



## Evidence based review: Bone Morphogenetic Proteins- 2 and 7

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Date of First Issue	April 2006

### Important Note:

This evidence based review summarises information on Bone Morphogenetic Proteins-2 and 7 (BMP-2, BMP-7) and commercial products incorporating these molecules. It is not intended to replace clinical judgement, or be used as a clinical protocol.

- A reasonable attempt has been made to find and review papers relevant to the focus of this EBH review. It does not claim to be exhaustive.
- The content of this document does not necessarily represent the official view of ACC or represent ACC policy.

## The evidence for the efficacy of Bone Morphogenetic Proteins in spinal fusion

### Executive Summary

This review assesses the evidence from clinical trials that bone morphogenetic proteins (BMP) are effective in spinal fusion.

Bone morphogenetic proteins are responsible for the growth and differentiation of bone forming cells. They form a large family of proteins with over 17 members. Two of the family are available as recombinant human molecules (rhBMP-2 and rhBMP-7) and have been incorporated into commercial products. They are used to induce bone deposition in a range of anatomical sites including long bones, the jaw and the spine. Initial evidence on the efficacy of BMP supported their use in tibial fractures. These products were initially approved by regulatory authorities for treatment of non-union of the tibia of several months duration, secondary to trauma (thus excluding pathological fractures) and in skeletally mature patients. In 2004 the US FDA extended their use to fusion of lumbar vertebrae, European and Australian authorities followed suite in 2005.

It is assumed in much of the evidence that if patients did not receive surgical intervention for their spinal conditions then relief/healing would be minimal. This assumption seems correct for the following reasons. Often one of the inclusion criteria for these studies was that patients' conditions had not responded to non-surgical intervention. The European Agency for the Evaluation of Medicinal Products (EMEA) considered the problem, and based on evidence, deemed it valid. Thus, in single treatment intervention trials where no comparative treatment is included, demonstration of bone fusion and/or pain relief could be considered as reasonable evidence of efficacy. However, in 2005 a literature review and a large multi-centre trial comparing the efficacy of surgery for degenerative lumbar spondylosis with a rehabilitation/education programme concluded that surgical interventions, in some situations were unnecessary.

#### rhBMP-2

RhBMP-2 has the trade name dibotermis alfa and is incorporated in to two commercial products called INFUSE® Bone Graft and InductOs™. Typically rhBMP-2 is applied in a matrix which is placed in or around the site where bone growth is required. Initially the matrix was a sponge of absorbable bovine collagen (ACS) which facilitates surgical implantation and retention of rhBMP-2 at the treatment site. For spinal fusions rhBMP-2/ACS may also be held within metal cages or other supporting vehicle.

Twenty papers were identified in which rhBMP-2 was used to attempt bone fusion in the spine. Sixteen papers dealt with fusion of the lumbar vertebrae and four papers with fusion of cervical vertebrae. There were ten papers in which patients received rhBMP-2 in the absence of any donor bone (allograft i.e. that is a bone donated by another person, or autograft i.e. bone taken from a patient and transplanted into another site of the same patient). In all of these ten papers some degree of successful bone fusions were observed. In the remaining eight papers either allo- or autograft bone was combined with rhBMP-2 in a single treatment; a design that does not allow the individual contribution of rhBMP to be assessed.

Convincing evidence on the ability of rhBMP-2 to fuse lumbar vertebrae arises from the assessment of InductOs™ by EMEA. Their report was made available in 2005. It was a thorough appraisal in which data was made available to the scrutinising committee that was not in the public domain. The pivotal trial sought to demonstrate that the efficacy of

InductOs™ with regard to fusion of the lumbar vertebrae was not inferior to an autograft of hip bone. The study was a well-designed randomised controlled trial (RCT) with random allocation of about 280 patients to one of two treatments. On the evidence, EMEA approved InductOs™ for use in adults with degenerative disc disease who have had at least six months of non-operative treatment for anterior lumbar spine fusion at a single level (L4-S1). In March 2006 one study reported that 23% of patients undergoing fusion of cervical vertebrae had complications. EMEA contraindicate the use of rhBMP-2 in fusion of cervical vertebrae. Another four RCT in which rhBMP-2 was used as a component of treatment were identified. These trials were of varied design and quality with relatively few patients per treatment. Two recent studies claimed that rhBMP-2 in combination with different matrices to collagen had superior efficacy to bone autograft.

### **rhBMP-7**

RhBMP7 is also known as osteogenic protein-1; its international non-proprietary name is eptoterminal alpha. It is manufactured by Stryker Biotech and marketed as OP-1 Implant®, OP-1 Putty® or in Europe as Osigraft. Fewer papers were identified using BMP-7 than rhBMP-2.

There have been only two studies where rhBMP-7 as OP-1 putty® was used in fusion of cervical vertebrae. Only 13 patients were involved. These studies were published prior to 2000 and no further information has been made available in the intervening six years. Further evidence for using rhBMP-7 for fusion of thoracic vertebrae is required.

In this review we identified two case series and two RCT where OP-1 putty® was used for fusion of lumbar vertebrae. In three of the four studies, with a total of 45 patients, OP-1 putty® was combined with bone autograft in to a single treatment. The combining of two potentially active components obfuscates the efficacy of rhBMP-7. The manufacturer of OP-1 Putty® is Stryker and their web site does not indicate any further published developments with regard to this product. The published evidence is insufficient to conclusively affirm that OP-1 putty® would be equal to a bone autograft in achieving fusion of lumbar vertebrae.

### **Conclusions**

The development of alternative methods to achieve fusion of spinal vertebrae without recourse to bone grafts continues to progress. Of the products presently being sold, more evidence is available for fusion of spinal vertebrae with products containing rhBMP-2 than rhBMP-7. The evidence does not support claims, nor are the manufactures making them, that rhBMP, compared to autograft of bone from the patient's hip, are superior in achieving bone fusion or quality of life. However the pain and complications associated with harvesting bone are removed and this is a considerable advantage. Future developments seem to focus on developing biomaterials that provide matrices for appropriate delivery of BMP at surgical sites.

The medical literature indicates a vigorous debate as to whether, in some circumstances, the outcomes of improved non-surgical interventions for degenerating lumbar discs compares favourably with induced bone fusion. These developments may shift the criteria for opting for bone fusion.

Several funders of health services have approved payment, and issued guidelines, for spinal fusions using BMP. These guidelines are similar to those issued by the US FDA.

## Bone Morphogenetic Proteins

### Background

BMP are responsible for the growth and differentiation of bone forming cells. These proteins belong to the superfamily of beta transforming growth factors ( $\beta$ -TGF). Membership is characterised by similar sequences of amino acid and their abilities to stimulate certain classes of receptors on the cell surface. There are over a hundred members of the  $\beta$ -TGF superfamily. Initially they were identified by their ability to induce cells to show cancerous properties. The effect is reversible since the cells revert to normal if the  $\beta$ -TGF is removed. It is the ability of  $\beta$ -TGF to transform the function of cells that offers therapeutic potential that may be coupled with possibly harmful consequences. A recent review identified over 17 BMP<sup>16</sup> although at present only two of the family (BMP-2 and BMP-7) have been incorporated into commercial products. These are available as recombinant (r) protein molecules of human (h) genes (rhBMP-2 and rhBMP-7). BMPs are commercially produced by inserting the gene into Chinese hamster ovary cells which then synthesise the protein. RhBMP-2 induces stem cells to differentiate in to progenitor cells and also aids the differentiation of the latter into osteoblasts. It is these cells that are responsible for synthesising new bone. In contrast, rhBMP-7 has little effect on stem cells but does aid the development of osteoblasts from progenitor cells.<sup>16</sup> The molecules are quickly inactivated or removed from the body and thus they are incorporated in to implant devices to facilitate retention and prevent leakage because the latter could lead to undesirable bone formation.

### rhBMP-2

rhBMP-2 has the international non-proprietary name dibotermis alfa. Typically, rhBMP-2 is applied to a matrix of absorbable collagen sponge made from purified bovine type-1 collagen (ACS) and the sponge placed in or around the site where bone growth is required. In some interventions the rhBMP-2/ACS may also be held within a metal cage or dowel of allo- or auto- graft bone. Improving the performance of vehicles that deliver and restrict rhBMP-2 to its appropriate anatomical site is a focus of recent articles.

Two companies, Wyeth and Medtronic Sofamor Danek produce rhBMP-2. In Europe rhBMP-2 is sold by Wyeth as InductOs™ initially it was approved for use in fractures of the tibia, but in February 2005 the European Agency for the Evaluation of Medicinal Products (EMA) approved InductOs™ for spinal applications. In the USA rhBMP-2 is sold as INFUSE® Bone Graft where it was also used for tibia fractures in addition to fusions of the spine. According to EMA, INFUSE® Bone Graft was approved only for anterior lumbar spine fusions in Canada and Mexico.<sup>1</sup> INFUSE® Bone Graft is not an approved medicine in New Zealand, but Medsafe has confirmed by email correspondence that it is being used in accordance with regulations for an unapproved medicine.

