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EXECUTIVE SUMMARY

A posterolateral fusion across the intertransverse space presents a challenging healing environment for spine surgeons.¹ The goal of the procedure is to stabilize two adjoining vertebrae by inducing bone to form across a space between two transverse processes – a location where bone previously never existed. The spinal anatomy involved in this type of procedure lacks some of the elements that support the bone generation process (i.e., limited bony surface area).²

In order to induce bone formation, a bone grafting material is required. While local bone, allograft, or ceramic substitutes may be used, the gold standard bone grafting material is autogenous bone taken from the iliac crest. However, as demonstrated in the current study, the procedure for harvesting autograft from the iliac crest can cause significant postoperative pain and morbidity. The harvesting procedure can also increase overall surgical time and patient blood loss.

AMPLIFY™ rhBMP-2 Matrix was designed to overcome the challenges of posterolateral fusion procedures while eliminating the need to harvest bone from a second surgical site. It combines the osteoinductive properties of recombinant bone morphogenetic protein-2 (rhBMP-2) with a compression resistant matrix (CRM) carrier at a concentration of 2.0 mg/cc. The CRM acts as a carrier for the rhBMP-2 and provides additional scaffolding for rhBMP-2 to induce new bone formation and generate a successful arthrodesis.

AMPLIFY™ rhBMP-2 Matrix is indicated as an alternative to autogenous bone graft for spinal fusion procedures in skeletally mature patients with degenerative disc disease (DDD) at one level from L1-S1. DDD is defined as discogenic back pain with degeneration of the disc confirmed by patient history and radiographic studies. DDD patients may also have up to Grade 1 spondylolisthesis or retrolisthesis at the involved level. Patients receiving AMPLIFY™ rhBMP-2 Matrix should have had at least 6 months of nonoperative treatment prior to implantation of AMPLIFY™ rhBMP-2 Matrix. AMPLIFY™ rhBMP-2 Matrix is to be implanted via a posterior approach and must be used in conjunction with metallic posterior spinal fixation that is indicated for temporary stabilization of the spine. This includes any such metallic device that is indicated for non-cervical posterior pedicle fixation for degenerative disc disease. After fusion has occurred, the temporary fixation devices may be removed.

¹ Boden SD, Schimandle JH, Hutton WC, Chen MI. 1995 Volvo Award in Basic Sciences. The use of an osteoinductive growth factor for lumbar spinal fusion. Part I: The biology of spinal fusion. *Spine* 1995;20:2626-32

² Boden SD. The biology of posterolateral lumbar spinal fusion. *Orthop Clin North Am* 1998;29:603-19.

Each AMPLIFY™ rhBMP-2 Matrix kit contains the necessary materials to reconstitute rhBMP-2 and to place it on the CRM. The contents of the kit are listed below:

AMPLIFY™ rhBMP-2 Matrix 40 mg (20 cc) Kit

Two (2) Vials of Sterile rhBMP-2 (20 mg each)

Two (2) Packages of Two (2) Sterile 5 cc Compression Resistant Matrices (CRM)
(4.67 cm L x 0.95 cm W x 1.13 cm H)

Two (2) Vials of Sterile Water for Injection (10 mL each)

Two (2) Sterile 10 mL Syringes with 20G 1½" Needles

Four (4) Sterile 3 mL Syringes with 20G 1½" Needles

The reconstituted rhBMP-2 from one 20 mg vial will be administered to two 5 cc blocks of CRM and applied to one side of the spine. The process is then repeated with the second rhBMP-2 vial and remaining CRM for the other side of the spine. As stated above, AMPLIFY™ rhBMP-2 Matrix must be used with commercially available metallic posterior spinal fixation.

Extensive nonclinical testing has been conducted to demonstrate that the AMPLIFY™ rhBMP-2 Matrix performs as intended for use in spinal fusion procedures. Detailed test reports were provided to FDA in the PMA submission and other documents:

- Nonclinical Mechanical Testing
- Nonclinical Safety
 - Intravenous Toxicity and Implant Toxicity
 - Biocompatibility Studies
 - Tumor Cell Activity
 - Fertility, Reproduction, and Teratology
 - Neurological Safety
 - Immunology-Antibody Response
- Nonclinical Efficacy
 - Bioactivity: Induction of Bone by rhBMP-2
 - Efficacy in Intended Posterolateral Fusion Indication
 - Efficacy in Other Interbody Fusion Indications
- Pharmacokinetics
 - Intravenous Pharmacokinetic Studies
 - Local Retention of rhBMP-2 Administered with CRM
- Pharmacodynamics: rhBMP-2 Activity in the Presence of Agents Affecting Bone Metabolism
- Inappropriate Usage of rhBMP-2

As a result of this body of nonclinical work, the safety (toxicology and pharmacokinetics) and bone-forming capacity (efficacy) of AMPLIFY™ rhBMP-2 Matrix have been thoroughly investigated and characterized.

The nonclinical safety of systemically delivered rhBMP-2 and locally delivered rhBMP-2 has been extensively examined, and no toxicities have been identified in these studies. The disposition of rhBMP-2 and rhBMP-2/CRM, as contained in AMPLIFY™ rhBMP-2 Matrix, is characterized by slow release of rhBMP-2 from the carrier and rapid systemic clearance. This profile results in minimal systemic exposure to rhBMP-2. rhBMP-2 was also evaluated for its effect on reproduction and fetal development. Studies examining use of rhBMP-2 at a range of doses found no evidence of maternal toxicity, embryoletality, fetotoxicity, or teratogenicity.

Application of rhBMP-2 results in the induction of normal bone locally at the site of implantation. This process includes the migration of mesenchymal cells into the site through chemotaxis and the apparent differentiation of these cells into bone-forming cells. The bone induced by rhBMP-2 remodels and assumes the structure appropriate to its location and function, as would be expected from host bone.

No evidence of any neurological abnormalities was found in studies performed to evaluate the safety of rhBMP-2 in the vicinity of the spinal cord and nerve roots. In addition, there was no evidence, based on blood and cerebrospinal fluid analyses, of any clinical abnormalities in the animals tested. There was also no radiographic or histologic evidence of mineralization within the thecal sac.

In nonclinical studies comparing fusion in the presence of AMPLIFY™ rhBMP-2 Matrix and autograft bone, the histological fusion rate was greater for animals treated with AMPLIFY™ rhBMP-2 Matrix than for animals receiving autograft bone. Rabbit testing has demonstrated that fusion masses induced with rhBMP-2/CRM were significantly stronger and stiffer than those treated with autograft. Furthermore, long-term testing in the rabbit model showed gradual resorption of the CRM carrier at three, six, and nine months postoperative, displaying the ability of the carrier to support new bone formation while resorbing over time without affecting long-term fusion.

Nonhuman primate studies examined the composition of the ceramic in the CRM carrier, demonstrating that the 15% hydroxyapatite to 85% β -tricalcium phosphate ceramic composition ratio was most appropriate for supporting new bone formation while resorbing over time. In addition, nonhuman primate testing was performed to determine the most effective rhBMP-2 concentration on the CRM carrier in the posterolateral environment. This testing showed that 2.0 mg/cc of rhBMP-2 on the CRM carrier was better than concentrations ranging from 0.6 mg/cc to 1.35 mg/cc and similar to a 2.7 mg/cc concentration for inducing reproducible bone formation and fusion. These nonhuman primate studies using the 2.0 mg/cc rhBMP-2/CRM demonstrated a 100% fusion rate, compared to a historical 33% fusion rate using autograft bone from the iliac crest. In summary, AMPLIFY™ rhBMP-2 Matrix has demonstrated effectiveness in promoting posterolateral spinal fusion in multiple nonclinical study models and

generated fusions that were shown to be statistically greater than autograft in both relative strength and stiffness.

After the successful completion of nonclinical work, AMPLIFY™ rhBMP-2 Matrix was evaluated in humans in a pivotal clinical trial. The goal of the clinical trial was to determine the safety and effectiveness of AMPLIFY™ rhBMP-2 Matrix with the CD HORIZON® Spinal System in the treatment of degenerative disc disease (DDD) at one level from L1 to S1. The assessment of safety and effectiveness of AMPLIFY™ rhBMP-2 Matrix was made by direct comparisons between clinical data collected from patients implanted with the investigational device and a similar group of patients who received surgical treatment with autogenous bone derived from the iliac crest (control) with the CD HORIZON® Spinal System.

The IDE pivotal study received full approval on December 31, 2001, and the first patient was enrolled in the study on March 29, 2002. During the course of the study, several IDE supplements were submitted to FDA. The most significant of these requested that 24-month evaluations of the study's clinical and radiographic variables be used as endpoints for the study, instead of 12-month evaluations. Twelve-month evaluations were originally designated in the protocol for the study's primary endpoints, but longer-term data at 24 months after surgery became available during review of the PMA. These were deemed as more clinically meaningful measurements, and the amendment was approved by the FDA. None of the supplements had any negative impact on the scientific soundness of the clinical trial.

The effectiveness of AMPLIFY™ rhBMP-2 Matrix was based on a patient having radiographically-demonstrated fusion and Oswestry pain/disability improvement. These factors, as well as the patient having maintained or improved neurological status, not having a serious implant-associated or implant/surgical procedure associated adverse event, or having a second surgery classified as a "failure," were used to determine whether a patient was an "overall success" – the primary endpoint for the clinical investigation. In addition, back pain, leg pain, graft site (hip) pain, general health status, and patient satisfaction were evaluated.

The safety of AMPLIFY™ rhBMP-2 Matrix and the control treatment was judged primarily on the nature and frequency of adverse events, device-related or not, over the entire course of the clinical trial. Neurological maintenance or improvement was also considered a safety endpoint. Antibody test results and radiographic review comments were other safety assessments used in this study.

Patients were evaluated preoperatively, at surgery/hospital discharge, and at 6 weeks, 3 months, 6 months, 12 months, and 24 months after surgery. As stated above, 24-month evaluations were used for the primary endpoint of the study – overall success. In anticipation of a potential post-approval study, patients were evaluated for long-term follow-up at 36 and 60 months postoperative.

Patients were randomized in a 1:1 manner to the investigational and control treatments. The study involved a total of 463 patients (239 investigational and 224 control) enrolled at 29 study sites. Demographic data were similar for the two treatment groups, with the exception of the category of ongoing spinal litigation. This rate was higher in the control group, but the number of patients involved in litigation was small in both groups. There was no difference noted between treatment groups for preoperative medical condition, medication usage, or disease characteristics.

Surgical and hospitalization data for the two groups were recorded. Patients in the investigational group were found to have shorter operative times (2.5 vs. 2.9 hours, respectively) and less blood loss (343.1 ml vs. 448.6 ml) than patients in the control group, with a probability of superiority value of essentially 100.0% in both cases. The average hospital stay in both treatment groups was approximately four days. No statistical difference for this parameter was demonstrated between the two treatment groups.

The results for patients receiving AMPLIFY™ rhBMP-2 Matrix were statistically non-inferior to the control group results for all effectiveness parameters at 24 months postoperative. The primary results are summarized in the table below.

Success Rates at 24 Months				
Primary Outcome Variable	Investigational Group	Control Group	Posterior Probabilities	
			Non-Inferiority ($\Delta = 10\%$)	Superiority
Fusion	95.9%	89.3%	~100.0%	99.2%
Oswestry	73.1%	72.7%	99.0%	53.7%
Neurological Status	87.0%	84.2%	~100.0%	78.5%
Overall Success	60.5%	55.5%	99.9%	83.9%

The overall success rate for the investigational group was slightly higher than the control group at 24 months following surgery (60.5% vs. 55.5%, respectively). The investigational overall success rate was found to be statistically non-inferior to the control group rate, thereby meeting the primary study objective.

The primary effectiveness endpoints for this clinical trial were fusion and pain/disability (Oswestry) improvement. As shown in the table above, the fusion rate at 24 months for the investigational group was over 6 percentage points higher than the fusion rate for the control group. This demonstrates that the investigational treatment was statistically superior to the control treatment in terms of fusion. The mean improvement in pain/disability (Oswestry) score for the investigational group from preoperative to 24 months was 26.7 points, versus 25.5 points for the control group. Bayesian statistical analyses yielded a posterior probability of non-inferiority to the control at 24 months of 99.0% for this variable.

The neurological status of study patients was assessed preoperatively and postoperatively using a neurological status scale. The success rates for both groups are given in the table above. Bayesian statistical analyses yielded a posterior probability of non-inferiority of the investigational group to the control group at 24 months of essentially 100%. These results indicated that the overall neurological success rate for the investigational group was non-inferior to that for the control group.

The adverse event rates in the investigational group were comparable to those of the control treatment group. There were two adverse event categories (graft site related and non-union) in which a statistical difference was noted; in both instances, this difference favored the investigational group. For graft site related adverse events, Bayesian statistical analysis showed a posterior probability of superiority of essentially 100%. This is considered a very positive result since one of the benefits of using AMPLIFY™ rhBMP-2 Matrix is that it eliminates the need for harvesting of bone graft and, in this case, reduces or eliminates a number of related adverse events. For the category of non-union events, the posterior probability of superiority was found to be 99.6% in favor of the investigational group. In addition to comparable adverse event rates, no statistical differences were found between treatment groups for any of the second surgery categories, except that the investigational group had statistically fewer device removals than the control group.

In the AMPLIFY™ clinical study report,³ a total of 13 cancers were reported in the investigational group through the 60-month time point; two of these were non-invasive skin cancers. Four (4) cancers were noted in the control group during the same time period. The difference in the number of cancers reported was not statistically significant.

An in-depth examination of cancer incidence was also performed for all rhBMP-2 clinical trials conducted by Medtronic and Pfizer, the manufacturer of rhBMP-2.⁴ The results of the statistical analyses of Medtronic's and Pfizer's clinical data showed no significant difference in the rate of malignancy between the rhBMP-2 and non-rhBMP-2 groups. In addition, a retrospective cohort study was conducted to assess whether the risk of pancreatic cancer increased among patients exposed to rhBMP-2 during lumbar spinal fusion surgery, compared to those without this exposure. The conclusion of this study of more than 90,000 elderly patients who underwent lumbar fusion surgery was that the risk of pancreatic cancer among patients exposed to BMP was not increased compared to the risk of those who were not exposed. All of the results support a conclusion that there is not a direct relationship between rhBMP-2 use and malignancy.

The rates of authentic antibody responses to rhBMP-2 and bovine collagen were compared between the two treatment groups. Using an IgAGM ELISA, the

³ Date of database closure for analysis in AMPLIFY™ report: February 3, 2009.

⁴ Date of database closure for analysis in malignancy report: December 22, 2008.

authentic antibody response rate to rhBMP-2 was determined to be 6.4% in the investigational group and 2.3% in the control group. A neutralizing antibody assay was run on samples from patients with positive antibodies to rhBMP-2. There were no neutralizing antibodies detected. The antibody response to bovine type I collagen was 16.7% in the investigational group and 21.2% in the control group. Patients who had positive antibody responses to bovine collagen were not found to have positive antibody responses to human Type I collagen.

In conclusion, through both extensive nonclinical and clinical testing, the AMPLIFY™ rhBMP-2 Matrix has been demonstrated to be safe and effective in the surgical treatment of symptomatic degenerative disc disease of the lumbar spine. AMPLIFY™ rhBMP-2 Matrix has been fully tested for the unique characteristics related to the proposed indication under this PMA. In addition, the testing demonstrates the AMPLIFY™ rhBMP-2 Matrix provides an alternative to the use of autogenous bone graft for posterolateral spinal fusion and is at least as safe and effective as autograft without the morbidity associated with harvesting bone from the iliac crest.

SUMMARY OF SAFETY AND EFFECTIVENESS DATA

I. GENERAL INFORMATION

Device Generic Name:	Filler, Recombinant Human Bone Morphogenetic Protein, Compression-Resistant Collagen Scaffold, Osteoinduction
Device Trade Name:	AMPLIFY™ rhBMP-2 Matrix
Applicant's Name and Address:	Medtronic Sofamor Danek USA, Inc. 1800 Pyramid Place Memphis, TN 38132
Premarket Approval Application (PMA) Number:	P050036
Date of Panel Recommendation	Pending
Date of Notice of Approval of Application:	Pending

II. INDICATIONS FOR USE

AMPLIFY™ rhBMP-2 Matrix is indicated as an alternative to autogenous bone graft for spinal fusion procedures in skeletally mature patients with degenerative disc disease (DDD) at one level from L1-S1. DDD is defined as discogenic back pain with degeneration of the disc confirmed by patient history and radiographic studies. DDD patients may also have up to Grade 1 spondylolisthesis or retrolisthesis at the involved level. Patients receiving AMPLIFY™ rhBMP-2 Matrix should have had at least 6 months of nonoperative treatment prior to implantation of AMPLIFY™ rhBMP-2 Matrix. AMPLIFY™ rhBMP-2 Matrix is to be implanted via a posterolateral approach and must be used in conjunction with a metallic posterior supplemental fixation device that is indicated for temporary stabilization of the spine.

III. CONTRAINDICATIONS

- AMPLIFY™ rhBMP-2 Matrix is contraindicated for patients with a known hypersensitivity to recombinant human Bone Morphogenetic Protein-2 (rhBMP-2), bovine Type I collagen, or other components of the formulation.
- AMPLIFY™ rhBMP-2 Matrix should not be used in the vicinity of a resected or extant tumor, in patients with any active malignancy, or in patients undergoing treatment for a malignancy.
- AMPLIFY™ rhBMP-2 Matrix should not be used in patients who are skeletally immature (<18 years of age or no radiographic evidence of epiphyseal closure).

- AMPLIFY™ rhBMP-2 Matrix should not be used in pregnant women. The potential effects of rhBMP-2 on the human fetus have not been evaluated.
- AMPLIFY™ rhBMP-2 Matrix should not be implanted in patients with an active infection at the operative site or with an allergy to one of the metals used in the posterior supplemental fixation device (such as titanium, stainless steel, or cobalt-chromium alloy).

IV. WARNINGS AND PRECAUTIONS

WARNINGS:

- In an experimental rabbit study, rhBMP-2 has been shown to elicit antibodies that are capable of crossing the placenta. Reduced ossification of the frontal and parietal bones of the skull was noted infrequently (<3%) in fetuses of rabbit dams immunized to rhBMP-2; however, there was no effect noted in limb bud development. There are no adequate and well-controlled studies in human pregnant women. Women of childbearing potential should be warned by their surgeon of potential risk to a fetus and informed of other possible orthopedic treatments.
- Women of childbearing potential should be advised that antibody formation to rhBMP-2 or its influence on human fetal development has not been completely assessed. In the clinical trial supporting the safety and effectiveness of AMPLIFY™ rhBMP-2 Matrix, 15/234 (6.4%) patients treated with AMPLIFY™ rhBMP-2 Matrix and 5/217 (2.3%) patients treated with autograft bone developed antibodies to rhBMP-2, based on an anti-human immunoglobulin antibody-based ELISA. The effect of maternal antibodies to rhBMP-2, as might be present for several months following device implantation, on the unborn fetus is unknown. Additionally, it is unknown whether fetal expression of BMP-2 could re-expose mothers who were previously antibody positive. Theoretically, re-exposure may elicit a more powerful immune response to BMP-2 with possible adverse consequences for the fetus. However, pregnancy did not lead to an increase in antibodies in the rabbit study. Studies in genetically altered mice indicate that BMP-2 is critical to fetal development and that a lack of BMP-2 activity may cause neonatal death or birth defects. It is not known if anti-BMP-2 antibodies may affect fetal development or the extent to which these antibodies may reduce BMP-2 activity.
- AMPLIFY™ rhBMP-2 Matrix should not be used immediately prior to or during pregnancy. Women of childbearing potential should be advised not to become pregnant for one year following treatment with AMPLIFY™ rhBMP-2 Matrix.
- The safety and effectiveness of AMPLIFY™ rhBMP-2 Matrix in nursing mothers has not been established. It is not known if BMP-2 is excreted in human milk.

- The safety and effectiveness of AMPLIFY™ rhBMP-2 Matrix with other spinal implants, implanted at locations other than the lower lumbar spine, or used in surgical techniques other than a posterolateral technique have not been established.
- Inappropriate use of the product, such as preparing it differently than prescribed or compressing the rhBMP-2/CRM construct more than necessary, may change the concentration of the rhBMP-2, which may cause complications.

PRECAUTION(S):

General

- The safety and effectiveness of repeat applications of AMPLIFY™ rhBMP-2 Matrix have not been established.
- AMPLIFY™ rhBMP-2 Matrix should only be used by surgeons who are experienced in spinal fusion procedures and have undergone adequate training with this device for posterolateral procedures.
- Posterior supplemental fixation (i.e., a metallic posterior supplemental fixation device) should be implanted on each side of the surgical level whenever possible.
- The posterior supplemental fixation components and instruments must be sterilized prior to use according to the sterilization instructions provided in the package insert for those components, unless supplied sterile and clearly labeled as such.
- AMPLIFY™ rhBMP-2 Matrix is intended for single use only. Discard unused product and use a different device for subsequent applications.
- Prior to use, inspect the packaging, vials, and stoppers for visible damage. If damage is visible, do not use the product. Retain the packaging and vials, and contact a Medtronic representative.
- Do not use after the printed expiration date on the label.

Hepatic and Renal Impairment

- The safety and effectiveness of AMPLIFY™ rhBMP-2 Matrix in patients with hepatic or renal impairment has not been established. Pharmacokinetic studies of rhBMP-2 indicate that the renal and hepatic systems are involved with its clearance.

Bone Formation

- The safety and effectiveness of AMPLIFY™ rhBMP-2 Matrix have not been demonstrated in patients with metabolic bone diseases.
- While not specifically evaluated in the clinical study, the potential for ectopic, heterotopic, or undesirable exuberant bone formation exists.

Antibody Formation/Allergic Reactions

- The safety and effectiveness of AMPLIFY™ rhBMP-2 Matrix have not been demonstrated in patients with autoimmune disease.
- The safety and effectiveness of AMPLIFY™ rhBMP-2 Matrix have not been demonstrated in patients with immunosuppressive disease or suppressed immune systems resulting from radiation therapy, chemotherapy, steroid therapy, or other treatments.

Immunogenicity

- As with all therapeutic proteins, there is a potential for immune responses to be generated to AMPLIFY™ rhBMP-2 Matrix. The immune response to AMPLIFY™ rhBMP-2 Matrix was evaluated in 234 investigational patients and 217 control patients receiving posterolateral lumbar fusions.
 - *Anti-rhBMP-2 antibodies:* 15/234 (6.4%) patients receiving AMPLIFY™ rhBMP-2 Matrix developed antibodies to rhBMP-2 vs. 5/217 (2.3%) in the control group, using an anti-human immunoglobulin antibody-based ELISA. No positive neutralizing antibodies were detected in patients with positive antibodies to rhBMP-2.
 - *Anti-bovine Type I collagen antibodies:* 16.7% (39/234) of patients receiving AMPLIFY™ rhBMP-2 Matrix developed antibodies to bovine Type I collagen vs. 21.2% (46/217) of control patients. No patients in either group developed anti-human Type I collagen antibodies.
- The incidence of antibody detection is highly dependent on the sensitivity and specificity of the assay. Additionally, the incidence of antibody detection may be influenced by several factors, including sample handling, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies for AMPLIFY™ rhBMP-2 Matrix with the incidence of antibodies for other products may be misleading.

V. DEVICE DESCRIPTION

AMPLIFY™ rhBMP-2 Matrix consists of two components: recombinant human Bone Morphogenetic Protein (rhBMP-2) and a Compression Resistant Matrix (CRM) carrier. The reconstituted rhBMP-2 is applied to the CRM. The CRM is then surgically implanted bilaterally across two adjacent transverse processes. Throughout the healing process, the CRM is resorbed by the body and replaced by newly-formed bone. These components must be used as a system for the prescribed indication. The bone morphogenetic protein solution component must not be used without the carrier/scaffold component or with a carrier/scaffold component different from the one described in this document. The AMPLIFY™ rhBMP-2 Matrix device must also be used with a commercially available metallic posterior supplemental fixation device. This device is not included in the AMPLIFY™ rhBMP-2 Matrix kit and must be procured separately. After fusion occurs, the metallic posterior supplemental fixation system may be removed.

Component Description

rhBMP-2 is the active agent in AMPLIFY™ rhBMP-2 Matrix. rhBMP-2 is a disulfide-linked dimeric protein molecule with two major subunit species of 114 and 131 amino acids. Each subunit is glycosylated at one site with high-mannose-type glycans. rhBMP-2 is produced by a genetically engineered Chinese hamster ovary (CHO) cell line and subsequently highly purified using a 3-step chromatography process.

rhBMP-2 and excipients are lyophilized. Upon reconstitution with 5.4 mL sterile water for injection (sWFI), the drug product yields 4.0 mg/mL dibotermis alfa, 0.5% (w/v) sucrose, 2.5% (w/v) glycine, 5 mM L-glutamic acid, 5 mM sodium chloride, and 0.01% (w/v) polysorbate 80 at pH 4.5. The reconstituted rhBMP-2 solution is clear and colorless to slightly yellow and is essentially free from plainly visible particulate matter.

The CRM is a white, compression-resistant, absorbent, implantable matrix for use with rhBMP-2. The CRM consists of absorbable bovine type I collagen obtained from the deep flexor (Achilles) tendon with resorbable biphasic calcium phosphate granules embedded into the collagen scaffold. The resorbable biphasic calcium phosphate consists of 15% hydroxyapatite and 85% β -tricalcium phosphate (HA/TCP). The CRM acts as a carrier for the rhBMP-2 and as a scaffold for new bone formation.

Each of the components is supplied sterile and is intended for single patient use.

Kit Description

AMPLIFY™ rhBMP-2 Matrix is provided in a 40 mg (20 cc) kit. One 40 mg (20 cc) kit is required per procedure. Each kit contains all the components necessary to prepare the AMPLIFY™ rhBMP-2 Matrix for implantation: rhBMP-2, which must be reconstituted; sterile water; compression resistant matrix; syringes with needles; package insert; Instructions for Preparation; and patient labels. The AMPLIFY™ rhBMP-2 Matrix kits are stored at room temperature (15-30°C or 59-86°F).

The rhBMP-2 is provided as a lyophilized powder in a vial delivering 20 mg of protein. After appropriate reconstitution, the concentration of rhBMP-2 is 4.0 mg/mL. The solution is then applied to the provided compression resistant matrix component(s). The concentration of rhBMP-2 on the CRM is 2.0 mg/cc. AMPLIFY™ rhBMP-2 Matrix is prepared at the time of surgery and allowed to stand a prescribed amount of time (no less than 5 minutes) before placement across the transverse processes. The Instructions for Preparation contain complete details on preparation of the AMPLIFY™ rhBMP-2 Matrix.

No other warranties, expressed or implied, are made. Implied warranties of merchantability and fitness for a particular purpose or use are specifically excluded.

VI. ALTERNATIVE PRACTICES OR PROCEDURES

Non-surgical alternatives to performing posterolateral fusion with AMPLIFY™ rhBMP-2 Matrix include, but are not limited to, watchful waiting with no surgical intervention, physical therapy, medications, external bracing, chiropractic care, spinal injections, bed rest, and exercising.

Surgical alternatives include Posterior Lumbar Interbody Fusion (PLIF) procedures with or without instrumentation, Anterior Lumbar Interbody Fusion (ALIF) procedures with or without instrumentation, combined anterior and posterolateral (i.e., 360°) fusion procedures, and fusions using anterior/anterolateral spinal systems (e.g., pedicle screw/rod and hook/rod systems). In each case, these fusions would involve the use of autograft, allograft bone, or ceramic substitutes. INFUSE® Bone Graft would only be available for use in an ALIF procedure with a Medtronic Titanium Threaded Interbody Fusion Device and without posterior instrumentation.

VII. MARKETING HISTORY

AMPLIFY™ rhBMP-2 Matrix has not been marketed for the combined use described in the PMA in the United States or any foreign country. AMPLIFY™ rhBMP-2 Matrix, manufactured by Medtronic Sofamor Danek, has only been used in IDE studies in the United States.

The rhBMP-2 and Compression Resistant Matrix (CRM) components of AMPLIFY™ rhBMP-2 Matrix have been marketed in the United States. rhBMP-2 is marketed in the United States as a component of INFUSE® Bone Graft (rhBMP-2 on an absorbable collagen sponge at a concentration of 1.5 mg/cc) for certain spine, trauma, and oromaxillofacial indications. INFUSE® Bone Graft is approved for use with a Medtronic Threaded Titanium Interbody Fusion Device for anterior lumbar interbody spinal fusion procedures (P000058). INFUSE® Bone Graft is also approved alone as a treatment for acute, open tibial shaft fractures (P000054) and as an alternative to autogenous bone graft for sinus augmentations, and for localized alveolar ridge augmentations for defects associated with extraction sockets (P050053). INFUSE® Bone Graft has not been withdrawn from the market for any reason.

The Compression Resistant Matrix (CRM) component has been marketed in the United States as MASTERGRAFT® Matrix (K023533) since 2003 and has not been withdrawn from the market for any reason.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Reported Adverse Events

The sponsor conducted a randomized, prospective, multicenter trial to assess the safety and effectiveness of AMPLIFY™ rhBMP-2 Matrix. Patients in the

investigational group received AMPLIFY™ rhBMP-2 Matrix with posterior supplemental fixation, while control patients received iliac crest autograft with posterior supplemental fixation. Both the investigational and control patients were implanted via a posterolateral surgical approach. This study is described in more detail beginning in Section X. The following section discusses the adverse events observed in the study.

The adverse effects, as shown in Table 1 below, were reported from the 239 investigational patients and 224 control patients enrolled in the clinical study. The adverse event rates presented are based on the number of patients having at least one occurrence for a particular adverse event divided by the total number of patients in that treatment group.

Table 1. All Adverse Events AMPLIFY™ rhBMP-2 Matrix Pivotal Study																						
Type of Adverse Event	Operative		1 Day- ≤1 Month		6 Weeks (=1-<2 Mos.)		3 Months (=2-<5 Mos.)		6 Months (=5-<9 Mos.)		12 Months (=9-<19 Mos.)		24 Months (=19-<30 Mos.)		# of Patients Reporting & Total Adverse Events		36 Months (=30-<42 Mos.)		48 Months (=42-<54 Mos.)		60 Months (≥54 Mos.)	
	Inv	Ctrl	Inv	Ctrl	Inv	Ctrl	Inv	Ctrl	Inv	Ctrl	Inv	Ctrl	Inv	Ctrl	Inv # (% of 239) Total Events	Ctrl # (% of 224) Total Events	Inv	Ctrl	Inv	Ctrl	Inv	Ctrl
	N=239	N=224	N=239	N=224	N=239	N=224	N=239	N=224	N=239	N=224	N=239	N=224	N=239	N=224								
Anatomical/Technical Difficulty	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1 (0.4%) 1	0 (0.0%) 0	0	0	0	0	0	0
Arthritis/Bursitis	0	0	3	1	1	1	7	2	4	3	6	6	3	6	23 (9.6%) 24	17 (7.6%) 19	7	5	4	7	2	3
Back and/or Leg Pain	0	0	18	8	11	5	15	13	21	30	37	31	37	23	105 (43.9%) 139	89 (39.7%) 110	39	36	30	26	11	18
Cancer	0	0	0	0	0	0	1	0	2	1	3	1	3	0	9 (3.8%) 9	2 (0.9%) 2	4	1	0	1	0	0
Cardiovascular	2	0	45	43	0	2	4	3	2	7	15	9	4	3	53 (22.2%) 72	54 (24.1%) 67	14	2	10	12	5	3
Carpal Tunnel Syndrome	0	0	0	0	0	0	0	0	2	1	4	3	3	2	9 (3.8%) 9	6 (2.7%) 6	0	1	0	0	0	1
Death	0	0	0	0	1	0	0	0	1	2	1	1	0	1	3 (1.3%) 3	4 (1.8%) 4	0	1	2	1	1	1
Dural Injury	13	18	1	0	0	0	0	0	0	0	0	0	0	0	14 (5.9%) 14	18 (8.0%) 18	0	1	0	0	0	1
Gastrointestinal	0	0	18	16	0	2	4	3	5	2	9	11	7	9	37 (15.5%) 43	33 (14.7%) 43	13	11	12	12	7	4
Graft Site Related	0	0	0	4	0	3	0	5	0	3	0	2	0	0	0 (0.0%) 0	17 (7.6%) 17	0	2	0	0	0	0
Implant Displacement/ Loosening	0	0	0	0	0	0	0	1	0	0	1	1	0	0	1 (0.4%) 1	2 (0.9%) 2	0	0	0	0	0	0
Infection	0	0	20	27	4	6	4	2	6	1	11	10	7	5	39 (16.3%) 52	45 (20.1%) 51	2	6	6	6	0	1
Malpositioned Implant	1	0	3	1	0	1	1	0	0	0	0	0	0	0	5 (2.1%) 5	2 (0.9%) 2	0	0	0	0	0	0
Neurological	0	0	9	7	2	9	19	14	19	17	20	14	16	13	70 (29.3%) 85	60 (26.8%) 74	12	16	9	5	7	3
Non-Union	0	0	0	0	0	0	1	8	0	6	8	6	1	3	10 (4.2%) 10	23 (10.3%) 23	1	1	0	0	0	1
Other*	1	0	43	34	7	7	7	8	6	11	18	14	19	17	70 (29.3%) 101	62 (27.7%) 91	26	26	37	20	10	10
Other Pain	0	0	2	3	2	0	1	1	6	5	11	4	9	19	29 (12.1%) 31	29 (12.9%) 32	8	13	11	7	8	7
Respiratory	0	0	8	7	0	1	1	1	0	1	5	3	3	0	16 (6.7%) 17	12 (5.4%) 13	0	0	0	4	0	1
Spinal Event – All**	0	0	1	1	0	2	3	3	5	2	5	12	4	2	17 (7.1%) 18	19 (8.5%) 22	6	2	3	1	3	1
Spinal Event - Cervical	0	0	0	0	0	2	1	1	4	1	3	8	2	0	9 (3.8%) 10	11(4.9%) 12	2	1	1	1	3	1
Spinal Event - Thoracic	0	0	1	0	0	0	2	2	1	1	1	4	2	2	7 (2.9%) 7	9 (4.0%) 9	4	1	2	0	0	0
Spinal Event - Lumbar	0	0	0	1	0	0	0	0	0	0	1	0	0	0	1 (0.4%) 1	1 (0.4%) 1	0	0	0	0	0	0
Trauma	0	0	2	3	2	8	8	7	13	16	36	19	30	17	69 (28.9%) 91	59 (26.3%) 70	22	16	12	12	6	6
Urogenital	0	0	10	6	2	2	5	3	4	3	5	5	2	5	27 (11.3%) 28	21 (9.4%) 24	4	3	3	2	2	3
Vertebral Fracture	3	3	0	0	0	0	0	0	0	0	0	0	0	1	3 (1.3%) 3	4 (1.8%) 4	0	0	0	0	0	0
Any Adverse Event															209 (87.4%) 756	197 (87.9%) 694	158	143	139	116	62	64

* * Other* adverse events include such events as anxiety, dental events, flu, insomnia, hypothyroidism, and insect bites.

** The category of "Spinal Event" has been subcategorized by region of the spine (i.e., cervical, thoracic, and lumbar). The sum of the events (i.e., "Spinal Event – All") was used in the calculation of the total number of adverse events.

For all of the categories described above, statistical differences were only noted for the categories for graft site related and non-union adverse events. Through 24 months postoperative, graft site related events occurred with greater frequency in the control group (7.6%) compared to the investigational group (0%). Non-union rates were also greater in the control group (10.3%) as compared to the investigational group (4.2%).

There were some adverse event categories in the table above that, while they were not statistically different between the investigational and control groups, occurred at rates that were greater than 10% at 24 months postoperative. Nine categories in the investigational group and eight categories in the control group had adverse event rates greater than 10% at 24 months postoperative. These included back and/or leg pain (43.9% investigational, 39.7% control); cardiovascular (22.2% investigational, 24.1% control); gastrointestinal (15.5% investigational, 14.7% control); infection (16.3% investigational, 20.1% control); neurological (29.3% investigational, 26.8% control); other (29.3% investigational, 27.7% control); other pain (12.1% investigational, 12.9% control); trauma (28.9% investigational, 26.3% control); and urogenital (11.3% investigational, 9.4% control).

The high adverse event rates reflect the fact that all adverse events were reported and captured, regardless of their relationship to the study treatment. As shown in the following table, only a minority of the adverse events reported were related to the study treatment.

Table 2. Adverse Events Related to the Study Treatment AMPLIFY™ rhBMP-2 Matrix Pivotal Study (Through 24 Months Postoperative)		
Adverse Event Type	# of Patients Reporting & Total Adverse Events	
	Inv # (% of 239) Total Events	Ctrl # (% of 224) Total Events
Arthritis/Bursitis	0 (0.0%) 0	2 (0.9%) 2
Back and/or Leg Pain	4 (1.7%) 4	5 (2.2%) 5
Dural Injury	0 (0.0%) 0	1 (0.4%) 1
Implant Displacement/ Loosening	1 (0.4%) 1	2 (0.9%) 2
Malpositioned Implant	4 (1.7%) 4	2 (0.9%) 2
Neurological	2 (0.8%) 2	1 (0.4%) 1
Non-Union	10 (4.2%) 10	22 (9.8%) 22
Trauma	1 (0.4%) 1	0 (0.0%) 0
Vertebral Fracture	0 (0.0%) 0	1 (0.4%) 1

Some of the reported adverse events required surgical interventions subsequent to the initial surgery. Some of these secondary surgical interventions, such as revisions, non-elective removals, and supplemental fixations, were considered second surgery failures in the clinical study. Secondary surgical intervention information for investigational and control treatment groups is summarized in the table below.

Table 3. Secondary Surgical Interventions AMPLIFY™ rhBMP-2 Matrix Pivotal Study							
Event	Total Events through 24-Month Time Point		# of Patients Reporting				Probability that the Second Surgery Rate of Inv. Group is Lower than the Control Group
	Inv N=239	Ctrl N=224	Inv N=239		Ctrl N=224		
Revisions	4	4	4	1.7%	4	1.8%	54.0%
Removals	13	29	13	5.4%	28	12.5%	99.6%
<i>Non-Elective</i>	10	23	10	4.2%	22	9.8%	-
<i>Elective</i>	3	6	3	1.3%	6	2.7%	-
Supplemental Fixations	6	9	6	2.5%	9	4.0%	81.4%
Reoperations	13	14	12	5.0%	11	4.9%	48.2%

For these safety comparisons, probabilities exceeding 97.5% are considered statistically significant, rather than the 95% criterion used for other endpoints. In the table above, it is clear that the investigational group had statistically fewer removals than the control group, while the other second surgeries were not statistically different between the two groups.

Potential Adverse Events

Potential risks associated with the use of the AMPLIFY™ rhBMP-2 Matrix include: 1) those commonly associated with any surgery; 2) those specifically associated with spinal surgery using a posterolateral approach; 3) those associated with a spinal implant, as well as those pertaining to the components of AMPLIFY™ rhBMP-2 Matrix (rhBMP-2 and CRM) specifically. However, the causality of these adverse events is not exclusive to these categories. There is also the risk that this surgical procedure will not be effective and may not relieve or may cause worsening of preoperative symptoms. Some of these effects may have been previously reported in the adverse events table or have been reported to the manufacturer.

- (1) Risks associated with any surgical procedure are those such as adverse reactions to anesthesia; pulmonary complications, such as pneumonia or atelectasis; infection of the wound; systemic infection; abscess; cellulitis; wound dehiscence; swelling; wound hematoma; wound necrosis; thrombosis; pulmonary embolism; thromboembolism; hemorrhage; seizure/convulsion; heart dysfunction, including arrhythmia, failure, or arrest; stroke or other type of cardiovascular system compromise; thrombophlebitis; complications of pregnancy, including miscarriage and fetal birth defects; nerve or muscular damage; memory loss, confusion, hallucination or other change in mental

status; and death. The incidence of these possible adverse events should be similar and comparable to those for any similar surgical procedure.

- (2) Risks associated with posterolateral lumbar spinal surgery include: hernia; paralytic ileus; temporary difficulty in micturition; urinary retention; damage to the ureter or the kidney; activation of kidney stones; urogenital nerve damage, which could result in retrograde ejaculation, sexual dysfunction, sterility, loss of bladder control, or other types of urological or reproductive system compromise; epidural bleeding; neurapraxia; warmth or tingling in the lower extremities; cauda equina damage; ileus; gastritis; bowel obstruction, loss of bowel control, or other types of gastrointestinal system compromise; and/or muscle loss.

Lumbar fusion risks include dural tears and leaking of spinal fluid; loss of disc height; loss of proper curvature, correction, height, or reduction of the spine; vertebral slipping; nerve root trauma; cerebrospinal fistula; scarring; herniation, disruption, or degeneration of adjacent discs; nerve damage possibly resulting in paralysis or pain and surrounding soft tissue damage; vascular damage or hemorrhage; failure to achieve fusion; failure of wound to heal; infection; spinal stenosis; and spondylolysis.

- (3) Risks associated with any implants in the spine are early or late loosening of any or all of the components; malpositioning of implant; sizing issues with components; anatomical or technical difficulties; disassembly; bending or breakage of any or all of the components; implant migration; generation of wear debris; loss of purchase; implant fracture; bone fracture; foreign body reactions to the implant, including infection and/or allergy; possible tissue reaction or tumor formation or graft rejection; bone resorption; cessation of bone growth of the operated portion of the spine; loss of neurological function; decreased leg strength; decreased reflexes; cord or nerve root injury; development of radiculopathy; myelopathy or pain; pseudarthrosis; fracture of the vertebral body; and tissue or nerve damage caused by improper positioning or placement of implants or instruments.

There are some risks that are specific to the use of the rhBMP-2/CRM in the investigational device. These include: excessive/ectopic bone formation; fusion at another level from excessive bone formation; spinal stenosis; delayed or failed healing; slow dissolving of the implant; implant migration; loss of purchase; implant fracture; fluid retention; foreign body reaction; abnormal cellular growth; formation of antibodies to parts or all of the implant; formation of blood clots; bone resorption; adhesion formation; allergic reaction; irritation; inflammation; interference with wound healing when used in the closure of skin incisions; edema; erythema; failure of bone induction; and abnormal structure of the newly-formed bone. A transient antibody response to rhBMP-2 has been detected in humans.

Risks specific to the collagen component of the CRM include: adhesion formation; allergic reaction; foreign body reaction; irritation; inflammation; interference with wound healing when used in the closure of skin incisions; and reduced strength of methyl-methacrylate adhesives when used to attach prosthetic devices to bone surfaces.

There are also risks associated with the implantation of metallic posterior supplemental fixation devices, which are required for use with AMPLIFY™ rhBMP-2 Matrix. For more information on these risks, please refer to the package insert for the appropriate metallic posterior supplemental fixation device.

NOTE: Additional surgery may be necessary to correct some of these potential adverse events.

IX. SUMMARY OF NONCLINICAL STUDIES

Extensive nonclinical testing has been conducted demonstrating that AMPLIFY™ rhBMP-2 Matrix performs as intended for use in spinal fusion procedures as designed. Testing was done in the following categories:

- Nonclinical Mechanical Testing
- Nonclinical Safety
 - Intravenous Toxicity and Implant Toxicity
 - Biocompatibility Studies
 - Tumor Cell Activity
 - Fertility, Reproduction, and Teratology
 - Neurological Safety
 - Immunology-Antibody Response
- Nonclinical Efficacy
 - Bioactivity: Induction of Bone by rhBMP-2
 - Efficacy in Intended Posterolateral Fusion Indication
 - Efficacy in Other Interbody Fusion Indications
- Pharmacokinetics
 - Intravenous Pharmacokinetic Studies
 - Local Retention of rhBMP-2 Administered with CRM
- Pharmacodynamics: rhBMP-2 Activity in the Presence of Agents Affecting Bone Metabolism
- Inappropriate Usage of rhBMP-2

Nonclinical Mechanical Testing

Muscle compression of the graft is a primary concern in posterolateral fusion applications, and the CRM resists soft tissue compression better than the absorbable collagen sponge (ACS) in the INFUSE® Bone Graft product. However, the CRM carrier is not a structural implant, and at no time does it bear any spinal loads. Laboratory bench top testing demonstrated that the average load necessary to cause 5 mm of compression was approximately ten (10) times

larger in CRM compared to ACS. Both materials were also evaluated *in vivo* for their mechanical properties in a posterolateral fusion model. The rhBMP-2/CRM produced better fusion results in comparison to rhBMP-2/ACS or autograft. The results of the studies are summarized below in Table 4.

Table 4. Mechanical Testing Studies			
Study Type (Species)	Groups No. Samples/ Sex	rhBMP-2 (mg/cc)	Relevant Findings
<i>In vitro</i> mechanical testing	2 10/NA	n/a	The average load at 5 mm of displacement was 489.2 ± 100.8 N for the CRM and 48.0 ± 2.5 for the ACS.
<i>In vivo</i> posterolateral fusion mechanical testing (Rabbit)	1 14/F	0.29 mg/cc	The strength and stiffness of the fusion was significantly better than the fusion produced by rhBMP-2/ACS or autograft. Histologic analysis confirmed normal new bone formed, which is capable of undergoing remodeling.

n/a = not applicable

Nonclinical Safety

Safety of rhBMP-2 Administered Intravenously: Acute and Repeated Dose

rhBMP-2 protein was studied in single- and multiple-dose general toxicology studies in the rat and dog. rhBMP-2 was administered intravenously (IV) at a range of doses. No treatment-related toxicities were observed in these studies. The findings are listed in Table 5.

Table 5: Intravenous (IV) Safety Test Findings			
Study Type (Species/Strain)	Groups No. Animals/ Sex	rhBMP-2 (mg/kg)	Relevant Findings
Acute toxicity with sacrifices on Days 2, 7 and 15 (Rat/Sprague-Dawley)	5 5/sex	saline vehicle 0.053 0.160 0.533	No toxicity observed. No-toxic-effect dose was 0.533 mg/kg IV.
Acute toxicity with sacrifices on Days 2 and 15 (Rat/Sprague-Dawley)	5 5/sex	saline vehicle 0.533 1.60 5.33	No treatment-related findings in animals sacrificed at Day 2 or Day 15. Slight-to-mild dose-related chondrogenesis at injection sites. No-toxic-effect dose was 5.33 mg/kg IV.
Acute toxicity with sacrifice on Day 15 (Dog/Beagle)	4 1/sex	vehicle 0.53 1.6 5.3	No toxicity observed. No-toxic-effect dose was 5.3 mg/kg IV.

Table 5: Intravenous (IV) Safety Test Findings			
Study Type (Species/Strain)	Groups No. Animals/ Sex	rhBMP-2 (mg/kg)	Relevant Findings
28-Day toxicity (Rat/Sprague-Dawley)	5 10/(5) ^a /sex	saline vehicle 0.016 0.05 0.16	Ten deaths unrelated to treatment (vehicle, 0.016, 0.05, 0.16). Dose-related soft tissue thickening and cartilage formation in subcutaneous tissue at injection sites. Following 28-day recovery period, the soft tissue thickening regressed and matured to bone. No-toxic-effect dose was 0.16 mg/kg/day IV.
28-Day toxicity (Dog/Beagle)	5 3/(2) ^a /sex	saline vehicle 0.016 0.05 0.16	Dose-related perivascular fibroplasia at injection site in all rhBMP-2-treated animals with bone formation in mid- to high-dose groups. No-toxic-effect dose was 0.16 mg/kg/day IV.
rhBMP-2 general pharmacology (mice, rats, guinea pigs, and dogs)	4-10 experiments <i>in vitro</i> and <i>in</i> <i>vivo</i> for each dose <i>Mice and Rats:</i> 5 5-10/M <i>Guinea Pigs:</i> 1 5-10/M <i>Dogs:</i> 1 5/mixed	<i>In vitro:</i> 10 ⁻⁸ g/ml 10 ⁻⁷ g/ml 10 ⁻⁶ g/ml 10 ⁻⁵ g/ml <i>In vivo:</i> 0.01 0.1 1.0	These experiments showed that rhBMP-2 had no effects on locomotion, the central nervous system, locomotor activity, respiration and cardiovascular systems, gastrointestinal systems, urinary system, and blood coagulation at the doses tested.

(n)^a = numbers of additional recovery sub-group animals in control and high-dose groups.

Chronic Toxicity

The long-term safety of implanted rhBMP-2 was evaluated in two studies – a 6-month study in beagle dogs and a 1-year study in Sprague-Dawley rats. These studies were designed to assess the potential long-term systemic and local effects of rhBMP-2 in two species at two skeletal sites. Implants containing rhBMP-2 had no systemic effects, and local effects were associated with the osteoinductive activity of rhBMP-2. Transient, low-titer immune responses were observed in the dog study. Findings are provided in Table 6 below.

Table 6: Chronic Toxicity Findings			
Study Type (Species/Strain)	Groups No. Animals/ Sex	rhBMP-2 (mg/kg)	Relevant Findings
6-month mandibular/ maxillofacial implant at inlay defect site (Dog/Beagle)	5 2/sex <i>Sacrificed at 3 and 6 months postimplantation</i>	sham surgery vehicle/ACS 0.078 mg/kg (0.4 mg/mL)/ACS 0.312 mg/kg (1.6 mg/mL)/ACS 0.781 mg/kg (4.0 mg/mL)/ ACS	No effects of treatment on clinical signs, hematology, or clinical chemistry. Dose-related post-surgical swelling. As swelling subsided (3-4 weeks), firm masses near the zygomatic and mandibular implant sites were detected in most rhBMP-2 treated animals. Histologically, the rhBMP-2-treated implant sites were composed of abundant fibrocellular tissue and/or new bone formation within and around the defect site. There were fluid-filled tissue cysts and occasionally strands of residual ACS material at implant sites with apparent regression between 3 and 6 months. Implant site changes were expected exaggerated pharmacologic responses to rhBMP-2/ACS and were not toxicologically significant. No-toxic-effect dose was 0.781 mg/kg (4.0 mg/mL concentration rhBMP-2). Transient low titer antibody responses were observed in 15/24 (62.5%) of the treated animals. No anti-bovine Type I collagen antibody response was found.
1-year femoral onlay implant toxicology (Rat/Sprague- Dawley)	5 10/sex <i>Sacrificed at 1, 6, and 12 months post-implantation</i>	vehicle/ACS 0.04 mg/kg (0.1 mg/mL)/ACS 0.3 mg/kg (0.75 mg/mL)/ACS 1.6 mg/kg (4.0 mg/mL)/ACS 1.6 mg/kg (4.0 mg/mL)/ACS opalescence	Slight increased incidence and severity of surgical site swelling at 1.6 mg/kg. Dose-related pharmacologic effect of increased incidence and/or severity of bone formation at implant site in all rhBMP-2/ACS treatment groups. No toxicity at any dose. Formation of antibodies to rhBMP-2 or bovine Type I collagen was not observed.

Biocompatibility Studies

The safety of CRM and rhBMP-2/CRM was evaluated in a series of biocompatibility tests. Under the conditions of these studies, there was no mortality or evidence of significant systemic toxicity in the mouse, no intracutaneous toxicity in the rabbit, no evidence of cell lysis or toxicity in the extract and overlay cytotoxicity tests, no evidence of hemolysis, and no evidence of cellular mutagenicity. Table 7 below lists the specific biocompatibility testing conducted and the results.

Table 7: Biocompatibility Test Summary			
Study Type (Species)	Groups No. Animals/ Sex	Route	Relevant Findings
Hemolysis Study – In Vitro Procedure (Extraction Method)/rabbit blood	n/a	n/a	The mean hemolytic index for the CRM test articles was 0%. The CRM test article extract was not hemolytic. The negative and positive controls performed as expected.
Cytotoxicity – ISO Elution Method/L929 mouse fibroblast cells	n/a	n/a	The 1X MEM test extract from the CRM showed no evidence of causing cell lysis or toxicity. The 1X MEM test extract met the requirements of the test since the grade was less than grade 2 (mild reactivity). The reagent control, negative control, and the positive control performed as anticipated.
ISO Acute Intracutaneous Toxicity (Rabbit)	1 3/(2 M and 1 F)	IC	There was no evidence of significant irritation or toxicity from the CRM extracts injected intracutaneously into rabbits. The Primary Irritation Index Characterization for the CRM extracts was negligible.
ISO Acute Reactivity (Mouse)	4 20/M	IV IP	There was no mortality or evidence of systemic toxicity from the CRM extracts. Each CRM test article extract met the requirements.
Kinetic-Chromogenic Limulus Amebocyte Lysate (LAL)	n/a	n/a	The level of endotoxins was found to be within specified levels.
<i>Salmonella tryphimurium</i> and <i>Escherichia coli</i> Reverse Mutation Assay I – ISO (AMES Assay)	n/a	n/a	The rhBMP-2/CRM test article is not mutagenic in the test species.
Rodent Bone Marrow Micronucleus Assay – ISO (Mouse)	5 19/sex	IV	The NaCl extract of the test article, rhBMP-2/CRM, at the tested concentration did not induce a statistically significant increase in micronucleated cells as compared to the negative control at 24 and 48 hours after dosing. The negative and positive controls performed as expected. rhBMP-2/CRM was considered non-mutagenic based on the criteria of the study protocol.
Mouse Lymphoma Mutagenesis Assay – ISO	n/a	n/a	Based on the test criteria, the test article, rhBMP-2/CRM, is considered non-mutagenic, under the experimental conditions utilized.

Table 7: Biocompatibility Test Summary			
Study Type (Species)	Groups No. Animals/ Sex	Route	Relevant Findings
L929 MEM Elution Test	n/a	n/a	No biological activity (Grade 0) was observed at 48 hours, post to the test article, rhBMP-2/CRM, extract. The positive and negative control performed as anticipated. The test article, rhBMP-2/CRM, is considered non-cytotoxic and meets the requirements of the Elution Test, ISO 10993-5.
Hemolysis – rabbit blood	n/a	n/a	The test article, rhBMP-2/CRM, is considered non-hemolytic under the experimental conditions employed.
Pyrogen Test/Material Mediated – ISO (Rabbit)	1 2/sex	IV	Based upon the criteria of the protocol, the test article, rhBMP-2/CRM, meets the requirements of the Pyrogen Test and is therefore considered non-pyrogenic.

n/a = not applicable

Carcinogenicity/Genotoxicity

In addition to the Ames Mutagenicity Assay, the Sponsor investigated the potential for rhBMP-2 to stimulate the proliferation of primary tumor cell isolates and tumor cell lines. rhBMP-2 was examined for growth potentiating activity *in vitro* on human tumor cell lines and primary tumor cell isolates. No growth potentiating activity was observed. rhBMP-2 inhibited growth of several carcinoma-derived tumors. Overall, studies investigating the potential effects of rhBMP-2 on tumor cell growth showed minimal evidence of growth potentiation, including studies of osteosarcoma cell lines. Table 8 below summarizes the findings of these studies.

Table 8: Carcinogenicity/Genotoxicity Studies			
Study Type (Species/Strain)	Groups No. Animals/ Sex	rhBMP-2 (mg/ml)	Relevant Findings
Growth potential on primary tumor isolates <i>in vitro</i> (Soda et al., <i>Anti-Cancer Drugs</i> , 1998)	n/a	10, 100, and 1000 ng/ml concentration <i>in vitro</i>	No tumor cell growth stimulation. Significant inhibition of colony forming units in 16 of 65 specimens at 1000 ng/ml.
Inhibition of tumor growth <i>in vitro</i> with human tumor cell lines	n/a	10, 100, and 1000 ng/ml concentration <i>in vitro</i>	No effect on osteosarcoma cell line growth. Inhibitory effects on several soft tissue carcinoma cell lines.

Table 8: Carcinogenicity/Genotoxicity Studies			
Study Type (Species/Strain)	Groups No. Animals/ Sex	rhBMP-2 (mg/ml)	Relevant Findings
Growth of human tumor xenografts (Nude mouse)	4 40/F	Sham Buffer/ACS (4.22 mg/ml)/ACS (0.422 mg/ml)/ACS	Surgical treatment with rhBMP-2/ACS did not increase the numbers of microscopically observed xenograft cell metastases. The exposure of 7 human tumor cell line xenografts in nude mice to rhBMP-2/ACS did not promote <i>in vivo</i> growth of any of the 7 tumor lines tested, which included tumor lines known to express mRNA for Type I or Type II components of the BMP-2 receptor complex.
<i>In vitro</i> proliferation of human cancer cell lines	n/a	3 ng/ml 10 ng/ml 30 ng/ml 100 ng/ml	In the presence of rhBMP-2, 10 of the 11 cell lines showed no additional mitogenic activity in comparison to identical cells grown in the absence of rhBMP-2. The remaining cell line, LnCap, was growth inhibited by rhBMP-2 in a dose dependent fashion.
Human tumor cell receptors (PCR screening)	n/a	n/a	It was determined that 10 of the 21 human tumor cells lines examined in this protocol express functionally relevant levels of BMPR-II and either BMPR-IA or BMPR-IB.

Fertility, Reproduction, and Teratology

Because BMP-2 participates in embryological development, rhBMP-2 was evaluated for any effect on reproduction or fetal development. Studies evaluated rhBMP-2 at a range of doses. The effect of rhBMP-2 on the reproduction and fertility of male and female Sprague-Dawley rats was studied. Maternal and paternal mating performance and reproductive parameters were not affected by treatment. Range-finding studies followed by developmental toxicity studies were conducted in both Sprague-Dawley rats and New Zealand white rabbits. No evidence of maternal toxicity, embryoletality, fetotoxicity, or teratogenicity was found. Findings are summarized in Table 9 below.

Table 9: Fertility, Reproduction, and Teratology Studies			
Study Type (Species/Strain)	Groups No. Animals/ Sex	rhBMP-2 (mg/kg)	Relevant Findings
Fertility (Rat/Sprague-Dawley)	5 40/F 40/M	saline vehicle 0.016 0.05 0.16	Maternal and paternal mating performance and reproductive parameters were not affected by treatment. No-toxic-effect dose was 0.16 mg/kg/day IV.

Table 9: Fertility, Reproduction, and Teratology Studies			
Study Type (Species/Strain)	Groups No. Animals/ Sex	rhBMP-2 (mg/kg)	Relevant Findings
Range-finding teratology (Rabbit/New Zealand White rabbit)	7 5/F	saline vehicle 0.016 0.05 0.16 0.5 1.6 <i>Days 6 to 18 gestation</i>	No maternal toxicity, embryoletality, or gross fetal abnormalities. No-toxic-effect level was 1.6 mg/kg/day IV.
Teratology (Rabbit/New Zealand White rabbit)	5 20/F	saline vehicle 0.016 0.5 1.6 <i>Days 6 to 18 gestation</i>	No maternal toxicity, embryoletality, or gross fetal abnormalities. No-toxic-effect level was 1.6 mg/kg/day IV. Definitive teratology study in rats. The incidences of malformations were not significantly different between control and treated groups.
Range-finding teratology (Rat/Sprague-Dawley)	7 6/F	saline vehicle 0.016 0.05 0.16 0.5 1.6 <i>Days 6 to 17 gestation</i>	No maternal toxicity, embryoletality, or gross fetal abnormalities. No-toxic-effect level was 1.6 mg/kg/day IV.
Teratology (Rat/Sprague-Dawley)	5 25/F	saline vehicle 0.16 0.5 1.6 <i>Days 6 to 17 gestation</i>	No maternal toxicity, embryoletality or fetal abnormalities. No-toxic effect dose was 1.6 mg/kg/day IV. The definitive teratology study in rats was repeated. In the initial study, there was a nonsignificant difference in skeletal formation between the rhBMP-2 groups and the saline and control groups. Examination of skeletal variance revealed a significant reduction in sternebral variance in all treated groups.
Repeat teratology (Rat/Sprague-Dawley)	2 25/F	vehicle 1.6 <i>Days 6 to 17 gestation</i>	It was hypothesized that the difference in skeletal formation in the preceding study was a result of the time of cesarean section rather than a treatment effect. This repeat study had a random order of selection for time of cesarean section. No maternal toxicity, embryoletality, fetotoxicity, or teratogenicity, and no difference in skeletal formation between the control and rhBMP-2 groups. No-toxic-effect level was 1.6 mg/kg/day IV.

Table 9: Fertility, Reproduction, and Teratology Studies			
Study Type (Species/Strain)	Groups No. Animals/ Sex	rhBMP-2 (mg/kg)	Relevant Findings
Development toxicity (Rabbit/New Zealand White rabbit)	1 30/F	Dose = 2.0 mg + TiterMax® Gold	Immunized adult does had an increased frequency of loose and decreased feces, but with no other effect to weight, feed consumption, or pregnancy incidences and outcomes. Fetuses consistently developed reduced ossification of the frontal and parietal bones with positive anti-BMP-2 titers. These findings are not toxicologically important because reduced ossification is considered to be a reversible phenomenon, and anti-BMP-2 antibody titer levels, with or without antibody neutralizing activity, did not correlate with effects on fetal bone ossification.

Neurological Safety

To evaluate the safety of rhBMP-2 for use in proximity to the spinal cord, neurological safety testing was conducted. The purpose of this study was to assess the effect of rhBMP-2 on exposed dura and neural tissue after standard decompressive lumbar laminectomy using a canine model. In addition, certain animals received puncture wounds to the dura with expression of cerebral spinal fluid at site of puncture. This study represented a worst case situation in which rhBMP-2 or autogenous bone graft was in direct contact with the spinal cord and, in some instances, a compromised dural barrier and found no evidence of safety concerns. The results are given in Table 10 below.

Table 10: Neurological Safety			
Study Type	Species/ Device Tested	rhBMP-2/ACS (mg/ml)	Relevant Findings
Implantation on exposed dura after laminectomy Meyer et al., <i>Spine</i> 1999	Dog/ rhBMP-2/ACS	0.10	Clinical observation, radiography, CT scans, neurological exam, histology: no neurological deficit, no spinal cord stenosis, and no mineralization of the dura when rhBMP-2 placed directly on exposed dura. There was no difference between animals that received a dural nick and those that did not.

Immunology-Antibody Response

Formation of antibodies to rhBMP-2 and Type I collagen in canines, rhesus monkeys, and rats was monitored using Enzyme Linked Immunosorbent Assays (ELISA). Immune responses to rhBMP-2 were observed in nonhuman primates

and in dogs. Two of these studies have already been summarized above in Table 6. Other findings are summarized in Table 11 below.

Table 11: Immunology Studies			
Study Type (Species/Strain)	Groups No. Animals/ Sex	rhBMP-2 (mg/kg)	Relevant Findings
Long bone critical-sized defect repair (Nonhuman primate pharmacology studies)	11 2-6/sex	Surgery only Autograft 0 mg/ml/ACS 0.05 mg/ml/ACS 0.2 mg/ml/ACS 0.4 mg/ml/ACS 0.8 mg/ml/ACS 1.3 mg/ml/ACS 1.5 mg/ml/ACS 1.9 mg/ml/ACS 3.1 mg/ml/ACS	Antibodies to rhBMP-2 were detected in 35% (7/20) of the animals treated with rhBMP-2/ACS, while anti-bovine Type I collagen antibodies were observed in 7% (1/14) of all animals exposed to ACS (either containing formulation buffer or rhBMP-2).

Animal Studies/Nonclinical Efficacy

Efficacy in Intended Posterolateral Fusion Indication

The efficacy studies listed below are relevant to the intended clinical indication and are presented as the primary data for the nonclinical efficacy studies for posterolateral fusion application of rhBMP-2/CRM. The research presented below was used to evaluate the optimal ceramic composition and rhBMP-2 concentration for use in posterolateral spine fusion. The evidence from the supporting studies is listed in Table 12.

Table 12: Posterolateral Spine Fusion Efficacy Studies			
Study Type (Species)	Groups No. Animals/ Sex	rhBMP-2 (mg/ml)	Relevant Findings
L5-L6 posterolateral fusion (New Zealand White rabbit) Suh et al., <i>Spine</i> 2002	1(1) ^a 14(14) ^a / F(F) ^a	0.29 mg/cc or 0.86 mg/side (0.43 mg/ml or 0.9 mg/side) ^a	The 5% HA/95% TCP (BCP) CRM achieved fusion in all 14 animals, but the new bone formation was limited to the periphery. In comparison to an early study delivering rhBMP-2 directly on 60% HA/40% TCP ceramic granules, the fusion masses produced were of comparable strength. However, the handling of the BCP/CRM had superior characteristics in comparison to the loose ceramic granules.

Table 12: Posterolateral Spine Fusion Efficacy Studies			
Study Type (Species)	Groups No. Animals/ Sex	rhBMP-2 (mg/ml)	Relevant Findings
Single-level lumbar posterolateral fusion (New Zealand White rabbit)	2 18/unknown	Buffer + CRM 0.43 mg/cc + CRM	The gross palpation scores for the rhBMP-2/CRM group were greater than the buffer/CRM group. In general, the amount of ceramic resorbed increased from 3 months to 6 months to 9 months, with little to no residual ceramic remaining at 9 months in the rhBMP-2 group.
L4-L5 spinal fusion (Non-human primate) Suh et al., <i>Spine</i> 2002	3 6/mixed	2.1 mg/cc + BCP (15%HA/85%TCP) CRM sponge 2.1 mg/cc + BCP (5%HA/95%TCP) CRM sponge 1.1 mg/cc + BCP (15%HA/85%TCP) CRM sponge	All animals treated with 2.1 mg/cc concentration resulted in a 100% fusion rate, with fusion limited to the confines of the CRM sponge, and at 6 months, histological evaluation of fusion masses revealed solid fusions with minimal residual ceramic.
Single-level lumbar posterolateral fusion (Non-human primate)	2 6/unknown	2.0 mg/cc + CRM 0.6 mg/cc + CRM	All three monkeys receiving the 2.0 mg/cc concentration achieved solid fusion. At 24 weeks, any residual ceramic was incorporated into the <i>de novo</i> bone. No adverse reactions were noted in the histology.
Side-by-side formulation comparison in posterolateral fusion (Non-human primate)	2 ^b 6 ^b /unknown	2.0 mg/cc + CRM (Clinical) ^b 2.0 mg/cc + CRM (High Glutamic Acid Buffer) ^b	Bone successfully formed between the intertransverse processes using rhBMP-2/CRM. The bone was formed through intramembranous ossification, contained both lamellar and woven bone, and incorporated residual ceramic.

Table 12: Posterolateral Spine Fusion Efficacy Studies			
Study Type (Species)	Groups No. Animals/ Sex	rhBMP-2 (mg/ml)	Relevant Findings
Single-level lumbar posterolateral fusion (New Zealand White rabbit)	4 ^c 24 ^c /unknown	2.0 mg/cc + CRM (Clinical) ^c 2.0 mg/cc + CRM (High Glutamic Acid Buffer) ^c	These results are focused on the clinical formulation since this will be used for AMPLIFY. At the 3 month time point, a rim of lamellar bone formed, filled with a mixture of woven and lamellar bone in the fusion mass. The 3 month samples also had less trabecular bone than the 5 week group. Osteoclastic resorption was noted at 5 weeks. Residual collagen was only seen at 5 weeks and never at 3 months. Residual ceramic was present at both time points but became more incorporated in the fusion mass over time. These residual ceramic fragments also increased the inflammatory response in the marrow of the fusion mass as phagocytosis by macrophages and in some cases foreign body giant cells. This response is normal for resorbable ceramics. An unusual finding in this study was the presence of blood filled and fluid filled cysts, regularly found adjacent to the fusion masses. The cause of these cysts is not known.

^a Fusion results and handling characteristics from the study were compared to a previous study.

^b The concentration of the two formulations were the equivalent, only the excipients differed. The commercial formulation was implanted in the left posterolateral gutter and the clinical formulation in the right.

^c Two treatments were examined at both 5-week and 3-month time points. Each treatment per time point group contained 6 animals.

Efficacy in Other Interbody Fusion Indications

The efficacy studies listed below are relevant to use of rhBMP-2/CRM to induce interbody fusion in various animal models. The research presented below was used to evaluate the bone forming capability of rhBMP-2/CRM in a healing environment very different from the posterolateral environment, as well as the compatibility of rhBMP-2/CRM with various interbody fusion devices. The evidence from these supporting studies is listed in Table 13.

Table 13: Interbody Spine Fusion Efficacy Studies			
Study Type (Species)	Groups No. Animals/ Sex	rhBMP-2 (mg/ml)	Relevant Findings
Multi-level (5) interbody fusion (Pig)	7 30 ^a /M	0.43 mg/cc + CRM 0.43 mg/ml + ACS + allograft chips 0.43 mg/ml + BSM Autologous rib graft Autologous iliac crest graft CRM only No graft material	Radiographic fusion scores for the rhBMP-2/CRM group trended higher than other treatments. Biomechanical testing showed that rhBMP-2/CRM displayed trends toward greater stiffness. Histologic and histomorphometric analysis demonstrated that rhBMP-2/CRM had the highest percentage of total new-bone area, expressed as a percentage of disc space area.
Two-level adjacent interbody fusion – INTER FIX™ Device (Sheep)	2 12/F	0.43 mg/cc + CRM + INTER FIX™ Device Autograft + INTER FIX™ Device	Histologic evaluation was significantly different between groups, as the rhBMP-2 +INTER FIX™ group had a 100% fusion rate (12/12 levels) and the autograft + INTER FIX™ group had a 66% fusion rate (8/12 levels).
Single-level interbody fusion – Pyramesh® Device (Sheep)	3 14 ^b /F	Autograft + Pyramesh® Device 0.43 mg/ml + ACS + Pyramesh® Device 0.43 mg/cc + CRM + Pyramesh® Device	The rhBMP-2 groups trended toward higher fusion scores in radiographic assessment. Biomechanical testing determined the rhBMP-2 groups had greater stiffness than the autograft group. Histologic assessment determined demonstrated greater fusion rates for rhBMP-2/CRM (8/8), in comparison to rhBMP-2/ACS (5/6) and autograft (3/6).

^a All groups contained 4 replicates except the rhBMP-2/CRM group, which contained 6 replicates.

^b All groups contained 6 replicates except the rhBMP-2/CRM group, which contained 8 replicates.

Pharmacokinetics

Intravenous Pharmacokinetic Studies

Although rhBMP-2 is intended to be delivered with a carrier as an implant, pharmacokinetic results obtained from intravenous (IV) dosing provide a means to evaluate the extent and duration of systemic exposure of rhBMP-2. Studies were conducted to characterize the pharmacokinetics of rhBMP-2 in the blood of rats and monkeys. A study conducted in juvenile and adult Sprague-Dawley rats revealed that juvenile rats, like adult rats, cleared rhBMP-2 rapidly. Results also showed a lower maximal concentration, higher clearance, and a larger initial volume of distribution for rhBMP-2 in juvenile rats as compared to adult rats. As a result of these pharmacokinetic characteristics, systemic presence of rhBMP-2

in the circulation was found to be minimal after IV dosing. The findings are summarized in Table 14 below.

Table 14: Intravenous Pharmacokinetic Studies			
Study Type (Species/Strain)	Groups No. Animals	rhBMP-2 Dose	Relevant Findings
PK & excretion Single dose (Rat/Sprague- Dawley)	4 12 (PK & excretion single dose)	0.43 µg/kg 4.3 µg/kg 43 µg/kg 860 µg/kg	Clearance of ¹²⁵ I rhBMP-2 was rapid and biexponential: T _{1/2α} ^a = 0.8 min and T _{1/2β} ^b = 15.3 min. Most of the administered dose (92%) was recovered by 24 hours in the urine as TCA-soluble counts per minute.
PK single dose (Nonhuman primate/cynomolgus monkey)	2 6	4.9 µg/kg	Clearance of ¹²⁵ I rhBMP-2 was rapid and biexponential: T _{1/2α} ^a = 1 min and T _{1/2β} ^b = 7 min.
Biodistribution (Rat/Sprague- Dawley)	8 24	4.3 µg/kg	Rapid localization to liver with metabolism and excretion into urine was noted. Biphasic disposition was observed with initial and terminal half-life of 0.8 and 31 minutes, respectively.
Biodistribution (Rat/Sprague- Dawley)	8 24	7.1 µg/kg	¹²⁵ I rhBMP-2 rapidly distributed to the highly perfused tissues; 1 minute after dosing, 82.4% of the dose was recovered in the liver, lung, kidney, and spleen. The liver was the predominant site of ¹²⁵ I rhBMP-2 localization throughout the study.
PK & excretion single dose, PK repeat dose (Rat/Sprague- Dawley)	1 4	5.3 mg/kg	Clearance of ¹²⁵ I rhBMP-2 was rapid and biexponential: T _{1/2α} ^a = 0.57 min and T _{1/2β} ^b = 16.7 min.
PK single dose: (Juvenile and adult rats/Sprague- Dawley)	2 24 juvenile and 12 adult	3.0 mg/kg	Clearance of ¹³¹ I rhBMP-2 was rapid and biexponential in both juvenile and adult rats as assessed by serum acid precipitable radioactivity and by ELISA.

T_{1/2α}^a = half-life of initial phase

T_{1/2β}^b = half-life of terminal phase

Local Retention of rhBMP-2 Administered with CRM

Local rhBMP-2 retention kinetics in rabbits has been studied with the Compression Resistant Matrix (CRM) carrier as well as with Biphasic Calcium Phosphate (BCP) granules. The study shows that CRM adequately retains rhBMP-2 protein at the desired site and facilitates bone formation, as described in Table 15.

Table 15: Local Retention Kinetics Studies			
Study Type (Species)	Groups No. Animals/ Sex	rhBMP-2 (mg/ml)	Relevant Findings
PK bioactivity (Rat)	4 48/M	0.1 mg/ml + ACS 0.02 mg/ml + ACS 0.004 mg/ml + ACS 0 mg/ml + ACS	The data obtained demonstrated the importance of the retention of rhBMP-2 in a rat ectopic implant model. When rhBMP-2 was implanted on ACS, the amount of plasmin-cleaved rhBMP-2 retained at the implantation site was significantly lower than native rhBMP-2 at all assessment time points over the 13-day study period. Early protein recoveries from implants at 3 hours were 55.7 and 17.6% for the native and plasmin-cleaved rhBMP-2, respectively.
Isotope-labeled retention (Rabbit)	2 18/F	2.1 mg/cc + BCP (5%HA/95%TCP) CRM 2.1 mg/cc + BCP (60%HA/40%TCP granules)	There was no statistical difference in the retention curve vs. time profile between the BCP and CRM carriers.
Louis-Ugbo et al., <i>J Orthop Res</i> 2002			
¹²⁵ I-rhBMP-2-labeled retention #1 (Rabbit)	1 18/unknown	2.0 mg/cc + CRM	The CRM retained 92%, 65%, 39%, 18%, 6%, and 3% of the administered rhBMP-2 at 24 hours, 1, 2, 3, 4, and 5 weeks, respectively. The average AUC was 1266 ± 168 %Retention*Days. The retention profile is shown in Figure 1 below.
¹²⁵ I-rhBMP-2-labeled retention #2 (Rabbit)	1 18/unknown	2.0 mg/cc + CRM	The CRM retained 82%, 55%, 31%, 13%, 5%, and 3% of the administered rhBMP-2 at 24 hours, 1, 2, 3, 4, and 5 weeks, respectively. The average AUC was 1211 ± 208 %Retention*Days. The retention profile is shown in Figure 1 below.
<i>In vivo</i> Incorporation (Rabbit)	2 16/M	1.5 mg/ml + 16 mM Glutamate 1.5 mg/ml + 25 mM Glutamate	The level of incorporation of the rhBMP-2 was insignificant on the <i>in vivo</i> retention kinetics.

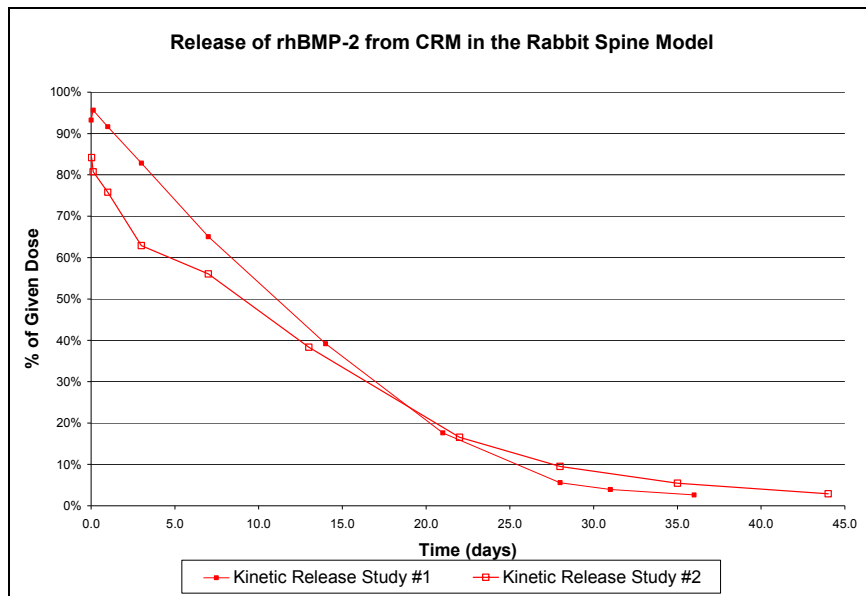


Figure 1. Retention of rhBMP-2 Following Implantation of rhBMP-2/CRM in the Rabbit

Pharmacodynamics: rhBMP-2 Activity in the Presence of Agents Affecting Bone Metabolism

A series of tests was performed showing that the bone induction activity of rhBMP-2 was not inhibited by agents that typically inhibit bone formation. These studies were performed in rat and rabbit models. In all cases, the induced bone integrated with the pre-existing bone and remodeled physiologically. Radiographic, biomechanical, and histological evaluations indicate that the new bone functions as native bone. The results are provided in Table 16.

Table 16. rhBMP-2 Activity in the Presence of Bone Metabolism Affecting Agents			
Study Type (Species)	Groups No. Animals/ Sex	rhBMP-2 (mg/ml)	Relevant Findings
Subcutaneous implant (Rat)	9 38 ^a /M	0.00 mg/ml + ACS + 4.5 µg/kg/min Nicotine 0.01 mg/ml + ACS + 4.5 µg/kg/min Nicotine 0.10 mg/ml + ACS + 4.5 µg/kg/min Nicotine 0.40 mg/ml + ACS + 4.5 µg/kg/min Nicotine 0.00 mg/ml + ACS 0.01 mg/ml + ACS 0.10 mg/ml + ACS 0.40 mg/ml + ACS 0.10 mg/ml + ACS + 0.0 µg/kg/min Nicotine	Systemic nicotine treatment did not inhibit the ability of rhBMP-2/ACS to induce bone formation.
Ulnar osteotomy repair (Rabbit)	3 38 ^b /M	0.20 mg/ml + ACS + 4.5 µg/kg/min Nicotine 0.20 mg/ml + ACS + 4.5 µg/kg/min Nicotine pretreatment 0.20 mg/ml + ACS + Saline	Nicotine did not affect the rate of fracture repair in this model.
Ulnar osteotomy repair (Rabbit) Luppen et al., <i>JBMR</i> 2002	4 49 ^c /M	0.20 mg/ml + ACS + 0.35 mg/kg/d, 3x/wk prednisolone (8 week SAC) 0.20 mg/ml + ACS + Saline (8 week SAC) 0.20 mg/ml + ACS + 0.35 mg/kg/d, 3x/wk prednisolone (6 week SAC) 0.20 mg/ml + ACS + Saline (6 week SAC)	Prednisolone treatment inhibited fracture healing. Treatment with rhBMP-2/ACS overcame this inhibition and enhanced healing in both the control and prednisolone treated animals.

Table 16. rhBMP-2 Activity in the Presence of Bone Metabolism Affecting Agents			
Study Type (Species)	Groups No. Animals/ Sex	rhBMP-2 (mg/ml)	Relevant Findings
Subcutaneous Implant (Rat)	7 47 ^d /M	0.01 mg/ml + ACS + 5 mg/kg/d 0.10 mg/ml + ACS + 5 mg/kg/d 0.40 mg/ml + ACS + 5 mg/kg/d 0.00 mg/ml + ACS + 0.9% NaCl 0.01 mg/ml + ACS + 0.9% NaCl 0.10 mg/ml + ACS + 0.9% NaCl 0.40 mg/ml + ACS + 0.9% NaCl	Prednisolone treatment dramatically inhibited bone growth and body mass gain. Prednisolone treatment also inhibited ectopic bone formation; however, the rhBMP-2/ACS overcame this inhibition.
Nicotine-induced pseudarthrosis posterolateral fusion (Rabbit) Lawrence et al., <i>Spine</i> 2007	4 64/F	No graft (n=16) Autograft (n=17) 1.5 mg/ml/ACS (n=15) 2.0 mg/ml/CRM (n=16)	All animals underwent a primary posterolateral fusion with autograft and 10 to 70 ng/ml nicotine levels to simulate smoking. Revision surgeries were performed on the animals that did not fuse (68/72). The spines were evaluated by manual palpation, and 1/16 fused with no graft, 5/17 with autograft, 15/15 with rhBMP-2/ACS, and 16/16 with rhBMP-2/CRM (rhBMP-2 fusion significantly higher). The same trend was seen in histological determination of fusion.

^a Each group had 4 animals, except the 0.10 mg/ml + ACS + 4.5 µg/kg/min Nicotine and 0.10 mg/ml + ACS + 0.0 µg/kg/min Nicotine group. Each of these groups had 5 animals.

^b Each of the groups had 13 animals except the Nicotine pretreatment group, which had 12 animals.

^c Both prednisolone groups had 13 animals each, while the saline group sacrificed at 8 weeks had 11 animals and the group sacrificed at 6 weeks had 12 animals.

^d Each group had 5 animals except 0.01 mg/ml + ACS + 5 mg/kg/d and 0.40 mg/ml + ACS + 5 mg/kg/d group. Each of these groups had 6 animals. The 0.00 mg/ml + ACS + 0.9% NaCl had 15 animals.

Inappropriate Use of rhBMP-2

Improper use of rhBMP-2 has been investigated in nonclinical studies to determine its effects and risks. These studies demonstrate that over-concentrating, over-stuffing, or using excess rhBMP-2 in certain locations can cause transient resorption and/or edema. These studies were used to support the current language in the AMPLIFY™ rhBMP-2 Matrix label regarding inappropriate use:

Inappropriate use of the product, such as preparing it differently than prescribed, compressing the rhBMP-2/CRM implant more than necessary,

may change the concentration of the rhBMP-2, which may cause complications.

The studies are summarized in Table 17 below.

Table 17. Effect of Inappropriate rhBMP-2 Usage Studies			
Study Type (Species)	Groups No. Animals/ Sex	rhBMP-2 (mg/ml)	Relevant Findings
Ectopic Muscle Pouch (Rat)	4 48/M (6 per time point per group)	<u>Group 1 (0.3 cc):</u> Buffer/ACS 0.1 mg/ml/ACS 0.43 mg/ml/ACS 1.5 mg/ml/ACS <u>Group 2 (0.3 cc):</u> Buffer/CRM 0.1 mg/ml/CRM 0.43 mg/ml/CRM 1.5 mg/ml/CRM <u>Group 3 (0.3 cc):</u> Buffer/Putty 0.1 mg/ml/Putty 0.43 mg/ml/Putty 1.5 mg/ml/Putty <u>Group 4 (0.1 cc):</u> 0.1 mg/ml/ACS 1.5 mg/ml/ACS 0.1 mg/ml injection 1.5 mg/ml injection	Each of the animals received four implants, one of each of the treatments in the separate groups, in the right and left latissimi and right and left glutei muscles. There were no differences in edema volumes between the low dose rhBMP-2 and the buffer control for any of the carriers (Group 1-3) at either 2 or 7 days post-implant. For ACS and CRM, edema volumes for the mid- and high dose appeared to plateau. However, both had higher edema volumes than the buffer control at both 2 and 7 days post-implant. Collagen-ceramic Putty (Putty) experienced dose dependent edema volumes from the 1x to 15x concentrations and did not plateau between the mid- and high dose. The data from group 4 demonstrated that the injection of rhBMP-2 into a muscle produced minimal local edema compared to a similar volume of rhBMP-2 on the ACS carrier.
Femoral Cancellous Defect (Sheep) Toth et al., <i>Spine</i> 2009	5 20/F	0.43 mg/cc/ACS 0.86 mg/cc/ACS 1.5 mg/cc/ACS 3.0 mg/cc/ACS Buffer	This study demonstrated that, as the local concentration of rhBMP-2 was increased, either by increasing the solution concentration or overfilling the defect with rhBMP-2/ACS, the rate of osteoclastic activity increased. This increased osteoclastic activity caused transient peri-implant resorption in the overfilled or hyperconcentrated groups. The normal fill, normal concentration group still experienced osteoclastic activity, however, to a much lesser extent.

Nonclinical Conclusions

In summary, the safety (toxicology and pharmacokinetics) and bone-forming capacity (efficacy) of the AMPLIFY™ rhBMP-2 Matrix have been extensively investigated and characterized. The nonclinical safety of systemically delivered rhBMP-2 and locally delivered rhBMP-2 has been thoroughly studied, and no toxicities have been identified in these studies. The disposition of rhBMP-2 and rhBMP-2/CRM is characterized by slow release of rhBMP-2 from the carrier and rapid systemic clearance. This profile results in minimal systemic exposure to rhBMP-2. Application of rhBMP-2 leads to the induction of normal bone locally at the site of implantation. This process includes the migration of mesenchymal cells into the site and the apparent differentiation into bone-forming cells. The bone induced by rhBMP-2 remodels and assumes the structure appropriate to its location and function, as would be expected from host bone.

No evidence of any neurological abnormalities was found in studies performed to evaluate the safety of rhBMP-2 in the vicinity of the spinal cord and nerve roots. In addition, there was no evidence, based on blood and cerebrospinal fluid analyses, of any clinical abnormalities in the animals tested. There was also no radiographic or histologic evidence of mineralization within the thecal sac.

In studies comparing fusion in the presence of rhBMP-2/CRM vs. autograft bone, the histological fusion rate was greater for the rhBMP-2/CRM treated animals than for animals receiving autograft bone. In a study comparing rhBMP-2/CRM to CRM alone, all animals treated with rhBMP-2/CRM had solid interbody fusions while none of the animals receiving CRM alone were fused. In addition, animals receiving the higher dose of rhBMP-2 had qualitatively denser bone compared to those in the lower dose group.

AMPLIFY™ rhBMP-2 Matrix (rhBMP-2/CRM) demonstrated effectiveness in promoting posterolateral spinal fusion in multiple nonclinical study models and was statistically higher than autograft in both relative strength and stiffness.

X. SUMMARY OF CLINICAL STUDIES

Study Background

Clinical data to support the safety and effectiveness of AMPLIFY™ rhBMP-2 Matrix were collected as part of a prospective, multi-center randomized study. Patients were randomized to the investigational or control grouping in a 1:1 manner. The investigational group was implanted with AMPLIFY™ rhBMP-2 Matrix and the CD HORIZON® Spinal System while the control group was implanted with iliac crest autograft bone and the CD HORIZON® Spinal System. In both cases, subjects received the device via a posterolateral surgical approach.

Neither the investigators nor the subjects were blinded to the treatment. Subject blinding was not possible due to the second surgical site required to collect the iliac crest grafts. The potential for investigator bias in the clinical outcome

parameters was reduced by having the subjects rate their outcome using objective self-assessments. The radiographic outcome measurements were performed by independent radiologists who were blinded to treatment. These were the only radiographic evaluations used for determining radiographic success.

Overall, the clinical trial enrolled a total of 463 patients (239 investigational; 224 control) at 29 study sites, with all centers following a common Clinical Investigational Plan (CIP).

Inclusion and Exclusion Criteria

Subjects were enrolled in this study according to the following inclusion/exclusion criteria.

Inclusion Criteria

- Degenerative disc disease (DDD), defined as back pain of discogenic origin, with or without leg pain, with degeneration of the disc confirmed by patient history and radiographic studies. DDD was determined to be present if one or more of the following were noted:
 - instability (defined as angulation $\geq 5^\circ$ and/or translation ≥ 4 mm, based on flexion/extension radiographs);
 - osteophyte formation;
 - decreased disc height;
 - thickening of ligamentous tissue;
 - disc degeneration or herniation; and/or
 - facet joint degeneration.
- Preoperative Oswestry score ≥ 30 .
- No greater than Grade 1 spondylolisthesis utilizing Meyerding's Classification.
- Requires fusion of a single level disc space from L1 to S1.
- At least 18 years of age, inclusive, at the time of surgery.
- Had not responded to non-operative treatment (e.g., bed rest, physical therapy, medications, spinal injections, manipulation, and/or TENS) for a period of six months.
- If of child-bearing potential, non-pregnant, non-nursing, and agreed to use adequate contraception for one year following surgery.
- Willing and able to comply with the study plan and signed the informed consent form.

Exclusion Criteria

- Primary diagnosis of a spinal disorder other than degenerative disc disease with Grade 1 or less spondylolisthesis at the involved level.
- Previous spinal fusion surgical procedure at the involved level.
- Required spinal fusion at more than one lumbar level.
- A condition which requires postoperative medications that interfered with fusion, such as steroids or prolonged use of nonsteroidal anti-inflammatory drugs excluding routine peri-operative nonsteroidal anti-inflammatory drugs. This did not include low-dose aspirin for prophylactic anticoagulation.

- Been previously diagnosed with osteopenia or osteomalacia.
- Conditions that might have been associated with diagnosis of osteoporosis including:
 - 1) postmenopausal non-black female over 60 years of age and weighed less than 140 pounds.
 - 2) postmenopausal female that had sustained a nontraumatic hip, spine, or wrist fracture.
 - 3) male over the age of 70.
 - 4) male over the age of 60 that had sustained a non-traumatic hip or spine fracture.

If the level of Bone Mineral Density (BMD) is a T score of < -3.5 (i.e. -3.6, -3.7, etc.) or a T score of < -2.5 (i.e. -2.6, -2.7, etc.) with vertebral crush fracture, then the patient was excluded from the study.

- Presence of active malignancy or prior history of malignancy (except for basal cell carcinoma of the skin).
- Overt or active bacterial infection, either local or systemic.
- Documented titanium alloy allergy or intolerance.
- Mentally incompetent.
- 'Waddell Signs of Inorganic Behavior' score of 3 or greater.
- Prisoner.
- Alcohol and/or drug abuser as defined by currently undergoing treatment for alcohol and/or drug abuse.
- Received drugs which may interfere with bone metabolism within two weeks prior to the planned date of spinal fusion surgery (e.g., steroids or methotrexate).
- History of autoimmune disease (e.g. Systemic Lupus Erythematosus or dermatomyositis).
- History of exposure to injectable collagen or silicone implants.
- History of hypersensitivity to protein pharmaceuticals (monoclonal antibodies or gamma globulins) or collagen.
- Received treatment with an investigational therapy within 28 days prior to implantation surgery or such treatment was planned during the 16 weeks following rhBMP-2/CRM implantation.
- Received any previous exposure to any/all BMPs of either human or animal extraction.
- History of allergy to bovine products or a history of anaphylaxis.
- History of endocrine or metabolic disorder known to affect osteogenesis.
- Unwilling or unable to cooperate or give written informed consent.

Postoperative Care

The recommended postoperative regimen included the use of an external orthosis (i.e., corset or brace) for ambulation for approximately 6 weeks following surgery; an abdominal strengthening program starting at 30 days postoperative; and avoidance of repetitive bending, stooping, lifting, or athletic activities until

fusion occurred or until it was determined that fusion would not occur. Patients were also advised to avoid prolonged use of nonsteroidal anti-inflammatory and steroidal drugs (low-dose aspirin for prophylactic anticoagulation was acceptable), as well as electrical bone growth stimulation for treatment of the lumbar spine during the 24 month follow-up period. Patients who smoked were also encouraged to discontinue smoking.

Assessments

Patients were evaluated preoperatively (within 6 months of surgery), intraoperatively, and postoperatively at 6 weeks (± 2 weeks), 3 months (± 2 weeks), 6 months (± 1 month), 12 months (± 1 month), and 24 months (± 2 months). Patients were also followed annually after 24 months until every patient in the clinical trial reached 24 months following surgery. In anticipation of a potential post-approval study, patients were also evaluated for long-term follow-up at 36 and 60 months postoperative. To date, all available patients have been evaluated at 60 months postoperative.

Complications and adverse events, device-related or not, were evaluated over the entire course of the clinical trial. At each evaluation time point, primary and secondary clinical and radiographic effectiveness parameters were measured. These are described in further detail in the following section. Success was determined from data collected during the initial 24 months of follow-up, with evaluations at 24 months postoperative serving as the primary endpoint of the study. Antibodies to rhBMP-2 and bovine Type I collagen were also assessed prior to surgery and after surgery at 6 weeks and at 3, 6, and 12 months. Antibodies to human Type I collagen were assessed if the antibody response to bovine Type I collagen was positive.

Outcomes Assessed and Success Criteria

Primary Study Assessments

The primary radiographic and clinical parameters assessed in this study were fusion at the involved level, pain and function (Oswestry), and neurological status.

- Fusion was assessed at 6, 12, and 24 months after surgery using plain radiographs (AP, lateral, and flexion/extension x-rays) and high resolution thin-slice CT scans. Fusion was defined as evidence of bridging trabecular bone (based on a continuous bony connection from the superior transverse process to the inferior transverse process on both sides); no evidence of motion (≤ 3 mm of translation and $< 5^\circ$ of angulation between flexion and extension as seen on lateral flexion/extension radiographs); and the absence of cracking, as evidenced by radiolucent lines completely through the fusion mass. All assessments were made from plain films except for the assessment of bridging bone, which was made using CT scans only if bridging bone could not be visualized on the plain radiograph.

- Pain and functional ability were measured using the Oswestry Low Back Pain Disability Questionnaire. Success was defined as a 15-point improvement in the Oswestry score from the preoperative baseline score.
- Neurological status consisted of measurements of four parameters – motor, sensory, reflexes, and straight leg raise (SLR). An algorithm was developed to transform the detailed scores for each parameter into an overall classification representing neurological status at a given time point. After determining the percentage scores, the postoperative subsection scores were then compared to the preoperative scores, and a successful outcome was declared if the difference in the postoperative and preoperative scores was greater than or equal to zero. Success in each individual parameter was required for a subject to be counted as a neurological success.

Secondary Study Assessments

The secondary clinical outcome measures assessed in this study were back pain, leg pain, general health status (SF-36), and donor site pain (control subjects only).

- Back pain was judged using a numerical rating scale. Both back pain intensity and duration were assessed on a scale from 0 to 10 and then added together to create a composite score, ranging from 0 to 20. A lower score represented a better condition. Back pain success was determined by comparing the postoperative composite back score to the preoperative score on a per subject basis.
- Leg pain was also measured using a numerical rating scale. Both leg pain intensity and duration were assessed on a scale from 0 to 10 and then added together to create a composite score, ranging from 0 to 20. A lower score represented a better condition. Leg pain success was determined by comparing the postoperative composite leg score to the preoperative score on a per subject basis.
- General health was assessed using with the Medical Outcomes Study 36-Item Short Form Health Survey (SF-36). This self-administered questionnaire consists of eight subscales that are summarized into two measures, i.e. the physical health summary (PCS) and the mental health summary (MCS). Success was defined as the proportion of subjects who demonstrated maintenance or improvement in the SF-36 subscores.
- Graft site (hip) pain was also recorded for control patients, who had bone graft harvested from the iliac crest for use with the control device. (Investigational patients did not undergo a bone harvest procedure and, therefore, did not experience graft site pain.) As with back and leg pain, graft site pain was rated on a numerical scale. Both graft site pain intensity and duration were assessed on a scale from 0 to 10 and then added together to create a composite score, ranging from 0 to 20. A lower score represented a better condition.

Primary Study Endpoint

The primary endpoint was determined at 24 months postoperative as a composite of the study's primary safety and effectiveness parameters. This endpoint, termed overall success, includes the following:

1. Demonstrated radiographic fusion;
2. A successful Oswestry outcome (at least 15 points from the baseline Oswestry score);
3. Neurological status maintenance or improvement;
4. No serious implant-associated or implant/surgical procedure-associated adverse event, and
5. No second surgery classified as a "failure."

Statistical Analysis Plan

The study was designed as a non-inferiority trial with a margin of 10%. Bayesian methods with non-informative, or uniform, priors were used to obtain the posterior probabilities of non-inferiority and superiority.

The study hypothesis was that the 24-month success rate of the AMPLIFY™ rhBMP-2 Matrix group would not be lower than that of the control group by more than 10%. The primary endpoint would be deemed successful (i.e., the AMPLIFY™ rhBMP-2 Matrix was non-inferior to the control) if the posterior probability was greater than 95% that the success rate of the investigational group was not lower than control group by more than 10%. If non-inferiority was demonstrated, analyses were also defined in the statistical plan to determine whether the investigational group had statistically superior outcomes as compared to the control group. No interim analyses were performed during the course of the study.

Data Analyses and Results

The results of the clinical study were evaluated using Bayesian statistical methods. The study was designed to use Bayesian methods with non-informative, or uniform, priors.

Study Results

Patient Demographics and Preoperative Data

The study involved a total of 463 patients (239 investigational and 224 control) enrolled at 29 study sites. Demographic data for these subjects are presented in Table 18.

Table 18. Subject Demographics		
	Investigational (n=239)	Control (n=224)
Age in years (range)	53.2 (20-81)	52.3 (18-86)
Weight (lbs)	187.2	188.5
Sex (Men/Women)	108/131	95/129
Race (% White)	91.2%	90.6%
Worker's Compensation Case (%)	27 (11.3)	28 (12.5)
Tobacco Used (%)	63 (26.4)	59 (26.3)
Previous Back Surgery (%)	73 (30.5)	62 (27.7)

There were no statistically significant differences between the two treatments in terms of the parameters presented in Table 18.

Surgical and Hospitalization Results

Surgical and hospitalization data for the two groups are shown in Table 19.

Table 19. Surgical and Hospitalization Information		
	Investigational (n=239)	Control (n=224)
Mean Operative Time (hrs)	2.5	2.9
Mean EBL (mL)	343.1	448.6
Hospital Stay (days)	4.1	4.0
Spinal Level Treated		
L1-L2	0	0
L2-L3	7	3
L3-L4	26	20
L4-L5	121	122
L5-S1	83	77
L5-L6	2	2

Patients in the investigational group were found to have shorter operative times (2.5 vs. 2.9 hours, respectively) and less blood loss (343.1 ml vs. 448.6 ml) than the control group patients, with a probability of superiority value of essentially 100.0% in both cases. The mean hospital stay of patients in both treatment groups was approximately four days. No statistical difference for this parameter was demonstrated between the two treatment groups in the analysis.

Results of Primary Effectiveness Analysis

The results for patients receiving AMPLIFY™ rhBMP-2 Matrix were statistically non-inferior to the control group results for all effectiveness parameters at 24 months postoperative. The overall success rate for the investigational group was slightly higher than the control group at 24 months following surgery (60.5% vs. 55.5%, respectively). The investigational overall success rate was found to be

statistically non-inferior to the control group rate, thereby meeting the primary study objective.

The primary effectiveness endpoints for this clinical trial were fusion and pain/disability (Oswestry) improvement. The fusion rate at 24 months for the investigational group was over 6 percentage points higher than the control group (95.9% vs. 89.3%, respectively). The pain/disability (Oswestry) mean improvement from preoperative for the investigational group at 24 months was 26.7 points, versus 25.5 points for the control group. Statistical analyses yielded a posterior probability of non-inferiority to the control at 24 months of essentially 100% for fusion and 99.0% for pain/disability.

Safety and Immune Response Evaluation

The neurological status of study subjects was assessed preoperatively and postoperatively using a neurological status scale. Neurological status success was defined as maintenance or improvement of the preoperative baseline score for each parameter. At 24 months following surgery, the overall success rate of neurological status for the investigational group was 87.0%, as compared to 84.2% for the control group. Statistical analyses at 24 months postoperative yielded a posterior probability of non-inferiority of the investigational group to the control group of essentially 100%. These results indicated that the overall neurological success rate for the investigational group was non-inferior to that for the control group.

A table showing the adverse event distribution over the course of the study is provided in Section VIII. The adverse event rates in the investigational group were comparable to those of the control treatment group. There were two adverse event categories (graft site related and non-union) in which a statistical difference was noted favoring the investigational group. For graft site related adverse events, the statistical analysis showed a posterior probability of superiority of essentially 100%. This is considered a very positive result since one of the benefits of using AMPLIFY™ rhBMP-2 Matrix is that it eliminates the need for harvesting of bone graft and, in this case, reduces or eradicates a number of related adverse events. For the category of non-union events, the posterior probability of superiority was found to be 99.6% in favor of the investigational group. In addition to comparable adverse event rates, no statistical differences were found between treatment groups for any of the second surgery categories, except that the investigational group had statistically fewer removals than the control group.

In the investigational group, a total of nine cancer events occurred in nine patients (3.8%) through 24 months postoperative. A total of two cancer events occurred in two control patients (0.9%) through 24 months. In addition, there were seven deaths in the clinical trial through 24 months postoperative – three in the investigational group and four in the control group. None of these events were considered related to the study procedure.

