS treated subjects and ABG subjects. The risk of heterotopic ossification can be adequately minimised by properly informing the HCPs on how to correctly use this device, by taking care not to overfill, prevent leakage and create a physical barrier between the device and neurological tissue. The update of the SmPC and the MAH's proposals for risk minimisation are considered adequate at the moment.

It is concluded that the efficacy and safety of the use of InductOs with other types of devices than the LT-cage, other types of surgery than the ALIF and higher lumbar level s that L4-S1 is acceptable.

The benefit-risk balance of InductOs for single-level lumbar interbody spine fusion as a substitute for autogenous bone graft in adults with degenerative disc disease who have had at least 6 months of non-operative treatment for this condition in the treatment of adults is considered positive.

4. Recommendations

☒ The application for broadening the use in single-level lumbar interbody spine fusion as a substitute for autogenous bone graft in adults with degenerative disc disease who have had at least 6 months of non-operative treatment for this condition, is approvable since other concerns and major objections have all been resolved.

Final Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following changes:

Variation accepted		Type
C.1.6 a)	Addition of a new therapeutic indication or modification of an approved one	II

Extension of the indication to broaden (anatomically) the use of InductOs in lumbar interbody spine fusion as a substitute for autogenous bone graft in adults with degenerative disc disease who have had at least 6 months of non-operative treatment for this condition in the treatment of adults. Consequently, sections 4.1, 4.2, 4.8, 4.9 and 5.1 of the SmPC have been updated. Further, SmPC section 4.4 has been updated with warnings related to type of surgery, device and spinal level, and sections 4.4, 4.5, 4.6, 5.1 and 5.3 of the SmPC based on supportive non-clinical and clinical data relating to immunogenicity, tumorigenicity or fusion success. The Package Leaflet was updated accordingly. Furthermore, the standard term has been updated from "kit for implant" to "powder, solvent and matrix", and the expression of the strength changed from “12mg” to “1.5 mg/ml” throughout the SmPC, labelling and Package leaflet. In addition, the MAH took the opportunity to implement the latest QRD template (version 9.0) and to make editorial changes throughout the annexes. A revised RMP version 2 was agreed as part of the procedure.

The requested variation proposed amendments to the SmPC, Annex II, Labelling and Package Leaflet.

Conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list)) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk management plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

When the submission of a PSUR and the update of a RMP coincide, they should be submitted at the same time.

In addition, an updated RMP should be submitted:

At the request of the European Medicines Agency;

Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

The Marketing Authorisation Holder (MAH) must agree the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The educational programme is aimed:

- at increasing awareness about the risk of heterotopic ossification and the potential risk of medication errors and incorrect use of InductOs and providing guidance on how to manage these risks.

The MAH shall ensure that in each Member State where InductOs is marketed, all healthcare professionals who are expected to use InductOs are provided with the following educational package:

- Healthcare professionals educational material

The healthcare professional educational material should contain:

- The Summary of Product Characteristics
- Healthcare professionals training material

  The healthcare professionals training material shall contain the following key elements:

  - Detailed description from the SmPC of the administration procedures of InductOs and of the measures that need to be taken to prevent medication errors, incorrect use, and minimise the risk of heterotopic ossification.