### rhBMP-7

rhBMP-7 is also known as osteogenic protein-1, its international non-proprietary name is opotermis alfa. It is manufactured by Stryker Biotech and marketed as OP-1 Implant® and OP-1 Putty®. In Europe it is marketed as Osigraft. The FDA approved its use in

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<sup>1</sup> <http://www.emea.eu.int/humandocs/PDFs/EPAR/inductos/318802en6.pdf>

fusions of the tibia in October 2001<sup>ii</sup> and this was extended to spinal fusions in April 2004.<sup>iii</sup> The EMEA<sup>iv</sup> and the Australian Therapeutic Goods Administration<sup>v</sup> (TGA) approved the use of OP-1® in 2001 for the treatment of fractures of the tibia that failed to heal. Like INFUSE® Bone Graft, rhBMP-7 and its products have not been approved for use in New Zealand, but Medsafe has confirmed by email correspondence that it is being used in accordance with regulations for an unapproved medicine.

## **Development of spinal fusion**

Spinal fusion is indicated for patients with degenerative disc disease and is usually offered after non-surgical treatments have failed. At present there is some debate about the respective merits of surgical versus non-surgical interventions for chronic low back pain.<sup>20;8;18</sup> Further consideration of this issue is beyond the scope of this review.

Cloward pioneered interbody fusions in the 1940s and approached the spine from the posterior anatomical aspect.<sup>15</sup> Anterior cervical fusions began in the 1950s. In the 1970s metallic cages were introduced to treat spinal instability in horses and comparable devices found their way into human medicine. Metal cages although strong, cause stiffness which leads to stress and implant subsidence. Also the radiological image of metal cages impairs imagery of new bone growth. Bone grafts have better properties for observing radiological imagery of bone fusion, but allografts from human cadavers have problems of availability and could transmit diseases. The alternative is autograft of bone taken from the patient's iliac crest (hip). Unfortunately pain is a common complaint after removal of bone from the iliac crest. For example, in one study a degree of pain persisted in 31% of patients after 24 months and in 16% the appearance of the graft donor site was graded as fair or poor.<sup>37</sup> Despite these constraints autograft bone graft is/was regarded as the "gold standard" by which to compare new treatments. The intricate anatomy of the spine is an important factor in achieving consistent successful bone fusion. For example collagen sponges placed posteriolaterally are subject to compressive forces that in early trials affected delivery of active ingredients.<sup>3</sup> Caution is required about incorporating pioneering evidence into a body of evidence that will be used to inform current opinion, especially if technology in this field has progressed.

It is these constraints that have driven research to develop osteoinductive products and delivery systems like INFUSE® Bone Graft and OP-1® which can be delivered in compatible and resorbable biomaterials.

There are several outcome measures used to assess the success of spinal fusion. These include radiographic imagery to assess the formation of bone and an assessment of the patient's disability due to their back pain. The latter is often measured by the Oswestry score; a ten section questionnaire that covers such items as pain intensity, walking, sleep patterns and the ability to undertake travel; the full questionnaire is reproduced in the appendices.

## **Objectives of this review**

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<sup>ii</sup> <http://www.fda.gov/cdrh/pdf/h010002a.pdf>.

<sup>iii</sup> <http://www.fda.gov/cdrh/pdf2/H020008a.pdf>.

<sup>iv</sup> <http://www.emea.eu.int/humandocs/PDFs/EPAR/osigraft/039301en1.pdf>.

<sup>v</sup> <http://www.tga.gov.au/search/cache.cgi?collection=tga-web&doc=http://www.tga.gov.au/docs/html/adecc/adecc0214.htm>.

To assess the evidence from clinical trials that bone morphogenetic proteins (BMP) are effective in spinal fusion.

## Criteria for selecting studies and information for this review

Similar selection procedures and search strategies were used for rhBMP-2 and BMP-7

**Types of Studies.** Randomised controlled studies, systematic reviews, other guidelines, case –control, case series studies.

**Types of Participants.** Human subjects requiring spinal fusion. Animal studies were excluded

**Types of Interventions.** Use of human bone morphogenetic protein with a supporting matrix and/or ancillary cages, rings, etc.

**Types of Outcome.** Measures of bone fusion rate, rate of secondary interventions, adverse reactions, measures of pain, patient satisfaction.

Evidence based on animal studies and abstracts of talks given at conferences are excluded from this review.

## Search Strategy

The following databases were searched for relevant literature:-

CINAHL, Medline in Process, Medline, Medline Daily Update, EMBASE, ACP Journal Club, DARE, CDSR, CCTR, and other Evidenced based healthcare websites.

The web sites of the US FDA, EMEA and Australian Therapeutic Goods Authority were consulted for information about the regulatory approvals for these products. We also looked at some clinical trial registers to ascertain if any clinical trials are in progress.

Inclusion criteria were; all papers found regardless of publication date, in English and more than 4 subjects included in the treatment group.

For BMP-2 the literature searches were undertaken October 2003, July 2004 and January 2006 with email alerts arriving up to March 2006. For BMP-7 searches were undertaken August 2004 and January 2006 with email alerts arriving up to March 2006.

## Methodological Quality

Primary source papers were assigned a design score according to the following SIGN criteria (Table 1).<sup>1</sup>

**Table 1 SIGN criteria for classifying studies.**

Score	Design
1++	High quality meta-analyses, systematic review of RCTs, or RCTs with a very low risk of bias
1+	Well conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
1-	Meta-analyses, systematic reviews of RCTs or RCTs with a high risk of bias
2++	High quality systematic reviews of case-control or cohort studies. High quality case-control or cohort studies with very low risk of confounding, bias or chance and a high probability that the relationship is causal
2+	Well conducted case control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal
2-	Case control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal.
3	Non-analytic studies
4	Expert opinion

## Presentation of information

Information is presented in the following sequence.

- Articles on rhBMP-2 are considered before those on rhBMP-7
- The papers are categorised by spinal level with cervical/thoracic fusions presented before lumbar fusions.
- Consideration is given to comments from regulatory authorities that have reviewed submissions by manufacturers of products containing these molecules.

## **Statistical considerations**

### **Case Series**

Authors of case series cited in this review seem to assume that if the target conditions for treatment with BMP did not receive surgical intervention, then relief/healing of their condition would be minimal. The validity of this assumption was raised by EMEA<sup>vi</sup> and based partly on the work of Fritzell<sup>19</sup>, they deemed the assumption valid. Also many of the studies have an inclusion criterion that patients have a long-standing failure of non-surgical intervention(s) for their spinal conditions. Thus, in some single treatment intervention trials, where no comparative treatment is included, demonstration of bone fusion with concomitant pain relief could be considered as reasonable evidence of efficacy. However this assumption is not universally accepted and a Cochrane Review of RCT concluded that in some circumstances, surgical intervention is probably no better than improved non-surgical interventions.<sup>20</sup> In a large multi centre trail a similar conclusion was formed.<sup>18</sup>

Although case series trials in the absence of a comparative treatment group provide some evidence of efficacy, they provide poor quality data for comparative analyses with other treatments.

### **Random Controlled Trials**

A strategy to develop better products to replace established treatments should include appropriate statistical testing. Often an established treatment may have undesirable side-effects that might be absent in the replacement treatment. Clearly in terms of preventing, curing or alleviating disease, the replacement treatment has only to be equal or non-inferior to the established treatment, for the former to be an attractive alternative. This seems to be true for products containing BMP since the “gold standard” of treatment in severe cases is usually an autograft of bone from the iliac crest. A statistical test of non-inferiority is not the same as accepting the null hypothesis because significant differences between two or more treatment groups were not detected.<sup>vii</sup> In many of the RCTs cited in this review the authors conclude that two treatments are comparable because the p-value for a comparison  $>0.05$  and the null hypothesis is accepted. An underpowered trial will almost certainly fail to reject the null hypothesis and wrongly conclude the treatments are similar. Non-inferiority tests seek assurance that the new treatment is no less efficacious than a comparative standard.

## **Literature review of rhBMP-2**

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<sup>vi</sup> <http://www.eudra.org/humandocs/Humans/EPAR/inductos/inductos.htm>.

<sup>vii</sup> <http://www.emea.eu.int/pdfs/human/ewp/215899en.pdf>.