The presence of antibodies to rhBMP-2 and bovine collagen was assessed in both treatment groups preoperatively and at 6 weeks, 3, 6 and 12 months postoperatively using ELISA. Both Protein G and IgAGM conjugates were used in parallel to detect BMP-2 antibodies. If there was a positive response to bovine Type I collagen, the serum was also tested for antibodies to human Type I collagen. The screening ELISA cutpoint for positive antibody responses was set to 5 times the standard deviation of sera from normal human donors. Subjects were considered to have an elevated immune response if the preoperative test was negative (titer < 50) and postoperative test was positive (titer \geq 50) or if the preoperative test was positive and the postoperative test was at least three times higher (Protein G) or two times higher (IgAGM) than the baseline titer.

The rates of authentic antibody responses to rhBMP-2 and bovine collagen were compared between the two treatment groups. Using an IgAGM ELISA, the authentic antibody response rate to rhBMP-2 was determined to be 6.4% in the investigational group and 2.3% in the control group. A neutralizing antibody assay was run on samples from patients with positive antibodies to rhBMP-2. There were no neutralizing antibodies detected. The antibody response to bovine type I collagen was 16.7% in the investigational group and 21.2% in the control group. Patients who had positive antibody responses to bovine collagen were not found to have positive antibody responses to human Type I collagen.

XI. CONCLUSIONS DRAWN FROM THE STUDIES

Through both extensive nonclinical and clinical testing, the AMPLIFY™ rhBMP-2 Matrix has been demonstrated to be safe and effective in the surgical treatment of symptomatic degenerative disc disease of the lumbar spine.

AMPLIFY™ rhBMP-2 Matrix has been fully tested for the unique characteristics related to the proposed indication under this PMA. This PMA application includes a combination of previously submitted testing and testing conducted specifically to assess the AMPLIFY™ rhBMP-2 Matrix for the proposed indication of posterolateral fusion.

All nonclinical and clinical testing support the conclusion that the AMPLIFY™ rhBMP-2 Matrix is safe and effective for its intended use. In addition, the testing demonstrates the AMPLIFY™ rhBMP-2 Matrix provides an alternative to the use of autogenous bone graft for posterolateral spinal fusion and is at least as safe and effective as autograft without the morbidity associated with harvesting bone from the iliac crest.



AMPLIFY™ rhBMP-2 MATRIX

Instructions for
Preparation: 40 mg Kit

Draft





AMPLIFY™ rhBMP-2 MATRIX

Instructions for Preparation: 40 mg Kit

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Introduction

A posterolateral fusion environment presents a challenging healing environment to spine surgeons.¹ The goal of the procedure is to stabilize two adjoining vertebrae by inducing bone to form across a space between two transverse processes — a location where bone previously never existed. The spinal anatomy involved in this type of procedure lacks some of the elements that support the bone generation process (i.e., limited bony surface area, etc.).²

AMPLIFY™ rhBMP-2 MATRIX was designed to overcome the challenges of posterolateral fusion procedures. It combines the osteoinductive properties of rhBMP-2 with a new compression resistant matrix (CRM) carrier. The compression resistant carrier maintains adequate space and provides additional scaffolding for rhBMP-2 to induce new bone formation and generate a successful arthrodesis.

The following instructions describe the preparation and implantation of AMPLIFY™ rhBMP-2 MATRIX. AMPLIFY™ rhBMP-2 MATRIX is used in conjunction with a Medtronic metallic posterior supplemental fixation device. For instructions on implanting the posterior supplemental fixation device, see the surgical technique for the specific device.

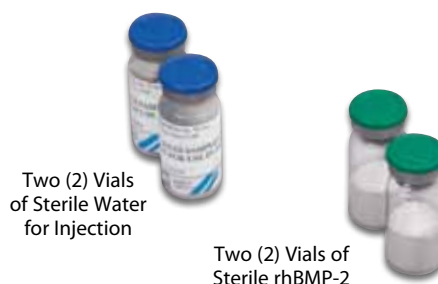


**AMPLIFY™ rhBMP-2 MATRIX with a
Medtronic metallic posterior supplemental fixation device**

40 mg Kit Contents

The AMPLIFY™ rhBMP-2 MATRIX 40 mg kit is designed specifically for use with a Medtronic metallic posterior supplemental fixation device to treat patients requiring a single-level posterolateral fusion. A single-level posterolateral fusion procedure requires one (1) 40 mg AMPLIFY™ rhBMP-2 MATRIX kit. One (1) 40 mg kit contains the following:

- » Two (2) Vials of Sterile rhBMP-2 (20 mg each)
- » Two (2) Packages of Two (2) Sterile 5 cc Compression Resistant Matrices (CRM)
4.67 cm L × 0.95 cm W × 1.13 cm H (each)
- » Two (2) Vials of Sterile Water for Injection (10 mL each)
- » Two (2) Sterile 10 mL Syringes with 20G 1½" Needles
- » Four (4) Sterile 3 mL Syringes with 20G 1½" Needles



**Contents of one (1) 40 mg
AMPLIFY™ rhBMP-2 MATRIX Kit**

1. Boden SD, Schimandle JH, Hutton WC, Chen MI. 1995 Volvo Award in Basic Sciences. The use of an osteoinductive growth factor for lumbar spinal fusion. Part I: The biology of spinal fusion. *Spine* 1995;20:2626-32.

2. Boden SD. The biology of posterolateral lumbar spinal fusion. *Orthop Clin North Am* 1998;29:603-19.

Instructions for Preparation: 40 mg Kit

The following instructions for preparation are for a 40 mg AMPLIFY™ rhBMP-2 MATRIX kit. A single-level posterolateral fusion procedure requires one (1) 40 mg AMPLIFY™ rhBMP-2 MATRIX kit.

Note: You will need to prepare a sterile and non-sterile field before beginning product preparation.

Total preparation time: Allow at least 15 minutes for preparation and an additional 5 minutes for protein to bind to the compression resistant matrices (CRM).

IN NON-STERILE FIELD

Step 1



Observing proper sterile technique, open both outer carrier packages. Place both inner carrier packages, each containing two 5 cc matrices, into the sterile field.

Open and place all four 3 mL syringes/needles into the sterile field. Both 10 mL syringes/needles should remain in the non-sterile field.

Step 2



Using one of the two 10 mL syringes/needles in the non-sterile field, withdraw 5.4 mL from one of the two vials of sterile water for injection.

Instructions for Preparation: 40 mg Kit

IN NON-STERILE FIELD

Step 3



SLOWLY reconstitute one of the two rhBMP-2 vials with 5.4 mL of sterile water. Inspect the solution. If dark particles are observed, do not use and return to sponsor. Discard used syringe/needle.

Step 4



GENTLY swirl (do not shake) the rhBMP -2 vial to ensure adequate mixing.

IN STERILE FIELD

Step 5



Using the second 10 mL syringe/needle in the non-sterile field, repeat steps 2 through 4 with the remaining vial of sterile water and vial of rhBMP-2.

Step 6

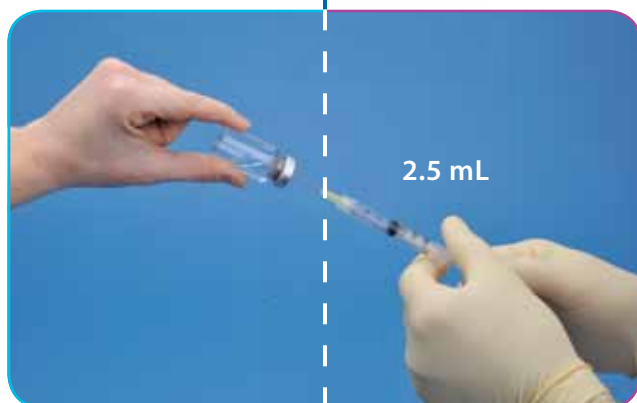


Open both inner carrier packages, leaving the four 5 cc matrices in the plastic trays.

Instructions for Preparation: 40 mg Kit

IN NON-STERILE FIELD

Step 7



Using one of the four 3 mL syringes/needles in the sterile field, the person in the sterile field withdraws 2.5 mL of reconstituted rhBMP-2 from the vial held by the person in the non-sterile field.

IN STERILE FIELD

Step 8



UNIFORMLY distribute 2.5 mL of reconstituted rhBMP-2 on one of the four 5 cc matrices. Inspect the sponge. If dark particles are observed, do not use and return to sponsor. Discard used syringe/needle.

IN STERILE FIELD

Step 9



Using a second 3 mL syringe/needle in the sterile field, repeat steps 7 and 8 for the second 5 cc matrix.

Step 10



Repeat steps 7 through 9 for the second vial of rhBMP-2 and remaining package of 5 cc matrices.

⌚ Before proceeding, allow wetted matrices to stand for a minimum of 5 minutes. Use within 2 hours.

Instructions for Preparation: 40 mg Kit

IN STERILE FIELD

Step 11



Decorticate both transverse processes on one side of the spine and carefully place one 5 cc matrix across the transverse processes. The matrix should be in direct contact with the decorticated surfaces of both transverse processes.

Step 12



A second 5 cc matrix should be placed lateral to the previously implanted graft material. Both matrices should be implanted on the same side of the spine and at the same motion segment.

Step 13



Identical implantation methods are required for implanting the remaining 5 cc matrices on the contralateral side of the motion segment.

✓ Note

- » The order of placement of the Medtronic metallic posterior supplemental fixation device relative to the AMPLIFY™ rhBMP-2 MATRIX is at the discretion of the surgeon (i.e., screws and/or rods may be placed before or after insertion of AMPLIFY™ rhBMP-2 MATRIX).
- » If a surgical drain is required, place the drain remotely from the implantation site or subcutaneously to the implantation site.



DO NOT irrigate or use suction in proximity to the implanted AMPLIFY™ rhBMP-2 MATRIX Device. During handling, avoid excess squeezing of the wetted CRM carrier.

Notes

Notes

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The surgical technique shown is for illustrative purposes only. The technique(s) actually employed in each case will always depend upon the medical judgment of the surgeon exercised before and during surgery as to the best mode of treatment for each patient.

Please see the package insert for the complete list of indications, warnings, precautions, and other important medical information.



AMPLIFY™ rhBMP-2 Matrix with Posterior Supplemental Fixation



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IMPORTANT INFORMATION ON AMPLIFY™ rhBMP-2 Matrix



For US Audiences Only

CAUTION: FEDERAL (USA) LAW RESTRICTS THIS DEVICE TO SALE BY OR ON THE ORDER OF A PHYSICIAN WITH APPROPRIATE TRAINING.

PURPOSE

The following contains important medical information on the use of AMPLIFY™ rhBMP-2 Matrix.

DESCRIPTION

AMPLIFY™ rhBMP-2 Matrix consists of two components: recombinant human Bone Morphogenetic Protein-2 (rhBMP-2) and a Compression Resistant Matrix (CRM) carrier. The reconstituted rhBMP-2 is applied to the CRM. The CRM is then surgically implanted bilaterally across two adjacent transverse processes. Throughout the healing process, the CRM is resorbed by the body and replaced by newly-formed bone. **These components must be used as a system for the prescribed indication described below. The bone morphogenetic protein solution component must not be used without the carrier/scaffold component or with a carrier/scaffold component different from the one described in this document. The AMPLIFY™ rhBMP-2 Matrix device must be used with a commercially available metallic posterior supplemental fixation device.**

AMPLIFY™ rhBMP-2 Matrix

AMPLIFY™ rhBMP-2 Matrix consists of recombinant human Bone Morphogenetic Protein-2 (rhBMP-2, known as diboterminal alfa) placed on a compression resistant matrix (CRM) carrier. AMPLIFY™ rhBMP-2 Matrix induces new bone formation at the site of implantation. Based on data from non-clinical studies, the bone formation process develops from the outside of the implant toward the center until the entire AMPLIFY™ rhBMP-2 Matrix device is replaced by trabecular bone.

rhBMP-2 is the active agent in AMPLIFY™ rhBMP-2 Matrix. rhBMP-2 is a disulfide-linked dimeric protein molecule with two major subunit species of 114 and 131 amino acids. Each subunit is glycosylated at one site with high-mannose-type glycans. rhBMP-2 is produced by a genetically engineered Chinese hamster ovary (CHO) cell line and subsequently highly purified using a 3-step chromatography process.

rhBMP-2 and excipients are lyophilized. Upon reconstitution, each milliliter of rhBMP-2 solution contains: 4.0 mg of rhBMP-2; 5.0 mg sucrose, NF; 25 mg glycine, USP; 0.74 mg L-glutamic acid, FCC; 0.29 mg sodium chloride, USP; 0.1 mg polysorbate 80, NF; and 1.0 mL of sterile water, USP. The reconstituted rhBMP-2 solution has a pH of 4.5, is clear and colorless to slightly yellow, and is essentially free from plainly visible particulate matter.

The CRM is a white, compression-resistant, absorbent, implantable matrix for use with rhBMP-2. The CRM consists of absorbable bovine type I collagen obtained from the deep flexor (Achilles) tendon with resorbable biphasic calcium phosphate granules embedded into the collagen scaffold. The resorbable biphasic calcium phosphate consists of 15% hydroxyapatite and 85% β -tricalcium phosphate (HA/TCP). The CRM acts as a carrier for the rhBMP-2 and a scaffold for new bone formation.

AMPLIFY™ rhBMP-2 Matrix is provided in a 40 mg (20 cc) kit. One 40 mg (20 cc) kit is required per procedure. The table below lists information about this kit.

40mg (20cc) AMPLIFY™ rhBMP-2 Matrix Kit		
Part #	Kit Name (size in cc)	Reconstituted rhBMP-2 Delivered on CRM
862XXXX	40 mg (20 cc) Kit	40 mg

Each kit contains all the components necessary to prepare AMPLIFY™ rhBMP-2 Matrix for implantation: rhBMP-2, which must be reconstituted; sterile water; compression resistant matrix; syringes with needles; package insert; and Instructions for Preparation.

The rhBMP-2 is provided as a lyophilized powder in a vial delivering 20 mg of protein. After appropriate reconstitution, the concentration of rhBMP-2 is 4.0 mg/ml. The solution is then applied to the provided compression resistant matrix component(s). The concentration of rhBMP-2 on the CRM is 2.0 mg/cc. AMPLIFY™ rhBMP-2 Matrix is prepared at the time of surgery and allowed to stand a prescribed amount of time (no less than 5 minutes) before placement across the transverse processes. The Instructions for Preparation contain complete details on preparation of AMPLIFY™ rhBMP-2 Matrix.

No warranties, expressed or implied, are made. Implied warranties of merchantability and fitness for a particular purpose or use are specifically excluded.

Posterior Supplemental Fixation Component

AMPLIFY™ rhBMP-2 Matrix is indicated for use with a metallic posterior supplemental fixation device. Any commercially available metallic posterior fixation device that is indicated for non-cervical posterior pedicle fixation for degenerative disc disease may be utilized with AMPLIFY™ rhBMP-2 Matrix. Its purpose is to provide temporary stabilization of the spine in order to facilitate fusion.

INDICATIONS

AMPLIFY™ rhBMP-2 Matrix is indicated as an alternative to autogenous bone graft for spinal fusion procedures in skeletally mature patients with degenerative disc disease (DDD) at one level from L₁-S₁. DDD is defined as discogenic back pain with degeneration of the disc confirmed by patient history and radiographic studies. DDD patients may also have up to Grade 1 spondylolisthesis or retrolisthesis at the involved level. Patients receiving AMPLIFY™ rhBMP-2 Matrix should have had at least 6 months of nonoperative treatment prior to implantation of AMPLIFY™ rhBMP-2 Matrix. AMPLIFY™ rhBMP-2 Matrix is to be implanted via a posterolateral approach and must be used in conjunction with a metallic posterior supplemental fixation device that is indicated for temporary stabilization of the spine.

CONTRAINDICATIONS

- AMPLIFY™ rhBMP-2 Matrix is contraindicated for patients with a known hypersensitivity to recombinant human Bone Morphogenetic Protein-2, bovine Type I collagen, or other components of the formulation.
- AMPLIFY™ rhBMP-2 Matrix should not be used in the vicinity of a resected or extant tumor, in patients with any active malignancy, or in patients undergoing treatment for a malignancy.
- AMPLIFY™ rhBMP-2 Matrix should not be used in patients who are skeletally immature (<18 years of age or no radiographic evidence of epiphyseal closure).
- AMPLIFY™ rhBMP-2 Matrix should not be used in pregnant women. The potential effects of rhBMP-2 on the human fetus have not been evaluated.
- AMPLIFY™ rhBMP-2 Matrix should not be implanted in patients with an active infection at the operative site or with an allergy to one of the metals used in the posterior supplemental fixation device (such as titanium, stainless steel, or cobalt-chromium alloy).

WARNING(S)

- In an experimental rabbit study, rhBMP-2 has been shown to elicit antibodies that are capable of crossing the placenta. Reduced ossification of the frontal and parietal bones of the skull was noted infrequently (<3%) in fetuses of rabbit dams immunized to rhBMP-2; however, there was no effect noted in limb bud development. There are no adequate and well-controlled studies in human pregnant women. Women of child bearing potential should be warned by their surgeon of potential risk to a fetus and informed of other possible orthopedic treatments.
 - Women of childbearing potential should be advised that antibody formation to rhBMP-2 or its influence on fetal development has not been completely assessed. In the clinical trial supporting the safety and effectiveness of AMPLIFY™ rhBMP-2 Matrix, 15/234 (6.4%) patients treated with AMPLIFY™ rhBMP-2 Matrix and 5/217 (2.3%) patients treated with autograft bone developed antibodies to rhBMP-2, based on an anti-human immunoglobulin antibody-based ELISA. The effect of maternal antibodies to rhBMP-2, as might be present for several months following device implantation, on the unborn fetus is unknown. Additionally, it is unknown whether fetal expression of BMP-2 could re-expose mothers who were previously antibody positive. Theoretically, re-exposure may elicit a more powerful immune response to BMP-2 with possible adverse consequences for the fetus. However, pregnancy did not lead to an increase in antibodies in the rabbit study. Studies in genetically altered mice indicate that BMP-2 is critical to fetal development and that a lack of BMP-2 activity may cause neonatal death or birth defects. It is not known if anti-BMP-2 antibodies may affect fetal development or the extent to which these antibodies may reduce BMP-2 activity.
 - AMPLIFY™ rhBMP-2 Matrix should not be used immediately prior to or during pregnancy. Women of childbearing potential should be advised not to become pregnant for one year following treatment with AMPLIFY™ rhBMP-2 Matrix.
 - The safety and effectiveness of AMPLIFY™ rhBMP-2 Matrix in nursing mothers has not been established. It is not known if BMP-2 is excreted in human milk.
-
- The safety and effectiveness of the use of AMPLIFY™ rhBMP-2 Matrix with other spinal implants, implanted at locations other than the lower lumbar spine, or used in surgical techniques other than a posterolateral technique have not been established.
 - Inappropriate use of the product, such as preparing it differently than prescribed or compressing the rhBMP-2/CRM construct more than necessary, may change the concentration of the rhBMP-2, which may cause complications.

PRECAUTION(S)

General

- The safety and effectiveness of repeat applications of AMPLIFY™ rhBMP-2 Matrix have not been established.
- AMPLIFY™ rhBMP-2 Matrix should only be used by surgeons who are experienced in spinal fusion procedures and have undergone adequate training with this device for posterolateral procedures.
- Posterior supplemental fixation (i.e., a metallic posterior supplemental fixation device) should be implanted on each side of the surgical level whenever possible.
- The posterior supplemental fixation components and instruments must be sterilized prior to use according to the sterilization instructions provided in the package insert for those components, unless supplied sterile and clearly labeled as such.
- AMPLIFY™ rhBMP-2 Matrix is intended for single use only. Discard unused product and use a different device for subsequent applications.
- Prior to use, inspect the packaging, vials, and stoppers for visible damage. If damage is visible, do not use the product. Retain the packaging and vials, and contact a Medtronic representative.
- Do not use after the printed expiration date on the label.

Hepatic and Renal Impairment

- The safety and effectiveness of AMPLIFY™ rhBMP-2 Matrix in patients with hepatic or renal impairment have not been established. Pharmacokinetic studies of rhBMP-2 indicate that the renal and hepatic systems are involved with its clearance.

Bone Formation

- The safety and effectiveness of AMPLIFY™ rhBMP-2 Matrix have not been demonstrated in patients with metabolic bone diseases.
- While not specifically evaluated in the clinical study, the potential for ectopic, heterotopic, or undesirable exuberant bone formation exists.

Antibody Formation/Allergic Reactions

- The safety and effectiveness of AMPLIFY™ rhBMP-2 Matrix have not been demonstrated in patients with autoimmune disease.
- The safety and effectiveness of AMPLIFY™ rhBMP-2 Matrix have not been demonstrated in patients with immunosuppressive disease or suppressed immune systems resulting from radiation therapy, chemotherapy, steroid therapy, or other treatments.

Immunogenicity

- As with all therapeutic proteins, there is a potential for immune responses to be generated to AMPLIFY™ rhBMP-2 Matrix. The immune response to AMPLIFY™ rhBMP-2 Matrix was evaluated in 234 investigational patients and 217 control patients receiving posterolateral lumbar fusions.
 - *Anti-rhBMP-2 antibodies:* 15/234 (6.4%) patients receiving AMPLIFY™ rhBMP-2 Matrix developed antibodies vs. 5/217 (2.3%) in the control group. No positive neutralizing antibodies were detected in patients with positive antibodies to rhBMP-2.
 - *Anti-bovine Type I collagen antibodies:* 16.7% (39/234) of patients receiving AMPLIFY™ rhBMP-2 Matrix developed antibodies to bovine Type I collagen vs. 21.2% (46/217) of control patients. No patients in either group developed anti-human Type I collagen antibodies.
- The incidence of antibody detection is highly dependent on the sensitivity and specificity of the assay. Additionally, the incidence of antibody detection may be influenced by several factors, including sample handling, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to AMPLIFY™ rhBMP-2 Matrix with the incidence of antibodies to other products may be misleading.

Patient samples that tested positive to anti-rhBMP-2 were also tested for their neutralizing activity. No patient samples demonstrated neutralizing activities.

PHYSICIAN NOTE: Although the physician is the learned intermediary between the company and the patient, the important medical information given in this document should be conveyed to the patient.

ADVERSE EVENTS

AMPLIFY™ rhBMP-2 Matrix with posterior supplemental fixation was implanted in 239 investigational patients and compared to 224 control patients who received posterior supplemental fixation with iliac crest autograft. Both the investigational and control patients were treated using a posterolateral surgical approach.

Adverse event rates presented are based on the number of patients having at least one occurrence for a particular adverse event divided by the total number of patients in that treatment group.

The active ingredient in AMPLIFY™ rhBMP-2 Matrix is rhBMP-2, provided in a concentration of 2.0mg/mL. This formulation of rhBMP-2 has not been used in previous studies. Adverse events observed in the pivotal study that utilized this formulation of rhBMP-2 are outlined below.

ALL ADVERSE EVENTS AMPLIFY™ rhBMP-2 Matrix Pivotal Study																							
Type of Adverse Event	Operative		1 Day- ≤1 Month		6 Weeks (=1-<2 Mos.)		3 Months (=2-<5 Mos.)		6 Months (=5-<9 Mos.)		12 Months (=9-<19 Mos.)		24 Months (=19-<30 Mos.)		# of Patients Reporting & Total Adverse Events		36 Months (=30-<42 Mos.)		48 Months (=42-<54 Mos.)		60 Months (≥54 Mos.)		
	Inv	Ctrl	Inv	Ctrl	Inv	Ctrl	Inv	Ctrl	Inv	Ctrl	Inv	Ctrl	Inv	Ctrl	Inv # (% of 239) Total Events	Ctrl # (% of 224) Total Events	Inv	Ctrl	Inv	Ctrl	Inv	Ctrl	
	N=239	N=224	N=239	N=224	N=239	N=224	N=239	N=224	N=239	N=224	N=239	N=224	N=239	N=224									
Anatomical/Technical Difficulty	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1 (0.4%) 1	0 (0.0%) 0	0	0	0	0	0	0	
Arthritis/Bursitis	0	0	3	1	1	1	7	2	4	3	6	6	3	6	23 (9.6%) 24	17 (7.6%) 19	7	5	4	7	2	3	
Back and/or Leg Pain	0	0	18	8	11	5	15	13	21	30	37	31	37	23	105 (43.9%) 139	89 (39.7%) 110	39	36	30	26	11	18	
Cancer	0	0	0	0	0	0	1	0	2	1	3	1	3	0	9 (3.8%) 9	2 (0.9%) 2	4	1	0	1	0	0	
Cardiovascular	2	0	45	43	0	2	4	3	2	7	15	9	4	3	53 (22.2%) 72	54 (24.1%) 67	14	2	10	12	5	3	
Carpal Tunnel Syndrome	0	0	0	0	0	0	0	0	2	1	4	3	3	2	9 (3.8%) 9	6 (2.7%) 6	0	1	0	0	0	1	
Death	0	0	0	0	1	0	0	0	1	2	1	1	0	1	3 (1.3%) 3	4 (1.8%) 4	0	1	2	1	1	1	
Dural Injury	13	18	1	0	0	0	0	0	0	0	0	0	0	0	14 (5.9%) 14	18 (8.0%) 18	0	1	0	0	0	1	
Gastrointestinal	0	0	18	16	0	2	4	3	5	2	9	11	7	9	37 (15.5%) 43	33 (14.7%) 43	13	11	12	12	7	4	
Graft Site Related	0	0	0	4	0	3	0	5	0	3	0	2	0	0	0 (0.0%) 0	17 (7.6%) 17	0	2	0	0	0	0	
Implant Displacement/ Loosening	0	0	0	0	0	0	0	1	0	0	1	1	0	0	1 (0.4%) 1	2 (0.9%) 2	0	0	0	0	0	0	
Infection	0	0	20	27	4	6	4	2	6	1	11	10	7	5	39 (16.3%) 52	45 (20.1%) 51	2	6	6	6	0	1	
Malpositioned Implant	1	0	3	1	0	1	1	0	0	0	0	0	0	0	5 (2.1%) 5	2 (0.9%) 2	0	0	0	0	0	0	
Neurological	0	0	9	7	2	9	19	14	19	17	20	14	16	13	70 (29.3%) 85	60 (26.8%) 74	12	16	9	5	7	3	
Non-Union	0	0	0	0	0	0	1	8	0	6	8	6	1	3	10 (4.2%) 10	23 (10.3%) 23	1	1	0	0	0	1	
Other*	1	0	43	34	7	7	7	8	6	11	18	14	19	17	70 (29.3%) 101	62 (27.7%) 91	26	26	37	20	10	10	
Other Pain	0	0	2	3	2	0	1	1	6	5	11	4	9	19	29 (12.1%) 31	29 (12.9%) 32	8	13	11	7	8	7	
Respiratory	0	0	8	7	0	1	1	1	0	1	5	3	3	0	16 (6.7%) 17	12 (5.4%) 13	0	0	0	4	0	1	
Spinal Event – All**	0	0	1	1	0	2	3	3	5	2	5	12	4	2	17 (7.1%) 18	19 (8.5%) 22	6	2	3	1	3	1	
Spinal Event - Cervical	0	0	0	0	0	2	1	1	4	1	3	8	2	0	9 (3.8%) 10	11(4.9%) 12	2	1	1	1	3	1	
Spinal Event - Thoracic	0	0	1	0	0	0	2	2	1	1	1	4	2	2	7 (2.9%) 7	9 (4.0%) 9	4	1	2	0	0	0	
Spinal Event - Lumbar	0	0	0	1	0	0	0	0	0	0	1	0	0	0	1 (0.4%) 1	1 (0.4%) 1	0	0	0	0	0	0	
Trauma	0	0	2	3	2	8	8	7	13	16	36	19	30	17	69 (28.9%) 91	59 (26.3%) 70	22	16	12	12	6	6	
Urogenital	0	0	10	6	2	2	5	3	4	3	5	5	2	5	27 (11.3%) 28	21 (9.4%) 24	4	3	3	2	2	3	
Vertebral Fracture	3	3	0	0	0	0	0	0	0	0	0	0	0	1	3 (1.3%) 3	4 (1.8%) 4	0	0	0	0	0	0	
Any Adverse Event																209 (87.4%) 756	197 (87.9%) 694	158	143	139	116	62	64

* * Other* adverse events include such events as anxiety, dental events, flu, insomnia, hypothyroidism, and insect bites.

** The category of "Spinal Event" has been subcategorized by region of the spine (i.e., cervical, thoracic, and lumbar). The sum of the events (i.e., "Spinal Event – All") was used in the calculation of the total number of adverse events.

The reported rates of several adverse events were high, but similar, in both the investigational and control groups.

Through 24 months, graft site related events occurred with greater frequency in the control group (7.6%) compared to the investigational group (0%). Non-union rates were greater in the control group (10.3%) as compared to the investigational group (4.2%).

The high adverse event rates reflect the fact that all adverse events were reported and captured, regardless of their relationship to the study treatment. As shown in the following table, only a minority of the adverse events reported were related to the study treatment.

ADVERSE EVENTS RELATED TO THE STUDY TREATMENT AMPLIFY™ rhBMP-2 Matrix Pivotal Study (Through 24 Months Postoperative)		
	# of Patients Reporting & Total Adverse Events	
ADVERSE EVENT TYPE	Inv # (% of 239) Total Events	Ctrl # (% of 224) Total Events
Arthritis/Bursitis	0 (0.0%) 0	2 (0.9%) 2
Back and/or Leg Pain	4 (1.7%) 4	5 (2.2%) 5
Dural Injury	0 (0.0%) 0	1 (0.4%) 1
Implant Displacement/ Loosening	1 (0.4%) 1	2 (0.9%) 2
Malpositioned Implant	4 (1.7%) 4	2 (0.9%) 2
Neurological	2 (0.8%) 2	1 (0.4%) 1
Non-Union	10 (4.2%) 10	22 (9.8%) 22
Trauma	1 (0.4%) 1	0 (0.0%) 0
Vertebral Fracture	0 (0.0%) 0	1 (0.4%) 1

Some of the reported adverse events required surgical interventions subsequent to the initial surgery. Some of these secondary surgical interventions, such as revisions, non-elective removals, and supplemental fixations, were considered second surgery failures in the clinical study. Secondary surgical intervention information for the investigational and control treatment groups is summarized in the table below.

SECONDARY SURGICAL INTERVENTIONS AMPLIFY™ rhBMP-2 Matrix Pivotal Study							
EVENT	Total Events through 24-Month Time Point		# of Patients Reporting				Probability that the Second Surgery Rate of Inv Group is Lower than the Ctrl Group
	Inv N=239	Ctrl N=224	Inv N=239		Ctrl N=224		
Revisions	4	4	4	1.7%	4	1.8%	54.0%
Removals	13	29	13	5.4%	28	12.5%	99.6%
Non-Elective	10	23	10	4.2%	22	9.8%	-
Elective	3	6	3	1.3%	6	2.7%	-
Supplemental Fixations	6	9	6	2.5%	9	4.0%	81.4%
Reoperations	13	14	12	5.0%	11	4.9%	48.2%

For these safety comparisons, probabilities exceeding 97.5% are considered statistically significant, rather than the 95% criterion used for other endpoints. In the table above, it is clear that the investigational group had statistically fewer removals than the control group, while the other second surgeries were not statistically different between the two groups.

POTENTIAL ADVERSE EVENTS

The following is a list of potential adverse events that may occur with spinal fusion surgery with AMPLIFY™ rhBMP-2 Matrix. Some of these adverse events may have been previously reported in the adverse events table or have been reported to the manufacturer:

- Allergic reaction.
- Anaphylactic reaction.
- Bone fracture.
- Cessation of any potential growth of the operated portion of the spine. Loss of spinal mobility or function.
- Change in mental status.
- Damage to blood vessels and cardiovascular system compromise.
- Damage to internal organs and connective tissue.
- Death.
- Development of respiratory problems.
- Disassembly, bending, breakage, loosening, and/or migration of components.
- Dural tears.
- Ectopic and/or exuberant bone formation.
- Edema (swelling).
- Elevated erythrocyte sedimentation rate.
- Erythematous tissue.
- Fetal development complications.
- Fluid-filled cysts or fluid collection.
- Foreign body (allergic) reaction.
- Gastrointestinal complications.
- Hematoma.
- Incisional complications.
- Infection.
- Inflammation.
- Itching.
- Loss of spinal mobility or function.
- Neurological system compromise.
- Non-union (or pseudarthrosis), delayed union, mal-union.
- Pain.
- Postoperative change in spinal curvature, loss of correction, height, and/or reduction.
- Scar formation.
- Seroma.
- Tissue or nerve damage.

Note: Additional surgery may be necessary to correct some of these potential adverse events.

CLINICAL RESULTS

Clinical data to support the safety and effectiveness of AMPLIFY™ rhBMP-2 Matrix were collected as part of a multi-center, prospective, randomized pivotal study. The investigational group received AMPLIFY™ rhBMP-2 Matrix with posterior supplemental fixation, while the control group was implanted with autograft bone from the iliac crest and posterior supplemental fixation. In both cases, a posterolateral surgical approach was used.

Neither the investigators nor the subjects were blinded to the treatment. Subject blinding was not possible due to the second surgical site required to collect autogenous bone graft from the iliac crest. The potential for investigator bias in the clinical outcome parameters was reduced by having subjects rate their outcome using objective self-assessments. The radiographic outcome parameters were assessed by independent radiologists who were not informed of treatment. These were the only radiographic evaluations used for determining radiographic success.

The indication studied was degenerative disc disease (DDD) accompanied by back pain with or without leg pain at a single level between L₁ and S₁, as confirmed by history and radiographic studies.

Clinical and Radiographic Effectiveness Parameters

Patients were evaluated preoperatively (within 6 months of surgery), intraoperatively, and postoperatively at 6 weeks and at 3, 6, 12, and 24 months. In addition, patients were assessed for long-term follow-up at 36 and 60 months. Complications and adverse events, device-related or not, were evaluated over the course of the clinical trial. At each time point, the primary and secondary clinical and radiographic outcome parameters were evaluated. Success was based on outcomes at 24 months postoperative. Antibodies to rhBMP-2 and bovine Type I collagen were measured preoperatively and at 6 weeks and 3, 6, and 12 months postoperative. Antibodies to human Type I collagen were assessed if the antibody response to bovine Type I collagen was positive.

Primary and secondary clinical and radiographic effectiveness outcome parameters were evaluated for all treated subjects at all follow-up time points identified above. The primary clinical outcome parameters assessed were pain, function, and neurological status. The secondary clinical outcome parameters assessed were back and leg pain, general health status, donor site pain (control subjects only), patient satisfaction, and patient global perceived effect of the treatment. The primary radiographic outcome parameter consisted of fusion evaluations.

Fusion was assessed at 6, 12, and 24 months postoperative using plain radiographs (AP, lateral, and flexion/extension films) and high resolution thin-slice CT scans. Fusion was defined as evidence of bridging trabecular bone (based on a continuous bony connection from the superior transverse process to the inferior transverse process on both sides); no evidence of motion (≤ 3 mm of translation and $< 5^\circ$ of angulation between flexion and extension as seen on lateral flexion/extension radiographs); and the absence of cracking, as evidenced by radiolucent lines completely through the fusion mass. All assessments were made from the plain films except for the assessment of bridging bone, which was made using CT scans only if bridging bone could not be visualized on the plain radiograph.

Pain and function were measured in all studies using the Oswestry Low Back Pain Disability Questionnaire. Success was defined as a 15-point improvement in the Oswestry score from the preoperative baseline score.

Neurological status consisted of measurements of four parameters - motor, sensory, reflexes, and straight leg raise (SLR). Neurological status success was defined as maintenance or improvement of the preoperative baseline score for each parameter. Success in each individual parameter was required for a subject to be counted as a neurological success.

Patient Demographics and Accountability

A total of 239 investigational and 224 control patients were enrolled in this randomized study and received the device. For the majority of the demographic parameters, there were no differences across the two populations.

Surgical Results and Hospitalization

Information related to the surgical procedures and postoperative hospitalizations of patients was collected and evaluated.

Surgical and Hospitalization Information			
	Investigational Group	Control Group	Probability of Superiority
Mean Operative Time (hrs)	2.5	2.9	~100.0%
Mean EBL (ml)	343.1	448.6	~100.0%
Hospitalization (days)	4.1	4.0	30.5

As the table above shows, patients in the investigational group had statistically shorter operative times and less blood loss than control patients.

Clinical and Radiographic Effectiveness Evaluation

Individual subject success was defined as success in each of the primary clinical and radiographic outcome parameters. Success for these parameters included:

1. the presence of radiographic fusion;
2. an improvement of at least 15 points from the baseline Oswestry score;
3. maintenance or improvement in neurological status;
4. the presence of no serious adverse event classified as implant-associated or implant/surgical procedure-associated; and
5. no additional surgical procedure classified as a "Failure."

The table below describes the success probabilities for the individual primary outcome parameters and overall success. All success probabilities were based on data from the 24-month follow-up evaluation, and posterior probabilities were calculated using Bayesian statistical methods.

Posterior Probabilities of Success at 24 Months				
Primary Outcome Variable	Investigational Group	Control Group	Posterior Probabilities	
	Posterior Mean (95% HPD Credible Interval)	Posterior Mean (95% HPD Credible Interval)	Non-Inferiority	Superiority
Fusion	95.4% (92.4%, 98.1%)	88.9% (84.1%, 93.4%)	~100.0%	99.2%
Oswestry	72.9% (66.9%, 78.9%)	72.4% (66.0%, 78.7%)	99.0%	53.7%
Neurological Status	86.6% (82.0%, 91.1%)	83.8% (78.5%, 89.0%)	~100.0%	78.5%
Overall Success	60.4% (53.6%, 67.1%)	55.4% (48.3%, 62.6%)	99.9%	83.9%

Non-inferiority of the investigational group to the control group was demonstrated for all of the endpoints listed above. Statistical superiority of the investigational group to the control group was demonstrated for fusion success.

For a patient receiving AMPLIFY™ rhBMP-2 Matrix with posterior supplemental fixation via a posterolateral technique, the chance (i.e., the probability) of overall success at 24 months would be 60.4%. Given the results of the trial, there is a 95% probability that the chance of success ranges from 53.6% to 67.1%. For a patient receiving the control treatment, the chance of overall success at 24 months would be 55.4%. Given the results of the trial, there is a 95% probability that the chance of success ranges from 48.3% to 62.6%.

Safety and Immune Response Evaluation

The assessment of safety consisted of an evaluation of the reported adverse events, as well as an evaluation of formation of antibodies to BMP-2, bovine Type I collagen, and human Type I collagen. The complete list of complications, adverse events, and subsequent interventions is described in the Adverse Events section above. The presence of antibodies was assessed

prior to surgery and at 6 weeks and 3, 6, and 12 months postoperative using ELISA. If a sample was positive for antibodies to bovine Type I collagen, the sample was also tested for antibodies to human Type I collagen. Subjects were considered to have an elevated antibody response if the preoperative result was negative (titer < 50) and at least one postoperative result was positive (titer ≥ 50) or if the preoperative result was positive and at least one postoperative result was positive with a two-fold higher titer than the preoperative test.

There were 20 subjects who had positive antibody responses to rhBMP-2 – 15 subjects in the investigational group and 5 subjects in the control group. The rate of positive antibody response to rhBMP-2 was 6.4% in the investigational group and 2.3% in the control group. A neutralizing antibody assay was run on samples from patients with positive antibodies to rhBMP-2. There were no neutralizing antibodies detected.

Eighty-five (85) subjects were considered to have an authentic elevated antibody response to bovine Type I collagen – 39 investigational subjects and 46 control subjects. The incidence rate in patients treated with rhBMP-2 was 16.7%, while the incidence in control patients was 21.2%. No subjects had positive responses to human Type I collagen.

Seventeen (17) cases of cancer were diagnosed during the course of the pivotal study (including after the 24-month time point) – 13 in the investigational group and four in the control group. Investigational subject cancer events included: laryngeal cancer, leukemia, lung cancer, melanoma, non-Hodgkin lymphoma, ovarian cancer, pancreatic cancer, prostate cancer (2), stomach cancer, thyroid cancer, basal cell carcinoma, and squamous cell carcinoma. Control malignancy events included: breast cancer, colon cancer, non-Hodgkin Lymphoma, and thyroid cancer.

HOW SUPPLIED

AMPLIFY™ rhBMP-2 Matrix is supplied in a single kit size containing all the components necessary to prepare the device, i.e., a vial with the lyophilized growth factor, the compression resistant matrix, a vial with sterile water for reconstituting the growth factor, syringes, and needles.

A metallic posterior supplemental fixation device must be used with AMPLIFY™ rhBMP-2 Matrix but is not provided as part of the device. The posterior supplemental fixation devices are procured separately and supplied in a variety of sizes which must be properly selected based on a specific patient's anatomy.

STORAGE CONDITIONS

Store AMPLIFY™ rhBMP-2 Matrix at room temperature (15° to 30°C/59° to 86°F).

DOSAGE AND ADMINISTRATION

AMPLIFY™ rhBMP-2 Matrix is prepared immediately prior to use from a kit containing all necessary components. Once prepared, AMPLIFY™ rhBMP-2 Matrix contains rhBMP-2 at a concentration of 2.0 mg/ml.

The amount of AMPLIFY™ rhBMP-2 Matrix to be implanted is consistent, a total of 40 mg, 20 mg per side. A surgical technique manual for AMPLIFY™ rhBMP-2 Matrix is available and provides more information.

Only store AMPLIFY™ rhBMP-2 Matrix in the manner described on the package, only mix the components in the manner described in the directions, only add the reconstituted rhBMP-2 to the CRM carrier provided in the manner described, and only use in the quantity and indication specified in the package insert. Any other storage, mixture, or administration may cause unanticipated adverse events.

DIRECTIONS FOR USE

AMPLIFY™ rhBMP-2 Matrix is prepared at the time of surgery by reconstituting the lyophilized rhBMP-2 with sterile water. The solution is then applied directly to the CRM, allowed to soak for at least 5 minutes, and then carefully placed across the transverse processes. AMPLIFY™ rhBMP-2 Matrix induces new bone tissue at the site of implantation. Temporary supplemental fixation is used to stabilize the site during healing. Throughout the healing process, the CRM is resorbed by the body and replaced by newly formed bone. After fusion occurs, the supplemental fixation system may be removed (see the Surgical Technique manual for the specific metallic posterior supplemental fixation device used). If AMPLIFY™ rhBMP-2 Matrix is not used within two hours after reconstitution, it must be discarded.

AMPLIFY™ rhBMP-2 Matrix must not be sterilized by the hospital. Please refer to the specific posterior supplemental fixation package insert for information on packaging, cleaning/decontamination, and sterilization of this component and its instruments.

PRODUCT COMPLAINTS

Any health care professional (e.g., customer or user of this system of products), who has any complaints or who has experienced any dissatisfaction in the product quality, identity, durability, reliability, safety, effectiveness, and/or performance of this product, should notify the distributor or Medtronic. Further, if any of the implanted AMPLIFY™ rhBMP-2 Matrix components ever "malfunction," (i.e., do not meet any of their performance specifications or otherwise do not perform as intended), or are suspected of doing so, the distributor should be notified immediately. If any Medtronic product ever "malfunctions" and may have caused or contributed to the death or serious injury of a patient, the distributor should be notified immediately by telephone, fax, or written correspondence. When filing a complaint, please provide the component(s) name and number, lot number(s), your name and address, the nature of the complaint, and notification of whether a written report from the distributor is requested.

DEVICE RETRIEVAL EFFORTS

Should it be necessary to remove AMPLIFY™ rhBMP-2 Matrix, please call Medtronic prior to the scheduled surgery to receive instructions regarding data collection, including histopathological, mechanical, and adverse event information.

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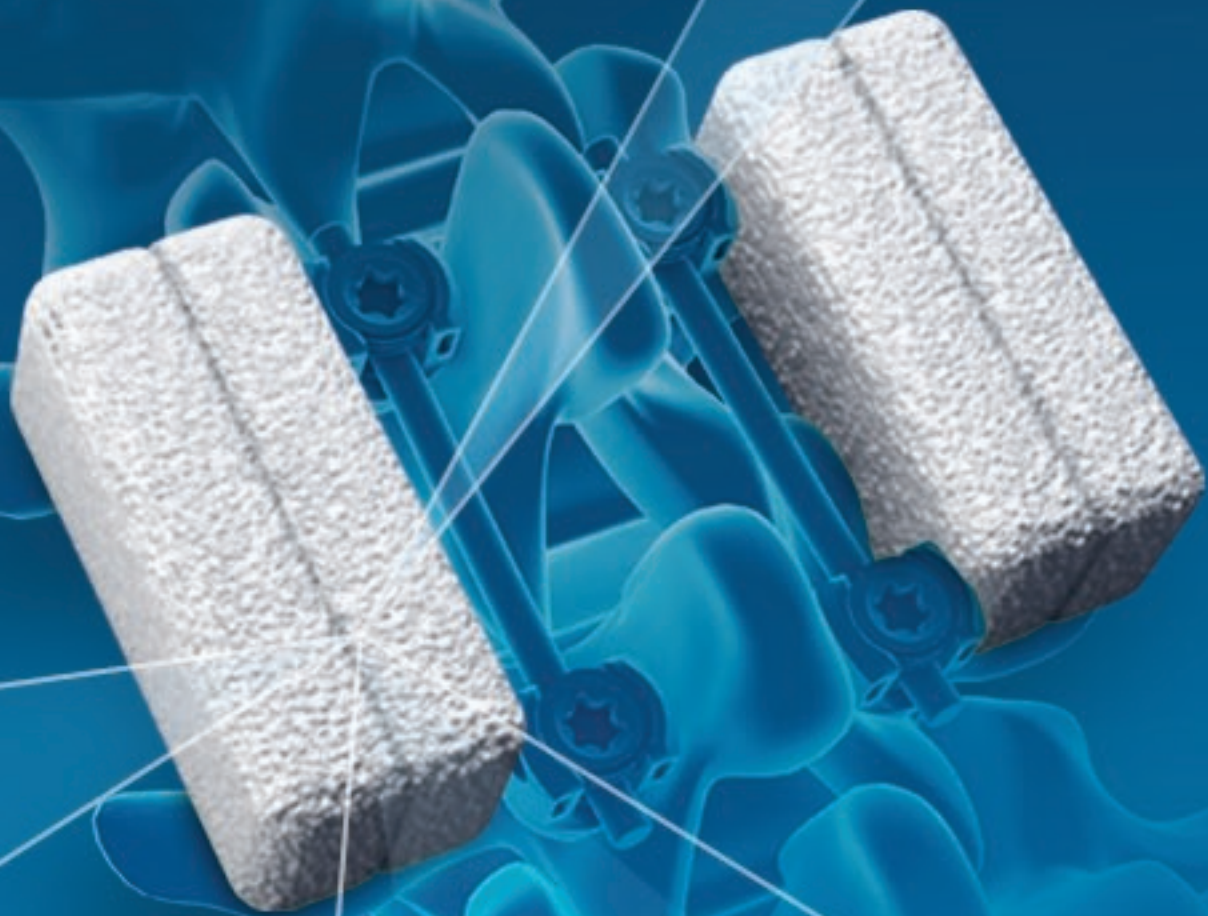
AMPLIFY™ rhBMP-2 Matrix
Box Sleeve



AMPLIFY™ rhBMP-2 Matrix

rhBMP-2 + CRM
(Compression Resistant Matrix)

40 mg Kit



AMPLIFY™ rhBMP-2 Matrix rhBMP-2 + CRM (Compression Resistant Matrix)



AMPLIFY™ rhBMP-2 Matrix rhBMP-2 + CRM (Compression Resistant Matrix)

Contents:

Two (2) Vials of Sterile rhBMP-2 (20 mg each)
Two (2) Packages of Two (2) Sterile 5 cc
Compression Resistant Matrices (CRM)
(4.67 cm L x 0.95 cm W x 1.13 cm H each)
Two (2) Vials of Sterile Water for Injection
(10 mL each)
Two (2) Sterile 10 mL Syringes with 20G 1½" Needles
Four (4) Sterile 3 mL Syringes with 20G 1½" Needles

Contents:

Two (2) Vials of Sterile rhBMP-2 (20 mg each)
Two (2) Packages of Two (2) Sterile 5 cc
Compression Resistant Matrices (CRM)
(4.67 cm L x 0.95 cm W x 1.13 cm H each)
Two (2) Vials of Sterile Water for Injection
(10 mL each)
Two (2) Sterile 10 mL Syringes with 20G 1½" Needles
Four (4) Sterile 3 mL Syringes with 20G 1½" Needles

40 mg Kit

Total rhBMP-2: **40 mg**
Total Graft Volume: **20 cc**
Concentration: **2.0 mg rhBMP-2 per cc CRM**

Contents:

Two (2) Vials of Sterile rhBMP-2 (20 mg each)
Two (2) Packages of Two (2) Sterile 5 cc
Compression Resistant Matrices (CRM)
(4.67 cm L x 0.95 cm W x 1.13 cm H each)
Two (2) Vials of Sterile Water for Injection (10 mL each)
Two (2) Sterile 10 mL Syringes with 20G 1½" Needles
Four (4) Sterile 3 mL Syringes with 20G 1½" Needles



Four (4) Sterile 5 cc CRMs

Four (4) Sterile 5 cc CRMs



Total rhBMP-2: **40 mg**
Total Graft Volume: **20 cc**
Concentration: **2.0 mg rhBMP-2 per cc CRM**

40 mg Kit

40 mg Kit

Total rhBMP-2: **40 mg**
Total Graft Volume: **20 cc**
Concentration: **2.0 mg rhBMP-2 per cc CRM**



Four (4) Sterile 5 cc CRMs

AMPLIFY™ rhBMP-2 Matrix
Kit Labels

AMPLIFY™ rhBMP-2 Matrix

**Medtronic**

LOT XXXXXXXX

EXP XXXX-XX-XX
YYYY-MM-DD

40 mg Kit

REF 862XXXX

DRAFT**Medtronic**1800 Pyramid Place
Memphis, TN 38132 USA
(901) 396-3133
(800) 933-2635

AMPLIFY™ rhBMP-2 Matrix

40 mg Kit

REF 862XXXX

Contents:

- Two (2) Vials of Sterile rhBMP-2 (20 mg each)
- Two (2) Packages of Two (2) Sterile 5 cc Compression Resistant Matrices (CRM) 4.67 cm L x 0.95 cm W x 1.13 cm H (each)
- Two (2) Vials of Sterile Water for Injection (10 mL each)
- Two (2) Sterile 10 mL Syringes with 20G 1½" Needles
- Four (4) Sterile 3 mL Syringes with 20G 1½" Needles

Store at controlled room temperature: 15 to 30°C (59 to 86°F).

DO NOT FREEZE**DO NOT USE KIT IF CONTENTS BECOME WET****DO NOT USE IF CONTENTS APPEAR DAMAGED****CAUTION:** Federal law (USA) restricts this device to sale by or on the order of a physician.

See package insert and instructions for preparation for labeling limitations and complete instructions on use.

Manufactured in Memphis, TN USA

MXXXXXXXXXX

AMPLIFY™ rhBMP-2 Matrix

CRM

One (1) Package of Two (2) Sterile 5 cc Compression Resistant
Matrices (CRM) for Use with rhBMP-2

Nonpyrogenic

Store at controlled room temperature: 15 to 30°C (59 to 86°F)

4.67 cm L x 0.95 cm W x 1.13 cm H (each)

USA: Rx only

STERILE EO



DRAFT

Manufactured for:

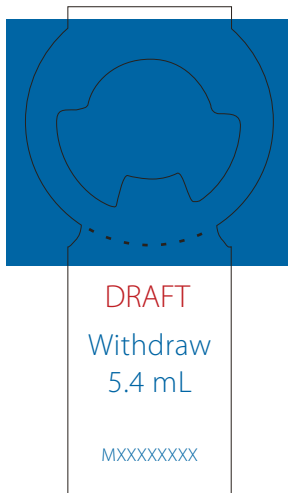
Medtronic Sofamor Danek USA, Inc.

Memphis, TN 38132 USA

Made in USA

Component of REF 862####

MXXXXXXXXX



LOT XXXXXXXXXX
EXP XXX-XX

Recombinant Human Bone Morphogenetic Protein-2 (rhBMP-2)
Component of 40 mg AMPLIFY™ rhBMP-2 MATRIX Kit
diboterminal alfa, 20 mg

862XXXX

Store at 5 to 30°C (41 to 86°F)
See package insert for complete information.
Protect from light.

DRAFT

Manufactured for: Medtronic Sofamor Danek USA, Inc.
Memphis, TN 38132 USA

MXXXXXXXXXXX

USA: Rx only



REF 862XXXX

AMPLIFY™ rhBMP-2 Matrix
40 mg Kit

LOT

DRAFT

STERILE

MXXXXXXXXXX

USE BY:



Medtronic

1800 Pyramid Place
Memphis, TN 38132 USA
Telephone: (800) 933-2635
(901) 396-3133

REF 862XXXX

AMPLIFY™ rhBMP-2 Matrix
40 mg Kit

LOT

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STERILE

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AMPLIFY™ rhBMP-2 Matrix
Patient Information Brochure



AMPLIFY™ rhBMP-2 Matrix

Patient Information
Brochure

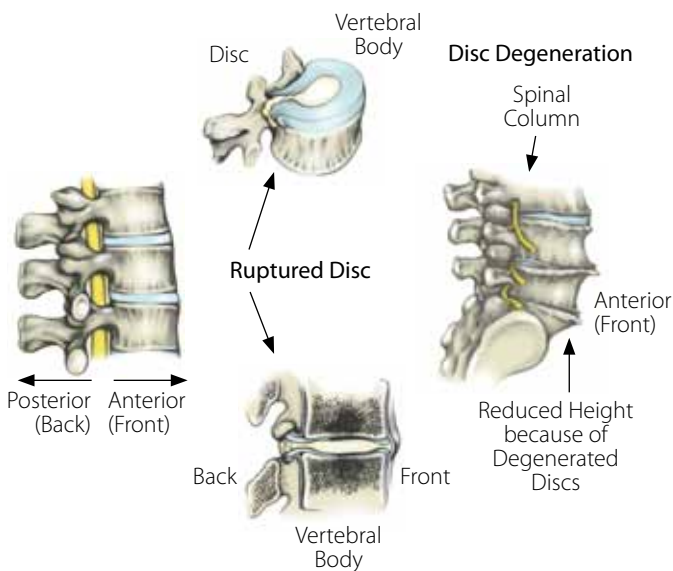


This patient information guide is designed to help you make an informed decision about treatment for your back pain and related problems. Your doctor has proposed surgery to relieve your back pain and related problems using AMPLIFY™ rhBMP-2 Matrix.



Your doctor has decided that you need spine surgery after carefully examining you, reviewing your history and x-rays, and taking into account the results of other diagnostic studies and previous non-surgical treatments. Specifically, your doctor has determined that you would benefit from having spinal surgery that fuses (connects) certain bones of your back together to prevent them from moving relative to each other.

Your Lower Back



The bony vertebrae, which encircle and protect your spinal cord, are separated by shock-absorbing discs. The discs give your spine the flexibility to move. Each disc has a spongy center (nucleus) surrounded by tough outer rings. Nerves branching from the spinal cord pass through openings in the vertebrae to other parts of your body. Several of these nerves form the sciatic nerve, which runs down your leg.

As discs lose their water content because of disease or age, they lose their height, bringing the vertebrae closer together. As a result, the nerve openings in your spine become more narrow, and the discs don't absorb the shocks as well, particularly when you are walking, running, or jumping. Wear and tear, poor posture, and incorrect body movements can also weaken the disc, causing disc degeneration. Disc degeneration may cause back and/or leg pain, as well as functional problems, such as tingling or numbness in your legs or buttocks or difficulty walking. Doctors call this degenerative disc disease (DDD).

What is AMPLIFY™ rhBMP-2 Matrix?



AMPLIFY™ rhBMP-2 Matrix is designed to aid in the treatment of degenerative disc disease (DDD) and is used to bridge the space between transverse processes. AMPLIFY™ rhBMP-2 Matrix consists of two parts: a solution containing rhBMP-2 (recombinant human bone morphogenetic protein-2) and a compression resistant matrix (CRM) carrier.

The protein is a manufactured (genetically engineered) version of a natural protein normally found in small quantities in the body. The purpose of the protein is to stimulate bone formation. During surgery, the protein solution is soaked into the CRM. The CRM acts as a “scaffold” for rhBMP-2 to induce new bone formation and generate a successful fusion. The CRM is manufactured from bovine (cow) Type I collagen embedded with ceramic particles. The CRM carrier is resorbed by the body during the bone formation process.

AMPLIFY™ rhBMP-2 Matrix is to be used in conjunction with a metallic posterior supplemental fixation device. After fusion has occurred, this device may be removed.

What are the potential benefits?

A potential advantage to having spinal fusion surgery using AMPLIFY™ rhBMP-2 Matrix is that it removes the need to collect bone from your hip (iliac crest autograft) to bridge the space between transverse processes. The use of autograft bone requires an alternative procedure and involves a second or larger incision that may be painful and/or take longer to heal. The time needed for your surgery and the amount of blood loss may be less if AMPLIFY™ rhBMP-2 Matrix is used.

Who is a candidate for AMPLIFY™ rhBMP-2 Matrix?



AMPLIFY™ rhBMP-2 Matrix is indicated as an alternative to autogenous bone graft for spinal fusion procedures in skeletally mature patients for the treatment of DDD at one level from L1-S1 (the lower part of the back). DDD is defined as a disc that has deteriorated and causes back pain. The disc deterioration is confirmed by patient history and radiographic (x-ray) studies. In addition to the disc degeneration, there may also be a small amount of slippage of one disc relative to the next at the diseased spinal level (known as Grade I spondylolisthesis or retrolisthesis). Prior to this surgery, you should have been non-responsive to at least six months of non-operative therapy. AMPLIFY™ rhBMP-2 Matrix is to be implanted via a posterior approach.

Who should not receive AMPLIFY™ rhBMP-2 Matrix?

AMPLIFY™ rhBMP-2 Matrix should not be used if:

- » You are pregnant or suspect that you might be pregnant.
- » You are sensitive to recombinant human bone morphogenetic protein-2, bovine (cow) Type I collagen, or one of the metals used in the posterior supplemental fixation device (such as titanium, stainless steel, or cobalt-chromium alloy).
- » You have an infection near the area of the surgical incision.
- » You had a tumor removed from the area surrounding the implantation site or currently have a tumor in that area.
- » You have or are currently being treated for cancer.
- » Your bones have not stopped growing.

Warnings and Precautions

This device has not been tested in pregnant women to determine if there is any effect on a developing fetus. This device has also not been studied in nursing mothers.

When tested in female rabbits that received the rhBMP-2, (a component of AMPLIFY™ rhBMP-2 Matrix), developed an immune response, and later became pregnant, the following was seen:

- » The antibodies developed by the mother were able to reach the developing rabbit fetus. The effect of these antibodies on the developing rabbit fetus is not currently known.
- » Some bone formation abnormalities were observed in a small number of the rabbit fetuses tested. It is not known if these changes would disappear as the rabbit fetus continued to develop or at some time after birth.

This device should not be used immediately prior to or during pregnancy. Women of childbearing potential should be advised not to get pregnant for one year following treatment with the device. Women of childbearing potential should be warned of potential risk to a fetus and should discuss other possible orthopedic treatments with their surgeon.

BMP-2 plays a critical role during fetal development in humans and other animals. It is not known whether a pregnant woman previously exposed to BMP-2 by implantation with the device might develop a second immune response to BMP-2 from the developing fetus, with adverse effects for the woman or baby. In a rabbit pregnancy study to investigate this issue, no increase in anti-BMP-2 antibodies was observed.

In addition, this device has not been tested:

- » To see if there are side effects by using it more than once in the same person.
- » In people with liver or kidney problems (this might be important, because these organs are involved in removing any by-products of the device).
- » In people with metabolic bone diseases, such as osteoporosis.
- » In people with an autoimmune or immunosuppressive disease, such as lupus or HIV/AIDS.
- » In people with immune deficiency due to other treatments, such as radiation therapy, chemotherapy, or steroid therapy.

Some patients may have an allergic reaction to AMPLIFY™ rhBMP-2 Matrix.

Please talk with your doctor about any of the above warnings and precautions.

How is the surgery performed?

AMPLIFY™ rhBMP-2 Matrix can be implanted through an opening in your lower back. This is known as a posterior surgical approach. You should speak to your doctor about the risk and benefits of this technique prior to surgery.

During your surgery, your doctor will prepare the area to allow the implants to be inserted. Rather than taking bone (autograft) from your hip or from the area in which the implants will be inserted, the surgeon will use AMPLIFY™ rhBMP-2 Matrix to connect the transverse processes. Your surgeon will also implant temporary posterior supplemental fixation in your back, which stabilizes the implant site until bone growth occurs.

There are alternative treatments to this surgery—both surgical and non-surgical. You should discuss these other options with your surgeon before you make your decision.



What can I expect after surgery?

Ask your doctor about your specific recovery plan following surgery. It is important to follow your doctor's instructions carefully to recover from surgery as quickly as possible and increase your chances of a successful outcome. Recovering from back pain and surgery is an ongoing process. How fast you recover depends on the type of surgery you had, your commitment to working closely with your physical therapist, and moving and exercising correctly, as recommended by your surgeon.

In most cases, immediately after surgery, your heart and lung function will continue to be monitored, a drainage tube may have been left in your wound, and your doctor may prescribe medicines to control pain and nausea. The average hospital stay for patients in the study used to evaluate AMPLIFY™ rhBMP-2 Matrix was just over four days for a posterior surgical approach.

A nurse will show you how to care for your wound before you are sent home, and your doctor will discuss a program to gradually increase your activity. You may be required to wear a back brace for at least one month after surgery, and you may be told to avoid repetitive bending, lifting, stooping, twisting, and athletic activities until fusion has occurred. You may also be cautioned to avoid vibrations, like you might experience when driving a car, for a period of time after your surgery.

Contact your doctor immediately if:

- » You get a fever.
- » The wound starts leaking fluids.
- » You have trouble swallowing or breathing.
- » You have trouble urinating.
- » You have new or increased back or leg pain or numbness.

Your doctor will schedule office visits to check on how you are doing and see if anything else needs to be done.

After surgery, your surgeon may refer you to a physical therapist who will teach you exercises to improve your strength and increase your mobility. The goal of physical therapy is to help you become active as soon as possible, using safe body movements that protect your back. This often includes abdominal strengthening exercises. You may also be taught different ways of standing, sitting, or lifting to avoid reinjuring your back.

What possible complications could occur?

As with any surgery, spinal surgery is not without risk. A variety of complications related to the use of AMPLIFY™ rhBMP-2 Matrix can occur. These may occur singly or in combination. Some of these may be severe, affecting your outcome. You may also need to have additional surgery to correct these complications. Some of the possible complications include:

- » Allergic reaction.
- » Anaphylactic reaction.
- » Bone fracture.
- » Cessation of any potential growth of the operated portion of the spine. Loss of spinal mobility or function.
- » Change in mental status.
- » Damage to blood vessels and cardiovascular system compromise.
- » Damage to internal organs and connective tissue.
- » Death.
- » Development of respiratory problems.
- » Disassembly, bending, breakage, loosening, and/or migration of components.
- » Dural tears.
- » Ectopic and/or exuberant bone formation.
- » Edema (swelling).
- » Elevated erythrocyte sedimentation rate.
- » Erythematous tissue.
- » Fetal development complications.
- » Fluid-filled cysts or fluid collection.
- » Foreign body (allergic) reaction.
- » Gastrointestinal complications.
- » Hematoma.
- » Incisional complications.
- » Infection.
- » Inflammation.
- » Itching.
- » Loss of spinal mobility or function.
- » Neurological system compromise.
- » Non-union (or pseudarthrosis), delayed union, or mal-union.
- » Pain.
- » Postoperative change in spinal curvature, loss of correction, height, and/or reduction.
- » Scar formation.
- » Seroma.
- » Tissue or nerve damage.

Talk to your doctor.

While this brochure has hopefully provided you with the information you need to make an informed decision about your treatment options, it is not intended to replace professional medical care or provide medical advice.



If you have any questions or need additional information about AMPLIFY™ rhBMP-2 Matrix, please call or see your doctor, who is the only one qualified to diagnose and treat your back. As with any surgical procedure, you should find a surgeon who is experienced in performing the specific surgery that you are considering.

Clinical results

A total of 463 patients participated in the clinical study of AMPLIFY™ rhBMP-2 Matrix. The AMPLIFY™ rhBMP-2 Matrix device was used with posterior supplemental fixation in 239 patients. A group of 224 control patients were implanted using bone taken from their hip, an alternative procedure, and the same posterior supplemental fixation as the investigational patients.

The following table compares the success rates at 24 months after surgery for the two groups of patients:

	Chance the investigational patients had a successful outcome	Chance the control patients had a successful outcome
Fusion	95.4%	88.9%
Pain and function	72.9%	72.4%
Neurological status	86.6%	83.8%
Overall success	60.4%	55.4%

The overall success rate describes the number of patients who had successful outcomes in fusion, pain and function, and neurological status. Also, to be considered an overall success, a patient could not have a serious complication associated with the device or have a second surgery because the first surgery was not successful.

In addition, two years after their surgery, 84.4% of the investigational patients and 78.7% of the control patients said that it was definitely true or mostly true that they were satisfied with the results of their surgery.

Patients in the study had blood collected to see if they generated antibodies (had a type of allergic reaction) to specific parts of the device—rhBMP-2 and bovine Type I collagen—as well as to human Type I collagen. Fifteen patients in the investigational group demonstrated a response to rhBMP-2, and 39 patients had a response to bovine Type I collagen. In the control group, five patients were noted to have a response to rhBMP-2, and 46 patients had a response to bovine Type I collagen. No patients in either group had a response to human Type I collagen. In addition, no positive neutralizing antibodies to rhBMP-2 were detected for either group.





BRIEF SUMMARY OF INDICATIONS, CONTRAINDICATIONS AND WARNINGS FOR:

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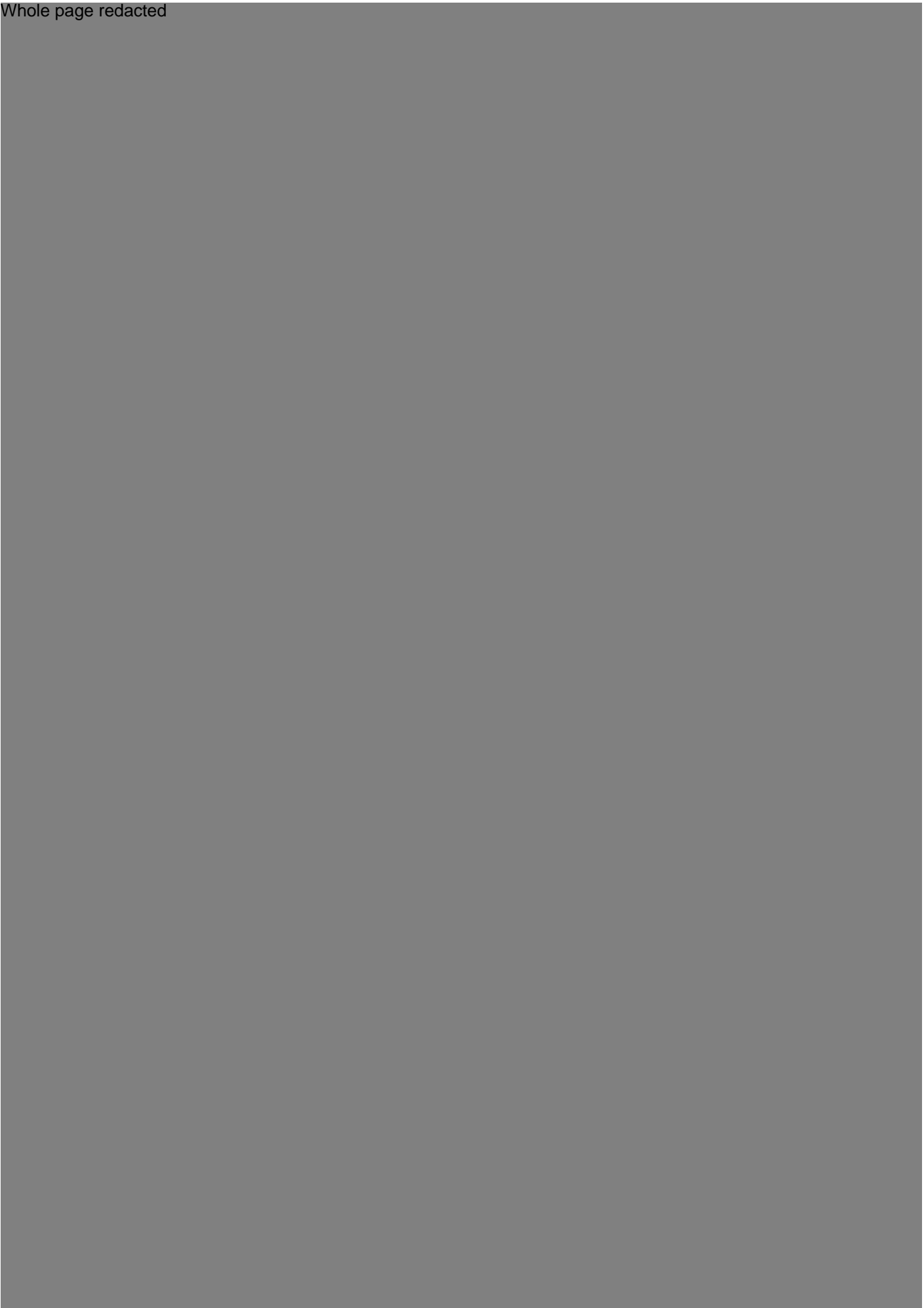
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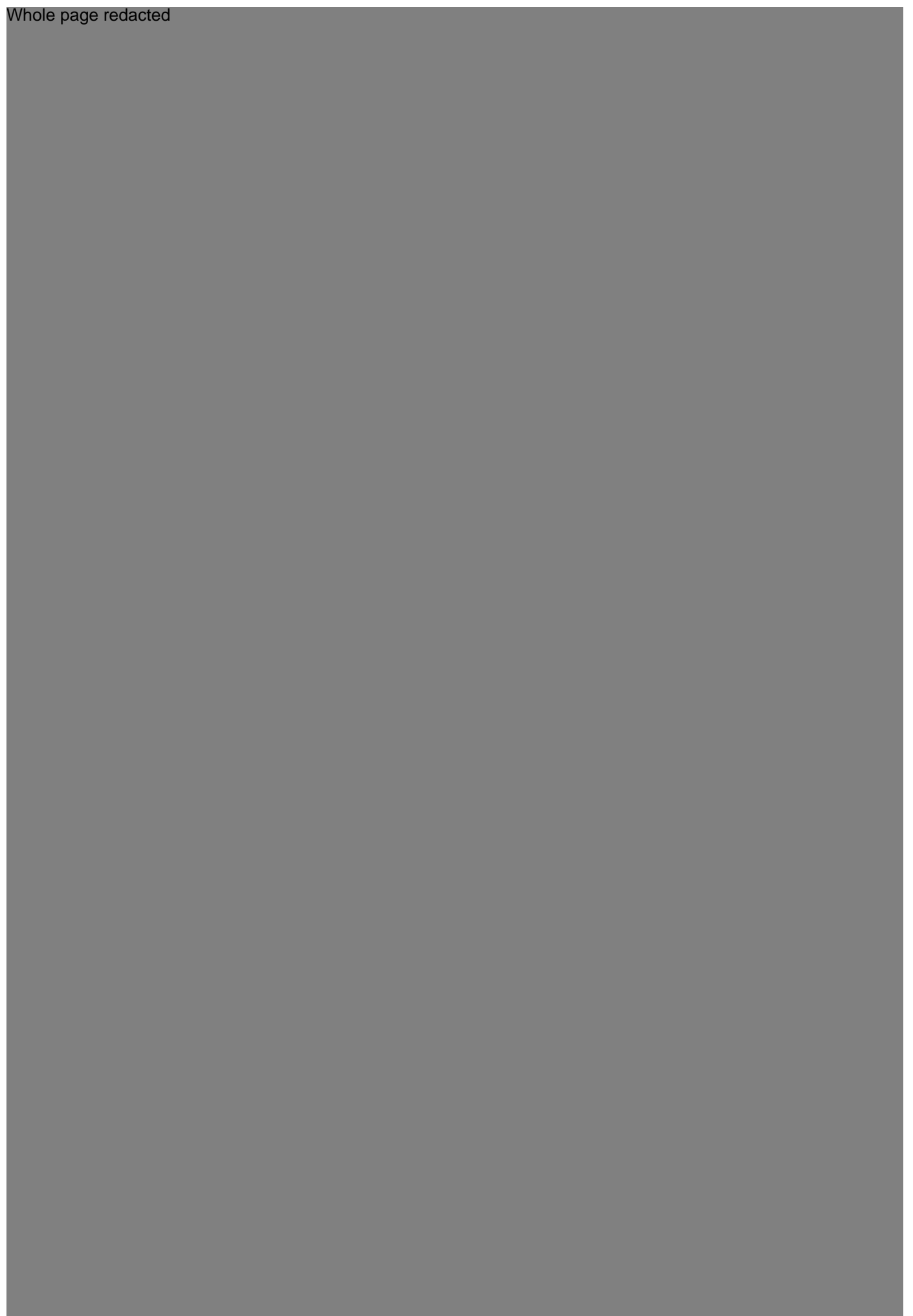


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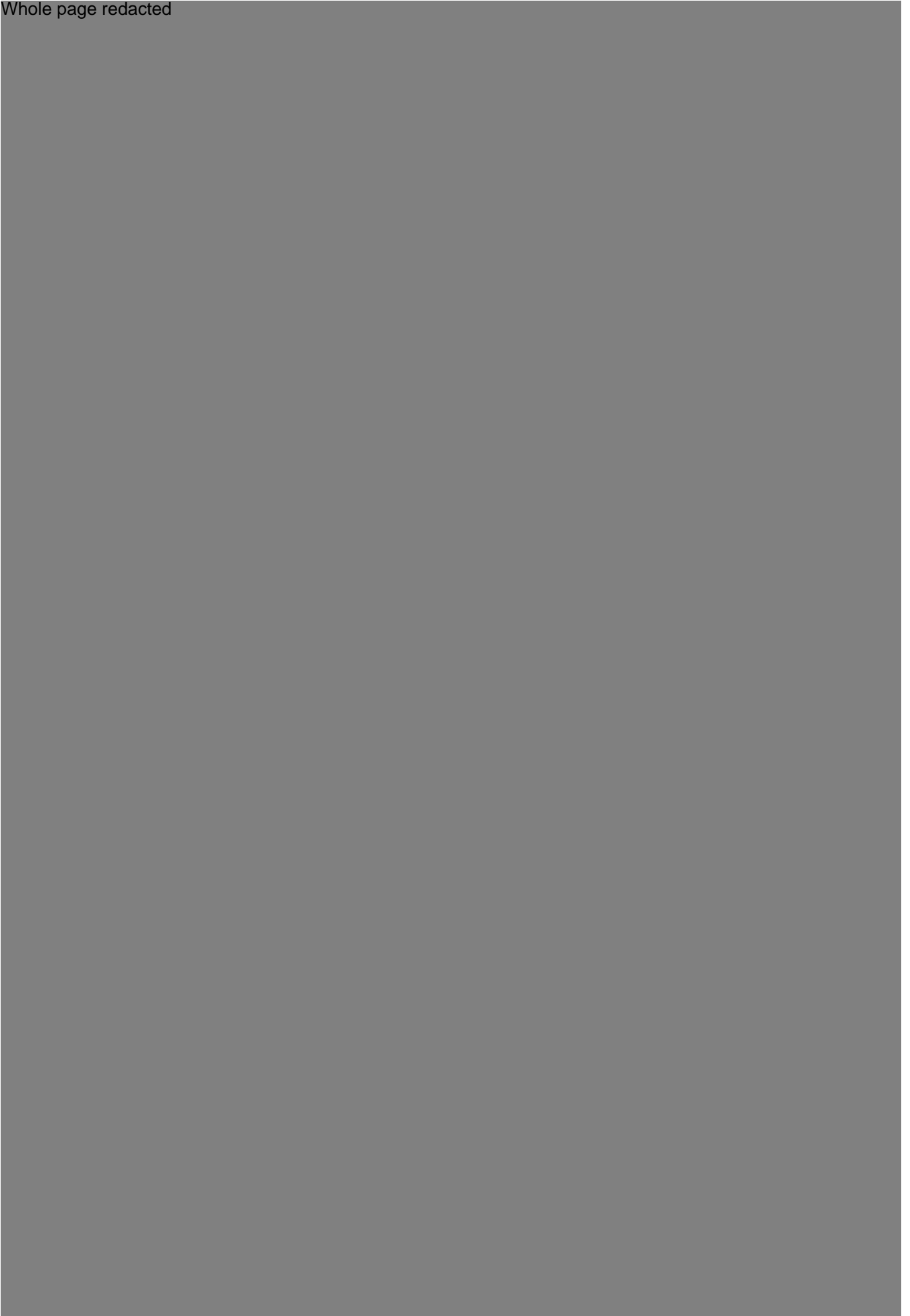


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DEVICE DESCRIPTION

The proposed 40 mg (20 cc) AMPLIFY™ rhBMP-2 Matrix commercial kit is made up of two components – a recombinant human bone morphogenetic protein and a carrier/scaffold for the bone morphogenetic protein and resulting bone formation. AMPLIFY™ rhBMP-2 Matrix must be used with a commercially available metallic posterior supplemental fixation device as temporary stabilization in order to facilitate fusion.

AMPLIFY™ rhBMP-2 Matrix Kit

AMPLIFY™ rhBMP-2 Matrix consists of recombinant human Bone Morphogenetic Protein-2 (rhBMP-2, known as diboterminal alfa) placed on a compression resistant matrix (CRM) carrier. AMPLIFY™ rhBMP-2 Matrix induces new bone tissue at the site of implantation. Based on data from nonclinical studies, the bone formation process develops from the outside of the implant toward the center until the entire AMPLIFY™ rhBMP-2 Matrix device is replaced by trabecular bone.

rhBMP-2 is the active agent in AMPLIFY™ rhBMP-2 Matrix. rhBMP-2 is a disulfide-linked dimeric protein molecule with two major subunit species of 114 and 131 amino acids. Each subunit is glycosylated at one site with high-mannose-type glycans. rhBMP-2 is produced by a genetically engineered Chinese hamster ovary cell line and subsequently highly purified using a 3-step chromatography process.

Each vial of rhBMP-2 contains a sterile lyophilized dosage form. Upon reconstitution, each milliliter of rhBMP-2 solution contains: 4.0 mg of rhBMP-2; 5.0 mg sucrose, NF; 25 mg glycine, USP; 0.74 mg L-glutamic acid, FCC; 0.29 mg sodium chloride, USP; 0.1 mg polysorbate 80, NF; and 1.0 mL of sterile water, USP. The reconstituted rhBMP-2 solution has a pH of 4.5, is clear and colorless to slightly yellow, and is essentially free from plainly visible particulate matter.

The Compression Resistant Matrix (CRM) acts as a carrier for the rhBMP-2 and serves as a scaffold for new bone formation. The CRM is a white, compression resistant, absorbent, implantable material. The CRM consists of absorbable bovine type I collagen (from Integra LifeSciences) with resorbable biphasic calcium phosphate granules embedded into the collagen scaffold. The resorbable biphasic calcium phosphate consists of 15% hydroxyapatite and 85% β -tricalcium phosphate (HA/TCP). The composition of CRM is 97.5% biphasic calcium phosphate and 2.5% type I bovine collagen by weight. This is the same composition as Medtronic's commercially available MasterGraft™ Matrix product (K023553).

Each AMPLIFY™ rhBMP-2 Matrix kit contains rhBMP-2, the CRM, and the necessary materials to reconstitute rhBMP-2 and to place it on the CRM. The reconstituted rhBMP-2 from one 20 mg vial will be applied to two 5 cc pieces of

CRM and applied to one side of the spine. The process is then repeated with the second rhBMP-2 vial and CRM pieces for the other side of the spine. The following components are contained in a 40 mg (20 cc) kit:

Commercial 40 mg (20 cc) Kit – AMPLIFY™ rhBMP-2 Matrix

Two (2) Vials of Sterile rhBMP-2 (20 mg each)

Two (2) Packages of Two (2) Sterile 5 cc Compression Resistant Matrices (CRM),
4.67 cm L x 0.95 cm W x 1.13 cm H (each)

Two (2) Vials of Sterile Water for Injection (10 mL each)

Two (2) Sterile 10 mL Syringes with 20G 1½" Needles

Four (4) Sterile 3 mL Syringes with 20G 1½" Needles

Temporary Posterior Supplemental Fixation

As stated above, AMPLIFY™ rhBMP-2 Matrix must be used with a commercially available metallic posterior supplemental fixation device. Any such metallic device that is indicated for posterior non-cervical pedicle fixation for degenerative disc disease may be used with AMPLIFY™ rhBMP-2 Matrix. The purpose of the posterior spinal fixation device is to provide temporary stabilization of the spine in order to facilitate bony fusion. The device used to provide temporary posterior fixation is not included in the AMPLIFY™ rhBMP-2 Matrix kit and must be obtained separately. After fusion has occurred, this device may be removed.

NONCLINICAL SUMMARY

rhBMP-2 Background

Bone morphogenetic proteins are members of the transforming growth factor-beta (TGF- β) superfamily. Human bone morphogenetic protein-2 (hBMP-2) is osteoinductive, inducing *de novo* bone formation *in vivo*. The primary mode of action for hBMP-2 is to differentiate mesenchymal cells derived from the periosteum (soft tissues surrounding the implant site) or the bone marrow stroma into cartilage and subsequently bone cells, resulting in endochondral or intramembranous bone formation. Recombinant human bone morphogenetic protein-2 (rhBMP-2) is secreted from cultures of Chinese hamster ovary (CHO) cells engineered to encode the rhBMP-2 protein gene. The active rhBMP-2 protein molecule consists of a disulfide-linked dimer with two major subunit species of 114 and 131 amino acids, respectively.

rhBMP-2 is typically applied to a carrier to assure local retention at the site of surgical implantation. AMPLIFY™ rhBMP-2 Matrix consists of rhBMP-2 placed on a compression resistant matrix (CRM) carrier. The AMPLIFY™ rhBMP-2 Matrix component induces new bone tissue formation at the site of implantation. The CRM is composed of an absorbable bovine type I collagen with resorbable biphasic calcium phosphate granules embedded into type I bovine collagen. The resorbable biphasic calcium phosphate is made up of 15% hydroxyapatite and 85% β -tricalcium phosphate (15:85 HA:TCP). The composition of CRM is 97.5% biphasic calcium phosphate and 2.5% type I bovine collagen. The CRM provides the matrix for the delivery of rhBMP-2 and serves as a scaffold for new bone formation.

At the time of surgery, surgeons prepare rhBMP-2/CRM by reconstituting a vial of lyophilized rhBMP-2 with sterile water. The reconstituted rhBMP-2 solution is then uniformly applied to the matrix. rhBMP-2 combined with CRM is then administered by surgical implantation in the intertransverse space on decorticated transverse processes.

Pharmacology studies have demonstrated that rhBMP-2 can induce bone formation in a variety of anatomical sites, including long bone segmental defects and various spine applications, such as interbody and posterolateral fusions. The induced bone biologically and structurally integrates with the pre-existing bone and remodels physiologically – that is, in a manner that is consistent with the biomechanical forces placed on it. In addition, the rhBMP-2-induced bone can repair itself following fracture in a manner indistinguishable from host bone. Radiographic, biomechanical, and histological evaluation of the tissue at the implant site indicates that the newly formed bone is appropriate for the anatomic site where it grows and that it functions biologically and biomechanically as native bone.

Histological analysis in many pharmacology studies has characterized the cellular events involved in the bone induction process initiated by rhBMP-2. Mesenchymal cells from the surrounding tissues first infiltrate the periphery of the carrier matrix. As the

carrier matrix is degraded, these cells differentiate and begin to form trabecular bone and/or cartilage. Vascular invasion is evident at the same time. The bone formation process temporarily extends from the outside of the implant toward the center until the entire rhBMP-2 implant is replaced by trabecular bone. Remodeling of the trabecular bone then occurs, depending on the physiologic form and function required.

The rhBMP-2 used in the AMPLIFY™ rhBMP-2 Matrix is the same as the rhBMP-2 that has been approved in three separate pre-market approvals as a component of INFUSE® Bone Graft. Therefore, the nonclinical safety, pharmacology and pharmacokinetic studies that were performed on rhBMP-2 during the development of INFUSE® Bone Graft are also relevant to and supportive of the AMPLIFY™ rhBMP-2 Matrix application. In addition to these studies, a number of nonclinical studies were performed to examine the feasibility and efficacy of rhBMP-2 on the CRM carrier. These included studies in rabbit and nonhuman primate posterolateral fusion models. Work in these areas identified limitations of the absorbable collagen sponge (ACS) carrier in the posterolateral fusion environment and were instrumental in determining the appropriate rhBMP-2 concentration for use with the CRM carrier. These studies are discussed in further detail below.

Relevant rhBMP-2 Safety Studies

Intravenous Toxicity and Implant Toxicity

The safety of rhBMP-2 has been evaluated in a series of toxicology studies of both the rhBMP-2 protein alone and rhBMP-2 on an absorbable collagen sponge (ACS). rhBMP-2 has been studied in single and multiple-dose general toxicology studies in the rat and canine with up to 28 days of daily dosing. rhBMP-2 was administered intravenously (IV) at doses that constituted a range that varied from slightly lower to substantially higher than the total doses (weight-based) of rhBMP-2 used in human clinical trials and proposed for commercial applications. There were no treatment-related toxicities observed in these studies. The tables below include detailed descriptions and relevant findings for individual studies.

Intravenous Safety Test Findings			
Study Type (Species/Strain)	Groups No. Animals/ Sex	rhBMP-2 (mg/kg)	Relevant Findings
Acute toxicity with sacrifices on Days 2, 7 and 15 (Rat/Sprague-Dawley)	5 5/sex	saline vehicle 0.053 0.160 0.533	No toxicity observed. No-toxic-effect dose was 0.533 mg/kg IV.
Acute toxicity with sacrifices on Days 2 and 15 (Rat/Sprague-Dawley)	5 5/sex	saline vehicle 0.533 1.60 5.33	No treatment-related findings in animals sacrificed at Day 2 or Day 15. Slight-to-mild dose-related chondrogenesis at injection sites. No- toxic-effect dose was 5.33 mg/kg IV.

Intravenous Safety Test Findings			
Study Type (Species/Strain)	Groups No. Animals/ Sex	rhBMP-2 (mg/kg)	Relevant Findings
Acute toxicity with sacrifice on Day 15 (Dog/Beagle)	4 1/sex	vehicle 0.53 1.6 5.3	No toxicity observed. No-toxic-effect dose was 5.3 mg/kg IV.
28-Day toxicity (Rat/Sprague-Dawley)	5 10/(5) ^a /sex	saline vehicle 0.016 0.05 0.16	Ten deaths unrelated to treatment (vehicle, 0.016, 0.05, 0.16). Dose- related soft tissue thickening and cartilage formation in subcutaneous tissue at injection sites. Following 28-day recovery period, the soft tissue thickening regressed and matured to bone. No-toxic-effect dose was 0.16 mg/kg/day IV.
28-Day toxicity (Dog/Beagle)	5 3/(2) ^a /sex	saline vehicle 0.016 0.05 0.16	Dose-related perivascular fibroplasia at injection site in all rhBMP-2-treated animals with bone formation in mid- to high-dose groups. No-toxic-effect dose was 0.16 mg/kg/day IV.
rhBMP-2 general pharmacology (mice, rats, guinea pigs, and dogs)	4-10 experiments <i>in vitro</i> and <i>in</i> <i>vivo</i> for each dose <i>Mice and Rats:</i> 5 5-10/M <i>Guinea Pigs:</i> 1 5-10/M <i>Dogs:</i> 1 5/mixed	<i>In vitro:</i> 10 ⁻⁸ g/ml 10 ⁻⁷ g/ml 10 ⁻⁶ g/ml 10 ⁻⁵ g/ml <i>In vivo:</i> 0.01 0.1 1.0	These experiments showed that rhBMP-2 had no effects on locomotion, the central nervous system, locomotor activity, respiration and cardiovascular systems, gastrointestinal systems, urinary system, and blood coagulation at the doses tested.

(n)^a = numbers of additional recovery sub-group animals in control and high-dose groups.

Chronic Toxicity Findings			
Study Type (Species/Strain)	Groups No. Animals/ Sex	rhBMP-2 (mg/kg)	Relevant Findings
6-month mandibular/ maxillofacial implant at inlay defect site (Dog/Beagle)	5 2/sex <i>Sacrificed at 3 and 6 months postimplantation</i>	sham surgery vehicle/ACS 0.078 mg/kg (0.4 mg/mL)/ACS 0.312 mg/kg (1.6 mg/mL)/ACS 0.781 mg/kg (4.0 mg/mL)/ ACS	No effects of treatment on clinical signs, hematology, or clinical chemistry. Dose-related post-surgical swelling. As swelling subsided (3-4 weeks), firm masses near the zygomatic and mandibular implant sites were detected in most rhBMP-2 treated animals. Histologically, the rhBMP-2-treated implant sites were composed of abundant fibrocellular tissue and/or new bone formation within and around the defect site. There were fluid-filled tissue cysts and occasionally strands of residual ACS material at implant sites with apparent regression between 3 and 6 months. Implant site changes were expected exaggerated pharmacologic responses to rhBMP-2/ACS and were not toxicologically significant. No-toxic-effect dose was 0.781 mg/kg (4.0 mg/mL concentration rhBMP-2). Transient low titer antibody responses were observed in 15/24 (62.5%) of the treated animals. No anti-bovine Type I collagen antibody response was found.
1-year femoral onlay implant toxicology (Rat/Sprague- Dawley)	5 10/sex <i>Sacrificed at 1, 6, and 12 months post-implantation</i>	vehicle/ACS 0.04 mg/kg (0.1 mg/mL)/ACS 0.3 mg/kg (0.75 mg/mL)/ACS 1.6 mg/kg (4.0 mg/mL)/ACS 1.6 mg/kg (4.0 mg/mL)/ACS opalescence	Slight increased incidence and severity of surgical site swelling at 1.6 mg/kg. Dose-related pharmacologic effect of increased incidence and/or severity of bone formation at implant site in all rhBMP-2/ACS treatment groups. No toxicity at any dose. Formation of antibodies to rhBMP-2 or bovine Type I collagen was not observed.

Fertility, Reproduction, and Teratology

Because BMP-2 participates in embryological development, rhBMP-2 was evaluated for any effect on reproduction or fetal development. rhBMP-2 was administered at doses that range from slightly lower to substantially higher than the total doses (weight-based) of rhBMP-2 used in human clinical trials and proposed for commercial applications. (up to 1 mg rhBMP-2/kg, total delivered dose). The effects of rhBMP-2 on the reproduction and fertility of male and female Sprague-Dawley rats were studied. Maternal and paternal mating performance and reproductive parameters were not affected by

treatment. Range-finding studies followed by definitive developmental toxicity studies were conducted in both Sprague-Dawley rats and New Zealand White rabbits. There was no evidence of maternal toxicity, embryoletality, fetotoxicity, or teratogenicity. The table below includes detailed descriptions and relevant findings for individual studies.

Fertility, Reproduction, and Teratology Studies			
Study Type (Species/Strain)	Groups No. Animals/ Sex	rhBMP-2 (mg/kg)	Relevant Findings
Fertility (Rat/Sprague-Dawley)	5 40/F 40/M	saline vehicle 0.016 0.05 0.16	Maternal and paternal mating performance and reproductive parameters were not affected by treatment. No-toxic-effect dose was 0.16 mg/kg/day IV.
Range-finding teratology (Rabbit/New Zealand White rabbit)	7 5/F	saline vehicle 0.016 0.05 0.16 0.5 1.6 <i>Days 6 to 18 gestation</i>	No maternal toxicity, embryoletality, or gross fetal abnormalities. No-toxic-effect level was 1.6 mg/kg/day IV.
Teratology (Rabbit/New Zealand White rabbit)	5 20/F	saline vehicle 0.016 0.5 1.6 <i>Days 6 to 18 gestation</i>	No maternal toxicity, embryoletality, or gross fetal abnormalities. No-toxic-effect level was 1.6 mg/kg/day IV. Definitive teratology study in rats. The incidences of malformations were not significantly different between control and treated groups.
Range-finding teratology (Rat/Sprague-Dawley)	7 6/F	saline vehicle 0.016 0.05 0.16 0.5 1.6 <i>Days 6 to 17 gestation</i>	No maternal toxicity, embryoletality, or gross fetal abnormalities. No-toxic-effect level was 1.6 mg/kg/day IV.
Teratology (Rat/Sprague-Dawley)	5 25/F	saline vehicle 0.16 0.5 1.6 <i>Days 6 to 17 gestation</i>	No maternal toxicity, embryoletality or fetal abnormalities. No-toxic effect dose was 1.6 mg/kg/day IV. The definitive teratology study in rats was repeated. In the initial study, there was a nonsignificant difference in skeletal formation between the rhBMP-2 groups and the saline and control groups. Examination of skeletal variance revealed a significant reduction in sternebral variance in all treated groups.

Fertility, Reproduction, and Teratology Studies			
Study Type (Species/Strain)	Groups No. Animals/ Sex	rhBMP-2 (mg/kg)	Relevant Findings
Repeat teratology (Rat/Sprague-Dawley)	2 25/F	vehicle 1.6 <i>Days 6 to 17 gestation</i>	It was hypothesized that the difference in skeletal formation in the preceding study was a result of the time of cesarean section rather than a treatment effect. This repeat study had a random order of selection for time of cesarean section. No maternal toxicity, embryolethality, fetotoxicity, or teratogenicity, and no difference in skeletal formation between the control and rhBMP-2 groups. No-toxic-effect level was 1.6 mg/kg/day IV.
Development toxicity (Rabbit/New Zealand White rabbit) <i>This study was a condition of approval study for the INFUSE® Bone Graft PMA and is included here to support the proposed device labeling.</i>	1 30/F	Dose = 2.0 mg + TiterMax® Gold	Immunized adult does had an increased frequency of loose and decreased feces, but with no other effect to weight, feed consumption, or pregnancy incidences and outcomes. Fetuses consistently developed reduced ossification of the frontal and parietal bones with positive anti-BMP-2 titers. These findings are not toxicologically important because reduced ossification is considered to be a reversible phenomenon, and anti-BMP-2 antibody titer levels, with or without antibody neutralizing activity, did not correlate with effects on fetal bone ossification.

Intravenous (IV) Pharmacokinetic Studies

Although rhBMP-2 is intended to be delivered with a carrier as an implant, pharmacokinetic results obtained from intravenous (IV) dosing provide a means to evaluate the extent and duration of systemic exposure to rhBMP-2. Pharmacokinetic studies following IV dosing showed minimal systemic exposure of rhBMP-2 due to the high clearance rate. Although the uptake of the rhBMP-2 by highly perfused tissues and organs is rapid, residence of the protein in these tissues is short. Catabolism of the protein is extensive and renal excretion of trichloroacetic acid (TCA)-soluble radioactivity is rapid (radioactivity not related to intact rhBMP-2). Studies were conducted to characterize the pharmacokinetics of rhBMP-2 in the blood of rats and monkeys. Following IV administration, rhBMP-2 was rapidly eliminated from the systemic circulation in rat and nonhuman primates ($t_{1/2}$ = 16 minutes in the rat and $t_{1/2}$ = 6.7 minutes in nonhuman primates). A study conducted in juvenile and adult Sprague-Dawley rats revealed that juvenile rats, like adult rats, cleared rhBMP-2 rapidly. Results also showed a lower maximal concentration, higher clearance, and a larger initial volume of distribution for rhBMP-2 in juvenile rats as compared to adult rats. As a result of these pharmacokinetic characteristics, systemic presence of

rhBMP-2 in the circulation was found to be minimal after IV dosing. The table below includes detailed descriptions and relevant findings for individual studies.

Intravenous Pharmacokinetic Studies			
Study Type (Species/Strain)	Groups No. Animals	rhBMP-2 Dose	Relevant Findings
PK & excretion Single dose (Rat/Sprague- Dawley)	4 12 (PK & excretion single dose)	0.43 µg/kg 4.3 µg/kg 43 µg/kg 860 µg/kg	Clearance of ¹²⁵ I rhBMP-2 was rapid and biexponential: T _{1/2α} ^a = 0.8 min and T _{1/2β} ^b = 15.3 min. Most of the administered dose (92%) was recovered by 24 hours in the urine as TCA-soluble counts per minute.
PK single dose (Nonhuman primate/cynomolgus monkey)	2 6	4.9 µg/kg	Clearance of ¹²⁵ I rhBMP-2 was rapid and biexponential: T _{1/2α} ^a = 1 min and T _{1/2β} ^b = 7 min.
Biodistribution (Rat/Sprague- Dawley)	8 24	4.3 µg/kg	Rapid localization to liver with metabolism and excretion into urine was noted. Biphasic disposition was observed with initial and terminal half-life of 0.8 and 31 minutes, respectively.
Biodistribution (Rat/Sprague- Dawley)	8 24	7.1 µg/kg	¹²⁵ I rhBMP-2 rapidly distributed to the highly perfused tissues; 1 minute after dosing, 82.4% of the dose was recovered in the liver, lung, kidney, and spleen. The liver was the predominant site of ¹²⁵ I rhBMP-2 localization throughout the study.
PK & excretion single dose, PK repeat dose (Rat/Sprague- Dawley)	1 4	5.3 mg/kg	Clearance of ¹²⁵ I rhBMP-2 was rapid and biexponential: T _{1/2α} ^a = 0.57 min and T _{1/2β} ^b = 16.7 min.
PK single dose: (Juvenile and adult rats/Sprague- Dawley)	2 24 juvenile and 12 adult	3.0 mg/kg	Clearance of ¹³¹ I rhBMP-2 was rapid and biexponential in both juvenile and adult rats as assessed by serum acid precipitable radioactivity and by ELISA.

T_{1/2α}^a = half-life of initial phase

T_{1/2β}^b = half-life of terminal phase

Neurological Safety

To evaluate the safety of rhBMP-2 for use in proximity to the spinal cord, neurological safety testing was conducted. The purpose of this study was to assess the effect of rhBMP-2 on exposed dura and neural tissue after standard decompressive lumbar laminectomy using a canine model. In addition, certain animals received puncture wounds to the dura with expression of cerebral spinal fluid at site of puncture. This study represented a worst case situation in which rhBMP-2 or autogenous bone graft was in direct contact with the spinal cord and, in some instances, a compromised dural barrier and found no evidence of safety concerns. The results are given in the table below.

Neurological Safety			
Study Type	Species/ Device Tested	rhBMP-2/ACS (mg/ml)	Relevant Findings
Implantation on exposed dura after laminectomy Mayer et al., <i>Spine</i> 1996	Dog/ rhBMP-2/ACS	0.10	Clinical observation, radiography, CT scans, neurological exam, histology: no neurological deficit, no spinal cord stenosis, and no mineralization of the dura when rhBMP-2 placed directly on exposed dura. There was no difference between animals that received a dural nick and those that did not.

CRM Properties and Development

Previous work [1] has demonstrated that rhBMP-2 on the absorbable collagen sponge (ACS) carrier is successful at inducing *de novo* bone formation when protected from significant compressive forces (e.g. muscle compression). Preclinical studies in both sheep [2,3] and nonhuman primate [4] interbody fusion models demonstrated that rhBMP-2/ ACS was effective at inducing reproducible bone growth and fusion when used within interbody fusion cages. In addition, rhBMP-2/ACS alone was shown to be capable of inducing reproducible bone formation and fusion in the rabbit posterolateral fusion model [5].

The successful fusion results with the ACS carrier in the rabbit posterolateral model and nonhuman primate interbody fusion model led to the investigation of rhBMP-2/ACS alone in a nonhuman primate posterolateral fusion model [1]. In this study, posterolateral fusion was performed at L4-L5 using different rhBMP-2 carrier formulations and rhBMP-2 doses. This study demonstrated that in six animals receiving rhBMP-2/ACS alone, only one treated with the high dose (8 mg rhBMP-2 at 1.7 mg/mL) achieved fusion. It was noted that this fusion mass was more robust at the transverse processes and narrower at the center of the intertransverse space. In the other animals treated with rhBMP-2/ACS alone, including the 2 mg and 4 mg doses, some bone formation was observed between the transverse processes. However, this bone growth was not continuous and led to pseudoarthrosis, as assessed by manual palpation. The minimal fusion mass volume and noncontiguous bone formation between adjacent transverse processes led the investigators to believe that soft tissue forces from the surrounding muscles compressed the sponge, resulting in limited and inconsistent bone formation. To test this theory, another group was examined, in which 9 mg of rhBMP-2 on ACS was covered by a protective polyethylene mesh shield. Results from this group confirmed that the shield protected the malleable rhBMP-2/ACS implant from compressive forces, allowing for more robust fusion masses to form.