## Cervical Fusions

Four papers examined the use of INFUSE® Bone Graft for interbody cervical fusion (Table 2). One paper was a RCT<sup>4</sup> and three were case series.<sup>5,29,38</sup>

**Table 2 Effect of rhBMP-2 on outcomes in patients undergoing cervical spinal fusion.**

Reference	Design Score	Intervention	Number in treatment group	Number in control group	Key results
Baskin DS, Ryan P, Sonntag V, et al. <sup>4</sup>	1-	RCT Anterior cervical discectomy and interbody fusion. The treatment group received a fibular allograft (Cornerstone-SR Allograft Ring) with INFUSE® Bone Graft along with an Atlantis anterior cervical plate. The control group received a fibular allograft with cancellous iliac crest autograft placed inside it, along with an Atlantis anterior cervical plate.	18	15	At 6, 12 and 24 months 100% fusion was achieved in all patients regardless of treatment. Improvement in the neck disability index was marginally superior in the treatment group compared to the control group at 24 months (p=0.03) as was arm pain (p=0.03). There was no difference at 24 months in neurologic status or neck pain score. The authors concluded that their pilot study demonstrated the feasibility of using rhBMP-2 safely and effectively in the cervical spine.
Lanman TH, Hopkins TJ. <sup>29</sup>	3	A prospective pilot case study with no comparative group. Treatment to assess efficacy of poly L and D lactide as a bioabsorbable bone implant containing rhBMP-2.	20	0	All patients achieved fusion by three months. This included two cases that required fusion at three levels. Hospital stay was mostly minimal with the procedure undertaken as outpatient. One patient had severe complications with dysphagia and a 32 day stay. Chief investigator was a paid consultant of Medtronic-the manufacturer.
Boakye M, Mummaneni PV, Garrett M, et al. <sup>5</sup>	3	A prospective case series report with no comparative group. Treatment to assess efficacy of incorporating polyetheretherketone (PEEK) a new biomaterial, in combination with rhBMP-2/ACS for bone fusion in the cervical region. Single level discectomy in 12 patients, 2 level in 9 and 3 levels in 3 patients.	24	0	No blinding took place in this trial. The mean follow up was 13 months. One quadriplegic patient died within 4 weeks of surgery. Clinical outcome in 21 out of 23 patients was considered good/excellent. In three patients heterotopic bone formation took place-subsequently patients now receive half dose rhBMP-2. Authors consider the first report using PEEK in this clinical setting.
Shields L, Raque G, Glassman S et al. <sup>38</sup> .	3	Multi centre retrospective case series, no comparative treatment group. Patients received higher than usual dose of rhBMP-2. Two procedures (a) anterior cervical discectomy and fusion 138 patients and (b) anterior vertebrectomy 13 patients. In both procedures autograft bone was also used	151	0	Survey of complications showed overall 9.9% patients had hematomas, 8.6% complaints without hematomas but experienced dysphagia/ respiratory problems. Another 6.6 % had a range of complaints. Overall complications attributed to rhBMP-2 was 23.2%. A higher than usual dose of rhBMP-2 was used which might explain why other investigations have not shown this high rate of adverse effects.

The RCT compared the effectiveness of a combined treatment of INFUSE® Bone Graft and bone allograft with the comparative group receiving iliac crest autograft.<sup>4</sup> The numbers of patients (18 and 15) in the treatment groups were relatively small. There was no significant difference between treatments upon the rates of bone fusion. However, those receiving INFUSE® Bone Graft had small, but significantly less pain in the neck and arm. In this trial INFUSE® Bone Graft appeared to be safe without the associated pain and complications of grafting. However the grafting technique was criticised by Dickman<sup>17</sup>

who considered the use of iliac crest bone in the control group was unnecessary. If this is so, the control intervention appears intrusive and the benefits of INFUSE® Bone Graft for cervical application contrived.

One case series study of 151 patients recorded a 23.2% complication rate which was considered higher than normal for fusion of cervical vertebrae. However the dose of rhBMP-2 was also higher and could have been responsible for the complications that included hematomas which displaced internal tissue and organs.<sup>38</sup> Two of the case series trials were testing new biomaterials within the implant (Table 3).<sup>5,29</sup> The properties of the implant could affect the kinetics of drug release and it is noticeable that in one trial, heterotopic bone formed, and the dose of rhBMP-2 was halved.<sup>5</sup>

### Lumbar Fusions

Up to January 2006 sixteen papers were reviewed on the use of rhBMP-2 for the fusion of discs in the lumbar region; fifteen presented some form of primary data and one<sup>36</sup> was a review (Table 3). Of the fifteen papers, five were case series and ten used some form of RCT. The surgical procedures and patients varied amongst these trials with some incorporating metal cages with bone grafts, whilst others used no bone graft. The approach to the spine also varied, some being anterior others posterior. One paper included data after laparoscopic surgery<sup>11</sup> and one dealt with deformities of the spine in adults.<sup>32</sup> These papers are summarised below and in Table 3. In the primary source material, one study<sup>12</sup> probably contains data previously published. In recent studies there seems to be an emphasis on developing new carrier vehicles for the active ingredient rhBMP-2.<sup>22,28,30</sup>

**Table 3 Effect of INFUSE® Bone Graft or related interventions on outcomes in patients undergoing lumbar spinal fusion.**

Reference	Design Score	Intervention	Number in treatment group	Number in control group	Key results
Boden SD, Zdeblick TA, Sandhu HS, Heim SE. <sup>7</sup>	1-	Anterior lumbar interbody arthodesis with 2 tapered cylindrical threaded fusion cages (Novus LT) filled with rhBMP-2/collagen sponge or autograft iliac crest bone. Four patients had laparoscopic surgery the rest open surgery.	11	3	No clinically relevant adverse events related to cage or graft materials observed. At 3 months 10/11 (91%) in the treatment group had solid fusions compared to 2/3 (66%) of the controls. At 12 and 24 months the entire treatment group had achieved fusion and 2/3 of the controls. The mean improvement in the Oswestry score was 25 points at 24 months in the treatment group and 15 points for the controls (Difference not significant). The control group was too small to reveal clinically relevant differences).
Kleeman TJ, Ahn UM, Talbot-Kleeman A. <sup>27</sup>	3	Laparoscopic anterior lumbar interbody fusion with rhBMP-2/collagen and 2 Novus LTCages.	22	0	Fusion was achieved in all patients by 6 months. Preoperation, the average Oswestry score was 47 but at 12 months it was 11. At 12 months 48% of those previously employed had recovered full function and had returned to work.
Burkus JK, Transfeldt EE, Kitchel SH, et al. <sup>13</sup>	1-	Anterior lumbar interbody fusion using threaded cortical allograft dowels filled in the treatment group with INFUSE® Bone Graft and in the control group with autograft from the iliac crest. All patients had complete discectomy.	24	22	At 12 and 24 months the treatment group showed higher rates of fusion compared to controls. Back pain and Oswestry scores were statistically significantly improved at 3, 6 and 24 months but not so at 12 months.

**Table 3 Effect of INFUSE® Bone Graft or related interventions on outcomes in patients undergoing lumbar spinal fusion.**