This study suggested that a carrier matrix capable of retaining and delivering rhBMP-2 while resisting muscle compression was needed for the challenging posterolateral fusion environment. Hence, the CRM carrier was developed. The CRM is called

“compressive resistant” because it is better at resisting muscle compression than the ACS. When hydrated with rhBMP-2 solution, the CRM carrier becomes soft and pliable but is still capable of resisting deformation due to compression. However, the CRM carrier is not a structural implant and at no time does the carrier support spinal loads. To compare the compression resistance of the ACS and CRM carriers, a laboratory bench test study was performed. In this study, the compression resistance of the ACS and CRM was measured using an MTS 810 Materials Test System. The hydrated samples were placed between two steel plates and loaded in compression at a displacement of 0.1 mm/s for a total of 5 mm. The force required to achieve this displacement was recorded. The average load at 5 mm of compression for CRM was 489.2 ± 100.8 N, compared to 48 ± 2.5 N for ACS.

To further examine CRM as an adequate carrier matrix for rhBMP-2, two rabbit posterolateral fusion studies were performed, examining *in vivo* retention kinetics and fusion. Nine animals per study underwent a posterolateral fusion using 2.0 mg/cc of rhBMP-2 on the CRM carrier. For one side of the spine, ^{125}I -labeled rhBMP-2 was added to the rhBMP-2 solution prior to addition of the protein to the carrier. The residual radioactivity was measured using gamma scintigraphy over a period of six weeks. Results demonstrated that the rhBMP-2 release from CRM was characterized by a small burst release followed by gradual release for a period of approximately five weeks, with less than 5% of the implanted protein present at the implantation site after 35 days. In addition, the half-life of the rhBMP-2 at the implantation site was nearly eight days. This slow release relative to the rapid clearance from circulation results in negligible systemic rhBMP-2 exposure following implantation on the CRM carrier. A 100% fusion rate was also achieved in these studies.

Efficacy Studies Using the CRM Carrier

Nonclinical testing in spinal applications has included indication-specific testing in interbody and/or posterolateral fusion models. The CRM carrier was designed for the posterolateral fusion application; therefore, testing included feasibility and efficacy studies in rabbit and nonhuman primate posterolateral fusion models. Previous nonclinical work demonstrated that the nonhuman primate was the most challenging model for inducing reproducible spinal fusion [1,4]. In particular, the nonhuman primate posterolateral fusion environment not only required higher doses of rhBMP-2 than the rabbit model, but also required protection from compressive soft tissue forces to be successful [1].

Initial feasibility work for rhBMP-2/CRM included multiple studies in the rabbit posterolateral fusion model. The purpose of one study was to evaluate the biomechanical and histological properties of a 5:95 Hydroxyapatite (HA): β -Tricalcium Phosphate (β -TCP) ceramic/collagen compression resistant matrix (CRM) as a carrier for rhBMP-2 [6]. Fourteen (14) skeletally mature New Zealand White rabbits underwent L5-L6 posterolateral fusion. Each animal was treated with 0.43 mg/cc rhBMP-2 on the CRM carrier. Animals were sacrificed at 5 weeks. All treated levels were fused with new bone marrow formation limited to the confines of the CRM. The spines were

explanted and tested in tension for stiffness and strength. Biomechanical testing demonstrated that the rhBMP-2/CRM spines were statistically superior with respect to relative strength and stiffness as compared to those tested previously with autograft bone in a similar model.

Results of Biomechanical Testing			
Material	Relative Strength	Relative Stiffness	Fusion Rate
rhBMP-2/CRM	2.60 ± 0.11	2.16 ± 0.12	100%
Autograft	1.70 ± 0.10	1.20 ± 0.10	42%

Another study was performed to examine the efficacy of rhBMP-2/CRM in a rabbit single-level lumbar posterolateral fusion model and to characterize the carrier's resorption profile over time. In this study, the CRM carrier consisted of collagen impregnated with biphasic calcium phosphate ceramic granules (15:85 HA:β-TCP). Nine animals were used in this study (n = 3 per time point). The treatment groups in this study included the following: 1) buffer solution on the CRM carrier (3 cc per side) and 2) 0.43 mg/cc rhBMP-2 on the CRM carrier (3 cc per side). The rabbits were sacrificed and evaluated by gross palpation, radiography, and histology after three, six, and nine months. At three, six, and nine months, the gross palpation scores for the rhBMP-2/CRM treated animals were all greater than the buffer/CRM group, except for two animals that demonstrated similar scores. In general, there was a steady decrease in the amount of residual ceramic between the 3-, 6-, and 9-month time points. There was minimal resorption of the ceramic at three months. However, at nine months, there was little to no residual ceramic. In addition, it appeared that the CRM soaked with rhBMP-2 had an increased rate of carrier resorption compared to the buffer-soaked CRM.

Ceramic Composition and rhBMP-2 Concentration Selection

The next steps in development of the rhBMP-2/CRM device included a series of preclinical efficacy studies to optimize the design and maximize fusion results with the carrier. More specifically, the ceramic composition (i.e., percentage HA and percentage β-TCP) of the CRM and the appropriate rhBMP-2 bulk concentration for reproducible fusion were investigated.

The initial work was performed by soaking blocks of biphasic calcium phosphate (BCP at 60% HA and 40% β-TCP) ceramic with rhBMP-2 solution, resulting in bulk rhBMP-2 concentrations of 0, 1.35, 2.0, and 2.7 mg/cc [7]. These groups were compared to primates treated with iliac crest bone graft (ICBG). The animals were sacrificed at 24 weeks, and fusion was assessed using manual palpation, CT scans, and histology. Manual palpation indicated that all animals receiving ICBG did not achieve fusion. All animals receiving the ceramic blocks with or without rhBMP-2 obtained fusion as determined via manual palpation. In addition, CT scans indicated the blocks loaded with rhBMP-2 resulted in complete graft incorporation. Histology demonstrated that animals receiving no rhBMP-2 on the composite sponge contained predominantly fibrous tissue surrounding residual ceramic with very little bone formation, which extended from the decorticated transverse processes. The 1.35 mg/cc rhBMP-2 group contained more variable amounts of bone formation compared to the 2.0 mg/cc and 2.7

mg/cc treated animals. In addition, both the 2.0 mg/cc and 2.7 mg/cc groups demonstrated comparable bone formation, indicating the possibility of an efficacious threshold level for rhBMP-2 on the ceramic blocks. One limitation of the BCP block carrier was that a significant amount of residual ceramic was left unremodeled at the 24-week sacrifice time. Ceramic is radiopaque, which makes it difficult to distinguish between new bone growth and residual ceramic, especially on plain film radiographs. Ultimately, the objective was to have a ceramic carrier capable of maintaining space for an adequate fusion mass to form while remodeling over time and eventually being replaced by new bone formation. To accomplish this, studies were conducted to investigate the overall impact of decreasing the amount of slow-resorbing HA and increasing the amount of faster-resorbing β -TCP.

Another study performed examined two different ceramic-collagen composite sponges in a nonhuman primate posterolateral fusion model [6]. Six skeletally mature rhesus monkeys underwent L4-L5 posterolateral spinal fusion. The animals were divided into three investigational groups, which examined: 1) CRM (15% HA and 85% β -TCP) with 2.1 mg/cc of rhBMP-2 (n = 2); 2) CRM (5% HA and 95% β -TCP) with 2.1 mg/cc of rhBMP-2 (n = 2); and 3) CRM (5% HA and 95% β -TCP) with 1.0 mg/cc of rhBMP-2 (n = 2). It should be noted that the 1.0 mg/cc group had the same overall rhBMP-2 dose as the 2.1 mg/cc groups, but this dose was delivered on twice the volume of carrier. The animals were sacrificed at 6 months. All animals treated with the 2.1 mg/cc of rhBMP-2, independent of ceramic composition, resulted in 100% fusion. The group treated with only 1.0 mg/cc of rhBMP-2 formed some new bone but did not achieve solid fusion. The fusion masses in the animals treated with the 15:85 HA:TCP composite sponge were larger than those treated with the relatively faster-degrading 5:95 HA:TCP composite sponge. Histological analysis revealed the fusion masses contained normal bone formation and minimal residual ceramic.

This study demonstrated that the 15:85 HA: β -TCP biphasic calcium phosphate composition was ideal for supporting new bone formation while resorbing over time. The study also showed that the bulk concentration of rhBMP-2 when placed on a ceramic/collagen composite matrix (i.e., milligrams of rhBMP-2 to volume of carrier) is more important to fusion success than the overall dose of rhBMP-2 supplied at the implantation site. Finally, similar to the earlier concentration dosing study on the BCP blocks, the 2.0 mg/cc rhBMP-2 concentration was the most consistent at inducing reproducible bone formation and fusion with a ceramic carrier in the posterolateral space.

A final preclinical study was performed to verify the efficacy of the 2.0 mg/cc rhBMP-2 bulk concentration on the 15:85 HA: β -TCP CRM carrier prior to initiating the pivotal investigational device exemption (IDE) trial [8]. In this study, six rhesus monkeys were treated with either rhBMP-2/CRM at 2.0 mg/cc bulk concentration (n = 3) or rhBMP-2/CRM at 0.6 mg/cc bulk concentration (n = 3). This was an uninstrumented single-level fusion model. CT scans at two, four, and six months postoperatively and histology results at sacrifice indicated that rhBMP-2/CRM at 2.0 mg/cc bulk concentration was successful at inducing 100% fusion. None of the animals receiving the 0.6 mg/cc rhBMP-2/CRM demonstrated fusion, indicating that the concentration was too low. This

study verified that rhBMP-2 on the CRM carrier at 2.0 mg/cc bulk concentration was effective at achieving fusion in the challenging uninstrumented nonhuman primate intertransverse posterolateral fusion model. Therefore, rhBMP-2/CRM at 2.0 mg/cc was selected as the formulation for the clinical IDE.

Building on the base of rhBMP-2 safety data and confidence in the ability of rhBMP-2 to induce new bone formation across a range of clinical applications, the compression resistant matrix was designed specifically for use in posterolateral spinal fusion, where muscle compression could impede efficacy. Early work showed the carrier to be more compression resistant than ACS and capable of binding and releasing rhBMP-2 over a prolonged period of time. Rabbit feasibility studies showed consistent bone formation and fusion, with early incorporation of the calcium phosphate granules followed by gradual replacement of the graft with new bone. Finally, the nonhuman primate posterolateral model was used to select the concentration to be used in clinical investigations. Overall, rhBMP-2/CRM demonstrated equivalent, if not better, bone formation than iliac crest autograft while providing a compression resistant matrix for a very challenging clinical application.

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REPORT OF CLINICAL TRIAL RESULTS – MARCH 2009

AMPLIFY™ rhBMP-2 MATRIX DEVICE (G000137)

I. Introduction

This report presents updated results for the clinical trial entitled “A Prospective, Randomized Clinical Investigation of Recombinant Human Bone Morphogenetic Protein-2 and Compression Resistant Matrix with the CD HORIZON® Spinal System for Posterolateral Lumbar Fusion in Patients with Symptomatic Degenerative Disc Disease.” This clinical trial was conducted to evaluate the safety and effectiveness of the investigational implant, rhBMP-2/CRM with temporary posterior supplemental fixation,¹ for the posterolateral fusion treatment of patients with symptomatic degenerative disc disease. The investigational implant was compared to a control treatment of bilateral posterolateral implantation of autogenous bone harvested from the iliac crest with temporary posterior supplemental fixation.

Medtronic Sofamor Danek filed its initial Investigational Device Exemption (IDE G000137) for a pilot clinical trial of the investigational device on May 16, 2000. This IDE requested 12 patients at four sites. The pilot IDE was conditionally approved by the FDA on November 2, 2000, and later received unconditional approval on December 14, 2000. On September 18, 2001, Medtronic Sofamor Danek asked FDA to expand the pilot study to a pivotal clinical trial. On October 17, 2001, FDA conditionally approved this request, limiting the trial to 480 patients at 30 sites. Full approval of the pivotal study was granted on December 31, 2001.

The first patient was enrolled in the study on March 29, 2002, and the last patient was enrolled on March 26, 2004. The study involved a total of 463 patients (239 investigational; 224 control) enrolled at 29 study sites, with all centers following a common Clinical Investigational Plan (CIP). At this time, all patients have reached the 24-month follow-up visit, with the last 24-month visit occurring on May 15, 2006.

During the course of the study, several IDE supplements were submitted to FDA. One supplement requested approval for two additional investigational sites; another supplement asked for an increase in the length of patient follow-up for the study from 24 months to 36 months. This supplement was later amended to increase the length of the study to 60 months and stipulated that patients would have completed their follow-up for the study after the 60-month visit. The most recent IDE supplement requested that 24-month evaluations of the study's clinical and radiographic variables be used as endpoints for the study, instead of 12-month evaluations as originally stated in the protocol and statistical considerations. This supplement was submitted on June 18, 2007. It was approved by FDA on July 19,

¹ Medtronic's CD HORIZON® Spinal System was used in the study for both the investigational and control treatment groups.

2007. None of these supplements were believed to have any negative effect on the scientific soundness of the clinical trial.

Clinical data from this IDE were originally submitted to FDA on September 26, 2005, in a pre-market approval (PMA) application (P050036) for the device. The results and conclusions submitted at that time were based on 12-month data. In November 2005, Medtronic received a deficiency letter stating that its PMA application was incomplete and would need additional information in order to be filed. Specifically, FDA requested additional animal and bench testing to compare the kit used in the clinical trial with the commercial kit proposed at that time. While the requested preclinical testing was being performed (over a period of approximately six months), all of the patients enrolled in the IDE study reached the 24-month time point for evaluation. Because a longer follow-up is desirable to provide a more complete assessment of safety and effectiveness of the treatment, the protocol was amended to use 24-month data for the study endpoints, and the statistical analyses were performed again utilizing 24-month data. The last clinical report, dated August 3, 2007, used 24-month data on the study endpoints as the basis for its conclusions. This current report also presents 24-month results, as well as additional data now available after 24 months through 60 months postoperative.

As stated in the PMA, the investigational product will be marketed under the name AMPLIFY™ rhBMP-2 MATRIX kit.

II. Methods

A. Clinical Trial Goals and Design

The goal of the Investigational Device Exemption (IDE) clinical trial was to evaluate the safety and effectiveness of rhBMP-2/CRM with the CD HORIZON® Spinal System in the treatment of degenerative disc disease (DDD) at one level from L1 to S1. DDD was defined as back pain of discogenic origin, with or without leg pain, with degeneration of the disc confirmed by patient history (e.g., pain [leg, back, or symptoms in the sciatic nerve distribution], function deficit, and/or neurological deficit) and radiographic studies (e.g., CT, MRI, x-ray, etc.) to include one or more of the following:

1. instability (defined as angular motion $\geq 5^\circ$ and/or translation ≥ 4 mm, based on flexion/extension radiographs);
2. osteophyte formation;
3. decreased disc height;
4. thickening of ligamentous tissue;
5. disc degeneration or herniation; and/or
6. facet joint degeneration.

The assessment of safety and effectiveness of rhBMP-2/CRM with the CD HORIZON® Spinal System was made by direct comparisons between clinical data collected from patients implanted with rhBMP-2/CRM and the CD HORIZON® Spinal System (investigational) and a similar group of patients who received surgical treatment utilizing the CD HORIZON® Spinal System with autogenous bone derived from the iliac crest (control). Patients were randomized in a 1:1 manner to the investigational and control treatments.

The effectiveness of rhBMP-2/CRM with the CD HORIZON® Spinal System is based on a patient having radiographically-demonstrated fusion and Oswestry pain/disability improvement, and maintenance or improvement in neurological status following surgery. These factors, as well as the patient not having a serious implant-associated or implant/surgical procedure associated adverse event or having a second surgery classified as a “failure,” are used to determine whether a patient is an “overall success” – the primary endpoint for the clinical investigation. In addition, back pain, leg pain, graft site (hip) pain, general health status, and patient satisfaction are evaluated.

The safety of rhBMP-2/CRM with the CD HORIZON® Spinal System and the control treatment is based primarily on the nature and frequency of adverse events during surgery and postoperatively. Neurological maintenance or improvement is also considered a safety endpoint. Antibody test results and radiographic review comments are other safety assessments used in this study.

Patients were evaluated preoperatively, at surgery/hospital discharge, and at 6 weeks, 3 months, 6 months, 12 months, and 24 months after surgery. Twenty-four (24) months postoperative evaluations are the endpoints of the study. All patients have now been evaluated at 24 months, and this report presents information on the primary endpoint – overall success at 24 months.

In addition, patients are continuing to be evaluated for long-term follow-up at 36 and 60 months, with some data obtained at 48 months (prior to the IDE amendment that identified the times for continued follow-up as 36 and 60 months). Any data collected from these additional time points is being included in this report in Section III.J. Five year follow-up on all patients is being evaluated in the IDE study as the basis for a possible post-approval study request from FDA.

B. Statistical Methodology

1. Clinical Trial Objectives and Hypotheses

The primary objective of the clinical trial was to determine if, at 24 months after surgery, the proportion of patients having favorable overall success outcomes (the primary endpoint) in the investigational treatment group was statistically non-inferior to the overall success rate in the control treatment group. Secondary objectives were also developed for the

clinical trial. One such secondary objective was to determine whether the investigational group demonstrated superior overall success results as compared to the control group. Other secondary objectives were to determine if the success rates for the individual effectiveness and radiographic variables, such as Oswestry success and fusion success, as well as neurological status, were statistically non-inferior for the investigational treatment group as compared to the control treatment group. In addition, if non-inferiority was established, analyses were pre-planned in the protocol to determine if the investigational group had superior outcomes when compared to the control group for those individual variables. As FDA recommended, a fixed value of 0.10 was used as the non-inferiority margin for assessing all of the non-inferiority hypotheses.

For adverse events, additional surgical procedures/interventions, and surgery and hospital information, only superiority hypotheses were proposed, and statistical comparisons were only done for reference purposes because of the large number of categories of individual adverse events and additional surgeries/interventions.

2. Analysis Datasets

Three different analysis datasets (primary, per-protocol, and missing-equals-failure datasets) were defined. The primary dataset consisted of all the patients who received study devices and completed surgical procedures. In the case where a patient received the other study treatment – that is, a patient was randomized as control but actually received the investigational treatment or vice versa – the patient was grouped according to the actual treatment that the patient received.² Primary statistical comparisons were based on the observed data, and missing data due to lost-to-follow-ups were not imputed. For patients who had additional surgical procedures/interventions that were classified as “failures,” they were deemed as failures for overall success, the primary endpoint. For other individual variables, the last observations taken before the additional surgical procedures/interventions were carried forward for all future evaluation periods.

The per-protocol dataset was a subset of patients who were included in the primary analysis dataset. Patients who had major protocol deviations, *i.e.*, those who did not meet the inclusion/exclusion criteria, those who received wrong study treatments (patients who were randomized as control but actually received the investigational treatment or vice versa), or those who had other major protocol deviations that could potentially affect clinical outcomes, were excluded from this dataset. A list of those patients

² There were two patients in this study who were randomized to the control group but received the investigational treatment.

and a brief description of their major protocol deviations are provided in Appendix A for this section. Additional surgical procedures or interventions and missing values due to lost-to-follow-ups were handled in the same manner as in the primary dataset. The per-protocol dataset was constructed only for the primary endpoint (overall success) and its component variables. Statistical comparisons using this dataset should be considered as a secondary analysis.

To assess the effects of lost-to-follow-ups and missing observations (including deaths) on study outcomes, a “missing-equals-failure” dataset was constructed for the primary endpoint overall success and its component variables. In this dataset, all missing responses in the patients who received study devices and completed surgical procedures were assumed to be failures, regardless of the reason. Success rates were computed and presented for each treatment group, but no formal statistical comparisons were performed with this dataset. Results of this type of analyses are largely dependent on the follow-up rates. It would bias against the control if the control group has a lower follow-up rate compared to the investigational group, as is the case in this study. We are presenting this analysis only because FDA/CDRH has traditionally requested it.

3. Statistical Methods and Computations

Bayesian statistical methods were pre-defined and used to determine non-inferiority and superiority of the investigational device to the control for success rates in overall success, individual effectiveness variables, and neurological status. Technical details of Bayesian methods were described in the Statistical Considerations section, provided in Appendix B. Independent uniform priors were used, and thus, the posterior distribution was simply a beta distribution.

With the non-inferiority margin d (delta), the posterior probability of non-inferiority, $P(p_0 - p_1 < d \mid \text{Data})$, was calculated. If the probability is at least 0.95 (corresponding to the significance level of 0.05), non-inferiority can be claimed. Similarly, the posterior probability of superiority, $P(p_0 - p_1 < 0 \mid \text{Data})$, was also calculated. If the probability is at least 0.95 (corresponding to the significance level of 0.05), a claim of superiority can be made. The minimum delta to achieve the non-inferiority with the probability of 95% was also estimated. The posterior distributions for p_0 , p_1 , and $p_0 - p_1$ are graphically presented, and the corresponding 95% highest posterior density (HPD) intervals are also reported.

Bayesian methods were also used for comparing surgery and safety data between the investigational group and the control group. For proportion data, independent uniform priors were used. Thus, the posterior distribution is a beta distribution. For continuous data, non-informative Jeffrey's priors were used. The resulting posterior distribution is a Student- t distribution.

Based on these, the 95% HPD intervals were estimated. If zero is included in the 95% HPD interval, the null hypothesis cannot be rejected. The posterior probability of superiority of the investigational device to the control, $P(p_1 - p_0 < 0 \mid \text{Data})$ or $P(\mu_1 - \mu_0 < 0 \mid \text{Data})$, was also calculated. If the probability is at least 0.975, then superiority of the investigational device to the control will be claimed.

4. Bayesian Interim and Final Analyses

The Statistical Considerations portion of the investigational plan originally pre-defined that the data would first be analyzed after approximately 250 investigational and control patients had reached 12-month evaluations. The data would also be summarized when the entire cohort of patients had reached the 12-month time point. Thus, one interim analysis and one final analysis were planned. If the probability of non-inferiority $P(p_0 - p_1 < d \mid \text{data})$ for the primary endpoint was at least 95% at any of those evaluations, then the corresponding data and their analyses would be developed into a PMA submission regarding non-inferiority. If, in addition, the probability of superiority $P(p_0 - p_1 < 0 \mid \text{data})$ was at least 95%, then this would be used to support a claim of superiority.

Because of the delays of filing the PMA for various reasons, no interim analyses were performed for either 12-month or 24-month outcomes. The latest FDA-approved versions of the study protocol and Statistical Considerations defined 24-month evaluations as the study endpoints.

This PMA application is based on the final analysis of the data evaluated through the 24-month time point for the whole study patient population, with long-term data added since the last submission. These data have been monitored in an appropriate manner, cleaned, and verified.

III. Results

A. Patient Accountability

Summaries of patient accountability in each group at the different clinical trial time points are provided in Tables 1 and 2. (NOTE: All tables follow the report in the subsequent section of the submission.) A total of 239 patients received the investigational treatment, and 224 patients received the control treatment. The date of database closure for analyses was February 3, 2009.

Table 1 presents patient accountability on the basis of having received any data on a patient at the study time periods. At 24 months postoperative, the follow-up rate was 89.4% in the investigational group and 84.5% for the control group. Table 2 presents patient accountability based on the availability of overall success outcomes, a more conservative interpretation of accountability. At 24 months postoperative, the follow-up rate was 84.7% in the investigational group

and 82.7% for the control group. These rates are somewhat lower than those in Table 1, mainly because fusion status could not be validly assessed in some patients due to poor quality of radiographic films.

The number of “expected” patients in both tables of patient accountability was the total number of patients who reached the anniversary date for a visit, minus the number of deaths. Second surgery failures are included in the “expected” number, because those patients are counted in the endpoint analyses, including overall success, by statistically carrying forward the last observation before the second surgery, regardless of whether a patient had an actual visit or not after the second surgery. Information on the number of second surgery failures by time periods can be found in Appendix C. In a conservative way, patients who withdrew from the study after surgery are included in the “expected” number, because they are considered as lost-to-follow-up in the statistical analyses. From the time after surgery through 24 months postoperative, four investigational patients and 16 control patients withdrew from the study. After the 24-month time point, an additional 23 investigational patients and 17 control patients withdrew from the study. These withdrawals were largely due to patients removing their consent for participation or sites withdrawing from the study.

B. Surgeon Information

Eighty-four (84) surgeons from 29 investigational centers (29 IRBs) participated in this clinical trial. Among them, 63 surgeons performed surgeries. A list of the investigators involved in the clinical trial is provided in Appendix D. It should be noted that three sites have now withdrawn from the study. While one withdrawal was due to an illness of the investigator, the other two were due to the demands required by the extended study.

C. Patient Demographics

Demographic data were evaluated for all of the patients enrolled in the study, and this information is summarized in Table 3. Statistical comparisons were made to determine whether the investigational and control groups had different patient population characteristics. The two treatment groups were very similar demographically, with only one variable showing a statistically significant difference ($p < 0.05$). More patients in the control group had an “unresolved spinal litigation case” than patients in the investigational group (6.7% vs. 2.5%, $p = 0.042$). Section III.I.9 of this report includes a statistical analysis of the primary endpoint, overall success, and its components in which data from patients participating in spinal litigation are excluded. This analysis demonstrated that the spinal litigation cases did not influence study conclusions with regard to clinical and radiographic outcomes.

D. Preoperative Medical Status

1. Preoperative Medical Condition and Medication Usage

Summaries of the patients' preoperative medical conditions and medication usage are provided in Table 4. There were no statistically significant differences ($p < 0.05$) for any of the variables.

2. Preoperative Summary of Degenerative Disc Disease Diagnostic Characteristics

A summary of preoperative radiographic characteristics of degenerative disc disease is listed in Table 5. These features were considered as part of the patient entry criteria into the study. As evident in the table, the radiographic characteristics of degenerative disc disease for the investigational and control patients were very similar. The proportions of patients who had multiple characteristics reported were also similar. Since investigators could mark one or more of the characteristics when enrolling patients, statistical analyses of the proportions are not considered appropriate. These data are being provided for informative purposes.

3. Preoperative Evaluations of Clinical Endpoints

Table 6 summarizes the preoperative status of the clinical trial endpoint parameters for the treatment groups. There were no statistically significant differences between the groups.

4. Summary

In summary, patients in both treatment groups had very similar preoperative medical conditions.

5. Study Patients vs. Non-Study Patients

Fifty-five (55) patients were randomized but were withdrawn from the study prior to receiving their assigned treatment. These patients are considered "non-study patients." Twenty-three (23) of these patients would have received the investigational treatment and 32 would have received the control treatment. Patients withdrew from the study preoperatively based on reasons listed in Table D-1 below. In addition, investigators withdrew patients preoperatively or intraoperatively after determining that the patient needed a different treatment or did not meet the inclusion criteria. A summary of the reasons given for withdrawal prior to receiving the device are as follows:

Table D-1. Reasons for Declining Participation Prior to Receiving Treatment		
	Investigational	Control
Different procedure required	7	12
Exclusion Criteria	1	4
Insurance Status or Denial	6	2
Patient Declined Participation	3	9
Patient Did Not Call to Schedule	3	3
Patient Did Not Complete Paperwork	1	1
Worker Compensation Issues	1	1
IRB Suspension of Study	1	0
TOTAL	23	32

Demographic and preoperative medical status data were collected for the non-study patients, and statistical comparisons were made to compare these patients to those who did receive the treatment. Note that also included in the count of non-study patients are four randomization numbers that were unintentionally skipped by the investigators, two in each treatment group. Table 7 presents the comparison of demographic information between the study and non-study patients. Table 8 presents a comparison of preoperative medication conditions and medication usage. Finally, Table 9 presents a comparison of preoperative evaluations of clinical endpoints.

In the investigational group, study and non-study patients had statistically different ($p < 0.05$) results in only two assessments. The non-study group had a higher percentage of unresolved spinal litigation cases and lower SF-36 PCS mean scores than the study group. For control patients, there were no statistically significant differences between any of the comparisons made between the study and non-study group patients.

The two statistical differences described above in the investigational group are believed to have no substantial impact on the clinical outcomes of the study. These comparisons demonstrate that the investigational and control patients who did participate in the study are very similar to those patients who did not participate in the study.

E. Surgery Information

Table 10 summarizes information related to the surgical procedures and postoperative hospitalizations of patients. The results of the Bayesian statistical analyses of the surgery data between the investigational and control groups are provided in Appendix E.

The mean operative times for the investigational and control treatment groups were 2.5 hours and 2.9 hours, respectively. These average operative times were found to be statistically different (probability of superiority is essentially 100.0%) based on Bayesian analyses. Investigational patients were found to

have less blood loss than the control group patients (343.1 mL versus 448.6 mL), with a probability of superiority value of essentially 100.0%.

The average length of hospital stay for patients in both treatment groups was approximately four days (4.1 and 4.0 days, respectively). No statistical difference of the two treatment groups for this parameter was demonstrated in the Bayesian analyses.

Even though statistical analyses were not performed, it is evident that the distributions of patients in the two treatment groups for the variables of treatment level, external orthosis, and outpatient/inpatient classification were very similar. These findings are considered beneficial for the clinical trial since they indicate that both investigational and control patients had similar procedures and were treated similarly postoperatively.

In summary, patients in the investigational group had shorter operative times and less blood loss than control group patients, most likely because a procedure for harvesting iliac crest graft was avoided in the investigational patients. The other operative parameters yielded similar results.

F. Safety Measurements

The safety variables measured in this study included assessment of adverse events, secondary surgical procedures, and neurological status. Radiographic reviewer findings were also examined, as were the results of antibody testing.

1. Adverse Events

The safety of the investigational device was evaluated based on comparisons of the nature and frequency of adverse events (AE) occurring in the treatment groups. Adverse events, or complications, vary in severity. Some may resolve without any subsequent treatment, some may require nonoperative medical intervention, and others may result in another surgical procedure. Narrative information pertaining to the adverse events from each treatment group is provided in Appendix F.

Adverse events were categorized by their nature. If the underlying cause of the adverse event was known, it was classified accordingly. If the underlying cause was unknown, the adverse event was classified according to the symptoms. For example, if a patient had back and/or leg pain secondary to a fall, the event was classified as "Trauma." On the other hand, if the cause of the back and/or leg pain was not known, the event was classified as "Back and/or Leg Pain."

In accordance with the clinical trial protocol, adverse events were classified according to their severity utilizing World Health Organization (WHO) criteria (mild, moderate, severe, or life threatening). If the adverse

event was graded as severe (“3”) or life threatening (“4”), it was considered “serious;” otherwise, it was considered “non-serious.” Typically, adverse events which resulted in an emergency room visit or a hospitalization were “serious.” Each adverse event summary provided in Appendix F has been classified according to these considerations.

Table 11 provides a time course summary of all operative and postoperative adverse events reported for investigational and control patients as a function of adverse event category. For this study, 23 main categories of adverse events were identified.³ The total number of occurrences per category is provided. One of the main categories, “Other,” was used to capture information about adverse events that occurred infrequently and did not fit into a particular category. For reference purposes, these “other” events have been broken out into separate tables (Tables 12 and 13) for the investigational and control groups, respectively.

A total of 209 (87.4%) investigational patients and 197 (87.9%) control patients had at least one adverse event within 24 months of the study surgery. Through 24 months, a total of 756 events were reported in the investigational patients, and 694 events were reported in the control patients. These adverse events varied in type, severity, and possible cause. The number of adverse events denotes the diligence that was undertaken to report all events that occurred to a patient, even though the event may not be related to the surgery or the implant. Therefore, adverse events such as anxiety, cough and cold, and trauma from motor vehicle accidents are included in the listing. This overall number of events also includes adverse events that were not considered serious.

To further distinguish what events are important to the study implant or implant/surgery being evaluated, additional breakdowns of adverse events are provided. Table 14 provides a summary of Grade 3 and 4 adverse events from the study. A total of 126 (52.7%) investigational patients and 125 (55.8%) control patients had at least one Grade 3 or Grade 4 adverse event within the first 24 months of the study. There were a total of 228 Grade 3 or 4 events in the investigational patient group and 234 events in the control patient group. While this table delineates the adverse events that are considered serious from the non-serious events, there are still events included in this listing that are not related to the implant.

The next two tables provide information that is more specific to the study surgery or device. Table 15 summarizes the adverse events that were thought to be possibly related to the study device or the device/surgical procedure. A total of 21 (8.8%) investigational patients and 34 (15.2%) control patients had at least one adverse event possibly related to the

³ One of these categories, “Spinal Event,” has been further subdivided into “Spinal Event – Cervical,” “Spinal Event – Thoracic,” and “Spinal Event – Lumbar.”

study device within 24 months of the study surgery. The 21 investigational patients had a total of 22 possibly related events and the 34 control patients had a total of 36 possibly related events through the 24-month time period.

Table 16 summarizes the Grade 3 or 4 adverse events that were possibly related to the study device at 24 months. Records show that, of those patients having an implant-associated or implant/surgical procedure-associated adverse event, only 15 (6.3%) investigational patients had 15 such events rated as Grade 3 or 4. This rate was less than the rate for the control group, with 27 (12.1%) patients having 28 events rated as Grade 3 or 4 and possibly related. The events that have been determined to be serious and possibly related to the study device include specific events mainly relating to back and leg pain, malpositioned implants, neurological events, and non-unions.

For all the categories considered in Table 11, statistical differences were noted between the categories for graft site related (0% investigational, 7.6% control) and non-union (4.2% investigational, 10.3% control) adverse events. The following information pertains to these events showing statistical differences:

Graft Site Related

The graft site related adverse event rate favored the investigational group. Graft site adverse events are restricted to the control group since rhBMP-2 eliminates the need to harvest bone. A total of 17 discrete graft site related events occurred in 17 patients in the control group (7.6%) through 24 months. Of these 17 graft site related events, one was classified as serious, with none related to the device. The majority of these events involved pain at the harvest graft site. As a result, the control group rate of graft site adverse events was statistically higher than the 0% rate for the investigational group. As expected, the Bayesian statistical analysis of adverse events in Appendix G shows a posterior probability of superiority of essentially 100%. This finding confirms one of the expected benefits of using rhBMP-2/CRM.

Non-Union

The rate of non-union adverse events also favored the investigational group. A total of ten events classified as non-unions occurred in ten patients in the investigational group (4.2%) through 24 months. These included seven instances of pseudoarthrosis, with three of these patients being asymptomatic; one incomplete fusion; one loosening of screws; and one back pain. Of these ten events, five were classified as serious, device-related events. Five patients underwent additional surgeries (four supplemental fixations and one removal). Five of these nonunion adverse

events have not resulted in an additional surgery to resolve the nonunion at this time.

By comparison, a total of 23 events classified as non-unions occurred in 23 patients in the control group (10.3%) through 24 months. These events included three events of back and/or leg pain; 19 instances of pseudoarthrosis, with one of these patients being asymptomatic; and one pseudoarthrosis with a right pedicle fracture. Of these 23 events, 18 were classified as serious, device-related events. Seventeen (17) patients underwent additional surgeries (four supplemental fixations, 11 removals, one supplemental fixation with adjacent level fusion, and one supplemental fixation with revision). Six of these nonunion adverse events have not resulted in an additional surgery at this time. The rate of the non-union adverse events in the investigational group was statistically lower than the rate of the control group, with a posterior probability of superiority of 99.6%.

The remaining categories yielded no statistical differences between treatment groups.

There were some categories in Table 11 that, while they were not statistically different between the investigational and control groups, had adverse event rates that were greater than 10% at 24 months postoperative. Nine categories in the investigational group and eight categories in the control group had adverse event rates greater than 10% at 24 months postoperative. These included back and/or leg pain (43.9% investigational, 39.7% control); cardiovascular (22.2% investigational, 24.1% control); gastrointestinal (15.5% investigational, 14.7% control); infection (16.3% investigational, 20.1% control); neurological (29.3% investigational, 26.8% control); other (29.3% investigational, 27.7% control); other pain (12.1% investigational, 12.9% control); trauma (28.9% investigational, 26.3% control); and urogenital (11.3% investigational, 9.4% control). In addition, events associated with the “Spinal Event – All” category are being discussed for their relevance to spinal surgery, even though the rates are less than 10% (7.1% investigational, 8.5% control). However, the significance of these categories should also be evaluated in terms of the seriousness of the events and the relationship to the implant. Appendix H has a further breakdown of these categories with information regarding the relationships and severity of the events.

Overall, only seven events from these nine categories were classified as implant or implant/surgical procedure related for the investigational patients. These events included four back and leg pain events, two neurological events (radiating pain and radiculopathy) and one trauma event (MVA resulting in pseudoarthrosis). In the control group, only six events were classified as implant or implant/surgical procedure related for the nine categories above. These events included five back and leg pain events and one neurological event (radiating pain).

This evaluation of categories with reporting rates of greater than 10% illustrates the diligence undertaken to report adverse events in the study, even though a large number of events are not serious or related to the study device.

In addition, two relevant categories with rates less than 10% will be discussed in the examination of safety in spinal surgery. These categories are deaths and cancers.

Cancers

A comprehensive report detailing the rates of cancer events reported with the worldwide use of rhBMP-2, as well as all of Medtronic Sofamor Danek's rhBMP-2 clinical trials, is included in Section III of this PMA amendment, entitled "Current Review of Malignancies and rhBMP-2."

In this study, a total of nine cancer events occurred in nine patients (3.8%) in the investigational group through 24 months. These cancer events included the following: one laryngeal cancer, one lung cancer, one non-Hodgkin lymphoma, one ovarian cancer, one pancreas cancer, one prostate cancer, one stomach cancer, one basal cell carcinoma, and one squamous cell carcinoma.

Three additional patients had four cancer events after 24 months postoperative. These four other cases included one case of leukemia, one malignant melanoma of the eye, one prostate cancer, and one thyroid cancer.

Of these events, all were classified as serious and not related to the device. Of the 13 total events, seven required additional surgeries: one lumpectomy of right groin, one tumor removal and total hysterectomy with bilateral salpingectomy and oophorectomy, one biopsy of the prostate, one implantation of a palladium seed in the prostate (for radiation therapy), one stomach surgery, one thyroidectomy, and one removal of basal cell carcinoma.

In the control group, a total of two cancer events occurred in two control patients (0.9%) through 24 months. These included one colon cancer and one non-Hodgkin's Lymphoma. In addition, one breast cancer and one thyroid cancer were reported after the 24-month time point. Of these events, all were classified as serious and not related to the device. All four events required additional surgeries: one colon resection, one left inguinal hernia repair and lymph node excision with ERCP and stent placement, one lumpectomy and lymph node dissection, and one thyroidectomy.

Deaths

A summary of each study patient who died at any time point during the study is provided in Appendix I. A total of six deaths occurred in the investigational group during the study, with three of these deaths taking place after the 24-month time point. In the control group, seven patients died, and three of these deaths occurred after the 24-month time point. None of the deaths were related to the study procedure.

2. Secondary Surgical Procedures

Some adverse events led to second surgical interventions after the clinical trial surgery. Each second surgical intervention was classified as one of five different kinds of procedures:

- Revision - A procedure that adjusts or in any way modifies the original implant configuration.
- Removal - A procedure that removes one or more components of the original implant configuration without replacement with the same type of device.
- Supplemental fixation - A procedure in which additional spinal devices not approved as part of the protocol are placed.
- Reoperation - Any surgical procedure at the involved level that does not remove, modify, or add any original implant components.
- “Other” surgical procedures are ones that do not fit into the previously mentioned categories and may not even involve the lumbar spine.

Table 17 summarizes secondary surgical interventions in each group. The statistical analyses of the rates of secondary surgical procedures between the two treatment groups are provided in Appendix J.

At 24 months postoperative, the second surgery rates for the two treatment groups were comparable for revisions, supplemental fixations, reoperations, and other procedures. However, there was a difference noted between groups for removals. A greater number of control patients (28, or 12.5%) required a removal when compared to the investigational group (13, or 5.4%). For non-elective removals, the rate was still different between the investigational group (4.2%) and the control group (9.8%).

Six investigational patients had supplemental fixations (2.5%). These surgeries were secondary to investigator diagnosis of non-union in four patients and complaints of back and leg pain in two patients. In the control group, nine patients had supplemental fixations (4.0%). This included three patients who had bone growth stimulators utilized post-operatively, as well as surgeries secondary to investigator diagnosis of non-union in four patients, complaints of back and leg pain in one patient, and trauma in another patient. There was no difference in the supplemental fixations between groups.

In accordance with the protocol, if a study patient had a revision, removal, or supplemental fixation procedure, the patient was then classified as a second surgery “failure.” These events are considered in the calculations of the “overall success” rate for the study. See Appendix C for a breakdown of these failures by time point.

3. Neurological Status

The neurological status of study subjects was assessed preoperatively and postoperatively. The neurological status assessment tool addressed motor function, sensory function, reflexes, and straight leg raise. An algorithm was developed to transform the detailed scores for each parameter into an overall classification representing maintenance or improvement in neurological status at a given postoperative time, as compared to a patient’s preoperative neurological status. The values were totaled for each neurological subsection (*i.e.*, motor, sensory, reflexes, and straight leg raise) and then expressed as a percent of the maximum possible score for that subsection. A normal parameter would have a score of 100, while an abnormal parameter would have a score of less than 100.

After determining the percentage scores, the postoperative subsection scores were compared to the preoperative scores. A successful outcome was declared if the difference between the postoperative and preoperative scores was greater than or equal to zero. The overall measure of neurological status was based on a successful result in each of the four parameters. The overall neurological status was deemed a success if and only if all four parameters were successes. If any one of the parameters was deemed a “failure,” the overall neurological status was considered a “failure.”

Table 18 lists the outcomes for overall neurological status success for both groups. At 24 months following surgery, the success rate of neurological status was 87.0% for the investigational group, as compared to 84.2% for the control group. No statistical difference of the two treatment groups for neurological success was demonstrated in the Bayesian analyses with a posterior probability of non-inferiority of virtually 100.0%. See Appendix K for more on these analyses.

4. Radiographic Reviewer Findings

Implant events based upon radiographic review are included in Table 19. In all reviews for the investigational group that were evaluated by two radiologists and adjudicated by a third radiologist, there were reports of CD HORIZON® Spinal System loosening in three patients. These patients, [REDACTED], [REDACTED], and [REDACTED], had designations of failure in overall success at six months, failure at six months, and failure at 12 months, respectively. In all reviews for the control group that were evaluated by two radiologists and adjudicated by a third radiologist, there were reports

of CD HORIZON® Spinal System loosening in one patient, [REDACTED]. This patient was designated as an overall success failure at six months. Additional comments concerning loosening of the CD HORIZON® Spinal System were made by one radiologist, but not confirmed by the second radiologist or adjudicator for two investigational patients, [REDACTED] and [REDACTED] and for two control patients, [REDACTED] and [REDACTED]. All of these patients were failures or had missing values for overall success at 24 months.⁴

Additional comments concerning broken implants or implant migration may have been noted by one radiologist, but the comments were not confirmed by the second radiologist or adjudicator. These comments included a broken graft mass (reported at discharge and six weeks) in investigational patient [REDACTED], migration (reported at three, six, and 24 months) in investigational patient [REDACTED] and fusion mass fracture (reported at 36 months) in control patient [REDACTED].

In addition to the observations pertaining to the implants and fusion mass, members of the radiographic review teams would occasionally write comments on the case report forms. The vast majority of these comments concerned the availability and/or quality of the films.

In addition, there were a few comments that pertained to other observations. It should be noted that the comments may have been made by only one of the radiologists and not by the other radiologist. Some comments indicated that the graft had extended above or below the level fused during the study surgery. This comment was made concerning nine investigational patients [REDACTED] and [REDACTED] and five control patients [REDACTED] and [REDACTED]. A few comments at six and 12 months indicated that the graft had resorbed. This particular comment was noted on six investigational patients [REDACTED], [REDACTED], and [REDACTED] and two control patients [REDACTED] and [REDACTED]. One comment on patient [REDACTED] (investigational) indicated the presence of “a sclerotic rim around the right proximal and left distal screw.” Another comment on patient [REDACTED] (control) indicated that there was extensive bone formation anterior to the level fused during the study surgery.

Further information concerning the radiologists’ comments, as well as the summaries of the answers to the implant status questions, can be found in the Data Listings provided on CD in Appendix L.

⁴ One additional investigational patient [REDACTED], had loosening of the CD HORIZON® Spinal System at 60 months postoperative.

5. Antibody Testing

The report of the antibody testing performed on the patients involved in this study was presented in the original PMA, dated September 26, 2005. A summary of the procedures and results are presented here for completeness of review of the safety of the treatment.

An evaluation of antibody testing was conducted to compare performance of two different enzyme-linked immunosorbent assays (ELISAs) designed to detect antibodies to rhBMP-2 in clinical samples. Formation of antibodies to rhBMP-2 was assessed in 451 patients in this clinical study. Of the 451 patients evaluated to date, 234 investigational patients were treated with rhBMP-2, and 217 control patients were treated with autogenous bone. Serum samples for antibody testing were collected prior to surgery and then again approximately at six weeks and at three, six, and 12 months after treatment. Forty-eight (48) patients (22 investigational, 26 control) were excluded from the analysis. These patients were considered non-evaluable because a serum sample was obtained at the preoperative time period, but no samples were obtained at the postoperative time intervals. Patient samples were analyzed in each of two ELISAs designed to measure antibodies specific for rhBMP-2. The original ELISA (used to test samples from previous clinical studies with rhBMP-2) uses protein G as a reagent to detect anti-rhBMP-2 antibodies in patient samples. The new ELISA uses an anti-human immunoglobulin antibody reagent for detection.

rhBMP-2 Antibody Results

Based upon the original protein G-based ELISA, the overall incidence of an elevated antibody response to rhBMP-2 was found to be 1.8% (8/451). The incidence in patients treated with rhBMP-2 was 3.4% (8/234), while the incidence in control patients was 0% (0/217).

Based on the new anti-human immunoglobulin antibody-based ELISA, the overall incidence of an elevated antibody response to rhBMP-2 was shown to be 4.4% (20/451). The incidence in patients treated with rhBMP-2 is 6.4% (15/234), which includes the eight patients identified by the original protein G-based ELISA. The incidence in control patients is 2.3% (5/217).

Of the 15 investigational patients [REDACTED] and [REDACTED] who exhibited authentic positive results to rhBMP-2 based on the new anti-immunoglobulin antibody-based ELISA, six patients [REDACTED], and [REDACTED] reported fifteen serious adverse events through 60 months postoperative. These events included one nerve root impingement, one wound infection, one osteoarthritis in the knees, one hip pain from hip replacement surgery, one cervical disc protrusion, two instances of

intolerance to foods and nausea, one cardiac after MVA, one gastric volvulus, one nausea and vomiting, two cataract surgeries, one snap in back, one instance of myoclonic jerks and loss of consciousness, and one renal failure. None of the fifteen serious adverse events or any of the non-serious events were considered implant- or implant/surgery-associated. Eight investigational patients [REDACTED], and [REDACTED] reported 10 adverse events that were undetermined in the relationship to the device (eight back and/or leg pain, one left foot drop and one back and radiating leg pain). Three investigational patients [REDACTED], [REDACTED] and [REDACTED] reported three adverse events that were surgery related (wound infection, nerve root impingement and urinary retention). In addition, there were 13 investigational patients [REDACTED], [REDACTED], and [REDACTED] who reported 52 adverse events that were not related to the device.

Of the five control patients [REDACTED], and [REDACTED] who exhibited authentic positive results to rhBMP-2 based on the new anti-immunoglobulin antibody-based ELISA, two patients reported seven serious adverse events. One patient [REDACTED] reported six serious adverse events (one abdominal pain, one gallstones, one nausea and vomiting, one pulmonary embolism, one obesity, and one rectal pain with hemorrhoids), and another patient ([REDACTED] reported one serious gastrointestinal (GERD) event. None of these seven serious adverse events or any of the non-serious events were considered implant- or implant/surgery-associated. One patient [REDACTED] reported one adverse event that was undetermined in relationship to the device (one back pain). One patient [REDACTED] had two adverse events reported that were surgery-related (one graft site related pain and one wound abscess/dehiscence). In addition, all five patients who exhibited authentic positive antibody results [REDACTED], and [REDACTED] reported adverse events that were not related to the device, for a total of 17 adverse events.

Bovine Type I Collagen Antibody Results

The overall incidence of elevated antibody response to bovine Type I collagen was found to be 18.8% (85/451). The incidence in patients treated with rhBMP-2 was 16.7% (39/234), while the incidence in control patients was 21.2% (46/217).

No patients who had an elevated antibody response to bovine Type I collagen exhibited an elevated antibody response to human Type I collagen.

Neutralizing Antibody Results

A neutralizing antibody assay was run on samples from patients with positive antibodies to rhBMP-2. There were no positive neutralizing antibodies detected.

Antibody Result Summary

The rates of authentic antibody responses to rhBMP-2 with either assay were very low for the two treatment groups. Neutralizing antibodies were not detected in these patients. In addition, the rates of authentic positive antibody responses to bovine Type I collagen were similar for the two treatment groups. Since the control patients were not exposed to the ACS during surgery, the positive response may be due to prior exposure to bovine collagen, possibly from hemostatic agents. Regardless, none of the patients in either treatment group had positive results for human Type I collagen. Also, there were no apparent negative clinical manifestations resulting from the existence of antibodies to rhBMP-2 or bovine collagen.

6. Safety Summary

In summary, rhBMP-2/CRM with posterior supplemental fixation was found to be at least as safe as the control treatment. The adverse event rates were comparable to those of the control treatment utilizing autogenous bone graft and posterior supplemental fixation. The only adverse event categories in which statistical differences were noted were graft site events and non-unions. The incidence of graft site adverse events favored the investigational group. This is considered a very positive result since one of the benefits of using rhBMP-2/CRM is that it precludes the harvesting of bone graft and, in this case, reduces or eliminates a number of related adverse events. The rate of non-union adverse events was higher in the control group. This result is also favorable for the investigational group since the investigational group had a reduction in second surgeries.

In addition to comparable adverse event rates, there were no statistical differences between treatment groups for any of the second surgery categories except removals. The investigational group had statistically fewer removals than the control group.

The rates of authentic antibody responses to rhBMP-2 were very low for the two treatment groups in both assays used. Neutralizing antibodies were not detected in these patients. In addition, the rates of authentic positive antibody responses to bovine Type I collagen were similar for the two treatment groups, and none of the patients in either treatment group had positive results for human Type I collagen. Also, there were no

apparent negative clinical manifestations resulting from the existence of antibodies to rhBMP-2 or bovine collagen.

G. Effectiveness Measurements

The effectiveness variables measured in this study included assessment of fusion at the involved level, Oswestry pain/disability status, back pain, leg pain, general health status, and graft site pain. In some cases, only partial data were available (*i.e.*, not all of the outcome measures were obtained for all patients at all follow-up points). In these cases, all available outcomes were summarized in the analyses. Therefore, the number of patients included in the assessment of the outcomes varies slightly due to missing data.

The results of statistical analyses of the effectiveness outcomes, as well as overall success, between the investigational and control treatment groups are provided in Appendix K.

1. Fusion

Fusion of the surgically treated vertebral bodies was determined using CT scans and A/P, lateral, and flexion/extension radiographs. The CT scans and radiographs were evaluated at Synarc. At Synarc, two teams of reviewers assessed the radiographs for fusion. Each team worked independently of the other. If their overall conclusions differed, a third independent Synarc reviewer was used to adjudicate the findings (break the tie). All reviewers were blinded to treatment group.

The fusion status of study patients was assessed at six, 12, and 24 months following surgery. Evidence of bridging trabecular bone, defined as a continuous bony connection from the superior transverse process to the inferior transverse process on both sides, was required for a patient to be considered fused. This determination was made with radiographs and CT scans. Additional criteria for fusion utilized radiographs. These criteria included no evidence of motion, as defined by no more than 3mm difference in translation on lateral flexion/extension radiographs and less than 5° difference in angular motion between flexion and extension, as seen on lateral flexion/extension radiographs. The final criterion for fusion was the absence of cracking, as evidenced by radiolucent lines completely through the fusion mass.

Table 20 presents the fusion results for patients in the investigational and control groups at six, 12, and 24 months following surgery. The fusion rates at all time periods were high for both treatment groups. At 24 months following surgery, the fusion rate of the investigational group was 95.9%, compared to 89.3% for the control group. These fusion success rates were found to be statistically different (posterior probability of superiority is 99.2%)

based on Bayesian analyses. Therefore, the investigational treatment is superior to the control treatment in terms of fusion.

There was extremely good agreement between the two independent radiographic reviewers in terms of assessing fusion. At 24 months after surgery, the percent agreement between the two reviewers was 96.7% for the investigational group and 96.2% for the control group with Cohen's kappa coefficients of 0.6079 and 0.7293, respectively (see Table 21).

2. Pain/Disability (Oswestry Disability Index)

The Oswestry Low Back Pain Disability Questionnaire (Fairbank, J. and P. Pynsent. The Oswestry Disability Index. *Spine* 2000; 15: 2940-53.) was used to measure the effects of back pain on a patient's ability to manage everyday life (*i.e.*, a combined measure of pain and disability). The Oswestry questionnaire is based on a patient's response to ten questions that focus on pain, personal care, lifting, walking, sitting, standing, sleeping, sex life, social life, and ability to travel. The responses to each question range from zero to five. A lower numeric score represents a better pain and disability status regarding that variable. A total Oswestry score can be determined by adding the scores of the individual questions and dividing that total by the maximum possible total score (*i.e.*, 50 if all questions are answered), yielding a percentage. Therefore, Oswestry scores are in a range of 0% to 100%, with a lower percentage indicating less pain and disability. The Oswestry Questionnaire was administered preoperatively as well as at each postoperative visit.

The mean Oswestry scores for the investigational and control patients at the different clinical trial periods are provided in Table 22. At all postoperative time periods for both treatment groups, the mean Oswestry scores improved as compared to the preoperative scores. The mean improvement in Oswestry scores was similar at the time periods for both treatment groups. For example, the Oswestry scores for investigational patients improved from preoperative to 24 months by an average of 26.7 points, as compared to a 25.5-point improvement for the control group.

Table 23 shows the distribution of patients demonstrating preoperative to postoperative improvements of at least 15 points in Oswestry score. Similar to the mean improvement scores, the Oswestry success rates were very similar for the investigational and control groups. At 24 months following surgery, the Oswestry success rate for the investigational group was 73.1%, as compared to a 72.7% rate for the control group, with a posterior probability of non-inferiority of 99.0%.

3. Back Pain

Numerical rating scales, adapted in part from *Measuring Health* (McDowell and Newell, 1996), were used to evaluate back pain. The back pain score is the summation of a patient's pain intensity and duration values as measured on numerical rating scales. Treatment group comparisons may be made based on actual measurements or changes in measurements from preoperative to postoperative scores.

A summary of back pain scores is provided in Table 24. The mean back pain scores at all postoperative time periods were less than the preoperative mean values for both treatment groups, indicating status improvement following surgery. In addition, the mean score and mean improvement scores were similar for the two treatment groups. At 24 months postoperative, the mean back pain score was 7.1 for patients in the investigational group and 7.8 for patients in the control group. The mean improvement was 8.5 and 7.9 points for the two groups, respectively.

Table 25 presents the distribution of patients with successful outcomes. At 24 months, the investigational group had a back pain success rate of 92.8%, and the control group had a success rate of 95.1%, with a posterior probability of non-inferiority of 99.9%.

4. Leg Pain

Numerical rating scales as described above were also used to measure leg pain. The leg pain score is the summation of a patient's pain intensity and duration values as measured on numerical rating scales. Treatment group comparisons may be made based on actual measurements or changes in measurements from preoperative to postoperative scores.

The summary of leg pain scores is provided in Table 26. The mean leg pain scores for each treatment group were similar, and there were improvements in condition at all time points following surgery. At 24 months postoperative, the mean leg pain score was 6.2 for patients in the investigational group and 6.7 for patients in the control group. The mean improvement was 7.6 and 7.3 points for the two groups, respectively.

Table 27 shows the distribution of successful leg pain outcomes. At 24 months following surgery, the leg pain success rates for the two treatment groups were very similar. The investigational group had a success rate for leg pain of 87.0%, and the control group had a success rate of 84.6%, with a posterior probability of non-inferiority of essentially 100%.

5. General Health (SF-36 Health Survey)

The Medical Outcomes Study 36-Item Short Form Health Survey (SF-36) was used to assess general health status of all study patients. The SF-36 is a self-administered test completed by the patient prior to surgery and at each postoperative visit. The SF-36 scale measures specific health concepts related to physical functioning and limitations, social functioning, and health perceptions. The questionnaire contains 36 questions that pertain to eight subscales of health status. These eight subscales are physical function, role-physical, pain index, general health perception, vitality, social function, role-emotional, and mental health. These eight SF-36 scales can be summarized into two measures pertaining to physical health and mental health. The physical health summary (PCS) is based primarily on the physical functioning, role-physical, bodily pain, and general health scales of the SF-36 survey. The mental health summary (MCS) is comprised primarily of the vitality, social functioning, role-emotional, and mental health scales. Table 28 presents the mean scores of the eight SF-36 scales, as well as the PCS and MCS scores at various study periods. Higher scores represent higher levels of health.

In terms of the mean PCS and MCS results, all postoperative scores through the 24 month time-point were higher than preoperative scores for both treatment groups. The mean improvements in PCS and MCS scores from preoperative to 24 months postoperative for the investigational group (13.2 and 6.1 points, respectively) were comparable to the values for the control group (12.3 and 6.0, respectively).

Table 29 presents the percent of patients who demonstrated maintenance or improvement in SF-36 results postoperatively as compared to the preoperative condition. With particular focus on the summary parameters, the PCS success rate at 24 months following surgery for the investigational group was slightly more than that for the control group (83.8% vs. 82.0%), with a posterior probability of non-inferiority of 99.9%. The MCS success rate was greater for the investigational group (71.1%) than for the control group (65.6%), with a posterior probability of non-inferiority of essentially 100%.

6. Graft Site Pain

Investigational patients did not undergo a bone harvest procedure and, therefore, did not experience graft site pain. The use of the investigational product eliminates the possibility of this pain.

Control patients had bone graft harvested from the iliac crest for use with the control device. The level of postoperative pain and morbidity associated with the graft harvest procedure was measured using numerical rating scales for pain intensity and duration.

A summary of the graft site (hip) pain scores is provided in Table 30. As expected, the highest level of hip pain was noted by control patients shortly after surgery, 11.3 points out of a maximum of 20 points. The pain scores improved over time following surgery. However, at 24 months postoperative, control patients continued to experience some graft site pain, with a mean graft site (hip) pain score of 5.1.

H. Overall Success

Overall success is the primary endpoint for the clinical trial and the parameter on which the success of the clinical trial is determined. Overall success is based on a patient demonstrating fusion, a successful Oswestry outcome, neurological status maintenance or improvement, no serious implant-associated or implant/surgical procedure-associated adverse event, and no second surgery classified as a “failure.” Therefore, this parameter encompasses important safety and effectiveness aspects of the treatment. Table 31 provides overall success information for the two treatment groups at the 6-, 12- and 24-month postoperative time periods, as well as those after 24 months.

The overall success rate for the investigational group was slightly higher than that of the control group at 24 months following surgery (60.5% vs. 55.5%, respectively). Bayesian statistical analyses yielded a posterior probability of non-inferiority at 24 months of 99.9%, as shown in Appendix K. The minimum delta value to show non-inferiority with a probability of 95% was 3.3%. The posterior probability of superiority was found to be 83.9%.

I. Other Analyses and Data Presentations

1. Patient Satisfaction

At each postoperative time point, patients were asked to respond to three questions pertaining to their satisfaction with the study treatment. These questions were as follows:

1. I am satisfied with the results of my surgery.
2. I was helped as much as I thought I would be with my surgery.
3. All things considered I would have the surgery again for the same condition.

Each question had a series of possible responses ranging from “definitely true” to “definitely false.” The results to this question are provided in Table 32. At 24 months following surgery, the results were fairly similar for both the investigational and control groups. For the first question, 84.4% of the investigational patients and 78.7% of the control patients responded as either “definitely true” or “mostly true.” For the second question, 80.1% of

the investigational patients and 79.2% of the control patients thought that they were helped as much as expected from their surgeries. Finally, 84.7% of the investigational patients said that they would have the surgery again, as opposed to a 75.7% rate for the control group. Based on these results, the investigational patients appear to be at least as satisfied with their procedures as patients in the control group.

2. Global Perceived Effect

At each postoperative time period, patients were asked to evaluate their overall impression of their change in low back pain. The seven possible answers ranged from “completely recovered” to “vastly worsened.” The results to this question are provided in Table 33. At 24 months following surgery, 78.3% of the investigational patients indicated that they had either “completely recovered” or were “much improved,” as compared to the 70.9% rate for the control group.

3. Doctor’s Perception of Results

At each postoperative visit, study investigators were asked to provide their perceptions of patients’ conditions. The possible responses were either “excellent,” “good,” “fair,” or “poor.” The results to this question are provided in Table 34. At 24 months following surgery, 91.3% of the doctors responded that the investigational patients were in “excellent” or “good” condition. This rate is lower for the control group, with a value of 79.9%. These findings show that a substantial majority of patients in both treatment groups were progressing well clinically in the overall opinions of the doctors.

4. Work Status

Table 35 shows the work status of patients at various time points in the clinical study. In many ways, the data are difficult to interpret since many factors affect whether a patient returns to work or not, as well as the nature of the work performed when they return to work. At 6 weeks postoperative, the work status of the investigational group was slightly better than the control group (9.4 % vs. 7.8%, respectively). At all other time points, the work status of the control patients appeared to be slightly better than the investigational patients; however, it should be noted that the investigational group had fewer patients working preoperative.

5. Medication Summaries

Summaries of the medications taken by investigational and control patients at the various study periods are summarized in Table 36.

6. Missing-Equals-Failure and Per-Protocol Analysis

A “missing-equals-failure” analysis was performed, and the results are presented in Table 37. In this analysis, deaths, patients lost-to-follow-up, and missing observations due to various reasons were considered as “failures.” By treating these patients as treatment failures, the clinical outcome rates in the “missing-equals-failure” analysis were lower than those observed in the clinical data. At 24 months postoperative, the investigational group’s “missing-equals-failure” overall success rate is higher than that for the control group (50.6% vs. 45.1%). No statistical comparisons were performed using the “missing-equals-failure” dataset.

A “per protocol” analysis was also performed, with the results presented in Table 38. The “per protocol” dataset was a subset of patients who were included in the primary analysis dataset. Patients who were excluded from the “per protocol” analysis had major protocol deviations (*i.e.*, did not meet the inclusion/exclusion criteria, received the wrong study treatment, or had other major protocol deviations that could potentially affect clinical outcomes). At 24 months postoperative, the overall success rates in the investigational group are again higher than those for the control group (61.0% vs. 56.3%). In the Bayesian analyses presented in Appendix K, every statistical comparison for the “per protocol” dataset yielded a posterior probability of non-inferiority of at least 98.5%, with fusion showing to be statistically different (probability of superiority is essentially 100.0%).

In summary, the “missing-equals-failure” and “per protocol” analyses of the data are consistent with the results from the primary dataset, with overall success rates for the investigational group found to be non-inferior to rates of the control group in the “per protocol” analysis. In addition, fusion success rates for the investigational group are statistically higher than the fusion rates for the control group in both the “per protocol” analyses and in the primary dataset analyses.

7. Examination of Effectiveness Variables by Investigator

Information pertaining to the effectiveness results (fusion, Oswestry, neurological, and overall success) at 12 and 24 months by investigational site is presented in Table 39 for both the investigational and control treatment groups. Based on the Breslow-Day test, the results appear to be homogenous across investigational sites. Thus, pooling the data across sites is justified.

8. Financial Disclosure of Clinical Investigators

Financial disclosure information pertaining to the investigators and co-investigators who participated in [REDACTED] is provided in Table 40.

The sites at which investigators reported financial interests were noted. The information indicates that 27 of 63 (42.9%) surgeons who performed surgeries at 29 sites have or have had a financial interest in Medtronic and/or Sofamor Danek during the course of this clinical trial. The surgeons with financial interests contributed 251 patients to both treatment groups, compared to surgeons without financial interests contributing 212 patients to both treatment groups. Five additional surgeons had a financial interest but did not perform surgeries in the study. No data were included in Table 40 involving these surgeons.

Overall success was compared between study investigators with and without financial interests. The overall success rate in the investigational patients at 24 months was 60.4% for investigators with financial interest, compared with 60.7% for investigators without financial interest. In the control patients at 24 months, the overall success was 54.3% vs. 57.1% for these two groups, respectively. Neither of these differences were statistically significant.

Based on these study site results, it is believed that the financial interests of the surgeons do not affect the results or conclusions of the clinical trial.

9. Analysis of Data Excluding Spinal Litigation Patients

As discussed in the section on patient demographics in this report, there is a statistical difference in the numbers of spinal litigation cases between the two treatment groups. Even though the difference is statistically different, the numbers of litigation cases were quite small – six in the investigational group and 15 in the control group. In order to assess the impact of spinal litigation cases on the study conclusion, a statistical analysis was performed on the primary endpoint, overall success, and its components, excluding the data from patients having spinal litigation. Table I-1 below summarizes the analysis results:

Table I-1. Summary and Comparison of Overall Success, Oswestry, Neurological Status, and Fusion Outcomes at 24 Months [Excluding Patients Having Spinal Litigation]				
Variable	Success Rate (%)		Posterior Probability	
	Investigational	Control	Non-inferiority (%)	Superiority (%)
Overall Success	118/194 (60.8%)	96/170 (56.5%)	99.7	80.0
Oswestry	149/202 (73.8%)	127/171 (74.3%)	98.3	45.8
Neurological	176/201 (87.6%)	145/172 (84.3%)	~100.0	81.8
Fusion	180/188 (95.7%)	140/157 (89.2%)	~100.0	99.0

The analysis shows that, when data from the spinal litigation patients are excluded, the results are very similar to the whole cohort data. This demonstrates that the spinal litigation cases did not influence the study conclusions with regard to clinical and radiographic outcomes.

10. Data Listings

Data listings for the investigational and control patients are provided on CD in Appendix L.

J. Long-Term Safety and Effectiveness Determination

As stated earlier in the report, the IDE study was amended to increase patient follow-up for the study from 24 months to 36 months and then to 60 months. At that point, it was stipulated that patients would have completed their follow-up for the study after the 60-month visit. This extended portion of the study was undertaken to gather long-term safety and effectiveness information about the device. The 60-month results are presented here for completeness, even though 24-month data is the study endpoint. The tables included in Section IV.B of this report incorporate data for patients at all time points through the 24-month study endpoint, as well as data for patients at 36 months, some patients who were seen at 48 months (which is not a protocol-defined evaluation time point), and patients at 60 months.

It should be noted that caution should be taken in interpreting follow-up data after 24 months. Because the last observations taken before additional surgical procedures/interventions that were classified as failures were carried forward for future evaluation periods, success rates are artificially low at time points after 24 months. This is because any second surgery failures occurring before a time point are cumulatively included in the success determination at that time point, even if the patient did not have an actual follow-up visit. Combined with relatively low follow-up rates after 24 months, this decreases the success rates in both treatment groups in a biased fashion.

1. Patient Accountability

Table 1 presents patient accountability information on the basis of having received any data on a patient at the specific study time period. At 60 months postoperative, the follow-up rate was 68.9% in the investigational group and 67.8% for the control group. Table 2 presents patient accountability based on the availability of overall success outcomes, a more conservative interpretation of accountability. At 60 months postoperative, the follow-up rate was 54.7% in the investigational group and 55.0% for the control group.

2. Safety Determination

Adverse Events

Additional safety information was obtained during the extended study periods and is included in the adverse event tables. A summary of the data indicates that through 60 months (including 36-, 48-, and 60-month time points) of follow-up, an additional 359 adverse events were reported in the investigational group, with an additional 323 adverse events in the control group. These adverse events varied in type, severity, and possible cause. To delineate what events are important to the study implant or implant/surgery being evaluated, the following breakdown of adverse events is provided.

An additional 137 Grade 3 or 4 adverse events were reported in 103 investigational patients through 60 months postoperative. In the control group, an additional 103 Grade 3 or 4 events were noted for 72 patients through 60 months of follow-up. Through 60 months of follow-up, three additional possibly related events were noted in the investigational group (two back and leg pain events and one nonunion event). In the control group, one other possibly related event was recorded (one back and leg pain event). Through 60 months of follow-up, both treatment groups had one additional Grade 3 or 4 adverse event that was possibly related to the study device. One investigational patient and one control patient both reported back and leg pain that was serious and possibly related to the study device.

Secondary Surgical Procedures

Additional secondary surgical interventions occurred in each group during the extended study period after 24 months postoperative through 60 months postoperative. Table 17 summarizes these additional secondary surgical interventions. In accordance with the protocol, if a study patient had a revision, non-elective removal, or supplemental fixation procedure, the patient was then classified as a second surgery “failure.” These events are considered in the calculations of the “overall success” rate for the study. See Appendix C for a breakdown of these failures by time point.

After 24 months, there were two additional revision surgeries in both the investigational and control groups. There were five additional non-elective removals in the investigational patients, compared to four in the control patients. There was one additional supplemental fixation in the control group (none in the investigational group) and one other reoperation in the control group (none in the investigational group).

3. Overall Success

Patients were also evaluated through the 36- and 60-month time periods to obtain long term data relating to overall success and its components. Table J-1 below is a summary of the primary endpoint data for the 36- and 60-month time points, but the tables included in Section IV.B of this report also include 48-month data on some patients, as well as secondary endpoint data.

Table J-1. Summary of Primary Endpoint Data at 36 and 60 Months Overall Success and Components				
Variable	36 Months		60 Months	
	Investigational	Control	Investigational	Control
Overall Success	74/150 (49.3%)	61/140 (43.6%)	54/123 (43.9%)	39/111 (35.1%)
Fusion Success	128/132 (97.0%)	109/118 (92.4%)	93/97 (95.9%)	70/79 (88.6%)
Oswestry Success	116/172 (67.4%)	109/164 (66.5%)	100/150 (66.7%)	85/135 (63.0%)
Neurological Success	151/172 (87.8%)	134/163 (82.2%)	132/150 (88.0%)	112/133 (84.2%)

4. Conclusion

Although success rates at 36 and 60 months are artificially low because second surgery failures are cumulatively carried forward and included in the success determination, the outcomes in the investigational treatment group are shown to be quite favorable as compared to the control treatment, although formal statistical comparisons were not performed because they are not protocol-defined study endpoints.

Based on these long-term follow-up results, no additional safety concerns were identified, and the study device continued to show favorable outcome results as compared to the control treatment for effectiveness.

IV. Overall Conclusions

The goal of the clinical trial of AMPLIFY™ rhBMP-2 MATRIX with posterior supplemental fixation (G000137) was to evaluate the safety and effectiveness of the device in the treatment of patients with symptomatic degenerative disc disease as compared to a control treatment, autogenous bone harvested from the iliac crest with posterior supplemental fixation. As demonstrated in this report, the use of AMPLIFY™ rhBMP-2 MATRIX with posterior supplemental fixation was at least as safe and effective as the control group, with a clear indication of superior fusion results with the investigational device.

The cohorts of patients in the investigational and control treatment groups were similar demographically and medically on a preoperative basis. This enhances the ability to interpret the effects associated with the different treatments since potentially confounding factors are similar for the two groups.

Patients receiving surgical implantation of the AMPLIFY™ rhBMP-2 MATRIX with posterior supplemental fixation experienced shorter operative times and less blood loss during surgery than patients in the control group. These findings for the investigational treatment group have positive safety implications and are believed to result from not having to harvest bone graft in patients receiving the AMPLIFY™ rhBMP-2 MATRIX.

The AMPLIFY™ rhBMP-2 MATRIX with posterior supplemental fixation was found to be at least as safe as the control treatment. The adverse event rates were comparable to those in the control treatment, which utilized the same approved spinal instrumentation device with autogenous bone graft. The only adverse event categories in which statistical differences were noted pertained to graft site related and non-union adverse events, both of which favored the investigational group. The graft site related adverse event result is considered a very positive result since one of the benefits of using the investigational device is that it eliminates the need for harvesting of bone graft and, in this case, seems to reduce or eliminate a number of related adverse events. The non-union adverse event result is also favorable for the investigational group since the investigational group had a reduction in second surgeries.

In addition to comparable adverse event rates, no statistical differences between treatment groups were found for any of the second surgery categories except removals. The investigational group had statistically fewer removals than the control group.

The rates of authentic antibody responses to rhBMP-2 and bovine collagen were comparable between the two treatment groups. Neutralizing antibodies were not detected in these patients. The authentic antibody response rate to rhBMP-2 was 6.4% in the investigational group, as compared to 2.3% in the control group. The antibody response to bovine Type I collagen was 16.7% in the investigational group and 21.2% in the control patients. It should be noted again that the control treatment did not expose patients to rhBMP-2 or CRM. Patients who had positive antibody responses to bovine collagen were not found to have positive antibody responses to human Type I collagen. There appeared to be no negative clinical consequences to positive antibody test results.

We believe the data from this study raise no new questions of safety as compared to the already PMA-approved INFUSE® Bone Graft device.

For effectiveness outcomes, the AMPLIFY™ rhBMP-2 MATRIX with posterior supplemental fixation results were statistically non-inferior to the control group results for all parameters at 24 months postoperative. In addition, fusion for the

AMPLIFY™ rhBMP-2 MATRIX group was statistically higher as compared to the control group.

The primary effectiveness endpoints for this clinical trial were fusion and pain/disability (Oswestry) improvement. The fusion failure rate at 24 months for the investigational group was only 4.1%, as compared to 10.7% in the control group. The pain/disability (Oswestry) mean improvement from preoperative to 24 months postoperative was 26.7 points for the investigational group, as compared to 25.5 points for the control group.

The overall success rate for the investigational group was 5% higher than that of the control group at 24 months following surgery (60.5% vs. 55.5%, respectively).

Therefore, based on these results, it can be concluded that the AMPLIFY™ rhBMP-2 MATRIX is safe and effective in the surgical treatment of symptomatic degenerative disc disease of the lumbar spine. The data and information presented in this PMA application provide a reasonable assurance of the safety and effectiveness of the device.

Table 1. STUDY PROGRESS SUMMARY
 BASED ON HAVING ANY DATA ON A PATIENT AT A GIVEN STUDY PERIOD
 (As of 03FEB2009)

Variable	Preoperative		Surgery		6 Weeks		3 Months		6 Months		12 Months		24 Months		36 Months		48 Months		60 Months	
	INV	Control	INV	Control	INV	Control	INV	Control	INV	Control	INV	Control	INV	Control	INV	Control	INV	Control	INV	Control
Number of Patients Enrolled	239	224	239	224	239	224	239	224	239	224	239	224	239	224	239	224	239	224	239	224
Theoretical Follow-up	239	224	239	224	239	224	239	224	239	224	239	224	239	224	239	224	239	224	239	224
Deaths (Cumulative)			0 (0)	0 (0)	1 (1)	0 (0)	0 (1)	0 (0)	0 (1)	1 (1)	0 (2)	0 (2)	0 (3)	1 (4)	0 (3)	1 (5)	0 (4)	1 (6)	0 (5)	0 (7)
Patients Evaluated Early &			0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Patients Not Yet Over Due			0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	9	15
Expected **	239	224	239	224	238	224	238	224	238	223	237	222	236	220	236	219	235	218	225	202
Evaluated of Expected	239	224	239	224	236	219	234	218	232	209	228	205	211	186	175	165	106	95	155	137
Percent Follow-up (%)	100.0	100.0	100.0	100.0	99.2	97.8	98.3	97.3	97.5	93.7	96.2	92.3	89.4	84.5	74.2	75.3	45.1	43.6	68.9	67.8

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* Expected = Theoretical - Cumulative Deaths - Additional Patients to be Evaluated + Patients Evaluated Early for visit.
 & Patients that completed follow-up visits early before the visit window.

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Table 2. PATIENT ACCOUNTABILITY
BASED ON AVAILABILITY OF OVERALL SUCCESS OUTCOMES

(As of 03FEB2009)

Variable	6 Months		12 Months		24 Months		36 Months		48 Months		60 Months	
	INV	Control	INV	Control	INV	Control	INV	Control	INV	Control	INV	Control
Number of Patients Enrolled	239	224	239	224	239	224	239	224	239	224	239	224
Theoretical Follow-up	239	224	239	224	239	224	239	224	239	224	239	224
Deaths (Cumulative)	0 (1)	1 (1)	0 (2)	0 (2)	0 (3)	1 (4)	0 (3)	1 (5)	0 (4)	1 (6)	0 (5)	0 (7)
Patients Evaluated Early \$	0	0	0	0	0	0	0	0	0	0	0	0
Patients Not Yet Over Due	0	0	0	0	0	0	0	0	0	0	9	15
Expected *	238	223	237	222	236	220	236	219	235	218	225	202
Number of Patients Who Had Overall Success Outcomes	204	189	214	197	200	182	150	140	102	82	123	111
Percent of Patients Who Had Overall Success Outcomes	85.7	84.8	90.3	88.7	84.7	82.7	63.6	63.9	43.4	37.6	54.7	55.0

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* Expected = Theoretical - Cumulative Deaths - Additional Patients to be Evaluated + Patients Evaluated Early for visit.

\$ Patients that completed follow-up visits early before the visit window.

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Table 3. Demographic Information

Variable	Investigational (N=239)	Control (N=224)	p-value *
Age (yr.)			
n	239	224	0.408
Mean	53.2	52.3	
Std	12.1	13.3	
Min	20.0	18.0	
Max	81.0	86.0	
Height (in.)			
n	239	224	0.380
Mean	67.1	66.8	
Std	3.9	4.0	
Min	59.0	58.0	
Max	79.0	78.0	
Weight (lbs.)			
n	239	224	0.720
Mean	187.2	188.5	
Std	38.9	41.6	
Min	104.0	99.0	
Max	362.0	312.0	
Sex [n (%)]			
Male	108 (45.2)	95 (42.4)	0.575
Female	131 (54.8)	129 (57.6)	
Race [n (%)]			
Caucasian	218 (91.2)	203 (90.6)	0.848
Black	11 (4.6)	14 (6.3)	
Asian	3 (1.3)	2 (0.9)	
Hispanic	4 (1.7)	4 (1.8)	
Other	3 (1.3)	1 (0.4)	
Marital Status [n (%)]			
Single	15 (6.3)	25 (11.2)	0.457
Married	176 (73.9)	155 (69.2)	
Divorced	29 (12.2)	27 (12.1)	
Separated	4 (1.7)	3 (1.3)	
Widowed	14 (5.9)	14 (6.3)	

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* For continuous variables, p-values are from ANOVA and for categorical variables, they are from Fisher's exact test.

Table 3. Demographic Information

Variable	Investigational (N=239)	Control (N=224)	p-value *
Education Level [n (%)]			
< High School	24 (10.0)	29 (13.1)	0.136
High School	64 (26.8)	73 (32.9)	
> High School	151 (63.2)	120 (54.1)	
Worker's Compensation Case [n (%)]			
Yes	27 (11.3)	28 (12.5)	0.774
No	212 (88.7)	196 (87.5)	
Unresolved Spinal Litigation Case [n (%)]			
Yes	6 (2.5)	15 (6.7)	0.042
No	233 (97.5)	209 (93.3)	
Tobacco Used [n (%)]			
Yes	63 (26.4)	59 (26.3)	1.000
No	176 (73.6)	165 (73.7)	
Alcohol Used [n (%)]			
Yes	90 (37.7)	78 (34.8)	0.562
No	149 (62.3)	146 (65.2)	
Preop Work Status [n (%)]			
Yes	83 (34.7)	92 (41.1)	0.180
No	156 (65.3)	132 (58.9)	

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* For continuous variables, p-values are from ANOVA and for categorical variables, they are from Fisher's exact test.

Table 4. Preoperative Medical Condition and Medication Usage
[Number (%) of Patients]

Variable	Investigational (N=239)	Control (N=224)	p-value *
Previous Back Surgery			
Yes	73 (30.5)	62 (27.7)	0.540
No	166 (69.5)	162 (72.3)	
Number of Previous Back Surgeries			
1	48 (65.8)	43 (69.4)	0.715
>1	25 (34.2)	19 (30.6)	
Diabetes			
Yes	17 (7.1)	27 (12.1)	0.081
No	222 (92.9)	197 (87.9)	
Liver Disease			
Yes	5 (2.1)	0 (0.0)	0.062
No	234 (97.9)	224 (100.0)	
Total Waddell Signs			
0 Positives	219 (91.6)	209 (93.3)	0.508
1 Positives	15 (6.3)	9 (4.0)	
2 Positives	5 (2.1)	6 (2.7)	
3 Positives	0 (0.0)	0 (0.0)	
4 Positives	0 (0.0)	0 (0.0)	
5 Positives	0 (0.0)	0 (0.0)	
Non-Narcotic Medications			
Yes	154 (64.7)	140 (62.5)	0.630
No	84 (35.3)	84 (37.5)	
Weak Narcotic Medications			
Yes	116 (48.5)	116 (51.8)	0.516
No	123 (51.5)	108 (48.2)	
Strong Narcotic Medications			
Yes	38 (16.0)	41 (18.4)	0.537
No	200 (84.0)	182 (81.6)	
Muscle Relaxant Medications			
Yes	55 (23.1)	55 (24.7)	0.743
No	183 (76.9)	168 (75.3)	

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* All p-values are from Fisher's exact test.

Table 3. Summary of Degenerative Disc Disease Diagnostic Characteristics
(Number (%) of Patients)

Variable	Investigational (N=239)	Control (N=224)
Characteristics of Degenerative Disc Disease		
A. Instability	30 (12.6)	24 (10.7)
B. Osteophyte Formation	55 (23.0)	60 (26.8)
C. Decreased Disc Height	143 (59.8)	136 (60.7)
D. Thickening of Ligamentous Tissue	48 (20.1)	49 (21.9)
E. Disc Herniation	206 (86.2)	201 (89.7)
F. Facet Joint Degeneration	98 (41.0)	106 (47.3)
Number of Characteristics Indicated		
1	59 (24.7)	44 (19.6)
2	86 (36.0)	84 (37.5)
3	50 (20.9)	50 (22.3)
4	24 (10.0)	22 (9.8)
5	17 (7.1)	18 (8.0)
6	3 (1.3)	6 (2.7)

Table 6. Preoperative Evaluations of Clinical Endpoints

Variable	Investigational (N=239)	Control (N=224)	p-value*
Oswestry Pain Score			
n	239	224	0.173
Mean	49.9	51.6	
Std	13.1	13.3	
Min	28.0	30.0	
Max	86.0	94.0	
SF-36 PCS			
n	236	224	0.509
Mean	27.8	27.4	
Std	6.3	6.7	
Min	15.3	9.1	
Max	48.7	45.2	
SF-36 MCS			
n	236	224	0.386
Mean	43.9	42.9	
Std	13.1	12.3	
Min	13.3	12.9	
Max	68.5	69.3	
Back Pain Score (0-20)			
n	238	224	0.568
Mean	15.6	15.8	
Std	3.5	3.6	
Min	0.0	0.0	
Max	20.0	20.0	
Leg Pain Score (0-20)			
n	238	223	0.942
Mean	14.0	14.0	
Std	4.8	5.3	
Min	0.0	0.0	
Max	20.0	20.0	

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* p-values are from analysis of variance.

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Table 7. Comparison of Demographic Information Between Study Patients and Non-Study Patients**

Variable	Investigational			Control		
	Study Patients (N=239)	Non-Study Patients (N=25)	p-value *	Study Patients (N=224)	Non-Study Patients (N=34)	p-value *
Age (yr.)						
n	239	22	0.196	224	31	0.804
Mean	53.2	49.7		52.3	51.6	
Std	12.1	13.9		13.3	13.9	
Min	20.0	21.0		18.0	19.0	
Max	81.0	71.0		86.0	76.0	
Height (in.)						
n	239	22	0.927	224	31	0.224
Mean	67.1	67.0		66.8	67.7	
Std	3.9	3.9		4.0	3.1	
Min	59.0	62.0		58.0	63.0	
Max	79.0	76.0		78.0	73.0	
Weight (lbs.)						
n	239	22	0.572	224	31	0.976
Mean	187.2	182.3		188.5	188.3	
Std	38.9	36.5		41.6	34.2	
Min	104.0	130.0		99.0	120.0	
Max	362.0	248.0		312.0	255.0	
Sex [n (%)]						
Male	108 (45.2)	11 (50.0)	0.663	95 (42.4)	15 (48.4)	0.565
Female	131 (54.8)	11 (50.0)		129 (57.6)	16 (51.6)	
Race [n (%)]						
Caucasian	218 (91.2)	18 (81.8)	0.179	203 (90.6)	27 (87.1)	0.432
Black	11 (4.6)	4 (18.2)		14 (6.3)	3 (9.7)	
Asian	3 (1.3)	0 (0.0)		2 (0.9)	1 (3.2)	
Hispanic	4 (1.7)	0 (0.0)		4 (1.8)	0 (0.0)	
Other	3 (1.3)	0 (0.0)		1 (0.4)	0 (0.0)	
Marital Status [n (%)]						
Single	15 (6.3)	4 (18.2)	0.215	25 (11.2)	3 (9.7)	0.802
Married	176 (73.9)	13 (59.1)		155 (69.2)	23 (74.2)	
Divorced	29 (12.2)	3 (13.6)		27 (12.1)	3 (9.7)	
Separated	4 (1.7)	0 (0.0)		3 (1.3)	1 (3.2)	
Widowed	14 (5.9)	2 (9.1)		14 (6.3)	1 (3.2)	

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* For continuous variables, p-values are from ANOVA and for categorical variables, they are from Fisher's exact test.

** Those who were randomized but did not receive study treatments for various reasons.

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Table 7. Comparison of Demographic Information between Study Patients and Non-Study Patients**

Variable	Investigational			Control		
	Study Patients (N=239)	Non-Study Patients (N=25)	p-value *	Study Patients (N=224)	Non-Study Patients (N=34)	p-value *
Education Level [n (%)]						
< High School	24(10.0)	2(9.1)	0.422	29(13.1)	5(16.1)	0.800
High School	64(26.8)	3(13.6)		73(32.9)	9(29.0)	
> High School	151(63.2)	17(77.3)		120(54.1)	17(54.8)	
Worker's Compensation Case [n (%)]						
Yes	27(11.3)	4(18.2)	0.310	28(12.5)	3(9.7)	1.000
No	212(88.7)	18(81.8)		196(87.5)	28(90.3)	
Unresolved Spinal Litigation Case [n (%)]						
Yes	6(2.5)	4(18.2)	0.006	15(6.7)	3(9.7)	0.467
No	233(97.5)	18(81.8)		209(93.3)	28(90.3)	
Tobacco Used [n (%)]						
Yes	63(26.4)	5(22.7)	0.805	59(26.3)	6(20.0)	0.513
No	176(73.6)	17(77.3)		165(73.7)	24(80.0)	
Alcohol Used [n (%)]						
Yes	90(37.7)	7(31.8)	0.652	78(34.8)	10(33.3)	1.000
No	149(62.3)	15(68.2)		146(65.2)	20(66.7)	
Preop Work Status [n (%)]						
Yes	83(34.7)	9(40.9)	0.642	92(41.1)	11(36.7)	0.696
No	156(65.3)	13(59.1)		132(58.9)	19(63.3)	

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* For continuous variables, p-values are from ANOVA and for categorical variables, they are from Fisher's exact test.

** Those who were randomized but did not receive study treatments for various reasons.

Table 8. Comparison of Preoperative Medical Condition and Medication Usage
Between Study Patients and Non-Study Patients**
(Number (%) of Patients)

Variable	Investigational			Control		
	Study Patients (N=239)	Non-Study Patients (N=25)	p-value *	Study Patients (N=224)	Non-Study Patients (N=34)	p-value *
Previous Back Surgery						
Yes	73 (30.5)	5 (22.7)	0.627	62 (27.7)	8 (26.7)	1.000
No	166 (69.5)	17 (77.3)		162 (72.3)	22 (73.3)	
Number of Previous Back Surgeries						
1	48 (65.8)	3 (60.0)	1.000	43 (69.4)	7 (87.5)	0.424
>1	25 (34.2)	2 (40.0)		19 (30.6)	1 (12.5)	
Diabetes						
Yes	17 (7.1)	1 (4.5)	1.000	27 (12.1)	4 (13.3)	0.771
No	222 (92.9)	21 (95.5)		197 (87.9)	26 (86.7)	
Liver Disease						
Yes	5 (2.1)	0 (0.0)	1.000	0 (0.0)	0 (0.0)	
No	234 (97.9)	22 (100.0)		224 (100.0)	30 (100.0)	
Total Waddell Signs						
0 Positives	219 (91.6)	22 (100.0)	0.760	209 (93.3)	27 (93.1)	0.836
1 Positives	15 (6.3)	0 (0.0)		9 (4.0)	1 (3.4)	
2 Positives	5 (2.1)	0 (0.0)		6 (2.7)	1 (3.4)	
3 Positives	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
4 Positives	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
5 Positives	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Non-Narcotic Medications						
Yes	154 (64.7)	13 (59.1)	0.645	140 (62.5)	19 (65.5)	0.840
No	84 (35.3)	9 (40.9)		84 (37.5)	10 (34.5)	
Weak Narcotic Medications						
Yes	116 (48.5)	11 (50.0)	1.000	116 (51.8)	14 (48.3)	0.844
No	123 (51.5)	11 (50.0)		108 (48.2)	15 (51.7)	
Strong Narcotic Medications						
Yes	38 (16.0)	5 (22.7)	0.379	41 (18.4)	6 (21.4)	0.797
No	200 (84.0)	17 (77.3)		182 (81.6)	22 (78.6)	
Muscle Relaxant Medications						
Yes	55 (23.1)	8 (36.4)	0.193	55 (24.7)	10 (37.0)	0.170
No	183 (76.9)	14 (63.6)		168 (75.3)	17 (63.0)	

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* All p-values are from Fisher's exact test.

** Those who were randomized but did not receive study treatments for various reasons.

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Table 9. Comparison of Preoperative Evaluations of Clinical Endpoints
Between Study Patients and Non-Study Patients**

Variable	Investigational			Control		
	Study Patients (N=239)	Non-Study Patients (N=25)	p-value *	Study Patients (N=224)	Non-Study Patients (N=34)	p-value *
Oswestry Pain Score						
n	239	22	0.665	224	31	0.962
Mean	49.9	48.7		51.6	51.5	
Std	13.1	12.5		13.3	13.0	
Min	28.0	30.0		30.0	22.0	
Max	86.0	72.0		94.0	76.0	
SF-36 PCS						
n	236	21	0.030	224	30	0.351
Mean	27.8	24.7		27.4	26.2	
Std	6.3	6.7		6.7	7.1	
Min	15.3	15.1		9.1	12.8	
Max	48.7	44.8		45.2	47.7	
SF-36 MCS						
n	236	21	0.404	224	30	0.212
Mean	43.9	46.4		42.9	45.8	
Std	13.1	12.6		12.3	11.7	
Min	13.3	22.6		12.9	18.5	
Max	68.5	63.3		69.3	68.7	
Back Pain Score (0-20)						
n	238	21	0.409	224	29	0.883
Mean	15.6	16.3		15.8	15.9	
Std	3.5	3.1		3.6	3.8	
Min	0.0	9.0		0.0	4.0	
Max	20.0	20.0		20.0	20.0	
Leg Pain Score (0-20)						
n	238	21	0.680	223	30	0.854
Mean	14.0	13.6		14.0	13.8	
Std	4.8	4.7		5.3	5.8	
Min	0.0	0.0		0.0	0.0	
Max	20.0	20.0		20.0	20.0	

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* P-values are from analysis of variance.