Reference	Design Score	Intervention	Number in treatment group	Number in control group	Key results
Burkus JK, Gornet MF, Dickman et al. <sup>10</sup>	1+	Anterior lumbar interbody fusion INFUSE® Bone Graft or autograft at a single level. LT Cage Lumbar Tapered Fusion Devices (Medtronic) were used in all patients after discectomy.	143	136	This is the pivotal trial from which data were submitted to regulatory authorities. It was a non-inferiority trial. Apart from the effect of bone grafting in the control group on pain and complications the clinical outcomes appear to be similar between treatment and controls and appear not to have been of statistical significance.
Boden SD, Kang J, Sandhu H, et al. <sup>6</sup>	1-	Use of rhBMP-2 to achieve posteriolateral lumbar spine fusion. Three treatment groups. Iliac crest autograft with Texas Scottish Rite Hospital pedicle screw instrumentation, (TRSH), rhBMP-2 + TRSH, or rhBMP-2 alone. rhBMP-2 was applied to 10cc of ceramic granules (biphasic calcium phosphate (Medtronic) per side of the spine and placed in the decorticated intertransverse process area.	Initial numbers per group were, autograft 5; rhBMP-2 + TRSH, 11; and rhBMP-2, 11 (9 at last follow up).		At a mean follow up time of 17 months, the fusion rate was 40% in the autograft group and 100% in the 2 groups receiving rhBMP-2. Comparing the autograft group with the rhBMP-2 + TRSH and the rhBMP-2 groups the differences were significant (P=0.018 and P=0.028 respectively). The rhBMP-2 group had a mean operative time of 2 hours compared to greater than 3 hours for the other 2 groups. Oswestry scores fell more quickly and to a greater extent in the rhBMP-2 group. At the last follow up the decrease in back pain score was greatest in the rhBMP-2 group (-6.2, -5.1 and -10.4 in the autograft, rhBMP-2 + TRSH and rhBMP-2 groups respectively). The difference between groups was significant, p = 0.025. Leg pain score was significantly lower in the rhBMP-2 group only compared to the preoperative score. No complications were attributed to the use of rhBMP-2. Resnick et al <sup>36</sup> consider the sample size of this trial inadequate.
Burkus J, Dorchak JD, Sanders DL. <sup>9</sup>	1-	Radiographic assessment of interbody fusion using rhBMP-2 on an absorbable collagen sponge within two tapered cylindrical fusion cages (LT-CAGE) inserted anteriorly after discectomy. The control group had iliac crest autograft placed in the cages.	22	20	Bone density increases within the interbody fusion device were observed at 6, 12 and 24 months in the rhBMP-2 and the autograft group. At 24 months new bone formation outside the cages (but within the confines of the disc space) was observed in 22 patients (100%) in the rhBMP-2 group and 19 (95%) in the autograft group. The authors concluded that high fusion rates associated with new bone formation inside and outside the cages can be achieved by using rhBMP-2.
Burkus JK, Heim SE, Gornet MF, et al. <sup>11</sup>	1-	A metaanalysis of 3 trials: an RCT using either the INFUSE® Bone Graft or autograft; a case series trial of INFUSE® Bone Graft system and a case series trial of iliac crest autografts. All trials used LT-CAGE Lumbar Tapered Fusion Device. Patients in the RCT trial had open surgery and an anterior approach. The 2 case series trials used an anterior laparoscopic method. All patients had 2 LT-CAGE devices implanted anteriorly and symmetrically at one lumbar level.	277	402	At 24 months the fusion rate in the rhBMP-2/collagen sponge group was 94.4% compared to 89.4% in the control group (p<0.022). According to the meta-analysis operation time, re-operations and time to return to work were notably more favourable for the rhBMP-2/collagen sponge group.

**Table 3 Effect of INFUSE® Bone Graft or related interventions on outcomes in patients undergoing lumbar spinal fusion.**

Reference	Design Score	Intervention	Number in treatment group	Number in control group	Key results
Lanman TH, Hopkins TJ. <sup>30</sup>	3	A prospective case study to assess the use of bioresorbable poly lactides in lumbar fusion. Device supplied by Medtronic). Various conditions within the treatment group including discogenic pain, spondylosis and non unions. No comparative group with regard to rhBMP-2.	43	0	At three month successful fusion in 45% increasing to 98% at 6 months. Oswestry score at pre-operation. Mean 49.7±14.5 and claims to fall although means are little changed to data to track changes within an individual is not available. The chief investigator is a paid consultant of Medtronic.
Kuklo TR, Rosner MK, and Polly DW. <sup>28</sup>	3	A prospective case series report with no comparative group. Treatment to assess efficacy of a incorporating bone implant cages made of polymers of the D and L isomers lactide, marketed as HYDROSORB by Medtronic Sofamor Danek. The cages are filled with rhBMP-2/ACS. Various bone diseases across 22 patients some required fusion at more than one level.	22	0	Although authors recognise no control group they claim from literature that operating time, blood loss and hospital stay compare favourable with other measures.
Haid RW, Branch CL, Alexander JT, et al. <sup>24</sup>	1+	A prospective randomised multi centre trial. Comparing the effect of rhBMP-2 with bone autograft. Implants delivered in titanium cages placed for posterior lumbar fusion. Radiographs and CT scans read blind. Major outcomes were Oswestry scores, pain in back and leg, radiographs and CT scans for bone fusion.	34	33	In both groups evidence of fusion at 6 months. Although slight decrease 12 months for intervention group. At 12 and 24 months fusion rates ~80-90% with no significant differences between groups. Between 65-75% patients had improved Oswestry scores no significant differences between groups. Back pain was less in the intervention, this highly significant at P=0.009 at 24 months. Authors have potential conflict of interest as paid consultants to Medtronic and also stock-holders.
Mummaneni PV, Pan J, Haid RW, et al. <sup>33</sup>	3	Three treatments (a) iliac crest bone graft (b) iliac bone graft with rhBMP-2 and (c) autograft bone taken from spine during their lumbar surgery.	(a) 19 (b) 14 (c) 11		Follow-up mean of 9 months on 40 of the 44 enrolled. Follow up period variable from 3-19 months. Group (a) 95% successful fusion (b) 100% and (c) 91%. Very successful fusion rate but all treatments had autograft bone.
Glassman SD, Dimar JR, Carreon LY, et al. <sup>22</sup>	1+	Prospective, randomised, trial to assess new ingredients, 15% hydroxyapatite and 85% tricalcium phosphate to improve rhBMP-2 impregnated collagen sponge. Comparative group had iliac crest autograft. Patients had single level lumbar degenerative disc disease. Bone fusion assessed by radiographs and CT scans at immediate post operative discharge, 6 and 12 months. CT scans read blind. Fusions classed on a five point scale the best being solid bilateral fusion.	38	36	At 6 months the intervention group i.e. those with rhBMP-2 with "improved" sponge had better mean fusion grades. This was also true at 12 months.

**Table 3 Effect of INFUSE® Bone Graft or related interventions on outcomes in patients undergoing lumbar spinal fusion.**

Reference	Design Score	Intervention	Number in treatment group	Number in control group	Key results
Villavicencio AT, Burneikiene S, Nelson EL, et al. <sup>43</sup>	3	Retrospective case series study on the effect upon fusion of rhBMP-2/ACS combined with autograft or allograft bone. Major objective of the study was to test treatment delivered transforaminally. No comparative group with regard to using rhBMP-2. Clinical assessment for treatment was blinded.	74	0	No failed fusions. Mean time to fusion was 4.1 months. Patient satisfaction was rated good. Not particularly informative study since bone grafts were used in all treatment groups.
Burkus JK, Sandhu HS, Gornet MF, et al. <sup>12</sup>	1-	Prospective randomised multi centre trial. rhBMP-2/ACS versus autograft bone from iliac crest. rhBMP and autograft bone were delivered by packing into a dowel of allogenic bone.	79	52	Length of surgery, blood loss and hospital stay were better with rhBMP/ACS treatment. Fusion rates were reported much better in rhBMP/ACS than control with values ~96-98% for 6-24 months compared with 89-76 in the control. Various pain parameters were reported better in the intervention. Oswestry scores seemed better in the in the intervention especially early in the trial, but at 24 months the improvement in this parameter was not significant.
Luhmann SJ, Bridwell KH, Cheng I, et al. <sup>32</sup>	3	Prospective case series to test the efficacy of rhBMP-2 on correcting a range of spinal deformity in adults. This was an off-label trial. Applied as INFUSE® Bone Graft in either anterior, posterior and sometimes both. Three treatments groups based on approach to spine and the presence or absence of bone graft. Radiographs read blind.	241		Similar fusion rates in the three treatments groups 93-100% success but no statistics performed. Overall there were 263 fusions since some patients required fusion at more than one level. Of these 263 fusions only 12 were regarded as not fused. No substantial complications were reported.
Resnick DK, Choudhri TF, Dailey AT, et al. <sup>36</sup>	1+	Literature review from 1966 to November 2003 to formulate guidelines on bone graft extenders and substitutes.			Although published in 2005 the cut-off date was November 2003. Identified 6 papers providing better than class III clinical evidence. All these papers were included in the EBH review of 2004 and gives critical appraisal. Recommends the use of autograft bone or rhBMP-2 bone graft substitute in anterior lumbar interbody fusion in conjunction with a threaded titanium cage.

The study by Burkus<sup>10</sup> warrants special mention since it is the pivotal study that formed submissions by Medtronic to FDA and EMEA. It was a relatively large RCT on 279 patients comparing the effects of using INFUSE® Bone Graft system with autograft bone. All patients had LT-CAGE Lumbar Fusion Devices deployed. Although a range of outcomes were measured none of the differences between the treatment groups were of statistical significance. This is not surprising and should not be misinterpreted as failure since the trial was designed as a non-inferiority trial. Twenty four months after surgery the fusion rate in the INFUSE® Bone Graft group was 94.5% compared to 88.7% in the autograft group. Back pain reduced dramatically in both groups but comparison between groups does not show any significant differences. Another RCT by the same group using anterior lumbar fusion, compared the use of INFUSE® Bone Graft presented at surgery in dowels of allograft bone with iliac crest bone autografts which were also combined with

allograft dowels. Although sample sizes were small (24 and 22) better fusion rates and improved outcomes were reported for Oswestry scores and back pain at 3, 6 and 24 months post surgery but not at 12 months.<sup>13</sup> In another study they presented radiographic evidence that rhBMP-2/ACS (plus fusion cage) induced bone formation six months after surgery.<sup>9</sup> Although bone growth occurred outside of the cages, it was confined to the disc space and caused no problems.<sup>9</sup>

An early pilot study in 2000 showed that osteoinduction occurred reliably in the 11 patients treated with rhBMP-2/carrier/fusion cage.<sup>7</sup> With only 3 patients in the control group comparisons of clinical outcomes were meaningless. A small case series study also reported the outcomes of laparoscopic anterior lumbar interbody fusion using rhBMP-2/collagen sponge and NOVUS LT cages.<sup>27</sup> Fusion was achieved in all patients by 6 months without adverse outcomes.

A meta-analysis<sup>11</sup> has been made using the data from one RCT<sup>10</sup> that compared the use of INFUSE® Bone Graft with grafting in an open anterior method and two case series trials.<sup>27</sup> Unfortunately the surgical procedures differed between studies. In the case series laparoscopy was used and baseline data for some parameters also varied, notably previous back surgery which could indicate more severe disease in that group were thus less amenable to successful outcomes. At 24 months the fusion rate in the rhBMP-2 was 94.4% compared to 89.4% in the control group ( $p < 0.022$ ). It is important to note that the original data from the relatively large RCT<sup>10</sup> showed no significant differences between treatments was included in the meta-analysis. The differences that were shown as a result of this meta-analysis presumably came from adding data from the two non-comparable case series, followed by statistical adjustment. A review of the INFUSE® Bone Graft data sometimes shows substantial differences in outcome between the open and laparoscopic methods used. The clinical differences reported between the INFUSE® Bone Graft and autograft groups, as a result of the meta-analysis, must therefore be viewed with caution.

A small RCT investigated the effect of using rhBMP-2 added to calcium phosphate granules for posterolateral spinal fusion.<sup>6</sup> There were three treatment groups, (a) iliac crest autograft with Texas Scottish Rite Hospital (TSRH) pedicle screw instrumentation, 5 patients, (b) TRSH Spinal System with rhBMP-2, 11 patients and (c) rhBMP-2 alone, 11 patients. Follow-up was at 17 months, the radiographic fusion rate was 40% in the autograft group and 100% in the 2 groups receiving rhBMP-2. Other clinical outcomes tended to be more favourable when rhBMP-2 alone was used. While some of these results were of statistical significance the small numbers especially in the control group (5 patients from which the authors derive a 40% success rate) make the validity of the comparisons doubtful.

All of the fifteen studies reporting primary data found no unexpected or serious adverse events attributable to the use of rhBMP-2.

In 2005 Burkus' group published a prospective randomised multi centre trial comparing the effects of rhBMP-2/ACS versus autograft bone from iliac crest on lumbar bone fusion. The study was performed between 1998-2001.<sup>12</sup> rhBMP-2 and autograft bone were delivered by packing into a dowel of allograft bone. Length of surgery, blood loss and hospital stay were better with rhBMP-2/ACS treatment. Fusion rates were also reported much better in rhBMP/ACS than control with values ~96-98% for 6-24 months compared with 89-76 in the control ( $p$  values for 6, 12 and 24 months 0.047, 0.036 and  $< 0.001$  respectively). Pain scores in the leg and back were reported better in the intervention group. Oswestry scores were also better in the intervention group especially early in the trial, curiously these

benefits were present six weeks after surgery, however at 12 and 24 months the improvement over baseline was not significant ( $p=0.074$  and  $0.119$  respectively). This trial appeared to demonstrate superiority of rhBMP-2 over a control treatment, where as the same authors, in the pivotal trial published three years earlier, such differences were not observed (the surgical procedures were different which might explain the discrepancy). However, another paper in 2005 by a different group of investigators who were investigating the effect of improved collagen matrices on posteriolateral lumbar fusions also claim better fusion rates over bone autografts.<sup>22</sup> In this investigation it is far from clear how the bone graft was positioned or held adjacent to the spine.

### **Comments from regulatory authorities on the use of rhBMP-2**

The FDA approved INFUSE® Bone Graft for spinal fusion between L4-S1 in July 2002. In February 2005 the Committee for products for human use (CHMP) of EMEA published its scientific discussion extending the approval of InductOs™ (the same product as INFUSE® Bone Graft) to include single level spinal fusion between L4-S1.<sup>viii</sup> This document contains very critical appraisal of the evidence presented in the pivotal trial by Burkus.<sup>10</sup> The trial was designed as a non-inferiority trial which sought to test that rhBMP-2 was not inferior to a standard treatment i.e. iliac crest autograft. In this trial a sample size of 270 with 135 in two treatment groups was estimated. After requesting further analyses, notably making tests two-sided rather than one-sided and treating missing data as treatment failures (a prudent step since failed treatments might drop out from the trial and thus cause bias) the reviewers were convinced that non-inferiority had been demonstrated with regard to both bone fusion and Oswestry scores for disability. EMEA approved InductOs™ with the limitations that are considered in the following section.

According to the Medtronic web site, on January 26 2006, the Australian TGA approved INFUSE® BONE GRAFT used with tapered lumbar cages for spinal fusions. The Australian TGA were contacted by email for details but they consider the information commercial-in-confidence and release is not authorised. Enquiries of MedSafe indicate that INFUSE® Bone Graft has not received regulatory approval in New Zealand but is being used in accordance with regulations that apply for an unapproved medicine.

This review identified only three papers on fusion of cervical vertebrae. None of the three regulatory authorities FDA, EMEA and TGA appears to have approved rhBMP-2 for use in the upper spine (see section below on contraindications).

### **Contraindications and cautionary notes for rhBMP-2**

It is important to note that BMP can be used at various levels in the spine, applied from two or three anatomical aspects (i.e. anterior, posterior etc), with different delivery systems (sponges, metal cages, resorbable biomaterials, for varying diseases from disc degeneration to malformations and in various age groups. Often the evidence to support efficacy in each of these specific circumstances is not available and regulatory authorities have restricted their approvals to specified clinical situations and caution about “off-label” use.

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<sup>viii</sup> <http://www.emea.eu.int/humandocs/PDFs/EPAR/inductos/InductOs-H-C-408-II-07.pdf>.

In October 2005 EMEA<sup>ix</sup> issued the following contraindications for using InductOs™ in patients with:

- 1) A known hypersensitivity to dibotermin alfa, bovine Type I collagen or to any of the other excipients of the medicinal product.
- 2) Skeletal immaturity.
- 3) Any active malignancy or patient undergoing treatment for a malignancy.
- 4) Pregnancy.
- 5) An active infection at the operative site.
- 6) Persistent compartment syndrome or neurovascular residua of compartment syndrome.
- 7) Pathological fractures such as those observed in (but not limited to) Paget's disease or in metastatic bone.
- 8) InductOs™ can cause initial resorption of surrounding trabecular bone. Therefore, in the absence of clinical data, the product should not be used for direct applications to trabecular bone when transient bone resorption may create a risk of bone fragility. When InductOs™ was used with the LT-CAGE device (as instructed in Section 4.2 of this SmPC) 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 autograft bone graft.
- 9) There are no data on the efficacy and safety of the product in concomitant use with bone graft.
- 10) In the absence of any experience, the repeated use of the medicinal product is not recommended.
- 11) The safety and efficacy of the use of InductOs™ in patients with known autoimmune disease, including rheumatoid arthritis, systemic lupus erythematosus, scleroderma, Sjögren's syndrome and dermatomyositis/polymyositis have not been established.
- 12) The safety and efficacy of InductOs™ have not been demonstrated in patients with metabolic bone diseases.
- 13) No studies have been performed in patients with hepatic or renal impairment.
- 14) 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.
- 15) Commonly, both dibotermin alfa and bovine Type I collagen have been found to elicit immune responses in patients.
- 16) In anterior lumbar spine fusion studies, 0.7% of patients receiving InductOs™ developed antibodies vs 0.8% of patients receiving autograft bone graft.
- 17) In anterior lumbar spine fusion studies, 19% of patients receiving InductOs™ developed antibodies to bovine Type I collagen vs. 13% of patients receiving autograft bone graft. In acute tibia fracture studies, 15.7% of patients receiving

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<sup>ix</sup> <http://www.emea.eu.int/humandocs/PDFs/EPAR/inductos/318802en7.pdf>.

InductOs™ developed antibodies to bovine Type I collagen vs. 11.8% of control patients. In either of the 2 indications, no patients who tested positive for anti-bovine Type I collagen antibodies developed antibodies to human Type I collagen.