** Those who were randomized but did not receive study treatments for various reasons.

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Table 10. Surgery and Discharge Information

Variable	Investigational (N=239)	Control (N=224)
Operative Time (hrs)		
n	239	224
Mean	2.5	2.9
Std	0.9	1.0
Min	0.9	1.2
Median	2.5	2.9
Max	5.4	8.5
Blood Loss (ml)		
n	239	224
Mean	343.1	448.6
Std	264.5	301.7
Min	50.0	50.0
Median	300.0	375.0
Max	1850.0	2400.0
Hospital Stay (days)		
n	239	224
Mean	4.1	4.0
Std	2.3	1.9
Min	1.0	1.0
Median	4.0	4.0
Max	23.0	19.0
Treatment Levels [n (%)]		
L1-L2	0(0.0)	0(0.0)
L2-L3	7(2.9)	3(1.3)
L3-L4	26(10.9)	20(8.9)
L4-L5	121(50.6)	122(54.5)
L5-S1	83(34.7)	77(34.4)
L5-L6	2(0.8)	2(0.9)
External Orthosis [n (%)]		
Low Profile Brace	78(32.6)	72(32.1)
High Profile Brace	35(14.6)	25(11.2)
Corset	78(32.6)	70(31.3)
Other	36(15.1)	44(19.6)
None	12(5.0)	13(5.8)
Patient Classified as [n (%)]		
Inpatient (>23 hours hospital stay)	239(100.0)	224(100.0)
Outpatient (<=23 hours hospital stay)	0(0.0)	0(0.0)

Table 11. Summary of All Adverse Events

Adverse Event Type	Investigational (N=239)											
	Operative		1 day-4 wks		6 weeks		3 months		6 months		12 months	
	Event	Patient n (%)	Event	Patient n (%)	Event	Patient n (%)	Event	Patient n (%)	Event	Patient n (%)	Event	Patient n (%)
Patients Who Had Any Adverse Events	21	20 (8.4)	183	114 (47.7)	32	30 (12.6)	81	61 (25.5)	96	72 (30.1)	195	107 (44.8)
Anatomical/Technical Difficulty	1	1 (0.4)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)
Arthritis/Bursitis	0	0 (0.0)	3	3 (1.3)	1	1 (0.4)	7	7 (2.9)	4	4 (1.7)	6	6 (2.5)
Back and/or Leg Pain	0	0 (0.0)	18	18 (7.5)	11	10 (4.2)	15	15 (6.3)	21	20 (8.4)	37	34 (14.2)
Cancer	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	1	1 (0.4)	2	2 (0.8)	3	3 (1.3)
Cardiovascular	2	2 (0.8)	45	37 (15.5)	0	0 (0.0)	4	4 (1.7)	2	2 (0.8)	15	13 (5.4)
Carpal tunnel Syndrome	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	2	2 (0.8)	4	4 (1.7)
Death	0	0 (0.0)	0	0 (0.0)	1	1 (0.4)	0	0 (0.0)	1	1 (0.4)	1	1 (0.4)
Dural Injury	13	13 (5.4)	1	1 (0.4)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)
Gastrointestinal	0	0 (0.0)	18	17 (7.1)	0	0 (0.0)	4	4 (1.7)	5	5 (2.1)	9	9 (3.8)
Graft site Related	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)
Implant Displacement/Loosening	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	1	1 (0.4)
Infection	0	0 (0.0)	20	19 (7.9)	4	3 (1.3)	4	4 (1.7)	6	4 (1.7)	11	11 (4.6)
Malpositioned Implant	1	1 (0.4)	3	3 (1.3)	0	0 (0.0)	1	1 (0.4)	0	0 (0.0)	0	0 (0.0)
Neurological	0	0 (0.0)	9	9 (3.8)	2	2 (0.8)	19	17 (7.1)	19	19 (7.9)	20	18 (7.5)
Non-Union	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	1	1 (0.4)	0	0 (0.0)	8	8 (3.3)
Other	1	1 (0.4)	43	35 (14.6)	7	7 (2.9)	7	6 (2.5)	6	5 (2.1)	18	14 (5.9)
Other Pain	0	0 (0.0)	2	2 (0.8)	2	2 (0.8)	1	1 (0.4)	6	6 (2.5)	11	11 (4.6)
Respiratory	0	0 (0.0)	8	8 (3.3)	0	0 (0.0)	1	1 (0.4)	0	0 (0.0)	5	4 (1.7)
Spinal Event-All	0	0 (0.0)	1	1 (0.4)	0	0 (0.0)	3	3 (1.3)	5	5 (2.1)	5	5 (2.1)
Spinal Event-Cervical	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	1	1 (0.4)	4	4 (1.7)	3	3 (1.3)
Spinal Event-Lumbar	0	0 (0.0)	1	1 (0.4)	0	0 (0.0)	2	2 (0.8)	1	1 (0.4)	1	1 (0.4)
Spinal Event-Thoracic	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	1	1 (0.4)
Trauma	0	0 (0.0)	2	2 (0.8)	2	2 (0.8)	8	8 (3.3)	13	12 (5.0)	36	33 (13.8)
Urogenital	0	0 (0.0)	10	10 (4.2)	2	2 (0.8)	5	5 (2.1)	4	4 (1.7)	5	5 (2.1)
Vertebral Fracture	3	3 (1.3)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)

Table 11. Summary of All Adverse Events

Adverse Event Type	Investigational (N=239)									
	24 months		Total (≤24 months)		36 months		48 months		60 months	
	Event	Patient n (%)	Event	Patient n (%)	Event	Patient n (%)	Event	Patient n (%)	Event	Patient n (%)
Patients Who Had Any Adverse Events	148	93(38.9)	756	209(87.4)	158	93(38.9)	139	81(33.9)	62	47(19.7)
Anatomical/Technical Difficulty	0	0(0.0)	1	1(0.4)	0	0(0.0)	0	0(0.0)	0	0(0.0)
Arthritis/Bursitis	3	2(0.8)	24	23(9.6)	7	7(2.9)	4	4(1.7)	2	2(0.8)
Back and/or Leg Pain	37	35(14.6)	139	105(43.9)	39	33(13.8)	30	29(12.1)	11	9(3.8)
Cancer	3	3(1.3)	9	9(3.8)	4	4(1.7)	0	0(0.0)	0	0(0.0)
Cardiovascular	4	4(1.7)	72	53(22.2)	14	13(5.4)	10	9(3.8)	5	5(2.1)
Carpal Tunnel Syndrome	3	3(1.3)	9	9(3.8)	0	0(0.0)	0	0(0.0)	0	0(0.0)
Death	0	0(0.0)	3	3(1.3)	0	0(0.0)	2	2(0.8)	1	1(0.4)
Dural Injury	0	0(0.0)	14	14(5.9)	0	0(0.0)	0	0(0.0)	0	0(0.0)
Gastrointestinal	7	6(2.5)	43	37(15.5)	13	12(5.0)	12	10(4.2)	7	7(2.9)
Graft Site Related	0	0(0.0)	0	0(0.0)	0	0(0.0)	0	0(0.0)	0	0(0.0)
Implant Displacement/Loosening	0	0(0.0)	1	1(0.4)	0	0(0.0)	0	0(0.0)	0	0(0.0)
Infection	7	6(2.5)	52	39(16.3)	2	2(0.8)	6	6(2.5)	0	0(0.0)
Malpositioned Implant	0	0(0.0)	5	5(2.1)	0	0(0.0)	0	0(0.0)	0	0(0.0)
Neurological	16	15(6.3)	85	70(29.3)	12	10(4.2)	9	9(3.8)	7	7(2.9)
Non-Union	1	1(0.4)	10	10(4.2)	1	1(0.4)	0	0(0.0)	0	0(0.0)
Other	19	17(7.1)	101	70(29.3)	26	18(7.5)	37	20(8.4)	10	8(3.3)
Other Pain	9	9(3.8)	31	29(12.1)	8	8(3.3)	11	11(4.6)	8	7(2.9)
Respiratory	3	3(1.3)	17	16(6.7)	0	0(0.0)	0	0(0.0)	0	0(0.0)
Spinal Event-All	4	4(1.7)	18	17(7.1)	6	6(2.5)	3	3(1.3)	3	3(1.3)
Spinal Event-Cervical	2	2(0.8)	10	9(3.8)	2	2(0.8)	1	1(0.4)	3	3(1.3)
Spinal Event-Lumbar	2	2(0.8)	7	7(2.9)	4	4(1.7)	2	2(0.8)	0	0(0.0)
Spinal Event-Thoracic	0	0(0.0)	1	1(0.4)	0	0(0.0)	0	0(0.0)	0	0(0.0)
Trauma	30	27(11.3)	91	69(28.9)	22	21(8.8)	12	12(5.0)	6	6(2.5)
Urogenital	2	2(0.8)	28	27(11.3)	4	4(1.7)	3	3(1.3)	2	2(0.8)
Vertebral Fracture	0	0(0.0)	3	3(1.3)	0	0(0.0)	0	0(0.0)	0	0(0.0)

Table 11. Summary of All Adverse Events

Adverse Event Type	Control (N=224)											
	Operative		1 day-4 wks		6 weeks		3 months		6 months		12 months	
	Event	Patient n (%)	Event	Patient n (%)	Event	Patient n (%)	Event	Patient n (%)	Event	Patient n (%)	Event	Patient n (%)
Patients Who Had Any Adverse Events	21	20 (8.9)	161	90 (40.2)	49	35 (15.6)	74	65 (29.0)	111	88 (39.3)	152	99 (44.2)
Anatomical/Technical Difficulty	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)
Arthritis/Bursitis	0	0 (0.0)	1	1 (0.4)	1	1 (0.4)	2	2 (0.9)	3	3 (1.3)	6	6 (2.7)
Back and/or Leg Pain	0	0 (0.0)	8	7 (3.1)	5	5 (2.2)	13	13 (5.8)	30	28 (12.5)	31	29 (12.9)
Cancer	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	1	1 (0.4)	1	1 (0.4)
Cardiovascular	0	0 (0.0)	43	39 (17.4)	2	2 (0.9)	3	3 (1.3)	7	7 (3.1)	9	8 (3.6)
Carpal Tunnel Syndrome	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	1	1 (0.4)	3	3 (1.3)
Death	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	2	2 (0.9)	1	1 (0.4)
Dural Injury	18	18 (8.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)
Gastrointestinal	0	0 (0.0)	16	15 (6.7)	2	2 (0.9)	3	3 (1.3)	2	2 (0.9)	11	6 (2.7)
Graft Site Related	0	0 (0.0)	4	4 (1.8)	3	3 (1.3)	5	5 (2.2)	3	3 (1.3)	2	2 (0.9)
Implant Displacement/Loosening	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	1	1 (0.4)	0	0 (0.0)	1	1 (0.4)
Infection	0	0 (0.0)	27	24 (10.7)	6	6 (2.7)	2	2 (0.9)	1	1 (0.4)	10	10 (4.5)
Malpositioned Implant	0	0 (0.0)	1	1 (0.4)	1	1 (0.4)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)
Neurological	0	0 (0.0)	7	6 (2.7)	9	7 (3.1)	14	13 (5.8)	17	17 (7.6)	14	14 (6.3)
Non-Union	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	8	8 (3.6)	6	6 (2.7)	6	6 (2.7)
Other	0	0 (0.0)	34	25 (11.2)	7	4 (1.8)	8	8 (3.6)	11	10 (4.5)	14	11 (4.9)
Other Pain	0	0 (0.0)	3	3 (1.3)	0	0 (0.0)	1	1 (0.4)	5	5 (2.2)	4	4 (1.8)
Respiratory	0	0 (0.0)	7	7 (3.1)	1	1 (0.4)	1	1 (0.4)	1	1 (0.4)	3	3 (1.3)
Spinal Event-All	0	0 (0.0)	1	1 (0.4)	2	1 (0.4)	3	3 (1.3)	2	2 (0.9)	12	11 (4.9)
Spinal Event-Cervical	0	0 (0.0)	0	0 (0.0)	2	1 (0.4)	1	1 (0.4)	1	1 (0.4)	8	8 (3.6)
Spinal Event-Lumbar	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	2	2 (0.9)	1	1 (0.4)	4	4 (1.8)
Spinal Event-Thoracic	0	0 (0.0)	1	1 (0.4)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)
Trauma	0	0 (0.0)	3	3 (1.3)	8	8 (3.6)	7	7 (3.1)	16	15 (6.7)	19	17 (7.6)
Urogenital	0	0 (0.0)	6	6 (2.7)	2	2 (0.9)	3	3 (1.3)	3	3 (1.3)	5	4 (1.8)
Vertebral Fracture	3	3 (1.3)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)

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Table 11. Summary of All Adverse Events

Adverse Event Type	Control (N=224)											
	24 months		Total (≤24 months)		36 months		48 months		60 months		Total (All)	
	Event	Patient n (%)	Event	Patient n (%)	Event	Patient n (%)	Event	Patient n (%)	Event	Patient n (%)	Event	Patient n (%)
Patients Who Had Any Adverse Events	126	86(38.4)	694	197(87.9)	143	82(36.6)	116	63(28.1)	64	43(19.2)	1017	210(93.8)
Anatomical/Technical Difficulty	0	0(0.0)	0	0(0.0)	0	0(0.0)	0	0(0.0)	0	0(0.0)	0	0(0.0)
Arthritis/Bursitis	6	6(2.7)	19	17(7.6)	5	5(2.2)	7	6(2.7)	3	3(1.3)	34	27(12.1)
Back and/or Leg Pain	23	23(10.3)	110	89(39.7)	36	31(13.8)	26	24(10.7)	18	18(8.0)	190	124(55.4)
Cancer	0	0(0.0)	2	2(0.9)	1	1(0.4)	1	1(0.4)	0	0(0.0)	4	4(1.8)
Cardiovascular	3	3(1.3)	67	54(24.1)	2	2(0.9)	12	9(4.0)	3	3(1.3)	84	63(28.1)
Carpal Tunnel Syndrome	2	2(0.9)	6	6(2.7)	1	1(0.4)	0	0(0.0)	1	1(0.4)	8	8(3.6)
Death	1	1(0.4)	4	4(1.8)	1	1(0.4)	1	1(0.4)	1	1(0.4)	7	7(3.1)
Dural Injury	0	0(0.0)	18	18(8.0)	1	1(0.4)	0	0(0.0)	1	1(0.4)	20	19(8.5)
Gastrointestinal	9	9(4.0)	43	33(14.7)	11	11(4.9)	12	8(3.6)	4	3(1.3)	70	51(22.8)
Graft Site Related	0	0(0.0)	17	17(7.6)	2	2(0.9)	0	0(0.0)	0	0(0.0)	19	19(8.5)
Implant Displacement/Loosening	0	0(0.0)	2	2(0.9)	0	0(0.0)	0	0(0.0)	0	0(0.0)	2	2(0.9)
Infection	5	5(2.2)	51	45(20.1)	6	6(2.7)	6	6(2.7)	1	1(0.4)	64	51(22.8)
Malpositioned Implant	0	0(0.0)	2	2(0.9)	0	0(0.0)	0	0(0.0)	0	0(0.0)	2	2(0.9)
Neurological	13	11(4.9)	74	60(26.8)	16	13(5.8)	5	5(2.2)	3	2(0.9)	98	72(32.1)
Non-Union	3	3(1.3)	23	23(10.3)	1	1(0.4)	0	0(0.0)	1	1(0.4)	25	25(11.2)
Other	17	15(6.7)	91	62(27.7)	26	20(8.9)	20	11(4.9)	10	9(4.0)	147	80(35.7)
Other Pain	19	18(8.0)	32	29(12.9)	13	12(5.4)	7	7(3.1)	7	6(2.7)	59	45(20.1)
Respiratory	0	0(0.0)	13	12(5.4)	0	0(0.0)	4	3(1.3)	1	1(0.4)	18	14(6.3)
Spinal Event-All	2	2(0.9)	22	19(8.5)	2	2(0.9)	1	1(0.4)	1	1(0.4)	26	22(9.8)
Spinal Event-Cervical	0	0(0.0)	12	11(4.9)	1	1(0.4)	1	1(0.4)	1	1(0.4)	15	14(6.3)
Spinal Event-Lumbar	2	2(0.9)	9	9(4.0)	1	1(0.4)	0	0(0.0)	0	0(0.0)	10	10(4.5)
Spinal Event-Thoracic	0	0(0.0)	1	1(0.4)	0	0(0.0)	0	0(0.0)	0	0(0.0)	1	1(0.4)
Trauma	17	16(7.1)	70	59(26.3)	16	14(6.3)	12	9(4.0)	6	5(2.2)	104	76(33.9)
Urogenital	5	5(2.2)	24	21(9.4)	3	3(1.3)	2	2(0.9)	3	3(1.3)	32	28(12.5)
Vertebral Fracture	1	1(0.4)	4	4(1.8)	0	0(0.0)	0	0(0.0)	0	0(0.0)	4	4(1.8)

**Table 12. rhBMP-2/CRM/CD HORIZON® Spinal System Pivotal Study
"Other" Adverse Events - Investigational Patients (N=239)**

Adverse Event Type	Operative			1 Day- <1 Month			6 Weeks (≥1-<2 Months)			3 Months (≥2-<5 Months)			6 Months (≥5-<9 Months)			12 Months (≥9-<19 Months)			24 Months (≥19-<30 Months)			Total Events (through 24 mos.)			36 Months (≥30-<42 Months)			48 Months (≥42-<54 Months)			60 Months (≥54 Months)			Total Events (all time points)		
	Event	n	(%)	Event	n	(%)	Event	n	(%)	Event	n	(%)	Event	n	(%)	Event	n	(%)	Event	n	(%)	Event	n	(%)	Event	n	(%)	Event	n	(%)	Event	n	(%)	Event	n	(%)
Patients Who Had Any "Other" Adverse Events	1	1	0.4%	43	35	14.6%	7	7	2.9%	7	6	2.5%	6	5	2.1%	18	14	5.9%	19	17	7.1%	101	70	29.3%	26	18	7.5%	37	20	8.4%	10	8	3.3%	174	89	37.2%
Abnormal Lab Values	0	0	0.0%	1	1	0.4%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%
Abnormal Mammogram	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	1	1	0.4%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%
Abnormal Pap Smear	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	0	0	0.0%	1	1	0.4%
Abnormal Thyroid Tissue	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%
Abscess - Wrist	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%
Adrenal Tumor - Benign	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%
Allergic Reaction	0	0	0.0%	2	2	0.8%	0	0	0.0%	1	1	0.4%	1	1	0.4%	0	0	0.0%	0	0	0.0%	4	4	1.7%	1	1	0.4%	1	1	0.4%	0	0	0.0%	6	6	2.5%
Ankle Sprain	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	1	1	0.4%
Ankle Swelling	0	0	0.0%	1	1	0.4%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%
Anxiety	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	2	2	0.8%	0	0	0.0%	3	3	1.3%
Autoimmune Disease	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%
Balance Problems	0	0	0.0%	1	1	0.4%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%
Bleeding at IV Site	0	0	0.0%	1	1	0.4%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%
Bleeding Incision	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%
Breast Mass	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%
Breast Reduction/ Pre-Cancerous Lesions	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%
Bug Bite	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	1	1	0.4%
Bunion	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	0	0	0.0%	1	1	0.4%
Buttocks Bruises	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	0	0	0.0%	1	1	0.4%
Cataracts	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	0	0	0.0%	2	1	0.4%	3	2	0.8%
Chemical Conjunctivitis	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%
Choking	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%
Chronic Allergies	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	0	0	0.0%	1	1	0.4%
Cough/Cold	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	2	2	0.8%	2	2	0.8%	2	2	0.8%	1	1	0.4%	0	0	0.0%	5	5	2.1%
Cutaneous Candida	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%
Cyst	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	1	1	0.4%	2	2	0.8%	0	0	0.0%	3	3	1.3%	1	1	0.4%	6	5	2.1%
Decreased Muscle Mass BLE	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	1	1	0.4%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%
Dehydration	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%
Dementia	0	0	0.0%	1	1	0.4%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	2	1	0.4%	0	0	0.0%	0	0	0.0%	0	0	0.0%	2	1	0.4%
Dental Event	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	1	1	0.4%	0	0	0.0%	1	1	0.4%	3	3	1.3%	0	0	0.0%	1	1	0.4%	0	0	0.0%	4	4	1.7%
Depression	0	0	0.0%	3	3	1.3%	0	0	0.0%	2	2	0.8%	0	0	0.0%	1	1	0.4%	2	2	0.8%	8	8	3.3%	0	0	0.0%	1	1	0.4%	1	1	0.4%	10	9	3.8%
Diabetes	0	0	0.0%	1	1	0.4%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	2	2	0.8%	2	2	0.8%	0	0	0.0%	2	2	0.8%	6	6	2.5%
Dog Bite	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%

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**Table 12. rhBMP-2/CRM/CD HORIZON® Spinal System Pivotal Study
"Other" Adverse Events - Investigational Patients (N=239)**

Adverse Event Type	Operative			1 Day- <1 Month			6 Weeks (≥1-<2 Months)			3 Months (≥2-<5 Months)			6 Months (≥5-<9 Months)			12 Months (≥9-<19 Months)			24 Months (≥19-<30 Months)			Total Events (through 24 mos.)			36 Months (≥30-<42 Months)			48 Months (≥42-<54 Months)			60 Months (≥54 Months)			Total Events (all time points)		
	Event	n	(%)	Event	n	(%)	Event	n	(%)	Event	n	(%)	Event	n	(%)	Event	n	(%)	Event	n	(%)	Event	n	(%)	Event	n	(%)	Event	n	(%)	Event	n	(%)	Event	n	(%)
Double Vision	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	1	1	0.4%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%
Drug Reaction	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	1	1	0.4%
Drug Withdrawal and Rehabilitation	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%
Dysphagia	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%
Eczema	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%
Elevated Blood Sugar	1	1	0.4%	2	2	0.8%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	4	4	1.7%	0	0	0.0%	0	0	0.0%	0	0	0.0%	4	4	1.7%
Elevated Creatinine	0	0	0.0%	1	1	0.4%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%
Elevated Lithium Level	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%
Elevated Liver Function Tests	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%
Elevated Vitamin B12 and Folate	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	1	1	0.4%
Enlarged Thyroid (goiter)	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	2	2	0.8%	0	0	0.0%	2	2	0.8%
Eyelash in Eye	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%
Fatigue	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	1	1	0.4%	0	0	0.0%	2	2	0.8%
Fatty Liver	0	0	0.0%	1	1	0.4%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%
Fever	0	0	0.0%	2	2	0.8%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	2	2	0.8%	0	0	0.0%	0	0	0.0%	0	0	0.0%	2	2	0.8%
Fibromyalgia	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%
Flat Foot	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%
Flu	0	0	0.0%	0	0	0.0%	1	1	0.4%	1	1	0.4%	0	0	0.0%	1	1	0.4%	0	0	0.0%	3	3	1.3%	0	0	0.0%	0	0	0.0%	0	0	0.0%	3	3	1.3%
Foot Pain	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%
Fungus	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	1	1	0.4%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%
Glaucoma	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	1	1	0.4%
Gout	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	1	1	0.4%
Heat Rash	0	0	0.0%	1	1	0.4%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%
Heel Spur Pain	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	1	1	0.4%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%
Hiccups	0	0	0.0%	1	1	0.4%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%
Hot Flashes	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	0	0	0.0%	1	1	0.4%
Hyperhomocysteinemia	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	1	1	0.4%
Hyperlipidemia	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	1	1	0.4%	1	1	0.4%	1	1	0.4%	0	0	0.0%	3	3	1.3%
Hypematremia	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%
Hypersomnolence and Daytime Sleep Disturbances	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%
Hypocalcemia	0	0	0.0%	2	2	0.8%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	2	2	0.8%	1	1	0.4%	0	0	0.0%	0	0	0.0%	3	2	0.8%
Hypoglycemia	0	0	0.0%	3	3	1.3%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	3	3	1.3%	0	0	0.0%	0	0	0.0%	0	0	0.0%	3	3	1.3%
Hypokalemia	0	0	0.0%	4	4	1.7%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	5	5	2.1%	0	0	0.0%	0	0	0.0%	0	0	0.0%	5	5	2.1%

**Table 12. rhBMP-2/CRM/CD HORIZON® Spinal System Pivotal Study
"Other" Adverse Events - Investigational Patients (N=239)**

Adverse Event Type	Operative			1 Day- <1 Month			6 Weeks (≥1-<2 Months)			3 Months (≥2-<5 Months)			6 Months (≥5-<9 Months)			12 Months (≥9-<19 Months)			24 Months (≥19-<30 Months)			Total Events (through 24 mos.)			36 Months (≥30-<42 Months)			48 Months (≥42-<54 Months)			60 Months (≥54 Months)			Total Events (all time points)		
	Event	n	(%)	Event	n	(%)	Event	n	(%)	Event	n	(%)	Event	n	(%)	Event	n	(%)	Event	n	(%)	Event	n	(%)	Event	n	(%)	Event	n	(%)	Event	n	(%)	Event	n	(%)
Hypothyroidism	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	1	1	0.4%	1	1	0.4%	1	1	0.4%	0	0	0.0%	3	3	1.3%
Hypovolemia	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%
Immunosuppressed	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%
Insomnia	0	0	0.0%	1	1	0.4%	1	1	0.4%	0	0	0.0%	1	1	0.4%	0	0	0.0%	0	0	0.0%	3	3	1.3%	1	1	0.4%	0	0	0.0%	0	0	0.0%	4	4	1.7%
Iron Deficiency	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%
Itching	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%
IV Infiltration	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%
Laryngeal Edema and Throat Swelling	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	1	1	0.4%
Leg and Foot Swelling	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	1	1	0.4%
Lesions on Feet	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%
Leukocytosis	0	0	0.0%	2	2	0.8%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	2	2	0.8%	0	0	0.0%	0	0	0.0%	0	0	0.0%	2	2	0.8%
Low Magnesium	0	0	0.0%	1	1	0.4%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%
Low Testosterone Level	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	1	1	0.4%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%
Lymphadenopathy	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	2	2	0.8%	0	0	0.0%	0	0	0.0%	2	2	0.8%
Mammogram	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	1	1	0.4%
Meningioma	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	0	0	0.0%	1	1	0.4%
Menstrual Cramps	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%
Mental Status Change	0	0	0.0%	2	2	0.8%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	2	2	0.8%	0	0	0.0%	0	0	0.0%	0	0	0.0%	2	2	0.8%
Methadone Overdose	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%
Oral Rash in Mouth	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%
Mood Disorder	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%
Morbid Obesity	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	1	1	0.4%	1	1	0.4%	0	0	0.0%	0	0	0.0%	2	2	0.8%
Morton's Neuroma	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	1	1	0.4%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%
Mumps	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%
Nail Puncture in Palm	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	1	1	0.4%
Neuroma, Foot	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	0	0	0.0%	1	1	0.4%
Nodules in Arm, Chest, and Abdomen	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%
Osteopenia/Osteoporosis	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	1	1	0.4%	1	1	0.4%	3	3	1.3%
Otitis Externa/Media	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	1	1	0.4%
Ovary Adhesions	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	0	0	0.0%	1	1	0.4%
Over-medicated	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	1	1	0.4%
Panic Attacks	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	1	1	0.4%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%
Pericardial Anemia	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	1	1	0.4%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%
Pharyngitis	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	1	1	0.4%

**Table 12. rhBMP-2/CRM/CD HORIZON® Spinal System Pivotal Study
"Other" Adverse Events - Investigational Patients (N=239)**

Adverse Event Type	Operative			1 Day- <1 Month			6 Weeks (≥1-<2 Months)			3 Months (≥2-<5 Months)			6 Months (≥5-<9 Months)			12 Months (≥9-<19 Months)			24 Months (≥19-<30 Months)			Total Events (through 24 mos.)			36 Months (≥30-<42 Months)			48 Months (≥42-<54 Months)			60 Months (≥54 Months)			Total Events (all time points)		
	Event	n	(%)	Event	n	(%)	Event	n	(%)	Event	n	(%)	Event	n	(%)	Event	n	(%)	Event	n	(%)	Event	n	(%)	Event	n	(%)	Event	n	(%)	Event	n	(%)	Event	n	(%)
PICC Line Kinked	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%
Plantar Fasciitis	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	1	1	0.4%	0	0	0.0%	2	2	0.8%
PMR	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	1	1	0.4%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%
Polydipsia	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	1	1	0.4%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%
Polymyalgia with Temporal Arteritis	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	1	1	0.4%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%
Polypharmacy	0	0	0.0%	3	3	1.3%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	3	3	1.3%	0	0	0.0%	0	0	0.0%	0	0	0.0%	3	3	1.3%
Popping in Back Without Pain	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	1	1	0.4%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%
Post-Myelogram Headache and Vomiting	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%
Pruritus	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%
Psychiatric - Rage	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%
R/O Parathyroidism	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%
Rash	0	0	0.0%	1	1	0.4%	1	1	0.4%	0	0	0.0%	0	0	0.0%	1	1	0.4%	1	1	0.4%	4	3	1.3%	1	1	0.4%	2	2	0.8%	0	0	0.0%	7	6	2.5%
Reaction to Medications	0	0	0.0%	1	1	0.4%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%
Restless Leg Syndrome	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%
Retained Remnant of Drain	0	0	0.0%	1	1	0.4%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%
Rheumatoid Arthritis	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	2	2	0.8%	0	0	0.0%	0	0	0.0%	0	0	0.0%	2	2	0.8%
Rhinitis	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	0	0.0%
Right Arm Weakness	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%
Rotator Cuff Tear	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	1	1	0.4%
Shingles	0	0	0.0%	1	1	0.4%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%
Side Effects from Chemotherapy	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	1	1	0.4%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%
Sinus Surgery	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%
Skin Breakdown	0	0	0.0%	1	1	0.4%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%
Skin Tear Over Groin	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%
Sleep Apnea	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	0	0	0.0%	2	2	0.8%	3	3	1.3%	0	0	0.0%	0	0	0.0%	0	0	0.0%	3	3	1.3%
Stress	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	1	1	0.4%
Sty	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	1	1	0.4%
Subarachnoid Hemorrhage	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%
Syncope	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	3	2	0.8%	1	1	0.4%	5	4	1.7%
Thyroid Nodule	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	1	1	0.4%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%
Toes Red	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	0	0	0.0%	1	1	0.4%

**Table 12. rhBMP-2/CRM/CD HORIZON® Spinal System Pivotal Study
"Other" Adverse Events - Investigational Patients (N=239)**

Adverse Event Type	Operative			1 Day- <1 Month			6 Weeks (≥1-<2 Months)			3 Months (≥2-<5 Months)			6 Months (≥5-<9 Months)			12 Months (≥9-<19 Months)			24 Months (≥19-<30 Months)			Total Events (through 24 mos.)			36 Months (≥30-<42 Months)			48 Months (≥42-<54 Months)			60 Months (≥54 Months)			Total Events (all time points)		
	Event	n	(%)	Event	n	(%)	Event	n	(%)	Event	n	(%)	Event	n	(%)	Event	n	(%)	Event	n	(%)	Event	n	(%)	Event	n	(%)	Event	n	(%)	Event	n	(%)	Event	n	(%)
Unacceptable Scar over Previous Surgery for Excision of Phlebitis	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%
Vertigo	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%
Viral Infection with Stomach Cramps	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%
Visual Disturbance	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%
Vitamin B12 Deficiency	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	1	1	0.4%
Wart/Mole	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	1	1	0.4%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%
Weight Loss	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%
Wound Drainage	0	0	0.0%	1	1	0.4%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%

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**Table 13. rhBMP-2/CRM/CD HORIZON® Spinal System Pivotal Study
"Other" Adverse Events - Control Patients (N=224)**

Adverse Event Type	Operative			1 Day- <1 Month			6 Weeks (≥1-<2 Months)			3 Months (≥2-<5 Months)			6 Months (≥5-<9 Months)			12 Months (≥9-<19 Months)			24 Months (≥19-<30 Months)			Total Events (through 24 mos.)			36 Months (≥30-<42 Months)			48 Months (≥42-<54 Months)			60 Months (≥54 Months)			Total Events (all time points)		
	Event	n	(%)	Event	n	(%)	Event	n	(%)	Event	n	(%)	Event	n	(%)	Event	n	(%)	Event	n	(%)	Event	n	(%)	Event	n	(%)	Event	n	(%)	Event	n	(%)	Event	n	(%)
Patients Who Had Any "Other" Adverse Events	0	0	0.0%	34	25	####	7	4	1.8%	8	8	3.6%	11	10	4.5%	14	11	4.9%	17	15	6.7%	91	62	27.7%	26	20	8.9%	20	11	4.9%	10	9	4.0%	147	80	35.7%
Abnormal Lab Values	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%
Abnormal Mammogram	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	1	1	0.4%
Abnormal Pap Smear	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%
Abnormal Thyroid Tissue	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	0	0	0.0%	1	1	0.4%
Abscess - Wrist	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	0	0	0.0%	1	1	0.4%
Adrenal Tumor - Benign	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	1	1	0.4%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%
Allergic Reaction	0	0	0.0%	3	3	1.3%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	4	4	1.8%	0	0	0.0%	0	0	0.0%	0	0	0.0%	4	4	1.8%
Ankle Sprain	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%
Ankle Swelling	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%
Anxiety	0	0	0.0%	2	1	0.4%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	3	1	0.4%	0	0	0.0%	0	0	0.0%	0	0	0.0%	3	1	0.4%
Autoimmune Disease	0	0	0.0%	1	1	0.4%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%
Balance Problems	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%
Bleeding at IV Site	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%
Bleeding Incision	0	0	0.0%	1	1	0.4%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%
Breast Mass	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	1	1	0.4%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%
Breast Reduction/ Pre-Cancerous Lesions	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	1	1	0.4%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%
Bug Bite	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%
Bunion	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	2	2	0.9%	0	0	0.0%	3	3	1.3%	0	0	0.0%	0	0	0.0%	0	0	0.0%	3	3	1.3%
Buttocks Bruises	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%
Cataracts	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	0	0	0.0%	2	2	0.9%	3	2	0.9%	0	0	0.0%	0	0	0.0%	0	0	0.0%	3	2	0.9%
Chemical Conjunctivitis	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	1	1	0.4%
Choking	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	0	0	0.0%	1	1	0.4%
Chronic Allergies	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%
Cough/Cold	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%
Cutaneous Candida	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	1	1	0.4%
Cyst	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	2	1	0.4%	2	2	0.9%	1	1	0.4%	6	5	2.2%
Decreased Muscle Mass BLE	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%
Dehydration	0	0	0.0%	1	1	0.4%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%
Dementia	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	1	1	0.4%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%
Dental Event	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	2	2	0.9%	1	1	0.4%	3	3	1.3%	0	0	0.0%	0	0	0.0%	0	0	0.0%	3	3	1.3%
Depression	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	3	3	1.3%	0	0	0.0%	2	2	0.9%	5	5	2.2%	2	2	0.9%	0	0	0.0%	2	2	0.9%	9	9	4.0%
Diabetes	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	1	1	0.4%	4	4	1.8%	0	0	0.0%	0	0	0.0%	5	5	2.2%
Dog Bite	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	1	1	0.4%

**Table 13. rhBMP-2/CRM/CD HORIZON® Spinal System Pivotal Study
"Other" Adverse Events - Control Patients (N=224)**

Adverse Event Type	Operative			1 Day- <1 Month			6 Weeks (≥1-<2 Months)			3 Months (≥2-<5 Months)			6 Months (≥5-<9 Months)			12 Months (≥9-<19 Months)			24 Months (≥19-<30 Months)			Total Events (through 24 mos.)			36 Months (≥30-<42 Months)			48 Months (≥42-<54 Months)			60 Months (≥54 Months)			Total Events (all time points)		
	Event	n	(%)	Event	n	(%)	Event	n	(%)	Event	n	(%)	Event	n	(%)	Event	n	(%)	Event	n	(%)	Event	n	(%)	Event	n	(%)	Event	n	(%)	Event	n	(%)	Event	n	(%)
Double Vision	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%
Drug Reaction	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%
Drug Withdrawal and Rehabilitation	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%
Dysphagia	0	0	0.0%	1	1	0.4%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	2	2	0.9%	1	1	0.4%	2	2	0.9%	0	0	0.0%	5	5	2.2%
Eczema	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%
Elevated Blood Sugar	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	0	0	0.0%	2	2	0.9%	3	3	1.3%	0	0	0.0%	0	0	0.0%	0	0	0.0%	3	3	1.3%
Elevated Creatinine	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%
Elevated Lithium Level	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	0	0	0.0%	1	1	0.4%
Elevated Liver Function Tests	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	1	1	0.4%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%
Elevated Vitamin B12 and Folate	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%
Enlarged Thyroid (goiter)	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%
Eyelash in Eye	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	1	1	0.4%
Fatigue	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%
Fatty Liver	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%
Fever	0	0	0.0%	6	6	2.7%	2	2	0.9%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	8	8	3.6%	1	1	0.4%	0	0	0.0%	1	1	0.4%	10	10	4.5%
Fibromyalgia	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	1	1	0.4%	0	0	0.0%	1	1	0.4%	0	0	0.0%	2	2	0.9%
Flat Foot	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	0	0	0.0%	1	1	0.4%	1	1	0.4%	0	0	0.0%	0	0	0.0%	2	2	0.9%
Flu	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	0	0	0.0%	1	1	0.4%
Foot Pain	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	0	0	0.0%	1	1	0.4%
Fungus	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%
Glaucoma	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%
Gout	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%
Heat Rash	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%
Heel Spur Pain	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%
Hiccups	0	0	0.0%	1	1	0.4%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%
Hot Flashes	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%
Hyperhomocysteinemia	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%
Hyperlipidemia	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	1	1	0.4%
Hypernatremia	0	0	0.0%	1	1	0.4%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%
Hypersomnolence and Daytime Sleep Disturbances	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	0	0	0.0%	1	1	0.4%
Hypocalcemia	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%
Hypoglycemia	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%
Hypokalemia	0	0	0.0%	2	2	0.9%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	2	2	0.9%	1	1	0.4%	1	1	0.4%	0	0	0.0%	4	3	1.3%

**Table 13. rhBMP-2/CRM/CD HORIZON® Spinal System Pivotal Study
"Other" Adverse Events - Control Patients (N=224)**

Adverse Event Type	Operative			1 Day- <1 Month			6 Weeks (≥1-<2 Months)			3 Months (≥2-<5 Months)			6 Months (≥5-<9 Months)			12 Months (≥9-<19 Months)			24 Months (≥19-<30 Months)			Total Events (through 24 mos.)			36 Months (≥30-<42 Months)			48 Months (≥42-<54 Months)			60 Months (≥54 Months)			Total Events (all time points)		
	Event	n	(%)	Event	n	(%)	Event	n	(%)	Event	n	(%)	Event	n	(%)	Event	n	(%)	Event	n	(%)	Event	n	(%)	Event	n	(%)	Event	n	(%)	Event	n	(%)	Event	n	(%)
Hypothyroidism	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	1	1	0.4%	0	0	0.0%	1	1	0.4%	0	0	0.0%	2	2	0.9%
Hypovolemia	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	0	0	0.0%	1	1	0.4%
Immunosuppressed	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%
Insomnia	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	1	1	0.4%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%
Iron deficiency	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%
Itching	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%
IV Infiltration	0	0	0.0%	1	1	0.4%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%
Laryngeal Edema and Throat Swelling	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%
Leg and Foot Swelling	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%
Lesions on Feet	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%
Leukocytosis	0	0	0.0%	1	1	0.4%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%
Low Magnesium	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%
Low Testosterone Level	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%
Lymphadenopathy	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	1	1	0.4%	1	1	0.4%	0	0	0.0%	0	0	0.0%	2	2	0.9%
Mammogram	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	0	0	0.0%	1	1	0.4%
Meningioma	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%
Menstrual Cramps	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%
Mental Status Change	0	0	0.0%	5	5	2.2%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	6	6	2.7%	0	0	0.0%	0	0	0.0%	0	0	0.0%	6	6	2.7%
Methadone Overdose	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%
Monilial Rash in Mouth	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	1	1	0.4%
Mood Disorder	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	0	0	0.0%	1	1	0.4%
Morbid Obesity	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%
Morton's Neuroma	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%
Mumps	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%
Nail Puncture in Palm	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%
Neuroma, Foot	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%
Nodules in Arm, Chest, and Abdomen	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	1	1	0.4%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%
Osteopenia/Osteoporosis	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	1	1	0.4%	0	0	0.0%	1	1	0.4%	0	0	0.0%	2	2	0.9%
Otitis Externa/Media	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	1	1	0.4%
Ovary Adhesions	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%
Over-medicated	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%
Panic Attacks	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	2	2	0.9%	0	0	0.0%	2	2	0.9%
Pernicious Anemia	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%
Pharyngitis	0	0	0.0%	1	1	0.4%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%

**Table 13. rhBMP-2/CRM/CD HORIZON® Spinal System Pivotal Study
"Other" Adverse Events - Control Patients (N=224)**

Adverse Event Type	Operative			1 Day- <1 Month			6 Weeks (≥1-<2 Months)			3 Months (≥2-<5 Months)			6 Months (≥5-<9 Months)			12 Months (≥9-<19 Months)			24 Months (≥19-<30 Months)			Total Events (through 24 mos.)			36 Months (≥30-<42 Months)			48 Months (≥42-<54 Months)			60 Months (≥54 Months)			Total Events (all time points)		
	Event	n	(%)	Event	n	(%)	Event	n	(%)	Event	n	(%)	Event	n	(%)	Event	n	(%)	Event	n	(%)	Event	n	(%)	Event	n	(%)	Event	n	(%)	Event	n	(%)	Event	n	(%)
PICC Line Kinked	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%
Plantar Fasciitis	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%
PMR	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%
Polydipsia	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%
Polymyalgia with Temporal Arteritis	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%
Polypharmacy	0	0	0.0%	1	1	0.4%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%
Popping in Back Without Pain	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%
Post-Myelogram Headache and Vomiting	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	1	1	0.4%
Pruritus	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%
Psychiatric - Rage	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%
R/O Parathyroidism	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	1	1	0.4%
Rash	0	0	0.0%	2	2	0.9%	1	1	0.4%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	3	3	1.3%	0	0	0.0%	1	1	0.4%	1	1	0.4%	5	4	1.8%
Reaction to Medications	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%
Restless Leg Syndrome	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	0	0	0.0%	1	1	0.4%
Retained Remnant of Drain	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%
Rheumatoid Arthritis	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	0	0	0.0%	1	1	0.4%
Rhinitis	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%
Right Arm Weakness	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	1	1	0.4%
Rotator Cuff Tear	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%
Shingles	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%
Side Effects from Chemotherapy	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%
Sinus Surgery	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%
Skin Breakdown	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%
Skin Tear Over Groin	0	0	0.0%	1	1	0.4%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%
Sleep Apnea	0	0	0.0%	1	1	0.4%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%
Stress	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%
Sty	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%
Subarachnoid Hemorrhage	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%
Syncope	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	1	1	0.4%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%
Thyroid Nodule	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%
Toes Red	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%

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**Table 13. rhBMP-2/CRM/CD HORIZON® Spinal System Pivotal Study
"Other" Adverse Events - Control Patients (N=224)**

Adverse Event Type	Operative			1 Day- <1 Month			6 Weeks (≥1-<2 Months)			3 Months (≥2-<5 Months)			6 Months (≥5-<9 Months)			12 Months (≥9-<19 Months)			24 Months (≥19-<30 Months)			Total Events (through 24 mos.)			36 Months (≥30-<42 Months)			48 Months (≥42-<54 Months)			60 Months (≥54 Months)			Total Events (all time points)		
	Event	n	(%)	Event	n	(%)	Event	n	(%)	Event	n	(%)	Event	n	(%)	Event	n	(%)	Event	n	(%)	Event	n	(%)	Event	n	(%)	Event	n	(%)	Event	n	(%)	Event	n	(%)
Unacceptable Scar Over Previous Surgery for Excision of Phlebitis	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	1	1	0.4%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%
Vertigo	0	0	0.0%	1	1	0.4%	0	0	0.0%	1	1	0.4%	0	0	0.0%	1	1	0.4%	0	0	0.0%	3	3	1.3%	0	0	0.0%	0	0	0.0%	2	2	0.9%	5	5	2.2%
Viral Infection with Stomach Cramps	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%
Visual Disturbance	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	0	0	0.0%	1	1	0.4%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%
Vitamin B12 Deficiency	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%
Wart/Mole	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%
Weight Loss	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	1	1	0.4%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%
Wound Drainage	0	0	0.0%	1	1	0.4%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	1	1	0.4%	1	1	0.4%	1	1	0.4%	0	0	0.0%	3	3	1.3%

Table 14. Summary of Grade 3 or 4 Adverse Events

Adverse Event Type	Investigational (N=239)											
	Operative		1 day-4 wks		6 weeks		3 months		6 months		12 months	
	Event	Patient n (%)	Event	Patient n (%)	Event	Patient n (%)	Event	Patient n (%)	Event	Patient n (%)	Event	Patient n (%)
Patients Who Had Any Adverse Events	2	2 (0.8)	61	51 (21.3)	10	10 (4.2)	22	20 (8.4)	31	27 (11.3)	61	42 (17.6)
Arthritis/Bursitis	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	2	2 (0.8)	1	1 (0.4)	3	3 (1.3)
Back and/or Leg Pain	0	0 (0.0)	5	5 (2.1)	1	1 (0.4)	2	2 (0.8)	4	4 (1.7)	8	8 (3.3)
Cancer	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	1	1 (0.4)	2	2 (0.8)	3	3 (1.3)
Cardiovascular	1	1 (0.4)	27	24 (10.0)	0	0 (0.0)	1	1 (0.4)	2	2 (0.8)	11	9 (3.8)
Carpal Tunnel Syndrome	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	1	1 (0.4)	2	2 (0.8)
Death	0	0 (0.0)	0	0 (0.0)	1	1 (0.4)	0	0 (0.0)	1	1 (0.4)	1	1 (0.4)
Dural Injury	0	0 (0.0)	1	1 (0.4)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)
Gastrointestinal	0	0 (0.0)	5	5 (2.1)	0	0 (0.0)	2	2 (0.8)	4	4 (1.7)	6	6 (2.5)
Graft Site Related	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)
Infection	0	0 (0.0)	7	7 (2.9)	2	2 (0.8)	0	0 (0.0)	0	0 (0.0)	3	3 (1.3)
Malpositioned Implant	0	0 (0.0)	3	3 (1.3)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)
Neurological	0	0 (0.0)	4	4 (1.7)	0	0 (0.0)	4	4 (1.7)	4	4 (1.7)	2	2 (0.8)
Non-Union	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	1	1 (0.4)	0	0 (0.0)	4	4 (1.7)
Other	0	0 (0.0)	4	4 (1.7)	2	2 (0.8)	1	1 (0.4)	1	1 (0.4)	1	1 (0.4)
Other Pain	0	0 (0.0)	0	0 (0.0)	1	1 (0.4)	1	1 (0.4)	2	2 (0.8)	1	1 (0.4)
Respiratory	0	0 (0.0)	1	1 (0.4)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	2	2 (0.8)
Spinal Event-All	0	0 (0.0)	1	1 (0.4)	0	0 (0.0)	3	3 (1.3)	2	2 (0.8)	3	3 (1.3)
Spinal Event-Cervical	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	1	1 (0.4)	2	2 (0.8)	2	2 (0.8)
Spinal Event-Lumbar	0	0 (0.0)	1	1 (0.4)	0	0 (0.0)	2	2 (0.8)	0	0 (0.0)	0	0 (0.0)
Spinal Event-Thoracic	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	1	1 (0.4)
Trauma	0	0 (0.0)	0	0 (0.0)	1	1 (0.4)	0	0 (0.0)	4	4 (1.7)	7	7 (2.9)
Urogenital	0	0 (0.0)	3	3 (1.3)	2	2 (0.8)	4	4 (1.7)	3	3 (1.3)	4	4 (1.7)
Vertebral Fracture	1	1 (0.4)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)

Table 14. Summary of Grade 3 or 4 Adverse Events

Adverse Event Type	Investigational (N=239)									
	24 months		Total (≤24 months)		36 months		48 months		60 months	
	Event	Patient n (%)	Event	Patient n (%)	Event	Patient n (%)	Event	Patient n (%)	Event	Patient n (%)
Patients Who Had Any Adverse Events	41	33 (13.8)	228	126 (52.7)	60	48 (20.1)	58	40 (16.7)	19	15 (6.3)
Arthritis/Bursitis	1	1 (0.4)	7	7 (2.9)	3	3 (1.3)	1	1 (0.4)	0	0 (0.0)
Back and/or Leg Pain	5	5 (2.1)	25	24 (10.0)	8	7 (2.9)	4	4 (1.7)	2	2 (0.8)
Cancer	3	3 (1.3)	9	9 (3.8)	4	4 (1.7)	0	0 (0.0)	0	0 (0.0)
Cardiovascular	3	3 (1.3)	45	36 (15.1)	9	9 (3.8)	9	8 (3.3)	2	2 (0.8)
Carpal Tunnel Syndrome	2	2 (0.8)	5	5 (2.1)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)
Death	0	0 (0.0)	3	3 (1.3)	0	0 (0.0)	2	2 (0.8)	1	1 (0.4)
Dural Injury	0	0 (0.0)	1	1 (0.4)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)
Gastrointestinal	6	5 (2.1)	23	21 (8.8)	11	10 (4.2)	10	8 (3.3)	3	3 (1.3)
Graft Site Related	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)
Infection	1	1 (0.4)	13	12 (5.0)	1	1 (0.4)	2	2 (0.8)	0	0 (0.0)
Malpositioned Implant	0	0 (0.0)	3	3 (1.3)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)
Neurological	1	1 (0.4)	15	15 (6.3)	2	2 (0.8)	2	2 (0.8)	2	2 (0.8)
Non-Union	0	0 (0.0)	5	5 (2.1)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)
Other	3	3 (1.3)	12	12 (5.0)	7	6 (2.5)	15	13 (5.4)	4	3 (1.3)
Other Pain	1	1 (0.4)	6	6 (2.5)	2	2 (0.8)	3	3 (1.3)	0	0 (0.0)
Respiratory	1	1 (0.4)	4	3 (1.3)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)
Spinal Event-All	2	2 (0.8)	11	10 (4.2)	2	2 (0.8)	1	1 (0.4)	1	1 (0.4)
Spinal Event-Cervical	1	1 (0.4)	6	5 (2.1)	1	1 (0.4)	1	1 (0.4)	1	1 (0.4)
Spinal Event-Lumbar	1	1 (0.4)	4	4 (1.7)	1	1 (0.4)	0	0 (0.0)	0	0 (0.0)
Spinal Event-Thoracic	0	0 (0.0)	1	1 (0.4)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)
Trauma	11	11 (4.6)	23	22 (9.2)	9	9 (3.8)	7	7 (2.9)	3	3 (1.3)
Urogenital	1	1 (0.4)	17	16 (6.7)	2	2 (0.8)	2	2 (0.8)	1	1 (0.4)
Vertebral Fracture	0	0 (0.0)	1	1 (0.4)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)

Table 14. Summary of Grade 3 or 4 Adverse Events

Adverse Event Type	Control (N=224)											
	Operative		1 day-4 wks		6 weeks		3 months		6 months		12 months	
	Event	Patient n (%)	Event	Patient n (%)	Event	Patient n (%)	Event	Patient n (%)	Event	Patient n (%)	Event	Patient n (%)
Patients Who Had Any Adverse Events	0	0 (0.0)	58	49 (21.9)	16	15 (6.7)	22	22 (9.8)	40	34 (15.2)	64	48 (21.4)
Arthritis/Bursitis	0	0 (0.0)	0	0 (0.0)	1	1 (0.4)	1	1 (0.4)	3	3 (1.3)	3	3 (1.3)
Back and/or Leg Pain	0	0 (0.0)	1	1 (0.4)	2	2 (0.9)	0	0 (0.0)	7	6 (2.7)	7	6 (2.7)
Cancer	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	1	1 (0.4)	1	1 (0.4)
Cardiovascular	0	0 (0.0)	33	33 (14.7)	0	0 (0.0)	1	1 (0.4)	5	5 (2.2)	7	7 (3.1)
Carpal Tunnel Syndrome	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	1	1 (0.4)	1	1 (0.4)
Death	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	2	2 (0.9)	1	1 (0.4)
Dural Injury	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)
Gastrointestinal	0	0 (0.0)	5	5 (2.2)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	8	4 (1.8)
Graft Site Related	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	1	1 (0.4)	0	0 (0.0)
Infection	0	0 (0.0)	7	7 (3.1)	3	3 (1.3)	0	0 (0.0)	0	0 (0.0)	4	4 (1.8)
Malpositioned Implant	0	0 (0.0)	1	1 (0.4)	1	1 (0.4)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)
Neurological	0	0 (0.0)	3	3 (1.3)	1	1 (0.4)	4	4 (1.8)	3	3 (1.3)	2	2 (0.9)
Non-Union	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	7	7 (3.1)	5	5 (2.2)	5	5 (2.2)
Other	0	0 (0.0)	5	4 (1.8)	1	1 (0.4)	3	3 (1.3)	4	4 (1.8)	5	5 (2.2)
Other Pain	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	1	1 (0.4)	0	0 (0.0)
Respiratory	0	0 (0.0)	0	0 (0.0)	1	1 (0.4)	1	1 (0.4)	1	1 (0.4)	2	2 (0.9)
Spinal Event-All	0	0 (0.0)	0	0 (0.0)	2	1 (0.4)	3	3 (1.3)	2	2 (0.9)	7	7 (3.1)
Spinal Event-Cervical	0	0 (0.0)	0	0 (0.0)	2	1 (0.4)	1	1 (0.4)	1	1 (0.4)	5	5 (2.2)
Spinal Event-Lumbar	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	2	2 (0.9)	1	1 (0.4)	2	2 (0.9)
Spinal Event-Thoracic	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)
Trauma	0	0 (0.0)	2	2 (0.9)	4	4 (1.8)	1	1 (0.4)	4	4 (1.8)	7	6 (2.7)
Urogenital	0	0 (0.0)	1	1 (0.4)	0	0 (0.0)	1	1 (0.4)	0	0 (0.0)	4	3 (1.3)
Vertebral Fracture	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)

Table 14. Summary of Grade 3 or 4 Adverse Events

Adverse Event Type	Control (N=224)											
	24 months		Total (≤24 months)		36 months		48 months		60 months		Total (All)	
	Event	Patient n (%)	Event	Patient n (%)	Event	Patient n (%)	Event	Patient n (%)	Event	Patient n (%)	Event	Patient n (%)
Patients Who Had Any Adverse Events	34	29(12.9)	234	125(55.8)	39	26(11.6)	42	27(12.1)	22	19(8.5)	337	148(66.1)
Arthritis/Bursitis	0	0(0.0)	8	7(3.1)	2	2(0.9)	2	1(0.4)	2	2(0.9)	14	11(4.9)
Back and/or Leg Pain	5	5(2.2)	22	18(8.0)	7	4(1.8)	3	3(1.3)	4	4(1.8)	36	27(12.1)
Cancer	0	0(0.0)	2	2(0.9)	1	1(0.4)	1	1(0.4)	0	0(0.0)	4	4(1.8)
Cardiovascular	0	0(0.0)	46	40(17.9)	1	1(0.4)	9	7(3.1)	3	3(1.3)	59	48(21.4)
Carpal Tunnel Syndrome	0	0(0.0)	2	2(0.9)	0	0(0.0)	0	0(0.0)	1	1(0.4)	3	3(1.3)
Death	1	1(0.4)	4	4(1.8)	1	1(0.4)	1	1(0.4)	1	1(0.4)	7	7(3.1)
Dural Injury	0	0(0.0)	0	0(0.0)	0	0(0.0)	0	0(0.0)	1	1(0.4)	1	1(0.4)
Gastrointestinal	5	5(2.2)	18	14(6.3)	6	6(2.7)	7	3(1.3)	4	3(1.3)	35	24(10.7)
Graft Site Related	0	0(0.0)	1	1(0.4)	0	0(0.0)	0	0(0.0)	0	0(0.0)	1	1(0.4)
Infection	3	3(1.3)	17	17(7.6)	2	2(0.9)	3	3(1.3)	0	0(0.0)	22	21(9.4)
Malpositioned Implant	0	0(0.0)	2	2(0.9)	0	0(0.0)	0	0(0.0)	0	0(0.0)	2	2(0.9)
Neurological	0	0(0.0)	13	13(5.8)	3	2(0.9)	1	1(0.4)	0	0(0.0)	17	15(6.7)
Non-Union	1	1(0.4)	18	18(8.0)	0	0(0.0)	0	0(0.0)	0	0(0.0)	18	18(8.0)
Other	5	5(2.2)	23	21(9.4)	7	6(2.7)	6	6(2.7)	2	2(0.9)	38	31(13.8)
Other Pain	5	5(2.2)	6	6(2.7)	3	3(1.3)	1	1(0.4)	0	0(0.0)	10	8(3.6)
Respiratory	0	0(0.0)	5	5(2.2)	0	0(0.0)	1	1(0.4)	0	0(0.0)	6	6(2.7)
Spinal Event-All	0	0(0.0)	14	12(5.4)	0	0(0.0)	0	0(0.0)	0	0(0.0)	14	12(5.4)
Spinal Event-Cervical	0	0(0.0)	9	8(3.6)	0	0(0.0)	0	0(0.0)	0	0(0.0)	9	8(3.6)
Spinal Event-Lumbar	0	0(0.0)	5	5(2.2)	0	0(0.0)	0	0(0.0)	0	0(0.0)	5	5(2.2)
Spinal Event-Thoracic	0	0(0.0)	0	0(0.0)	0	0(0.0)	0	0(0.0)	0	0(0.0)	0	0(0.0)
Trauma	6	6(2.7)	24	23(10.3)	4	4(1.8)	6	4(1.8)	3	3(1.3)	37	31(13.8)
Urogenital	3	3(1.3)	9	6(2.7)	2	2(0.9)	1	1(0.4)	1	1(0.4)	13	10(4.5)
Vertebral Fracture	0	0(0.0)	0	0(0.0)	0	0(0.0)	0	0(0.0)	0	0(0.0)	0	0(0.0)

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Table 15. Summary of Adverse Events That Are Possibly Related* to Study Device

Adverse Event Type	Investigational (N=239)											
	Operative		1 day-4 wks		6 weeks		3 months		6 months		12 months	
	Event	Patient n (%)	Event	Patient n (%)	Event	Patient n (%)	Event	Patient n (%)	Event	Patient n (%)	Event	Patient n (%)
Patients Who Had Any Adverse Events	0	0 (0.0)	5	5 (2.1)	0	0 (0.0)	2	2 (0.8)	2	2 (0.8)	12	12 (5.0)
Arthritis/Bursitis	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)
Back and/or Leg Pain	0	0 (0.0)	1	1 (0.4)	0	0 (0.0)	0	0 (0.0)	1	1 (0.4)	2	2 (0.8)
Dural Injury	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)
Implant Displacement/Loosening	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	1	1 (0.4)
Malpositioned Implant	0	0 (0.0)	3	3 (1.3)	0	0 (0.0)	1	1 (0.4)	0	0 (0.0)	0	0 (0.0)
Neurological	0	0 (0.0)	1	1 (0.4)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	1	1 (0.4)
Non-Union	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	1	1 (0.4)	0	0 (0.0)	8	8 (3.3)
Trauma	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	1	1 (0.4)	0	0 (0.0)
Vertebral Fracture	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)

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* Possibly related: device related and device/surgical procedure related.

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Table 15. Summary of Adverse Events That Are Possibly Related* to Study Device

Adverse Event Type	Investigational (N=239)											
	24 months		Total (≤24 months)		36 months		48 months		60 months		Total (All)	
	Event	Patient n (%)	Event	Patient n (%)	Event	Patient n (%)	Event	Patient n (%)	Event	Patient n (%)	Event	Patient n (%)
Patients Who Had Any Adverse Events	1	1 (0.4)	22	21 (8.8)	2	2 (0.8)	1	1 (0.4)	0	0 (0.0)	25	23 (9.6)
Arthritis/Bursitis	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)
Back and/or Leg Pain	0	0 (0.0)	4	4 (1.7)	1	1 (0.4)	1	1 (0.4)	0	0 (0.0)	6	6 (2.5)
Dural Injury	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)
Implant Displacement/Loosening	0	0 (0.0)	1	1 (0.4)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	1	1 (0.4)
Malpositioned Implant	0	0 (0.0)	4	4 (1.7)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	4	4 (1.7)
Neurological	0	0 (0.0)	2	2 (0.8)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	2	2 (0.8)
Non-Union	1	1 (0.4)	10	10 (4.2)	1	1 (0.4)	0	0 (0.0)	0	0 (0.0)	11	11 (4.6)
Trauma	0	0 (0.0)	1	1 (0.4)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	1	1 (0.4)
Vertebral Fracture	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)

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* Possibly related: device related and device/surgical procedure related.

Table 15. Summary of Adverse Events That Are Possibly Related* to Study Device

Adverse Event Type	Control (N=224)											
	Operative		1 day-4 wks		6 weeks		3 months		6 months		12 months	
	Event	Patient n (%)	Event	Patient n (%)	Event	Patient n (%)	Event	Patient n (%)	Event	Patient n (%)	Event	Patient n (%)
Patients Who Had Any Adverse Events	2	2 (0.9)	1	1 (0.4)	2	2 (0.9)	10	10 (4.5)	9	9 (4.0)	9	9 (4.0)
Arthritis/Bursitis	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	1	1 (0.4)	1	1 (0.4)
Back and/or Leg Pain	0	0 (0.0)	0	0 (0.0)	1	1 (0.4)	0	0 (0.0)	3	3 (1.3)	1	1 (0.4)
Dural Injury	1	1 (0.4)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)
Implant Displacement/Loosening	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	1	1 (0.4)	0	0 (0.0)	1	1 (0.4)
Malpositioned Implant	0	0 (0.0)	1	1 (0.4)	1	1 (0.4)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)
Neurological	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	1	1 (0.4)	0	0 (0.0)	0	0 (0.0)
Non-Union	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	8	8 (3.6)	5	5 (2.2)	6	6 (2.7)
Trauma	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)
Vertebral Fracture	1	1 (0.4)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)

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* Possibly related: device related and device/surgical procedure related.

Table 15. Summary of Adverse Events That Are Possibly Related* to Study Device

Adverse Event Type	Control (N=224)											
	24 months		Total (≤24 months)		36 months		48 months		60 months		Total (All)	
	Event	Patient n (%)	Event	Patient n (%)	Event	Patient n (%)	Event	Patient n (%)	Event	Patient n (%)	Event	Patient n (%)
Patients Who Had Any Adverse Events	3	3 (1.3)	36	34 (15.2)	1	1 (0.4)	0	0 (0.0)	0	0 (0.0)	37	35 (15.6)
Arthritis/Bursitis	0	0 (0.0)	2	2 (0.9)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	2	2 (0.9)
Back and/or Leg Pain	0	0 (0.0)	5	5 (2.2)	1	1 (0.4)	0	0 (0.0)	0	0 (0.0)	6	6 (2.7)
Dural Injury	0	0 (0.0)	1	1 (0.4)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	1	1 (0.4)
Implant Displacement/Loosening	0	0 (0.0)	2	2 (0.9)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	2	2 (0.9)
Malpositioned Implant	0	0 (0.0)	2	2 (0.9)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	2	2 (0.9)
Neurological	0	0 (0.0)	1	1 (0.4)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	1	1 (0.4)
Non-Union	3	3 (1.3)	22	22 (9.8)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	22	22 (9.8)
Trauma	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)
Vertebral Fracture	0	0 (0.0)	1	1 (0.4)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	1	1 (0.4)

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* Possibly related: device related and device/surgical procedure related.

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Table 16. Summary of Grade 3 or 4 Adverse Events That Are Possibly Related* to Study Device

Adverse Event Type	Investigational (N=239)											
	Operative		1 day-4 wks		6 weeks		3 months		6 months		12 months	
	Event	Patient n (%)	Event	Patient n (%)	Event	Patient n (%)	Event	Patient n (%)	Event	Patient n (%)	Event	Patient n (%)
Patients Who Had Any Adverse Events	0	0 (0.0)	5	5 (2.1)	0	0 (0.0)	1	1 (0.4)	2	2 (0.8)	7	7 (2.9)
Arthritis/Bursitis	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)
Back and/or Leg Pain	0	0 (0.0)	1	1 (0.4)	0	0 (0.0)	0	0 (0.0)	1	1 (0.4)	2	2 (0.8)
Malpositioned Implant	0	0 (0.0)	3	3 (1.3)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)
Neurological	0	0 (0.0)	1	1 (0.4)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	1	1 (0.4)
Non-Union	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	1	1 (0.4)	0	0 (0.0)	4	4 (1.7)
Trauma	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	1	1 (0.4)	0	0 (0.0)

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* Possibly related: device related and device/surgical procedure related.

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Table 16. Summary of Grade 3 or 4 Adverse Events That Are Possibly Related* to Study Device

	Investigational (N=239)											
	24 months		Total (≤24 months)		36 months		48 months		60 months		Total (All)	
Adverse Event Type	Event	Patient n (%)	Event	Patient n (%)	Event	Patient n (%)	Event	Patient n (%)	Event	Patient n (%)	Event	Patient n (%)
Patients Who Had Any Adverse Events	0	0(0.0)	15	15(6.3)	1	1(0.4)	0	0(0.0)	0	0(0.0)	16	16(6.7)
Arthritis/Bursitis	0	0(0.0)	0	0(0.0)	0	0(0.0)	0	0(0.0)	0	0(0.0)	0	0(0.0)
Back and/or Leg Pain	0	0(0.0)	4	4(1.7)	1	1(0.4)	0	0(0.0)	0	0(0.0)	5	5(2.1)
Malpositioned Implant	0	0(0.0)	3	3(1.3)	0	0(0.0)	0	0(0.0)	0	0(0.0)	3	3(1.3)
Neurological	0	0(0.0)	2	2(0.8)	0	0(0.0)	0	0(0.0)	0	0(0.0)	2	2(0.8)
Non-Union	0	0(0.0)	5	5(2.1)	0	0(0.0)	0	0(0.0)	0	0(0.0)	5	5(2.1)
Trauma	0	0(0.0)	1	1(0.4)	0	0(0.0)	0	0(0.0)	0	0(0.0)	1	1(0.4)

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* Possibly related: device related and device/surgical procedure related.

Table 16. Summary of Grade 3 or 4 Adverse Events That Are Possibly Related* to Study Device

	Control (N=224)											
	Operative		1 day-4 wks		6 weeks		3 months		6 months		12 months	
Adverse Event Type	Event	Patient n (%)	Event	Patient n (%)	Event	Patient n (%)	Event	Patient n (%)	Event	Patient n (%)	Event	Patient n (%)
Patients Who Had Any Adverse Events	0	0(0.0)	1	1(0.4)	2	2(0.9)	8	8(3.6)	9	9(4.0)	7	7(3.1)
Arthritis/Bursitis	0	0(0.0)	0	0(0.0)	0	0(0.0)	0	0(0.0)	1	1(0.4)	1	1(0.4)
Back and/or Leg Pain	0	0(0.0)	0	0(0.0)	1	1(0.4)	0	0(0.0)	3	3(1.3)	1	1(0.4)
Malpositioned Implant	0	0(0.0)	1	1(0.4)	1	1(0.4)	0	0(0.0)	0	0(0.0)	0	0(0.0)
Neurological	0	0(0.0)	0	0(0.0)	0	0(0.0)	1	1(0.4)	0	0(0.0)	0	0(0.0)
Non-Union	0	0(0.0)	0	0(0.0)	0	0(0.0)	7	7(3.1)	5	5(2.2)	5	5(2.2)
Trauma	0	0(0.0)	0	0(0.0)	0	0(0.0)	0	0(0.0)	0	0(0.0)	0	0(0.0)

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* Possibly related: device related and device/surgical procedure related.

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Table 16. Summary of Grade 3 or 4 Adverse Events That Are Possibly Related* to Study Device

Adverse Event Type	Control (N=224)											
	24 months		Total (≤24 months)		36 months		48 months		60 months		Total (All)	
	Event	Patient n (%)	Event	Patient n (%)	Event	Patient n (%)	Event	Patient n (%)	Event	Patient n (%)	Event	Patient n (%)
Patients Who Had Any Adverse Events	1	1 (0.4)	28	27 (12.1)	1	1 (0.4)	0	0 (0.0)	0	0 (0.0)	29	28 (12.5)
Arthritis/Bursitis	0	0 (0.0)	2	2 (0.9)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	2	2 (0.9)
Back and/or Leg Pain	0	0 (0.0)	5	5 (2.2)	1	1 (0.4)	0	0 (0.0)	0	0 (0.0)	6	6 (2.7)
Malpositioned Implant	0	0 (0.0)	2	2 (0.9)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	2	2 (0.9)
Neurological	0	0 (0.0)	1	1 (0.4)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	1	1 (0.4)
Non-Union	1	1 (0.4)	18	18 (8.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	18	18 (8.0)
Trauma	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)

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* Possibly related: device related and device/surgical procedure related.

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TABLE 17. IDE SECOND SURGERIES¹
rhBMP-2/CRM/CD HORIZON® Spinal System Pivotal Study

Type of Secondary Surgical Procedure	Operative		1 Day- <1 Month		6 Weeks (21-42 Months)		3 Months (42-51 Months)		6 Months (51-69 Months)		12 Months (69-81 Months)		24 Months (81-93 Months)		Total Events (Thru 24 Months)		# of Patients Reporting				36 Months (93-105 Months)		48 Months (105-117 Months)		60 Months (117-129 Months)		Total Events (All Time Points)		# of Patients Reporting			
	INV	Control	INV	Control	INV	Control	INV	Control	INV	Control	INV	Control	INV	Control	INV	Control	INV	Control	INV	Control	INV	Control	INV	Control	INV	Control	INV	Control	INV	Control	INV	Control
	INV	Control	INV	Control	INV	Control	INV	Control	INV	Control	INV	Control	INV	Control	INV	Control	INV	Control	INV	Control	INV	Control	INV	Control	INV	Control	INV	Control	INV	Control	INV	Control
Revisions	0	0	2	0	0	2	0	0	0	0	0	1	2	1	4	4	4	1.7%	4	1.8%	1	1	0	1	1	0	6	6	6	2.5%	6	2.7%
Removals	0	0	1	0	0	1	2	0	2	2	4	17	4	9	13	29	13	5.4%	28	12.5%	6	4	3	0	0	2	22	35	22	9.2%	34	15.2%
Non-elective	0	0	1	0	0	1	2	0	1	1	4	17	2	4	10	23	10	4.2%	22	9.8%	3	2	2	0	0	2	15	27	15	6.3%	26	11.6%
Elective	0	0	0	0	0	0	0	0	1	1	0	0	2	5	3	6	3	1.3%	6	2.7%	3	2	1	0	0	0	7	8	7	2.9%	8	3.6%
Supplemental Fixations	0	0	0	0	0	1	0	1	0	2	5	5	1	0	6	9	6	2.6%	9	4.0%	0	1	0	0	0	0	6	10	6	2.5%	10	4.5%
Reoperations	0	0	10	4	2	7	1	1	0	0	0	0	0	2	13	14	12	5.0%	11	4.9%	1	0	0	0	0	0	14	14	13	5.4%	11	4.9%
Other	0	0	2	4	2	0	7	9	15	13	37	33	31	35	94	94	62	25.9%	60	26.8%	43	21	37	27	13	14	187	156	99	41.4%	87	38.6%

¹ Secondary surgeries classified as Revisions, Non-Elective Removals and Supplemental Fixations are typically classified as "Failures."

For rhBMP-2/CRM/CD HORIZON® patients, there were a total of 27 Revisions, Non-Elective Removals and Supplemental Fixations that were classified as "Failures". Please note that 6 patients [redacted] and [redacted] had both a Non-Elective Removal and a Supplemental Fixation during the same second surgery, and 2 patients [redacted] had both a Revision and a Supplemental Fixation during the same second surgery. These were counted as one event on the second surgery table and were classified as one second surgery "Failure."

For control patients, there were a total of 43 Revisions, Non-Elective Removals, and Supplemental Fixations that were classified as "Failures." Please note that 17 patients [redacted] and [redacted] had both a Non-Elective Removal and a Supplemental Fixation during the same second surgery, 2 patients ([redacted] and [redacted]) had both a Revision and a Supplemental Fixation during the same second surgery. These were counted as one event on the second surgery table and were classified as one second surgery "Failure." Five patients ([redacted] and [redacted]) had a third surgery (Non-Elective Removal) after they had already been counted as a second surgery "Failure" because of undergoing previous Revisions, Non-Elective Removals, or Supplemental Fixations. These 5 Non-Elective Removals are included as events on the second surgery table, but are not classified as additional "Failures" because of their previous second surgery "Failure" status. There are three control patients [redacted] who had external bone growth stimulators. While these are not considered true surgical interventions, external bone growth stimulators are categorized as supplemental fixations and study failures and are included in the table above.

Table 18. Summary of Success* Rates of Neurological Status
[Number (%) of Patients]

Period	Variable	Investigational (N=239)	Control (N=224)
6 Weeks	Motor		
	Success	229 (98.3)	207 (95.8)
	Failure	4 (1.7)	9 (4.2)
	Sensory		
	Success	223 (95.7)	206 (95.4)
	Failure	10 (4.3)	10 (4.6)
	Reflexes		
	Success	225 (96.6)	210 (97.2)
	Failure	8 (3.4)	6 (2.8)
	Straight Leg Raise		
3 Months	Success	232 (99.6)	210 (97.2)
	Failure	1 (0.4)	6 (2.8)
	Overall		
	Success	215 (92.3)	191 (88.4)
	Failure	18 (7.7)	25 (11.6)
	Motor		
	Success	226 (97.8)	211 (97.7)
	Failure	5 (2.2)	5 (2.3)
	Sensory		
	Success	217 (93.9)	205 (94.9)
6 Months	Failure	14 (6.1)	11 (5.1)
	Reflexes		
	Success	221 (95.7)	207 (95.8)
	Failure	10 (4.3)	9 (4.2)
	Straight Leg Raise		
	Success	225 (97.4)	213 (98.6)
	Failure	6 (2.6)	3 (1.4)
	Overall		
	Success	205 (88.7)	192 (88.9)
	Failure	26 (11.3)	24 (11.1)
6 Months	Motor		
	Success	225 (98.3)	199 (96.1)
	Failure	4 (1.7)	8 (3.9)
	Sensory		
	Success	213 (93.0)	194 (93.7)
	Failure	16 (7.0)	13 (6.3)
	Reflexes		
	Success	216 (94.3)	198 (95.7)
	Failure	13 (5.7)	9 (4.3)
	Straight Leg Raise		
6 Months	Success	224 (97.8)	204 (98.6)
	Failure	5 (2.2)	3 (1.4)
	Overall		
	Success	200 (87.3)	182 (87.9)
	Failure	29 (12.7)	25 (12.1)

* Success for each component: Post Score - Pre Score \geq 0.
 Success for overall neuro: All successes of the 4 components.

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Table 18. Summary of Success* Rates of Neurological Status
(Number (%) of Patients)

Period	Variable	Investigational (N=239)	Control (N=224)
12 Months	Motor		
	Success	222(98.7)	193(95.1)
	Failure	3(1.3)	10(4.9)
	Sensory		
	Success	210(93.3)	194(95.6)
	Failure	15(6.7)	9(4.4)
	Reflexes		
	Success	212(94.2)	194(95.6)
	Failure	13(5.8)	9(4.4)
	Straight Leg Raise		
24 Months	Success	220(97.8)	199(98.0)
	Failure	5(2.2)	4(2.0)
	Overall		
	Success	197(87.6)	180(88.7)
	Failure	28(12.4)	23(11.3)
	Motor		
	Success	204(98.6)	170(92.9)
	Failure	3(1.4)	13(7.1)
	Sensory		
	Success	194(93.7)	171(93.4)
36 Months	Failure	13(6.3)	12(6.6)
	Reflexes		
	Success	195(94.2)	174(95.1)
	Failure	12(5.8)	9(4.9)
	Straight Leg Raise		
	Success	204(98.6)	177(96.7)
	Failure	3(1.4)	6(3.3)
	Overall		
	Success	180(87.0)	154(84.2)
	Failure	27(13.0)	29(15.8)
36 Months	Motor		
	Success	169(98.3)	149(91.4)
	Failure	3(1.7)	14(8.6)
	Sensory		
	Success	163(94.8)	151(92.6)
	Failure	9(5.2)	12(7.4)
	Reflexes		
	Success	162(94.2)	154(94.5)
	Failure	10(5.8)	9(5.5)
	Straight Leg Raise		
36 Months	Success	168(97.7)	158(96.9)
	Failure	4(2.3)	5(3.1)
	Overall		
36 Months	Success	151(87.8)	134(82.2)
	Failure	21(12.2)	29(17.8)

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* Success for each component: Post Score - Pre Score \geq 0.
 Success for overall neuro: All successes of the 4 components.

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Table 18. Summary of Success* Rates of Neurological Status
[Number (%) of Patients]

Period	Variable	Investigational (N=239)	Control (N=224)
48 Months	Motor		
	Success	103 (98.1)	88 (93.6)
	Failure	2 (1.9)	6 (6.4)
	Sensory		
	Success	99 (94.3)	87 (92.6)
	Failure	6 (5.7)	7 (7.4)
	Reflexes		
	Success	99 (94.3)	88 (93.6)
	Failure	6 (5.7)	6 (6.4)
	Straight Leg Raise		
60 Months	Success	103 (98.1)	88 (93.6)
	Failure	2 (1.9)	6 (6.4)
	Overall		
	Success	92 (87.6)	75 (79.8)
	Failure	13 (12.4)	19 (20.2)
	Motor		
	Success	145 (96.7)	125 (93.3)
	Failure	5 (3.3)	9 (6.7)
	Sensory		
	Success	142 (94.7)	125 (93.3)
	Failure	8 (5.3)	9 (6.7)
	Reflexes		
	Success	142 (94.7)	126 (94.7)
	Failure	8 (5.3)	7 (5.3)
	Straight Leg Raise		
	Success	148 (98.7)	131 (97.8)
	Failure	2 (1.3)	3 (2.2)
	Overall		
	Success	132 (88.0)	112 (84.2)
	Failure	18 (12.0)	21 (15.8)

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* Success for each component: Post Score - Pre Score \geq 0.
 Success for overall neuro: All successes of the 4 components.

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rhBMP-2/CRM/CD HORIZON® Spinal System-Pivotal Study

Table 19. Summary of Implant Events based on Radiographic Review
[Number (%) of Patients]

Period	Variable	Investigational (N=239)			Control (N=224)		
		Reader 1	Reader 2	Adjudicated	Reader 1	Reader 2	Adjudicated
Discharge	rhBMP-/CRM or Bone Graft Migration						
	Yes	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
	No	216(100.0)	220(100.0)	220(100.0)	198(100.0)	209(100.0)	206(100.0)
	rhBMP-/CRM or Bone Graft Broken						
	Yes	1(0.5)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
	No	215(99.5)	220(100.0)	220(100.0)	198(100.0)	209(100.0)	206(100.0)
	rhBMP-/CRM or Bone Graft Fusion Mass Fracture						
	Yes	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
	No	216(100.0)	220(100.0)	220(100.0)	198(100.0)	209(100.0)	206(100.0)
	CD HORIZON® Implant Loosening						
	Yes	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
	No	216(100.0)	220(100.0)	220(100.0)	198(100.0)	209(100.0)	206(100.0)
	CD HORIZON® Implant Bent						
	Yes	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
	No	216(100.0)	220(100.0)	220(100.0)	198(100.0)	209(100.0)	206(100.0)
	CD HORIZON® Implant Broken						
	Yes	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
	No	216(100.0)	220(100.0)	220(100.0)	198(100.0)	209(100.0)	206(100.0)
	CD HORIZON® Implant Migration						
	Yes	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
	No	216(100.0)	220(100.0)	220(100.0)	198(100.0)	209(100.0)	206(100.0)

rhBMP-2/CRM/CD HORIZON® Spinal System-Pivotal Study

Table 19. Summary of Implant Events based on Radiographic Review
[Number (%) of Patients]

Period	Variable	Investigational (N=239)			Control (N=224)		
		Reader 1	Reader 2	Adjudicated	Reader 1	Reader 2	Adjudicated
6 Weeks	rhBMP-/CRM or Bone Graft Migration						
	Yes	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
	No	235(100.0)	234(100.0)	234(100.0)	215(100.0)	216(100.0)	216(100.0)
	rhBMP-/CRM or Bone Graft Broken						
	Yes	1(0.4)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
	No	234(99.6)	234(100.0)	234(100.0)	215(100.0)	216(100.0)	216(100.0)
	rhBMP-/CRM or Bone Graft Fusion Mass Fracture						
	Yes	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
	No	235(100.0)	234(100.0)	234(100.0)	215(100.0)	216(100.0)	216(100.0)
	CD HORIZON® Implant Loosening						
	Yes	1(0.4)	1(0.4)	1(0.4)	1(0.5)	1(0.5)	1(0.5)
	No	234(99.6)	233(99.6)	233(99.6)	214(99.5)	215(99.5)	215(99.5)
	CD HORIZON® Implant Bent						
	Yes	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
	No	235(100.0)	234(100.0)	234(100.0)	215(100.0)	216(100.0)	216(100.0)
	CD HORIZON® Implant Broken						
	Yes	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
	No	235(100.0)	234(100.0)	234(100.0)	215(100.0)	216(100.0)	216(100.0)
	CD HORIZON® Implant Migration						
	Yes	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
	No	235(100.0)	234(100.0)	234(100.0)	215(100.0)	216(100.0)	216(100.0)

Table 19. Summary of Implant Events based on Radiographic Review
[Number (%) of Patients]

Period	Variable	Investigational (N=239)			Control (N=224)		
		Reader 1	Reader 2	Adjudicated	Reader 1	Reader 2	Adjudicated
3 Months	rhBMP-/CRM or Bone Graft Migration						
	Yes	1(0.4)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
	No	230(99.6)	232(100.0)	232(100.0)	216(100.0)	217(100.0)	217(100.0)
	rhBMP-/CRM or Bone Graft Broken						
	Yes	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
	No	231(100.0)	232(100.0)	232(100.0)	216(100.0)	217(100.0)	217(100.0)
	rhBMP-/CRM or Bone Graft Fusion Mass Fracture						
	Yes	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
	No	231(100.0)	232(100.0)	232(100.0)	216(100.0)	217(100.0)	217(100.0)
	CD HORIZON® Implant Loosening						
	Yes	2(0.9)	1(0.4)	1(0.4)	1(0.5)	1(0.5)	1(0.5)
	No	229(99.1)	231(99.6)	231(99.6)	215(99.5)	216(99.5)	216(99.5)
	CD HORIZON® Implant Bent						
	Yes	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
	No	231(100.0)	232(100.0)	232(100.0)	216(100.0)	217(100.0)	217(100.0)
	CD HORIZON® Implant Broken						
	Yes	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
	No	231(100.0)	232(100.0)	232(100.0)	216(100.0)	217(100.0)	217(100.0)
	CD HORIZON® Implant Migration						
	Yes	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
	No	231(100.0)	232(100.0)	232(100.0)	216(100.0)	217(100.0)	217(100.0)

rhBMP-2/CRM/CD HORIZON® Spinal System-Pivotal Study

Table 19. Summary of Implant Events based on Radiographic Review
[Number (%) of Patients]

Period	Variable	Investigational (N=239)			Control (N=224)		
		Reader 1	Reader 2	Adjudicated	Reader 1	Reader 2	Adjudicated
6 Months	rhBMP-/CRM or Bone Graft Migration						
	Yes	1(0.4)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
	No	228(99.6)	228(100.0)	228(100.0)	209(100.0)	206(100.0)	208(100.0)
	rhBMP-/CRM or Bone Graft Broken						
	Yes	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
	No	229(100.0)	228(100.0)	228(100.0)	209(100.0)	206(100.0)	208(100.0)
	rhBMP-/CRM or Bone Graft Fusion Mass Fracture						
	Yes	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
	No	229(100.0)	228(100.0)	228(100.0)	209(100.0)	206(100.0)	208(100.0)
	CD HORIZON® Implant Loosening						
	Yes	3(1.3)	3(1.3)	3(1.3)	2(1.0)	1(0.5)	1(0.5)
	No	226(98.7)	225(98.7)	225(98.7)	207(99.0)	205(99.5)	206(99.5)
	CD HORIZON® Implant Bent						
	Yes	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
	No	229(100.0)	228(100.0)	228(100.0)	209(100.0)	206(100.0)	208(100.0)
	CD HORIZON® Implant Broken						
	Yes	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
	No	229(100.0)	228(100.0)	228(100.0)	209(100.0)	206(100.0)	208(100.0)
	CD HORIZON® Implant Migration						
	Yes	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
	No	229(100.0)	228(100.0)	228(100.0)	209(100.0)	206(100.0)	208(100.0)

rhBMP-2/CRM/CD HORIZON® Spinal System-Pivotal Study

Table 19. Summary of Implant Events based on Radiographic Review
[Number (%) of Patients]

Period	Variable	Investigational (N=239)			Control (N=224)		
		Reader 1	Reader 2	Adjudicated	Reader 1	Reader 2	Adjudicated
12 Months	rhBMP-/CRM or Bone Graft Migration						
	Yes	1(0.4)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
	No	226(99.6)	226(100.0)	227(100.0)	204(100.0)	204(100.0)	204(100.0)
	rhBMP-/CRM or Bone Graft Broken						
	Yes	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
	No	227(100.0)	226(100.0)	227(100.0)	204(100.0)	204(100.0)	204(100.0)
	rhBMP-/CRM or Bone Graft Fusion Mass Fracture						
	Yes	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
	No	227(100.0)	226(100.0)	227(100.0)	204(100.0)	204(100.0)	204(100.0)
	CD HORIZON® Implant Loosening						
	Yes	4(1.8)	3(1.3)	3(1.3)	0(0.0)	0(0.0)	0(0.0)
	No	223(98.2)	223(98.7)	224(98.7)	204(100.0)	204(100.0)	204(100.0)
	CD HORIZON® Implant Bent						
	Yes	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
	No	227(100.0)	226(100.0)	227(100.0)	204(100.0)	204(100.0)	204(100.0)
	CD HORIZON® Implant Broken						
	Yes	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
	No	227(100.0)	226(100.0)	227(100.0)	204(100.0)	204(100.0)	204(100.0)
	CD HORIZON® Implant Migration						
	Yes	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
	No	227(100.0)	226(100.0)	227(100.0)	204(100.0)	204(100.0)	204(100.0)

rhBMP-2/CRM/CD HORIZON® Spinal System-Pivotal Study

Table 19. Summary of Implant Events based on Radiographic Review
[Number (%) of Patients]

Period	Variable	Investigational (N=239)			Control (N=224)		
		Reader 1	Reader 2	Adjudicated	Reader 1	Reader 2	Adjudicated
24 Months	rhBMP-/CRM or Bone Graft Migration						
	Yes	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
	No	206(100.0)	207(100.0)	207(100.0)	177(100.0)	181(100.0)	180(100.0)
	rhBMP-/CRM or Bone Graft Broken						
	Yes	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
	No	206(100.0)	207(100.0)	207(100.0)	177(100.0)	181(100.0)	180(100.0)
	rhBMP-/CRM or Bone Graft Fusion Mass Fracture						
	Yes	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
	No	206(100.0)	207(100.0)	207(100.0)	177(100.0)	181(100.0)	180(100.0)
	CD HORIZON® Implant Loosening						
	Yes	3(1.5)	2(1.0)	1(0.5)	0(0.0)	2(1.1)	0(0.0)
	No	203(98.5)	205(99.0)	205(99.5)	177(100.0)	179(98.9)	180(100.0)
	CD HORIZON® Implant Bent						
	Yes	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
	No	206(100.0)	207(100.0)	207(100.0)	177(100.0)	181(100.0)	180(100.0)
	CD HORIZON® Implant Broken						
	Yes	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
	No	206(100.0)	207(100.0)	207(100.0)	177(100.0)	181(100.0)	180(100.0)
	CD HORIZON® Implant Migration						
	Yes	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
	No	206(100.0)	207(100.0)	207(100.0)	177(100.0)	181(100.0)	180(100.0)

rhBMP-2/CRM/CD HORIZON® Spinal System-Pivotal Study

Table 19. Summary of Implant Events based on Radiographic Review
[Number (%) of Patients]

Period	Variable	Investigational (N=239)			Control (N=224)		
		Reader 1	Reader 2	Adjudicated	Reader 1	Reader 2	Adjudicated
36 Months	rhBMP-/CRM or Bone Graft Migration						
	Yes	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
	No	168(100.0)	167(100.0)	167(100.0)	154(100.0)	154(100.0)	154(100.0)
	rhBMP-/CRM or Bone Graft Broken						
	Yes	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
	No	168(100.0)	167(100.0)	167(100.0)	154(100.0)	154(100.0)	154(100.0)
	rhBMP-/CRM or Bone Graft Fusion Mass Fracture						
	Yes	0(0.0)	0(0.0)	0(0.0)	1(0.6)	0(0.0)	0(0.0)
	No	168(100.0)	167(100.0)	167(100.0)	153(99.4)	154(100.0)	154(100.0)
	CD HORIZON® Implant Loosening						
	Yes	1(0.6)	2(1.2)	1(0.6)	0(0.0)	1(0.6)	0(0.0)
	No	167(99.4)	165(98.8)	165(99.4)	154(100.0)	153(99.4)	153(100.0)
	CD HORIZON® Implant Bent						
	Yes	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
	No	168(100.0)	167(100.0)	167(100.0)	154(100.0)	154(100.0)	154(100.0)
	CD HORIZON® Implant Broken						
	Yes	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
	No	168(100.0)	167(100.0)	167(100.0)	154(100.0)	154(100.0)	154(100.0)
	CD HORIZON® Implant Migration						
	Yes	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
	No	168(100.0)	167(100.0)	167(100.0)	154(100.0)	154(100.0)	154(100.0)

rhBMP-2/CRM/CD HORIZON® Spinal System-Pivotal Study

Table 19. Summary of Implant Events based on Radiographic Review
[Number (%) of Patients]

Period	Variable	Investigational (N=239)			Control (N=224)		
		Reader 1	Reader 2	Adjudicated	Reader 1	Reader 2	Adjudicated
48 Months	rhBMP-/CRM or Bone Graft Migration						
	Yes	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
	No	93(100.0)	93(100.0)	93(100.0)	69(100.0)	71(100.0)	70(100.0)
	rhBMP-/CRM or Bone Graft Broken						
	Yes	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
	No	93(100.0)	93(100.0)	93(100.0)	69(100.0)	71(100.0)	70(100.0)
	rhBMP-/CRM or Bone Graft Fusion Mass Fracture						
	Yes	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
	No	93(100.0)	93(100.0)	93(100.0)	69(100.0)	71(100.0)	70(100.0)
	CD HORIZON® Implant Loosening						
	Yes	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
	No	93(100.0)	93(100.0)	93(100.0)	69(100.0)	71(100.0)	70(100.0)
	CD HORIZON® Implant Bent						
	Yes	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
	No	93(100.0)	93(100.0)	93(100.0)	69(100.0)	71(100.0)	70(100.0)
	CD HORIZON® Implant Broken						
	Yes	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
	No	93(100.0)	93(100.0)	93(100.0)	69(100.0)	71(100.0)	70(100.0)
	CD HORIZON® Implant Migration						
	Yes	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
	No	93(100.0)	93(100.0)	93(100.0)	69(100.0)	71(100.0)	70(100.0)

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rhBMP-2/CRM/CD HORIZON® Spinal System-Pivotal Study

Table 19. Summary of Implant Events based on Radiographic Review
[Number (%) of Patients]

Period	Variable	Investigational (N=239)			Control (N=224)		
		Reader 1	Reader 2	Adjudicated	Reader 1	Reader 2	Adjudicated
60 Months	rhBMP-/CRM or Bone Graft Migration						
	Yes	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	No	110(100.0)	109(100.0)	109(100.0)	90(100.0)	90(100.0)	87(100.0)
	rhBMP-/CRM or Bone Graft Broken						
	Yes	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	No	110(100.0)	109(100.0)	109(100.0)	90(100.0)	90(100.0)	87(100.0)
	rhBMP-/CRM or Bone Graft Fusion Mass Fracture						
	Yes	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	No	110(100.0)	109(100.0)	109(100.0)	90(100.0)	90(100.0)	87(100.0)
	CD HORIZON® Implant Loosening						
	Yes	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.2)	0 (0.0)
	No	110(100.0)	109(100.0)	109(100.0)	90(100.0)	88 (97.8)	86(100.0)
	CD HORIZON® Implant Bent						
	Yes	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	No	110(100.0)	109(100.0)	109(100.0)	90(100.0)	90(100.0)	87(100.0)
	CD HORIZON® Implant Broken						
	Yes	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	No	110(100.0)	109(100.0)	109(100.0)	90(100.0)	90(100.0)	87(100.0)
	CD HORIZON® Implant Migration						
	Yes	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	No	110(100.0)	109(100.0)	109(100.0)	90(100.0)	90(100.0)	87(100.0)

Table 20. Summary of Success* Rates of Fusion Status
[Number (%) of Patients]

Variable	Investigational (N=239)	Control (N=224)
6 Months		
Success	155(79.1)	119(65.3)
Failure	41(20.9)	61(34.7)
12 Months		
Success	182(87.5)	151(82.5)
Failure	26(12.5)	32(17.5)
24 Months		
Success	186(95.9)	151(89.3)
Failure	8(4.1)	18(10.7)
36 Months		
Success	128(97.0)	109(92.4)
Failure	4(3.0)	9(7.6)
48 Months		
Success	87(95.6)	58(86.6)
Failure	4(4.4)	9(13.4)
60 Months		
Success	93(95.9)	70(88.6)
Failure	4(4.1)	9(11.4)

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* If discrepancies between the first two reviewers could not be resolved by the third reviewer, the fusion success status is considered as missing.

Table 21. Summary of Agreement on Radiographic Fusion Status Reviewed by Two Independent Radiologists

Period	Treatment	Fusion Status * (Reviewer 1 - Reviewer 2)				N	Agree** (%)	p-value from McNemar Test	Cohen's Kappa Coefficient		
		S-S	F-F	S-F	F-S				Coef.	Lower 95% Limit	Upper 95% Limit
6 Months	Investigational	143	34	5	5	187	94.7	1.0000	0.8380	0.7408	0.9352
	Control	110	56	3	5	174	95.4	0.4795	0.8983	0.8295	0.9671
12 Months	Investigational	181	23	1	2	207	98.6	0.5637	0.9306	0.8527	1.0084
	Control	150	26	4	3	183	96.2	0.7055	0.8586	0.7563	0.9608
24 Months	Investigational	170	5	2	4	181	96.7	0.4142	0.6079	0.3210	0.8949
	Control	141	9	2	4	156	96.2	0.4142	0.7293	0.5230	0.9356

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Note: Second surgery failures are not taken into account in calculating Fusion status in this table.

* Number of Patient in:

S-S: Success (Reviewer 1)-Success (Reviewer 2)

F-F: Failure (Reviewer 1)-Failure (Reviewer 2)

S-F: Success (Reviewer 1)-Failure (Reviewer 2)

F-S: Failure (Reviewer 1)-Success (Reviewer 2)

** The percentage of patients who had the same fusion statuses.

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Table 22. Summary of Oswestry Low Back Pain Disability Scores

Period	Variable	Investigational (N=239)	Control (N=224)
Preoperative	Pain Score		
	n	239	224
	Mean	49.9	51.6
	Std	13.1	13.3
	Min	28.0	30.0
	Max	86.0	94.0
6 Weeks	Pain Score		
	n	231	214
	Mean	37.1	37.5
	Std	18.6	16.8
	Min	0.0	5.0
	Max	82.0	76.0
	Change from Preoperative		
	n	231	214
	Mean	-12.9	-13.9
	Std	20.1	17.2
	Min	-74.0	-76.0
	Max	36.0	30.2
	P-Value *	<0.001	<0.001
3 Months	Pain Score		
	n	229	213
	Mean	27.8	30.2
	Std	17.3	17.4
	Min	0.0	0.0
	Max	84.0	80.0
	Change from Preoperative		
	n	229	213
	Mean	-22.1	-21.2
	Std	19.4	17.3
	Min	-74.0	-92.0
	Max	34.0	16.9
	P-Value *	<0.001	<0.001

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* P-values for change from preoperative in each group are from paired t-test.

Table 22. Summary of Oswestry Low Back Pain Disability Scores

Period	Variable	Investigational (N=239)	Control (N=224)
6 Months	Pain Score		
	n	226	206
	Mean	24.2	27.0
	Std	18.6	17.7
	Min	0.0	0.0
	Max	82.0	74.0
	Change from Preoperative		
	n	226	206
	Mean	-26.0	-24.5
	Std	18.9	17.0
	Min	-84.0	-80.0
	Max	34.0	21.3
	P-Value *	<0.001	<0.001
12 Months	Pain Score		
	n	223	203
	Mean	23.2	26.0
	Std	19.9	18.2
	Min	0.0	0.0
	Max	82.0	82.0
	Change from Preoperative		
	n	223	203
	Mean	-26.9	-25.6
	Std	19.9	19.0
	Min	-78.0	-88.0
	Max	34.0	21.1
	P-Value *	<0.001	<0.001
24 Months	Pain Score		
	n	208	183
	Mean	22.9	26.4
	Std	19.3	21.2
	Min	0.0	0.0
	Max	82.0	82.0
	Change from Preoperative		
	n	208	183
	Mean	-26.7	-25.5
	Std	19.9	20.7
	Min	-76.0	-86.0
	Max	34.0	21.1
	P-Value *	<0.001	<0.001

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* P-values for change from preoperative in each group are from paired t-test.

Table 22. Summary of Oswestry Low Back Pain Disability Scores

Period	Variable	Investigational (N=239)	Control (N=224)
36 Months	Pain Score		
	n	172	164
	Mean	24.8	27.0
	Std	21.3	19.8
	Min	0.0	0.0
	Max	84.0	82.0
	Change from Preoperative		
	n	172	164
	Mean	-25.0	-23.6
	Std	20.5	19.8
	Min	-73.3	-86.0
	Max	34.0	21.1
	P-Value *	<0.001	<0.001
48 Months	Pain Score		
	n	104	94
	Mean	28.4	29.0
	Std	22.0	20.9
	Min	0.0	0.0
	Max	82.0	82.0
	Change from Preoperative		
	n	104	94
	Mean	-22.8	-21.4
	Std	22.9	20.5
	Min	-78.0	-86.0
	Max	34.0	21.1
	P-Value *	<0.001	<0.001
60 Months	Pain Score		
	n	150	135
	Mean	25.2	28.1
	Std	20.3	20.3
	Min	0.0	0.0
	Max	82.0	82.0
	Change from Preoperative		
	n	150	135
	Mean	-24.5	-23.5
	Std	19.7	21.2
	Min	-76.0	-94.0
	Max	34.0	21.1
	P-Value *	<0.001	<0.001

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* P-values for change from preoperative in each group are from paired t-test.

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Table 23. Summary of Success* Rates of Oswestry Low Back Pain Measures
[Number (%) of Patients]

Variable	Investigational (N=239)	Control (N=224)
6 Weeks		
Success	107(46.3)	93(43.5)
Failure	124(53.7)	121(56.5)
3 Months		
Success	140(61.1)	128(60.1)
Failure	89(38.9)	85(39.9)
6 Months		
Success	170(75.2)	149(72.3)
Failure	56(24.8)	57(27.7)
12 Months		
Success	159(71.3)	150(73.9)
Failure	64(28.7)	53(26.1)
24 Months		
Success	152(73.1)	133(72.7)
Failure	56(26.9)	50(27.3)
36 Months		
Success	116(67.4)	109(66.5)
Failure	56(32.6)	55(33.5)
48 Months		
Success	65(62.5)	59(62.8)
Failure	39(37.5)	35(37.2)
60 Months		
Success	100(66.7)	85(63.0)
Failure	50(33.3)	50(37.0)

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* Success; Pre Score - Post Score \geq 15.

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Table 24. Summary of Back Pain Scores

Period	Variable	Investigational (N=239)	Control (n=224)
Preoperative	Pain Score		
	n	238	224
	Mean	15.6	15.8
	Std	3.5	3.6
	Min	0.0	0.0
	Max	20.0	20.0
6 Weeks	Pain Score		
	n	231	213
	Mean	8.7	8.1
	Std	5.2	5.1
	Min	0.0	0.0
	Max	20.0	20.0
	Change from Preoperative		
	n	230	213
	Mean	-6.9	-7.7
	Std	5.8	5.6
	Min	-19.0	-20.0
	Max	7.0	7.0
	P-Value *	<0.001	<0.001
3 Months	Pain Score		
	n	228	213
	Mean	7.0	7.8
	Std	5.2	5.4
	Min	0.0	0.0
	Max	20.0	20.0
	Change from Preoperative		
	n	227	213
	Mean	-8.6	-7.9
	Std	5.6	5.5
	Min	-20.0	-20.0
	Max	6.0	13.0
	P-Value *	<0.001	<0.001

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* P-values for change from preoperative in each group are from paired t-test.

Table 24. Summary of Back Pain Scores

Period	Variable	Investigational (N=239)	Control (n=224)
6 Months	Pain Score		
	n	226	206
	Mean	6.8	7.9
	Std	5.6	5.6
	Min	0.0	0.0
	Max	20.0	20.0
	Change from Preoperative		
	n	225	206
	Mean	-8.9	-7.9
	Std	6.0	5.8
	Min	-20.0	-20.0
	Max	7.0	13.0
	P-Value *	<0.001	<0.001
12 Months	Pain Score		
	n	223	203
	Mean	6.6	8.1
	Std	5.7	5.9
	Min	0.0	0.0
	Max	20.0	20.0
	Change from Preoperative		
	n	222	203
	Mean	-9.0	-7.7
	Std	6.0	5.8
	Min	-20.0	-20.0
	Max	5.0	8.0
	P-Value *	<0.001	<0.001
24 Months	Pain score		
	n	208	183
	Mean	7.1	7.8
	Std	5.9	6.3
	Min	0.0	0.0
	Max	20.0	20.0
	Change from Preoperative		
	n	207	183
	Mean	-8.5	-7.9
	Std	6.3	5.9
	Min	-20.0	-20.0
	Max	8.0	5.0
	P-Value *	<0.001	<0.001

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* P-values for change from preoperative in each group are from paired t-test.

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Table 24. Summary of Back Pain Scores

Period	Variable	Investigational (N=239)	Control (n=224)
36 Months	Pain Score		
	n	171	164
	Mean	7.8	8.8
	Std	6.2	6.4
	Min	0.0	0.0
	Max	20.0	20.0
	Change from Preoperative		
	n	171	164
	Mean	-7.9	-6.7
	Std	6.4	6.3
	Min	-20.0	-20.0
	Max	7.0	12.0
	P-Value *	<0.001	<0.001
48 Months	Pain Score		
	n	104	93
	Mean	8.7	9.5
	Std	6.3	6.3
	Min	0.0	0.0
	Max	20.0	20.0
	Change from Preoperative		
	n	104	93
	Mean	-7.4	-6.5
	Std	6.5	6.2
	Min	-20.0	-20.0
	Max	6.0	8.0
	P-Value *	<0.001	<0.001
60 Months	Pain Score		
	n	150	135
	Mean	8.0	9.5
	Std	6.1	6.3
	Min	0.0	0.0
	Max	20.0	20.0
	Change from Preoperative		
	n	149	135
	Mean	-7.7	-6.5
	Std	6.3	6.2
	Min	-20.0	-20.0
	Max	5.0	9.0
	P-Value *	<0.001	<0.001

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* P-values for change from preoperative in each group are from paired t-test.

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Table 25. Summary of Back Pain Success* Rates
[Number (%) of Patients]

Variable	Investigational (N=239)	Control (N=224)
6 Weeks		
Success	208(90.4)	197(92.5)
Failure	22(9.6)	16(7.5)
3 Months		
Success	213(93.8)	200(93.9)
Failure	14(6.2)	13(6.1)
6 Months		
Success	214(95.1)	193(93.7)
Failure	11(4.9)	13(6.3)
12 Months		
Success	209(94.1)	189(93.1)
Failure	13(5.9)	14(6.9)
24 Months		
Success	192(92.8)	174(95.1)
Failure	15(7.2)	9(4.9)
36 Months		
Success	158(92.4)	143(87.2)
Failure	13(7.6)	21(12.8)
48 Months		
Success	92(88.5)	84(90.3)
Failure	12(11.5)	9(9.7)
60 Months		
Success	136(91.3)	121(89.6)
Failure	13(8.7)	14(10.4)
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* Success: Pre Score - Post Score >= 0.

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Table 26. Summary of Leg Pain Scores

Period	Variable	Investigational (N=239)	Control (n=224)
Preoperative	Pain Score		
	n	238	223
	Mean	14.0	14.0
	Std	4.8	5.3
	Min	0.0	0.0
	Max	20.0	20.0
6 Weeks	Pain Score		
	n	231	213
	Mean	6.1	5.6
	Std	5.9	5.9
	Min	0.0	0.0
	Max	20.0	20.0
	Change from Preoperative		
	n	230	212
	Mean	-7.9	-8.3
	Std	6.9	6.7
	Min	-20.0	-20.0
	Max	15.0	7.0
	P-Value *	<0.001	<0.001
3 Months	Pain Score		
	n	229	213
	Mean	5.6	5.8
	Std	5.8	5.9
	Min	0.0	0.0
	Max	20.0	20.0
	Change from Preoperative		
	n	228	212
	Mean	-8.3	-8.1
	Std	6.7	6.7
	Min	-20.0	-20.0
	Max	10.0	8.0
	P-Value *	<0.001	<0.001

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* P-values for change from preoperative in each group are from paired t-test.

Table 26. Summary of Leg Pain Scores

Period	Variable	Investigational (N=239)	Control (n=224)
6 Months	Pain Score		
	n	226	206
	Mean	5.8	5.9
	Std	6.0	6.2
	Min	0.0	0.0
	Max	20.0	20.0
	Change from Preoperative		
	n	225	205
	Mean	-8.1	-8.1
	Std	6.7	6.7
	Min	-20.0	-20.0
	Max	8.0	9.0
	P-Value *	<0.001	<0.001
12 Months	Pain Score		
	n	223	203
	Mean	6.1	6.3
	Std	6.3	6.4
	Min	0.0	0.0
	Max	20.0	20.0
	Change from Preoperative		
	n	222	202
	Mean	-7.7	-7.7
	Std	7.1	7.1
	Min	-20.0	-20.0
	Max	11.0	9.0
	P-Value *	<0.001	<0.001
24 Months	Pain Score		
	n	208	183
	Mean	6.2	6.7
	Std	6.3	6.7
	Min	0.0	0.0
	Max	20.0	20.0
	Change from Preoperative		
	n	207	182
	Mean	-7.6	-7.3
	Std	7.0	7.0
	Min	-20.0	-20.0
	Max	11.0	11.0
	P-Value *	<0.001	<0.001

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* P-values for change from preoperative in each group are from paired t-test.

Table 26. Summary of Leg Pain Scores

Period	Variable	Investigational (N=239)	Control (n=224)
36 Months	Pain Score		
	n	171	164
	Mean	7.1	7.1
	Std	6.7	6.7
	Min	0.0	0.0
	Max	20.0	20.0
	Change from Preoperative		
	n	171	163
	Mean	-6.8	-7.0
	Std	7.5	7.0
	Min	-20.0	-20.0
	Max	16.0	9.0
	P-Value *	<0.001	<0.001
48 Months	Pain Score		
	n	104	93
	Mean	7.9	7.2
	Std	6.7	6.5
	Min	0.0	0.0
	Max	20.0	20.0
	Change from Preoperative		
	n	104	92
	Mean	-6.2	-6.7
	Std	7.8	7.6
	Min	-20.0	-20.0
	Max	15.0	16.0
	P-Value *	<0.001	<0.001
60 Months	Pain Score		
	n	150	135
	Mean	7.3	7.5
	Std	6.4	6.8
	Min	0.0	0.0
	Max	20.0	20.0
	Change from Preoperative		
	n	149	135
	Mean	-6.4	-6.6
	Std	7.0	6.9
	Min	-20.0	-20.0
	Max	11.0	15.0
	P-Value *	<0.001	<0.001

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* P-values for change from preoperative in each group are from paired t-test.

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Table 27. Summary of Leg Pain Success* Rates
[Number (%) of Patients]

Variable	Investigational (N=239)	Control (N=224)
6 Weeks		
Success	202 (87.8)	189 (89.2)
Failure	28 (12.2)	23 (10.8)
3 Months		
Success	212 (93.0)	191 (90.1)
Failure	16 (7.0)	21 (9.9)
6 Months		
Success	201 (89.3)	188 (91.7)
Failure	24 (10.7)	17 (8.3)
12 Months		
Success	190 (85.6)	177 (87.6)
Failure	32 (14.4)	25 (12.4)
24 Months		
Success	180 (87.0)	154 (84.6)
Failure	27 (13.0)	28 (15.4)
36 Months		
Success	145 (84.8)	139 (85.3)
Failure	26 (15.2)	24 (14.7)
48 Months		
Success	85 (81.7)	78 (84.8)
Failure	19 (18.3)	14 (15.2)
60 Months		
Success	126 (84.6)	118 (87.4)
Failure	23 (15.4)	17 (12.6)

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* Success: Pre Score - Post Score >= 0.

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Table 28. Summary of SF-36 Health Survey Scores

Period	Variable	Investigational (N=239)	Control (N=224)
Preoperative	PCS		
	n	236	224
	Mean	27.8	27.4
	Std	6.3	6.7
	MCS		
	n	236	224
	Mean	43.9	42.9
	Std	13.1	12.3
	Physical Function		
	n	238	224
	Mean	28.6	27.3
	Std	20.3	19.3
	Role-Physical		
	n	237	224
	Mean	8.3	6.7
	Std	21.6	19.0
	Pain Index		
	n	237	224
	Mean	22.4	20.8
	Std	13.2	13.6
	Gen. Health Percept.		
	n	237	224
	Mean	67.3	65.6
	Std	20.9	21.2
	Social Function		
	n	237	224
	Mean	40.0	39.5
	Std	23.6	23.7
	Mental Health		
	n	237	224
	Mean	61.9	60.3
	Std	23.2	22.4
	Role-Emotional		
	n	238	224
	Mean	44.7	39.9
	Std	45.3	43.9
	Vitality		
	n	237	224
	Mean	33.7	32.2
	Std	21.4	19.7

Table 28. Summary of SF-36 Health Survey Scores

Period	Variable	Investigational (N=239)	Control (N=224)
6 Weeks	PCS		
	n	228	212
	Mean	31.6	31.9
	Std	7.5	7.7
	PCS Change from Preop		
	n	225	212
	Mean	3.8	4.5
	Std	8.0	8.7
	MCS		
	n	228	212
	Mean	48.4	47.4
	Std	11.9	11.5
	MCS Change from Preop		
	n	225	212
	Mean	4.5	4.2
	Std	11.6	11.0
	Physical Function		
	n	230	214
	Mean	40.1	39.5
	Std	22.3	23.3
	Phys. Func. Change from Preop		
	n	229	214
	Mean	11.7	12.3
	Std	24.0	26.1
	Role-Physical		
	n	230	213
	Mean	10.4	12.0
	Std	23.8	26.6
	Role-Phys. Change from Preop		
	n	228	213
	Mean	2.2	5.2
	Std	30.3	30.0
	Pain Index		
	n	230	213
	Mean	41.0	39.9
	Std	23.2	21.1
	Pain Index Change from Preop		
	n	228	213
	Mean	18.6	18.9
	Std	23.3	22.0

Table 28. Summary of SF-36 Health Survey Scores

Period	Variable	Investigational (N=239)	Control (N=224)
6 Weeks	Gen. Health Percept.		
	n	231	213
	Mean	72.4	72.9
	Std	19.3	18.5
	Gen. Health Change from Preop		
	n	229	213
	Mean	4.7	6.5
	Std	17.0	16.3
	Social Function		
	n	230	213
	Mean	49.9	49.6
	Std	27.5	27.2
	Social Func. Change from Preop		
	n	228	213
	Mean	10.3	9.6
	Std	29.0	30.3
	Mental Health		
	n	230	213
	Mean	71.1	69.9
	Std	19.9	20.5
	Mental Health Change from Preop		
	n	228	213
	Mean	9.3	9.4
	Std	20.5	18.4
	Role-Emotional		
	n	231	213
	Mean	54.8	51.8
	Std	46.0	44.2
	Role-Emot. Change from Preop		
	n	230	213
	Mean	10.4	11.1
	Std	47.7	48.5
	Vitality		
	n	230	213
	Mean	46.1	44.3
	Std	21.5	20.8
	vitality Change from Preop		
	n	228	213
	Mean	12.5	11.8
	Std	24.6	23.5

Table 28. Summary of SF-36 Health Survey Scores

Period	Variable	Investigational (N=239)	Control (N=224)
3 Months	PCS		
	n	228	210
	Mean	37.4	36.1
	Std	9.7	9.7
	PCS Change from Preop		
	n	226	210
	Mean	9.5	8.8
	Std	10.2	10.0
	MCS		
	n	228	210
	Mean	49.6	49.4
	Std	12.6	12.2
	MCS Change from Preop		
	n	226	210
	Mean	5.8	6.4
	Std	12.6	10.9
	Physical Function		
	n	229	213
	Mean	53.3	50.6
	Std	24.9	24.0
	Phys. Func. Change from Preop		
	n	228	213
	Mean	24.5	23.2
	Std	26.8	27.6
	Role-Physical		
	n	228	212
	Mean	30.7	28.5
	Std	38.1	38.8
	Role-Phys. Change from Preop		
	n	227	212
	Mean	22.7	21.9
	Std	40.6	40.2
	Pain Index		
	n	229	212
	Mean	52.7	49.8
	Std	24.7	23.4
	Pain Index Change from Preop		
	n	227	212
	Mean	30.3	28.9
	Std	23.9	23.0

Table 28. Summary of SF-36 Health Survey Scores

Period	Variable	Investigational (N=239)	Control (N=224)
3 Months	Gen. Health Percept.		
	n	229	212
	Mean	71.4	72.2
	Std	20.6	19.9
	Gen. Health Change from Preop		
	n	227	212
	Mean	3.7	6.3
	Std	16.4	15.6
	Social Function		
	n	229	212
	Mean	67.6	63.9
	Std	28.1	28.2
	Social Func. Change from Preop		
	n	227	212
	Mean	27.9	24.1
	Std	30.4	28.8
	Mental Health		
	n	229	212
	Mean	71.8	70.9
	Std	22.8	21.2
	Mental Health Change from Preop		
	n	227	212
	Mean	9.9	10.3
	Std	22.9	18.2
	Role-Emotional		
	n	229	211
	Mean	58.8	63.2
	Std	45.0	42.3
	Role-Emot. Change from Preop		
	n	228	211
	Mean	14.8	23.2
	Std	47.7	47.8
	Vitality		
	n	229	212
	Mean	54.8	50.7
	Std	23.1	22.9
	Vitality Change from Preop		
	n	227	212
	Mean	20.9	18.9
	Std	25.8	23.8

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Table 28. Summary of SF-36 Health Survey Scores

Period	Variable	Investigational (N=239)	Control (N=224)
6 Months	PCS		
	n	224	206
	Mean	40.7	38.4
	Std	11.0	10.4
	PCS Change from Preop		
	n	221	206
	Mean	12.9	11.0
	Std	11.0	11.1
	MCS		
	n	224	206
	Mean	49.4	49.8
	Std	12.8	12.0
	MCS Change from Preop		
	n	221	206
	Mean	5.6	6.7
	Std	13.1	12.0
	Physical Function		
	n	226	206
	Mean	60.4	57.4
	Std	27.1	25.1
	Phys. Func. Change from Preop		
	n	225	206
	Mean	31.7	30.3
	Std	26.9	28.8
	Role-Physical		
	n	225	206
	Mean	48.8	39.3
	Std	44.1	41.3
	Role-Phys. Change from Preop		
	n	223	206
	Mean	40.1	33.1
	Std	47.3	41.4
	Pain Index		
	n	226	206
	Mean	56.1	52.7
	Std	25.5	26.1
	Pain Index Change from Preop		
	n	224	206
	Mean	33.8	32.0
	Std	25.0	25.0

Table 28. Summary of SF-36 Health Survey Scores

Period	Variable	Investigational (N=239)	Control (N=224)
6 Months	Gen. Health Percept.		
	n	225	206
	Mean	71.3	69.6
	Std	21.4	21.5
	Gen. Health Change from Preop		
	n	223	206
	Mean	3.9	3.5
	Std	16.9	18.1
	Social Function		
	n	226	206
	Mean	73.0	69.5
	Std	28.1	27.5
	Social Func. Change from Preop		
	n	224	206
	Mean	33.4	29.6
	Std	30.6	29.1
	Mental Health		
	n	226	206
	Mean	72.8	72.0
	Std	22.9	21.8
	Mental Health Change from Preop		
	n	224	206
	Mean	11.2	11.3
	Std	23.4	20.2
	Role-Emotional		
	n	225	206
	Mean	64.0	66.5
	Std	44.4	42.2
	Role-Emot. Change from Preop		
	n	224	206
	Mean	18.5	26.7
	Std	50.2	53.1
	Vitality		
	n	226	206
	Mean	54.0	52.3
	Std	25.1	23.4
	Vitality Change from Preop		
	n	224	206
	Mean	20.5	19.8
	Std	25.2	22.2

Table 28. Summary of SF-36 Health Survey Scores

Period	Variable	Investigational (N=239)	Control (N=224)
12 Months	PCS		
	n	223	201
	Mean	41.5	39.1
	Std	12.1	11.1
	PCS Change from Preop		
	n	220	201
	Mean	13.7	11.7
	Std	11.9	11.4
	MCS		
	n	223	201
	Mean	49.4	49.0
	Std	13.0	11.5
	MCS Change from Preop		
	n	220	201
	Mean	5.3	5.7
	Std	14.0	12.5
	Physical Function		
	n	223	202
	Mean	62.7	57.9
	Std	28.9	28.0
	Phys. Func. Change from Preop		
	n	222	202
	Mean	33.7	30.8
	Std	29.5	30.5
	Role-Physical		
	n	223	203
	Mean	51.9	43.0
	Std	44.6	43.8
	Role-Phys. Change from Preop		
	n	221	203
	Mean	43.8	36.2
	Std	47.7	45.5
	Pain Index		
	n	223	203
	Mean	59.1	51.6
	Std	29.7	26.4
	Pain Index Change from Preop		
	n	221	203
	Mean	36.6	30.9
	Std	27.8	25.2

Table 28. Summary of SF-36 Health Survey Scores

Period	Variable	Investigational (N=239)	Control (N=224)
12 Months	Gen. Health Percept.		
	n	223	203
	Mean	69.9	69.5
	Std	22.5	21.4
	Gen. Health Change from Preop		
	n	221	203
	Mean	1.6	2.7
	Std	18.2	19.9
	Social Function		
	n	223	203
	Mean	73.3	69.4
	Std	30.3	28.5
	Social Func. Change from Preop		
	n	221	203
	Mean	33.4	29.5
	Std	30.8	31.1
	Mental Health		
	n	223	203
	Mean	73.0	70.2
	Std	23.2	21.4
	Mental Health Change from Preop		
	n	221	203
	Mean	10.6	9.3
	Std	23.9	21.7
	Role-Emotional		
	n	223	202
	Mean	65.5	64.5
	Std	43.4	43.6
	Role-Emot. Change from Preop		
	n	222	202
	Mean	19.8	23.8
	Std	53.7	56.6
	Vitality		
	n	223	203
	Mean	54.4	52.2
	Std	26.8	23.6
	Vitality Change from Preop		
	n	221	203
	Mean	20.4	19.7
	Std	27.7	24.0

Table 28. Summary of SF-36 Health Survey Scores

Period	Variable	Investigational (N=239)	Control (N=224)
24 Months	PCS		
	n	207	183
	Mean	40.9	39.7
	Std	11.7	12.0
	PCS Change from Preop		
	n	204	183
	Mean	13.2	12.3
	Std	11.9	12.3
	MCS		
	n	207	183
	Mean	50.7	49.2
	Std	11.8	12.2
	MCS Change from Preop		
	n	204	183
	Mean	6.1	6.0
	Std	12.8	12.4
	Physical Function		
	n	208	183
	Mean	60.9	57.9
	Std	28.9	30.4
	Phys. Func. Change from Preop		
	n	207	183
	Mean	32.5	30.7
	Std	29.1	32.3
	Role-Physical		
	n	208	183
	Mean	54.6	49.4
	Std	46.4	43.1
	Role-Phys. Change from Preop		
	n	206	183
	Mean	46.0	42.4
	Std	49.7	44.7
	Pain Index		
	n	208	183
	Mean	58.1	55.0
	Std	27.7	28.2
	Pain Index Change from Preop		
	n	206	183
	Mean	35.4	34.2
	Std	26.9	26.0

Table 28. Summary of SF-36 Health Survey Scores

Period	Variable	Investigational (N=239)	Control (N=224)
24 Months	Gen. Health Percept.		
	n	208	183
	Mean	69.2	68.3
	Std	21.9	21.6
	Gen. Health Change from Preop		
	n	206	183
	Mean	0.7	1.2
	Std	18.6	21.0
	Social Function		
	n	208	183
	Mean	73.9	69.5
	Std	28.7	30.0
	Social Func. Change from Preop		
	n	206	183
	Mean	33.7	29.6
	Std	30.3	29.8
	Mental Health		
	n	207	183
	Mean	74.4	71.2
	Std	22.5	22.4
	Mental Health Change from Preop		
	n	205	183
	Mean	11.1	10.1
	Std	22.7	21.6
	Role-Emotional		
	n	208	183
	Mean	69.7	66.8
	Std	41.9	42.6
	Role-Emot. Change from Preop		
	n	207	183
	Mean	23.7	26.0
	Std	51.8	52.0
	Vitality		
	n	208	183
	Mean	55.6	53.1
	Std	25.6	26.5
	Vitality Change from Preop		
	n	206	183
	Mean	21.1	20.4
	Std	25.4	25.1

Table 28. Summary of SF-36 Health Survey Scores

Period	Variable	Investigational (N=239)	Control (N=224)
36 Months	PCS		
	n	171	162
	Mean	39.6	37.8
	Std	11.9	11.5
	PCS Change from Preop		
	n	170	162
	Mean	12.1	10.1
	Std	12.4	11.5
	MCS		
	n	171	162
	Mean	50.3	49.6
	Std	11.9	12.5
	MCS Change from Preop		
	n	170	162
	Mean	5.8	6.8
	Std	10.8	12.2
	Physical Function		
	n	172	164
	Mean	59.9	54.0
	Std	29.2	28.7
	Phys. Func. Change from Preop		
	n	172	164
	Mean	32.0	26.9
	Std	30.1	30.9
	Role-Physical		
	n	172	163
	Mean	49.3	44.2
	Std	44.4	42.6
	Role-Phys. Change from Preop		
	n	172	163
	Mean	42.3	37.3
	Std	47.4	44.0
	Pain Index		
	n	171	163
	Mean	53.5	50.8
	Std	28.9	28.3
	Pain Index Change from Preop		
	n	170	163
	Mean	31.0	29.9
	Std	27.6	26.8

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Table 28. Summary of SF-36 Health Survey Scores

Period	Variable	Investigational (N=239)	Control (N=224)
36 Months	Gen. Health Percept.		
	n	171	163
	Mean	68.3	66.7
	Std	22.1	22.0
	Gen. Health Change from Preop		
	n	170	163
	Mean	-0.4	-0.3
	Std	19.4	19.6
	Social Function		
	n	171	163
	Mean	73.0	67.9
	Std	29.4	30.2
	Social Func. Change from Preop		
	n	170	163
	Mean	33.2	28.4
	Std	31.3	32.9
	Mental Health		
	n	171	163
	Mean	73.8	70.4
	Std	21.1	23.0
	Mental Health Change from Preop		
	n	170	163
	Mean	10.3	10.6
	Std	19.1	21.8
	Role-Emotional		
	n	172	164
	Mean	66.3	67.5
	Std	42.3	42.1
	Role-Emot. Change from Preop		
	n	172	164
	Mean	21.5	28.5
	Std	48.7	49.4
	Vitality		
	n	171	163
	Mean	54.2	51.7
	Std	26.6	27.0
	Vitality Change from Preop		
	n	170	163
	Mean	19.9	19.1
	Std	25.9	26.8

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Table 28. Summary of SF-36 Health Survey Scores

Period	Variable	Investigational (N=239)	Control (N=224)
48 Months	PCS		
	n	103	93
	Mean	37.9	36.9
	Std	11.9	11.9
	PCS Change from Preop		
	n	102	93
	Mean	9.9	9.3
	Std	12.7	11.6
	MCS		
	n	103	93
	Mean	48.8	48.6
	Std	12.3	11.9
	MCS Change from Preop		
	n	102	93
	Mean	5.5	6.5
	Std	12.5	12.1
	Physical Function		
	n	104	94
	Mean	52.7	52.4
	Std	30.8	29.6
	Phys. Func. Change from Preop		
	n	104	94
	Mean	24.0	24.4
	Std	33.9	31.4
	Role-Physical		
	n	104	94
	Mean	45.7	43.6
	Std	46.0	42.9
	Role-Phys. Change from Preop		
	n	104	94
	Mean	36.5	37.0
	Std	50.0	43.2
	Pain Index		
	n	103	94
	Mean	51.3	46.4
	Std	28.6	28.8
	Pain Index Change from Preop		
	n	102	94
	Mean	29.9	26.7
	Std	28.0	27.3

Table 28. Summary of SF-36 Health Survey Scores

Period	Variable	Investigational (N=239)	Control (N=224)
48 Months	Gen. Health Percept.		
	n	103	93
	Mean	66.0	65.8
	Std	22.8	21.6
	Gen. Health Change from Preop		
	n	102	93
	Mean	-2.5	-0.5
	Std	20.7	19.8
	Social Function		
	n	103	94
	Mean	68.7	65.6
	Std	30.9	30.4
	Social Func. Change from Preop		
	n	102	94
	Mean	30.4	27.0
	Std	32.3	32.7
	Mental Health		
	n	103	94
	Mean	70.2	69.7
	Std	22.0	22.6
	Mental Health Change from Preop		
	n	102	94
	Mean	8.2	10.6
	Std	20.7	19.3
	Role-Emotional		
	n	104	94
	Mean	61.5	63.8
	Std	44.0	43.6
	Role-Emot. Change from Preop		
	n	104	94
	Mean	20.5	24.8
	Std	52.2	55.3
	Vitality		
	n	103	94
	Mean	51.0	50.3
	Std	26.5	24.9
	Vitality Change from Preop		
	n	102	94
	Mean	17.2	17.6
	Std	23.7	24.7

Table 28. Summary of SF-36 Health Survey Scores

Period	Variable	Investigational (N=239)	Control (N=224)
60 Months	PCS		
	n	149	134
	Mean	40.3	37.0
	Std	11.7	12.2
	PCS Change from Preop		
	n	147	134
	Mean	12.3	9.4
	Std	12.1	12.0
	MCS		
	n	149	134
	Mean	49.6	49.9
	Std	12.3	11.6
	MCS Change from Preop		
	n	147	134
	Mean	5.3	7.6
	Std	12.1	12.5
	Physical Function		
	n	150	135
	Mean	59.2	52.8
	Std	29.8	30.5
	Phys. Func. Change from Preop		
	n	149	135
	Mean	29.5	25.6
	Std	31.4	33.0
	Role-Physical		
	n	150	134
	Mean	53.5	41.6
	Std	45.0	42.9
	Role-Phys. Change from Preop		
	n	149	134
	Mean	44.5	35.8
	Std	50.6	44.3
	Pain Index		
	n	149	135
	Mean	55.5	49.0
	Std	27.7	28.9
	Pain Index Change from Preop		
	n	147	135
	Mean	32.8	29.6
	Std	24.6	27.1

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Table 28. Summary of SF-36 Health Survey Scores

Period	Variable	Investigational (N=239)	Control (N=224)
60 Months	Gen. Health Percept.		
	n	149	135
	Mean	67.1	66.4
	Std	22.3	21.1
	Gen. Health Change from Preop		
	n	147	135
	Mean	-1.7	-1.3
	Std	20.7	19.5
	Social Function		
	n	149	135
	Mean	73.0	66.8
	Std	29.9	29.9
	Social Func. Change from Preop		
	n	147	135
	Mean	33.7	28.9
	Std	31.0	34.2
	Mental Health		
	n	149	135
	Mean	72.5	71.8
	Std	22.4	21.9
	Mental Health Change from Preop		
	n	147	135
	Mean	9.4	12.3
	Std	21.6	22.3
	Role-Emotional		
	n	150	134
	Mean	66.0	66.4
	Std	44.6	42.8
	Role-Emot. Change from Preop		
	n	149	134
	Mean	19.2	28.6
	Std	50.0	52.2
	Vitality		
	n	149	135
	Mean	53.3	50.1
	Std	26.1	26.5
	Vitality Change from Preop		
	n	147	135
	Mean	18.8	18.5
	Std	23.9	26.3

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rhBMP-2/CRM/CD HORIZON® Spinal System-Pivotal Study

Table 29. Summary of Success* Rates of SF-36 Health Survey
[Number (%) of Patients]

Period	Variable	Investigational (N=239)	Control (N=224)
6 Weeks	PCS		
	Success	152 (67.6)	142 (67.0)
	Failure	73 (32.4)	70 (33.0)
	MCS		
	Success	144 (64.0)	132 (62.3)
	Failure	81 (36.0)	80 (37.7)
	Physical Function		
	Success	168 (73.4)	157 (73.4)
	Failure	61 (26.6)	57 (26.6)
	Role-Physical		
	Success	196 (86.0)	188 (88.3)
	Failure	32 (14.0)	25 (11.7)
	Pain Index		
	Success	190 (83.3)	186 (87.3)
	Failure	38 (16.7)	27 (12.7)
	Gen. Health Percept.		
	Success	158 (69.0)	152 (71.4)
	Failure	71 (31.0)	61 (28.6)
	Social Function		
	Success	164 (71.9)	154 (72.3)
	Failure	64 (28.1)	59 (27.7)
	Mental Health		
	Success	173 (75.9)	163 (76.5)
	Failure	55 (24.1)	50 (23.5)
	Role-Emotional		
	Success	195 (84.8)	173 (81.2)
	Failure	35 (15.2)	40 (18.8)
	Vitality		
	Success	172 (75.4)	159 (74.6)
	Failure	56 (24.6)	54 (25.4)

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* Success: Post Score - Pre Score >= 0.

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Table 29. Summary of Success* Rates of SF-36 Health Survey
[Number (%) of Patients]

Period	Variable	Investigational (N=239)	Control (N=224)
3 Months	PCS		
	Success	187(82.7)	173(82.4)
	Failure	39(17.3)	37(17.6)
	MCS		
	Success	159(70.4)	155(73.8)
	Failure	67(29.6)	55(26.2)
	Physical Function		
	Success	193(84.6)	182(85.4)
	Failure	35(15.4)	31(14.6)
	Role-Physical		
	Success	210(92.5)	197(92.9)
	Failure	17(7.5)	15(7.1)
	Pain Index		
	Success	213(93.8)	201(94.8)
	Failure	14(6.2)	11(5.2)
	Gen. Health Percept.		
	Success	143(63.0)	151(71.2)
	Failure	84(37.0)	61(28.8)
	Social Function		
	Success	200(88.1)	185(87.3)
	Failure	27(11.9)	27(12.7)
	Mental Health		
	Success	161(70.9)	164(77.4)
	Failure	66(29.1)	48(22.6)
	Role-Emotional		
	Success	195(85.5)	187(88.6)
	Failure	33(14.5)	24(11.4)
	Vitality		
	Success	192(84.6)	178(84.0)
	Failure	35(15.4)	34(16.0)

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* Success: Post Score - Pre Score >= 0.

Table 29. Summary of Success* Rates of SF-36 Health Survey
[Number (%) of Patients]

Period	Variable	Investigational (N=239)	Control (N=224)
6 Months	PCS		
	Success	190 (86.0)	177 (85.9)
	Failure	31 (14.0)	29 (14.1)
	MCS		
	Success	151 (68.3)	143 (69.4)
	Failure	70 (31.7)	63 (30.6)
	Physical Function		
	Success	202 (89.8)	185 (89.8)
	Failure	23 (10.2)	21 (10.2)
	Role-Physical		
	Success	209 (93.7)	197 (95.6)
	Failure	14 (6.3)	9 (4.4)
	Pain Index		
	Success	216 (96.4)	200 (97.1)
	Failure	8 (3.6)	6 (2.9)
	Gen. Health Percept.		
	Success	145 (65.0)	126 (61.2)
	Failure	78 (35.0)	80 (38.8)
	Social Function		
	Success	206 (92.0)	183 (88.8)
	Failure	18 (8.0)	23 (11.2)
	Mental Health		
	Success	174 (77.7)	156 (75.7)
	Failure	50 (22.3)	50 (24.3)
	Role-Emotional		
	Success	193 (86.2)	182 (88.3)
	Failure	31 (13.8)	24 (11.7)
	Vitality		
	Success	190 (84.8)	173 (84.0)
	Failure	34 (15.2)	33 (16.0)

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* Success: Post Score - Pre Score \geq 0.

Table 29. Summary of Success* Rates of SF-36 Health Survey
[Number (%) of Patients]

Period	Variable	Investigational (N=239)	Control (N=224)
12 Months	PCS		
	Success	187 (85.0)	174 (86.6)
	Failure	33 (15.0)	27 (13.4)
	MCS		
	Success	152 (69.1)	138 (68.7)
	Failure	68 (30.9)	63 (31.3)
	Physical Function		
	Success	198 (89.2)	184 (91.1)
	Failure	24 (10.8)	18 (8.9)
	Role-Physical		
	Success	210 (95.0)	193 (95.1)
	Failure	11 (5.0)	10 (4.9)
	Pain Index		
	Success	207 (93.7)	191 (94.1)
	Failure	14 (6.3)	12 (5.9)
	Gen. Health Percept.		
	Success	140 (63.3)	123 (60.6)
	Failure	81 (36.7)	80 (39.4)
	Social Function		
	Success	200 (90.5)	182 (89.7)
	Failure	21 (9.5)	21 (10.3)
	Mental Health		
	Success	167 (75.6)	147 (72.4)
	Failure	54 (24.4)	56 (27.6)
	Role-Emotional		
	Success	190 (85.6)	174 (86.1)
	Failure	32 (14.4)	28 (13.9)
	Vitality		
	Success	183 (82.8)	172 (84.7)
	Failure	38 (17.2)	31 (15.3)

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* Success: Post Score - Pre Score \geq 0.

Table 29. Summary of Success* Rates of SF-36 Health Survey
[Number (%) of Patients]

Period	Variable	Investigational (N=239)	Control (N=224)
24 Months	PCS		
	Success	171(83.8)	150(82.0)
	Failure	33(16.2)	33(18.0)
	MCS		
	Success	145(71.1)	120(65.6)
	Failure	59(28.9)	63(34.4)
	Physical Function		
	Success	185(89.4)	159(86.9)
	Failure	22(10.6)	24(13.1)
	Role-Physical		
	Success	196(95.1)	175(95.6)
	Failure	10(4.9)	8(4.4)
	Pain Index		
	Success	192(93.2)	174(95.1)
	Failure	14(6.8)	9(4.9)
	Gen. Health Percept.		
	Success	125(60.7)	108(59.0)
	Failure	81(39.3)	75(41.0)
	Social Function		
	Success	190(92.2)	166(90.7)
	Failure	16(7.8)	17(9.3)
	Mental Health		
	Success	158(77.1)	135(73.8)
	Failure	47(22.9)	48(26.2)
	Role-Emotional		
	Success	179(86.5)	162(88.5)
	Failure	28(13.5)	21(11.5)
	Vitality		
	Success	176(85.4)	150(82.0)
	Failure	30(14.6)	33(18.0)

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* Success: Post Score - Pre Score >= 0.

Table 29. Summary of Success* Rates of SF-36 Health Survey
[Number (%) of Patients]

Period	Variable	Investigational (N=239)	Control (N=224)
36 Months	PCS		
	Success	141 (82.9)	127 (78.4)
	Failure	29 (17.1)	35 (21.6)
	MCS		
	Success	127 (74.7)	118 (72.8)
	Failure	43 (25.3)	44 (27.2)
	Physical Function		
	Success	152 (88.4)	139 (84.8)
	Failure	20 (11.6)	25 (15.2)
	Role-Physical		
	Success	165 (95.9)	155 (95.1)
	Failure	7 (4.1)	8 (4.9)
	Pain Index		
	Success	150 (88.2)	151 (92.6)
	Failure	20 (11.8)	12 (7.4)
	Gen. Health Percept.		
	Success	94 (55.3)	81 (49.7)
	Failure	76 (44.7)	82 (50.3)
	Social Function		
	Success	154 (90.6)	140 (85.9)
	Failure	16 (9.4)	23 (14.1)
	Mental Health		
	Success	131 (77.1)	119 (73.0)
	Failure	39 (22.9)	44 (27.0)
	Role-Emotional		
	Success	151 (87.8)	151 (92.1)
	Failure	21 (12.2)	13 (7.9)
	Vitality		
	Success	141 (82.9)	127 (77.9)
	Failure	29 (17.1)	36 (22.1)

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* Success: Post Score - Pre Score >= 0.

Table 29. Summary of Success* Rates of SF-36 Health Survey
[Number (%) of Patients]

Period	Variable	Investigational (N=239)	Control (N=224)
48 Months	PCS		
	Success	76(74.5)	71(76.3)
	Failure	26(25.5)	22(23.7)
	MCS		
	Success	70(68.6)	68(73.1)
	Failure	32(31.4)	25(26.9)
	Physical Function		
	Success	81(77.9)	78(83.0)
	Failure	23(22.1)	16(17.0)
	Role-Physical		
	Success	98(94.2)	91(96.8)
	Failure	6(5.8)	3(3.2)
	Pain Index		
	Success	89(87.3)	87(92.6)
	Failure	13(12.7)	7(7.4)
	Gen. Health Percept.		
	Success	55(53.9)	45(48.4)
	Failure	47(46.1)	48(51.6)
	Social Function		
	Success	91(89.2)	81(86.2)
	Failure	11(10.8)	13(13.8)
	Mental Health		
	Success	71(69.6)	71(75.5)
	Failure	31(30.4)	23(24.5)
	Role-Emotional		
	Success	90(86.5)	80(85.1)
	Failure	14(13.5)	14(14.9)
	Vitality		
	Success	85(83.3)	76(80.9)
	Failure	17(16.7)	18(19.1)

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* Success: Post Score - Pre Score >= 0.

Table 29. Summary of Success* Rates of SF-36 Health Survey
[Number (%) of Patients]

Period	Variable	Investigational (N=239)	Control (N=224)
60 Months	PCS		
	Success	122 (83.0)	102 (76.1)
	Failure	25 (17.0)	32 (23.9)
	MCS		
	Success	103 (70.1)	100 (74.6)
	Failure	44 (29.9)	34 (25.4)
	Physical Function		
	Success	125 (83.9)	114 (84.4)
	Failure	24 (16.1)	21 (15.6)
	Role-Physical		
	Success	141 (94.6)	130 (97.0)
	Failure	8 (5.4)	4 (3.0)
	Pain Index		
	Success	138 (93.9)	126 (93.3)
	Failure	9 (6.1)	9 (6.7)
	Gen. Health Percept.		
	Success	80 (54.4)	65 (48.1)
	Failure	67 (45.6)	70 (51.9)
	Social Function		
	Success	134 (91.2)	116 (85.9)
	Failure	13 (8.8)	19 (14.1)
	Mental Health		
	Success	106 (72.1)	106 (78.5)
	Failure	41 (27.9)	29 (21.5)
	Role-Emotional		
	Success	129 (86.6)	119 (88.8)
	Failure	20 (13.4)	15 (11.2)
	Vitality		
	Success	126 (85.7)	110 (81.5)
	Failure	21 (14.3)	25 (18.5)

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* Success: Post Score - Pre Score \geq 0.

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Table 30. Summary of Hip (Donor Site) Pain in the Control Group Patients

Period	Statistic	Control (N=224)
Discharge	Pain Score	
	n	216
	Mean	11.3
	Std	5.7
	Min	0.0
	Max	20.0
	P-Value *	<0.001
6 Weeks	Pain Score	
	n	213
	Mean	7.9
	Std	6.0
	Min	0.0
	Max	20.0
	P-Value *	<0.001
3 Months	Pain Score	
	n	215
	Mean	6.3
	Std	5.9
	Min	0.0
	Max	20.0
	P-Value *	<0.001
6 Months	Pain Score	
	n	206
	Mean	5.7
	Std	5.8
	Min	0.0
	Max	20.0
	P-Value *	<0.001
12 Months	Pain Score	
	n	202
	Mean	5.2
	Std	5.5
	Min	0.0
	Max	20.0
	P-Value *	<0.001

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* P-values are from t-test comparing mean with zero.

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Table 30. Summary of Hip (Donor Site) Pain in the Control Group Patients

Period	Statistic	Control (N=224)
24 Months	Pain Score	
	n	180
	Mean	5.1
	Std	6.0
	Min	0.0
	Max	20.0
	P-Value *	<0.001
36 Months	Pain Score	
	n	156
	Mean	5.4
	Std	6.4
	Min	0.0
	Max	20.0
	P-Value *	<0.001
48 Months	Pain Score	
	n	71
	Mean	4.9
	Std	5.7
	Min	0.0
	Max	20.0
	P-Value *	<0.001
60 Months	Pain Score	
	n	125
	Mean	5.3
	Std	6.2
	Min	0.0
	Max	20.0
	P-Value *	<0.001

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* P-values are from t-test comparing mean with zero.

Table 31. Summary of Overall Success Rates
(Number (%) of Patients)

Period	Variable	Investigational (N=239)	Control (N=224)
6 Months	Fusion		
	Success	155 (79.1)	115 (65.3)
	Failure	41 (20.9)	61 (34.7)
	Oswestry Pain		
	Success	170 (75.2)	149 (72.3)
	Failure	56 (24.8)	57 (27.7)
	Neurological		
	Success	200 (87.3)	182 (87.9)
	Failure	29 (12.7)	25 (12.1)
	Second Surgery Failure		
	Yes	5	5
	Serious Associated AE		
	Yes	5	8
	Overall Success		
	Success	102 (50.0)	76 (40.2)
	Failure	102 (50.0)	113 (59.8)

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Note: A patient is considered as an overall success if the patient had successes in fusion, oswestry pain, and neurological status and had no additional surgery classified as 'failure' and no serious, device or device/surgical procedure associated, adverse event.

Table 31. Summary of Overall Success Rates
[Number (%) of Patients]

Period	Variable	Investigational (N=239)	Control (N=224)
12 Months	Fusion		
	Success	182(87.5)	151(82.5)
	Failure	26(12.5)	32(17.5)
	Oswestry Pain		
	Success	159(71.3)	150(73.9)
	Failure	64(28.7)	53(26.1)
	Neurological		
	Success	197(87.6)	180(88.7)
	Failure	28(12.4)	23(11.3)
	Second Surgery Failure		
	Yes	6	14
	Serious Associated AE		
	Yes	13	20
	Overall Success		
	Success	117(54.7)	106(53.8)
	Failure	97(45.3)	91(46.2)

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Note: A patient is considered as an overall success if the patient had successes in fusion, oswestry pain, and neurological status and had no additional surgery classified as 'failure' and no serious, device or device/surgical procedure associated, adverse event.

Table 31. Summary of Overall Success Rates
[Number (%) of Patients]

Period	Variable	Investigational (N=239)	Control (N=224)
24 Months	Fusion		
	Success	186(95.9)	151(89.3)
	Failure	8(4.1)	18(10.7)
	Oswestry Pain		
	Success	152(73.1)	133(72.7)
	Failure	56(26.9)	50(27.3)
	Neurological		
	Success	180(87.0)	154(84.2)
	Failure	27(13.0)	29(15.8)
	Second Surgery Failure		
	Yes	16	28
	Serious Associated AE		
	Yes	15	24
	Overall Success		
	Success	121(60.5)	101(55.5)
	Failure	79(39.5)	81(44.5)

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Note: A patient is considered as an overall success if the patient had successes in fusion, oswestry pain, and neurological status and had no additional surgery classified as 'failure' and no serious, device or device/surgical procedure associated, adverse event.

Table 31. Summary of Overall Success Rates
[Number (%) of Patients]

Period	Variable	Investigational (N=239)	Control (N=224)
36 Months	Fusion		
	Success	128(97.0)	109(92.4)
	Failure	4(3.0)	9(7.6)
	Oswestry Pain		
	Success	116(67.4)	109(66.5)
	Failure	56(32.6)	55(33.5)
	Neurological		
	Success	151(87.8)	134(82.2)
	Failure	21(12.2)	29(17.8)
	Second Surgery Failure		
	Yes	23	33
	Serious Associated AE		
	Yes	16	28
	Overall Success		
	Success	74(49.3)	61(43.6)
	Failure	76(50.7)	79(56.4)

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Note: A patient is considered as an overall success if the patient had successes in fusion, oswestry pain, and neurological status and had no additional surgery classified as 'failure' and no serious, device or device/surgical procedure associated, adverse event.

Table 31. Summary of Overall Success Rates
[Number (%) of Patients]

Period	Variable	Investigational (N=239)	Control (N=224)
48 Months	Fusion		
	Success	87 (95.6)	58 (86.6)
	Failure	4 (4.4)	9 (13.4)
	Oswestry Pain		
	Success	65 (62.5)	59 (62.8)
	Failure	39 (37.5)	35 (37.2)
	Neurological		
	Success	92 (87.6)	75 (79.8)
	Failure	13 (12.4)	19 (20.2)
	Second Surgery Failure		
	Yes	26	35
	Serious Associated AE		
	Yes	16	28
	Overall Success		
	Success	49 (48.0)	26 (31.7)
	Failure	53 (52.0)	56 (68.3)

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Note: A patient is considered as an overall success if the patient had successes in fusion, oswestry pain, and neurological status and had no additional surgery classified as 'failure' and no serious, device or device/surgical procedure associated, adverse event.

Table 31. Summary of Overall Success Rates
(Number (%) of Patients)

Period	Variable	Investigational (N=239)	Control (N=224)
60 Months	Fusion		
	Success	93 (95.9)	70 (88.6)
	Failure	4 (4.1)	9 (11.4)
	Oswestry Pain		
	Success	100 (66.7)	85 (63.0)
	Failure	50 (33.3)	50 (37.0)
	Neurological		
	Success	132 (88.0)	112 (84.2)
	Failure	18 (12.0)	21 (15.8)
	Second Surgery Failure		
	Yes	26*	37*
	Serious Associated AE		
	Yes	15	28
	Overall Success		
	Success	54 (43.9)	39 (35.1)
	Failure	69 (56.1)	72 (64.9)

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Note: A patient is considered as an overall success if the patient had successes in fusion, oswestry pain, and neurological status and had no additional surgery classified as 'failure' and no serious, device or device/surgical procedure associated, adverse event.

* At 60 Months, Patients [REDACTED] (Inv.) and [REDACTED] (Control) had not yet reached the 60-month window to carry forward the last observation. As a result, the number of second surgery failures in this table is one less for both groups than that shown in Table 17 (Second Surgery Table).

Table 32. Summary of Patient Satisfaction with Result of Surgery
(Number (%) of Patients)

Period	Variable	Investigational (N=239)	Control (N=224)
6 Weeks	I am satisfied with the results of my surgery		
	Definitely True	129(56.3)	125(58.7)
	Mostly True	66(28.8)	64(25.4)
	Do not Know	31(13.5)	31(14.6)
	Mostly False	0(0.0)	1(0.5)
	Definitely False	3(1.3)	2(0.9)
	I was helped as much as I thought I would be by my surgery		
	Definitely True	118(52.0)	116(54.5)
	Mostly True	62(27.3)	49(23.0)
	Do not Know	43(18.9)	45(21.1)
	Mostly False	3(1.3)	2(0.9)
	Definitely False	1(0.4)	1(0.5)
	All things considered I would have the surgery again for the same condition		
	Definitely True	147(64.8)	126(59.2)
	Mostly True	40(17.6)	38(17.8)
	Do not Know	31(13.7)	39(18.3)
	Mostly False	3(1.3)	3(1.4)
	Definitely False	6(2.6)	7(3.3)
3 Months	I am satisfied with the results of my surgery		
	Definitely True	130(56.8)	119(56.1)
	Mostly True	65(28.4)	60(28.3)
	Do not Know	30(13.1)	28(13.2)
	Mostly False	0(0.0)	3(1.4)
	Definitely False	4(1.7)	2(0.9)
	I was helped as much as I thought I would be by my surgery		
	Definitely True	111(49.3)	114(53.8)
	Mostly True	72(32.0)	54(25.5)
	Do not Know	34(15.1)	33(15.6)
	Mostly False	6(2.7)	6(2.8)
	Definitely False	2(0.9)	5(2.4)
	All things considered I would have the surgery again for the same condition		
	Definitely True	134(59.8)	127(59.9)
	Mostly True	58(25.9)	47(22.2)
	Do not Know	17(7.6)	26(12.3)
	Mostly False	7(3.1)	4(1.9)
	Definitely False	8(3.6)	8(3.8)
6 Months	I am satisfied with the results of my surgery		
	Definitely True	138(61.3)	111(53.9)
	Mostly True	51(22.7)	57(27.7)
	Do not Know	25(11.1)	29(14.1)
	Mostly False	7(3.1)	8(3.9)
	Definitely False	4(1.8)	1(0.5)
	I was helped as much as I thought I would be by my surgery		
	Definitely True	124(55.6)	103(50.7)
	Mostly True	61(27.4)	68(33.5)
	Do not Know	21(9.4)	19(9.4)
	Mostly False	13(5.8)	9(4.4)
	Definitely False	4(1.8)	4(2.0)
	All things considered I would have the surgery again for the same condition		
	Definitely True	151(67.4)	123(60.6)
	Mostly True	38(17.0)	43(21.2)
	Do not Know	24(10.7)	25(12.3)
	Mostly False	4(1.8)	5(2.5)
	Definitely False	7(3.1)	7(3.4)

Table 32. Summary of Patient Satisfaction with Result of Surgery
(Number (%) of Patients)

Period	Variable	Investigational (N=239)	Control (N=224)
12 Months	I am satisfied with the results of my surgery		
	Definitely True	131 (58.7)	112 (55.2)
	Mostly True	55 (24.7)	52 (25.6)
	Do not Know	21 (9.4)	22 (10.8)
	Mostly False	11 (4.9)	12 (5.9)
	Definitely False	5 (2.2)	5 (2.5)
	I was helped as much as I thought I would be by my surgery		
	Definitely True	125 (56.3)	98 (48.3)
	Mostly True	53 (23.9)	56 (27.6)
	Do not Know	18 (8.1)	23 (11.3)
	Mostly False	19 (8.6)	16 (7.9)
	Definitely False	7 (3.2)	10 (4.9)
	All things considered I would have the surgery again for the same condition		
	Definitely True	147 (66.2)	114 (56.4)
	Mostly True	35 (15.8)	42 (20.8)
	Do not Know	23 (10.4)	25 (12.4)
	Mostly False	8 (3.6)	7 (3.5)
	Definitely False	9 (4.1)	14 (6.9)
24 Months	I am satisfied with the results of my surgery		
	Definitely True	123 (60.0)	98 (53.6)
	Mostly True	50 (24.4)	46 (25.1)
	Do not Know	21 (10.2)	25 (13.7)
	Mostly False	8 (3.9)	8 (4.4)
	Definitely False	3 (1.5)	6 (3.3)
	I was helped as much as I thought I would be by my surgery		
	Definitely True	112 (54.4)	88 (48.4)
	Mostly True	53 (25.7)	56 (30.8)
	Do not Know	20 (9.7)	18 (9.9)
	Mostly False	16 (7.8)	10 (5.5)
	Definitely False	5 (2.4)	10 (5.5)
	All things considered I would have the surgery again for the same condition		
	Definitely True	143 (70.4)	105 (58.0)
	Mostly True	29 (14.3)	32 (17.7)
	Do not Know	19 (9.4)	25 (13.8)
	Mostly False	4 (2.0)	7 (3.9)
	Definitely False	8 (3.9)	12 (6.6)
36 Months	I am satisfied with the results of my surgery		
	Definitely True	105 (61.4)	89 (55.3)
	Mostly True	43 (25.1)	36 (22.4)
	Do not Know	11 (6.4)	17 (10.6)
	Mostly False	6 (3.5)	11 (6.8)
	Definitely False	6 (3.5)	8 (5.0)
	I was helped as much as I thought I would be by my surgery		
	Definitely True	102 (60.0)	82 (51.3)
	Mostly True	32 (18.8)	44 (27.5)
	Do not Know	17 (10.0)	10 (6.3)
	Mostly False	13 (7.6)	9 (5.6)
	Definitely False	6 (3.5)	15 (9.4)
	All things considered I would have the surgery again for the same condition		
	Definitely True	119 (70.0)	90 (56.6)
	Mostly True	24 (14.1)	28 (17.6)
	Do not Know	16 (9.4)	21 (13.2)
	Mostly False	1 (0.6)	3 (1.9)
	Definitely False	10 (5.9)	17 (10.7)

Table 32. Summary of Patient Satisfaction with Result of Surgery
(Number (%) of Patients)

Period	Variable	Investigational (N=239)	Control (N=224)
48 Months	I am satisfied with the results of my surgery		
	Definitely True	61 (59.8)	52 (55.3)
	Mostly True	23 (22.5)	19 (20.2)
	Do not Know	11 (10.8)	11 (11.7)
	Mostly False	3 (2.9)	9 (9.6)
	Definitely False	4 (3.9)	3 (3.2)
	I was helped as much as I thought I would be by my surgery		
	Definitely True	60 (58.3)	50 (54.3)
	Mostly True	17 (16.5)	21 (22.8)
	Do not Know	14 (13.6)	6 (6.5)
	Mostly False	8 (7.8)	5 (5.4)
	Definitely False	4 (3.9)	10 (10.9)
	All things considered I would have the surgery again for the same condition		
	Definitely True	67 (65.0)	53 (57.6)
	Mostly True	14 (13.6)	17 (18.5)
	Do not Know	19 (18.4)	12 (13.0)
	Mostly False	0 (0.0)	4 (4.3)
	Definitely False	3 (2.9)	6 (6.5)
60 Months	I am satisfied with the results of my surgery		
	Definitely True	88 (58.7)	67 (49.6)
	Mostly True	44 (29.3)	37 (27.4)
	Do not Know	10 (6.7)	16 (11.9)
	Mostly False	4 (2.7)	9 (6.7)
	Definitely False	4 (2.7)	6 (4.4)
	I was helped as much as I thought I would be by my surgery		
	Definitely True	88 (58.7)	66 (48.9)
	Mostly True	36 (24.0)	35 (25.9)
	Do not Know	14 (9.3)	13 (9.6)
	Mostly False	8 (5.3)	11 (8.1)
	Definitely False	4 (2.7)	10 (7.4)
	All things considered I would have the surgery again for the same condition		
	Definitely True	103 (68.7)	83 (61.9)
	Mostly True	21 (14.0)	24 (17.9)
	Do not Know	17 (11.3)	15 (11.2)
	Mostly False	3 (2.0)	2 (1.5)
	Definitely False	6 (4.0)	10 (7.5)

Table 33. Summary of Patient's Perceived Effect of Surgical Treatment
[Number (%) of Patients]

Period	Variable	Investigational (N=239)	Control (N=224)
6 Weeks	Perceived Effect of Surgical Treatment		
	Completely Recovered	17(7.4)	17(8.0)
	Much Improved	143(62.2)	130(61.3)
	Slightly Improved	55(23.9)	50(23.6)
	No Change	9(3.9)	10(4.7)
	Slightly Worsened	3(1.3)	2(0.9)
	Much Worsened	2(0.9)	3(1.4)
	Vastly Worsened	1(0.4)	0(0.0)
3 Months	Perceived Effect of Surgical Treatment		
	Completely Recovered	25(11.0)	27(12.7)
	Much Improved	146(64.0)	129(60.6)
	Slightly Improved	46(20.2)	46(21.6)
	No Change	5(2.2)	2(0.9)
	Slightly Worsened	3(1.3)	5(2.3)
	Much Worsened	2(0.9)	3(1.4)
	Vastly Worsened	1(0.4)	1(0.5)
6 Months	Perceived Effect of Surgical Treatment		
	Completely Recovered	36(15.9)	28(13.6)
	Much Improved	135(59.7)	126(61.2)
	Slightly Improved	40(17.7)	35(17.0)
	No Change	8(3.5)	5(2.4)
	Slightly Worsened	5(2.2)	9(4.4)
	Much Worsened	1(0.4)	3(1.5)
	Vastly Worsened	1(0.4)	0(0.0)
12 Months	Perceived Effect of Surgical Treatment		
	Completely Recovered	63(28.3)	32(15.8)
	Much Improved	108(48.4)	104(51.5)
	Slightly Improved	29(13.0)	49(24.3)
	No Change	7(3.1)	3(1.5)
	Slightly Worsened	12(5.4)	7(3.5)
	Much Worsened	3(1.3)	6(3.0)
	Vastly Worsened	1(0.4)	1(0.5)

Table 33. Summary of Patient's Perceived Effect of Surgical Treatment
[Number (%) of Patients]

Period	Variable	Investigational (N=239)	Control (N=224)
24 Months	Perceived Effect of Surgical Treatment		
	Completely Recovered	71 (34.3)	49 (26.9)
	Much Improved	91 (44.0)	80 (44.0)
	Slightly Improved	25 (12.1)	31 (17.0)
	No Change	5 (2.4)	5 (2.7)
	Slightly Worsened	11 (5.3)	6 (3.3)
	Much Worsened	3 (1.4)	9 (4.9)
	Vastly Worsened	1 (0.5)	2 (1.1)
36 Months	Perceived Effect of Surgical Treatment		
	Completely Recovered	57 (33.3)	45 (28.1)
	Much Improved	73 (42.7)	64 (40.0)
	Slightly Improved	24 (14.0)	28 (17.5)
	No Change	3 (1.8)	7 (4.4)
	Slightly Worsened	9 (5.3)	6 (3.8)
	Much Worsened	5 (2.9)	8 (5.0)
	Vastly Worsened	0 (0.0)	2 (1.3)
48 Months	Perceived Effect of Surgical Treatment		
	Completely Recovered	31 (30.1)	20 (21.5)
	Much Improved	44 (42.7)	41 (44.1)
	Slightly Improved	14 (13.6)	18 (19.4)
	No Change	3 (2.9)	1 (1.1)
	Slightly Worsened	8 (7.8)	6 (6.5)
	Much Worsened	3 (2.9)	5 (5.4)
	Vastly Worsened	0 (0.0)	2 (2.2)
60 Months	Perceived Effect of Surgical Treatment		
	Completely Recovered	53 (35.3)	34 (25.4)
	Much Improved	63 (42.0)	57 (42.5)
	Slightly Improved	20 (13.3)	27 (20.1)
	No Change	5 (3.3)	3 (2.2)
	Slightly Worsened	6 (4.0)	3 (2.2)
	Much Worsened	3 (2.0)	9 (6.7)
	Vastly Worsened	0 (0.0)	1 (0.7)

Table 34. Summary of Doctor's Perception of Results
(Number (%) of Patients)

Period	Variable	Investigational (N=239)	Control (N=224)
6 Weeks	Doctor's Perception		
	Excellent	102 (44.2)	90 (41.5)
	Good	115 (49.8)	109 (50.2)
	Fair	13 (5.6)	17 (7.8)
	Poor	1 (0.4)	1 (0.5)
3 Months	Doctor's Perception		
	Excellent	109 (47.2)	91 (42.3)
	Good	101 (43.7)	104 (48.4)
	Fair	19 (8.2)	19 (8.8)
	Poor	2 (0.9)	1 (0.5)
6 Months	Doctor's Perception		
	Excellent	126 (55.0)	93 (44.9)
	Good	81 (35.4)	90 (43.5)
	Fair	18 (7.9)	15 (7.2)
	Poor	4 (1.7)	9 (4.3)
12 Months	Doctor's Perception		
	Excellent	121 (54.0)	84 (41.4)
	Good	79 (35.3)	83 (40.9)
	Fair	17 (7.6)	24 (11.8)
	Poor	7 (3.1)	12 (5.9)
24 Months	Doctor's Perception		
	Excellent	120 (58.0)	84 (45.7)
	Good	69 (33.3)	63 (34.2)
	Fair	10 (4.8)	26 (14.1)
	Poor	8 (3.9)	11 (6.0)
36 Months	Doctor's Perception		
	Excellent	95 (55.2)	73 (44.8)
	Good	55 (32.0)	59 (36.2)
	Fair	15 (8.7)	22 (13.5)
	Poor	7 (4.1)	9 (5.5)
48 Months	Doctor's Perception		
	Excellent	55 (52.4)	41 (43.6)
	Good	38 (36.2)	32 (34.0)
	Fair	6 (5.7)	14 (14.9)
	Poor	6 (5.7)	7 (7.4)
60 Months	Doctor's Perception		
	Excellent	81 (54.4)	57 (43.5)
	Good	52 (34.9)	50 (38.2)
	Fair	9 (6.0)	15 (11.5)
	Poor	7 (4.7)	9 (6.9)

Table 35. Summary of Patient Work Information
[Number (%) of Patients]

Period	Variable	Investigational (N=239)	Control (N=224)
Preoperative	Work Status		
	Working	83 (34.7)	92 (41.1)
	Not Working	156 (65.3)	132 (58.9)
6 Weeks	Work Status		
	Working	22 (9.4)	17 (7.8)
	Not Working	95 (40.8)	103 (47.5)
	Was not working prior to surgery/ Not applicable	116 (49.8)	97 (44.7)
3 Months	Work Status		
	Working	53 (22.9)	57 (26.5)
	Not Working	67 (29.0)	58 (27.0)
	Was not working prior to surgery/ Not applicable	111 (48.1)	100 (46.5)
6 Months	Work Status		
	Working	77 (33.6)	86 (41.5)
	Not Working	48 (21.0)	29 (14.0)
	Was not working prior to surgery/ Not applicable	104 (45.4)	92 (44.4)
12 Months	Work Status		
	Working	94 (41.8)	95 (46.8)
	Not Working	39 (17.3)	25 (12.3)
	Was not working prior to surgery/ Not applicable	92 (40.9)	83 (40.9)
24 Months	Work Status		
	Working	89 (43.0)	89 (48.4)
	Not Working	33 (15.9)	25 (13.6)
	Was not working prior to surgery/ Not applicable	85 (41.1)	70 (38.0)
36 Months	Work Status		
	Working	73 (42.4)	77 (47.2)
	Not Working	22 (12.8)	23 (14.1)
	Was not working prior to surgery/ Not applicable	77 (44.8)	63 (38.7)
48 Months	Work Status		
	Working	47 (44.8)	43 (45.7)
	Not Working	14 (13.3)	18 (19.1)
	Was not working prior to surgery/ Not applicable	44 (41.9)	33 (35.1)
60 Months	Work Status		
	Working	66 (44.0)	63 (47.4)
	Not Working	20 (13.3)	21 (15.8)
	Was not working prior to surgery/ Not applicable	64 (42.7)	49 (36.8)

Table 36. Summary of Pain and Muscle Relaxant Medications
[Number (%) of Patients]

Period	Variable	Investigational (N=239)	Control (N=224)
Preoperative	Non-Narcotic Medications		
	Not at all	84(35.3)	84(37.5)
	Once a week/as needed	15(6.3)	7(3.1)
	1 every couple of days	15(6.3)	21(9.4)
	1 or 2 a day	71(29.8)	69(30.8)
	3 or more a day	53(22.3)	43(19.2)
	Weak Narcotic Medications		
	Not at all	123(51.5)	108(48.2)
	Once a week/as needed	12(5.0)	9(4.0)
	1 every couple of days	15(6.3)	10(4.5)
	1 or 2 a day	40(16.7)	42(18.8)
	3 or more a day	49(20.5)	55(24.6)
	Strong Narcotic Medications		
	Not at all	200(84.0)	182(81.6)
	Once a week/as needed	4(1.7)	7(3.1)
	1 every couple of days	4(1.7)	5(2.2)
	1 or 2 a day	11(4.6)	14(6.3)
	3 or more a day	19(8.0)	13(6.7)
	Muscle Relaxant Medications		
	Not at all	183(76.9)	168(75.3)
	Once a week/as needed	5(2.1)	9(4.0)
	1 every couple of days	10(4.2)	7(3.1)
	1 or 2 a day	23(9.7)	26(11.7)
	3 or more a day	17(7.1)	13(5.8)

Table 36. Summary of Pain and Muscle Relaxant Medications
[Number (%) of Patients]

Period	Variable	Investigational (N=239)	Control (N=224)
6 Weeks	Non-Narcotic Medications		
	Not at all	141(61.0)	135(63.1)
	Once a week/as needed	16(6.9)	8(3.7)
	1 every couple of days	14(6.1)	21(9.8)
	1 or 2 a day	44(19.0)	31(14.5)
	3 or more a day	16(6.9)	19(8.9)
	Weak Narcotic Medications		
	Not at all	103(44.6)	83(39.2)
	Once a week/as needed	22(9.5)	19(9.0)
	1 every couple of days	18(7.8)	14(6.6)
	1 or 2 a day	45(19.5)	50(23.6)
	3 or more a day	43(18.6)	46(21.7)
	Strong Narcotic Medications		
	Not at all	178(77.7)	167(78.0)
	Once a week/as needed	7(3.1)	2(0.9)
	1 every couple of days	4(1.7)	2(0.9)
	1 or 2 a day	18(7.9)	22(10.3)
	3 or more a day	22(9.6)	21(9.8)
	Muscle Relaxant Medications		
	Not at all	154(67.2)	149(69.6)
	Once a week/as needed	11(4.8)	5(2.3)
	1 every couple of days	15(6.6)	7(3.3)
	1 or 2 a day	36(15.7)	36(16.8)
	3 or more a day	13(5.7)	17(7.9)

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Table 36. Summary of Pain and Muscle Relaxant Medications
[Number (%) of Patients]

Period	Variable	Investigational (N=239)	Control (N=224)
3 Months	Non-Narcotic Medications		
	Not at all	134 (59.0)	121 (56.8)
	Once a week/as needed	11 (4.8)	22 (10.3)
	1 every couple of days	15 (6.6)	18 (8.5)
	1 or 2 a day	49 (21.6)	40 (18.8)
	3 or more a day	18 (7.9)	12 (5.6)
	Weak Narcotic Medications		
	Not at all	133 (58.1)	118 (55.4)
	Once a week/as needed	11 (4.8)	9 (4.2)
	1 every couple of days	22 (9.6)	9 (4.2)
	1 or 2 a day	40 (17.5)	42 (19.7)
	3 or more a day	23 (10.0)	35 (16.4)
	Strong Narcotic Medications		
	Not at all	196 (85.6)	183 (85.9)
	Once a week/as needed	5 (2.2)	5 (2.3)
	1 every couple of days	3 (1.3)	0 (0.0)
	1 or 2 a day	10 (4.4)	12 (5.6)
	3 or more a day	15 (6.6)	13 (6.1)
	Muscle Relaxant Medications		
	Not at all	170 (74.2)	155 (73.1)
	Once a week/as needed	13 (5.7)	10 (4.7)
	1 every couple of days	13 (5.7)	7 (3.3)
	1 or 2 a day	22 (9.6)	28 (13.2)
	3 or more a day	11 (4.8)	12 (5.7)

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Table 36. Summary of Pain and Muscle Relaxant Medications
[Number (%) of Patients]

Period	Variable	Investigational (N=239)	Control (N=224)
6 Months	Non-Narcotic Medications		
	Not at all	119(52.7)	91(44.6)
	Once a week/as needed	13(5.8)	20(9.8)
	1 every couple of days	25(11.1)	24(11.8)
	1 or 2 a day	48(21.2)	55(27.0)
	3 or more a day	21(9.3)	14(6.9)
	Weak Narcotic Medications		
	Not at all	144(63.7)	126(61.2)
	Once a week/as needed	12(5.3)	11(5.3)
	1 every couple of days	18(8.0)	12(5.8)
	1 or 2 a day	33(14.6)	30(14.6)
	3 or more a day	19(8.4)	27(13.1)
	Strong Narcotic Medications		
	Not at all	209(92.5)	179(87.3)
	Once a week/as needed	2(0.9)	0(0.0)
	1 every couple of days	3(1.3)	3(1.5)
	1 or 2 a day	5(2.2)	10(4.9)
	3 or more a day	7(3.1)	13(6.3)
	Muscle Relaxant Medications		
	Not at all	179(79.2)	153(75.6)
	Once a week/as needed	7(3.1)	9(4.4)
	1 every couple of days	10(4.4)	7(3.4)
	1 or 2 a day	20(8.8)	19(9.3)
	3 or more a day	10(4.4)	15(7.3)

Table 36. Summary of Pain and Muscle Relaxant Medications
[Number (%) of Patients]

Period	Variable	Investigational (N=239)	Control (N=224)
12 Months	Non-Narcotic Medications		
	Not at all	121(54.3)	86(42.6)
	Once a week/as needed	20(9.0)	17(8.4)
	1 every couple of days	13(5.8)	22(10.9)
	1 or 2 a day	49(22.0)	51(25.2)
	3 or more a day	20(9.0)	26(12.9)
	Weak Narcotic Medications		
	Not at all	154(69.4)	132(65.0)
	Once a week/as needed	12(5.4)	12(5.9)
	1 every couple of days	12(5.4)	10(4.9)
	1 or 2 a day	25(11.3)	25(12.3)
	3 or more a day	19(8.6)	24(11.8)
	Strong Narcotic Medications		
	Not at all	202(91.0)	177(87.2)
	Once a week/as needed	3(1.4)	2(1.0)
	1 every couple of days	3(1.4)	1(0.5)
	1 or 2 a day	6(2.7)	14(6.9)
	3 or more a day	8(3.6)	9(4.4)
	Muscle Relaxant Medications		
	Not at all	174(78.4)	157(78.1)
	Once a week/as needed	10(4.5)	6(3.0)
	1 every couple of days	7(3.2)	8(4.0)
	1 or 2 a day	22(9.9)	14(7.0)
	3 or more a day	9(4.1)	16(8.0)

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Table 36. Summary of Pain and Muscle Relaxant Medications
[Number (%) of Patients]

Period	Variable	Investigational (N=239)	Control (N=224)
24 Months	Non-Narcotic Medications		
	Not at all	102(49.3)	82(45.3)
	Once a week/as needed	20(9.7)	24(13.3)
	1 every couple of days	17(8.2)	18(9.9)
	1 or 2 a day	47(22.7)	39(21.5)
	3 or more a day	21(10.1)	18(9.9)
	Weak Narcotic Medications		
	Not at all	142(68.6)	125(68.3)
	Once a week/as needed	14(6.8)	10(5.5)
	1 every couple of days	12(5.8)	8(4.4)
	1 or 2 a day	20(9.7)	19(10.4)
	3 or more a day	19(9.2)	21(11.5)
	Strong Narcotic Medications		
	Not at all	185(89.4)	164(90.1)
	Once a week/as needed	6(2.9)	1(0.5)
	1 every couple of days	2(1.0)	2(1.1)
	1 or 2 a day	8(3.9)	9(4.9)
	3 or more a day	6(2.9)	6(3.3)
	Muscle Relaxant Medications		
	Not at all	167(80.7)	142(78.5)
	Once a week/as needed	5(2.4)	7(3.9)
	1 every couple of days	10(4.8)	7(3.9)
	1 or 2 a day	19(9.2)	14(7.7)
	3 or more a day	6(2.9)	11(6.1)

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Table 36. Summary of Pain and Muscle Relaxant Medications
[Number (%) of Patients]

Period	Variable	Investigational (N=239)	Control (N=224)
36 Months	Non-Narcotic Medications		
	Not at all	91 (53.2)	67 (41.6)
	Once a week/as needed	13 (7.6)	14 (8.7)
	1 every couple of days	14 (8.2)	17 (10.6)
	1 or 2 a day	34 (19.9)	43 (26.7)
	3 or more a day	19 (11.1)	20 (12.4)
	Weak Narcotic Medications		
	Not at all	110 (64.3)	112 (69.6)
	Once a week/as needed	9 (5.3)	6 (3.7)
	1 every couple of days	12 (7.0)	5 (3.1)
	1 or 2 a day	20 (11.7)	17 (10.6)
	3 or more a day	20 (11.7)	21 (13.0)
	Strong Narcotic Medications		
	Not at all	146 (85.9)	140 (87.0)
	Once a week/as needed	4 (2.4)	3 (1.9)
	1 every couple of days	4 (2.4)	3 (1.9)
	1 or 2 a day	7 (4.1)	7 (4.3)
	3 or more a day	9 (5.3)	8 (5.0)
	Muscle Relaxant Medications		
	Not at all	133 (77.8)	132 (82.0)
	Once a week/as needed	6 (3.5)	4 (2.5)
	1 every couple of days	7 (4.1)	6 (3.7)
	1 or 2 a day	17 (9.9)	12 (7.5)
	3 or more a day	8 (4.7)	7 (4.3)

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Table 36. Summary of Pain and Muscle Relaxant Medications
[Number (%) of Patients]

Period	Variable	Investigational (N=239)	Control (N=224)
48 Months	Non-Narcotic Medications		
	Not at all	48 (46.6)	43 (45.7)
	Once a week/as needed	9 (8.7)	9 (9.6)
	1 every couple of days	11 (10.7)	11 (11.7)
	1 or 2 a day	24 (23.3)	21 (22.3)
	3 or more a day	11 (10.7)	10 (10.6)
	Weak Narcotic Medications		
	Not at all	62 (60.2)	64 (68.1)
	Once a week/as needed	8 (7.8)	6 (6.4)
	1 every couple of days	5 (4.9)	3 (3.2)
	1 or 2 a day	11 (10.7)	7 (7.4)
	3 or more a day	17 (16.5)	14 (14.9)
	Strong Narcotic Medications		
	Not at all	83 (80.6)	81 (86.2)
	Once a week/as needed	1 (1.0)	2 (2.1)
	1 every couple of days	3 (2.9)	0 (0.0)
	1 or 2 a day	6 (5.8)	6 (6.4)
	3 or more a day	10 (9.7)	5 (5.3)
	Muscle Relaxant Medications		
	Not at all	71 (69.6)	79 (84.0)
	Once a week/as needed	4 (3.9)	4 (4.3)
	1 every couple of days	6 (5.9)	0 (0.0)
	1 or 2 a day	12 (11.8)	5 (5.3)
	3 or more a day	9 (8.8)	6 (6.4)

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Table 36. Summary of Pain and Muscle Relaxant Medications
[Number (%) of Patients]

Period	Variable	Investigational (N=239)	Control (N=224)
60 Months	Non-Narcotic Medications		
	Not at all	71(48.0)	65(48.1)
	Once a week/as needed	20(13.5)	7(5.2)
	1 every couple of days	14(9.5)	17(12.6)
	1 or 2 a day	27(18.2)	31(23.0)
	3 or more a day	16(10.8)	15(11.1)
	Weak Narcotic Medications		
	Not at all	102(68.0)	87(64.9)
	Once a week/as needed	14(9.3)	4(3.0)
	1 every couple of days	4(2.7)	4(3.0)
	1 or 2 a day	18(12.0)	16(11.9)
	3 or more a day	12(8.0)	23(17.2)
	Strong Narcotic Medications		
	Not at all	125(84.5)	117(86.7)
	Once a week/as needed	4(2.7)	1(0.7)
	1 every couple of days	2(1.4)	1(0.7)
	1 or 2 a day	5(3.4)	7(5.2)
	3 or more a day	12(8.1)	9(6.7)
	Muscle Relaxant Medications		
	Not at all	123(82.0)	108(80.6)
	Once a week/as needed	6(4.0)	5(3.7)
	1 every couple of days	6(4.0)	2(1.5)
	1 or 2 a day	10(6.7)	8(6.0)
	3 or more a day	5(3.3)	11(8.2)

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Table 37. Summary of Overall Success Rates by Assuming Missing-Equals-Failure Analysis*
[Number (%) of Patients]

Period	Variable	Investigational (N=239)	Control (N=224)
12 Months	Fusion		
	Success	182 (76.2)	151 (67.4)
	Failure	57 (23.8)	73 (32.6)
	Oswestry Pain		
	Success	159 (66.5)	150 (67.0)
	Failure	80 (33.5)	74 (33.0)
	Neurological		
	Success	197 (82.4)	180 (80.4)
	Failure	42 (17.6)	44 (19.6)
	Overall		
24 Months	Success	117 (49.0)	106 (47.3)
	Failure	122 (51.0)	118 (52.7)
	Fusion		
	Success	186 (77.8)	151 (67.4)
	Failure	53 (22.2)	73 (32.6)
	Oswestry Pain		
	Success	152 (63.6)	133 (59.4)
	Failure	87 (36.4)	91 (40.6)
	Neurological		
	Success	180 (75.3)	154 (68.8)
	Failure	59 (24.7)	70 (31.3)
	Overall		
	Success	121 (50.6)	101 (45.1)
	Failure	118 (49.4)	123 (54.9)

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* All missing observations are considered as treatment failures.

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Table 38. Summary of Overall Success Rates by Per-Protocol Patients
[Number (%) of Patients]

Period	Variable	Investigational (N=211)	Control (N=195)
6 Months	Fusion		
	Success	140 (79.5)	101 (65.2)
	Failure	36 (20.5)	54 (34.8)
	Oswestry Pain		
	Success	149 (74.5)	131 (72.4)
	Failure	51 (25.5)	50 (27.6)
	Neurological		
	Success	176 (86.7)	160 (87.9)
	Failure	27 (13.3)	22 (12.1)
	Second Surgery Failure		
	Yes	5	2
	Serious Associated AE		
	Yes	5	4
	Overall Success		
	Success	89 (48.9)	68 (41.2)
	Failure	93 (51.1)	97 (58.8)

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Note: A patient is considered as an overall success if the patient had successes in fusion, oswestry pain, and neurological status and had no additional surgery classified as 'failure' and no serious, device or device/surgical procedure associated, adverse event.

Table 38. Summary of Overall Success Rates by Per-Protocol Patients
(Number (%) of Patients)

Period	Variable	Investigational (N=211)	Control (N=195)
12 Months	Fusion		
	Success	163 (88.1)	132 (81.5)
	Failure	22 (11.9)	30 (18.5)
	Oswestry Pain		
	Success	140 (70.0)	133 (75.1)
	Failure	60 (30.0)	44 (24.9)
	Neurological		
	Success	178 (88.1)	156 (88.1)
	Failure	24 (11.9)	21 (11.9)
	Second Surgery Failure		
	Yes	5	9
	Serious Associated AE		
	Yes	10	15
	Overall Success		
	Success	103 (53.9)	93 (54.7)
	Failure	88 (46.1)	77 (45.3)

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Note: A patient is considered as an overall success if the patient had successes in fusion, oswestry pain, and neurological status and had no additional surgery classified as 'failure' and no serious, device or device/surgical procedure associated, adverse event.

Table 38. Summary of Overall Success Rates by Per-Protocol Patients
[Number (%) of Patients]

Period	Variable	Investigational (N=211)	Control (N=195)
24 Months	Fusion		
	Success	167(97.1)	132(88.6)
	Failure	5(2.9)	17(11.4)
	Oswestry Pain		
	Success	135(73.4)	117(73.1)
	Failure	49(26.6)	43(26.9)
	Neurological		
	Success	159(86.9)	136(85.0)
	Failure	24(13.1)	24(15.0)
	Second Surgery Failure		
	Yes	12	22
	Serious Associated AE		
	Yes	12	18
	Overall Success		
	Success	108(61.0)	89(56.3)
	Failure	69(39.0)	69(43.7)

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Note: A patient is considered as an overall success if the patient had successes in fusion, oswestry pain, and neurological status and had no additional surgery classified as 'failure' and no serious, device or device/surgical procedure associated, adverse event.

Table 38. Summary of Overall Success Rates by Per-Protocol Patients
[Number (%) of Patients]

Period	Variable	Investigational (N=211)	Control (N=195)
36 Months	Fusion		
	Success	116(99.1)	96(92.3)
	Failure	1(0.9)	8(7.7)
	Oswestry Pain		
	Success	103(66.9)	96(68.1)
	Failure	51(33.1)	45(31.9)
	Neurological		
	Success	137(89.0)	118(83.7)
	Failure	17(11.0)	23(16.3)
	Second Surgery Failure		
	Yes	19	25
	Serious Associated AE		
	Yes	13	20
	Overall Success		
	Success	67(50.0)	55(46.6)
	Failure	67(50.0)	63(53.4)

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Note: A patient is considered as an overall success if the patient had successes in fusion, oswestry pain, and neurological status and had no additional surgery classified as 'failure' and no serious, device or device/surgical procedure associated, adverse event.

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Table 38. Summary of Overall Success Rates by Per-Protocol Patients
[Number (%) of Patients]

Period	Variable	Investigational (N=211)	Control (N=195)
48 Months	Fusion		
	Success	76 (98.7)	52 (86.7)
	Failure	1 (1.3)	8 (13.3)
	Oswestry Pain		
	Success	55 (61.1)	52 (64.2)
	Failure	35 (38.9)	29 (35.8)
	Neurological		
	Success	81 (89.0)	63 (77.8)
	Failure	10 (11.0)	18 (22.2)
	Second Surgery Failure		
	Yes	22	27
	Serious Associated AE		
	Yes	13	20
	Overall Success		
	Success	41 (46.6)	24 (34.8)
	Failure	47 (53.4)	45 (65.2)

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Note: A patient is considered as an overall success if the patient had successes in fusion, oswestry pain, and neurological status and had no additional surgery classified as 'failure' and no serious, device or device/surgical procedure associated, adverse event.

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Table 38. Summary of Overall Success Rates by Per-Protocol Patients
[Number (%) of Patients]

Period	Variable	Investigational (N=211)	Control (N=195)
60 Months	Fusion		
	Success	82 (98.8)	62 (88.6)
	Failure	1 (1.2)	8 (11.4)
	Oswestry Pain		
	Success	86 (65.2)	72 (63.2)
	Failure	46 (34.8)	42 (36.8)
	Neurological		
	Success	117 (88.6)	97 (85.8)
	Failure	15 (11.4)	16 (14.2)
	Second Surgery Failure		
	Yes	22	29
	Serious Associated AE		
	Yes	12	20
	Overall Success		
	Success	45 (42.1)	35 (37.6)
	Failure	62 (57.9)	58 (62.4)

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Note: A patient is considered as an overall success if the patient had successes in fusion, oswestry pain, and neurological status and had no additional surgery classified as 'failure' and no serious, device or device/surgical procedure associated, adverse event.

Table 39. Summary of Fusion, Oswestry, Neurological, and Overall Success Status at 12 Months and 24 Months by Study Sites
[Number (%) of Patients]

Period	Variable	Study Site									
		1016 (N=10)		1110 (N=6)		1169 (N=42)		1361 (N=1)		1389 (N=25)	
		Inv. (N=5)	Control (N=5)	Inv. (N=3)	Control (N=3)	Inv. (N=21)	Control (N=21)	Inv. (N=1)	Control (N=0)	Inv. (N=13)	Control (N=12)
12 Months	Fusion										
	Success	4(100.0)	4(100.0)	2(100.0)	2(66.7)	18(94.7)	15(88.2)	0(0.0)	0(0.0)	5(45.5)	7(70.0)
	Failure	0(0.0)	0(0.0)	0(0.0)	1(33.3)	1(5.3)	2(11.8)	1(100.0)	0(0.0)	6(54.5)	3(30.0)
	Oswestry										
	Success	5(100.0)	5(100.0)	2(100.0)	3(100.0)	14(70.0)	13(68.4)	1(100.0)	0(0.0)	9(75.0)	8(66.7)
	Failure	0(0.0)	0(0.0)	0(0.0)	0(0.0)	6(30.0)	6(31.6)	0(0.0)	0(0.0)	3(25.0)	4(33.3)
	Neurological										
	Success	5(100.0)	5(100.0)	3(100.0)	3(100.0)	19(95.0)	18(94.7)	1(100.0)	0(0.0)	8(66.7)	9(75.0)
	Failure	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(5.0)	1(5.3)	0(0.0)	0(0.0)	4(33.3)	3(25.0)
	Overall Success										
24 Months	Success	4(100.0)	4(100.0)	1(100.0)	2(66.7)	12(63.2)	9(47.4)	0(0.0)	0(0.0)	2(18.2)	4(36.4)
	Failure	0(0.0)	0(0.0)	0(0.0)	1(33.3)	7(36.8)	10(52.6)	1(100.0)	0(0.0)	9(81.8)	7(63.6)
	Fusion										
	Success	0(0.0)	3(100.0)	3(100.0)	2(66.7)	16(94.1)	13(92.9)	0(0.0)	0(0.0)	8(88.9)	10(83.3)
	Failure	1(100.0)	0(0.0)	0(0.0)	1(33.3)	1(5.9)	1(7.1)	0(0.0)	0(0.0)	1(11.1)	2(16.7)
	Oswestry										
	Success	2(66.7)	3(100.0)	2(66.7)	3(100.0)	13(76.5)	13(72.2)	1(100.0)	0(0.0)	7(70.0)	7(58.3)
	Failure	1(33.3)	0(0.0)	1(33.3)	0(0.0)	4(23.5)	5(27.8)	0(0.0)	0(0.0)	3(30.0)	5(41.7)
	Neurological										
	Success	3(100.0)	3(100.0)	3(100.0)	3(100.0)	15(88.2)	17(94.4)	1(100.0)	0(0.0)	6(60.0)	9(75.0)
	Failure	0(0.0)	0(0.0)	0(0.0)	0(0.0)	2(11.8)	1(5.6)	0(0.0)	0(0.0)	4(40.0)	3(25.0)
	Overall Success										
	Success	0(0.0)	3(100.0)	2(66.7)	2(66.7)	11(64.7)	10(58.8)	0(0.0)	0(0.0)	3(33.3)	6(50.0)
	Failure	2(100.0)	0(0.0)	1(33.3)	1(33.3)	5(35.3)	7(41.2)	0(0.0)	0(0.0)	5(66.7)	6(50.0)

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* P-values are from the Breslow-Day test for homogeneity across sites.
Insignificance indicates the consistent result among the sites.

(1) Sites are not combined.

(2) Sites (1110,1361,1439,1516,1627,1629,2098,2472,2574,2597,2598,2716,2788)
with fewer than 10 patients are combined into a single site.

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Table 39. Summary of Fusion, Oswestry, Neurological, and Overall Success Status at 12 Months and 24 Months by Study Sites
(Number (%) of Patients)

Period	Variable	Study Site									
		1433(N=5)		1469(N=20)		1516(N=6)		1576(N=54)		1598(N=21)	
		Inv. (N=3)	Control (N=2)	Inv. (N=10)	Control (N=10)	Inv. (N=4)	Control (N=2)	Inv. (N=28)	Control (N=26)	Inv. (N=11)	Control (N=10)
12 Months	Fusion										
	Success	0(0.0)	0(0.0)	5(62.5)	7(77.8)	3(100.0)	1(100.0)	22(91.7)	17(81.0)	10(100.0)	7(77.8)
	Failure	0(0.0)	1(100.0)	3(37.5)	2(22.2)	0(0.0)	0(0.0)	2(8.3)	4(19.0)	0(0.0)	2(22.2)
	Oswestry										
	Success	2(66.7)	1(100.0)	6(66.7)	9(90.0)	3(75.0)	0(0.0)	19(76.0)	19(82.6)	7(70.0)	6(66.7)
	Failure	1(33.3)	0(0.0)	3(33.3)	1(10.0)	1(25.0)	1(100.0)	6(24.0)	4(17.4)	3(30.0)	3(33.3)
	Neurological										
	Success	2(66.7)	1(100.0)	7(77.8)	8(80.0)	3(75.0)	1(100.0)	25(100.0)	22(95.7)	10(100.0)	9(100.0)
	Failure	1(33.3)	0(0.0)	2(22.2)	2(20.0)	1(25.0)	0(0.0)	0(0.0)	1(4.3)	0(0.0)	0(0.0)
	Overall Success										
24 Months	Success	0(0.0)	0(0.0)	4(44.4)	5(50.0)	3(75.0)	0(0.0)	16(64.0)	13(61.9)	7(70.0)	5(55.6)
	Failure	1(100.0)	1(100.0)	5(55.6)	5(50.0)	1(25.0)	1(100.0)	9(36.0)	8(38.1)	3(30.0)	4(44.4)
	Fusion										
	Success	0(0.0)	1(100.0)	8(100.0)	8(88.9)	3(100.0)	1(100.0)	25(96.2)	18(85.7)	10(100.0)	6(75.0)
	Failure	0(0.0)	0(0.0)	0(0.0)	1(11.1)	0(0.0)	0(0.0)	1(3.8)	3(14.3)	0(0.0)	2(25.0)
	Oswestry										
	Success	0(0.0)	1(100.0)	7(87.5)	8(88.9)	3(100.0)	0(0.0)	18(69.2)	17(77.3)	7(70.0)	5(62.5)
	Failure	1(100.0)	0(0.0)	1(12.5)	1(11.1)	0(0.0)	1(100.0)	8(30.8)	5(22.7)	3(30.0)	3(37.5)
	Neurological										
	Success	0(0.0)	1(100.0)	6(85.7)	7(77.8)	3(100.0)	0(0.0)	26(100.0)	21(95.5)	9(90.0)	7(87.5)
	Failure	1(100.0)	0(0.0)	1(14.3)	2(22.2)	0(0.0)	1(100.0)	0(0.0)	1(4.5)	1(10.0)	1(12.5)
	Overall Success										
	Success	0(0.0)	1(100.0)	5(62.5)	5(55.6)	3(100.0)	0(0.0)	17(63.0)	12(57.1)	7(70.0)	3(37.5)
	Failure	1(100.0)	0(0.0)	3(37.5)	4(44.4)	0(0.0)	1(100.0)	10(37.0)	9(42.9)	3(30.0)	5(62.5)

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* p-values are from the Breslow-Day test for homogeneity across sites.
Insignificance indicates the consistent result among the sites.

(1) Sites are not combined.

(2) Sites (1110,1361,1433,1516,1627,1629,2099,2472,2574,2597,2598,2716,2789)
with fewer than 10 patients are combined into a single site.

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Table 39. Summary of Fusion, Oswestry, Neurological, and Overall Success Status at 12 Months and 24 Months by Study Sites
(Number (%) of Patients)

Period	Variable	Study Site									
		1627 (N=6)		1629 (N=2)		1749 (N=10)		1980 (N=96)		2098 (N=7)	
		Inv. (N=4)	Control (N=2)	Inv. (N=1)	Control (N=1)	Inv. (N=5)	Control (N=5)	Inv. (N=47)	Control (N=49)	Inv. (N=4)	Control (N=3)
12 Months	Fusion										
	Success	4(100.0)	2(100.0)	1(100.0)	1(100.0)	3(75.0)	2(66.7)	42(95.5)	38(88.4)	2(50.0)	2(100.0)
	Failure	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(25.0)	1(33.3)	2(4.5)	5(11.6)	2(50.0)	0(0.0)
	Oswestry										
	Success	4(100.0)	1(50.0)	1(100.0)	0(0.0)	4(80.0)	3(60.0)	25(54.3)	34(75.6)	2(50.0)	2(100.0)
	Failure	0(0.0)	1(50.0)	0(0.0)	1(100.0)	1(20.0)	2(40.0)	21(45.7)	11(24.4)	2(50.0)	0(0.0)
	Neurological										
	Success	4(100.0)	2(100.0)	1(100.0)	0(0.0)	5(100.0)	4(80.0)	39(84.8)	39(86.7)	3(75.0)	2(100.0)
	Failure	0(0.0)	0(0.0)	0(0.0)	1(100.0)	0(0.0)	1(20.0)	7(15.2)	6(13.3)	1(25.0)	0(0.0)
	Overall Success	4(100.0)	1(50.0)	1(100.0)	0(0.0)	2(50.0)	1(25.0)	21(45.7)	27(60.0)	1(25.0)	2(66.7)
24 Months	Fusion										
	Success	3(100.0)	2(100.0)	1(100.0)	1(100.0)	3(100.0)	4(100.0)	38(100.0)	33(89.2)	3(75.0)	2(100.0)
	Failure	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	4(10.8)	1(25.0)	0(0.0)
	Oswestry										
	Success	3(100.0)	1(50.0)	1(100.0)	0(0.0)	4(80.0)	5(100.0)	27(67.5)	26(68.4)	2(50.0)	2(100.0)
	Failure	0(0.0)	1(50.0)	0(0.0)	1(100.0)	1(20.0)	0(0.0)	13(32.5)	12(31.6)	2(50.0)	0(0.0)
	Neurological										
	Success	2(66.7)	0(0.0)	1(100.0)	0(0.0)	5(100.0)	5(100.0)	36(90.0)	32(86.3)	2(50.0)	1(50.0)
	Failure	1(33.3)	2(100.0)	0(0.0)	1(100.0)	0(0.0)	0(0.0)	4(10.0)	5(13.5)	2(50.0)	1(50.0)
	Overall Success	2(66.7)	0(0.0)	1(100.0)	0(0.0)	2(66.7)	4(100.0)	24(60.0)	22(56.4)	1(25.0)	1(33.3)
	Failure	1(33.3)	2(100.0)	0(0.0)	1(100.0)	1(33.3)	0(0.0)	16(40.0)	17(43.6)	3(75.0)	2(66.7)

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* P-values are from the Breslow-Day test for homogeneity across sites.
Insignificance indicates the consistent result among the sites.

(1) Sites are not combined.

(2) Sites (1110,1361,1433,1516,1627,1629,2098,2472,2574,2597,2598,2716,2788)
with fewer than 10 patients are combined into a single site.

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Table 39. Summary of Fusion, Oswestry, Neurological, and Overall Success Status at 12 Months and 24 Months by Study Sites
(Number (%) of Patients)

Period	Variable	Study Site									
		2257 (N=15)		2294 (N=10)		2322 (N=18)		2323 (N=19)		2334 (N=12)	
		Inv. (N=8)	Control (N=7)	Inv. (N=5)	Control (N=5)	Inv. (N=9)	Control (N=9)	Inv. (N=10)	Control (N=9)	Inv. (N=7)	Control (N=5)
12 Months	Fusion										
	Success	6 (85.7)	6 (85.7)	5 (100.0)	5 (100.0)	6 (66.7)	9 (100.0)	8 (80.0)	7 (100.0)	6 (100.0)	2 (66.7)
	Failure	1 (14.3)	1 (14.3)	0 (0.0)	0 (0.0)	3 (33.3)	0 (0.0)	2 (20.0)	0 (0.0)	0 (0.0)	1 (33.3)
	Oswestry										
	Success	7 (87.5)	6 (85.7)	4 (80.0)	5 (100.0)	8 (88.9)	4 (50.0)	9 (90.0)	7 (77.8)	5 (83.3)	3 (75.0)
	Failure	1 (12.5)	1 (14.3)	1 (20.0)	0 (0.0)	1 (11.1)	4 (50.0)	1 (10.0)	2 (22.2)	1 (16.7)	1 (25.0)
	Neurological										
	Success	8 (100.0)	7 (100.0)	4 (80.0)	5 (100.0)	9 (100.0)	5 (62.5)	10 (100.0)	9 (100.0)	7 (100.0)	3 (75.0)
24 Months	Failure	0 (0.0)	0 (0.0)	1 (20.0)	0 (0.0)	0 (0.0)	3 (37.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (25.0)
	Overall Success										
	Success	5 (71.4)	4 (57.1)	3 (60.0)	5 (100.0)	6 (66.7)	3 (37.5)	7 (70.0)	6 (75.0)	5 (83.3)	2 (66.7)
	Failure	2 (28.6)	3 (42.9)	2 (40.0)	0 (0.0)	3 (33.3)	5 (62.5)	3 (30.0)	2 (25.0)	1 (16.7)	1 (33.3)
	Fusion										
	Success	8 (100.0)	6 (100.0)	5 (100.0)	4 (100.0)	7 (87.5)	7 (100.0)	7 (77.8)	9 (100.0)	6 (100.0)	4 (100.0)
	Failure	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)	0 (0.0)	2 (22.2)	0 (0.0)	0 (0.0)	0 (0.0)
	Oswestry										
	Success	6 (75.0)	5 (83.3)	3 (60.0)	4 (100.0)	7 (77.8)	4 (50.0)	10 (100.0)	8 (88.9)	4 (66.7)	4 (100.0)
	Failure	2 (25.0)	1 (16.7)	2 (40.0)	0 (0.0)	2 (22.2)	4 (50.0)	0 (0.0)	1 (11.1)	2 (33.3)	0 (0.0)
	Neurological										
	Success	7 (87.5)	6 (100.0)	4 (80.0)	3 (75.0)	9 (100.0)	5 (62.5)	10 (100.0)	7 (77.8)	6 (100.0)	4 (100.0)
	Failure	1 (12.5)	0 (0.0)	1 (20.0)	1 (25.0)	0 (0.0)	3 (37.5)	0 (0.0)	2 (22.2)	0 (0.0)	0 (0.0)
	Overall Success										
	Success	6 (75.0)	4 (66.7)	3 (60.0)	3 (75.0)	5 (62.5)	3 (37.5)	7 (77.8)	7 (77.8)	4 (66.7)	4 (100.0)
	Failure	2 (25.0)	2 (33.3)	2 (40.0)	1 (25.0)	3 (37.5)	5 (62.5)	2 (22.2)	2 (22.2)	2 (33.3)	0 (0.0)

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* P-values are from the Breslow-Day test for homogeneity across sites.
Insignificance indicates the consistent result among the sites.

(1) Sites are not combined.

(2) Sites (1110,1361,1433,1516,1627,1629,2098,2472,2574,2597,2598,2716,2788)
with fewer than 10 patients are combined into a single site.

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Table 39. Summary of Fusion, Oswestry, Neurological, and Overall Success Status at 12 Months and 24 Months by Study Sites
(Number (%) of Patients)

Period	Variable	Study Site									
		2472 (N=3)		2547 (N=18)		2574 (N=6)		2597 (N=7)		2598 (N=4)	
		Inv. (N=1)	Control (N=2)	Inv. (N=9)	Control (N=9)	Inv. (N=4)	Control (N=2)	Inv. (N=4)	Control (N=3)	Inv. (N=2)	Control (N=2)
12 Months	Fusion										
	Success	1(100.0)	2(100.0)	5(100.0)	2(66.7)	3(75.0)	2(100.0)	3(100.0)	2(66.7)	1(50.0)	2(100.0)
	Failure	0(0.0)	0(0.0)	0(0.0)	1(33.3)	1(25.0)	0(0.0)	0(0.0)	1(33.3)	1(50.0)	0(0.0)
	Oswestry										
	Success	1(100.0)	2(100.0)	5(71.4)	2(28.6)	3(75.0)	1(50.0)	2(66.7)	3(100.0)	0(0.0)	2(100.0)
	Failure	0(0.0)	0(0.0)	2(28.6)	5(71.4)	1(25.0)	1(50.0)	1(33.3)	0(0.0)	2(100.0)	0(0.0)
	Neurological										
	Success	1(100.0)	2(100.0)	3(42.9)	5(71.4)	4(100.0)	2(100.0)	3(100.0)	3(100.0)	2(100.0)	2(100.0)
	Failure	0(0.0)	0(0.0)	4(57.1)	2(28.6)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
	Overall Success										
	Success	1(100.0)	2(100.0)	1(16.7)	0(0.0)	2(50.0)	1(50.0)	2(66.7)	2(66.7)	0(0.0)	2(100.0)
	Failure	0(0.0)	0(0.0)	5(83.3)	7(100.0)	2(50.0)	1(50.0)	1(33.3)	1(33.3)	2(100.0)	0(0.0)
24 Months	Fusion										
	Success	1(100.0)	1(100.0)	7(100.0)	2(100.0)	4(100.0)	2(100.0)	2(100.0)	3(100.0)	2(100.0)	2(100.0)
	Failure	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
	Oswestry										
	Success	1(100.0)	1(100.0)	5(71.4)	1(25.0)	4(100.0)	1(50.0)	1(50.0)	3(100.0)	1(50.0)	2(100.0)
	Failure	0(0.0)	0(0.0)	2(28.6)	3(75.0)	0(0.0)	1(50.0)	1(50.0)	0(0.0)	1(50.0)	0(0.0)
	Neurological										
	Success	1(100.0)	1(100.0)	4(57.1)	4(80.0)	4(100.0)	1(50.0)	2(100.0)	3(100.0)	1(50.0)	2(100.0)
	Failure	0(0.0)	0(0.0)	3(42.9)	1(20.0)	0(0.0)	1(50.0)	0(0.0)	0(0.0)	1(50.0)	0(0.0)
	Overall Success										
	Success	1(100.0)	1(100.0)	3(42.9)	0(0.0)	4(100.0)	1(50.0)	1(50.0)	3(100.0)	1(50.0)	2(100.0)
	Failure	0(0.0)	0(0.0)	4(57.1)	4(100.0)	0(0.0)	1(50.0)	1(50.0)	0(0.0)	1(50.0)	0(0.0)

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* P-values are from the Breslow-Day test for homogeneity across sites.
Insignificance indicates the consistent result among the sites.

(1) Sites are not combined.

(2) Sites (1110,1361,1433,1516,1627,1629,2098,2472,2574,2597,2598,2716,2788)
with fewer than 10 patients are combined into a single site.

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Table 39. Summary of Fusion, Oswestry, Neurological, and Overall Success Status at 12 Months and 24 Months by Study Sites
(Number (%) of Patients)

Period	Variable	Study Site								Total (N=463)		p-value *	
		2716 (N=8)		2788 (N=7)		3221 (N=11)		3304 (N=14)		Inv. (N=239)	Control (N=224)	(1)	(2)
		Inv. (N=4)	Control (N=4)	Inv. (N=4)	Control (N=3)	Inv. (N=5)	Control (N=6)	Inv. (N=7)	Control (N=7)				
12 Months	Fusion												
	Success	4(100.0)	3(75.0)	4(100.0)	0(0.0)	2(100.0)	1(33.3)	7(100.0)	4(57.1)	182(87.5)	151(82.5)	0.049	0.110
	Failure	0(0.0)	1(25.0)	0(0.0)	1(100.0)	0(0.0)	2(66.7)	0(0.0)	3(42.9)	26(12.5)	32(17.5)		
	Oswestry												
	Success	4(100.0)	3(75.0)	3(75.0)	2(100.0)	2(100.0)	2(66.7)	2(28.6)	4(57.1)	159(71.3)	150(73.9)	0.130	0.370
	Failure	0(0.0)	1(25.0)	1(25.0)	0(0.0)	0(0.0)	1(33.3)	5(71.4)	3(42.9)	64(28.7)	53(26.1)		
	Neurological												
	Success	4(100.0)	4(100.0)	0(0.0)	0(0.0)	2(100.0)	3(100.0)	5(71.4)	7(100.0)	197(87.6)	180(88.7)	0.282	0.258
	Failure	0(0.0)	0(0.0)	4(100.0)	2(100.0)	0(0.0)	0(0.0)	2(28.6)	0(0.0)	28(12.4)	23(11.3)		
	Overall Success												
	Success	4(100.0)	3(75.0)	0(0.0)	0(0.0)	2(100.0)	1(33.3)	1(14.3)	2(28.6)	117(54.7)	106(53.8)	0.284	0.575
	Failure	0(0.0)	1(25.0)	4(100.0)	2(100.0)	0(0.0)	2(66.7)	6(85.7)	5(71.4)	97(45.3)	91(46.2)		
24 Months	Fusion												
	Success	3(100.0)	1(50.0)	4(100.0)	0(0.0)	3(100.0)	1(50.0)	6(100.0)	5(83.3)	186(95.9)	151(89.3)	0.030	0.044
	Failure	0(0.0)	1(50.0)	0(0.0)	1(100.0)	0(0.0)	1(50.0)	0(0.0)	1(16.7)	8(4.1)	18(10.7)		
	Oswestry												
	Success	4(100.0)	1(33.3)	3(75.0)	2(100.0)	4(100.0)	2(66.7)	2(28.6)	4(57.1)	152(73.1)	133(72.7)	0.073	0.539
	Failure	0(0.0)	2(66.7)	1(25.0)	0(0.0)	0(0.0)	1(33.3)	5(71.4)	3(42.9)	56(26.9)	50(27.3)		
	Neurological												
	Success	4(100.0)	3(100.0)	0(0.0)	0(0.0)	4(100.0)	3(100.0)	6(85.7)	6(85.7)	180(87.0)	154(84.2)	0.190	0.591
	Failure	0(0.0)	0(0.0)	4(100.0)	2(100.0)	0(0.0)	0(0.0)	1(14.3)	1(14.3)	27(13.0)	29(15.8)		
	Overall Success												
	Success	3(100.0)	1(33.3)	0(0.0)	0(0.0)	3(100.0)	1(33.3)	2(28.6)	2(28.6)	121(60.3)	101(55.5)	0.080	0.342
	Failure	0(0.0)	2(66.7)	4(100.0)	2(100.0)	0(0.0)	2(66.7)	5(71.4)	5(71.4)	79(39.5)	81(44.5)		

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* P-values are from the Breslow-Day test for homogeneity across sites.
Insignificance indicates the consistent result among the sites.

(1) Sites are not combined.

(2) Sites (1110,1361,1433,1516,1627,1629,2098,2472,2574,2597,2598,2716,2788) with fewer than 10 patients are combined into a single site.

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Table 40. Summary of Effectiveness Variables by Financial Interests of Investigators at 12 and 24 Months
[Number (%) of Patients]

			Study Site								
Period	Treatment Group	Variable	1016 (N=10)	1110* (N=6)	1169 (N=42)	1361 (N=1)	1389 (N=25)	1433 (N=5)	1469 (N=20)	1516 (N=6)	1576* (N=54)
12 Months	Investigational	Fusion									
		Success	4(100.0)	2(100.0)	18(94.7)	0(0.0)	5(45.5)	0(0.0)	5(62.5)	3(100.0)	22(91.7)
		Failure	0(0.0)	0(0.0)	1(5.3)	1(100.0)	6(54.5)	0(0.0)	3(37.5)	0(0.0)	2(8.3)
		Oswestry									
		Success	5(100.0)	2(100.0)	14(70.0)	1(100.0)	9(75.0)	2(66.7)	6(66.7)	3(75.0)	19(76.0)
		Failure	0(0.0)	0(0.0)	6(30.0)	0(0.0)	3(25.0)	1(33.3)	3(33.3)	1(25.0)	6(24.0)
		Neurological									
		Success	5(100.0)	3(100.0)	19(95.0)	1(100.0)	8(66.7)	2(66.7)	7(77.8)	3(75.0)	25(100.0)
		Failure	0(0.0)	0(0.0)	1(5.0)	0(0.0)	4(33.3)	1(33.3)	2(22.2)	1(25.0)	0(0.0)
		Overall Success									
		Success	4(100.0)	1(100.0)	12(63.2)	0(0.0)	2(18.2)	0(0.0)	4(44.4)	3(75.0)	16(64.0)
		Failure	0(0.0)	0(0.0)	7(36.8)	1(100.0)	9(81.8)	1(100.0)	5(55.6)	1(25.0)	9(36.0)
	Control	Fusion									
		Success	4(100.0)	2(66.7)	15(88.2)	0(0.0)	7(70.0)	0(0.0)	7(77.8)	1(100.0)	17(81.0)
		Failure	0(0.0)	1(33.3)	2(11.8)	0(0.0)	3(30.0)	1(100.0)	2(22.2)	0(0.0)	4(19.0)
		Oswestry									
		Success	5(100.0)	3(100.0)	13(68.4)	0(0.0)	8(66.7)	1(100.0)	9(90.0)	0(0.0)	19(82.6)
		Failure	0(0.0)	0(0.0)	6(31.6)	0(0.0)	4(33.3)	0(0.0)	1(10.0)	1(100.0)	4(17.4)
		Neurological									
		Success	5(100.0)	3(100.0)	18(94.7)	0(0.0)	9(75.0)	1(100.0)	8(80.0)	1(100.0)	22(95.7)
		Failure	0(0.0)	0(0.0)	1(5.3)	0(0.0)	3(25.0)	0(0.0)	2(20.0)	0(0.0)	1(4.3)
		Overall Success									
		Success	4(100.0)	2(66.7)	9(47.4)	0(0.0)	4(36.4)	0(0.0)	5(50.0)	0(0.0)	13(61.9)
		Failure	0(0.0)	1(33.3)	10(52.6)	0(0.0)	7(63.6)	1(100.0)	5(50.0)	1(100.0)	8(38.1)

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* Investigators at those sites reported financial interests.

** P-values are from Fisher's exact test for comparing with-financial-interests with without-financial-interests.

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Table 40. Summary of Effectiveness Variables by Financial Interests of Investigators at 12 and 24 Months
(Number (%) of Patients)

Period	Treatment Group	Variable	Study Site									
			1598 (N=21)	1627 (N=6)	1629* (N=2)	1749 (N=10)		1980* (N=96)	2098 (N=7)	2257 (N=13)	2294* (N=10)	2322 (N=18)
						A (N=1)	B* (N=9)					
12 Months	Investigational	Fusion										
		Success	10(100.0)	4(100.0)	1(100.0)	1(100.0)	2(66.7)	42(95.5)	2(50.0)	6(85.7)	5(100.0)	2(66.7)
		Failure	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(33.3)	2(4.5)	2(50.0)	1(14.3)	0(0.0)	1(33.3)
		Oswestry										
		Success	7(70.0)	4(100.0)	1(100.0)	0(0.0)	4(100.0)	25(54.3)	2(50.0)	7(87.5)	4(80.0)	3(100.0)
		Failure	3(30.0)	0(0.0)	0(0.0)	1(100.0)	0(0.0)	21(45.7)	2(50.0)	1(12.5)	1(20.0)	0(0.0)
		Neurological										
		Success	10(100.0)	4(100.0)	1(100.0)	1(100.0)	4(100.0)	39(84.8)	3(75.0)	8(100.0)	4(80.0)	3(100.0)
		Failure	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	7(15.2)	1(25.0)	0(0.0)	1(20.0)	0(0.0)
		Overall Success										
		Success	7(70.0)	4(100.0)	1(100.0)	0(0.0)	2(66.7)	21(45.7)	1(25.0)	5(71.4)	3(60.0)	2(66.7)
		Failure	3(30.0)	0(0.0)	0(0.0)	1(100.0)	1(33.3)	25(54.3)	3(75.0)	2(28.6)	2(40.0)	1(33.3)
	Control	Fusion										
		Success	7(77.8)	2(100.0)	1(100.0)	0(0.0)	2(66.7)	38(88.4)	2(100.0)	6(85.7)	5(100.0)	2(100.0)
		Failure	2(22.2)	0(0.0)	0(0.0)	0(0.0)	1(33.3)	5(11.6)	0(0.0)	1(14.3)	0(0.0)	0(0.0)
		Oswestry										
		Success	6(66.7)	1(50.0)	0(0.0)	0(0.0)	3(60.0)	34(75.6)	2(100.0)	6(85.7)	5(100.0)	1(50.0)
		Failure	3(33.3)	1(50.0)	1(100.0)	0(0.0)	2(40.0)	11(24.4)	0(0.0)	1(14.3)	0(0.0)	1(50.0)
		Neurological										
		Success	9(100.0)	2(100.0)	0(0.0)	0(0.0)	4(80.0)	39(86.7)	2(100.0)	7(100.0)	5(100.0)	1(50.0)
		Failure	0(0.0)	0(0.0)	1(100.0)	0(0.0)	1(20.0)	6(13.3)	0(0.0)	0(0.0)	0(0.0)	1(50.0)
		Overall Success										
		Success	5(55.6)	1(50.0)	0(0.0)	0(0.0)	1(25.0)	27(60.0)	2(66.7)	4(57.1)	5(100.0)	0(0.0)
		Failure	4(44.4)	1(50.0)	1(100.0)	0(0.0)	3(75.0)	18(40.0)	1(33.3)	3(42.9)	0(0.0)	2(100.0)

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* Investigators at those sites reported financial interests.