- 18) 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. Special consideration of risks and benefits should be given for patients who have previously received injectable collagen. The possibility of an immune response to the product should be evaluated in cases where an undesirable effect with immunological background is suspected.
- 19) Failure to follow the Instructions for Use for InductOs™ may compromise its effectiveness.
- 20) Localised oedema associated with the use of InductOs™ has been reported in patients undergoing cervical spine surgery. The oedema was delayed in onset and, in some cases, 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.
- 21) The safety and efficacy of InductOs™ used with spinal implants other than the LT-CAGE device, implanted at locations other than L4-S1 in the lower lumbar spine, or used in surgical techniques other than anterior open or anterior laparoscopic approaches have not been established. When degenerative disc disease was treated by a posterior lumbar interbody fusion procedure with cylindrical threaded cages and diboterminal alfa, posterior bone formation was observed in some instances.

This comprehensive list from EMEA is similar to that issued by FDA and reflects ongoing caution about these products especially about long term consequences. Attention is drawn to the penultimate contraindication in cautioning use in fusion of cervical vertebrae.

### **Guidelines issued by funders of health services**

Although not an exhaustive survey several organisations have issued their own guidelines on using BMP-2 for spinal fusion. The US Government Centers for Medicare and Medicaid Services (CMS) has approved payments for spinal fusion with BMP-2. The commercial companies that approved payments and have issued guidelines on payment include Aetna<sup>x</sup>, Blue Shield Blue Cross<sup>xi</sup> and CIGNA.<sup>xii</sup>

### **Economic evaluation of rhBMP-2 and INFUSE® Bone Graft**

There were two papers addressing the on the economic costs in the US of using rhBMP-2 for lumbar fusions prior to 2004, but none recently.<sup>2,34</sup> No new articles on the economic valuation of using rhBMP-2 have been identified since the first review. More recent developments in this field incorporate a range of biomaterials to replace allograft bone and metal cages. The costs of these evolving biomaterials on the overall costs of these procedures are unclear.

### **Conclusions rhBMP-2**

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<sup>x</sup> <http://www.aetna.com/cpb/data/CPBA0411.html>

<sup>xi</sup> [http://www.bcbsnc.com/services/medical-policy/pdf/bone\\_morphogenetic\\_protein.pdf](http://www.bcbsnc.com/services/medical-policy/pdf/bone_morphogenetic_protein.pdf)

<sup>xii</sup> [http://www.cigna.com/health/provider/medical/procedural/coverage\\_positions/medical/mm\\_0118\\_coverage\\_positioncriteria\\_recombinant\\_human\\_bone\\_morphogenetic\\_protein.pdf](http://www.cigna.com/health/provider/medical/procedural/coverage_positions/medical/mm_0118_coverage_positioncriteria_recombinant_human_bone_morphogenetic_protein.pdf)

There were thirteen papers, out of a total of nineteen, in which evidence was based on case series. In these studies some treatment groups would have received rhBMP-2 in conjunction with bone graft (either allo- or auto- graft) and therefore it is difficult to conclude that rhBMP-2 alone was responsible for bone fusion. However, in ten studies (6 RCT and 4 case series) a treatment group received rhBMP-2 in the absence of any donated bone. In these studies some degree of clinically successful bone fusion was observed. Based on the assumption that for the patients treated in these trials, bone fusion is better than any non-surgical interventions<sup>xiii</sup> at relieving chronic low back pain, then these studies present good evidence of overall efficacy of rhBMP-2.

The trial published by Burkus<sup>11</sup> with 279 patients was the pivotal trial and with a meta-analysis that followed a year later<sup>11</sup> these publications are still the most substantial single body of evidence from a RCT to date. The data have been reviewed by FDA, EMEA and TGA and products (INFUSE® Bone Graft and InductOs™) have received approvals for achieving bone fusion in the lower back. However the crucial question is-are these products superior to bone grafts with regard to rates of fusion, pain relief and complications? Most primary source studies are case series and therefore do not address this issue. The EMEA's scientific discussion on the approval of InductOs™ was published in 2005.<sup>xiv</sup> It is a rigorous appraisal and takes a prudent approach to data analysis requesting a reanalysis classifying missing data as treatment failures. EMEA concluded that INFUSE® Bone Graft is not inferior to autograft bone implants with regard to achieving bone fusion and Oswestry scores. No statistical tests of superiority were undertaken.

What seems remarkable is that in order to conclude that rhBMP-2 was no less clinically effective than bone autografts the sample size calculations for the RCT conducted by Burkus required ~135 subjects in each treatment group. No other trials, even though they investigate similar parameters of bone fusion and Oswestry scores and use broadly similar surgical techniques come close to that sample size. However two trials one by Burkus<sup>12</sup> and another by Glassman<sup>22</sup> claim superiority of rhBMP-2 products over bone autografts. The question of superiority with respect to bone fusion is unresolved.

From a patient's perspective what matters is the relief of pain, improvement in mobility and future prospects. Unfortunately many of the studies which included a comparative treatment did so by comparing rhBMP-2 with an autograft which is known to cause pain. Therefore it is possible that patients, knowing their treatment, reported pain in which they "confused" pain from the hip with pain from spinal disease. Never-the-less a review of the studies where pain was reported 24 months after surgery is shown in Table 4. Seven papers were identified in which some parameter of pain was measured in trials comparing rhBMP-2 with autograft. In three trials, at twenty four months pain was reported to be less in the rhBMP-2 group compared to autograft.<sup>13,6,11</sup> Of the remaining four, three had marginally non-significant p values<sup>7,12,24</sup> and one, the large pivotal trial showed no benefit of rhBMP-2 with regard to pain.<sup>10</sup>

**Table 4 Summary of parameters of pain in studies where rhBMP-2 was used to fuse lumbar vertebrae.**

Studies where some aspect of pain was reported less in the group receiving rhBMP-2	Studies where some aspect of pain was reported to be no different in the group receiving rhBMP-2
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<sup>xiii</sup> <http://www.emea.eu.int/humandocs/PDFs/EPAR/inductos/InductOs-H-C-408-II-07.pdf>.

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**Table 4 Summary of parameters of pain in studies where rhBMP-2 was used to fuse lumbar vertebrae.**

Studies where some aspect of pain was reported less in the group receiving rhBMP-2	Studies where some aspect of pain was reported to be no different in the group receiving rhBMP-2
RhBMP-2 delivered in allograft versus autograft. Back pain at 24 months less p=0.047. <sup>13</sup>	rhBMP-2 versus autograft. At 24 months after surgery difference in back pain p=0.12. <sup>7</sup>
Three treatment trial with (a) iliac crest autograft with Texas Scottish Rite Hospital (TSRH) (b) TRSH Spinal System with rhBMP-2 and (c) rhBMP-2 alone. P=0.049 for a comparison between rhBMP-2 groups ((b+c versus a). <sup>6</sup>	The pivotal trial by Burkus <sup>10</sup> . Pain parameters in rhBMP-2 and autograft decreased over time to the same extent. Therefore no difference in treatment groups. A meta-analysis contradicts these findings.
A meta-analysis of three trial with mixed treatments but consistent use of Oswestry scores claims for use of rhBMP-2/ACS versus autograft bone p=0.0041. <sup>11</sup>	rhBMP-2 in allograft dowels compared to autograft bone, also in allograft dowels. Statistically significantly greater improvements in Oswestry scores in rhBMP-2 versus autograft at 3 and 6 months p=0.021 and 0.031. At 12 and 24 months improvement marginally non-significant p=0.074 and 0.119. <sup>12</sup>
	rhBMP-2/ACS delivered in metal cages compared to autograft in the same cages. At 24 months Oswestry scores and SF-36 questionnaire no significant differences. Reports highly significant improvement in back pain at 24 months and this improvement is greater than in the control p=0.009. However the starting values for back pain between the groups seem different. <sup>24</sup>

The evidence that using rhBMP-2 is better than bone autograft at achieving long-term pain relief is not strong.

In circumstances where autograft or allograft is not an option, INFUSE® Bone Graft and InductOs™ may achieve desirable outcomes. In many cases, although autograft is feasible, rhBMP-2 may still be preferable because benefits other than bone fusion and pain relief are possible e.g. reduced complications arising from removing autograft bone, length of hospital stay.

At present the benefits of rhBMP-2 have to be judged against potential harm in the future. This is true of most medical innovations. There are several contraindications and the relative infancy of the procedure has not allowed any long term consequences to emerge. It is a condition of some regulatory authorities that manufacturers initiate pro active monitoring for increased risk of cancers. One might expect these contraindications to be assessed and if warranted their number reduced.

In 2005 editors of major medical journals agreed that it was requirement for future publication that clinical trials be registered before being undertaken. Trial registers in the US, Australia and UK contained no entries for BMP-2 products. This may seem surprising, but the manufacturers of INFUSE® Bone Graft and InductOs™ have regulatory approval for their products and may see little need for future large scale trials.