** P-values are from Fisher's exact test for comparing with-financial-interests with without-financial-interests.

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Table 40. Summary of Effectiveness Variables by Financial Interests of Investigators at 12 and 24 Months
(Number (%) of Patients)

			Study Site									
			2322 (N=18)				2547 (N=18)		2597 (N=7)		2598 (N=4)	
Period	Treatment Group	Variable	B* (N=12)	2323* (N=19)	2334 (N=12)	2472 (N=3)	A (N=2)	B* (N=16)	2574 (N=6)	A (N=5)	B* (N=2)	A (N=2)
12 Months	Investigational	Fusion										
		Success	4 (66.7)	8 (80.0)	6 (100.0)	1 (100.0)	0 (0.0)	5 (100.0)	3 (75.0)	3 (100.0)	0 (0.0)	0 (0.0)
		Failure	2 (33.3)	2 (20.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	0 (0.0)	1 (100.0)
		Oswestry										
		Success	5 (83.3)	9 (90.0)	5 (83.3)	1 (100.0)	1 (100.0)	4 (66.7)	3 (75.0)	2 (66.7)	0 (0.0)	0 (0.0)
		Failure	1 (16.7)	1 (10.0)	1 (16.7)	0 (0.0)	0 (0.0)	2 (33.3)	1 (25.0)	1 (33.3)	0 (0.0)	1 (100.0)
		Neurological										
		Success	6 (100.0)	10 (100.0)	7 (100.0)	1 (100.0)	1 (100.0)	2 (33.3)	4 (100.0)	3 (100.0)	0 (0.0)	1 (100.0)
		Failure	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (66.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
		Overall Success										
		Success	4 (66.7)	7 (70.0)	5 (83.3)	1 (100.0)	0 (0.0)	1 (16.7)	2 (50.0)	2 (66.7)	0 (0.0)	0 (0.0)
		Failure	2 (33.3)	3 (30.0)	1 (16.7)	0 (0.0)	0 (0.0)	5 (83.3)	2 (50.0)	1 (33.3)	0 (0.0)	1 (100.0)
	Control	Fusion										
		Success	6 (100.0)	7 (100.0)	2 (66.7)	2 (100.0)	0 (0.0)	2 (66.7)	2 (100.0)	0 (0.0)	2 (100.0)	1 (100.0)
		Failure	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	1 (100.0)	0 (0.0)	0 (0.0)
		Oswestry										
		Success	3 (50.0)	7 (77.8)	3 (75.0)	2 (100.0)	0 (0.0)	2 (33.3)	1 (50.0)	1 (100.0)	2 (100.0)	1 (100.0)
		Failure	3 (50.0)	2 (22.2)	1 (25.0)	0 (0.0)	1 (100.0)	4 (66.7)	1 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)
		Neurological										
		Success	4 (66.7)	9 (100.0)	3 (75.0)	2 (100.0)	1 (100.0)	4 (66.7)	2 (100.0)	1 (100.0)	2 (100.0)	1 (100.0)
		Failure	2 (33.3)	0 (0.0)	1 (25.0)	0 (0.0)	0 (0.0)	2 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
		Overall Success										
		Success	3 (50.0)	6 (75.0)	2 (66.7)	2 (100.0)	0 (0.0)	0 (0.0)	1 (50.0)	0 (0.0)	2 (100.0)	1 (100.0)
		Failure	3 (50.0)	2 (25.0)	1 (33.3)	0 (0.0)	1 (100.0)	6 (100.0)	1 (50.0)	1 (100.0)	0 (0.0)	0 (0.0)

* Investigators at those sites reported financial interests.

** P-values are from Fisher's exact test for comparing with-financial-interests with without-financial-interests.

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Table 40. Summary of Effectiveness Variables by Financial Interests of Investigators at 12 and 24 Months
[Number (%) of Patients]

Period	Treatment Group	Variable	Study Site						Total (N=463)		p-value **		
			2598 (N=4)	2716 (N=8)	2788 (N=7)			3221 (N=11)	3304* (N=14)	With Interests (N=251)		Without Interests (N=212)	
			B* (N=2)	A (N=5)	B* (N=3)	A (N=1)	B* (N=6)						
12 Months	Investigational	Fusion											
		Success	1(100.0)	3(100.0)	1(100.0)	1(100.0)	3(100.0)	2(100.0)	7(100.0)	103(92.0)	79(82.3)	0.057	
		Failure	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	9(8.0)	17(17.7)		
		Oswestry										0.138	
		Success	0(0.0)	3(100.0)	1(100.0)	1(100.0)	2(66.7)	2(100.0)	2(28.6)	78(66.7)	81(76.4)		
		Failure	1(100.0)	0(0.0)	0(0.0)	0(0.0)	1(33.3)	0(0.0)	5(71.4)	39(33.3)	25(23.6)		
		Neurological										0.421	
		Success	1(100.0)	3(100.0)	1(100.0)	0(0.0)	0(0.0)	2(100.0)	5(71.4)	101(85.6)	96(89.7)		
		Failure	0(0.0)	0(0.0)	0(0.0)	1(100.0)	3(100.0)	0(0.0)	2(28.6)	17(14.4)	11(10.3)		
		Overall Success										0.213	
		Success	0(0.0)	3(100.0)	1(100.0)	0(0.0)	0(0.0)	2(100.0)	1(14.3)	58(50.4)	59(59.6)		
		Failure	1(100.0)	0(0.0)	0(0.0)	1(100.0)	3(100.0)	0(0.0)	6(85.7)	57(49.6)	40(40.4)		
	Control	Fusion											
		Success	1(100.0)	2(100.0)	1(50.0)	0(0.0)	0(0.0)	1(33.3)	4(57.1)	88(83.8)	63(80.8)	0.695	
		Failure	0(0.0)	0(0.0)	1(50.0)	0(0.0)	1(100.0)	2(66.7)	3(42.9)	17(16.2)	15(19.2)		
		Oswestry										1.000	
		Success	1(100.0)	2(100.0)	1(50.0)	0(0.0)	2(100.0)	2(66.7)	4(57.1)	86(73.5)	64(74.4)		
		Failure	0(0.0)	0(0.0)	1(50.0)	0(0.0)	0(0.0)	1(33.3)	3(42.9)	31(26.5)	22(25.6)		
		Neurological										0.506	
		Success	1(100.0)	2(100.0)	2(100.0)	0(0.0)	0(0.0)	3(100.0)	7(100.0)	102(87.2)	78(90.7)		
		Failure	0(0.0)	0(0.0)	0(0.0)	0(0.0)	2(100.0)	0(0.0)	0(0.0)	15(12.8)	8(9.3)		
		Overall Success										0.565	
		Success	1(100.0)	2(100.0)	1(50.0)	0(0.0)	0(0.0)	1(33.3)	2(28.6)	63(55.8)	43(51.2)		
		Failure	0(0.0)	0(0.0)	1(50.0)	0(0.0)	2(100.0)	2(66.7)	5(71.4)	50(44.2)	41(48.8)		

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* Investigators at those sites reported financial interests.

** P-values are from Fisher's exact test for comparing with-financial-interests with without-financial-interests.

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Table 40. Summary of Effectiveness Variables by Financial Interests of Investigators at 12 and 24 Months
(Number (%) of Patients)

			Study Site								
Period	Treatment Group	Variable	1016 (N=10)	1110* (N=6)	1169 (N=12)	1361 (N=1)	1389 (N=25)	1433 (N=5)	1469 (N=20)	1516 (N=6)	1576* (N=54)
24 Months	Investigational	Fusion									
		Success	0 (0.0)	3 (100.0)	16 (94.1)	0 (0.0)	8 (88.9)	0 (0.0)	8 (100.0)	3 (100.0)	25 (96.2)
		Failure	1 (100.0)	0 (0.0)	1 (5.9)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.8)
		Oswestry									
		Success	2 (66.7)	2 (66.7)	13 (76.5)	1 (100.0)	7 (70.0)	0 (0.0)	7 (87.5)	3 (100.0)	18 (69.2)
		Failure	1 (33.3)	1 (33.3)	4 (23.5)	0 (0.0)	3 (30.0)	1 (100.0)	1 (12.5)	0 (0.0)	8 (30.8)
		Neurological									
		Success	3 (100.0)	3 (100.0)	15 (88.2)	1 (100.0)	6 (60.0)	0 (0.0)	6 (85.7)	3 (100.0)	26 (100.0)
		Failure	0 (0.0)	0 (0.0)	2 (11.8)	0 (0.0)	4 (40.0)	1 (100.0)	1 (14.3)	0 (0.0)	0 (0.0)
		Overall Success									
		Success	0 (0.0)	2 (66.7)	11 (64.7)	0 (0.0)	3 (33.3)	0 (0.0)	5 (62.5)	3 (100.0)	17 (63.0)
		Failure	2 (100.0)	1 (33.3)	6 (35.3)	0 (0.0)	6 (66.7)	1 (100.0)	3 (37.5)	0 (0.0)	10 (37.0)
	Control	Fusion									
		Success	3 (100.0)	2 (66.7)	13 (92.9)	0 (0.0)	10 (83.3)	1 (100.0)	8 (88.9)	1 (100.0)	18 (85.7)
		Failure	0 (0.0)	1 (33.3)	1 (7.1)	0 (0.0)	2 (16.7)	0 (0.0)	1 (11.1)	0 (0.0)	3 (14.3)
		Oswestry									
		Success	3 (100.0)	3 (100.0)	13 (72.2)	0 (0.0)	7 (58.3)	1 (100.0)	8 (88.9)	0 (0.0)	17 (77.3)
		Failure	0 (0.0)	0 (0.0)	5 (27.8)	0 (0.0)	5 (41.7)	0 (0.0)	1 (11.1)	1 (100.0)	5 (22.7)
		Neurological									
		Success	3 (100.0)	3 (100.0)	17 (94.4)	0 (0.0)	9 (75.0)	1 (100.0)	7 (77.8)	0 (0.0)	21 (95.5)
		Failure	0 (0.0)	0 (0.0)	1 (5.6)	0 (0.0)	3 (25.0)	0 (0.0)	2 (22.2)	1 (100.0)	1 (4.5)
		Overall Success									
		Success	3 (100.0)	2 (66.7)	10 (58.8)	0 (0.0)	6 (50.0)	1 (100.0)	5 (55.6)	0 (0.0)	12 (57.1)
		Failure	0 (0.0)	1 (33.3)	7 (41.2)	0 (0.0)	6 (50.0)	0 (0.0)	4 (44.4)	1 (100.0)	9 (42.9)

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* Investigators at those sites reported financial interests.

** P-values are from Fisher's exact test for comparing with-financial-interests with without-financial-interests.

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Table 40. Summary of Effectiveness Variables by Financial Interests of Investigators at 12 and 24 Months
[Number (%) of Patients]

			Study Site										
			1749 (N=10)								2322 (N=18)		
Period	Treatment Group	Variable	1598 (N=21)	1627 (N=6)	1629* (N=2)	A (N=1)	B* (N=9)	1980* (N=96)	2098 (N=7)	2257 (N=15)	2294* (N=10)	A (N=6)	
24 Months	Investigational Fusion	Success	10(100.0)	3(100.0)	1(100.0)	1(100.0)	2(100.0)	38(100.0)	3(75.0)	6(100.0)	5(100.0)	2(100.0)	
		Failure	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(25.0)	0(0.0)	0(0.0)	0(0.0)	
		Oswestry											
		Success	7(70.0)	3(100.0)	1(100.0)	0(0.0)	4(100.0)	27(67.5)	2(50.0)	6(75.0)	3(60.0)	2(66.7)	
		Failure	3(30.0)	0(0.0)	0(0.0)	1(100.0)	0(0.0)	13(32.5)	2(50.0)	2(25.0)	2(40.0)	1(33.3)	
		Neurological											
		Success	9(90.0)	2(66.7)	1(100.0)	1(100.0)	4(100.0)	36(90.0)	2(50.0)	7(87.5)	4(80.0)	3(100.0)	
		Failure	1(10.0)	1(33.3)	0(0.0)	0(0.0)	0(0.0)	4(10.0)	2(50.0)	1(12.5)	1(20.0)	0(0.0)	
		Overall Success											
		Success	7(70.0)	2(66.7)	1(100.0)	0(0.0)	2(100.0)	24(60.0)	1(25.0)	6(75.0)	3(60.0)	1(50.0)	
		Failure	3(30.0)	1(33.3)	0(0.0)	1(100.0)	0(0.0)	16(40.0)	3(75.0)	2(25.0)	2(40.0)	1(50.0)	
	Control	Fusion											
		Success	6(75.0)	2(100.0)	1(100.0)	0(0.0)	4(100.0)	33(89.2)	2(100.0)	6(100.0)	4(100.0)	1(100.0)	
		Failure	2(25.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	4(10.8)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	
		Oswestry											
		Success	5(62.5)	1(50.0)	0(0.0)	0(0.0)	5(100.0)	26(68.4)	2(100.0)	5(83.3)	4(100.0)	2(100.0)	
		Failure	3(37.5)	1(50.0)	1(100.0)	0(0.0)	0(0.0)	12(31.6)	0(0.0)	1(16.7)	0(0.0)	0(0.0)	
		Neurological											
		Success	7(87.5)	0(0.0)	0(0.0)	0(0.0)	5(100.0)	32(86.5)	1(50.0)	6(100.0)	3(75.0)	1(50.0)	
		Failure	1(12.5)	2(100.0)	1(100.0)	0(0.0)	0(0.0)	5(13.5)	1(50.0)	0(0.0)	1(25.0)	1(50.0)	
		Overall Success											
		Success	3(37.5)	0(0.0)	0(0.0)	0(0.0)	4(100.0)	22(58.4)	1(33.3)	4(66.7)	3(75.0)	1(50.0)	
		Failure	5(62.5)	2(100.0)	1(100.0)	0(0.0)	0(0.0)	17(43.6)	2(66.7)	2(33.3)	1(25.0)	1(50.0)	

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* Investigators at those sites reported financial interests.

** P-values are from Fisher's exact test for comparing with-financial-interests with without-financial-interests.

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Table 40. Summary of Effectiveness Variables by Financial Interests of Investigators at 12 and 24 Months
[Number (%) of Patients]

Period	Treatment Group	Variable	Study Site									
			2322 (N=18)				2547 (N=18)		2597 (N=7)		2598 (N=4)	
			B* (N=12)	2323* (N=19)	2334 (N=12)	2472 (N=3)	A (N=2)	B* (N=16)	2574 (N=6)	A (N=5)	B* (N=2)	A (N=2)
24 Months	Investigational	Fusion										
		Success	5(83.3)	7(77.8)	6(100.0)	1(100.0)	1(100.0)	6(100.0)	4(100.0)	2(100.0)	0(0.0)	1(100.0)
		Failure	1(16.7)	2(22.2)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
		Oswestry										
		Success	5(83.3)	10(100.0)	4(66.7)	1(100.0)	1(100.0)	4(66.7)	4(100.0)	1(50.0)	0(0.0)	0(0.0)
		Failure	1(16.7)	0(0.0)	2(33.3)	0(0.0)	0(0.0)	2(33.3)	0(0.0)	1(50.0)	0(0.0)	1(100.0)
		Neurological										
		Success	6(100.0)	10(100.0)	6(100.0)	1(100.0)	0(0.0)	4(66.7)	4(100.0)	2(100.0)	0(0.0)	0(0.0)
		Failure	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(100.0)	2(33.3)	0(0.0)	0(0.0)	0(0.0)	1(100.0)
		Overall Success										
		Success	4(66.7)	7(77.8)	4(66.7)	1(100.0)	0(0.0)	3(50.0)	4(100.0)	1(50.0)	0(0.0)	0(0.0)
		Failure	2(33.3)	2(22.2)	2(33.3)	0(0.0)	1(100.0)	3(50.0)	0(0.0)	1(50.0)	0(0.0)	1(100.0)
	Control	Fusion										
		Success	6(100.0)	9(100.0)	4(100.0)	1(100.0)	0(0.0)	2(100.0)	2(100.0)	1(100.0)	2(100.0)	1(100.0)
		Failure	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
		Oswestry										
		Success	2(33.3)	8(88.9)	4(100.0)	1(100.0)	0(0.0)	1(25.0)	1(50.0)	1(100.0)	2(100.0)	1(100.0)
		Failure	4(66.7)	1(11.1)	0(0.0)	0(0.0)	0(0.0)	3(75.0)	1(50.0)	0(0.0)	0(0.0)	0(0.0)
		Neurological										
		Success	4(66.7)	7(77.8)	4(100.0)	1(100.0)	0(0.0)	4(80.0)	1(50.0)	1(100.0)	2(100.0)	1(100.0)
		Failure	2(33.3)	2(22.2)	0(0.0)	0(0.0)	0(0.0)	1(20.0)	1(50.0)	0(0.0)	0(0.0)	0(0.0)
		Overall Success										
		Success	2(33.3)	7(77.8)	4(100.0)	1(100.0)	0(0.0)	0(0.0)	1(50.0)	1(100.0)	2(100.0)	1(100.0)
		Failure	4(66.7)	2(22.2)	0(0.0)	0(0.0)	0(0.0)	4(100.0)	1(50.0)	0(0.0)	0(0.0)	0(0.0)

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* Investigators at those sites reported financial interests.

** P-values are from Fisher's exact test for comparing with-financial-interests with without-financial-interests.

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Table 40. Summary of Effectiveness Variables by Financial Interests of Investigators at 12 and 24 Months
(Number (%) of Patients)

Period	Treatment Group	Variable	Study Site						Total (N=463)		p-value **		
			2598 (N=4)	2716 (N=8)	2788 (N=7)			3221 (N=11)	3304* (N=14)	With Interests (N=251)		Without Interests (N=212)	
			B* (N=2)	A (N=5)	B* (N=3)	A (N=1)	B* (N=6)						
24 Months	Investigational	Fusion											
		Success	1(100.0)	2(100.0)	1(100.0)	1(100.0)	3(100.0)	3(100.0)	6(100.0)	103(96.3)	83(95.4)	1.000	
		Failure	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	4(3.7)	4(4.6)		
		Oswestry											
		Success	1(100.0)	3(100.0)	1(100.0)	1(100.0)	2(66.7)	4(100.0)	2(28.6)	80(70.8)	72(75.8)	0.437	
		Failure	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(33.3)	0(0.0)	5(71.4)	33(29.2)	23(24.2)		
		Neurological											
		Success	1(100.0)	3(100.0)	1(100.0)	0(0.0)	0(0.0)	4(100.0)	6(85.7)	102(90.3)	78(83.0)	0.148	
		Failure	0(0.0)	0(0.0)	0(0.0)	1(100.0)	3(100.0)	0(0.0)	1(14.3)	11(9.7)	16(17.0)		
		Overall Success	1(100.0)	2(100.0)	1(100.0)	0(0.0)	0(0.0)	3(100.0)	2(28.6)	67(60.4)	54(60.7)	1.000	
		Failure	0(0.0)	0(0.0)	0(0.0)	1(100.0)	3(100.0)	0(0.0)	5(71.4)	44(39.6)	35(39.3)		
	Control	Fusion											
		Success	1(100.0)	1(100.0)	0(0.0)	0(0.0)	0(0.0)	1(50.0)	5(83.3)	87(88.8)	64(90.1)	1.000	
		Failure	0(0.0)	0(0.0)	1(100.0)	0(0.0)	1(100.0)	1(50.0)	1(16.7)	11(11.2)	7(9.9)		
		Oswestry											
		Success	1(100.0)	1(100.0)	0(0.0)	0(0.0)	2(100.0)	2(66.7)	4(57.1)	75(70.8)	58(75.3)	0.508	
		Failure	0(0.0)	0(0.0)	2(100.0)	0(0.0)	0(0.0)	1(33.3)	3(42.9)	31(29.2)	19(24.7)		
		Neurological											
		Success	1(100.0)	1(100.0)	2(100.0)	0(0.0)	0(0.0)	3(100.0)	6(85.7)	90(84.9)	64(83.1)	0.838	
		Failure	0(0.0)	0(0.0)	0(0.0)	0(0.0)	2(100.0)	0(0.0)	1(14.3)	16(15.1)	13(16.9)		
		Overall Success	1(100.0)	1(100.0)	0(0.0)	0(0.0)	0(0.0)	1(33.3)	2(28.6)	57(54.3)	44(57.1)	0.763	
		Failure	0(0.0)	0(0.0)	2(100.0)	0(0.0)	2(100.0)	2(66.7)	5(71.4)	48(45.7)	33(42.9)		

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* Investigators at those sites reported financial interests.

** P-values are from Fisher's exact test for comparing with-financial-interests with without-financial-interests.

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Pivotal Study with the rhBMP-2/CRM/CD HORIZON® SPINAL SYSTEM
Bayesian Analyses for Surgery Data

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Results from Bayesian Analyses for Comparisons of
Surgery Data
between Investigational Device and Control Device Groups

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Pivotal Study with the rhBMP-2/CRM/CD HORIZON® SPINAL SYSTEM Bayesian Analyses for Surgery Data

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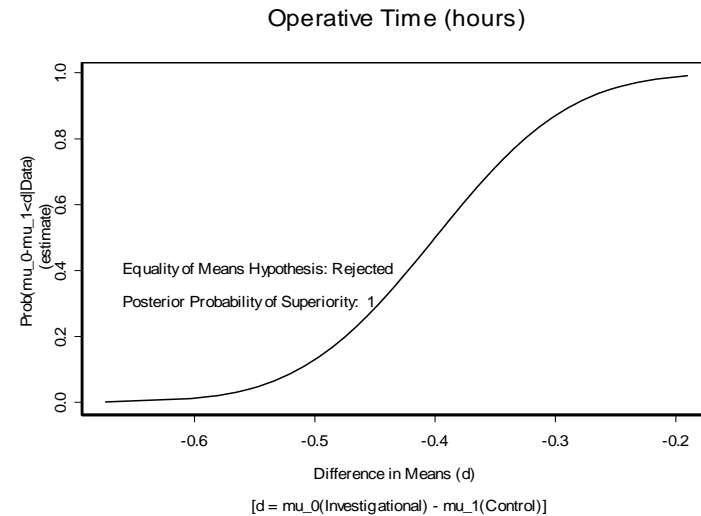
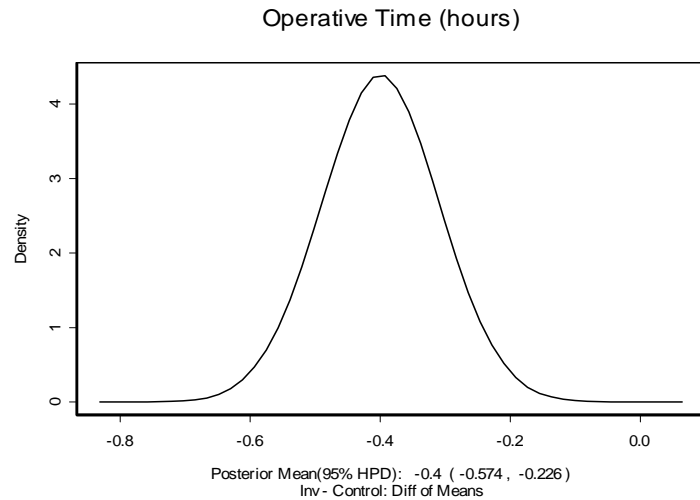
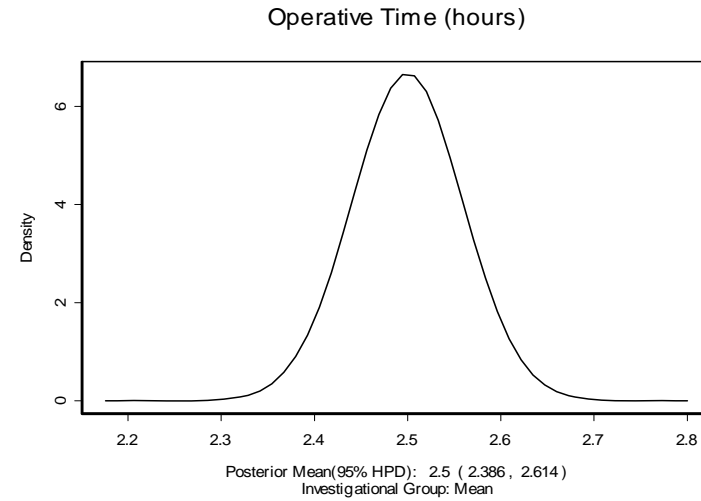
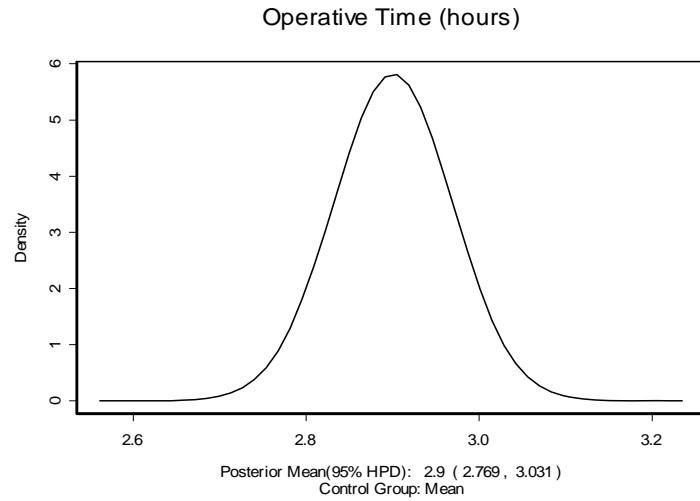
Summary of 95% Highest Posterior Density (HPD) Intervals of Surgery Data

Variable	Null Hypothesis Accepted	Probability of Superiority (%)	95% HPD								
			μ_0 (Control)			μ_1 (Investigational)			$\mu_1 - \mu_0$		
			Mean	Lower	Upper	Mean	Lower	Upper	Mean	Lower	Upper
Operative Time (hours)	Rejected	~100.0	2.900	2.769	3.031	2.500	2.386	2.614	-0.400	-0.574	-0.226
Blood Loss (mls)	Rejected	~100.0	448.6	409.1	488.1	343.1	309.6	376.6	-105.5	-157.3	-53.7
Hospital Stay (days)	Accepted	30.5	4.00	3.75	4.25	4.10	3.81	4.39	0.10	-0.28	0.48

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Pivotal Study with the rhBMP-2/CRM/CD HORIZON® SPINAL SYSTEM Bayesian Analyses for Surgery Data

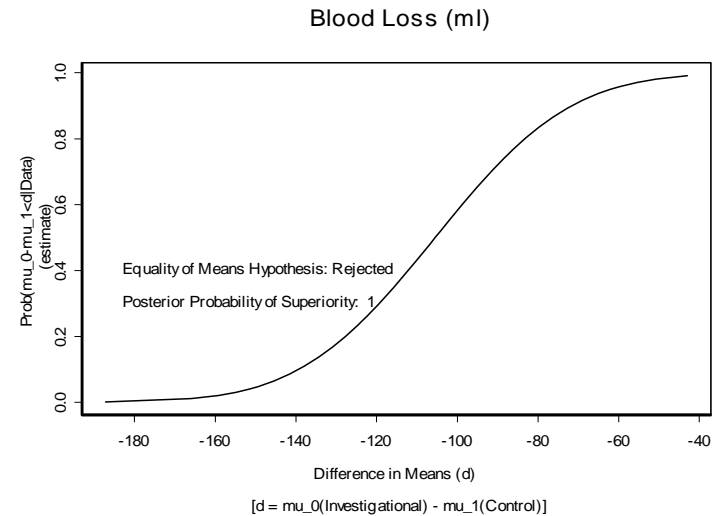
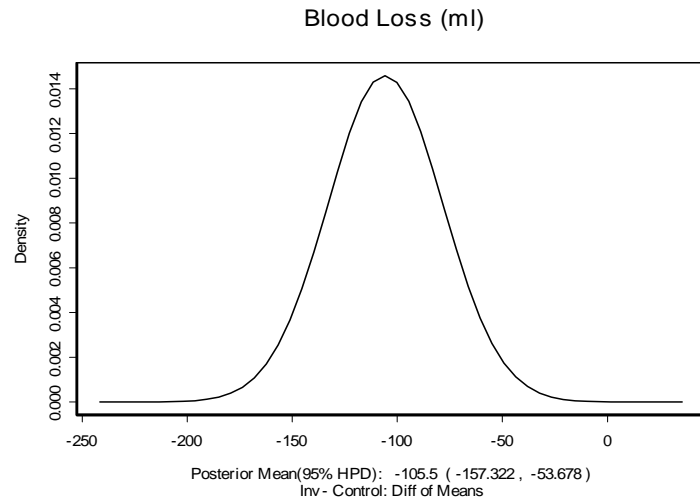
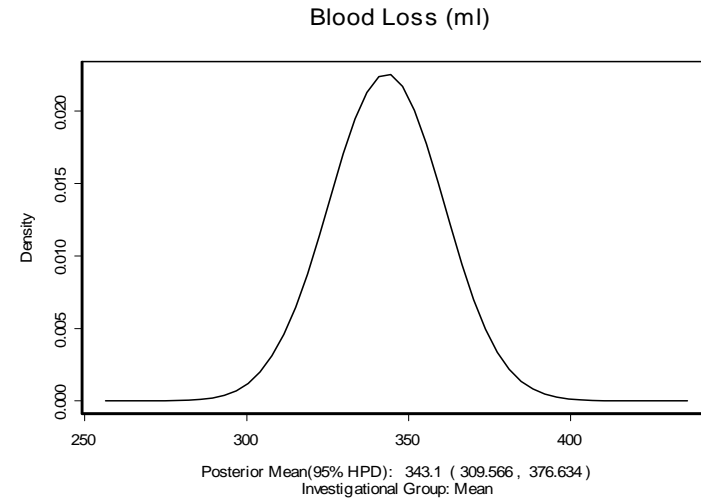
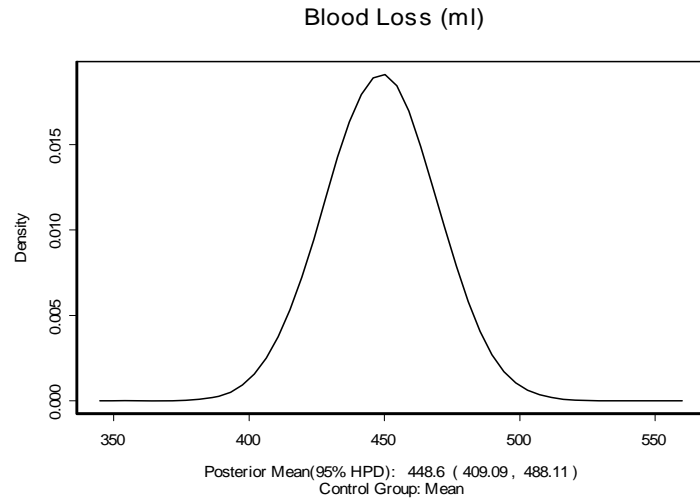
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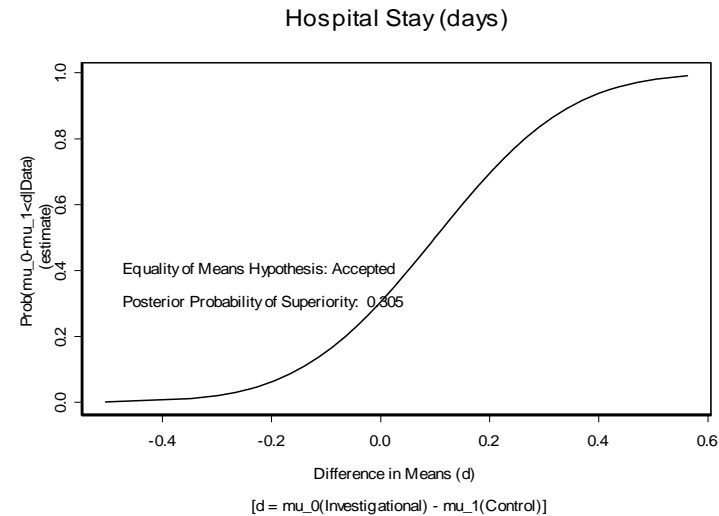
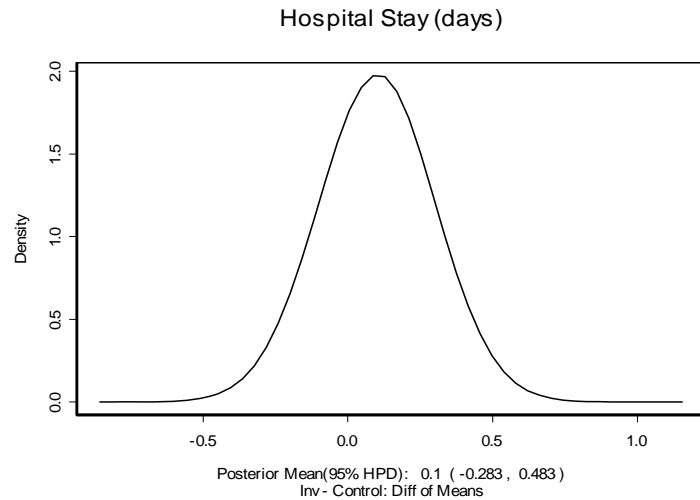
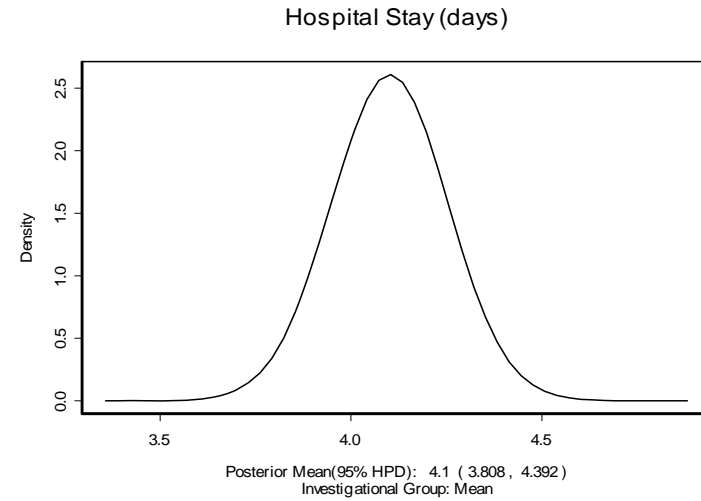
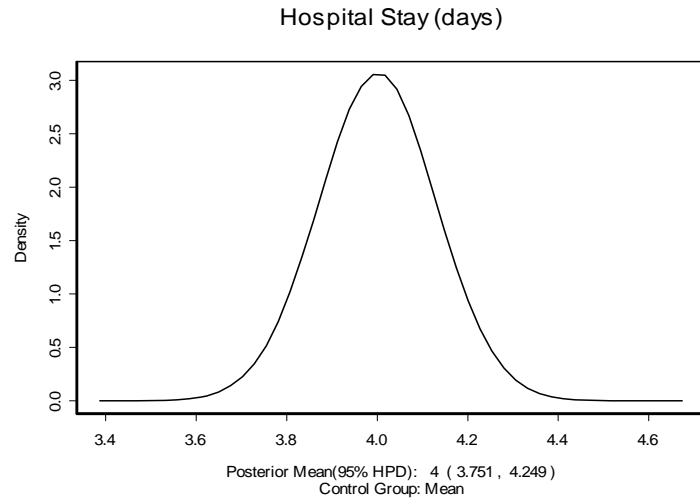
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Pivotal Study with the rhBMP-2/CRM/CD HORIZON® SPINAL SYSTEM Bayesian Analyses for Surgery Data

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Pivotal Study with the rhBMP-2/CRM/CD HORIZON® SPINAL SYSTEM
Bayesian Analyses for Adverse Events

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Results from Bayesian Analyses for Comparisons of
Adverse Events
between Investigational Device and Control Device Groups

[Evaluations up to the 24-Month Visit]

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Pivotal Study with the rhBMP-2/CRM/CD HORIZON® SPINAL SYSTEM

Bayesian Analyses for Adverse Events

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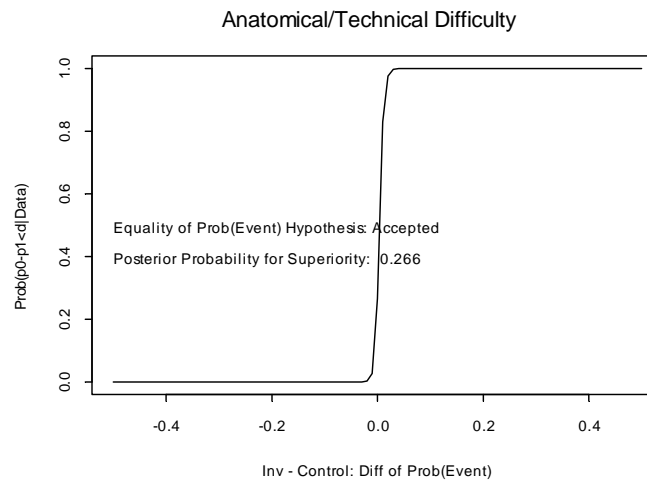
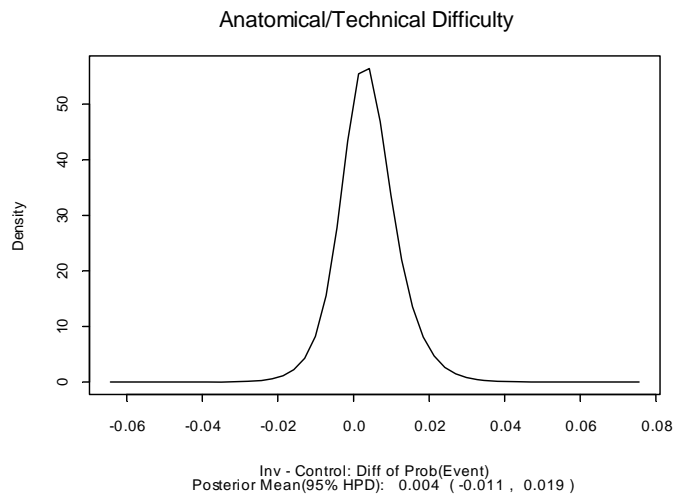
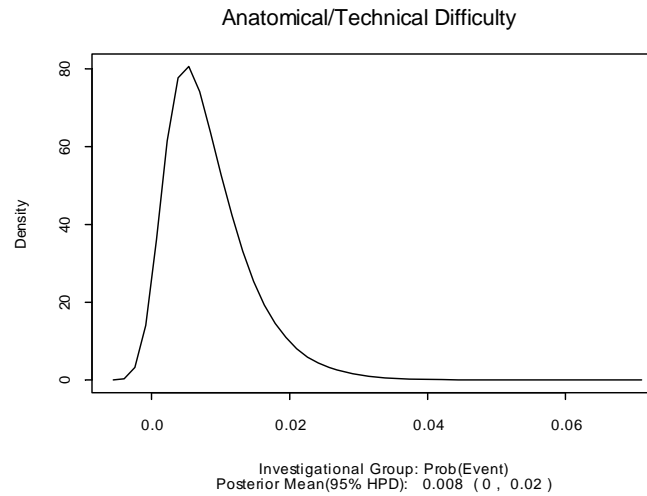
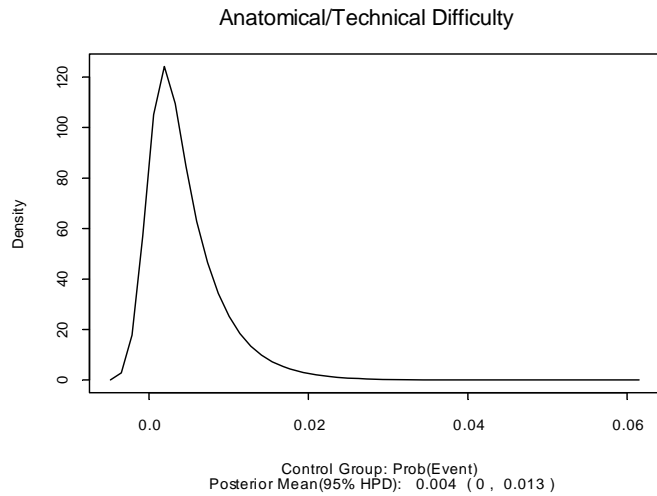
Summary of 95% Highest Posterior Density (HPD) Intervals of Adverse Events

Event	Null Hypothesis Accepted	Probability of Superiority (%)	95% HPD								
			p0 (Control)			p1 (Investigational)			p1 - p0		
			Mean	Lower	Upper	Mean	Lower	Upper	Mean	Lower	Upper
Anatomical/ Technical Difficulty	Accepted	26.6	0.004	0.000	0.013	0.008	0.000	0.020	0.004	-0.011	0.019
Arthritis/Bursitis	Accepted	20.2	0.080	0.046	0.115	0.010	0.063	0.138	0.020	-0.031	0.072
Back and/or Leg Pain	Accepted	18.1	0.398	0.335	0.462	0.440	0.377	0.502	0.042	-0.047	0.132
Cancer	Accepted	2.4	0.013	0.001	0.028	0.041	0.018	0.067	0.028	-0.001	0.058
Cardiovascular	Accepted	68.9	0.243	0.188	0.299	0.224	0.172	0.278	-0.019	-0.097	0.056
Carpal Tunnel Syndrome	Accepted	26.5	0.031	0.010	0.053	0.041	0.019	0.067	0.011	-0.023	0.045
Death	Accepted	67.3	0.022	0.005	0.042	0.017	0.003	0.033	-0.006	-0.032	0.020
Dural Injury	Accepted	82.0	0.084	0.049	0.120	0.062	0.033	0.093	-0.022	-0.070	0.042
Gastrointestinal	Accepted	41.3	0.150	0.106	0.199	0.158	0.112	0.204	0.007	-0.057	0.073
Graft Site Related	Rejected	~100.0	0.080	0.045	0.115	0.004	0.000	0.012	-0.075	-0.112	-0.040
Implant Displacement/Loosening	Accepted	71.2	0.013	0.001	0.028	0.008	0.000	0.020	-0.005	-0.025	0.014
Infection	Accepted	85.3	0.204	0.152	0.257	0.166	0.120	0.213	-0.038	-0.107	0.033
Malpositioned Implant	Accepted	16.5	0.013	0.001	0.028	0.025	0.008	0.045	0.012	-0.013	0.037
Neurological	Accepted	27.6	0.270	0.212	0.327	0.295	0.237	0.351	0.025	-0.057	0.106
Non-Union	Rejected	99.6	0.115	0.075	0.157	0.050	0.024	0.078	-0.065	-0.114	-0.015
Other	Accepted	35.2	0.279	0.220	0.336	0.295	0.239	0.353	0.016	-0.065	0.098
Other Pain	Accepted	60.5	0.133	0.090	0.177	0.124	0.084	0.166	-0.008	-0.054	0.054
Respiratory	Accepted	27.9	0.058	0.029	0.089	0.071	0.040	0.103	0.013	-0.031	0.058
Spinal Event	Accepted	70.8	0.088	0.053	0.126	0.075	0.043	0.108	-0.014	-0.063	0.026
Trauma	Accepted	27.3	0.265	0.209	0.325	0.290	0.233	0.347	0.025	-0.057	0.105
Urogenital	Accepted	25.3	0.097	0.060	0.136	0.116	0.077	0.157	0.019	-0.038	0.074
Vertebral Fracture	Accepted	67.3	0.022	0.006	0.041	0.017	0.003	0.033	-0.006	-0.031	0.020
Any Adverse Event	Accepted	56.2	0.876	0.832	0.917	0.871	0.828	0.912	-0.005	-0.065	0.055

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Pivotal Study with the rhBMP-2/CRM/CD HORIZON® SPINAL SYSTEM Bayesian Analyses for Adverse Events

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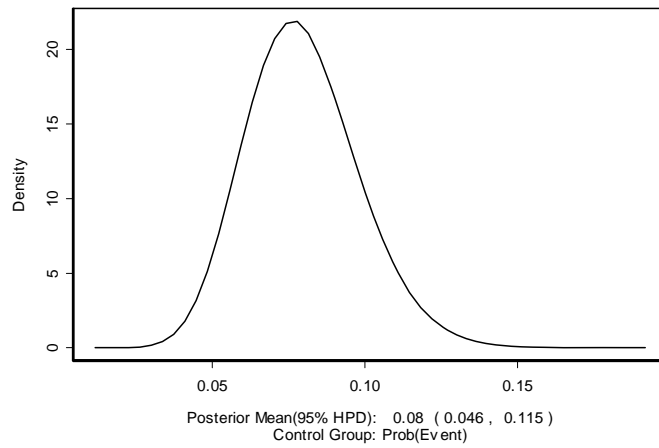


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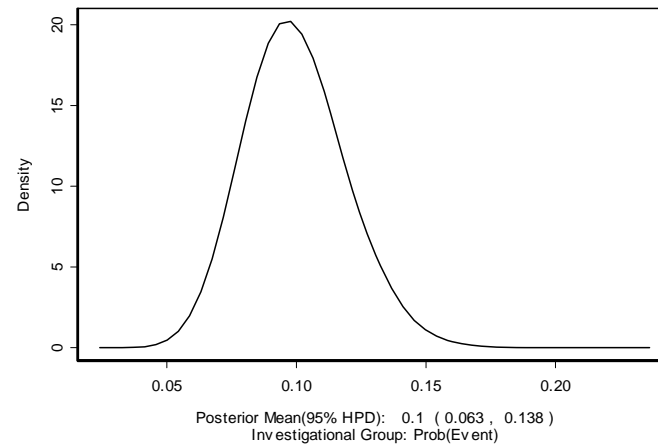
Pivotal Study with the rhBMP-2/CRM/CD HORIZON® SPINAL SYSTEM Bayesian Analyses for Adverse Events

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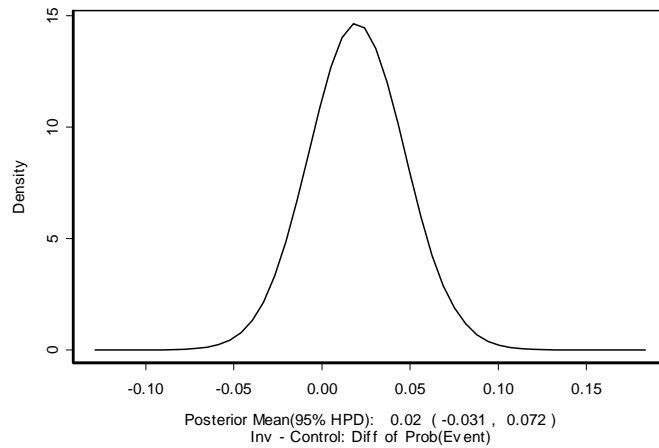
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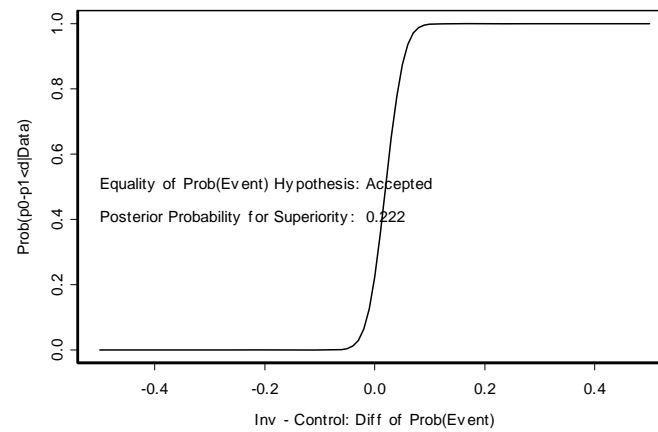
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Arthritis/Bursitis



Arthritis/Bursitis



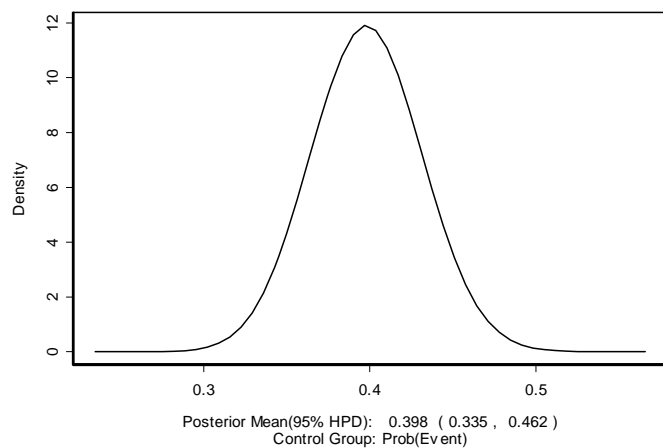
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Pivotal Study with the rhBMP-2/CRM/CD HORIZON® SPINAL SYSTEM

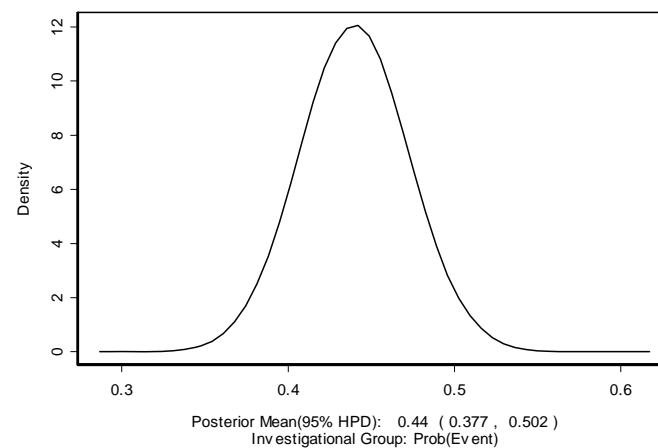
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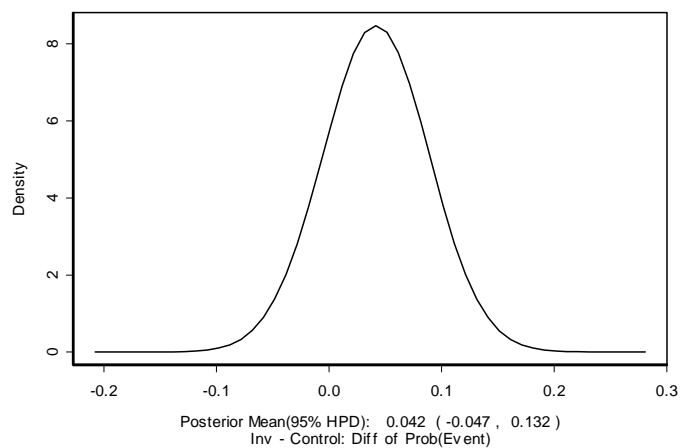
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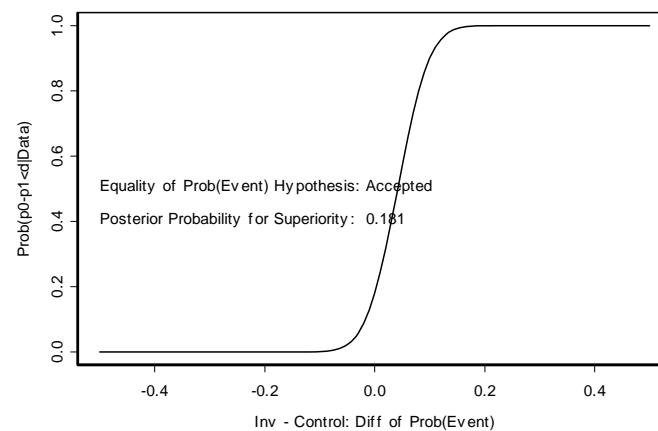
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Back and/or Leg Pain



Back and/or Leg Pain

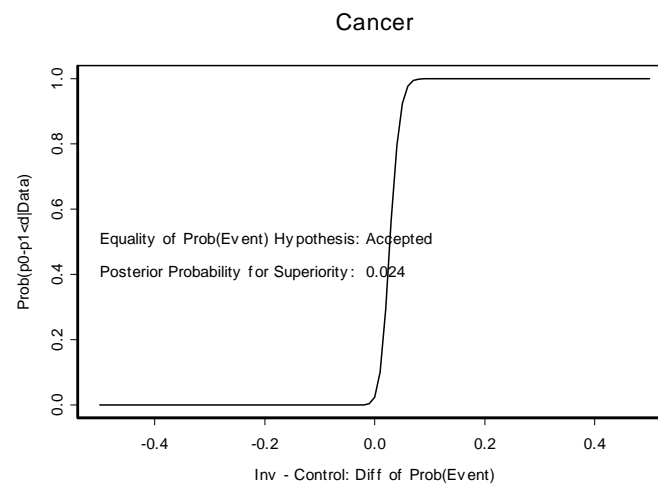
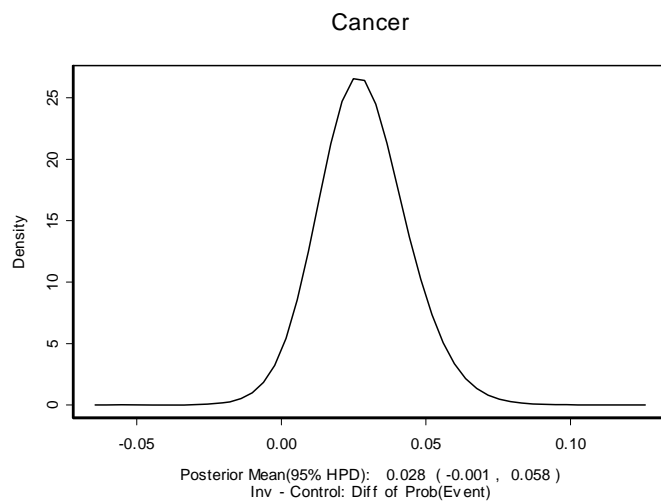
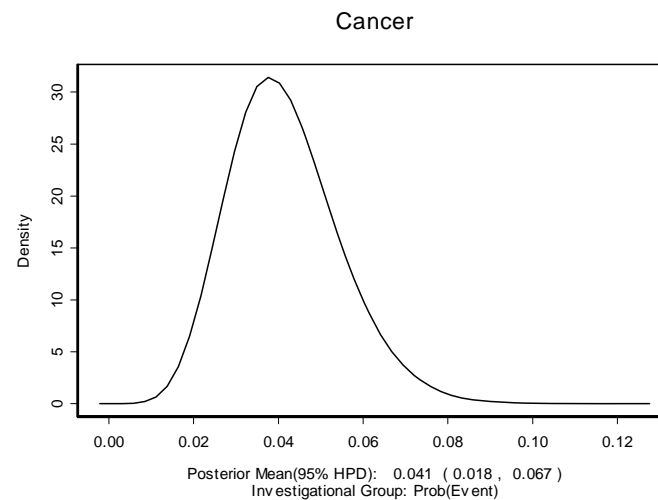
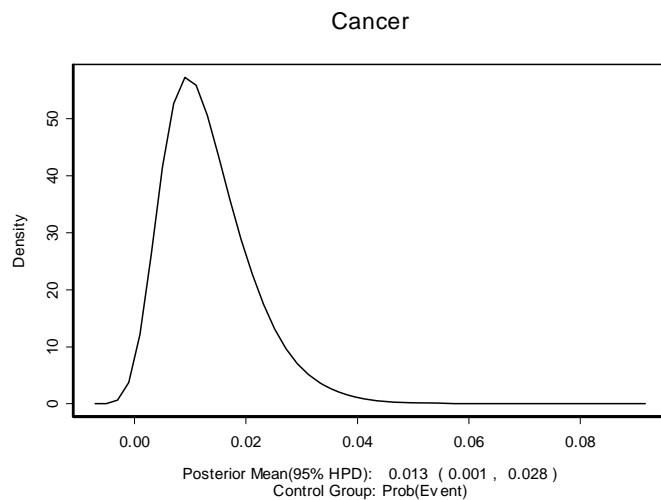


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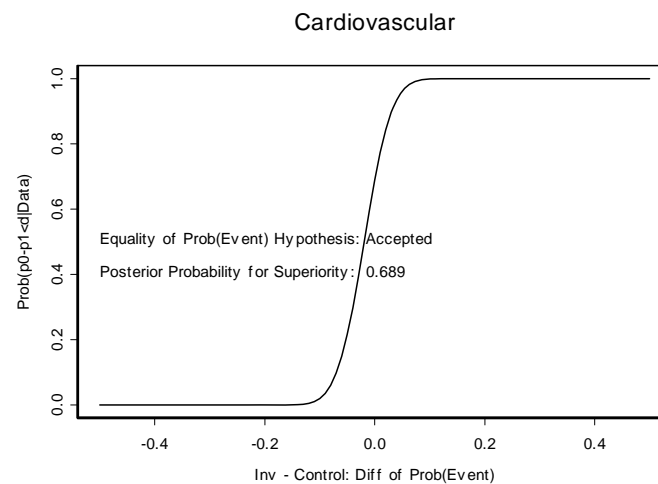
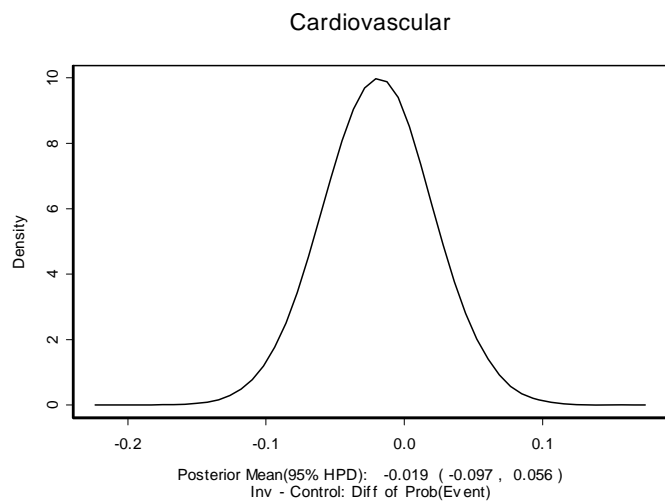
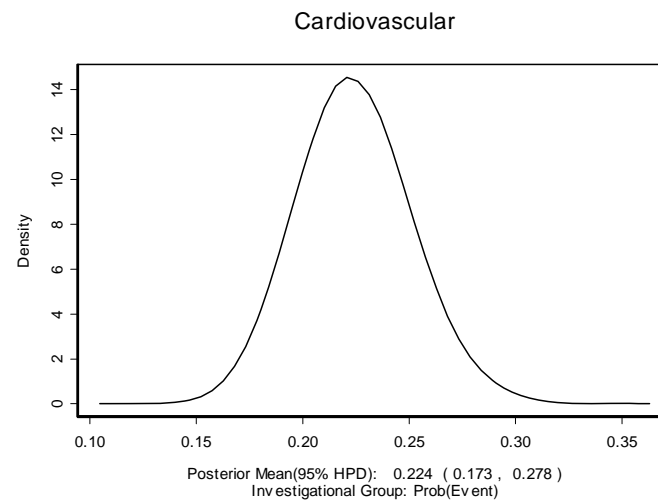
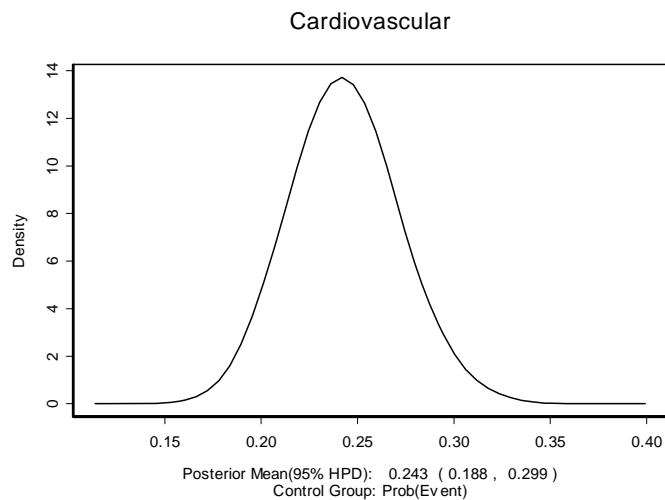


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Pivotal Study with the rhBMP-2/CRM/CD HORIZON® SPINAL SYSTEM

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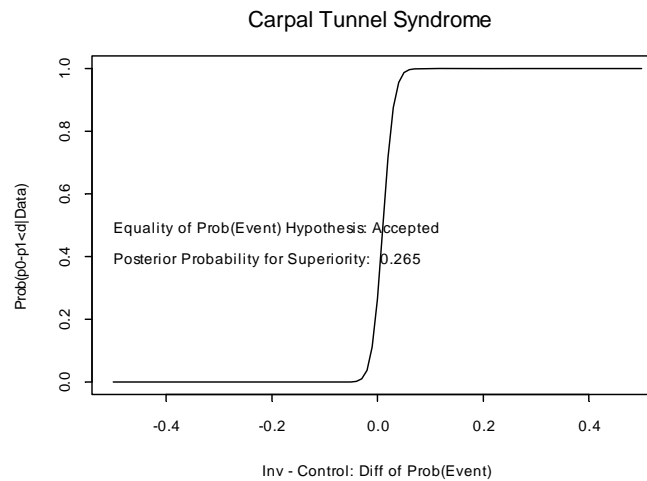
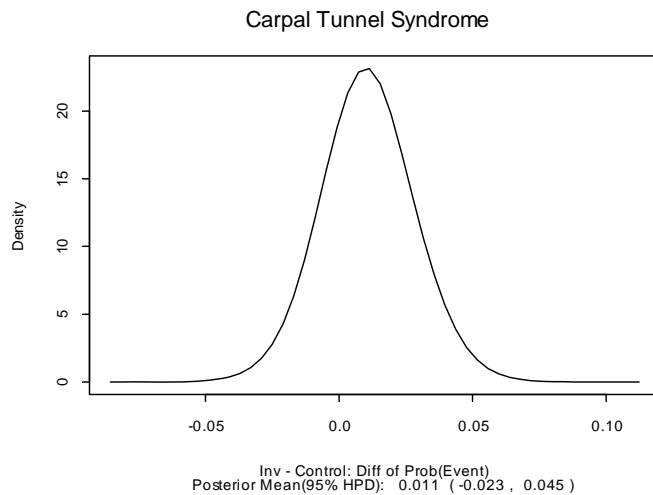
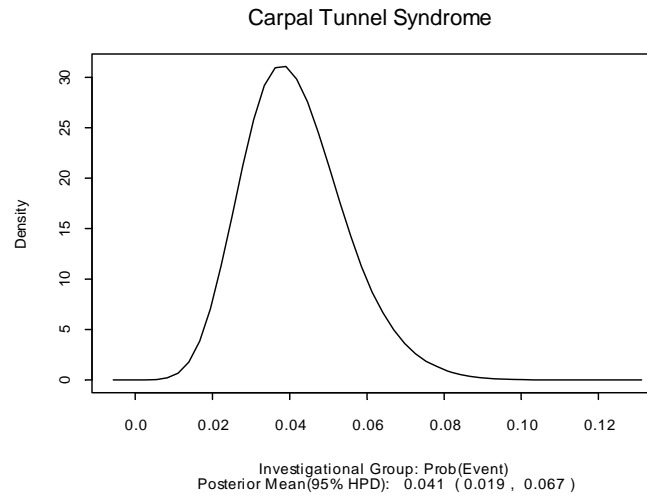
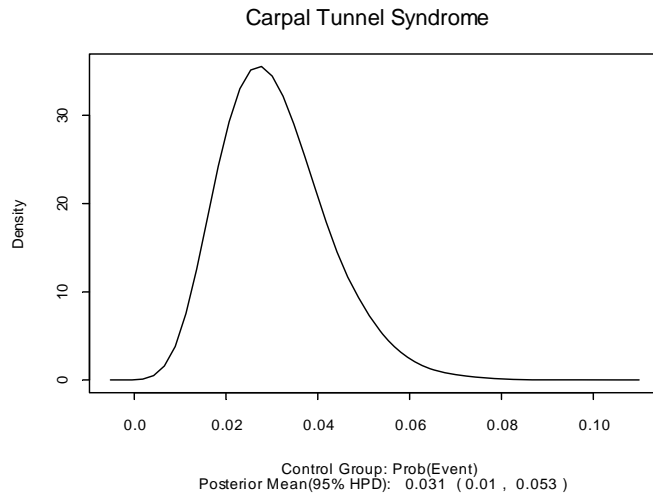
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Pivotal Study with the rhBMP-2/CRM/CD HORIZON® SPINAL SYSTEM Bayesian Analyses for Adverse Events

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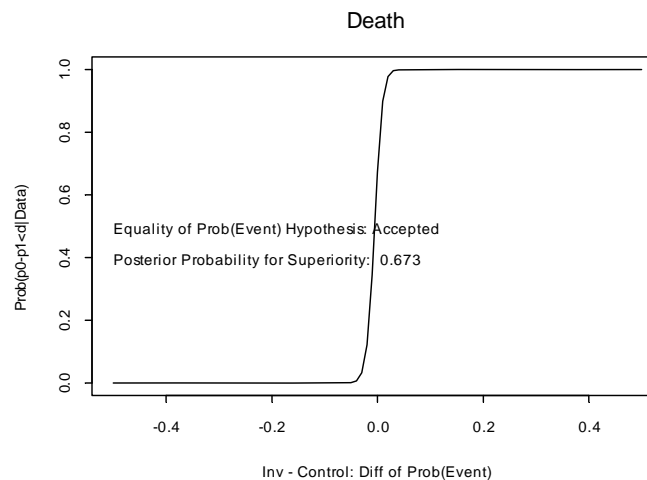
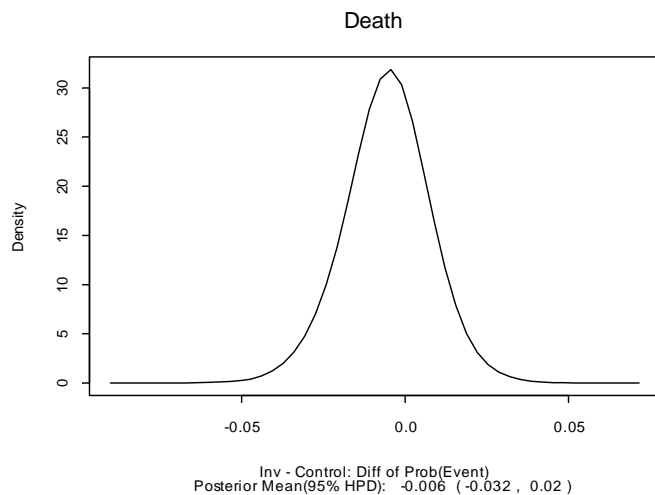
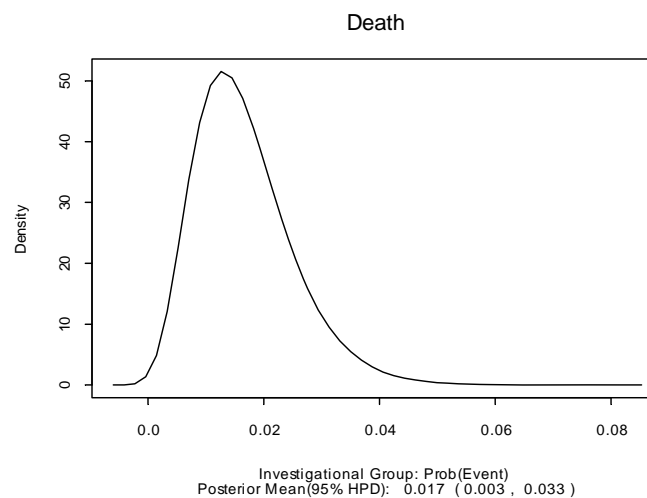
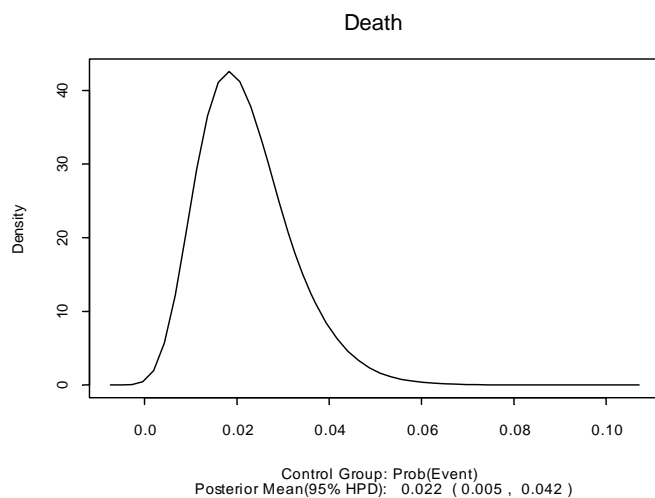


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Pivotal Study with the rhBMP-2/CRM/CD HORIZON® SPINAL SYSTEM

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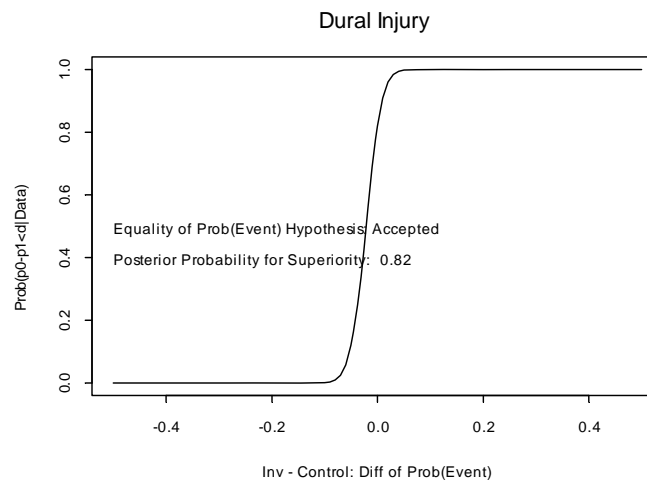
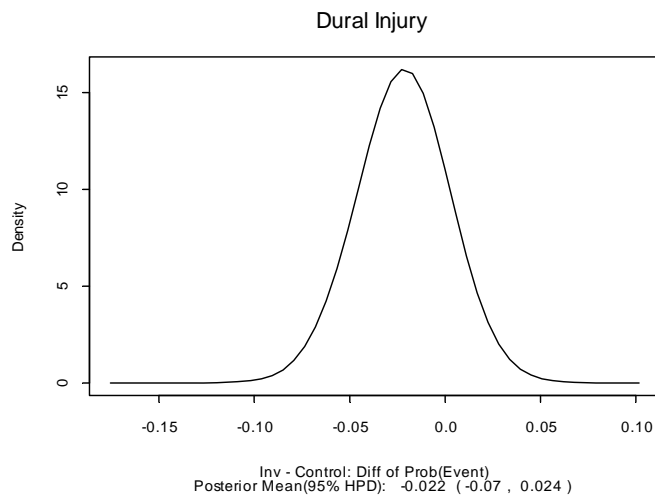
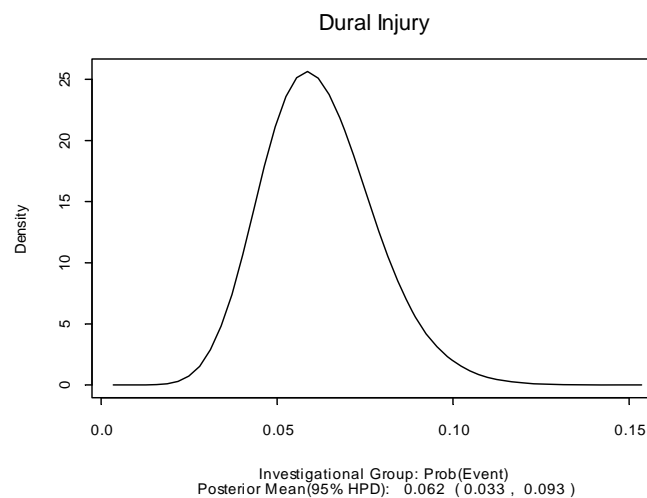
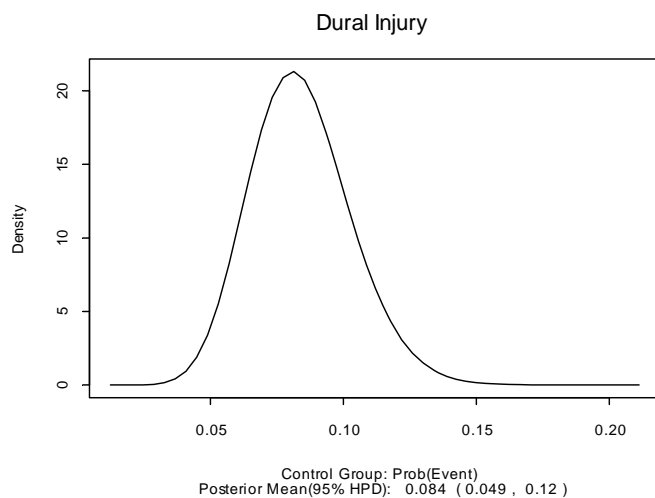


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Pivotal Study with the rhBMP-2/CRM/CD HORIZON® SPINAL SYSTEM

Bayesian Analyses for Adverse Events

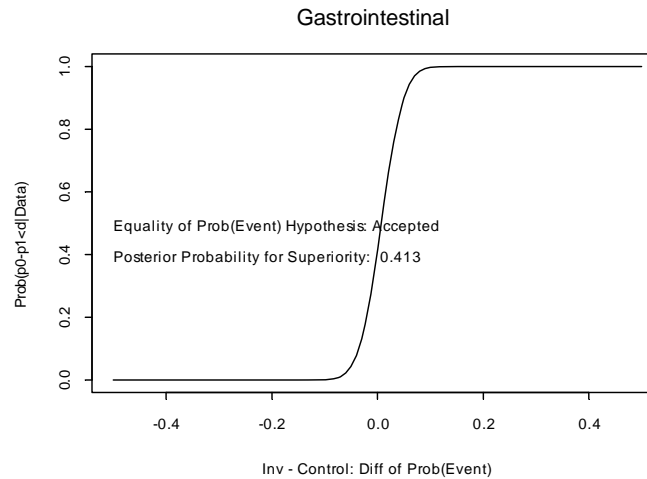
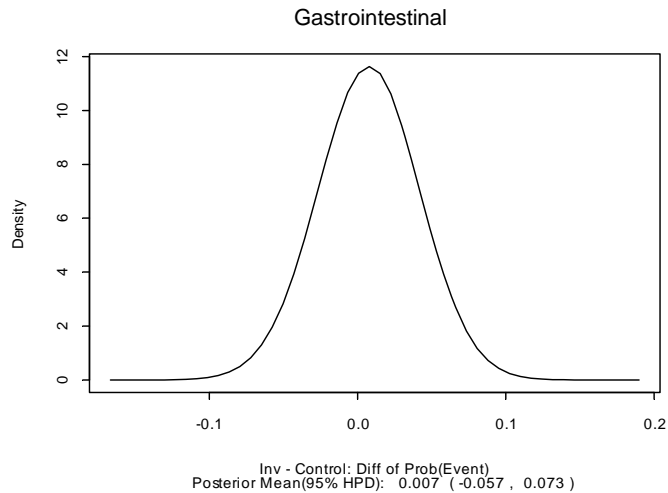
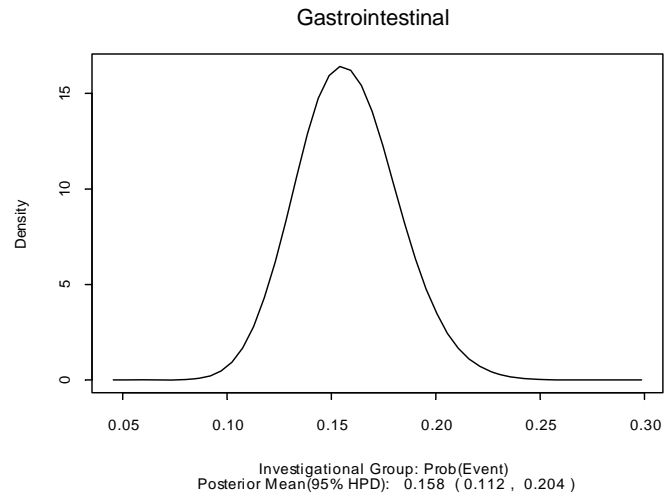
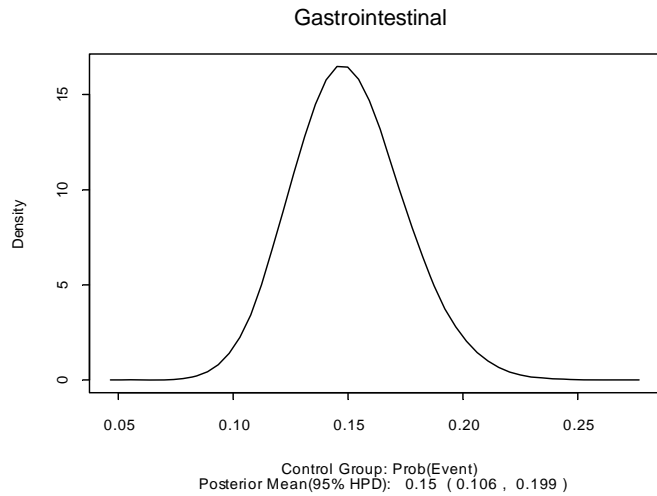
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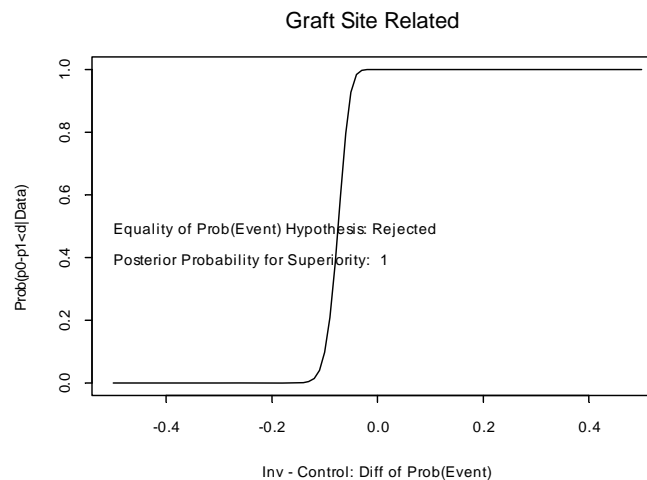
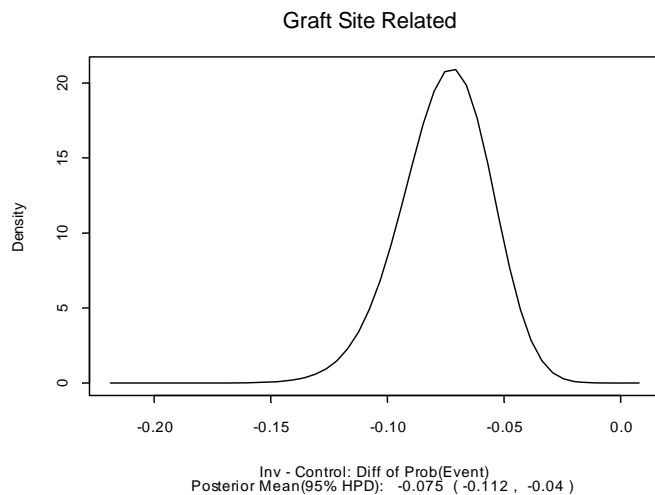
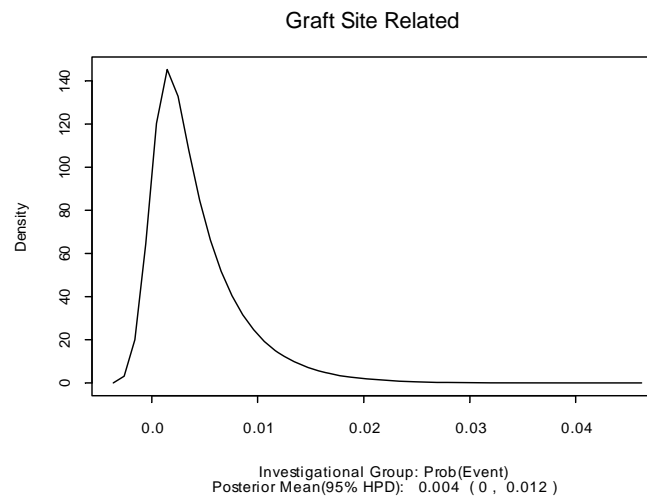
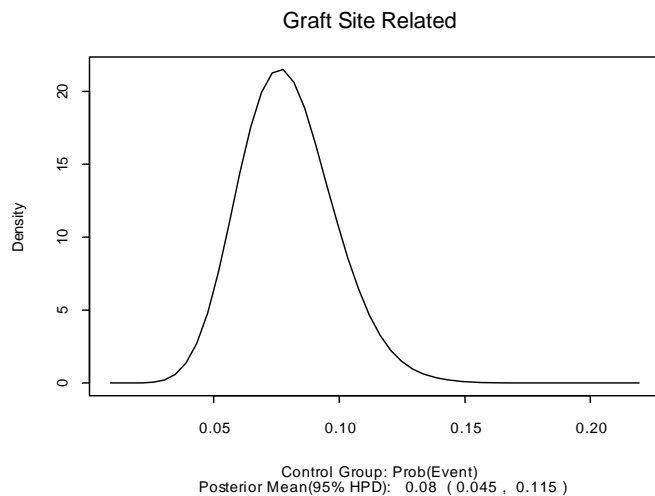


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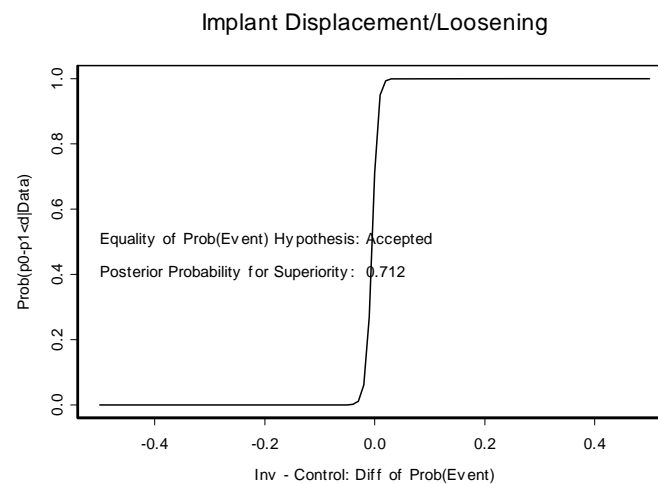
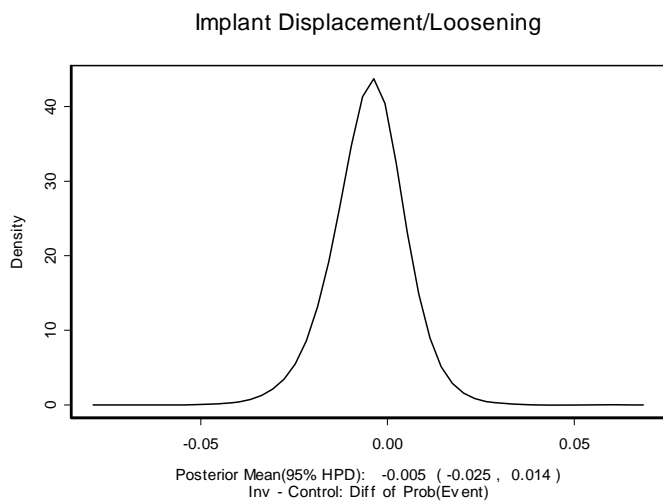
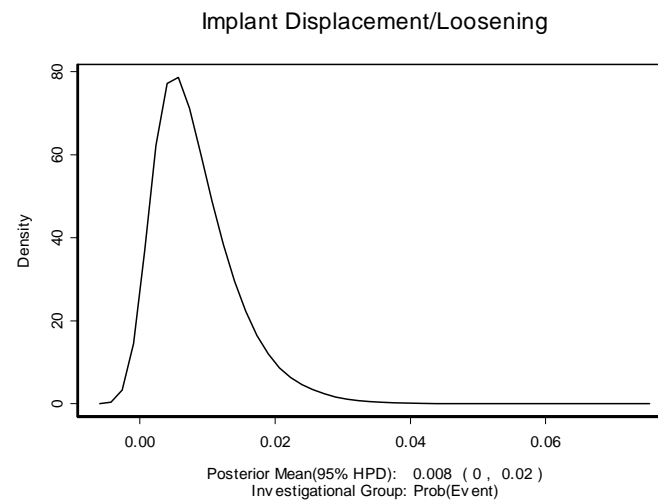
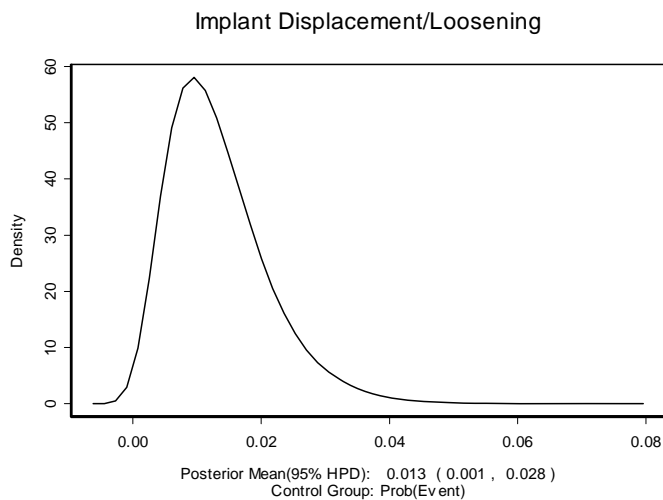


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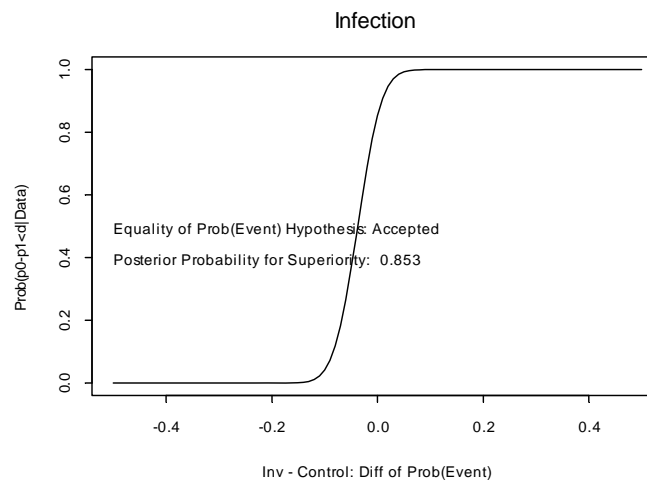
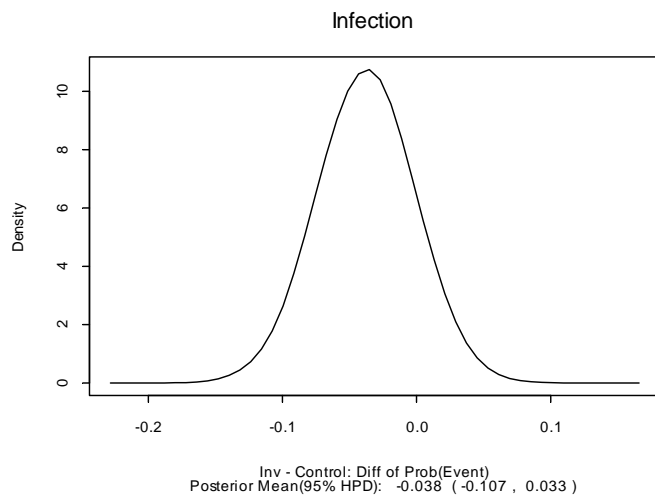
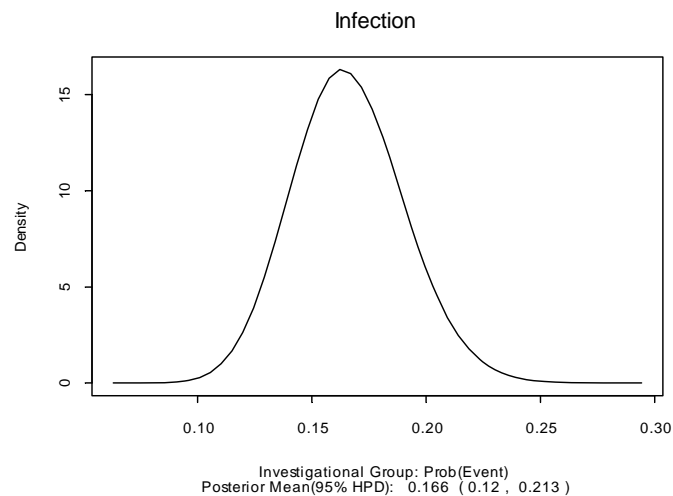
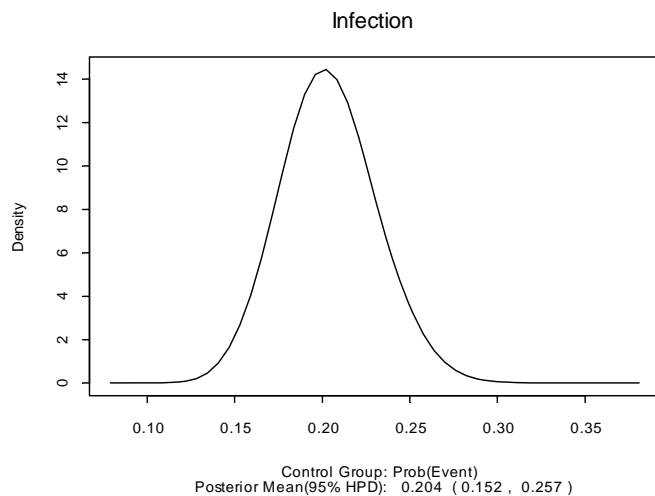


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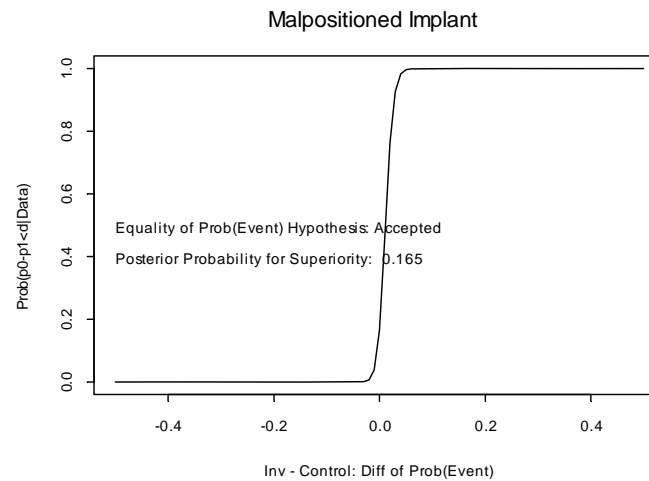
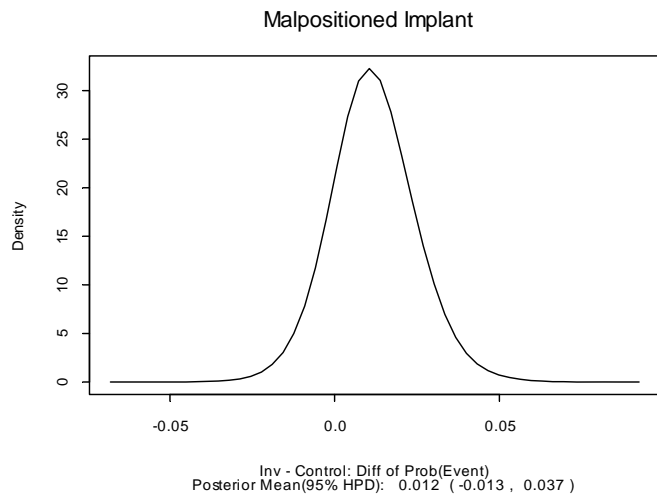
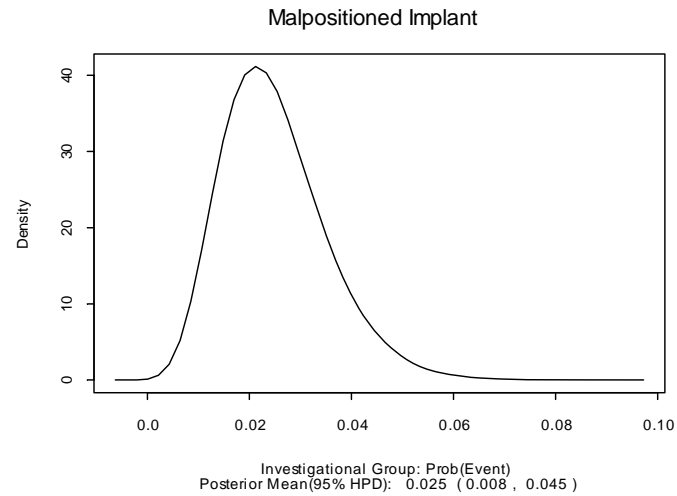
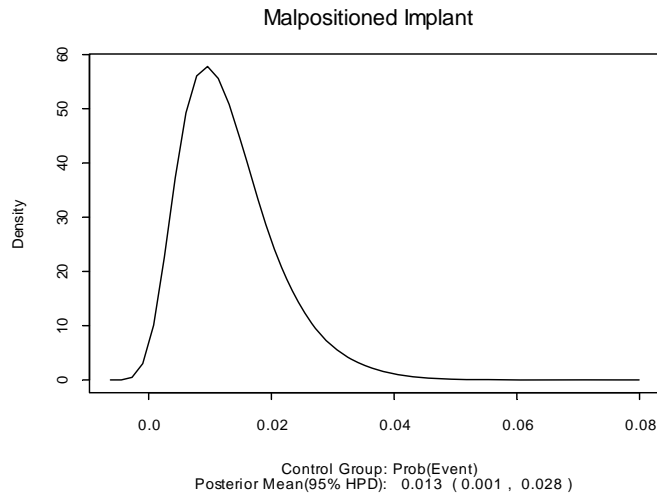
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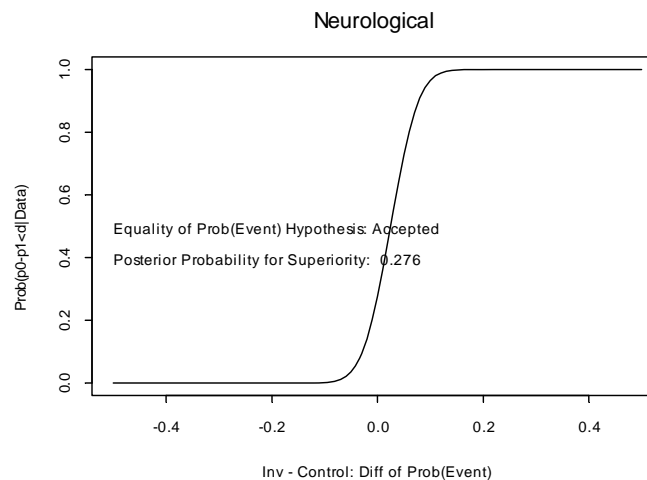
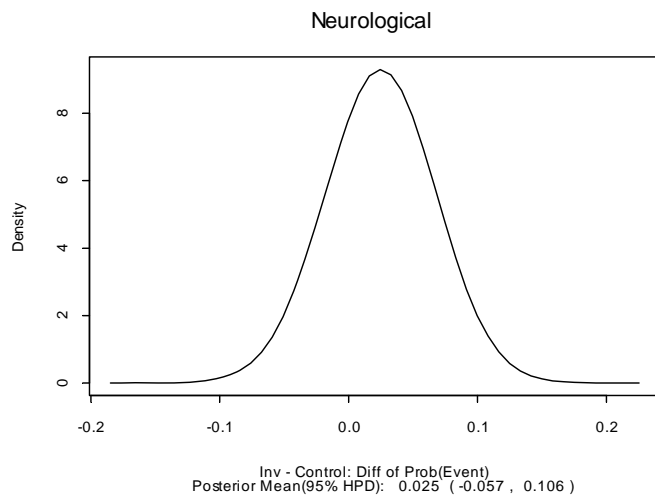
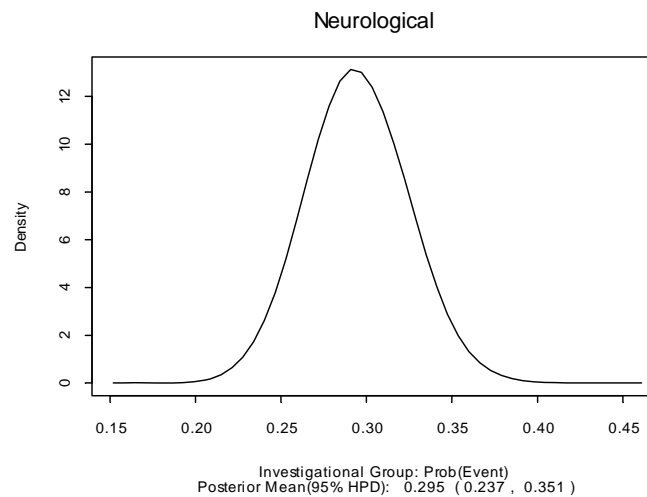
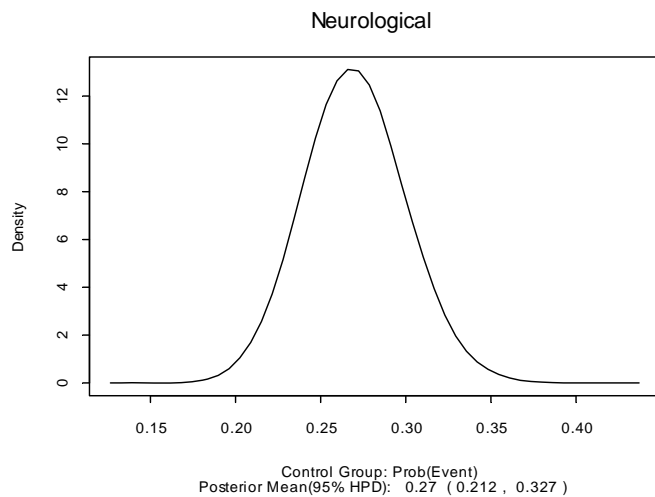


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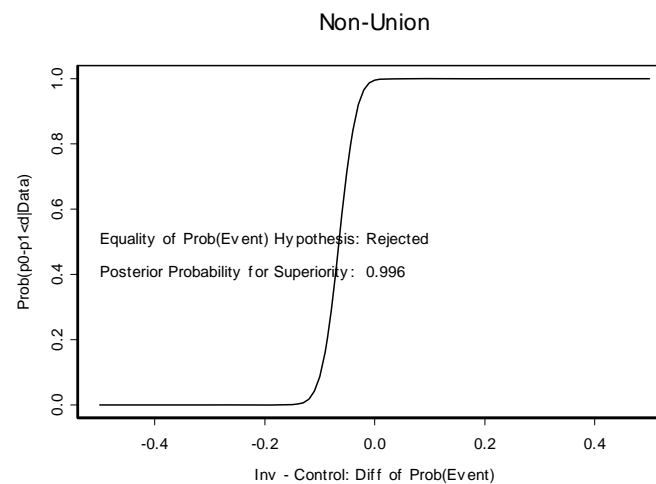
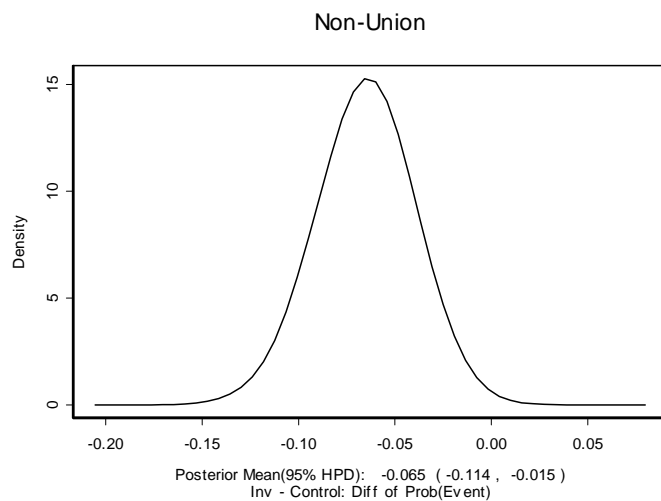
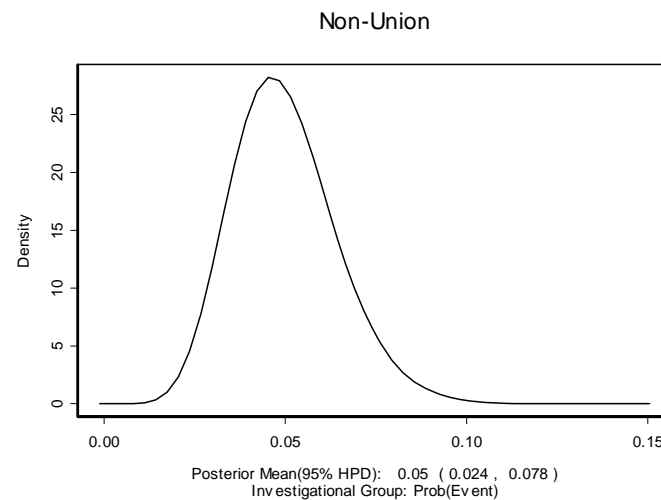
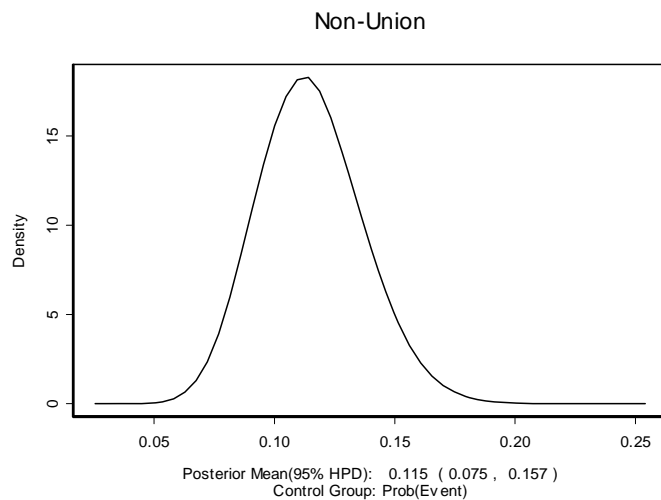


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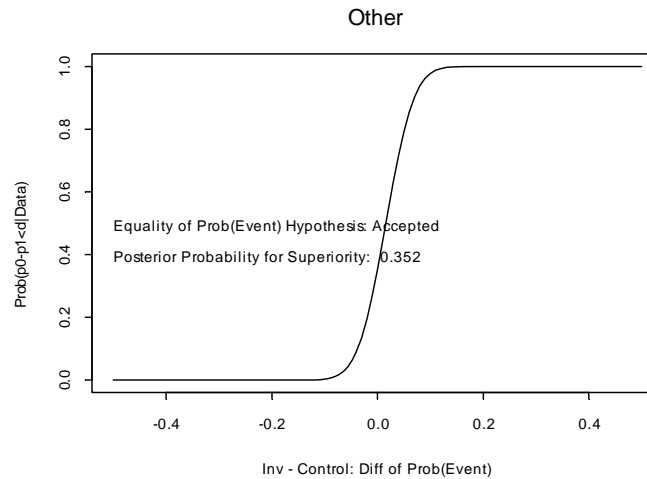
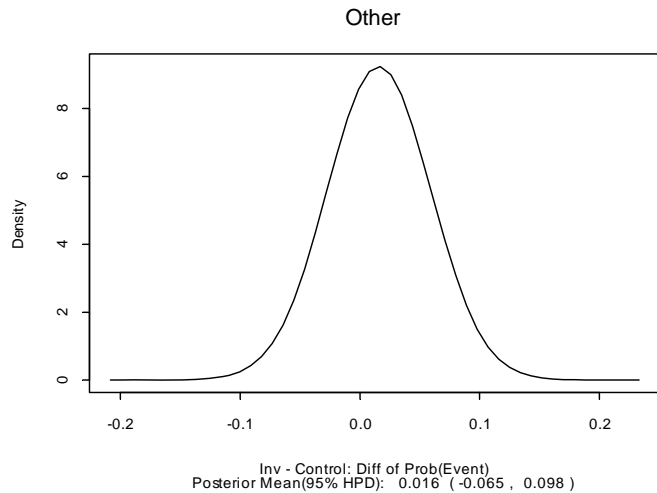
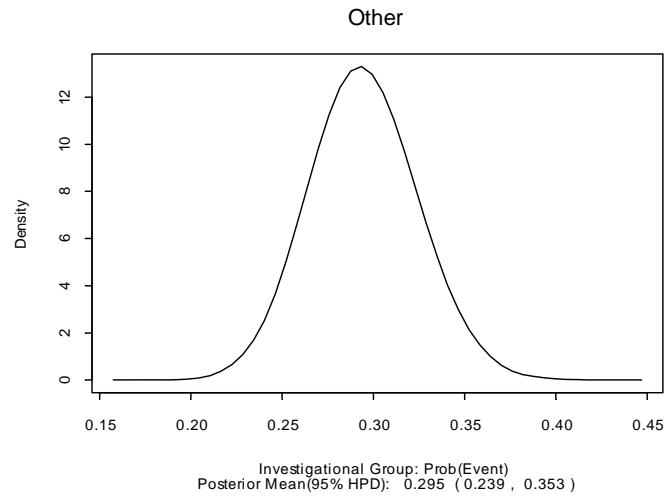
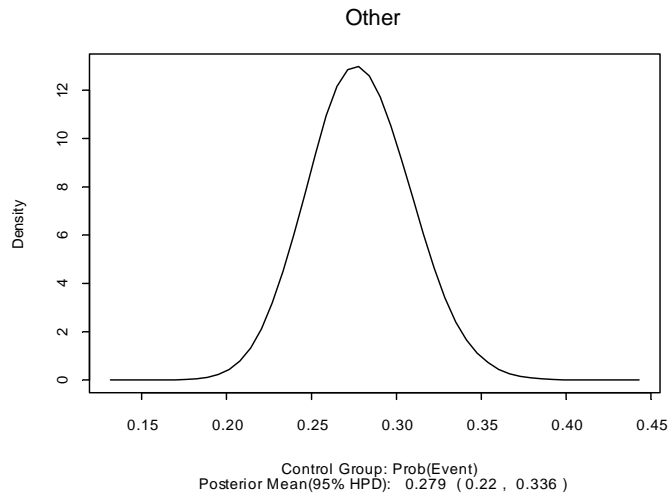
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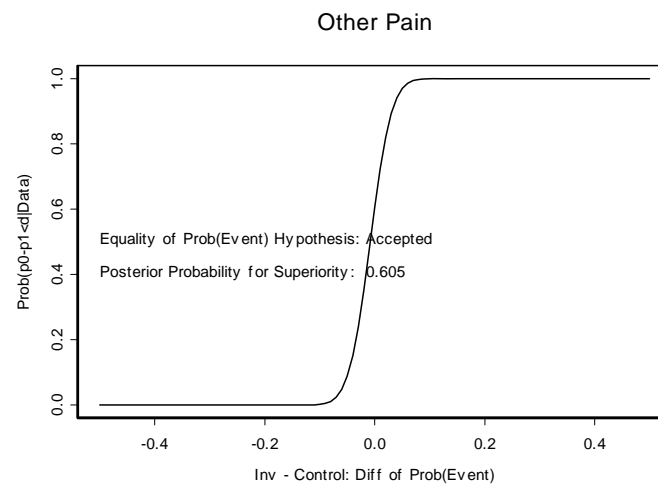
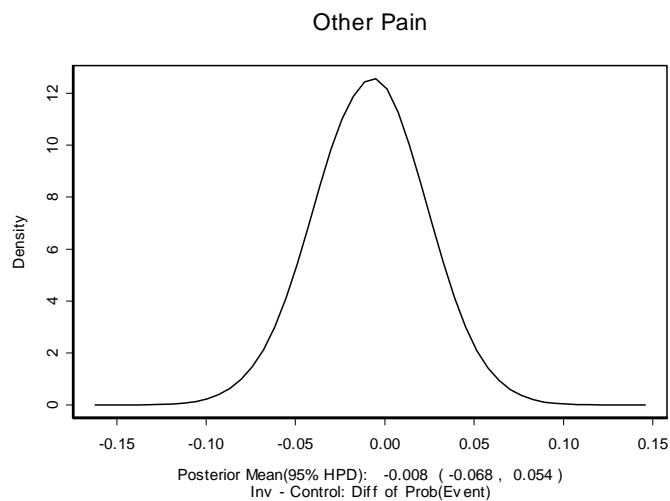
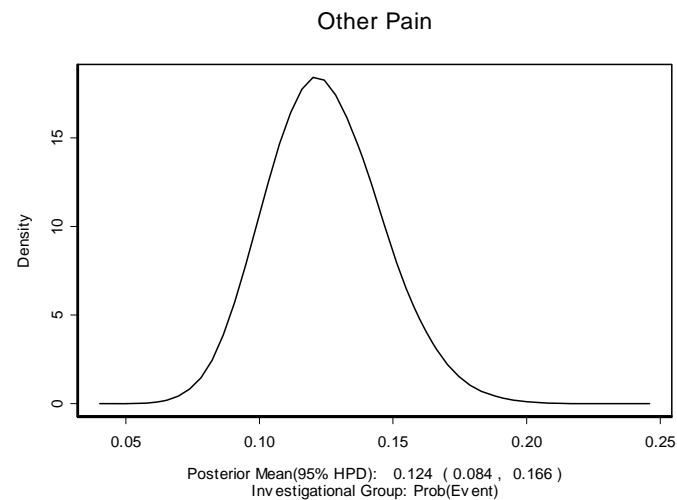
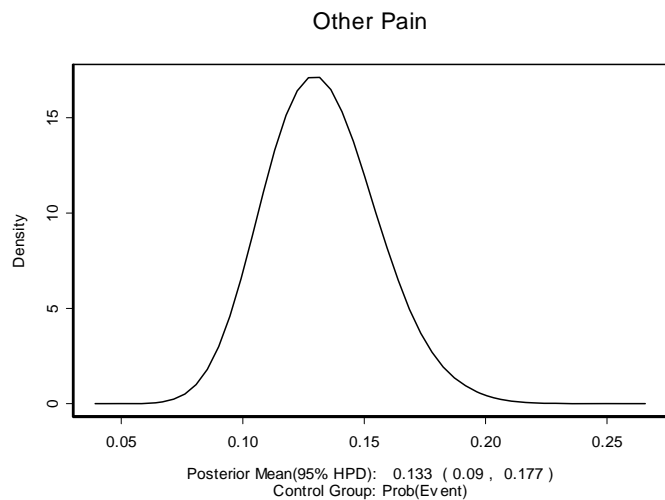


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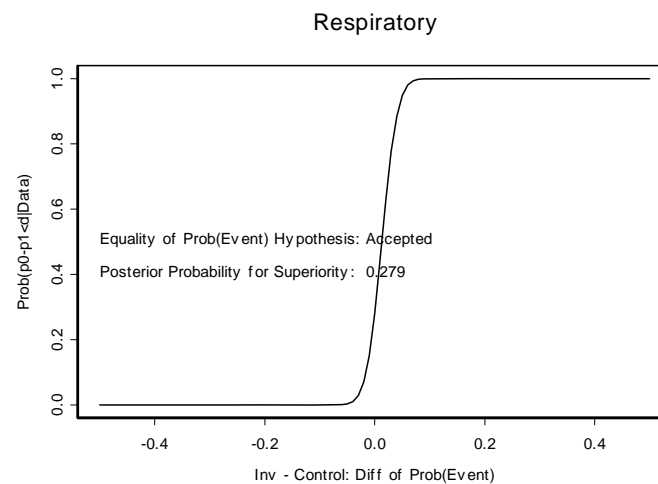
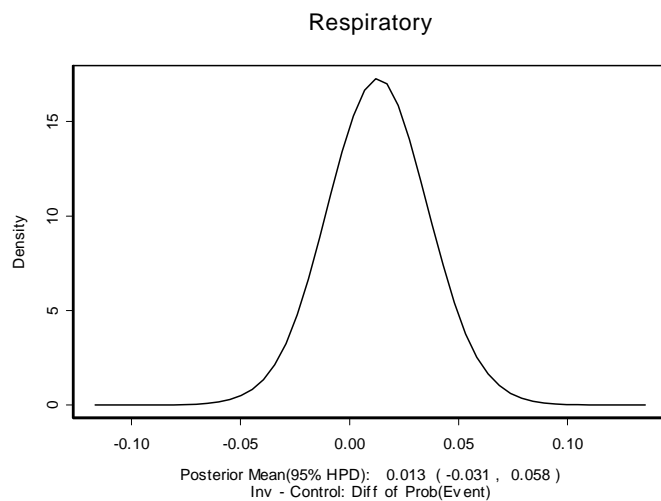
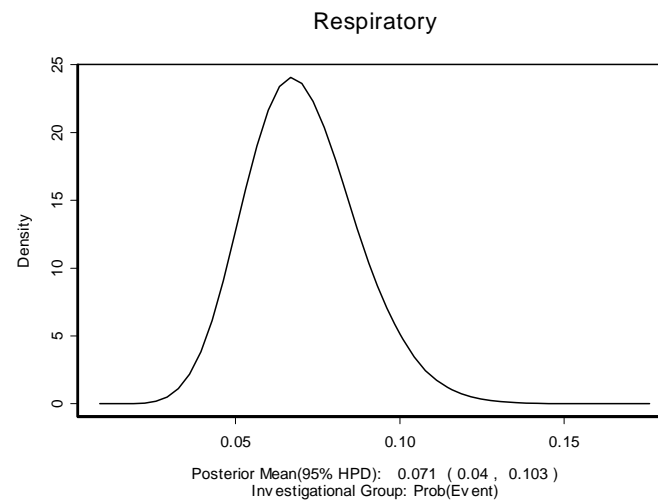
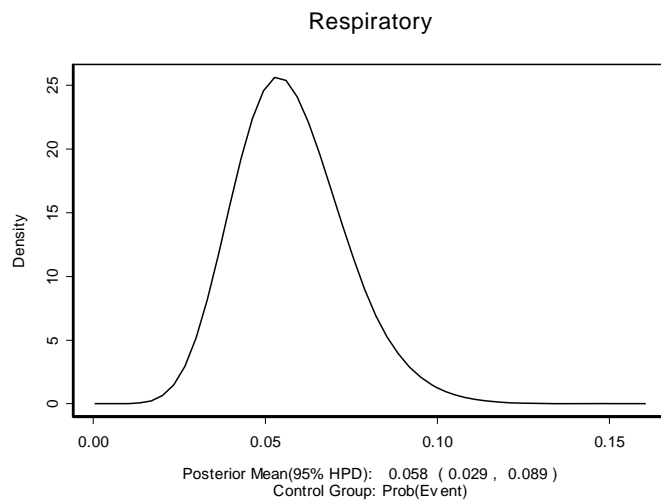


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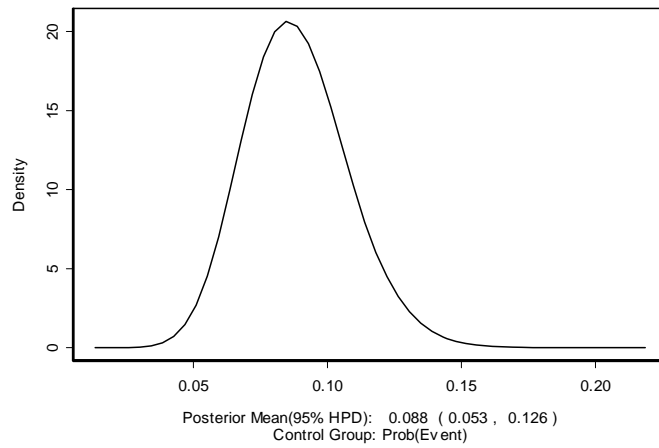


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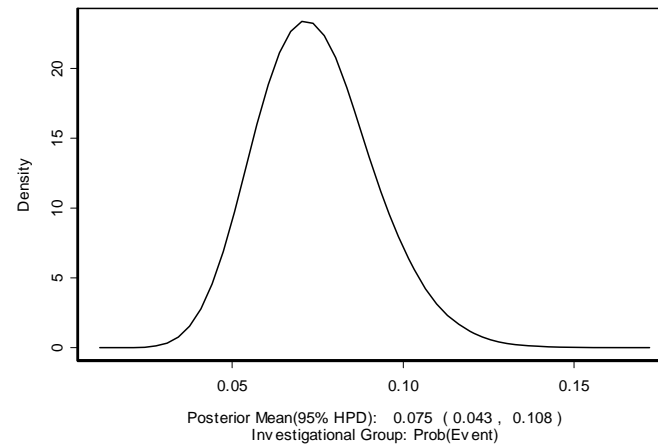
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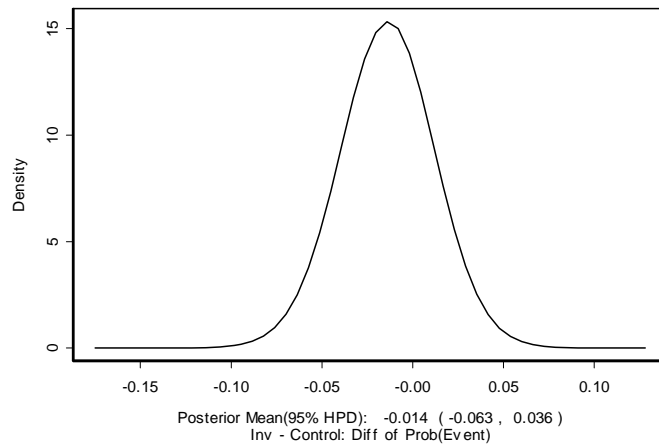
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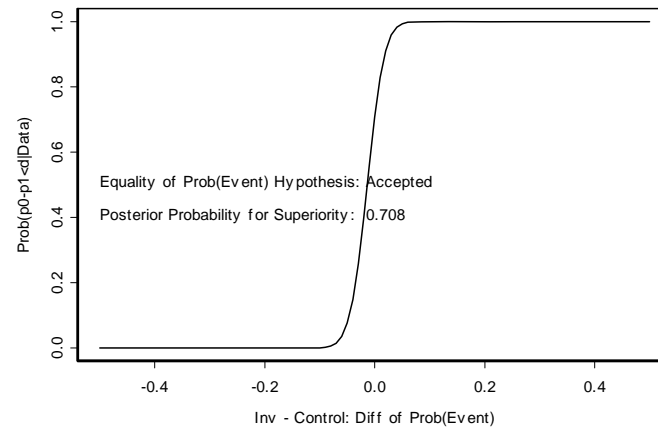
Spinal Event



Spinal Event



Spinal Event

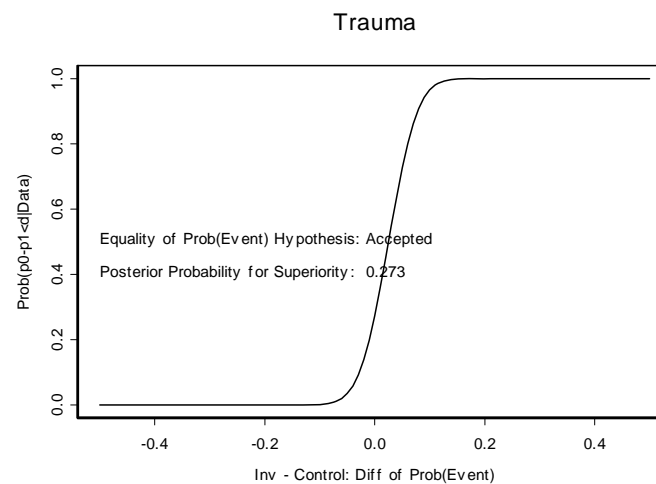
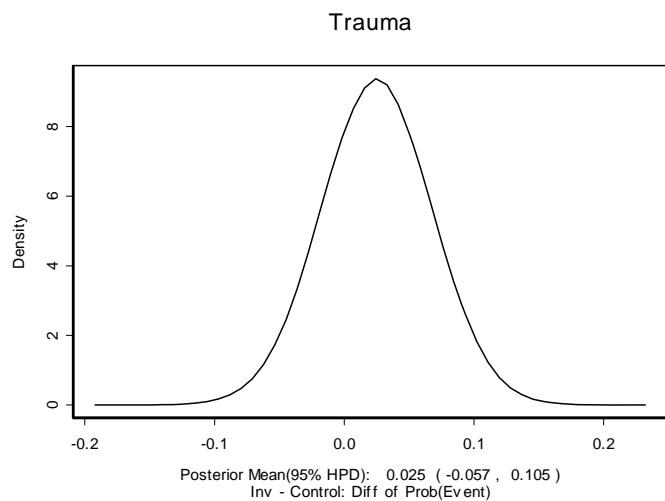
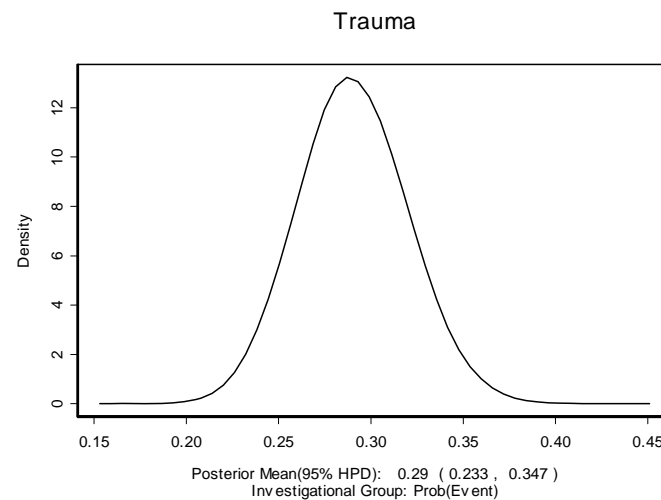
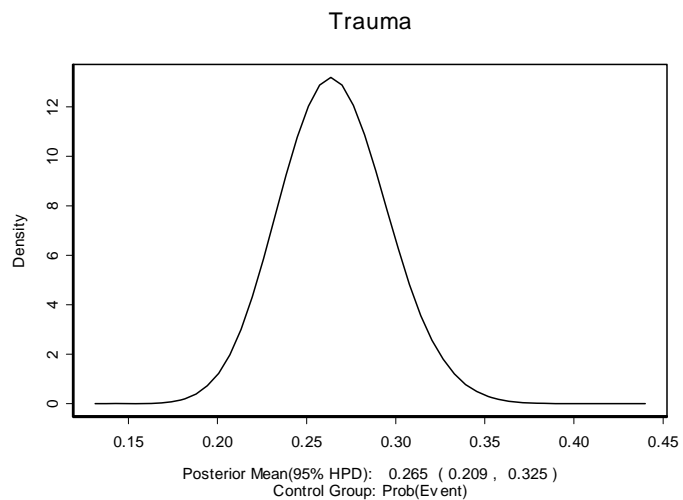


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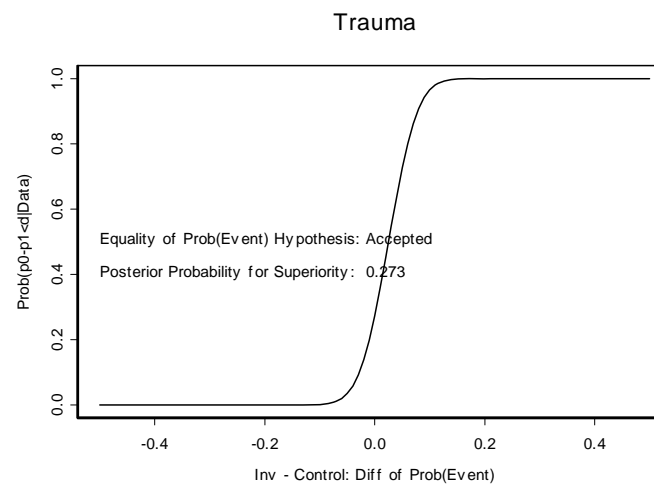
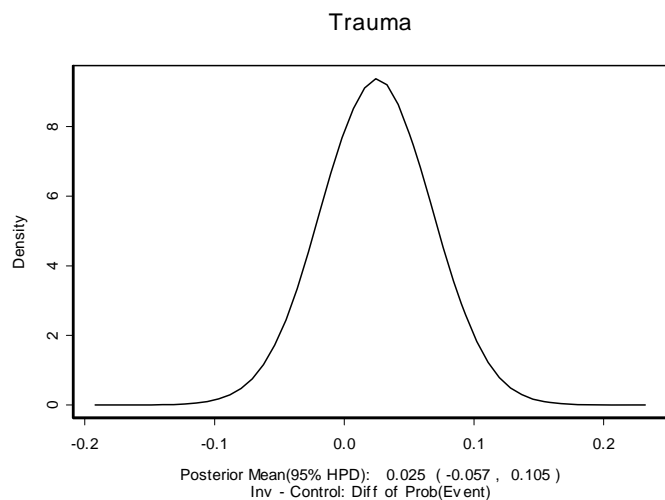
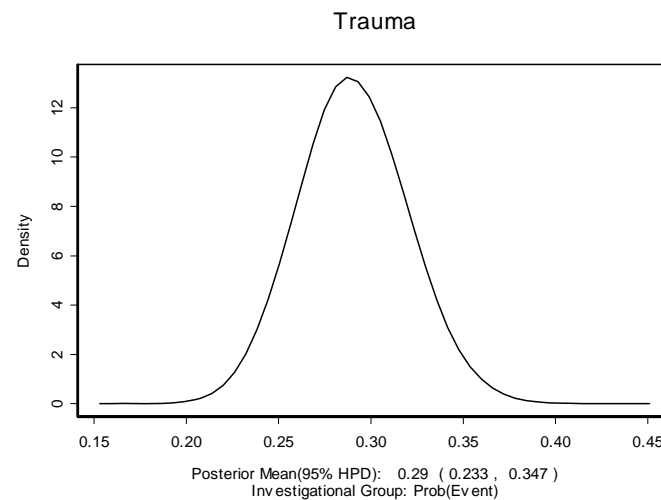
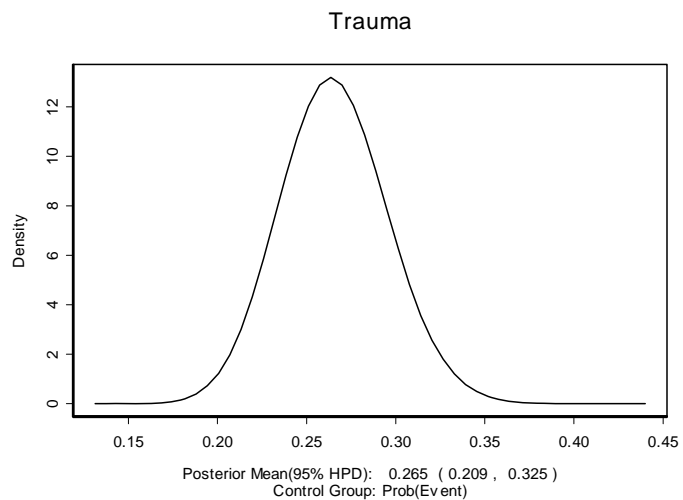


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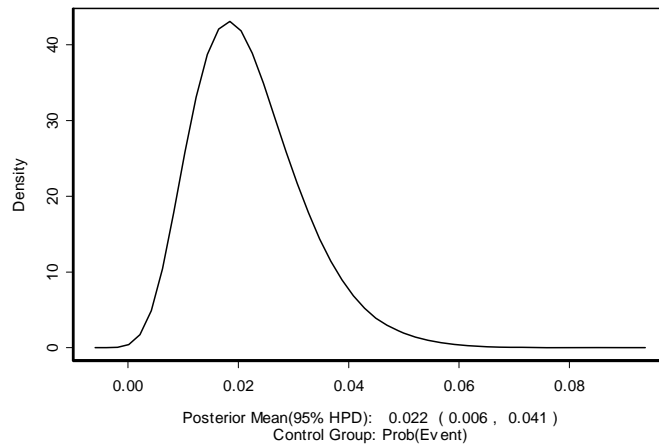


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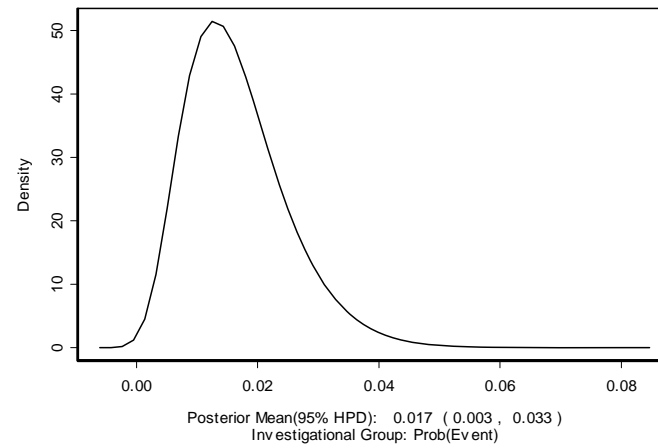
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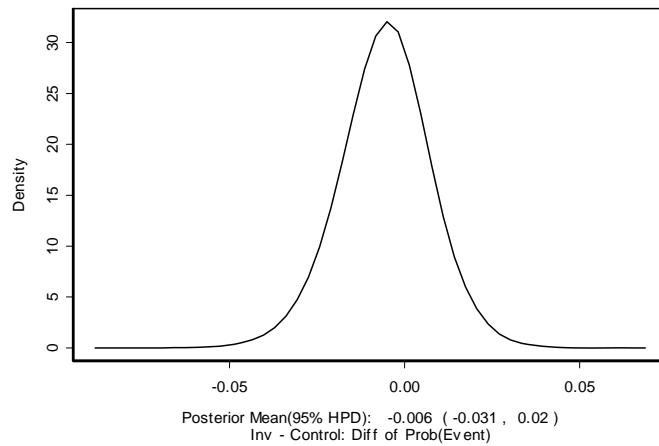
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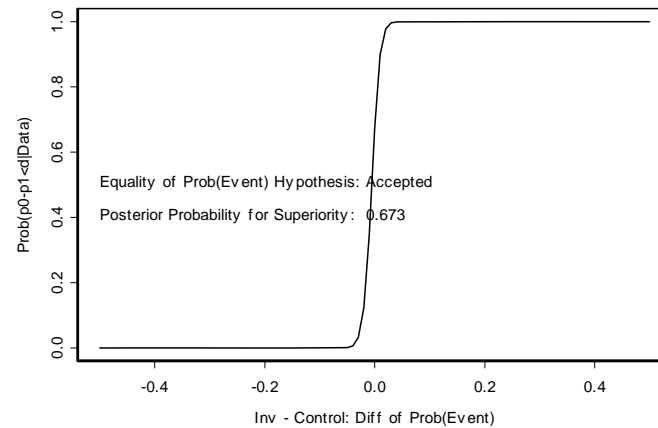
Vertebral Fracture



Vertebral Fracture



Vertebral Fracture

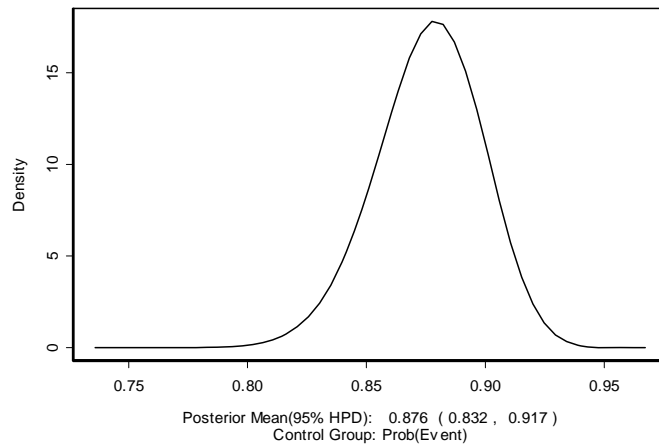


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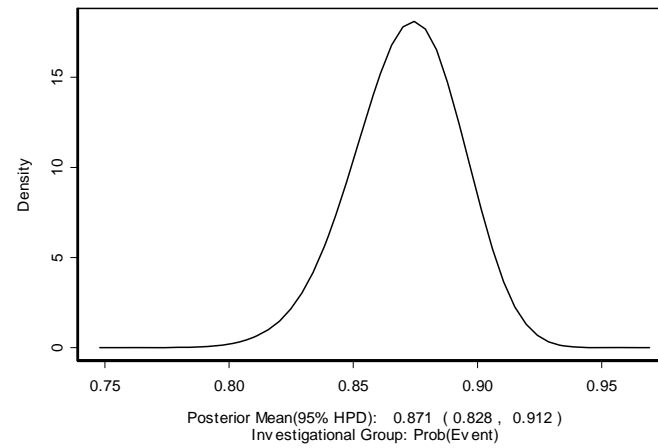
Pivotal Study with the rhBMP-2/CRM/CD HORIZON® SPINAL SYSTEM Bayesian Analyses for Adverse Events

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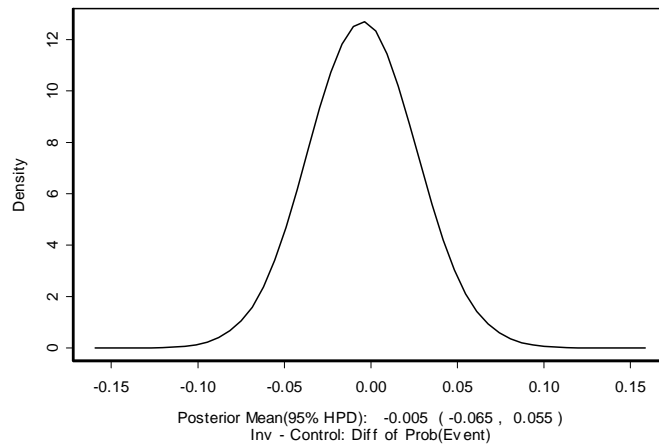
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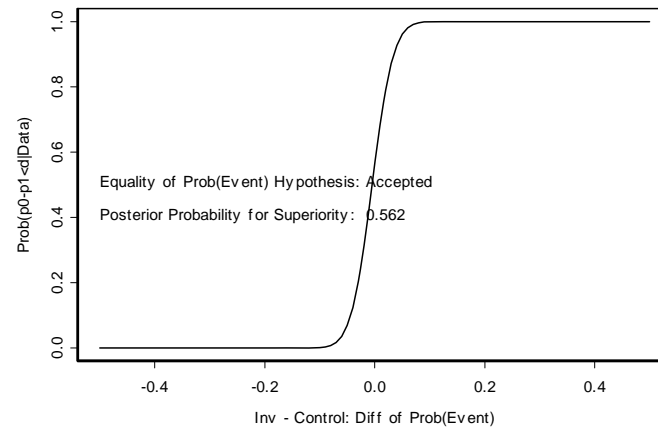
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Any Adverse Event



Any Adverse Event



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Pivotal Study with the rhBMP-2/CRM/CD HORIZON® SPINAL SYSTEM
Bayesian Analyses for Secondary Surgical Events

Page 1 of 7

Results from Bayesian Analyses for Comparisons of
Secondary Surgical Events
between Investigational Device and Control Device Groups

[Evaluations up to the 24-Month Visit]

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Pivotal Study with the rhBMP-2/CRM/CD HORIZON® SPINAL SYSTEM Bayesian Analyses for Secondary Surgical Events

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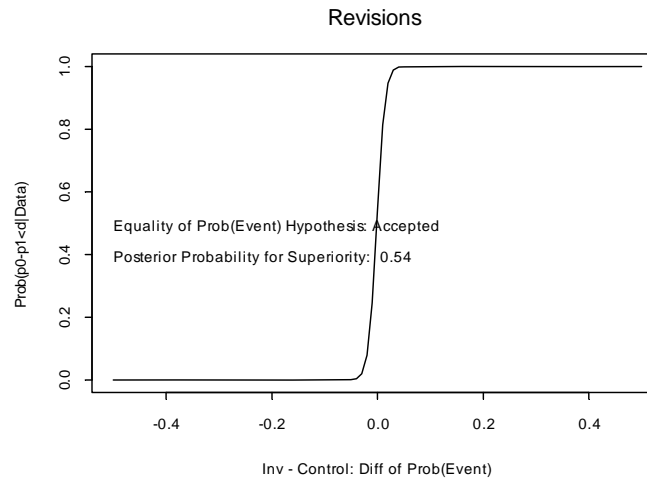
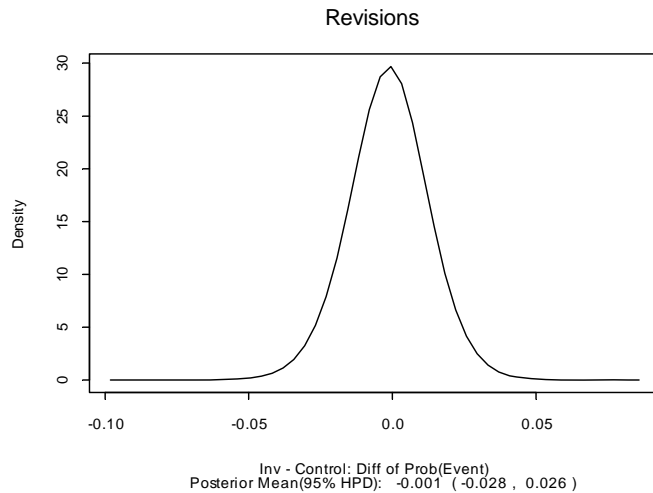
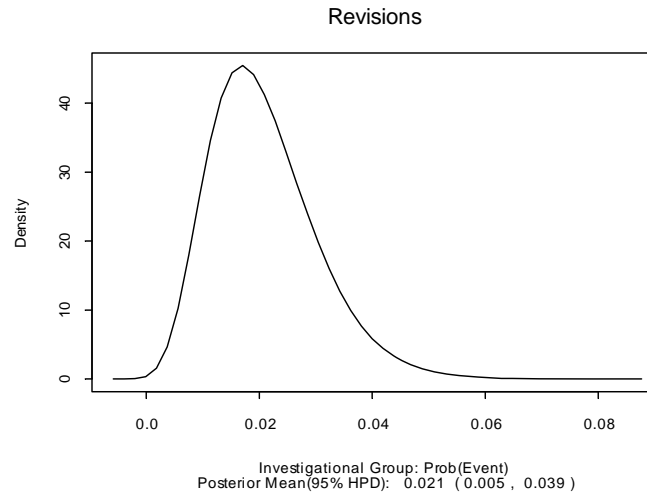
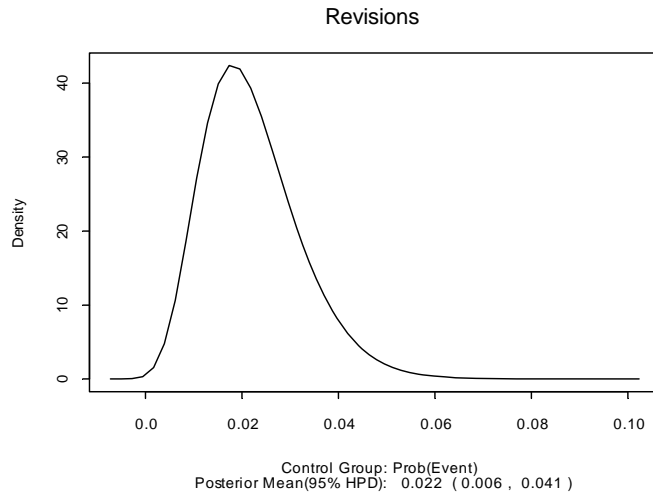
Summary of 95% Highest Posterior Density (HPD) Intervals of Secondary Surgical Events

Event	Null Hypothesis Accepted	Probability of Superiority (%)	95% HPD								
			p0 (Control)			p1 (Investigational)			p1 - p0		
			Mean	Lower	Upper	Mean	Lower	Upper	Mean	Lower	Upper
Revisions	Accepted	54.0	0.022	0.006	0.041	0.021	0.005	0.039	-0.001	-0.028	0.026
Removals	Rejected	99.6	0.128	0.086	0.172	0.058	0.030	0.088	-0.070	-0.123	-0.018
Supplemental Fixations	Accepted	81.4	0.044	0.019	0.071	0.029	0.010	0.050	-0.015	-0.051	0.018
Reoperations	Accepted	48.2	0.053	0.026	0.083	0.054	0.027	0.083	0.001	-0.041	0.041
Others	Accepted	58.2	0.270	0.212	0.328	0.261	0.207	0.317	-0.009	-0.088	0.072

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Pivotal Study with the rhBMP-2/CRM/CD HORIZON® SPINAL SYSTEM Bayesian Analyses for Secondary Surgical Events

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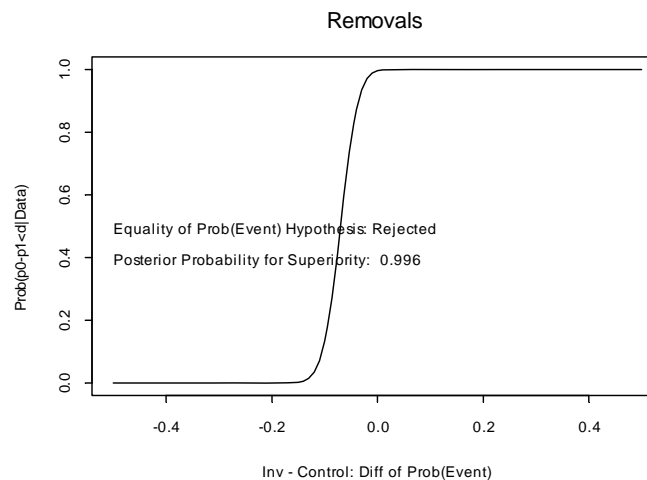
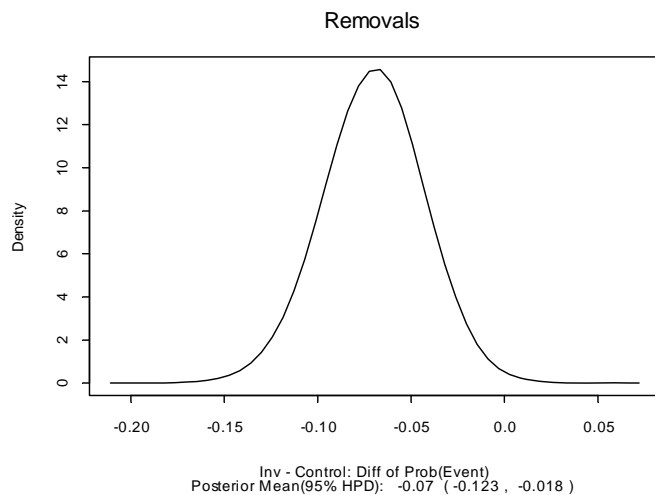
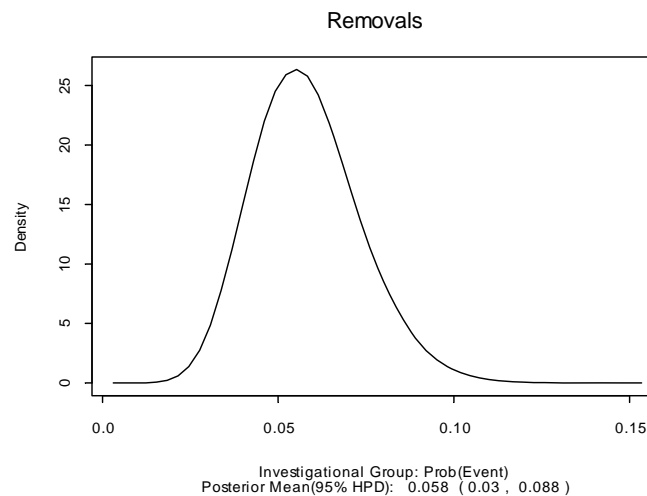
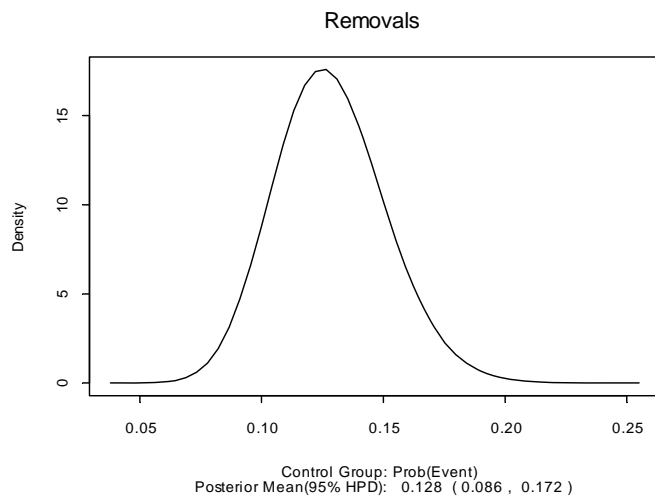


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Pivotal Study with the rhBMP-2/CRM/CD HORIZON® SPINAL SYSTEM

Bayesian Analyses for Secondary Surgical Events

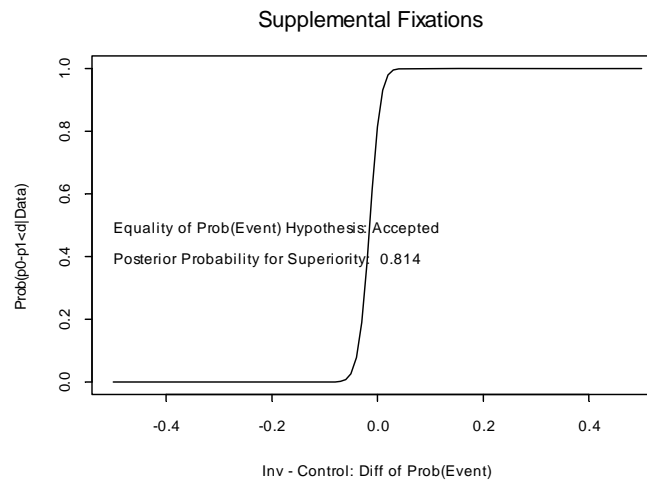
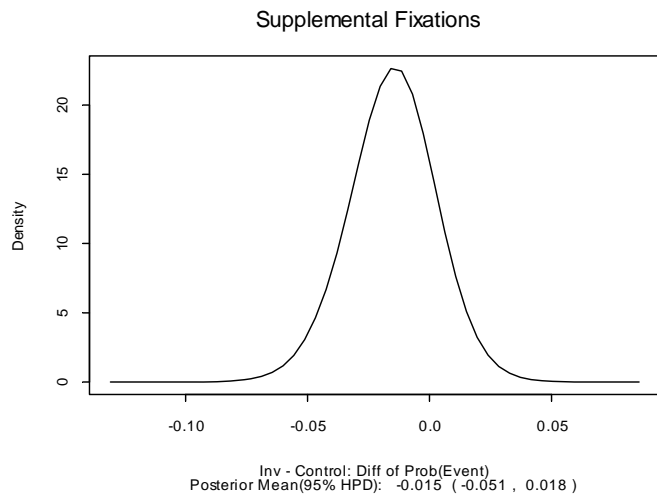
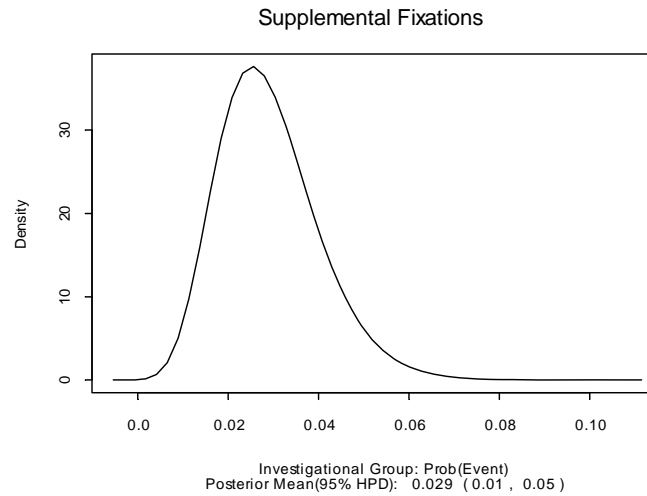
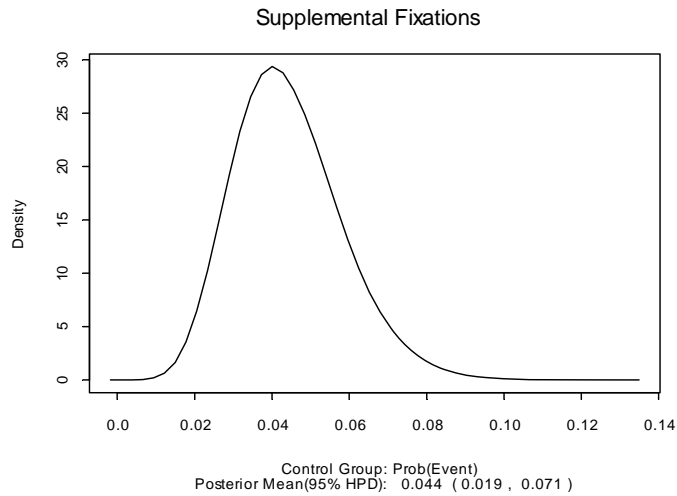
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Pivotal Study with the rhBMP-2/CRM/CD HORIZON® SPINAL SYSTEM Bayesian Analyses for Secondary Surgical Events

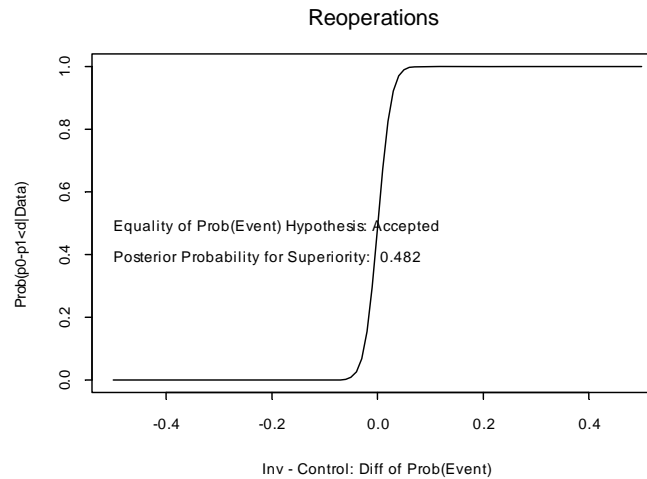
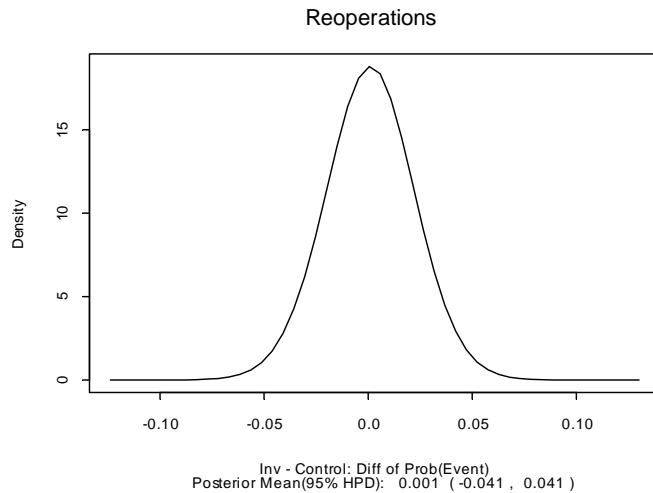
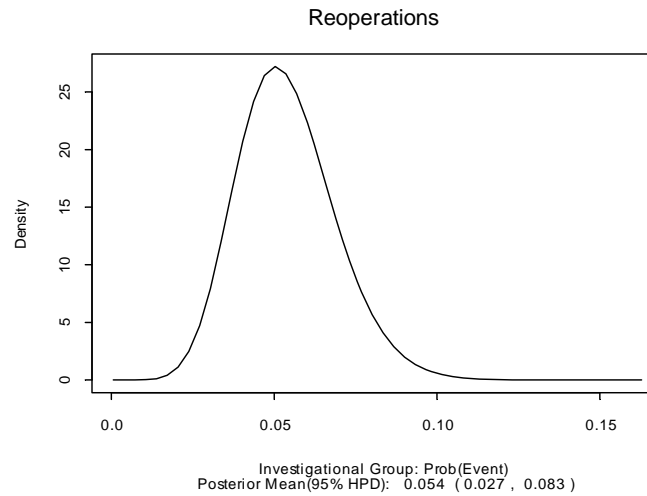
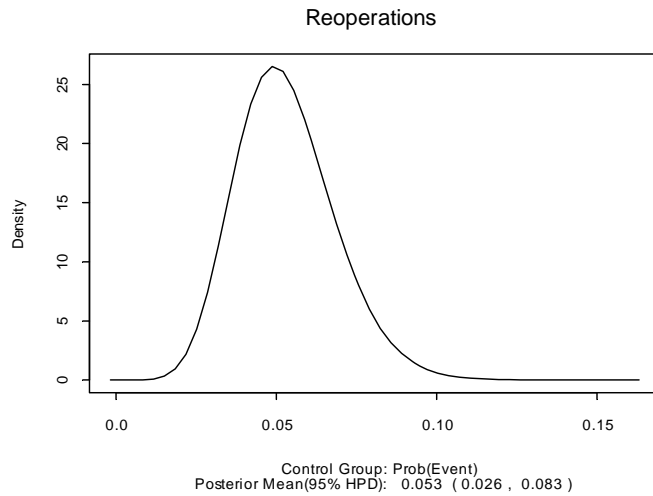
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Pivotal Study with the rhBMP-2/CRM/CD HORIZON® SPINAL SYSTEM Bayesian Analyses for Secondary Surgical Events

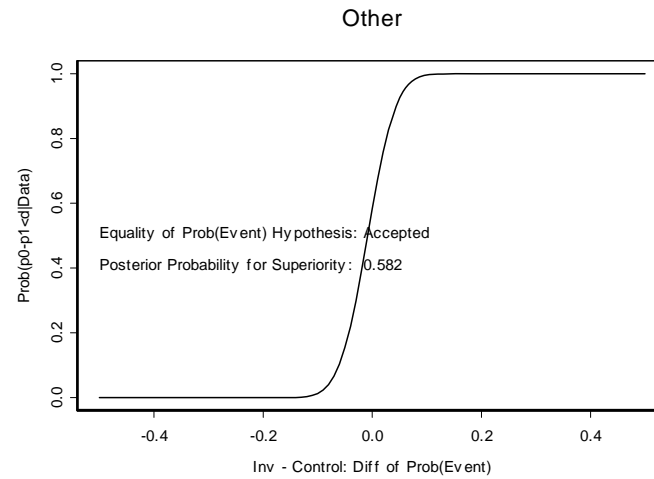
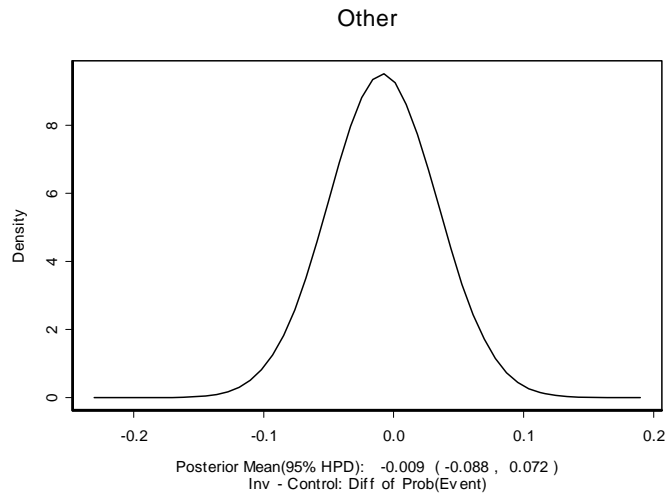
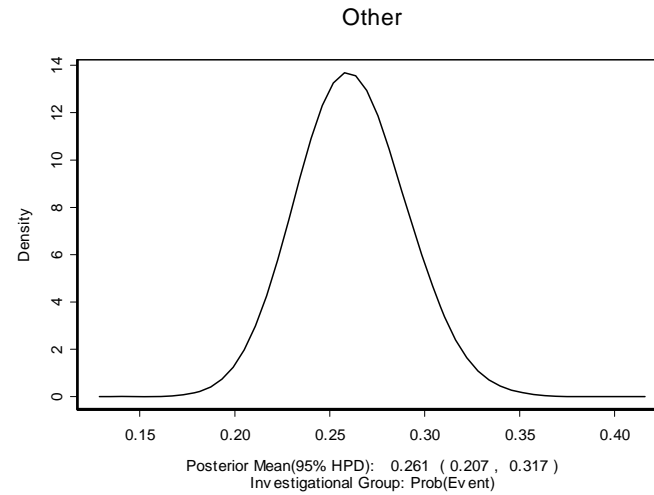
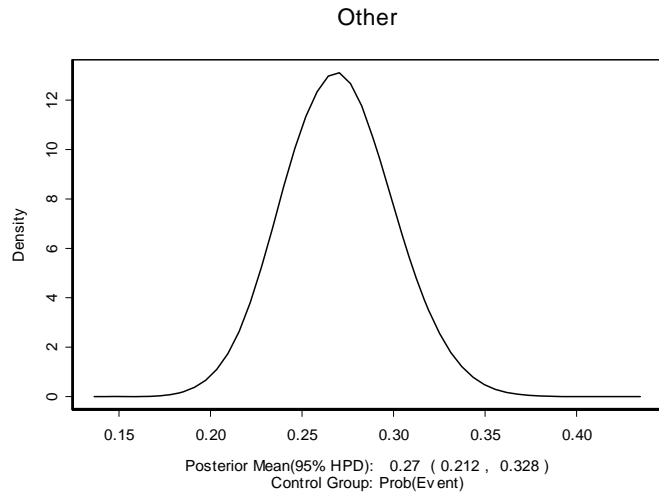
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Pivotal Study with the rhBMP-2/CRM/CD HORIZON® SPINAL SYSTEM Bayesian Analyses for Secondary Surgical Events

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Pivotal Study with the rhBMP-2/CRM/CD HORIZON® SPINAL SYSTEM

Bayesian Analyses for Effectiveness Variables

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**Results from Bayesian Analyses for Comparison of
Effectiveness and Neurological Variables at 24 Months
between Investigational Device and Control Device Groups**

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Pivotal Study with the rhBMP-2/CRM/CD HORIZON® SPINAL SYSTEM

Bayesian Analyses for Effectiveness Variables

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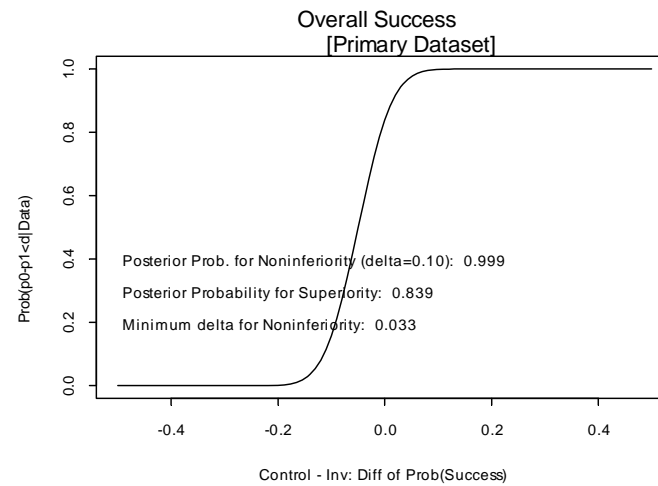
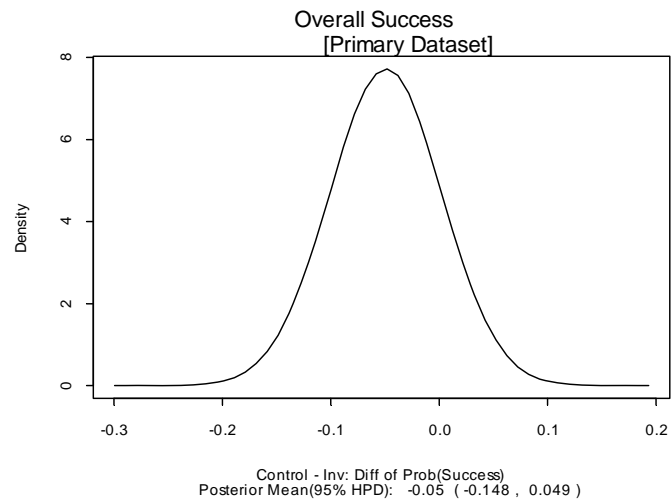
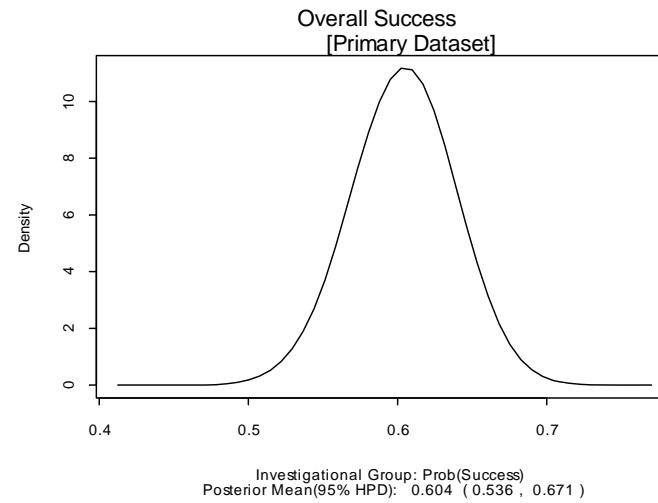
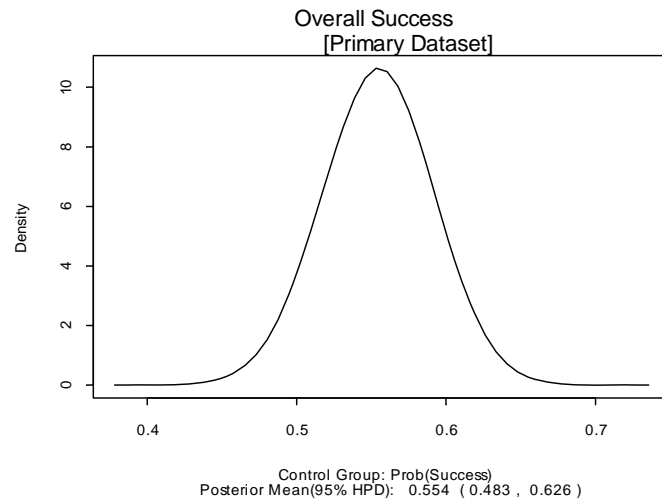
Summary of Posterior Probabilities of Non-inferiority and Superiority and 95% Highest Posterior Density (HPD) Intervals of Success for Effectiveness Variables

Variable	Probability of Non-inferiority (delta=0.10) (%)	Probability of Superiority (%)	95% HPD								
			p0 (Control)			p1 (Investigational)			p0 - p1		
			Mean	Lower	Upper	Mean	Lower	Upper	Mean	Lower	Upper
Primary Dataset											
Overall Success	99.9	83.9	0.554	0.483	0.626	0.604	0.536	0.671	-0.050	-0.148	0.049
Oswestry Pain	99.0	53.7	0.724	0.660	0.787	0.729	0.669	0.789	-0.004	-0.092	0.084
Fusion	~100.0	99.2	0.889	0.841	0.934	0.954	0.924	0.981	-0.065	-0.122	-0.011
Neurological Status	~100.0	78.5	0.838	0.785	0.890	0.866	0.820	0.911	-0.028	-0.099	0.042
Back Pain	99.9	17.8	0.946	0.912	0.976	0.923	0.887	0.957	0.023	-0.026	0.071
Leg Pain	~100.0	74.6	0.842	0.789	0.893	0.866	0.818	0.910	-0.024	-0.093	0.040
SF-36 PCS	99.9	68.7	0.816	0.759	0.870	0.835	0.783	0.884	-0.019	-0.094	0.057
SF-36 MCS	~100.0	87.7	0.654	0.587	0.723	0.709	0.647	0.770	-0.055	-0.147	0.038
Per-Protocol Dataset											
Overall Success	99.7	80.7	0.562	0.486	0.639	0.609	0.538	0.680	-0.046	-0.150	0.060
Oswestry Pain	98.5	52.2	0.728	0.660	0.796	0.731	0.666	0.793	-0.003	-0.094	0.093
Fusion	~100.0	99.9	0.881	0.828	0.930	0.966	0.938	0.990	-0.085	-0.143	-0.027
Neurological Status	99.9	69.4	0.846	0.790	0.900	0.865	0.815	0.912	-0.019	-0.094	0.055

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Pivotal Study with the rhBMP-2/CRM/CD HORIZON® SPINAL SYSTEM Bayesian Analyses for Effectiveness Variables

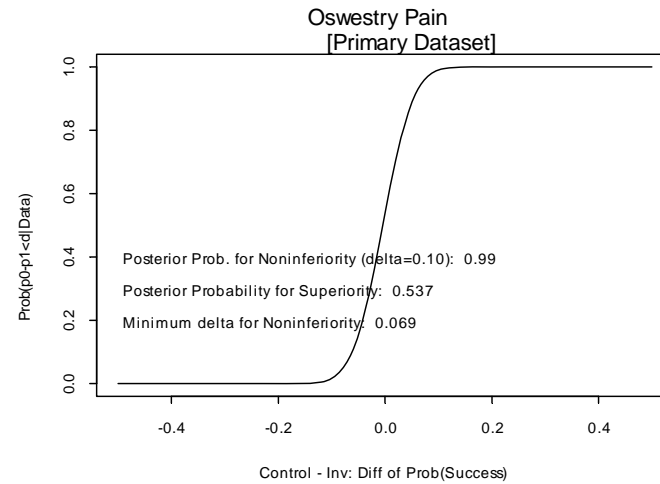
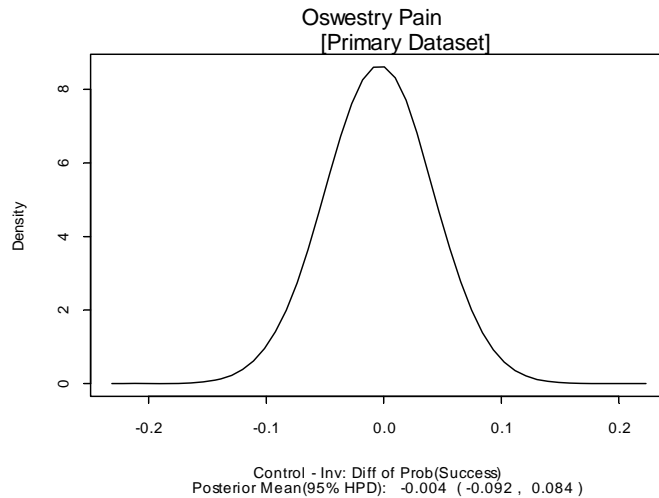
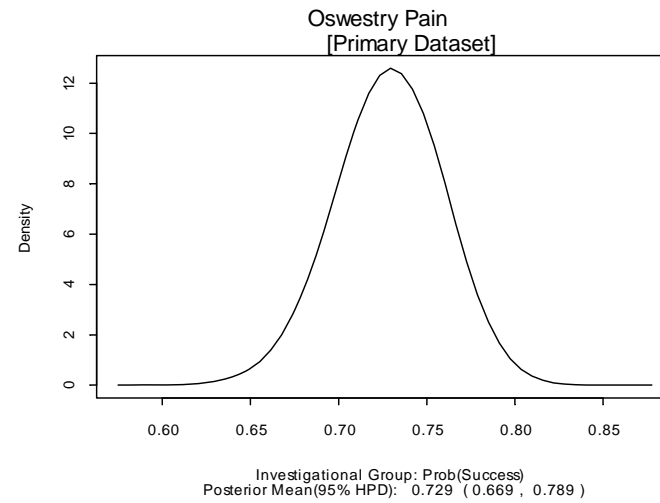
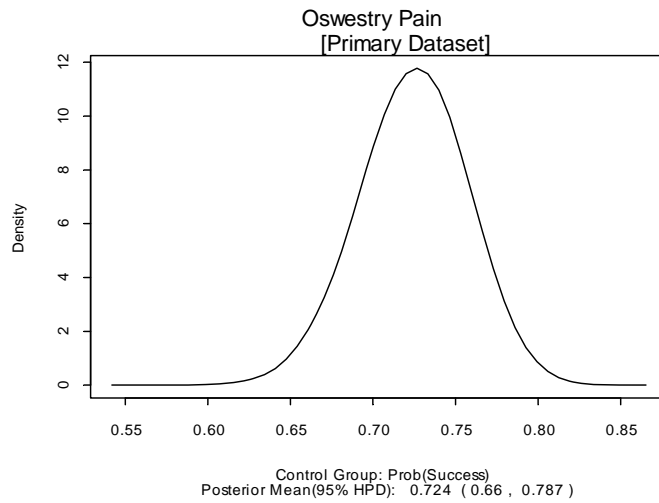
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Pivotal Study with the rhBMP-2/CRM/CD HORIZON® SPINAL SYSTEM Bayesian Analyses for Effectiveness Variables

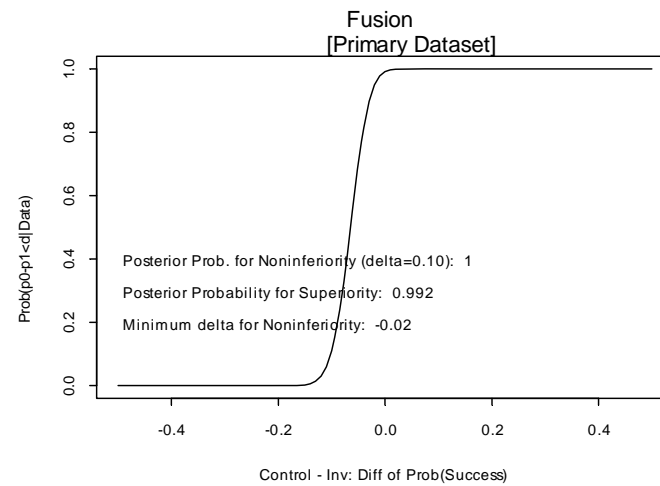
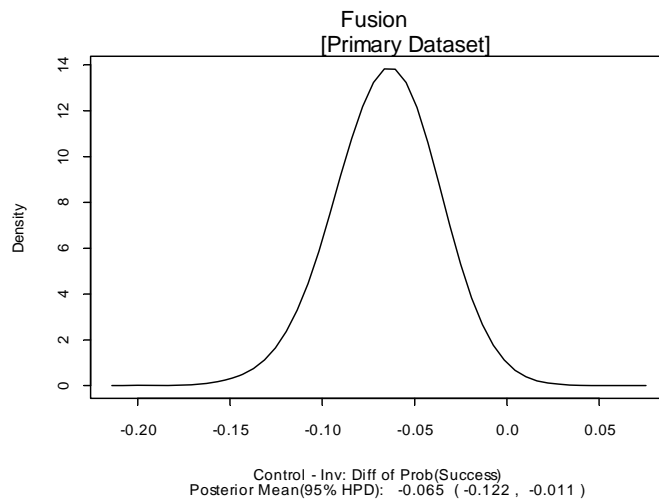
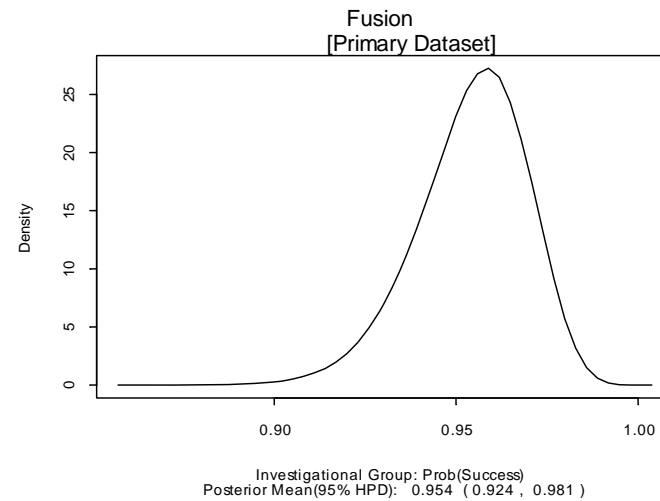
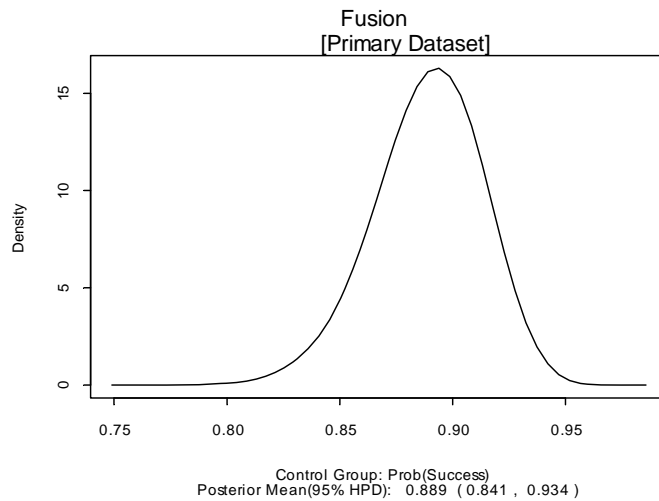
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Pivotal Study with the rhBMP-2/CRM/CD HORIZON® SPINAL SYSTEM Bayesian Analyses for Effectiveness Variables

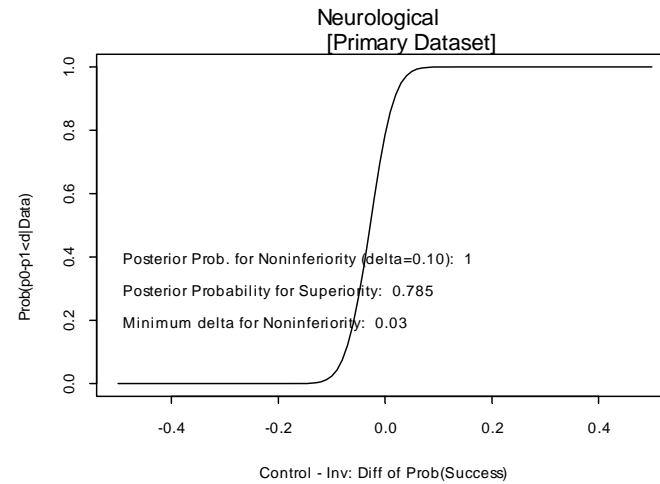
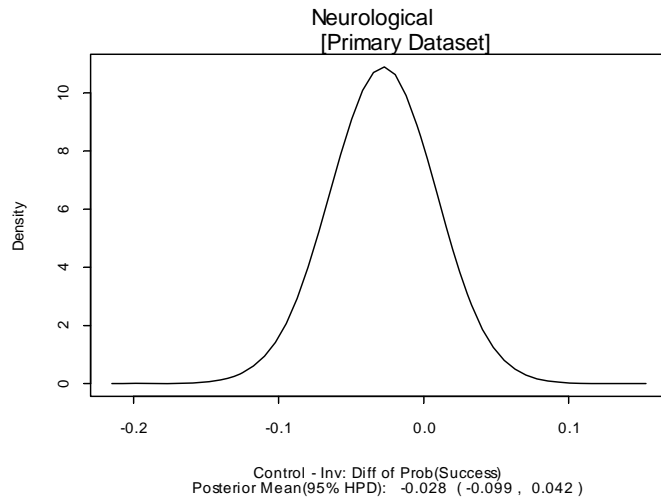
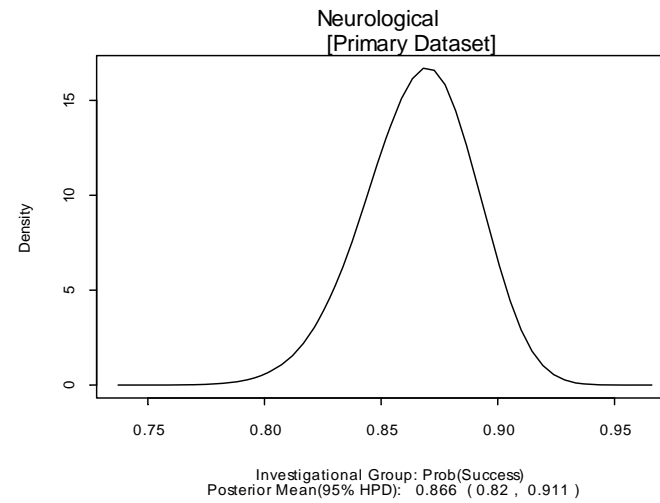
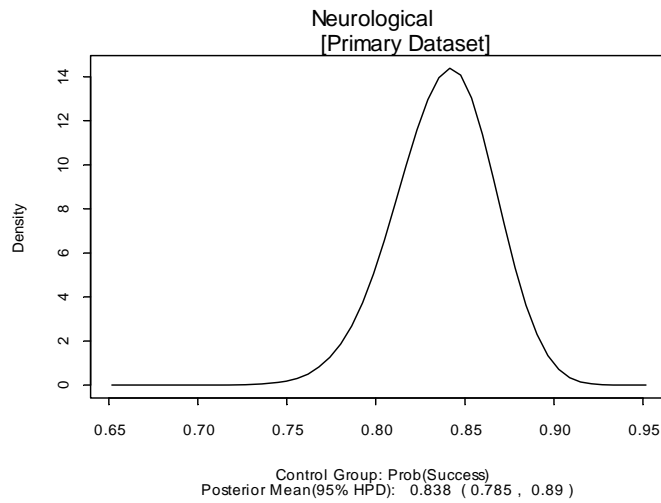
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Pivotal Study with the rhBMP-2/CRM/CD HORIZON® SPINAL SYSTEM Bayesian Analyses for Effectiveness Variables

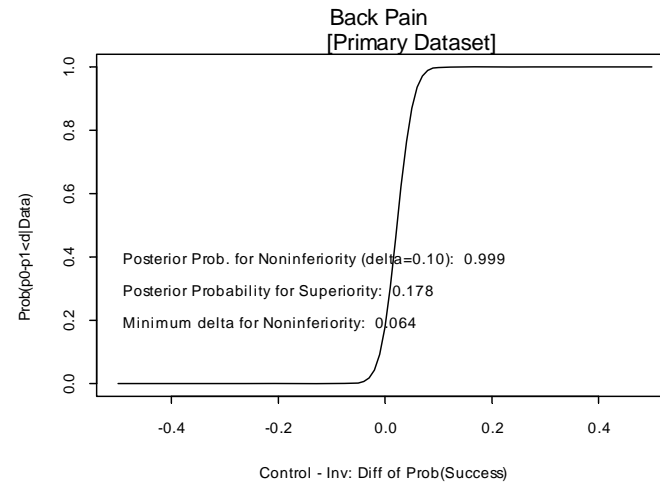
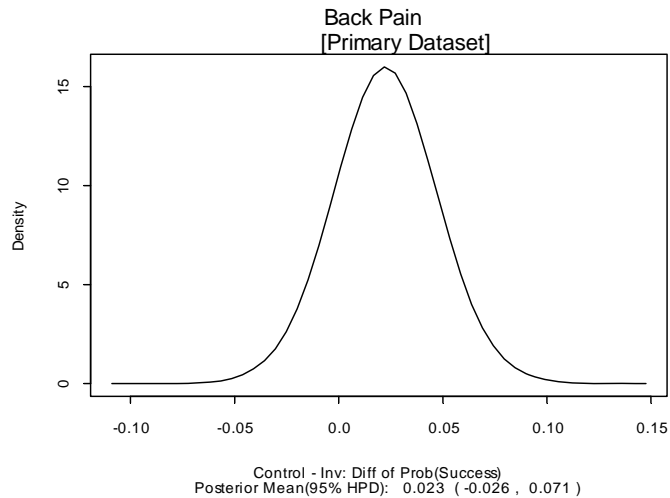
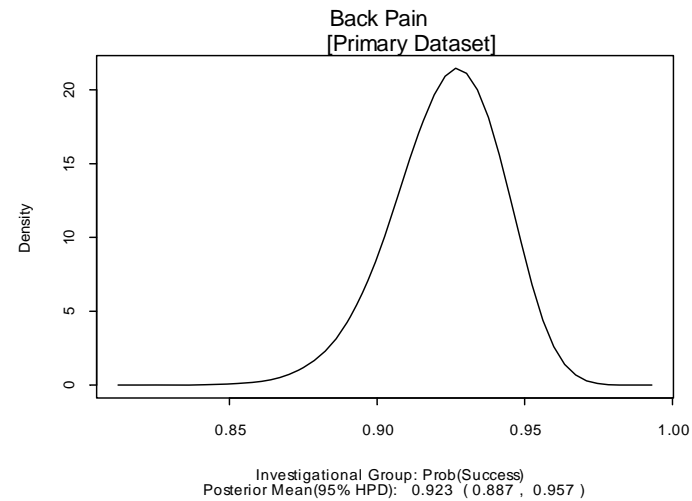
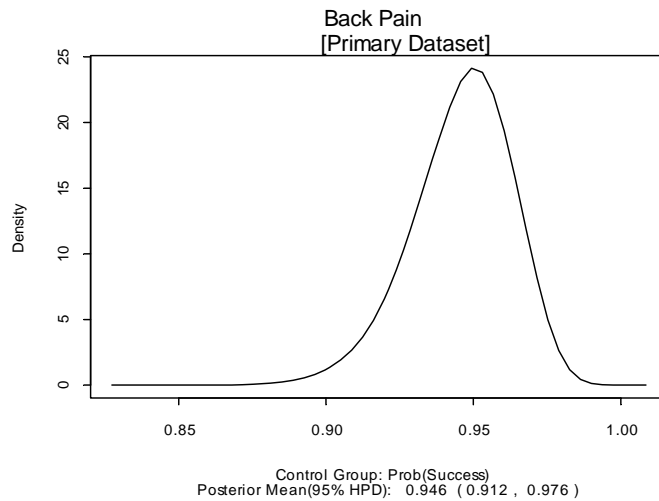
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Pivotal Study with the rhBMP-2/CRM/CD HORIZON® SPINAL SYSTEM Bayesian Analyses for Effectiveness Variables

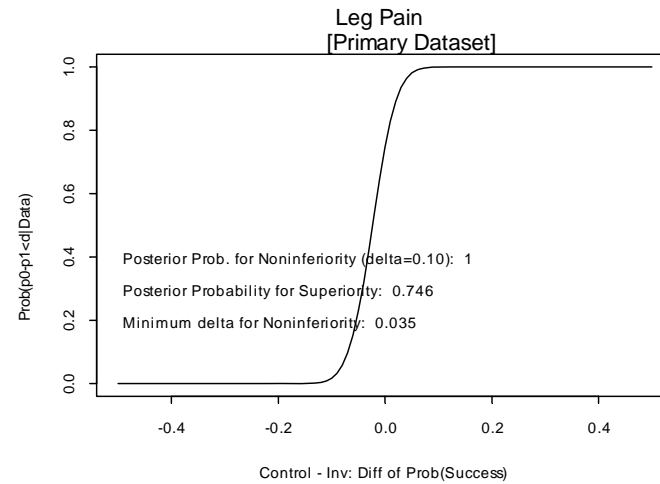
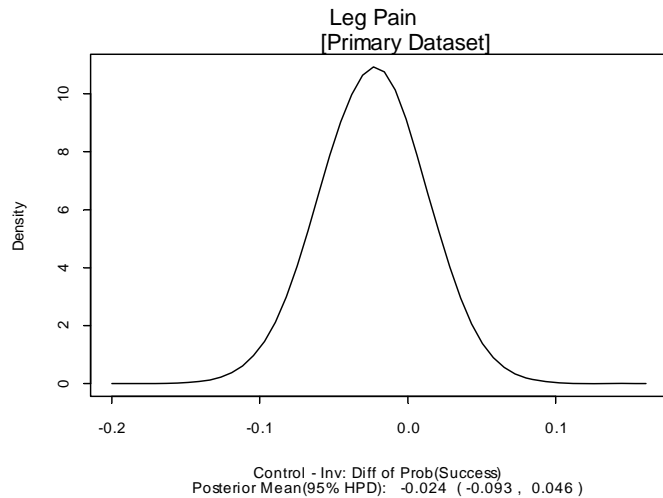
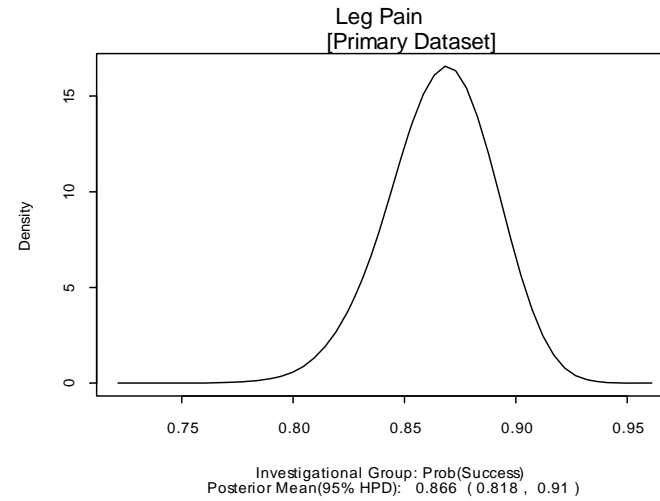
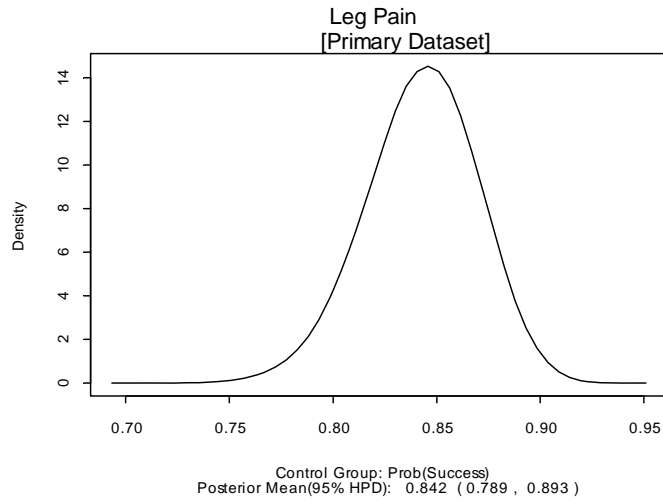
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Pivotal Study with the rhBMP-2/CRM/CD HORIZON® SPINAL SYSTEM Bayesian Analyses for Effectiveness Variables

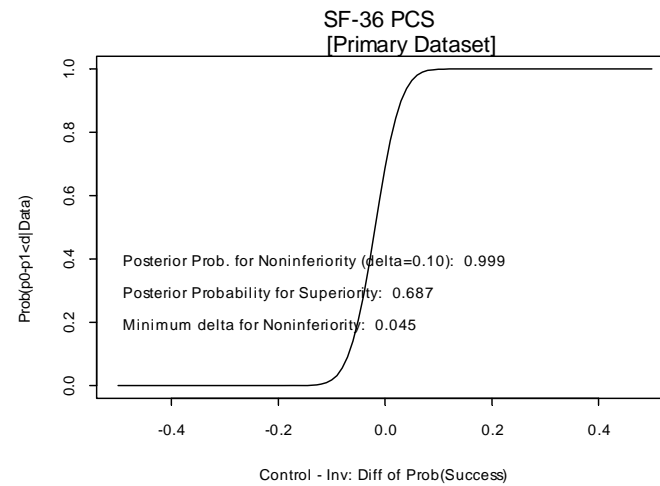
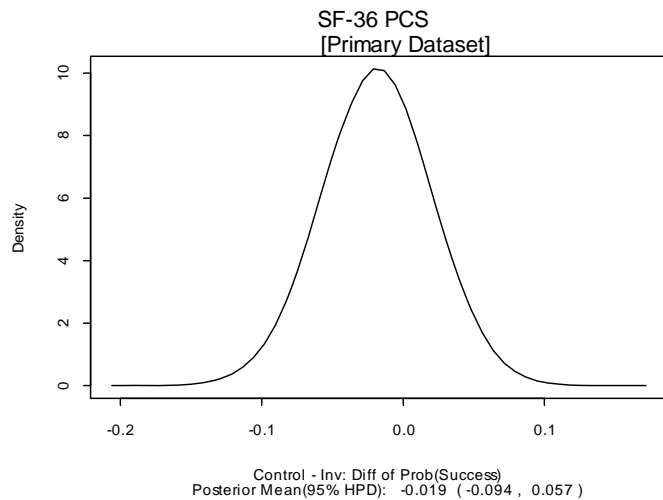
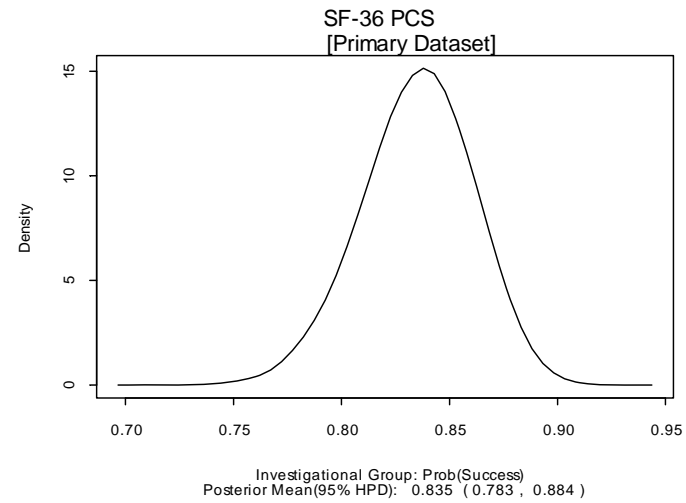
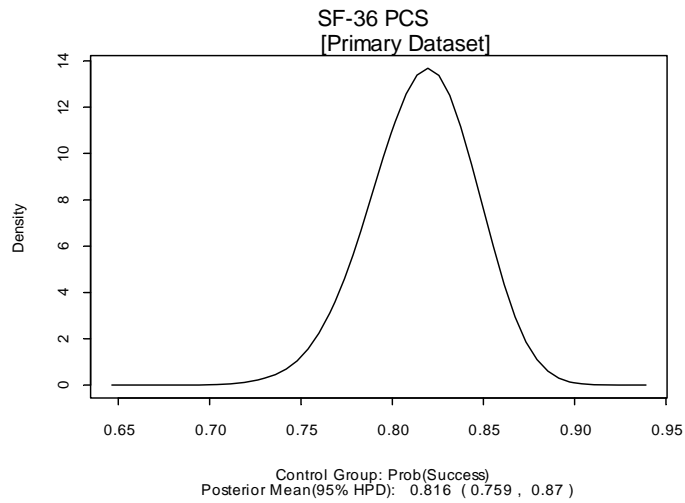
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Pivotal Study with the rhBMP-2/CRM/CD HORIZON® SPINAL SYSTEM Bayesian Analyses for Effectiveness Variables

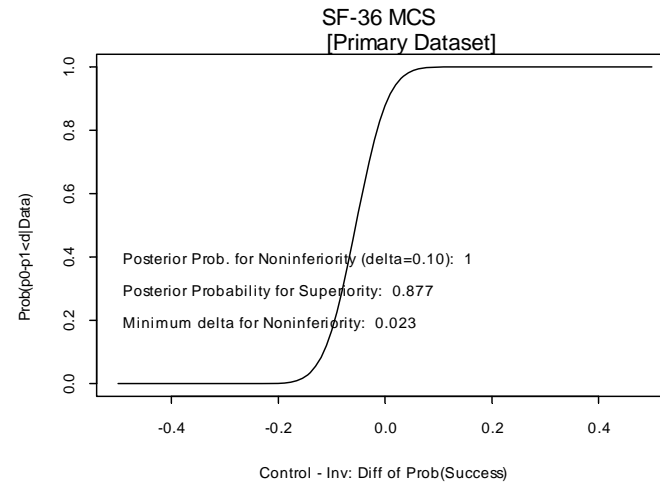
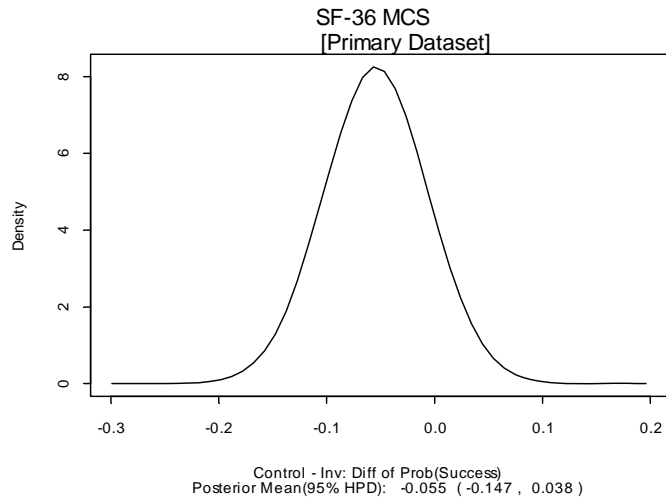
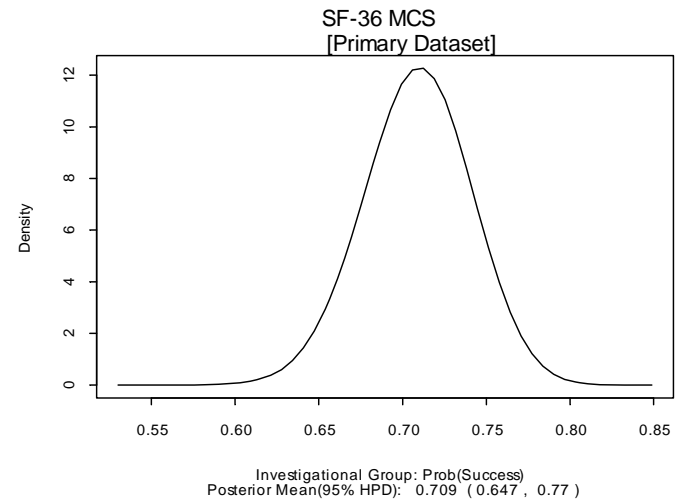
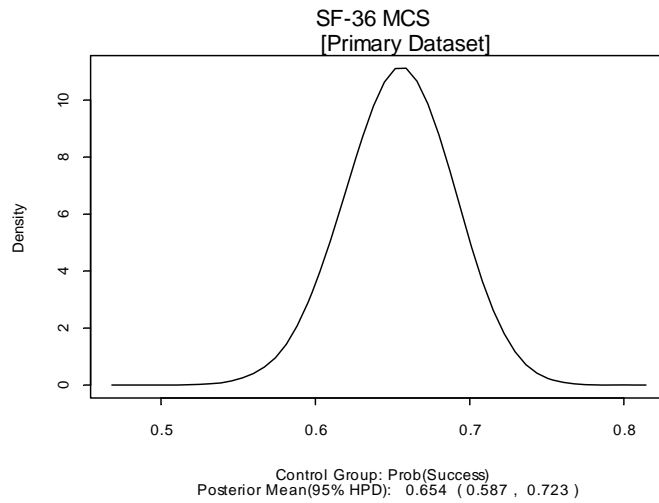
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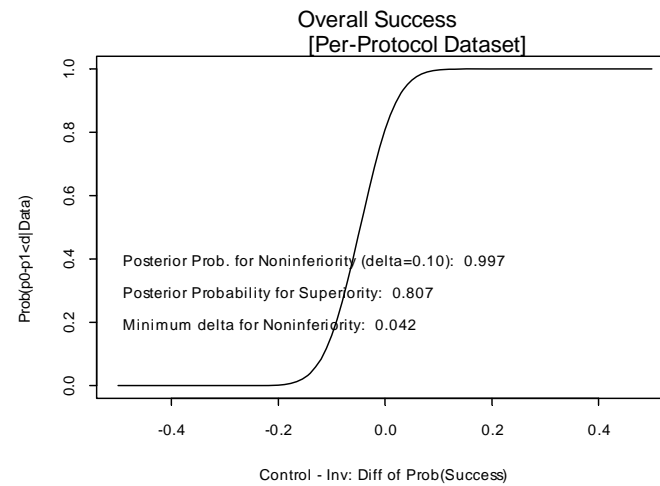
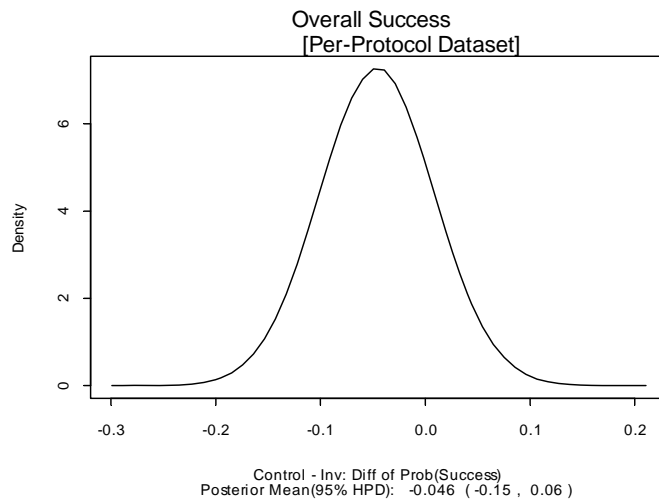
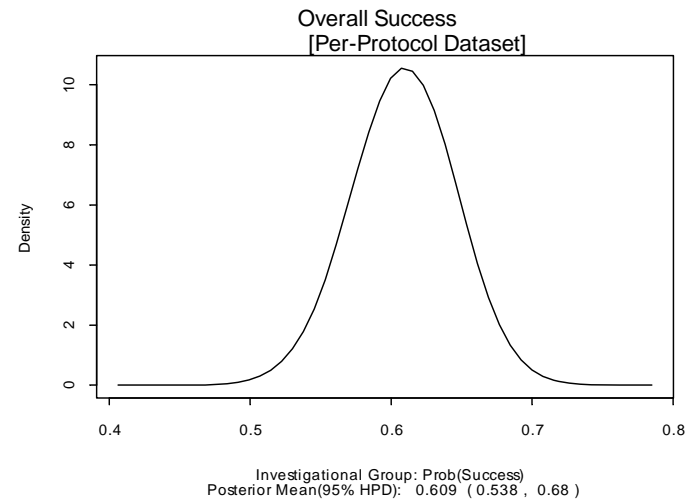
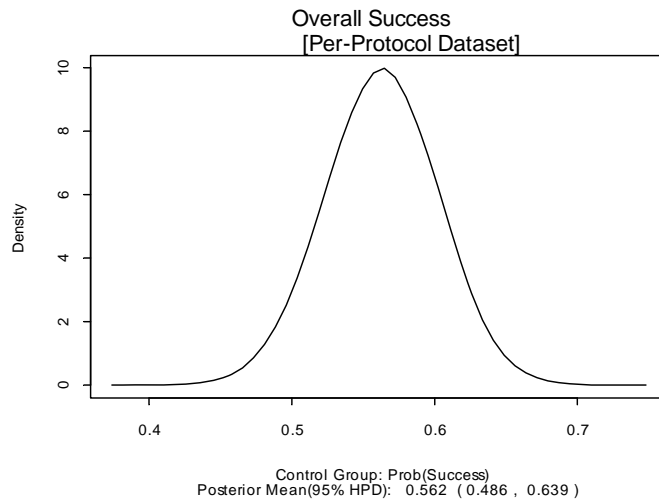


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Pivotal Study with the rhBMP-2/CRM/CD HORIZON® SPINAL SYSTEM

Bayesian Analyses for Effectiveness Variables

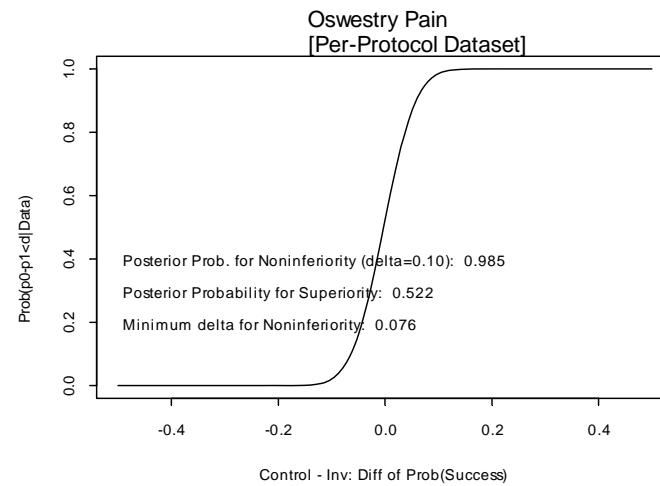
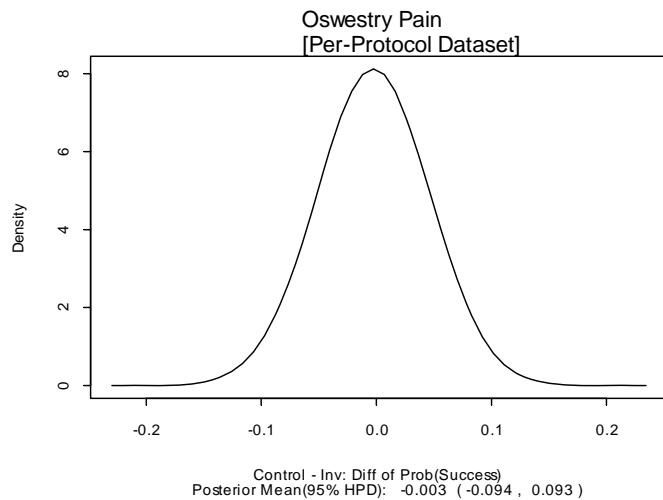
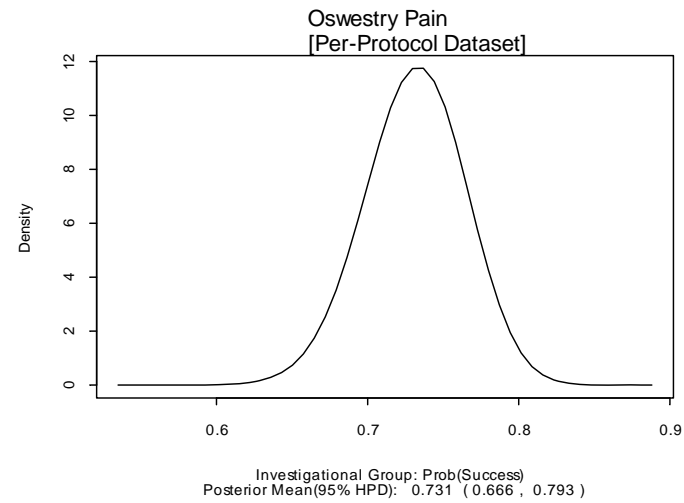
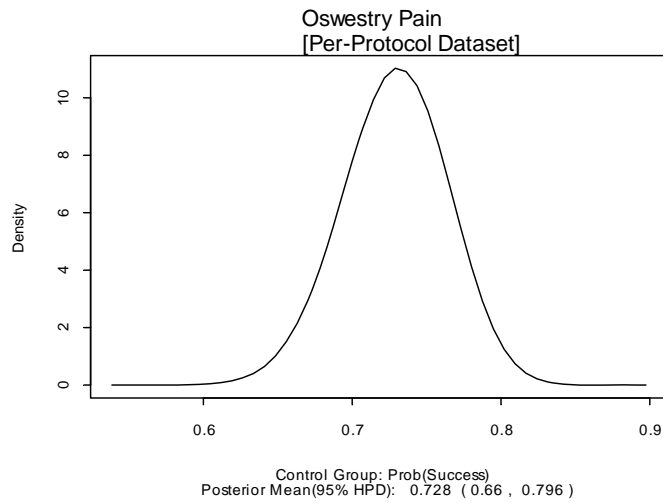
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Pivotal Study with the rhBMP-2/CRM/CD HORIZON® SPINAL SYSTEM Bayesian Analyses for Effectiveness Variables

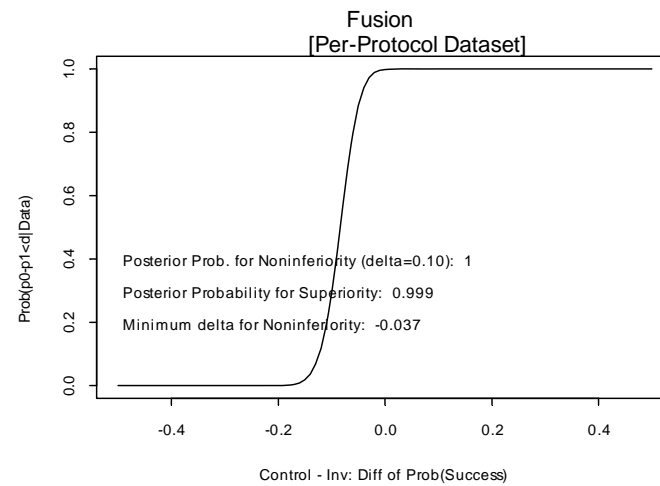
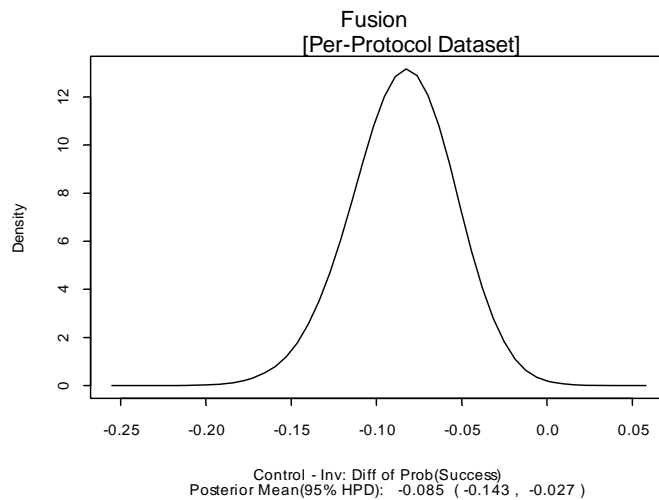
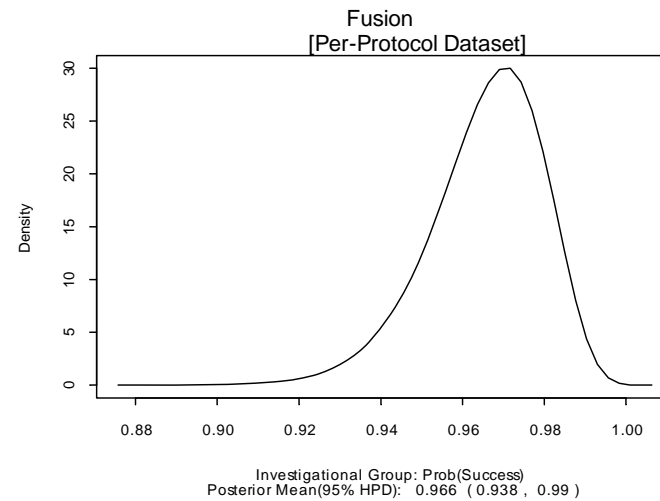
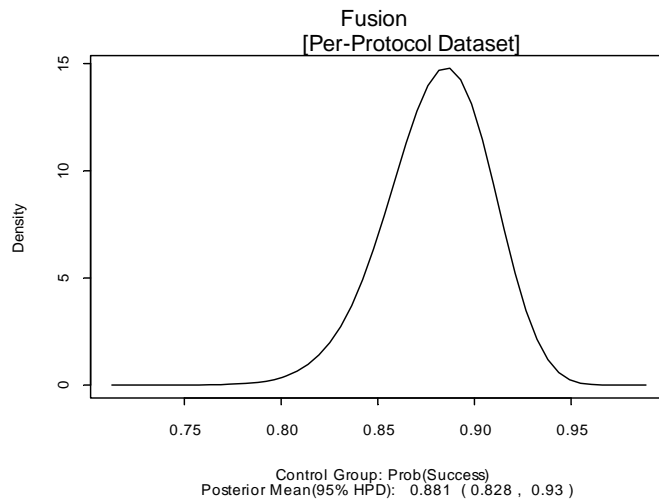
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Pivotal Study with the rhBMP-2/CRM/CD HORIZON® SPINAL SYSTEM Bayesian Analyses for Effectiveness Variables

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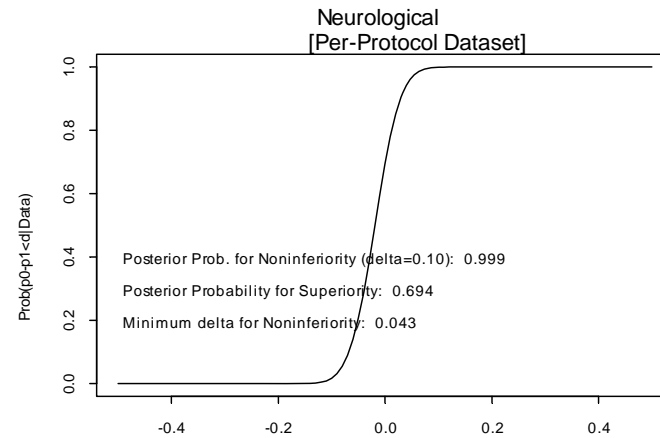
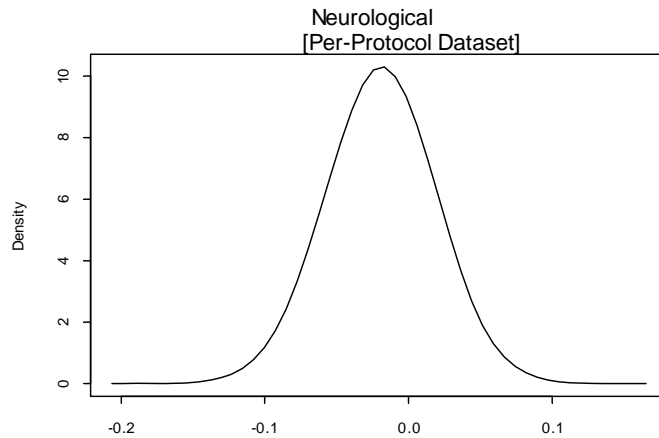
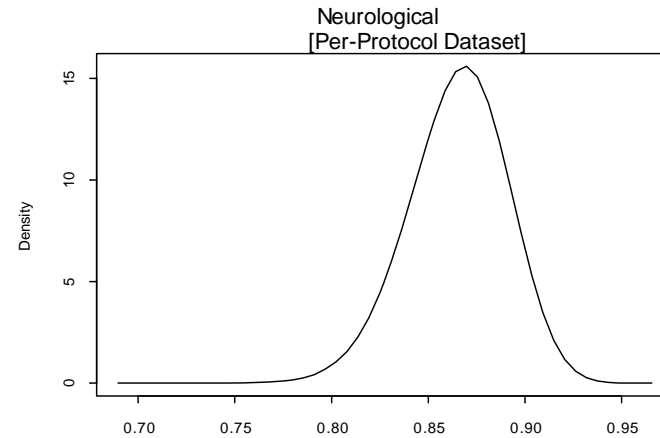
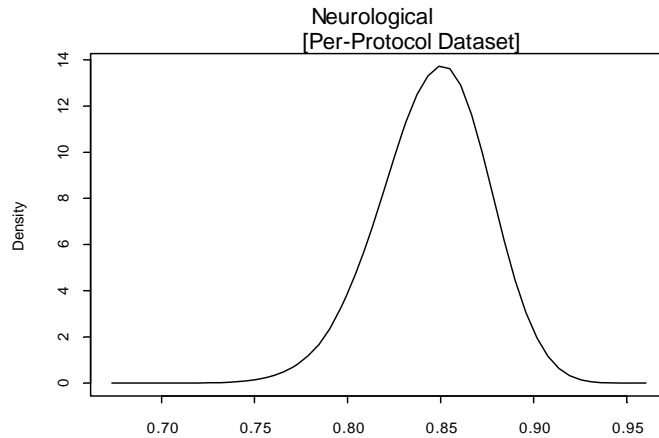


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Pivotal Study with the rhBMP-2/CRM/CD HORIZON® SPINAL SYSTEM

Bayesian Analyses for Effectiveness Variables

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Current Review of Malignancies and rhBMP-2

In order to address concerns raised in a deficiency letter to Medtronic Sofamor Danek's pre-market approval (PMA) application P050036 for the AMPLIFY™ rhBMP-2 Matrix product, Medtronic, together with its business partner, Wyeth (now Pfizer), commissioned an updated analysis of all known malignancy data reported with the use of rhBMP-2. Attached are two of the five sections of the report. (The remaining three sections, which contained a summary of malignancies reported in worldwide commercial use, a bibliography, and current labeling on rhBMP-2 products, [REDACTED] They are omitted here for space considerations.)