## Literature review of rhBMP-7

### Cervical Fusions

There have two reports of using BMP-7 in cervical vertebrae and none within the last three years (Table 5). Jeppsson *et al.* implanted OP-1® in four patients with cervical spinal instability due to rheumatoid disease.<sup>25</sup> One patient had signs of new bone formation at two months follow-up, but three patients showed no signs of bone growth at six or ten

month consequently recruitment was abandoned. Another study included patients who required either cervical (5 patients) or lumbar fusions (4 patients).<sup>23</sup> The patients were high risk with diverse presentation.

**Table 5. Effect of rhBMP-7 on outcomes in patients undergoing cervical spinal fusion.**

Reference	Design Score	Intervention	Number in treatment group	Number in control group	Key results
Jeppsson C, Saveland H, Rydholm U, et al. <sup>25</sup>	3	Subjects with rheumatoid disease causing instability of the atlanto-axial joint and with neurological symptoms. Initially intended to test 10 patients but recruitment was halted after poor results.	4	0	At 2 months no patient had radiographic signs of bone formation. At 6 months one patient had bone formation in a patient who complained of impaired neck motion and had removed neck collar – a redislocation occurred. At 10 months, no detectable bone formation was found in the other 3 patients.
Govender PV, Yoga RR, Rickards L, et al. <sup>23</sup>	3	Case series on spinal fusion with OP-1® putty combined with iliac crest autograft bone and pedicle screws.	9	0	All nine patients suffered from different primary diseases and co-morbidities. Labelled high risk patients with fusions of lumbar or cervical vertebrae. This makes comparisons and firm conclusions impossible. Authors write case reports on each patient and claim in some cases bone fusion and improved Oswestry scores. No adverse effects noted.

### Lumbar Fusions

There were five reported studies using BMP-7 in lumbar fusions, although the last by Vaccaro may partially repeat data from patients in an earlier study (Table 6). Two studies were partially-blinded RCT in which the effectiveness of OP-1® in posterolateral lumbar fusion with autograft in patients with spondylolysis.<sup>26,42</sup> Radiostereometric analysis at one year indicated that there were a similar rates of stabilisation in the affected vertebra in both treatment groups in sagittal and transverse axes, but more stabilisation in the autograft group along the vertical axis (p=0.03). There was no difference in the rate of bone bridging at one year between groups and the proportion reporting pain was similar. There were no unusual adverse effects of the procedures.

Two reports were of case series of lumbar spinal fusion using a combination of OP-1® and autograft bone.<sup>23,41</sup> In twelve patients with lumbar spondylolisthesis, OP-1 Putty® mixed with autograft bone was implanted posterolaterally.<sup>41</sup> At twelve months, success as defined by a 20% improvement in the Oswestry score, was achieved in nine patients and radiographic evidence of fusion in six. Bridging bone between transverse processes was observed in ten patients. The authors report no adverse events were caused by OP-1® (those not attributed to the device included pseudoarthrosis, increased back pain, and donor site pain). Since this study combined within each patient the elements of a new treatment (OP-1 Putty®) and a standard treatment (autograft) and had no comparative group its difficult to draw a major conclusion other than the combined treatment was, to some degree, successful. A single case series was found in which patients' fractured vertebra at the thoraco-lumbar junction was transplanted with OP-1®.<sup>31</sup> OP-1® was sealed by collagen sponge in one patient and by autograft bone in four others. Although the procedures involved in each case were different none achieved successful healing. Severe bone resorption occurred in one individual.

**Table 6. Effect of rhBMP-7 on outcomes in patients undergoing lumbar spinal fusion.**

Reference	Design Score	Intervention	Number in treatment group	Number in control	Key results
Laursen, M, Hoy K, Hansen ES, et al. <sup>31</sup>	3	Subjects with acute unstable single-level, fracture at the thoracolumbar spine junction, and no neurologic impairment Transpedicular transplantation of the fractured vertebra using OP-1® & bovine bone-derived collagen type-I carrier as bone graft substitute, then sealed by collagen sponge in one case and autograft bone in the other 4. Myelography was carried out, then a standard bilateral posterolateral autograft bone transplantation was performed with material from iliac crest. Seems to be a slightly different procedure in each case.	5	0	Initially severe resorption at transplantation site. Vertebra contour visible at 12 months as a result of new bone formation. Bone mineral density at fracture level increased up to 3 months then decreased slightly at 6, 12 months. Radiographs revealed loosened screw  Increased bone mineral density at fracture level, satisfactory correction achieved post-operatively and stable at 6 months  Correction achieved in surgery was lost during follow up, compression at fracture level increased beyond pre-operative level. BMD initially increased then decreased, patient reported no back pain but some tiredness in back. Partial loss of correction during follow up, BMD increased at fracture level, no complaints.
Johnsson, R., B. Stromqvist, and P. Aspenberg P. <sup>26</sup>	1+	RCT. Non-instrumented posterolateral lumbar fusion with either OP-1® (n=10) or iliac crest autograft bone (n=10). All patients instructed to keep spine straight for 5 months using soft lumbosacral brace with dorsal rigid reinforcement worn day and night.	10	10	At 1 year, there was bilateral bridging bone in 6 OP-1® patients, partial bone formation in 3, and no bone formation in 1. There were 8, 2 and 0 patients, in these categories respectively, in the autograft group. There was no statistically significant difference between the groups (p=0.39).  At 1 year after surgery, 4 patients in OP-1® group had no back pain, 4 had minor back pain and 2 had major back pain; compared with 5, 2 and 3 in each category among the autograft group. There were no intraoperative complications, and no early, late, local or systemic adverse effects of the OP-1® Implant. One patient in the autograft group had persistent minor pain at the bone harvest site.
Vaccaro AR, Patel T, Fischgrund J, et al. <sup>41</sup>	3	Case series. Iliac crest autograft mixed with OP-1® putty. Patients with single-level, grade I or II degenerative lumbar spondylolisthesis and neurogenic claudication. Patients fitted with lumbosacral brace for 3 months.	12	0	Oswestry scores indicated clinical success in 9 of 12 patients (75%). Radiologic fusion at 12 months was achieved in 6 of 11 patients (55%). No patient had progression of the spondylolisthesis. Adverse events: pseudarthrosis, increased back pain, donor site pain, surgical complications. No cases of systemic toxicity, ectopic bone formation or recurrence of spinal stenosis.
Vaccaro AR, Patel T, Fischgrund J, et al. <sup>42</sup>	1-	Prospective randomised multi-centre trial. Comparing clinical and radiographic outcomes after treatment with OP-1® putty and autograft iliac crest bone graft for single level lumbar fusions (L3-L4 or L4-L5). Approach was posterior lateral. Radiological assessments were read blind.	24 recruited but success at follow-up variable	11 recruited but 10 at follow-up	Radiological success rates were 73.7% for OP-1® and 60% bone graft. Unfortunately 5/25 in the OP-1® treatment were not, for various reasons, evaluated at 12 months. The authors recognise that this loss may bias results. Oswestry scores in both groups improved over time-the degree of improvement was similar in both groups. No differences were reported in adverse events between the two groups.
Vaccaro AR, Anderson DG, Patel T, et al. <sup>39</sup>	1-	The same study design and probably same patients as in the above trial. Follow-up extended to 36 months.	24 But success at follow-up variable	11 recruited but 10 at follow-up	Varying degree of patient compliance and data at 12.24 36 months. Radiological bone fusion observed in 55% at 24 and 36 months compared with 40% autograft bone graft. With only 10 subjects receiving bone grafts the accuracy of measure is probably poor.

In some of these trials OP-1 Putty® is combined with a bone autograft into a single treatment which is then compared to treatment with bone autograft alone.<sup>39,41,42</sup> Since the OP-1 Putty® was not given to a group of patients in the absence of bone autograft, it makes the efficacy of rhBMP-7 in these trials inconclusive. Patients were assessed initially at 12 months after surgery and in a subsequent paper the same group of patients are assessed 24 months.<sup>40</sup> The sample sizes were 24 in the group receiving OP-1 Putty® and 11 in the control. If the study by Burkus et al<sup>10</sup> reflects adequate sample sizes for a trial of this nature, then either this trial was underpowered or the authors had high therapeutic expectations.

### **Comments from regulatory authorities on the use of rhBMP-7**

In April 2004 the US FDA notified Stryker Biotech that OP-1 Putty®<sup>xv</sup> had been approved for use in patients requiring posterolateral lumbar spinal fusion.

Between 1999 and 2004 EMEA published several articles on Osigraft the product that contains OP-1, including, in 2004, its scientific discussion on OP-1.<sup>xvi</sup> As far as I can tell this agency has not approved OP-1 for use in spinal applications. The scientific discussions of the EMEA committee concerned assessment of data on fusions of the tibia

### **Contraindications and cautionary notes for rhBMP-7**

Both the FDA and EMEA have published their opinions on the safety of OP-1 (although these views are not restricted to spine). In general they are similar to those for rhBMP-2. The US FDA contraindications for the use of OP-1 Putty® include:

1. OP-1 Putty® should not be used to treat patients who have a known hypersensitivity to the active substance or to collagen.
2. OP-1 Putty® should not be applied at or near the vicinity of a resected tumor or in patients with a history of malignancy.
3. OP-1 Putty® should not be administered to patients who are skeletally immature (<18 years of age or no radiographic evidence of closure of epiphyses).
4. OP-1 Putty® should not be administered to pregnant women. The potential effects of OP-I treatment on the human fetus have not been evaluated. Studies in rats injected with high doses of OP-I have shown that small amounts of OP-1 will cross the placental barrier.

One of the major safety concerns with rhBMP is the development of neutralising antibodies that could compromise normal bone turnover/repair or even cross the placenta if women became pregnant. After its initial recommendation in 2004 to develop assays and monitor for neutralising antibodies the EMEA reported in June 2005 a high incidence of such antibodies.<sup>xvii</sup> Several authors have also published reviews on the safety of OP-1.<sup>14,21,35</sup> Their views are similar to FDA and EMEA. In 2002 one incident of hyperostosis after use of OP-1® was reported to New Zealand's Medicines Adverse Reactions Committee.<sup>xviii</sup> The committee did not recommend any further action and recorded the causal link as 'probable'.

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<sup>xv</sup> <http://www.fda.gov/cdrh/pdf2/H020008a.pdf>.

<sup>xvi</sup> <http://www.emea.eu.int/humandocs/PDFs/EPAR/osigraft/039301en6.pdf>.

<sup>xvii</sup> <http://www.emea.eu.int/humandocs/PDFs/EPAR/osigraft/039301en8b.pdf>.

<sup>xviii</sup> <http://www.medsafe.govt.nz/Profs/adverse/Minutes112.htm>

### **Guidelines issued by funders of health services**

Payment for treatment with OP-1 putty® has been approved by the same agencies that that approved BMP-2.

### **Cost effectiveness**

No information directly relevant to the cost effectiveness of OP-1® was identified.

### **Discussion of rhBMP-7, OP-1 putty®**

OP-1 putty® was originally approved in 2001 by FDA for fusion of the tibia and in 2004 usage was extended to cover lumbar fusion.

There have been three studies where rhBMP-7 as OP-1 putty® was used in fusion of cervical vertebrae. These were case series of four, nine and five patients, and hence only 18 patients have been involved. The last study was published in 2002 and apparently no further information has been made available in the intervening period. The evidence for using rhBMP-7 for fusion of cervical/thoracic vertebrae seems scant and unconvincing.

In this review we identified two case series and two RCT where OP-1 putty® was used for lumbar spinal fusion. The major outcomes for these studies were bone fusion measurements and Oswestry scores. The total number of patients in lumbar fusion studies was 76, of which 55 received OP-1®. In three of the four studies, with a total of 45 patients, OP-1 putty® was combined with bone autograft in to a single treatment. The combining of OP-1 putty® with bone autograft obfuscates the efficacy of rhBMP-7. The 2004 review concluded there was a shortage of large, well designed, randomised studies on the use of OP-1 Putty® to promote bone repair and fusion in the spine. Recent published evidence is insufficient to overturn that view. The manufacturer of OP-1 Putty® is Stryker and their web site does not indicate any further published developments with regard to this product.

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## Appendices

### OSWESTRY 2.0

INSTRUCTIONS: Could you please complete this questionnaire. It is designed to give us information as to how your back (or leg) trouble has affected your ability to manage in every day life. Please answer every section. Mark one box only in each section that most closely describes you **today**.

#### **Section 1 – Pain intensity:**

- I have no pain at the moment. (0 points)
- The pain is very mild at the moment. (1 points)
- The pain is moderate at the moment. (2 points)
- The pain is fairly severe at the moment. (3 points)
- The pain is very severe at the moment. (4 points)
- The pain is the worst imaginable at the moment. (5 points)

#### **Section 2 – Personal care:**

- I can look after myself normally without causing extra pain. (0 points)
- I can look after myself normally, but it is very painful. (1 points)
- It is painful to look after myself, and I am slow and careful. (2 points)
- I need some help, but I manage most of my personal care. (3 points)
- I need help every day in most aspects of self care. (4 points)
- I do not get dressed, I wash with difficulty, I stay in bed. (5 points)

#### **Section 3 – Lifting:**

- I can lift heavy weights without extra pain. (0 points)
- I can lift heavy weights, but it gives me extra pain. (1 points)
- Pain prevents me from lifting heavy weights off the floor, but I can manage if they are conveniently positioned, e.g., on a table. (2 points)
- Pain prevents me from lifting heavy weights off the floor, but I can manage light to medium weights if they are conveniently positioned. (3 points)
- I can only lift very light weights. (4 points)
- I cannot lift or carry anything at all. (5 points)

#### **Section 4 – Walking:**

- Pain does not prevent me from walking any distance. (0 points)
- Pain prevents me from walking more than 1 mile. (1 point)
- Pain prevents me from walking more than ½ of a mile. (2 points)
- Pain prevents me from walking more than 100 yards. (3 points)
- I can only walk using a stick or crutches. (4 points)
- I am in bed most of the time and have to crawl to the toilet. (5 points)

#### **Section 5 – Sitting:**

- I can sit in any chair for as long as I like. (0 points)
- I can sit in my favorite chair for as long as I like. (1 point)
- Pain prevents me from sitting more than 1 hour. (2 points)
- Pain prevents me from sitting more than ½ an hour. (3 points)
- Pain prevents me from sitting more than 10 minutes. (4 points)
- Pain prevents me from sitting at all. (5 points)

#### **Section 6 – Standing:**

- I can stand as long as I want without extra pain. (0 points)
- I can stand as long as I want but it gives me extra pain. (1 point)
- Pain prevents me from standing for more than 1 hour. (2 points)
- Pain prevents me from standing for more than ½ an hour. (3 points)
- Pain prevents me from standing for more than 10 minutes. (4 points)
- Pain prevents me from standing at all. (5 points)

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### **Section 7 – Sleeping**

- My sleep is never disturbed by pain. (0 points)
- My sleep is occasionally disturbed by pain. (1 point)
- Because of pain, I have less than 6 hours of sleep. (2 points)
- Because of pain, I have less than 4 hours of sleep. (3 points)
- Because of pain, I have less than 2 hours of sleep. (4 points)
- Pain prevents me from sleeping at all. (5 points)

### **Section 8 – Sex Life (if applicable)**

- My sex life is normal and causes no extra pain. (0 points)
- My sex life is normal but causes some extra pain. (1 point)
- My sex life is nearly normal but is very painful. (2 points)
- My sex life is severely restricted by pain. (3 points)
- My sex life is nearly absent because of pain. (4 points)
- Pain prevents any sex life at all. (5 points)

### **Section 9 – Social Life:**

- My social life is normal and causes me no extra pain. (0 points)
- My social life is normal but increases the degree of pain. (1 point)
- Pain has no significant effect on my social life apart from limiting my more energetic interests, e.g., sports, etc. (2 points)
- Pain has restricted my social life and I do not go out as often. (3 points)
- Pain has restricted social life to my home. (4 points)
- I have no social life because of pain. (5 points)

### **Section 10 – Traveling:**

- I can travel anywhere without pain. (0 points)
- I can travel anywhere, but it gives extra pain. (1 point)
- Pain is bad, but I manage journeys over two hours. (2 points)
- Pain restricts me to journeys less than one hour. (3 points)
- Pain restricts me to short necessary journeys less than 30 minutes. (4 points)
- Pain prevents me from traveling except to receive treatment. (5 points)

### **Scoring:**

Simply count up all the points and divide 50 (or 45 if they leave out one section) and multiply by 100 to get your score.

Example: on my last ODI I scored a 16. So,  $16/50 \times 100 = 32\%$  disability:

### **Categories:**

**0% to 20%:** minimal disability: The patient can cope with most living activities. Usually no treatment is indicated apart from advice on lifting sitting and exercise.

**21%-40%:** moderate disability: The patient experiences more pain and difficulty with sitting lifting and standing. Travel and social life are more difficult and they may be disabled from work. Personal care sexual activity and sleeping are not grossly affected and the patient can usually be managed by conservative means.

**41%-60%:** severe disability: Pain remains the main problem in this group but activities of daily living are affected. These patients require a detailed investigation.

**61%-80%:** crippled: Back pain impinges on all aspects of the patient's life. Positive intervention is required.

**81%-100%:** These patients are either bed-bound or exaggerating their symptoms.