The first section is a summary of the currently available data on the relationship that may potentially exist between rhBMP-2 and malignancy. This section consists of two main parts: 1) a review of the scientific literature investigating the effects of rhBMP-2 on cancer cell lines, pharmacokinetic release studies, and tumor promotion studies; and 2) an evaluation of the incidence of malignancy in clinical trials conducted both by Medtronic and Wyeth, the manufacturer of rhBMP-2. Statistical and epidemiological analyses were performed to determine if the data from the clinical studies suggested any association between rhBMP-2 and the incidence of cancer. Two general conclusions were derived. First, the overall number of malignancies for the analyzed groups was comparable to that expected in the general population and was not significantly different from that in the control group. Second, while the incidence rates of some individual cancer types were found to be higher than expected in patients in the rhBMP-2 group, most of these rates were not shown to be statistically different from the rates expected in the population at large. The exception was in the rates of pancreatic and thyroid cancer in Medtronic's rhBMP-2 group. Both incidence rates were shown to be both numerically higher than those expected in the general population. However, once these rates were adjusted for multiplicity and a potentially pre-existing pancreatic case was eliminated from the analysis, the difference was not statistically significant.

The second section of the report contains a previously-submitted report on the incidence of pancreatic cancer in rhBMP-2 patients. The report, titled "Diboterminalfa [recombinant human Bone Morphogenetic Protein-2; rhBMP-2] (InductOs) and Pancreatic Cancer: A Retrospective Cohort Study," summarizes research performed by Dr. Gregory S. Cooper, MD, Professor of Medicine at Case Western Reserve University and commissioned by Wyeth. Wyeth decided to undertake the epidemiological investigation to evaluate a signal that rhBMP-2 use was associated with an increased risk of pancreatic cancer, based on a *post hoc* analysis of clinical trials that involved multiple comparisons. In this study, Wyeth investigated the potential association between rhBMP-2 exposure and risk of pancreatic cancer using a retrospective cohort of Medicare patients who underwent lumbar spinal fusion surgery between October 2003 and December 2005. The epidemiological study found that patients exposed to rhBMP-2 were not at an increased risk of pancreatic cancer, as compared to patients who did not receive rhBMP-2.

Medtronic Report

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1.0 INTRODUCTION

The purpose of this report is to present the information currently available on any potential relationship between rhBMP-2 and malignancy. While information from a variety of sources, including scientific literature, pharmacokinetic release studies, and tumor promotion studies, is provided, the primary focus of this report is data on the incidence of malignancy in clinical studies of rhBMP-2 performed by Medtronic Sofamor Danek and Wyeth. Data from Medtronic's 18 completed or ongoing clinical trials with rhBMP-2 and 26 Wyeth-sponsored clinical studies of rhBMP-2 will be analyzed to determine if an increased rate of malignancy occurs with the use of rhBMP-2. To date, Medtronic and Wyeth have carefully monitored all cases of malignancy reported with the use of rhBMP-2 in clinical studies.

This report is organized as follows:

- Section 2.0 describes the currently approved indications for rhBMP-2.
- Section 3.0 presents a general discussion of bone morphogenetic proteins.
- Section 4.0 includes a summary of the current literature regarding the incidence of malignancy with the use of rhBMP-2.
- Section 5.0 provides relevant pharmacokinetic information about rhBMP-2.
- Section 6.0 presents information on specific preclinical studies performed to investigate tumor promotion.
- Section 7.0 summarizes Medtronic and Wyeth's clinical trial experiences to date with rhBMP-2.
- Section 8.0 presents the plan for the statistical and epidemiological analysis of the available malignancy data from Medtronic and Wyeth's clinical studies, as well as the results of this analysis.
- Section 9.0 reviews the key points of the report.

This document is the first section of a larger document examining the relationship between rhBMP-2 and tumor formation. The remaining sections of the report, as described in the Executive Summary, are included following this report.

2.0 SUMMARY OF CURRENT INDICATIONS

As of February 2009, rhBMP-2/ACS (at a concentration of 1.5 mg/cc) has been approved in the United States for three indications. The first approval was granted in 2002, when rhBMP-2/ACS was approved for use in the lumbar spine in combination with Medtronic's LT-CAGE® Lumbar Tapered Fusion Device. The product was initially indicated for use in anterior lumbar interbody spinal fusion procedures to treat skeletally mature patients with degenerative disc disease (DDD) at a single level from L4-S1. The approval

for this indication was based on data from three clinical trials (a pilot study and two pivotal studies) conducted by Medtronic (IDE G960065/PMA P000058). In addition, 15 other Medtronic clinical trials to investigate the use of rhBMP-2 in the spine have been completed or are currently ongoing. These trials are described in Tables A1-1 and A1-2 of Attachment 1.

In 2004, rhBMP-2/ACS was also approved for use in the treatment of acute tibial fractures, based on data from a clinical study conducted by Wyeth. This study examined the efficacy and safety of rhBMP-2/ACS in the treatment of acute, open tibial shaft fractures that have been stabilized with IM nail fixation after appropriate wound management. Wyeth transferred ownership of this PMA to Medtronic after the PMA was approved by the FDA. Most recently, rhBMP-2/ACS received PMA approval in 2007 for oral maxillofacial use as an alternative to autogenous bone graft for sinus augmentations, and for localized alveolar ridge augmentations for defects associated with extraction sockets. This approval was based on the combined results of five different clinical studies performed by Wyeth. Medtronic submitted the PMA for the oral maxillofacial indications to FDA after completion of the clinical studies by Wyeth. Besides the six clinical studies represented in these two PMA approvals, Wyeth has conducted 20 other clinical trials examining the use of rhBMP-2 in various indications. All of Wyeth's studies are summarized in Table A1-3 of Attachment 1.



In addition to the US approvals, rhBMP-2/ACS has also been approved for two indications in Europe. Wyeth Europa was granted marketing authorization by the European Commission for use of rhBMP-2/ACS in the treatment of acute tibia fractures on 09 September 2002. On 29 March 2005, this authorization was expanded to include the use of rhBMP-2/ACS in the treatment of degenerative disc disease of the lumbar spine.*

3.0 OVERVIEW OF BONE MORPHOGENETIC PROTEINS

Bone morphogenetic proteins (BMPs) are a member of a large family of proteins collectively known as the Transforming Growth Factor- β (TGF- β)

* rhBMP-2/ACS has also been approved for use in various indications in Canada, Mexico, Israel, India, Brazil, Australia, Argentina, and Singapore.

superfamily. This large group of signaling polypeptides plays a key role in cell differentiation and growth. Besides the TGF- β isoforms, this group includes activin/inhibin, Mullerian inhibiting substance, and more than 20 proteins within the BMP family.¹ The biological activity of BMP was first identified by Dr. Marshall Urist, who demonstrated that protein extracts derived from mammalian bone were capable of inducing the formation of cartilage and bone when implanted into non-bony (ectopic) sites in rats. BMPs are the only known growth factors or hormones that induce new bone in this assay system.

The BMPs, like other members of the TGF- β family, initiate signaling from the cell surface transmembrane serine-threonine kinase receptors. However, the BMPs signal through receptors distinct from that of TGF- β . BMPs can interact with two distinct Type I receptors that are activin receptor-like kinases (ALK). These Type I receptors are termed BMPR-IA (ALK-3) and BMPR-IB (ALK-6), and they are structurally similar to one another. BMPs can also interact with three distinct Type II receptors (BMPR-II, ActR-II, and ActR-IIB). However, the majority of BMP signaling utilizes the BMPR-II receptor. BMP-2 binds to the Type IA and IB receptors with low affinity, but binding is enhanced in the presence of the Type II receptor, which is specific for BMPs. Upon binding of BMP ligand to the BMP receptor complex, either the Smad-dependent pathway or the Smad-independent signaling pathway is activated. BMPR-IA, BMPR-IB, and BMPR-II are expressed differentially in various cells, and the pattern of receptor expression can influence cellular responses to BMPs. Because the specificity of intracellular signals is determined by Type I receptors, the differential expression of BMPR-IA and BMPR-IB may be significant in understanding the pleiotropic effects of BMP action.

The Smad family of proteins acts as the main mediators of BMP signal transduction. The receptor/ligand interaction results in phosphorylation of the receptor regulated Smads, including Smad1, Smad5, and Smad8, which then form heteromeric complexes with Smad4. Smad4 is the common signal transduction mediator of the TGF- β family, and it induces transcription of the specific genes once translocated into the nucleus. Other members of the Smad family of molecules, such as Smad6, appear to down-regulate the BMP signal. The MAP kinase pathway, which mediates signaling of several growth factors and cytokines, also appears to be involved in BMP signal transduction.

Wyeth scientists have been able to isolate and produce large quantities of a recombinant version of human BMP-2 (rhBMP-2) for use in a variety of indications. rhBMP-2 is manufactured by cell culture using Chinese hamster ovary (CHO) cells that express the coding sequence for rhBMP-2. It is a glycosylated, disulfide-bonded, dimeric protein with two major subunit species of 114 and 131 amino acids. rhBMP-2 is thought to induce the differentiation of mesenchymal cells into cartilage and bone cells with the attendant endochondral (induction of cartilage followed by replacement with bone) and

intramembranous (direct induction of bone) bone formation. It is clear, however, that the physiological properties of the BMPs are not limited to bone; they have been shown to be multifunctional proteins affecting a variety of cells, including neuronal and epithelial cells.²

For various orthopedic indications, rhBMP-2 has been tested using different dosages, surgical approaches, and various matrices (carriers), such as ceramic and ceramic/bovine collagen matrices. For the currently approved indications, rhBMP-2 is reconstituted and applied to an absorbable collagen sponge (ACS). The ACS, manufactured from US-sourced tendon Type I bovine collagen, has been approved as a medical device for use as an intraoperative agent.

4.0 REVIEW OF LITERATURE

As noted in the previous section, BMP-2 is expressed in a variety of tissues and cell types, including malignant cells. BMPs have been shown to be expressed in many epithelial-derived neoplasms, including those found in the prostate, pancreas, and breast, as well as those in the oral cavity. Review of the current literature investigating the effects of direct exposure of rhBMP-2 on cancer cell lines has suggested both positive and negative effects, depending on the cell culture medium used, exposure regimen, and type and stage of progression of cell line used. Signaling is commonly up-regulated or down-regulated in neoplastic tissue, as compared to normal tissue. These variables should be considered when interpreting the data in publications.

Pancreatic cancer is an area of particular interest, as a previous analysis of clinical trial data produced a potential signal that rhBMP-2 use was associated with an increased risk of pancreatic cancer. While pancreatic cancer is not as common as either breast cancer or prostate cancer, it is not as rare as it is often perceived. Pancreatic cancer is the tenth most common cancer in men and the fourth leading cause of cancer death in men and women. According to the National Cancer Institute, it is estimated that there were 37,680 new cases of pancreatic cancer in the United States in 2008.[†] It is also expected that 34,290 deaths will occur this year from this disease.[‡] Most pancreatic tumors are diagnosed as adenocarcinomas. Other pancreatic tumors include serous cystadenomas, acinar cell cancers, and pancreatic neuroendocrine tumors.[§] Patients diagnosed with pancreatic cancer, particularly adenocarcinomas, typically have a poor prognosis partly because the cancer usually causes no symptoms early on, leading to locally advanced or metastatic disease at the time of diagnosis. Pancreatic cancers are commonly classified as resectable, locally

[†] <http://www.cancer.gov/cancertopics/types/pancreatic>.

[‡] Statistics adapted from the American Cancer Society's publication, Cancer Facts & Figures, 2008.

[§] Ghaneh P, Costello E, Neoptolemos JP. "Biology and management of pancreatic cancer." Gut 2007;56(8):1134-1152.

advanced, or metastatic. Resectable tumors are within the pancreas or may extend beyond it; however, there is no involvement of the blood vessels and no evidence of spreading (10-15% of patients are diagnosed at this stage). Locally advanced tumors are located within the pancreas but have involvement with local organs and blood vessels. For this reason, these tumors cannot be surgically removed although they present no evidence of spread to distant locations (35-40% of patients are diagnosed at this stage). Metastatic tumors have spread beyond the pancreas and involve distant organs (45-55% of tumors are diagnosed at this stage).^{**} Common risk factors for pancreatic cancer include advanced age (over 60 years old), male gender, African-American ethnicity, smoking, alcoholism, obesity, diabetes mellitus, chronic pancreatitis, history of gastrectomy or cholecystectomy, family history of pancreatic cancer, and a diet low in fruits and vegetables and high in red meat.

A survey of the available literature on all malignancies, including pancreatic cancer, was performed, and a brief summary of the findings from the various investigations is included below. The results are divided into two sections. The first describes the effect of rhBMP-2 on the inhibition of cancer progression; the second describes the effect of rhBMP-2 on the promotion of cancer progression.

4.1 Inhibition of Cancer Progression

- Orui et al. tested three osteosarcoma lines and one prostate and breast cell line. Cell cultures were supplemented with 1% fetal bovine serum (FBS). rhBMP-2 (50-500 ng/mL) inhibited cell growth in two of the osteosarcoma lines and had no effect on the other clones.³
- Ide et al. demonstrated that rhBMP-2 inhibited the growth of the androgen-sensitive prostate cancer cell line (LNCaP) but had no effect on three other androgen-insensitive prostate cancer cell lines.⁴ The cell culture was supplemented with 10% FBS. When LNCaP cells were incubated in serum-free media, rhBMP-2 enhanced cell growth (rhBMP-2 with exogenous androgens in serum-free media resulted in inhibition). The authors noted that BMPR-IB was up-regulated by androgens. They hypothesized that BMPR-IA and B may differentially regulate cell prostate cancer growth in response to BMP. Further, they speculated that androgens present in the FBS might partially explain the disparate results noted above.
- Tada et al. showed that BMP-2 suppressed growth of A549 lung cancer cell and induced cytoskeletal microfilament formation; similar findings were noted with addition of TFG- β .⁵ The A549 cells were maintained in a medium supplemented with 5% fetal calf serum.

^{**} <http://www.cancer.net/patient/Cancer+Types/Pancreatic+Cancer>.

- Arnold et al. found that rhBMP-2 decreased the proliferation of MDA-MBA-231 breast cancer cells to a greater extent than the less metastatic breast cancer cell line, MCF-7.⁶ Semiquantitative RT-PCR revealed that both lines contained BMP receptors IA, IB, and II.
- Beck et al. showed that BMP-2 induced growth suppression in colon cancer cells, and this is mediated in part by improved protein stability of the p21(WAF1).⁷
- Ghosh-Choudhury et al. demonstrated that BMP-2 inhibits both basal and estradiol-induced proliferation on MCF-7 breast cancer cells *in vitro*.⁸ In a separate publication, Ghosh-Choudhury et al. found that BMP-2 treatment inhibits epidermal growth factor induced growth of MDA-MB-231 human breast cancer cells by inducing hypophosphorylation of retinoblastoma, a key regulator of cell cycle progression.⁹
- Hallahan et al. showed that BMP-2 protein caused medulloblastoma cell apoptosis. BMP-2 induced this effect in both retinoid-sensitive and retinoid-resistant cells.¹⁰
- Nakamura et al. demonstrated the BMP-2 causes growth arrest and neuronal differentiation of human neuroblastoma derived cells by inducing p27(KIP1) accumulation.¹¹
- Tomari et al. found that BMP-2 inhibits dihydrotestosterone induced growth of LNCap prostate cancer cells through a decrease in E2F protein expression and suppression of E2F activity by hypophosphorylation of retinoblastoma.¹²
- Wen et al. showed that BMP-2 dose dependently inhibited the growth of OUMS37 rat gastric cells and MKN74 human gastric cancer cells through a p21/WAF1/COP1 pathway. The authors note that this inhibition is due to G1 phase cell cycle arrest. BMP-2 was also shown to increase the expression of pepsinogen II, a differentiation marker of the stomach, in MKN74 cells.¹³
- Steinert et al. found a difference in altered gene expression between single dose BMP-2 exposure and constant high level exposure of BMP-2. The authors grouped the genes of interest and found that apoptosis-related genes were predominantly upregulated under the single-dose application of BMP-2.¹⁴

4.2 Promotion of Cancer Progression

- Clement et al. reported that BMP-2 does not induce apoptosis in MCF-7 breast cancer cells. BMP-2 treatment induced increased expression of Id-1, Id-2, and Id-3 and decreased caspase-3 expression.¹⁵ In another publication, Clement also reports that, after short exposure to BMP-2, MCF-7 cells are able to migrate through matrigel. In a xenograft model without estrogen supplementation, MCF-7/BMP-2 cells formed tumors that were characterized by enhanced vascularization and formation of chondroid and osseous structures.¹⁶
- Feeley et al. reported that BMP-2 was able to stimulate cell migration and invasion of LAPC-4 and LAPC-9 prostate cancer cells in a dose dependent fashion.¹⁷ Noggin was able to inhibit this BMP dependent migration and invasion in LAPC-4 cells. In a separate investigation, Feeley et al. showed that BMP-2 stimulated PC-3 prostate cancer cell migration and invasion in a dose-dependent manner and that BMP-2 induced cell proliferation.¹⁸
- Fong et al. found that BMP-2 increases migration of human chondrosarcoma cells and acts through the PI3K/Akt pathway leading to beta 1 integrin activation and contributing to migration.¹⁹
- Gordon et al. discovered that BMP-2 induces an epithelial-to-mesenchymal transition and increases Panc-1 pancreatic cell invasiveness through a Smad-1 dependent mechanism.²⁰ The increased invasiveness is due in part to the BMP-2 induction of increased MMP-2 expression and activity.
- Katsuno et al. found that BMP-2 promoted motility and invasiveness in MDA-231-D cells *in vitro*.²¹ The authors also claim that dominant-negative receptors for TGF- β and/or BMPs inhibited bone metastasis in their mouse xenograft model.
- Langenfeld et al. reported that, though BMP-2 slightly suppressed growth of the A549 cell line *in vitro* (cells were cultured in 5% fetal calf serum), it stimulated the migration and invasiveness of A549 and H7249 lung carcinoma lines.²² The authors noted that BMP-2 was over-expressed in human non-small cell lung cancer. When BMP-2 was co-injected with A549 cells into nude mice, tumor growth *in vivo* was enhanced. In a follow-up article, the same authors note that BMP-2 stimulated neovascularization in tumors from A549 cells injected subcutaneously into (athymic) nude mice.²³ In a separate investigation, Langenfeld reported that BMP-2 treatment of A549 cells also induces the PI3K/mTOR signaling cascade in lung cancer cell lines. The authors also note that forced expression of BMP-2 in A549 cells (not addition of rhBMP-2) formed more

foci than that of vector controls. Rapamycin, an mTOR antagonist, prevented foci formation of the A549/BMP-2 cells.²⁴

- Kleeff et al. reported that, when cultured in serum-free media, BMP-2 enhanced the growth of two pancreatic cell lines, inhibited growth in one line, and had no effect in three others.¹ Kleeff et al. showed higher expression of BMP-2 and BMP-2 receptors (BMPR-IA and BMPR-II) in pancreatic carcinoma (compared to the normal pancreas and chronic pancreatitis). Further, the authors noted that increased BMP-2 immunostaining in pancreatic cancer was associated with shorter survival. The group tested the response of six pancreatic cell lines to BMP-2 *in vitro* in serum-free media; two showed enhanced growth. Both cell lines (ASPC-1 and CAPAN-1) had a mutation in the Smad4 gene. Transfection of full length Smad4 constructs led to attenuation or complete loss of the BMP-2 stimulatory effects on these two lines. The authors hypothesize that Smad4 mutation may result in BMP-2 acting as a mitogen, as opposed to leading to growth inhibition. Similar findings were noted by Dr. Reiss and colleagues with regard to TGF- β .²⁵ In Smad4-deficient pancreatic cancer cell lines, TGF- β did not induce suppression of growth but, rather, promoted cell motility and invasiveness.

As previously noted, Smad4 is a key factor in the signal transduction of BMP-2 (and other growth factors in the TGF- β family). The Smad4 protein is encoded by the Deleted in Pancreatic Cancer locus-4 (DPC4) gene, which was initially identified by Dr. Kern and colleagues, and resides on chromosome 18.²⁶ Bi-allelic loss of this tumor and suppressor gene is noted in 50-60% of patients with pancreatic cancer and in a minority of patients with other cancers such as colon cancer.²⁷

5.0 PHARMACOKINETIC INFORMATION

Information on a product's pharmacokinetic (PK) release profile can also help to explain the impact of systemic exposure to that product. However, PK studies were not feasible for rhBMP-2 in humans. Therefore, two sets of data have been relied upon to infer human PK: 1) formal PK studies in animals utilizing radiolabeled rhBMP-2; and 2) BMP-2 serum levels in human patients after implantation utilizing enzyme-linked immunosorbent assays (ELISA).

5.1 Animal Studies

Pharmacokinetic studies in rats and monkeys after intravenous (IV) administration of rhBMP-2 demonstrated that rhBMP-2 was rapidly cleared from the systemic circulation. After a single IV dose, concentrations of rhBMP-2 in rats declined bi-exponentially, with a terminal half-life of approximately 16 minutes. The terminal half-life in monkeys was 6.7 minutes.

The rapid initial decline of rhBMP-2 from blood after IV administration of a single dose suggests a rapid distribution of the protein from the systemic circulation to tissues. In rats, one minute after IV dosing, ¹²⁵I-rhBMP-2 was extensively distributed to highly perfused organs. Over 82% of the administered dosage was detected in the liver, kidney, spleen, and lung.

The decline of radioactivity from tissues was also rapid, indicating that the residence of the protein in organs was short. At 24 hours, only trace amounts of radioactivity (0.5% of the dosage) were detected in tissues; 92% of the BMP-2 associated radioactivity was excreted in the urine and approximately 3.4% in feces. The available data suggest that rhBMP-2 is extensively catabolized before being excreted, with 92% of the radioactivity in the urine no longer associated with intact protein.

The pharmacokinetics of rhBMP-2 following surgical implantation of rhBMP-2/ACS in rats was assessed, once again utilizing radiolabeled rhBMP-2. In a rat femoral onlay model, the loss of radioactivity was tri-phasic. The mean residence time at the site of implantation was four to eight days. Peak radioactivity in the systemic circulation was observed six hours post-implantation and represented approximately 0.1% of the administered dose.

The pharmacokinetics of rhBMP-2 on a collagen/calcium phosphate composite carrier was also assessed in a rabbit posterolateral fusion model. In this study, the mean residence time was 7.6 days. No measurable radioactivity was detected in the systemic circulation at any time point.

Overall, the relatively slow release of rhBMP-2 from the implant site, rapid clearance of rhBMP-2 from the systemic circulation, and high degree of catabolism of the protein prior to excretion suggest that the systemic exposure to implanted rhBMP-2 is negligible. Even assuming that peak systemic concentration in humans reached that observed in rats, the systemic exposure would be orders of magnitude below levels that were deemed to be non-toxic in acute toxicity studies. If 40 mg were implanted in the lumbar spine and 0.1% was detectable in the circulation, it would represent a potential systemic exposure dose of 0.04 mg. In rat and canine toxicity studies, an IV dose of 5.3 mg/kg (the equivalent of 371 mg in a 70 kg person) showed no toxic effects.

5.2 Human Serum Testing

Serum levels of BMP-2 were also tested in human subjects to determine the amount of rhBMP-2 remaining in the body after implantation. These levels were analyzed at various time periods in three studies utilizing various carriers. The results are described below:

- In the first study, serum levels were assessed in 24 patients with fractures of the distal femur or forearm who received rhBMP-2 (0.1 mg/cc) combined with a PLA/PLGA matrix (bioerodible particles). The lower level of detection in the ELISA assay used was 4 ng/mL; none of the patients had detectable levels 24 hours after treatment.
- In the second study, 22 patients with open tibial shaft fractures were randomized to receive control therapy or rhBMP-2/ACS at either 0.75 mg/cc or 1.5 mg/cc. The maximum dose of rhBMP-2 in the study was 12 mg. The lower limit of detection of the ELISA utilized in the study was 10 ng/mL. One control patient had a positive ELISA prior to treatment, but did not have measurable levels following therapy. The results were negative in all of the other patients.
- Systemic release was also evaluated in a clinical study in which rhBMP-2 was injected within a calcium phosphate matrix (CPM). Eleven (11) subjects were evaluated for serum levels of the BMP-2 protein before treatment and at six hours and four weeks after injection with rhBMP-2/CPM. These time points were based on peak and long-term release kinetics observed in animal studies. None of the patients had detectable levels (lower level of detection 2 ng/mL).

6.0 PRECLINICAL TUMOR PROMOTION STUDIES

The Wyeth Drug Safety and Metabolism group conducted a series of experiments to test the potential of rhBMP-2 to enhance tumor growth *in vitro* and *in vivo*.^{††} These studies are briefly summarized below. The last three studies were performed as FDA-mandated conditions of approval for PMA P000058 (INFUSE® Bone Graft with the LT-CAGE® Lumbar Tapered Fusion Device in the lumbar spine) and for PMA P000054 (INFUSE® Bone Graft).

- Initially, 65 different tumor cells lines were tested using a colony-forming assay. Concentrations of rhBMP-2 at 10, 100, and 1000 ng/mL had no stimulatory effect; growth was inhibited in 16 of the lines tested. These cell lines were not screened for the presence of BMP-2 receptors.
- In a follow-up study, 21 different human tumor lines were screened for the presence of functionally relevant expression of BMP-2 receptors by comparing levels of messenger RNA (using quantitative polymerase chain reaction) to those in cells known to be responsive to BMP-2. Ten of the lines tested were determined to have functionally relevant levels of BMPR-IA, BMPR-IB, and BMPR-II.

^{††} All of the *in vitro* studies were performed in culture media supplemented with 10-20% fetal bovine serum.

- These ten lines and an osteosarcoma cell line were tested *in vitro* for response to exogenously added rhBMP-2 (3-100 ng/mL). No effect was noted in ten of the cases. In the other line, growth was inhibited in a concentration-dependent fashion (LnCap, prostate cancer).
- The effects of rhBMP-2/ACS on the *in vivo* growth of seven of the aforementioned lines were further tested. Athymic nu/nu female mice were implanted subcutaneously with a pre-defined number of tumor cells. Once the tumor xenografts attained a mass of 70-170 mg, the mice were randomized to four cohorts: 1) sham surgery; 2) ACS; 3) ACS + 4.22 mg/mL rhBMP-2; and 4) ACS + 0.422 mg/mL rhBMP-2. In each case, the surgery was performed in the flank opposite to the one implanted with tumor cells. rhBMP-2 had no effect on four cell lines and reduced the growth (at some time periods) in the other three.

Overall, these studies did not demonstrate a pro-oncogenic effect of rhBMP-2. Additional details on these preclinical studies are provided in Attachment 2.

7.0 CLINICAL EXPERIENCE

7.1 Summary of Clinical Trials

The previous sections provided the latest available information from the scientific literature regarding the effect of rhBMP-2 on malignancy, as well as results of release and tumor promotion studies performed to examine this relationship. However, the primary focus of this report is malignancy data from Medtronic and Wyeth's clinical studies of rhBMP-2. While Medtronic's studies address the area of spinal fusion, Wyeth's clinical trials examine other uses of rhBMP-2, including various orthopedic indications and oral maxillofacial surgery. Specific information on Medtronic and Wyeth's clinical trials is provided in Attachment 1.

Patients in these studies who had any follow-up visit information after their treatment were considered part of the patient population for the analyses described in subsequent sections. Data from patients in Medtronic's clinical studies were compiled into a composite Medtronic treatment group, with separate arms for the patients who received treatment with rhBMP-2 and those who did not. The same procedure was performed with Wyeth study data. A basic demographic analysis was then completed on the data from both groups. The full results of this analysis are provided for the Medtronic and Wyeth treatment groups in Tables A3-1 and A3-2 of Attachment 3, respectively.

In Medtronic's 18 clinical studies of rhBMP-2, 1152 patients received rhBMP-2, and 1008 received a non-rhBMP-2 treatment. The average age of

patients in Medtronic's rhBMP-2 group was 47.0 years; for the non-rhBMP-2 group, the mean age was 45.2. Both groups had a slightly larger percentage of women than men. The rhBMP-2 group had 526 men and 626 women (45.7% vs. 54.3%). The non-rhBMP-2 group had 475 men and 533 women (47.1% vs. 52.9%). The total follow-up duration was 3774 patient-years for the rhBMP-2 group and 3234 patient-years for the non-rhBMP-2 group.

In the 26 Wyeth-sponsored studies, 1006 patients received treatment with rhBMP-2, while 749 patients were not treated with rhBMP-2. The average age of the two patient groups in Wyeth's studies was very close; patients in the rhBMP-2 group were an average of 42.6 years old, and patients in the non-rhBMP-2 group had a mean age of 42.3 years old. Both of Wyeth's treatment groups had significantly more men than women. The rhBMP-2 group had 708 men, compared to 298 women (70.4% vs. 29.6%). The non-rhBMP-2 group had 508 men and 241 women (67.8% vs. 32.2%). The total follow-up duration was 1417 patient-years for the rhBMP-2 group and 989 patient-years for the non-rhBMP-2 group.

Patients in Medtronic's rhBMP-2 group had an average of 3.3 years of systematic follow-up, while patients in the non-rhBMP-2 group had slightly less at 3.2 years. Patients in Wyeth's rhBMP-2 group were followed for an average of 1.4 years, and patients in the non-rhBMP-2 group had 1.3 years of follow-up. The discrepancy in follow-up rates between the Medtronic and Wyeth groups is due to differences in study design. Almost all of Medtronic's studies were designed with a 24-month post-treatment time point, which required patients to continue participation until every patient in the study had reached 24 months after surgery. Many of the Wyeth studies only required patients to complete follow-up through one year post-treatment.

In addition to differences in study endpoints and required follow-up time, it is also important to note other variations in the study designs that contributed to the difference in the amount of systematic follow-up between the rhBMP-2 group and non-rhBMP-2 groups. Some of the clinical trials were not randomized and had single-arm designs with rhBMP-2 treatment only. Some had a randomization ratio other than 1:1. Others had post-approval studies that required longer-term follow-up of rhBMP-2 patients only.

7.2 Reported Malignancy Cases

The following section provides a summary of the malignancies reported in both Medtronic and Wyeth's clinical trials. All cancers were classified using categories defined by the U.S. National Cancer Institute's Surveillance, Epidemiology and End Result (SEER) program. This program is an epidemiological surveillance tumor registry designed to track cancer incidence and survival in the U.S. Table 1 shows the specific 24 categories of malignancies captured in the SEER program. In addition, the SEER program

reports statistics for “All Sites (Invasive).” Non-invasive cancers (i.e., some non-serious skin cancers) are not captured in these categories.

Table 1: SEER* MALIGNANCIES		
Brain and Other Nervous System	Kidney and Renal Pelvis	Oral Cavity and Pharynx
Breast	Larynx	Ovary
Cervix Uteri	Leukemia	Pancreas
Colon and Rectum	Liver and Bile Duct	Prostate
Corpus Uteri	Lung and Bronchus	Stomach
Esophagus	Melanoma of the Skin	Testis
Hodgkin Lymphoma	Multiple Myeloma	Thyroid
Kaposi’s Sarcoma	Non-Hodgkin Lymphoma	Urinary Bladder

* SEER = Surveillance, Epidemiology and End Result

To date, there have been 23 SEER malignancies reported in the rhBMP-2 group of Medtronic’s clinical trials. Eleven (11) SEER malignancies have been reported in Medtronic’s non-rhBMP-2 group. In the Wyeth studies, there were nine SEER malignancies reported in the rhBMP-2 group^{‡‡} and six in the non-rhBMP-2 group. A breakdown of these malignancies, by category, is provided in Table 2.

^{‡‡} This number includes a case of mesothelioma (cancer of the abdominal lining) that is not considered a SEER malignancy. However, because this cancer is considered an invasive cancer, it was included in the “All Sites” category for the SIR analysis.

Table 2: SEER* MALIGNANCIES REPORTED FROM rhBMP-2 CLINICAL TRIALS

SEER Cancer Classification	Reported from Medtronic Clinical Trials (as of 12/22/08)		Reported to Date from Wyeth Clinical Trials (as of 09/03/08)	
	rhBMP-2 Arms (n = 1152)	Non-rhBMP-2 Arms (n = 1008)	rhBMP-2 Arms (n = 1006)	Non-rhBMP-2 Arms (n = 749)
Brain and Other Nervous System	0	0	0	1
Breast	3	2	2	3**
Cervix Uteri	0	0	0	0
Colon and Rectum	1	1	1	0
Corpus Uteri	0	1	0	0
Esophagus	0	0	0	0
Hodgkin Lymphoma	0	1	0	0
Kaposi's Sarcoma	0	0	0	0
Kidney and Renal Pelvis	1**	0	0	0
Larynx	1	0	0	0
Leukemia	1	0	0	0
Liver and Bile Duct	1	0	0	0
Lung and Bronchus	1	0	0	0
Melanoma of the Skin	3	0	0	1
Myeloma	0	0	1	0
Non-Hodgkin Lymphoma	1	1	0	0
Oral Cavity and Pharynx	0	0	0	1
Ovary	1	0	0	0
Pancreas	3**	0	0	0
Prostate	2	2	4	0
Stomach	0	0	0	0
Testis	1	0	0	0
Thyroid	3	3	0	0
Urinary Bladder	0	0	0	0
<i>Other (Mesothelioma)[†]</i>	0	0	1	0
TOTAL	23	11	9	6

* SEER = Surveillance, Epidemiology and End Result

** Denotes pre-existing or potentially pre-existing malignancy. Only one of the three cases of pancreatic cancer in the Medtronic group and one of the three breast cancer cases in the Wyeth group were considered pre-existing or potentially pre-existing.

[†] While this cancer is not considered a SEER malignancy, it is considered an invasive cancer and was included in the "All Sites" category for the SIR analysis.

In addition to the cancers listed above, there have also been non-SEER malignancies reported in both Medtronic and Wyeth's clinical trials. These are primarily non-invasive skin cancers. In Medtronic's studies, there were four non-SEER cancers in the rhBMP-2 group, and a single non-SEER cancer in the non-rhBMP-2 group. There were five non-SEER malignancies

in Wyeth's rhBMP-2 group, and four non-SEER cases in the non-rhBMP-2 group. The non-SEER cases are summarized in Table 3 below.

Table 3: NON-SEER* MALIGNANCIES REPORTED FROM rhBMP-2 CLINICAL TRIALS

Classification	Reported from Medtronic Clinical Trials (as of 12/22/08)		Reported to Date from Wyeth Clinical Trials (as of 09/03/08)	
	rhBMP-2 Arms (n = 1152)	Non-rhBMP-2 Arms (n = 1008)	rhBMP-2 Arms (n = 1006)	Non-rhBMP-2 Arms (n = 749)
Basal Cell Carcinoma	1	0	1	2
Epithelioma**	0	0	1	0
Melanoma <i>in situ</i> [†]	1	0	0	0
Merkel Cell Carcinoma**	0	1	0	0
Squamous Cell Carcinoma	2	0	3 ^{††}	2
TOTAL	4	1	5	4

* SEER = Surveillance, Epidemiology and End Result

** Both epithelioma and Merkel cell carcinoma are non-melanoma types of skin cancer.

[†] This cancer is being counted as a non-SEER cancer because it was originally an *in situ* cancer that was reported to be completely excised at the time of first diagnosis. The same patient was later diagnosed as having melanoma and was counted as SEER case in Table 2.

^{††} Denotes pre-existing malignancy. Only one of the three cases of squamous cell cancer in the Wyeth group was considered pre-existing.

Detailed case histories for both the SEER and non-SEER malignancies in Medtronic's clinical trials are provided in Attachments 4 and 5. Similar information is provided for the Wyeth studies in Attachments 6 and 7.

8.0 STATISTICAL AND EPIDEMIOLOGICAL ANALYSIS OF MALIGNANCIES

8.1 Analysis Methods

In order to assess and compare the occurrence of malignancies between patients who received rhBMP-2 treatments and those who did not, three types of statistical analyses were performed with Medtronic and Wyeth worldwide clinical trial data. Standardized incidence ratio (SIR) analysis was also conducted to compare the clinical trial patients with the general US population of similar age, gender, and race. Results of the various analyses are presented for the Medtronic and Wyeth groups separately and for a combination of the two groups.

Some of the malignancy cases reported in the clinical trials were either non-invasive (i.e., certain skin cancers) or pre-existing at the time of original treatment. Most of the analyses have been performed with these cases both included and excluded.

8.1.1 Simple Comparison of Malignancy Cases Between rhBMP-2 and Non-rhBMP-2 Patients

Fisher's exact test was used to compare the pooled numbers (rates) of malignancy cases in rhBMP-2 patients and non-rhBMP-2 patients in the clinical trials. This is a naïve type of analysis, since not all of the clinical trials were randomized, some of the trials had single-arm designs with rhBMP-2 treatment only, and some of the trials went into the post-approval study phase with longer-term follow-ups of rhBMP-2 patients only. This analysis ignored the fact that the rhBMP-2 patients have had a longer mean follow-up duration.

8.1.2 Time-to-Event Analysis for Comparing the Time from Treatment to Diagnosis of Malignancy Between rhBMP-2 and non- rhBMP-2 Patients

A simple time-to-event (Kaplan-Meier) analysis and a Cox regression model (PHREG) analysis – adjusting for patient age, sex, and race – were performed to assess the difference in the time from treatment to diagnosis of malignancy between the rhBMP-2 and non-rhBMP-2 patients. These analyses took into account the difference in follow-up duration between the two groups, as well as the difference in the time to diagnosis. The adjustment for age, sex, and race in the Cox regression analysis was inherently based on the internal regression relationship between occurrence of malignancy and those factors that were built on data from the clinical trial patients. As a comparison, the standardized incidence ratio (SIR) analysis described below was based on the external relationship built with patient registry/general population data.

8.1.3 Comparison of Incidence Rates

Incidence rates were calculated as the number of cases per 1000 patient-years of follow-up. The incidence rates between the rhBMP-2 and non-rhBMP-2 patients were then compared. The mid-p exact approach was used for calculating p-values and 95% confidence intervals. This analysis took account of the difference in follow-up duration between the two groups.

8.1.4 Standardized Incidence Ratio (SIR) Analysis

In epidemiology, standardized incidence rates of occurrence of disease are measures of primary interest. Standardization is a tool to minimize distortion during the comparisons of rates. A standardized incidence ratio (SIR) analysis was used to assess whether the frequency of malignancy among patients who were exposed to rhBMP-2 in clinical trials was consistent with the frequency of malignancy in the general population (of similar age, gender, and race). The SIR is defined as the number of observed cases of an event divided by the expected number of that event.

As described above, population-based cancer incidence estimates from the Surveillance, Epidemiology and End Result (SEER) program were used to

calculate the expected numbers of malignancies. The 2004 SEER dataset, in which age-specific^{§§} cancer rates were based on 1997-2001 registry data, was used for this analysis.²⁸ The expected numbers were calculated by matching race, gender, and age of the study patients to the SEER cancer rates and then multiplying the rates by the duration of patient follow-up. For example, a white male patient who is 55 years old has an expected rate of 125/100,000 to have a lung cancer diagnosed in a year according to the SEER statistics. If the patient had a follow-up duration of 3.5 years in the clinical trial, he would contribute $3.5 \times 125/100,000$ to the expected number for lung cancer. The summation of such values for all the rhBMP-2 patients would be the expected number for the rhBMP-2 group.

To determine the observed malignancies in such an epidemiological analysis, the case-definition should be consistent with the SEER definition of incident cancer. As mentioned above, non-serious skin cancers are not captured in the SEER program and are not feasibly included in the analyses presented here. In addition, consistent with the SEER malignancy case definition, we did not count reports of “carcinoma-in-situ” in the SIR analyses.

SIRs for “all sites” and 24 SEER individual cancer categories were examined and calculated by the number of observed cases divided by the expected number for each category. The 95% confidence intervals (CIs) for the SIRs were calculated using the Approximation to Mid-p approach, which is the most conservative method according to an article by Ng, Filardo, and Zheng,^{***} since it gives the shortest expected interval.²⁹ An interval containing the value of “1” indicates the observed incidence is not significantly different from the matched general population.

Because there were 24 SEER cancer categories examined, the number of observed cases in one or more categories could statistically deviate from the expected for the population simply by chance alone, even if no real difference existed. This is a statistically well-known, so-called “multiplicity” issue. Therefore, using the Bonferroni approach to adjust for multiplicity, we also calculated the $(1-0.05/24) = 99.79\%$ confidence intervals for each of the 24 individual SEER cancer categories. These confidence intervals were multiplicity-adjusted. The number 24 used for the adjustment is a conservative number, which did not consider separate, multiple comparisons for Medtronic data, Wyeth data, and the pooled data.

8.2 Analysis Results

Cumulative malignancy data were collected from Medtronic and Wyeth’s rhBMP-2 clinical trials, and analyses of this data were performed as described

^{§§} By 5-year age group.

^{***} The Approximation to Mid-p approach was referred to as “M8” in the article.

in Section 8.1. The Medtronic database was closed for this analysis on 22 December 2008, while the Wyeth data were last updated on 03 September 2008.^{†††} The results of the analyses are summarized in the text and tables below; the full results are also provided in Attachment 3.

In some of the tables, a footnote references four pre-existing or “potentially pre-existing” cancers. Of these four malignancies, three (a renal cancer in Medtronic’s rhBMP-2 group, an instance of skin cancer in Wyeth’s rhBMP-2 group, and a case of breast cancer in Wyeth’s non-rhBMP-2 group) were documented in patient case histories as present prior to study treatment and are thought to be clearly pre-existing. The fourth case is thought to be “potentially pre-existing” based on the time of onset of the cancer and results of laboratory tests for a specific cancer marker.

In this instance, a male patient in Medtronic’s study of rhBMP-2/ACS with MasterGraft™ Granules presented with “painless” jaundice in mid-January 2004, one month after receiving treatment with rhBMP-2 in December 2003. In early February, the patient’s Carbohydrate Antigen (CA) 19-9 level, a pancreatic cancer tumor marker, was tested and found to be 377 U/mL (normal < 37 U/mL). On 27 February 2004, a fine needle biopsy of the head of the pancreas revealed the presence of an adenocarcinoma, and a follow-up CT scan on 01 March 2004 confirmed a 2.9 x 3.2 cm mass in the head of the pancreas.

In December 2004, the patient’s levels of CA 19-9 were measured from stored blood serum samples (obtained at the pre-operative, 6-week, 3-month, and 6-month evaluations). All available CA 19-9 levels are shown in Table 4 below.

Table 4: CA 19-9 Levels for Patient	
Date	CA 19-9 Level (U/mL) [Normal < 37 U/mL]
09 December 2003 (pre-operative stored sample)	138
16 January 2004 (6-week evaluation stored sample)	209
02 February 2004 (oncology consult – separate laboratory)	377
08 March 2004 (3-month evaluation stored sample)	637
09 July 2004 (6-month evaluation stored sample)	71.6*

* Patient initiated chemotherapy and radiation therapy on 05 April 2004.

These results, coupled with the short time to onset, seem to imply that the patient’s cancer was present prior to receiving rhBMP-2/ACS. As a result, this malignancy is considered “potentially pre-existing.”^{‡‡‡}

^{†††} Data received after these cut-off dates are not included in the analyses, but available information from them is provided in Attachment 8.

^{‡‡‡} This patient’s complete case history is provided in Attachment 4 of this document.

Where applicable, the statistical analyses for this report were performed both with these pre-existing four cancers included and excluded. Considering pre-existing cancers in an analysis is thought by some to be an overly conservative approach. Performing the analyses both ways provides a means to determine the influence of pre-existing cancers on the results.

8.2.1 Results of Simple Comparison of Malignancy Cases Between rhBMP-2 and Non-rhBMP-2 Patients

As described in Section 8.1.1, Fisher's exact test was used to compare the rates of malignancy cases in rhBMP-2 patients and non-rhBMP-2 patients in both Medtronic and Wyeth's clinical studies. To determine the malignancy rate, the number of patients with a reported cancer was divided by the total number of patients (i.e., the number of patients in the particular study group who had any follow-up visit after their treatment). The results are summarized in Tables 5 and 6 below. In both tables, patients are grouped by treatment arm (rhBMP-2 vs. non-rhBMP-2); information on both SEER-designated and non-SEER cancers is included.

Table 5. Simple Comparison of Malignancy Cases (rhBMP-2 vs. non-rhBMP-2 Patients): Analysis Including Pre-Existing Cases*						
Source	Malignancy Type	rhBMP-2 Group		Non-rhBMP-2 Group		p-value (Fisher's exact test)
		Number of Cases	Number (%) of Patients	Number of Cases	Number (%) of Patients	
Medtronic			(n = 1152)		(n = 1008)	
	SEER malignancies	23	23 (2.0%)	11	11 (1.1%)	0.118
	Non-SEER malignancies	4	4 (0.3%)	1	1 (0.1%)	0.381
	Total malignancies	27	25 (2.2%)**	12	12 (1.2%)	0.096
Wyeth			(n = 1006)		(n = 749)	
	SEER malignancies	9	9 (0.9%)	6	6 (0.8%)	1.000
	Non-SEER malignancies	5	5 (0.5%)	4	4 (0.5%)	1.000
	Total malignancies	14	12 (1.2%)**	10	10 (1.3%)	0.830
Pooled			(n = 2158)		(n = 1757)	
	SEER malignancies	32	32 (1.5%)	17	17 (1.0%)	0.192
	Non-SEER malignancies	9	9 (0.4%)	5	5 (0.3%)	0.595
	Total malignancies	41	37 (1.7%)**	22	22 (1.3%)	0.291

n = number of patients who had any follow-up visit after treatment.

* Pre-existing or "potentially pre-existing" cases included: 1 renal cancer and 1 pancreatic cancer from the Medtronic rhBMP-2 group; 1 skin cancer from the Wyeth rhBMP-2 group; and 1 breast cancer in the Wyeth non-rhBMP-2 group.

** Two patients in both the Medtronic and Wyeth rhBMP-2 groups reported both a SEER and non-SEER cancer. This explains the discrepancy in the number of cases vs. the number of patients.

As shown in Table 5, 27 cases of cancer were reported in 25 patients in Medtronic's rhBMP-2 treatment groups. Of these cases, four cancers were designated as non-SEER malignancies (i.e., non-invasive skin cancers). The total malignancy rate for Medtronic's rhBMP-2 group was determined to be 2.2% (25/1152). The rate of SEER malignancies, excluding the patients with non-SEER cancers, was found to be 2.0% (23/1152). For patients in Medtronic's studies who did not receive rhBMP-2, the malignancy rate is slightly lower. In all, 12 malignancies were reported, with one of these cases designated as a non-SEER malignancy (Merkel cell carcinoma, a type of skin cancer). The total malignancy rate for this group was calculated to be 1.2% (12/1008); the SEER malignancy rate was just less at 1.1% (11/1008).

While a numerical difference in the number of patients with malignancies exists between the two groups in Medtronic's clinical studies, this difference was not shown to be statistically significant, based on the p-values calculated from Fisher's exact test ($p=0.096$, total rate; $p=0.118$, SEER rate). It is important to note again that this is a naïve type of analysis that does not account for variations in study design and length of follow-up. As stated before, not all of Medtronic's clinical trials were randomized, some had single-arm designs with the rhBMP-2 treatment only, and others went into the post-approval study phase with longer-term follow-ups of rhBMP-2 patients only.

In the Wyeth studies, 14 malignancies were noted for 12 patients who received rhBMP-2. Of these malignancies, five were designated as non-SEER cancers. The total malignancy rate for Wyeth's rhBMP-2 group was 1.2% (12/1006), with a SEER malignancy rate of 0.9% (9/1006). These rates were virtually the same for patients who did not receive rhBMP-2. Ten cancers were reported in Wyeth's non-rhBMP-2 treatment groups, and four of these were non-SEER malignancies. The total malignancy rate was calculated to be 1.3% (10/749); the SEER malignancy rate was just less at 0.8% (6/749). Fisher's exact test showed no significant difference in these rates ($p=0.830$, total rate; $p=1.000$, SEER rate).

When the results of the Medtronic and Wyeth groups were pooled, the total malignancy rate for the combined rhBMP-2 group was 1.7% (37/2158), and the SEER malignancy rate was 1.5% (32/2158). For the pooled non-rhBMP-2 group, the total cancer rate was 1.3% (22/1757), with a SEER malignancy rate of 1.0% (17/1757). While the rates for the non-rhBMP-2 group were slightly less than those for the rhBMP-2 group, the difference was not shown to be statistically significant ($p=0.291$, total rate; $p=0.192$, SEER rate).

As described before, the same analysis was also performed excluding pre-existing and “potentially pre-existing” malignancy cases. The results are presented in Table 6.

Table 6. Simple Comparison of Malignancy Cases (rhBMP-2 vs. non-rhBMP-2 Patients): Analysis Excluding Pre-Existing Cases*						
Source	Malignancy Type	rhBMP-2 Group		Non-rhBMP-2 Group		p-value (Fisher's exact test)
		Number of Cases	Number (%) of Patients	Number of Cases	Number (%) of Patients	
Medtronic			(n = 1152)		(n = 1008)	
	SEER malignancies	21	21 (1.8%)	11	11 (1.1%)	0.211
	Non-SEER malignancies	4	4 (0.3%)	1	1 (0.1%)	0.381
	Total malignancies	25	23 (2.0%)**	12	12 (1.2%)	0.172
Wyeth			(n = 1006)		(n = 749)	
	SEER malignancies	9	9 (0.9%)	5	5 (0.7%)	0.788
	Non-SEER malignancies	4	4 (0.4%)	4	4 (0.5%)	0.730
	Total malignancies	13	11 (1.1%)**	9	9 (1.2%)	0.825
Pooled			(n = 2158)		(n = 1757)	
	SEER malignancies	30	30 (1.4%)	16	16 (0.9%)	0.182
	Non-SEER malignancies	8	8 (0.4%)	5	5 (0.3%)	0.784
	Total malignancies	38	34 (1.6%)**	21	21 (1.2%)	0.341

n = number of patients who had any follow-up visit after the treatment.

* Pre-existing or “potentially pre-existing” cases excluded: 1 renal cancer and 1 pancreatic cancer from the Medtronic rhBMP-2 group; 1 skin cancer from the Wyeth rhBMP-2 group; and 1 breast cancer in the Wyeth non-rhBMP-2 group.

** Two patients in both the Medtronic and Wyeth rhBMP-2 group reported both a SEER and non-SEER cancer. This explains the discrepancy in the number of cases vs. the number of patients.

With two cancers excluded from the analysis of Medtronic’s rhBMP-2 group, the total malignancy rate was calculated to be 2.0% (23/1152), down from 2.2% in the original analysis. The rate of SEER malignancies, excluding the patients with non-SEER cancers, was found to be 1.8% (21/1152), less than the original 2.0%. The rate of malignancies for the non-rhBMP-2 group did not change in either category. The p-values were re-calculated with the new rates, and they increased, showing less of a difference between the two groups than before.

Two cancers were also excluded from the analysis of the Wyeth data – one non-SEER malignancy from the rhBMP-2 group and a SEER malignancy from the non-rhBMP-2 group. For Wyeth’s rhBMP-2 group, the total malignancy rate was determined to be 1.1% (11/1006), down from 1.2%. The SEER

malignancy rate did not change for Wyeth's rhBMP-2 group. For the non-rhBMP-2 group, the total malignancy rate declined slightly with the exclusion of the pre-existing breast cancer, to 1.2% (9/749) from the original 1.3%. The SEER malignancy rate also decreased, from the original 0.8% to 0.7% (5/749). The p-values did not show a significant difference between the rates in the two groups for this analysis.

Finally, when the results of the Medtronic and Wyeth groups (excluding pre-existing and potentially pre-existing cancers) were pooled, the total malignancy rate for the combined rhBMP-2 group was 1.6% (34/2158), and the SEER malignancy rate was 1.4% (30/2158). For the non-rhBMP-2 group, the total cancer rate was 1.2% (21/1757), with a SEER malignancy rate of 0.9% (16/1757). Again, the difference between the two groups was not shown to be statistically significant (p=0.341, total rate; p=0.182, SEER rate).

8.2.2 Results of Time-to-Event Analysis for Malignancy Cases Between rhBMP-2 and non-rhBMP-2 Patients

A simple time-to-event (Kaplan-Meier) analysis and a Cox regression model (PHREG) analysis were performed to assess the difference in the time from treatment to malignancy diagnosis between patients in the rhBMP-2 and non-rhBMP-2 groups, as outlined in Section 8.1.2 above. Unlike the simple comparisons performed in Section 8.2.1, these analyses took into account the difference in follow-up duration between the two groups, in addition to the difference in the time to diagnosis. The Cox regression analysis also adjusted for the variables of age, race, and sex. Due to the nature of time-to-event analyses, pre-existing cases (as discussed above) were excluded from the analyses. The results are presented in Table 7.

Table 7. Time-to-Event Analyses of Time from Treatment to Malignancy Diagnosis Between rhBMP-2/non-rhBMP-2 Patients				
Source	Malignancy Type	p-value from Kaplan-Meier Analysis		p-value from Cox Regression Analysis, Adjusting for Age, Race, & Sex
		Log-Rank Test	Wilcoxon Test	
Medtronic	SEER malignancies	0.204	0.234	0.297
	Total malignancies	0.169	0.136	0.258
Wyeth	SEER malignancies	0.788	0.702	0.636
	Total malignancies	0.635	0.414	0.779
Pooled	SEER malignancies	0.182	0.441	0.236
	Total malignancies	0.333	0.558	0.423

Regardless of the analysis performed or the data source (Medtronic, Wyeth, or pooled), the results did not show a statistical difference between the rhBMP-2 and non-rhBMP-2 treatment groups ($p < 0.05$).

8.2.3 Results of Comparison of Incidence Rates Between rhBMP-2 and non-rhBMP-2 Patients

The rate of cancer incidence was determined for the rhBMP-2 and non-rhBMP-2 groups in both Medtronic and Wyeth's clinical studies. To allow for equal comparison, this rate was calculated as the number of cases per 1000 patient-years of follow-up. In addition, the rate ratio between the rhBMP-2 and non-rhBMP-2 groups was determined. A rate ratio of 1 indicates that the groups have no difference in incidence rate.

As with the simple comparisons in Section 8.2.1, these analyses were performed both with pre-existing cases (described earlier) included and excluded. The results are presented in Tables 8 and 9.

Table 8. Incidence Rates Between rhBMP-2 and non-rhBMP-2 Patients: Analysis Including Pre-Existing Cases*							
Source	Malignancy Type	rhBMP-2 Group		Non-rhBMP-2 Group		Comparison	
		Number of Case Patients	Incidence Rate (95% CI) (per 1,000 patient-years)	Number of Case Patients	Incidence Rate (95% CI) (per 1,000 patient-years)	Rate Ratio (95% CI)	p-value (Mid-p exact)
Medtronic	Total Follow-up (patient-years)		3774		3234		
	SEER malignancies	23	6.094 (3.862, 9.145)	11	3.401 (1.696, 6.086)	1.792 (0.882, 3.817)	0.109
	Total malignancies	25	6.624 (4.286, 9.779)	12	3.711 (1.915, 6.482)	1.785 (0.906, 3.676)	0.096
Wyeth	Total Follow-up (patient-years)		1417		989		
	SEER malignancies	9	6.351 (2.898, 12.060)	6	6.067 (2.216, 13.200)	1.047 (0.368, 3.161)	0.945
	Total malignancies	12	8.469 (4.371, 14.790)	10	10.110 (4.841, 18.600)	0.838 (0.357, 1.999)	0.679
Pooled	Total Follow-up (patient-years)		5191		4223		
	SEER malignancies	32	6.165 (4.216, 8.703)	17	4.026 (2.344, 6.446)	1.531 (0.856, 2.817)	0.155
	Total malignancies	37	7.128 (5.018, 9.825)	22	5.210 (3.264, 7.888)	1.368 (0.810, 2.353)	0.246

* Pre-existing or "potentially pre-existing" cases included: 1 renal cancer and 1 pancreatic cancer from the Medtronic rhBMP-2 group; 1 skin cancer from the Wyeth rhBMP-2 group; and 1 breast cancer in the Wyeth non-rhBMP-2 group.

The incidence rate in the Medtronic studies was numerically higher for the rhBMP-2 group than for the non-rhBMP-2 group in both total and SEER malignancies. However, the difference in the incidence rate between the two groups was not shown to be statistically significant ($p=0.096$, total rate; $p=0.109$, SEER rate).

In the Wyeth studies, the rhBMP-2 group had a numerically lower incidence rate for total malignancies than the non-rhBMP-2 group, and the rate ratio was less than one as a result. For the number of SEER malignancies, the incidence rate was virtually the same for both treatment groups (rate ratio=1.047). The difference in the total and SEER malignancy rates between Wyeth treatment groups was not found to be statistically significant in either case ($p=0.679$, total rate; $p=0.945$, SEER rate).

When data from Medtronic and Wyeth were pooled, the incidence rate was found to be slightly greater in the rhBMP-2 group than the non-rhBMP-2 group for both total and SEER malignancies. The total malignancy incidence rate ratio was 1.368 (95% CI: 0.810, 2.353), and the SEER malignancy incidence rate ratio was 1.531 (95% CI: 0.856, 2.817). However, the differences were not statistically significant ($p=0.246$, total rate; $p=0.155$, SEER rate).

When pre-existing cases are excluded from the same analysis, the values change slightly, as shown in Table 9.

Table 9. Incidence Rates Between rhBMP-2 and non-rhBMP-2 Patients: Analysis Excluding Pre-Existing Cases*							
Source	Malignancy Type	rhBMP-2 Group		Non-rhBMP-2 Group		Comparison	
		Number of Case Patients	Incidence Rate (95% CI) (per 1,000 patient-years)	Number of Case Patients	Incidence Rate (95% CI) (per 1,000 patient-years)	Rate Ratio (95% CI)	p-value (Mid-p exact)
Medtronic	Total Follow-up (patient-years)		3774		3234		
	SEER malignancies	21	5.564 (3.443, 8.506)	11	3.401 (1.696, 6.086)	1.636 (0.795, 3.519)	0.187
	Total malignancies	23	6.094 (3.862, 9.145)	12	3.711 (1.915, 6.482)	1.642 (0.823, 3.410)	0.163
Wyeth	Total Follow-up (patient-years)		1417		989		
	SEER malignancies	9	6.351 (2.898, 12.060)	5	5.056 (1.629, 11.800)	1.256 (0.421, 4.136)	0.703
	Total malignancies	11	7.763 (3.870, 13.890)	9	9.100 (4.153, 17.280)	0.853 (0.348, 2.135)	0.723
Pooled	Total Follow-up (patient-years)		5191		4223		
	SEER malignancies	30	5.779 (3.899, 8.250)	16	3.789 (2.164, 6.153)	1.525 (0.837, 2.863)	0.172
	Total malignancies	34	6.550 (4.535, 9.153)	21	4.973 (3.077, 7.602)	1.317 (0.767, 2.303)	0.324

* Pre-existing or "potentially pre-existing" cases excluded: 1 renal cancer and 1 pancreatic cancer from the Medtronic rhBMP-2 group; 1 skin cancer from the Wyeth rhBMP-2 group; and 1 breast cancer in the Wyeth non-rhBMP-2 group.

As shown above, the total and SEER malignancy incidence rates and rate ratios decreased for Medtronic's rhBMP-2 group with the exclusion of one pre-existing and one "potentially pre-existing" cancer. The p-values, which still show no significant difference, also increased. Wyeth's total malignancy incidence rate became lower for the rhBMP-2 group when one pre-existing non-SEER cancer was omitted from the analysis. Both the total and SEER malignancy rates were less for Wyeth's non-rhBMP-2 group with the exclusion of a pre-existing SEER malignancy. This slightly increased the rate ratios for the total and SEER malignancies from those calculated in the previous analysis for the Wyeth data, but it did not create a statistically significant difference. The cumulative effect of the exclusion of the pre-existing cases was to decrease the overall incidence rates and rate ratios for the pooled Medtronic and Wyeth groups.

8.2.4 Results of Standardized Incidence Ratio (SIR) Analysis

Standardized incidence ratios (SIRs) for “All Sites” and 24 individual SEER cancer categories were calculated by the number of observed cases divided by the expected number for each category. Confidence intervals (CIs) for those SIRs were determined to show whether or not a malignancy rate significantly deviates from the general population. As described in Section 8.1.4, if the confidence interval contains the value “1,” it indicates the observed incidence is not significantly different from the matched general population.

In order to determine the sensitivity of this analysis, it was performed both including and excluding the cases thought to be pre-existing. The non-SEER malignancies were not incorporated in the analysis because information on these cancers is not available in the SEER database. The results in Tables 10-14 only include comparisons of rhBMP-2 patients with the general population. Comparisons of the non-rhBMP-2 patients with the general population can be found in Tables A3-3 through A3-14 of Attachment 3.

Table 10. Standardized Incidence Ratio (SIR) of rhBMP-2 Patients: Analysis of Medtronic Data, Including Pre-Existing Cases					
Malignancy SEER Category	Number of Expected	Number of Observed	SIR		
			Observed SIR*	Unadjusted** 95% CI	Adjusted*** 95% CI
All Cancer Sites	23.84	23	0.965	(0.589, 1.355)	
Brain & Other Nervous System	0.323	0	0.000	(0.000, 8.537)	(0.000, 18.684)
Breast	4.748	3	0.632	(0.152, 1.582)	(0.044, 2.434)
Cervix Uteri	0.258	0	0.000	(0.000, 10.674)	(0.000, 23.359)
Colon and Rectum	2.256	1	0.443	(0.035, 1.996)	(0.000, 3.545)
Corpus Uteri	0.861	0	0.000	(0.000, 3.204)	(0.000, 7.013)
Esophagus	0.221	0	0.000	(0.000, 12.486)	(0.000, 27.326)
Hodgkin Lymphoma	0.113	0	0.000	(0.000, 24.364)	(0.000, 53.321)
Kaposi's Sarcoma	0.036	0	0.000	(0.000, 76.170)	(0.000, 166.700)
Kidney and Renal Pelvis	0.606	1	1.650	(0.131, 7.433)	(0.001, 13.198)
Larynx	0.214	1	4.681	(0.373, 21.083)	(0.003, 37.437)
Leukemia	0.488	1	2.049	(0.163, 9.228)	(0.001, 16.386)
Liver and Bile Duct	0.210	1	4.765	(0.379, 21.420)	(0.003, 38.035)
Lung and Bronchus	3.090	1	0.324	(0.026, 1.458)	(0.000, 2.588)
Melanoma of the Skin	1.101	3	2.726	(0.658, 6.824)	(0.192, 10.500)
Myeloma	0.246	0	0.000	(0.000, 11.211)	(0.000, 24.535)
Non-Hodgkin Lymphoma	0.937	1	1.068	(0.085, 4.810)	(0.001, 8.540)
Oral Cavity and Pharynx	0.575	0	0.000	(0.000, 4.793)	(0.000, 10.489)
Ovary	0.461	1	2.170	(0.173, 9.773)	(0.001, 17.354)
Pancreas	0.463	3	6.485	(1.565, 16.234)	(0.456, 24.978)
Prostate	3.557	2	0.562	(0.097, 1.702)	(0.016, 2.765)
Stomach	0.290	0	0.000	(0.000, 9.504)	(0.000, 20.799)
Testis	0.134	1	7.490	(0.596, 33.738)	(0.004, 59.907)
Thyroid	0.431	3	6.961	(1.680, 17.426)	(0.490, 26.813)
Urinary Bladder	0.905	0	0.000	(0.000, 3.047)	(0.000, 6.668)

* SIR = the number of the observed cases divided by number of the expected cases.

** The 95% confidence intervals for SIRs are not adjusted for the number of multiple comparisons examined (multiplicity).

*** The 95% confidence intervals for SIRs of individual SEER categories are adjusted for the multiplicity.

Table 10 presents the results from Medtronic's rhBMP-2 group and includes the two pre-existing malignancy cases in the analysis. The number of observed cancers for "All Sites" was 23, which is almost the same as the expected value of 23.84. The observed SIR was 0.965, indicating that the total number of observed malignancy cases was virtually the same as what would be expected for the general population of the same age, sex, and race.

The results of examining the individual SEER categories revealed that the number of observed cases for the majority of the categories were within the statistically expected ranges and were not deviated from the general population. That is, their 95% confidence intervals for the SIR values

contained the value “1,” even without adjusting for multiplicity (multiple comparisons).

The categories for pancreatic and thyroid cancer had elevated SIR values with unadjusted confidence intervals not containing the number “1.” This seems to imply that the rates of incidence are higher than the general population. However, as discussed above, such comparisons for individual categories suffer from the multiplicity issue. When the confidence intervals were adjusted for multiplicity using the Bonferroni approach, the interval for both of these cancers included “1.” These intervals are in bold print in Table 10. Statistically, this shows that, while numerically higher than the expected rate, the observed rate was no different from that found in the general population. Even in this conservative type of analysis (i.e., including pre-existing cancer cases), the difference in the expected and observed values can be explained.

In addition, while the number of observed thyroid malignancies may seem numerically high at three, it should be noted that three cases of thyroid cancer were also observed in the non-rhBMP-2 group of Medtronic’s studies, where the expected number is actually smaller for the non-rhBMP-2 group. This information is documented in Table A3-3 in Attachment 3 and in the Medtronic SEER case narratives in Attachment 4.

Table 11 provides the results of the same analysis of Medtronic's rhBMP-2 group, with the pre-existing cases excluded.

Table 11. Standardized Incidence Ratio (SIR) rhBMP-2 Patients: Analysis of <u>Medtronic</u> Data, Excluding Pre-Existing Cases					
Malignancy SEER Category	Number of Expected	Number of Observed	SIR		
			Observed SIR*	Unadjusted** 95% CI	Adjusted*** 95% CI
<i>All Cancer Sites</i>	23.84	21	0.881	(0.525, 1.257)	
Brain & Other Nervous System	0.323	0	0.000	(0.000, 8.537)	(0.000, 18.684)
Breast	4.748	3	0.632	(0.152, 1.582)	(0.044, 2.434)
Cervix Uteri	0.258	0	0.000	(0.000, 10.674)	(0.000, 23.359)
Colon and Rectum	2.256	1	0.443	(0.035, 1.996)	(0.000, 3.545)
Corpus Uteri	0.861	0	0.000	(0.000, 3.204)	(0.000, 7.013)
Esophagus	0.221	0	0.000	(0.000, 12.486)	(0.000, 27.326)
Hodgkin Lymphoma	0.113	0	0.000	(0.000, 24.364)	(0.000, 53.321)
Kaposi's Sarcoma	0.036	0	0.000	(0.000, 76.170)	(0.000, 166.700)
Kidney and Renal Pelvis	0.606	0	0.000	(0.000, 4.550)	(0.000, 9.959)
Larynx	0.214	1	4.681	(0.373, 21.083)	(0.003, 37.437)
Leukemia	0.488	1	2.049	(0.163, 9.228)	(0.001, 16.386)
Liver and Bile Duct	0.210	1	4.756	(0.379, 21.420)	(0.003, 38.035)
Lung and Bronchus	3.090	1	0.324	(0.026, 1.458)	(0.000, 2.588)
Melanoma of the Skin	1.101	3	2.726	(0.658, 6.824)	(0.192, 10.500)
Myeloma	0.246	0	0.000	(0.000, 11.211)	(0.000, 24.535)
Non-Hodgkin Lymphoma	0.937	1	1.068	(0.085, 4.810)	(0.001, 8.540)
Oral Cavity and Pharynx	0.575	0	0.000	(0.000, 4.793)	(0.000, 10.489)
Ovary	0.461	1	2.170	(0.173, 9.773)	(0.001, 17.354)
Pancreas	0.463	2	4.323	(0.745, 13.088)	(0.120, 21.260)
Prostate	3.557	2	0.562	(0.097, 1.702)	(0.016, 2.765)
Stomach	0.290	0	0.000	(0.000, 9.504)	(0.000, 20.799)
Testis	0.134	1	7.490	(0.596, 33.738)	(0.004, 59.907)
Thyroid	0.431	3	6.961	(1.680, 17.426)	(0.490, 26.813)
Urinary Bladder	0.905	0	0.000	(0.000, 3.047)	(0.000, 6.668)

* SIR = the number of the observed cases divided by number of the expected cases.

** The 95% confidence intervals for SIRs are not adjusted for the number of multiple comparisons examined (multiplicity).

*** The 95% confidence intervals for SIRs of individual SEER categories are adjusted for the multiplicity.

With the pre-existing renal and pancreatic cancer cases removed from the analysis of Medtronic's data, the number of observed cancers for "All Sites" dropped to 21 (from 23 in the previous analysis). As a result, the overall SIR value also decreased, from 0.965 to 0.881. The exclusion of the pre-existing cases only affected two individual SEER categories – Kidney and Renal Pelvis and Pancreas, in bold text above. The observed number of cases for Kidney and Renal Pelvis dropped from one to zero. The more notable change was for the Pancreas category. This demonstrated that, once the pre-existing cancer is removed from the analysis, there was no difference between the rate of

pancreatic cancers observed and the number expected in the general population, even without adjusting for multiplicity.

The same analysis was performed with Wyeth's rhBMP-2 group, and the results are given in Table 12. As there were no pre-existing cancers in the Wyeth rhBMP-2 group, there were no cases specifically excluded.

Table 12. Standardized Incidence Ratio (SIR) of rhBMP-2 Patients: Analysis of Wyeth Data					
Malignancy SEER Category	Number of Expected	Number of Observed*	SIR		
			Observed SIR**	Unadjusted*** 95% CI	Adjusted† 95% CI
<i>All Cancer Sites</i>	8.781	9	1.025	(0.460, 1.759)	
Brain & Other Nervous System	0.117	0	0.000	(0.000, 23.609)	(0.000, 51.669)
Breast	1.379	2	1.451	(0.250, 4.392)	(0.040, 7.135)
Cervix Uteri	0.066	0	0.000	(0.000, 41.915)	(0.000, 91.733)
Colon and Rectum	0.910	1	1.098	(0.087, 4.947)	(0.001, 8.784)
Corpus Uteri	0.262	0	0.000	(0.000, 10.526)	(0.000, 23.037)
Esophagus	0.090	0	0.000	(0.000, 30.579)	(0.000, 66.923)
Hodgkin Lymphoma	0.046	0	0.000	(0.000, 60.545)	(0.000, 132.505)
Kaposi's Sarcoma	0.019	0	0.000	(0.000, 148.739)	(0.000, 325.521)
Kidney and Renal Pelvis	0.226	0	0.000	(0.000, 12.215)	(0.000, 26.733)
Larynx	0.083	0	0.000	(0.000, 33.170)	(0.000, 72.594)
Leukemia	0.195	0	0.000	(0.000, 14.111)	(0.000, 30.883)
Liver and Bile Duct	0.083	0	0.000	(0.000, 33.028)	(0.000, 72.282)
Lung and Bronchus	1.216	0	0.000	(0.000, 2.269)	(0.000, 4.965)
Melanoma of the Skin	0.356	0	0.000	(0.000, 7.745)	(0.000, 16.950)
Myeloma	0.098	1	10.165	(0.810, 45.787)	(0.006, 81.302)
Non-Hodgkin Lymphoma	0.356	0	0.000	(0.000, 7.743)	(0.000, 16.946)
Oral Cavity and Pharynx	0.216	0	0.000	(0.000, 12.792)	(0.000, 27.995)
Ovary	0.137	0	0.000	(0.000, 20.182)	(0.000, 44.169)
Pancreas	0.187	0	0.000	(0.000, 14.768)	(0.000, 32.321)
Prostate	1.529	4	2.617	(0.770, 5.828)	(0.294, 8.632)
Stomach	0.120	0	0.000	(0.000, 22.918)	(0.000, 50.158)
Testis	0.064	0	0.000	(0.000, 42.773)	(0.000, 93.610)
Thyroid	0.116	0	0.000	(0.000, 23.672)	(0.000, 51.807)
Urinary Bladder	0.377	0	0.000	(0.000, 7.308)	(0.000, 15.994)

* One cancer of the abdominal lining (mesothelioma) in the BMP group was counted in "All Sites," but the individual SIR analysis was not performed because the SEER Statistics do not include information for this category.

** SIR = the number of the observed cases divided by number of the expected cases.

*** The 95% confidence intervals for SIRs are not adjusted for the number of multiple comparisons examined (multiplicity).

† The 95% confidence intervals for SIRs of individual SEER categories are adjusted for the multiplicity.

As shown in the table, the number of observed cancers for "All Sites" was 9, which is essentially the same as expected. This indicated that the observed rate was not different from the general population. The observed SIR was calculated to be 1.025. The expected number from any of the individual SEER categories is not significantly different from that expected from the general

population, as the 95% confidence intervals for each SIR contained the value of “1,” even without adjusting for multiplicity.

The results of the analysis of pooled data (from both Medtronic and Wyeth’s rhBMP-2 groups) are provided in Table 13.

Table 13. Standardized Incidence Ratio (SIR) of rhBMP-2 Patients: Analysis of Pooled Medtronic and Wyeth Data, Including Pre-Existing Cases					
Malignancy SEER Category	Number of Expected	Number of Observed*	SIR		
			Observed SIR**	Unadjusted*** 95% CI	Adjusted† 95% CI
All Cancer Sites	32.62	32	0.981	(0.647, 1.308)	
Brain & Other Nervous System	0.440	0	0.000	(0.000, 6.270)	(0.000, 13.722)
Breast	6.127	5	0.816	(0.275, 1.675)	(0.123, 2.412)
Cervix Uteri	0.324	0	0.000	(0.000, 8.507)	(0.000, 18.618)
Colon and Rectum	3.167	2	0.632	(0.109, 1.912)	(0.017, 3.106)
Corpus Uteri	1.123	0	0.000	(0.000, 2.457)	(0.000, 5.376)
Esophagus	0.311	0	0.000	(0.000, 8.866)	(0.000, 19.403)
Hodgkin Lymphoma	0.159	0	0.000	(0.000, 17.373)	(0.000, 38.021)
Kaposi's Sarcoma	0.055	0	0.000	(0.000, 50.373)	(0.000, 110.244)
Kidney and Renal Pelvis	0.832	1	1.202	(0.096, 5.415)	(0.001, 9.616)
Larynx	0.297	1	3.369	(0.268, 15.177)	(0.002, 26.950)
Leukemia	0.684	1	1.463	(0.117, 6.590)	(0.001, 11.702)
Liver and Bile Duct	0.294	1	3.404	(0.271, 15.333)	(0.002, 27.225)
Lung and Bronchus	4.306	1	0.232	(0.018, 1.046)	(0.000, 1.858)
Melanoma of the Skin	1.457	3	2.060	(0.497, 5.156)	(0.145, 7.933)
Myeloma	0.344	1	2.904	(0.231, 13.080)	(0.002, 23.226)
Non-Hodgkin Lymphoma	1.293	1	0.774	(0.062, 3.485)	(0.000, 6.187)
Oral Cavity and Pharynx	0.791	0	0.000	(0.000, 3.486)	(0.000, 7.630)
Ovary	0.598	1	1.674	(0.133, 7.538)	(0.001, 13.385)
Pancreas	0.649	3	4.620	(1.115, 11.566)	(0.325, 17.795)
Prostate	5.086	6	1.180	(0.439, 2.279)	(0.217, 3.207)
Stomach	0.410	0	0.000	(0.000, 6.718)	(0.000, 14.702)
Testis	0.198	1	5.051	(0.402, 22.751)	(0.003, 40.399)
Thyroid	0.547	3	5.480	(1.322, 13.718)	(0.386, 21.107)
Urinary Bladder	1.282	0	0.000	(0.000, 2.150)	(0.000, 4.706)

* One cancer of the abdominal lining (mesothelioma) in the BMP group was counted in “All Sites,” but the individual SIR analysis was not performed because the SEER Statistics do not include information for this category.

** SIR = the number of the observed cases divided by number of the expected cases.

*** The 95% confidence intervals for SIRs are not adjusted for the number of multiple comparisons examined (multiplicity).

† The 95% confidence intervals for SIRs of individual SEER categories are adjusted for the multiplicity.

When both groups were combined, the number of observed cancers for “All Sites,” including potentially pre-existing cases, was 32, which is slightly less than the expected value of 32.62. This yielded an observed SIR of 0.981. As before, most of the individual SEER categories were within the statistically expected ranges and were not deviated from the general population. As

before, the Pancreas and Thyroid SEER categories had elevated SIR values, with unadjusted confidence intervals not containing the number “1.” However, when the confidence intervals were adjusted for multiplicity using the Bonferroni approach, the interval for both of these cancers included “1.” It should also be noted that the SIRs decreased for both the Pancreas and Thyroid categories from the values calculated from the Medtronic-only data (Pancreas: 6.485 to 4.620; Thyroid: 6.961 to 5.480). The results from these categories are in bold print in Table 13.

Finally, the analysis of the pooled Medtronic and Wyeth rhBMP-2 clinical data was repeated, excluding pre-existing malignancies. The results are shown in Table 14.

Table 14. Standardized Incidence Ratio (SIR) of rhBMP-2 Patients: Analysis of <u>Pooled</u> Medtronic and Wyeth Data, Excluding Pre-Existing Cases					
Malignancy SEER Category	Number of Expected	Number of Observed*	SIR		
			Observed SIR**	Unadjusted*** 95% CI	Adjusted† 95% CI
All Cancer Sites	32.62	30	0.920	(0.598, 1.238)	
Brain & Other Nervous System	0.440	0	0.000	(0.000, 6.270)	(0.000, 13.722)
Breast	6.127	5	0.816	(0.275, 1.675)	(0.123, 2.412)
Cervix Uteri	0.324	0	0.000	(0.000, 8.507)	(0.000, 18.618)
Colon and Rectum	3.167	2	0.632	(0.109, 1.912)	(0.017, 3.106)
Corpus Uteri	1.123	0	0.000	(0.000, 2.457)	(0.000, 5.376)
Esophagus	0.311	0	0.000	(0.000, 8.866)	(0.000, 19.403)
Hodgkin Lymphoma	0.159	0	0.000	(0.000, 17.373)	(0.000, 38.021)
Kaposi's Sarcoma	0.055	0	0.000	(0.000, 50.373)	(0.000, 110.244)
Kidney and Renal Pelvis	0.832	0	0.000	(0.000, 3.315)	(0.000, 7.256)
Larynx	0.297	1	3.369	(0.268, 15.177)	(0.002, 26.950)
Leukemia	0.684	1	1.463	(0.117, 6.590)	(0.001, 11.702)
Liver and Bile Duct	0.294	1	3.404	(0.271, 15.333)	(0.002, 27.225)
Lung and Bronchus	4.306	1	0.232	(0.018, 1.046)	(0.000, 1.858)
Melanoma of the Skin	1.457	3	2.060	(0.497, 5.156)	(0.145, 7.933)
Myeloma	0.344	1	2.904	(0.231, 13.080)	(0.002, 23.226)
Non-Hodgkin Lymphoma	1.293	1	0.774	(0.062, 3.485)	(0.000, 6.187)
Oral Cavity and Pharynx	0.791	0	0.000	(0.000, 3.486)	(0.000, 7.630)
Ovary	0.598	1	1.674	(0.133, 7.538)	(0.001, 13.385)
Pancreas	0.649	2	3.080	(0.531, 9.324)	(0.085, 15.146)
Prostate	5.086	6	1.180	(0.439, 2.279)	(0.217, 3.207)
Stomach	0.410	0	0.000	(0.000, 6.718)	(0.000, 14.702)
Testis	0.198	1	5.051	(0.402, 22.751)	(0.003, 40.399)
Thyroid	0.547	3	5.480	(1.322, 13.718)	(0.386, 21.107)
Urinary Bladder	1.282	0	0.000	(0.000, 2.150)	(0.000, 4.706)

* One cancer of the abdominal lining (mesothelioma) in the BMP group was counted in “All Sites,” but the individual SIR analysis was not performed because the SEER Statistics do not include information for this category.

** SIR = the number of the observed cases divided by number of the expected cases.

*** The 95% confidence intervals for SIRs are not adjusted for the number of multiple comparisons examined (multiplicity).

† The 95% confidence intervals for SIRs of individual SEER categories are adjusted for the multiplicity.

The results of the pooled analysis (excluding the pre-existing cancers) were much the same as before. With the pre-existing cancers removed from the analysis of the combined data, the number of observed cancers for “All Sites” dropped to 30 (from 32 in the previous analysis). This was slightly less than the expected number of 32.62. As a result, the overall SIR value also decreased, from 0.981 to 0.920. Again, when the pre-existing renal and pancreatic cancers were left out of the analysis, the SIR for the Kidney and Renal Pelvis category became zero, and the observed rate of pancreatic cancer showed no significant difference from that expected in the general population, even without adjusting for multiplicity. The SIR for pancreatic cancer was observed to be 3.080, with an unadjusted 95% confidence interval of (0.531, 9.324).

8.2.5 Summary of Analysis Results

The results of all of these analyses of clinical data demonstrate that there does not seem to be an increased rate of malignancy with the use of rhBMP-2. Even with the naïve statistical analysis of Fisher’s exact test, which ignores the difference in follow-up duration between the rhBMP-2 group and the non-rhBMP-2 group, the rates of malignancies observed were not significantly different, although the rates in the rhBMP-2 group were numerically higher in the Medtronic-sponsored trials. Both time-to-event analyses (Kaplan-Meier and Cox regression) showed no significant difference between the rhBMP-2 and non-rhBMP-2 groups. The comparison of incidence rates also showed no significant difference between the rhBMP-2 and non-rhBMP-2 groups.

The epidemiological analysis confirmed the results of the statistical analyses. The SIR analysis of the total SEER malignancy cases (All Sites) in the rhBMP-2 patient groups revealed that the number of observed cases did not significantly deviate from the general population of the same age, sex, and race. The total number of cases, in fact, was the same as expected. The SIR analysis for individual SEER categories showed the observed cases did not significantly deviate from the general population, except for the categories of pancreatic and thyroid cancers. However, such an analysis of individual SEER categories suffers from multiplicity; after adjusting for multiplicity, the numbers of observed cases for these two categories were not significantly different from the general population. It was also likely that one of the three pancreatic cancers was pre-existing. With the exclusion of this case, the remaining number of cases (two) does not significantly deviate from the expected number, even without adjusting for multiplicity. In addition, it may seem that the number of observed thyroid malignancies in Medtronic’s study is numerically high (three cases). However, it should be noted that three cases of thyroid cancer were also observed in the non-rhBMP-2 group of Medtronic’s studies, where the expected number of thyroid cancers is actually less for the non-rhBMP-2 group.

9.0 CONCLUSION

Though bone morphogenetic proteins (BMPs) have been shown to stimulate the formation of bone and cartilage, it is apparent that these molecules may regulate the growth and differentiation of various cells, possibly including tumor cells. The goal of this report was to provide a thorough presentation of the available data on the relationship that may exist between rhBMP-2 and tumor formation. Information was presented from a variety of sources, including current literature, pharmacokinetic release studies, and tumor promotion studies. While the survey of the literature provides somewhat conflicting perspectives on the role of rhBMP-2 in tumor initiation and promotion, results from the preclinical studies suggest that rhBMP-2 has a limited systemic effect and a lack of oncogenic potential.

The results of the statistical analyses of Medtronic and Wyeth's clinical data showed no significant difference in the rate of malignancy between the rhBMP-2 and non-rhBMP-2 groups. The total malignancy rate for Medtronic's rhBMP-2 group was determined to be 2.2% (25/1152). For patients in Medtronic's studies who did not receive rhBMP-2, the malignancy rate was slightly lower at 1.2% (12/1008). The total malignancy rate for Wyeth's rhBMP-2 group was 1.2% (12/1006), which was virtually the same as for patients who did not receive rhBMP-2 (1.3%, 10/749). Even with the naïve statistical analysis of Fisher's exact test, the rates of malignancies observed were not significantly different, although the rates in the rhBMP-2 group were numerically higher in the Medtronic-sponsored trials ($p=0.096$, total rate for Medtronic studies). Time-to-event analyses and comparison of incidence rates also showed no significant difference between the rhBMP-2 and non-rhBMP-2 groups.

The epidemiological analysis of the clinical data showed similar results to the statistical analyses. The SIR analysis of the total SEER malignancy cases (All Sites) in the rhBMP-2 patient revealed that the number of observed cases was not significantly different from the number expected in the general population of the same age, sex, and race. The SIR analysis for individual SEER categories showed the observed cases also did not deviate from the general population, except for the categories of pancreatic and thyroid cancers. After adjusting for multiplicity and omitting potentially pre-existing cases, the numbers of observed cases for these two categories were not significantly different from the general population.

Together, all of these results seem to support a conclusion that there is not a direct relationship between rhBMP-2 use and malignancy.

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ATTACHMENT 1: CLINICAL STUDY SUMMARIES: MEDTRONIC AND WYETH

Medtronic Clinical Studies

A total of 18 completed or ongoing clinical studies have been performed by Medtronic to evaluate the safety and efficacy of rhBMP-2. Three of these clinical trials were conducted in the U.S. by Medtronic to evaluate the safety and efficacy of rhBMP-2/ACS in combination with the LT-CAGE® Lumbar Tapered Fusion Device in single-level spinal fusion procedures from L4-S1 to treat degenerative disc disease (DDD) in skeletally mature patients. These data, taken from a pilot study and two pivotal studies, were submitted and received premarket approval in the U.S.^{§§§} As a condition of PMA approval, Medtronic was required to conduct a post-approval study to obtain a total of six years of postoperative data from patients implanted with the investigational device. Control patients were not required to be followed, and as a result, significantly more data were collected from the investigational patients. This accounts for some of the discrepancy in follow-up time that exists between rhBMP-2 and non-rhBMP-2 patients in Medtronic's clinical studies.

Information on these three clinical trials, including IDE and PMA numbers, are shown in Table A1-1.

^{§§§} Data from these studies were also submitted through a Type II Variation in support of this indication in the European Union.

Table A1-1. Medtronic Studies in Support of rhBMP-2/ACS with the LT-CAGE® Device (IDE G960065/PMA P000058)					
Type of Study	Study Title	rhBMP-2 Concentration (mg/cc)	rhBMP-2 Dose (mg)	# of Patients Who Had Any Follow-Up (Total Patient-Years of Follow-Up)	
				rhBMP-2 Group	Non- rhBMP-2 Group
Pilot Study		1.5 mg/cc	3.9-7.8	11 (23)	3 (6)
Pivotal Study: Open Approach		1.5 mg/cc	4.2-8.4	143* (646)	136 (265)
Pivotal Study: Laparoscopic Approach		1.5 mg/cc	4.2-8.4	134* (611)	- **

* Patients continued to post-approval study.

** Single-arm study only.

Fifteen (15) other clinical trials have been conducted or are ongoing in North America by Medtronic to investigate rhBMP-2 in combination with different devices or carriers, surgical approaches, and/or at various doses and concentrations. The other trials have been or are being conducted in patients with degenerative disc disease. Some of the trials are comprised of both “pilot” and “pivotal” phases. In one of the studies, the use of rhBMP-2/ACS with the LT-CAGE® Device was used as a control treatment for evaluating a lumbar artificial disc replacement therapy.

One of these other studies is also the basis of a PMA currently under review for the AMPLIFY™ rhBMP-2 MATRIX (P050036). This trial was a U.S. IDE clinical study of rhBMP-2 and the Compression Resistant Matrix (CRM) with the CD HORIZON® Spinal System (G000137). This treatment was studied for use in skeletally mature patients with symptomatic lumbar degenerative disc disease (DDD) at one level from L1-S1.

The protocol numbers and titles of all 15 Medtronic clinical trials are shown in Table A1-2.

Table A1-2. Fifteen (15) Medtronic Studies of rhBMP-2 with Alternative Concentrations, Devices, or Carriers in the Spine							
IDE (G#) or Protocol #	Study Title	rhBMP-2 Concentration (mg/cc)	rhBMP-2 Dose (mg)	rhBMP-2 Carrier Used	Spine Region	# of Patients Who Had Any Follow-Up (Total Patient-Years of Follow-Up)	
						rhBMP-2 Group	Non-rhBMP-2 Group
Protocol #1187		2.2 or 3.0	15.0 or 40.0			15 (16)	-
G970124 (pilot)		1.5	8.1-11.7			24 (91)	22 (86)
G970124 (pivotal)		1.5	8.1-11.7			55 (106)	30 (56)
G980207		1.5	8.4-16.8			25 (51)	19 (35)
G980306		1.5	4.2 or 8.4			34 (66)	33 (66)
G980320		2.1	42.0			22 (45)	5 (9)

Table A1-2. Fifteen (15) Medtronic Studies: rhBMP-2 with Alternative Concentrations, Devices, or Carriers in the Spine (cont.)							
IDE (G#) or Protocol #	Study Title	rhBMP-2 Concentration (mg/cc)	rhBMP-2 Dose (mg)	rhBMP-2 Carrier Used	Spine Region	# of Patients Who Had Any Follow-Up (Total Patient-Years of Follow-Up)	
						rhBMP-2 Group	Non-rhBMP-2 Group
Protocol #9807		2.1	42.0 or 63.0			98 (308)	98 (315)
G990056 (pilot)		1.5	0.6 or 1.2			18 (33)	15 (30)
G990056 (pivotal)		1.5	0.6 or 1.2			2 (5)	1 (2)
G000137		2.0	40.0			239 (957)	221 (842)
G010354		1.5	4.2-12.0			172 (604)	404 (1475)

Table A1-2. Fifteen (15) Medtronic Studies: rhBMP-2 with Alternative Concentrations, Devices, or Carriers in the Spine (cont.)							
IDE (G#) or Protocol #	Study Title	rhBMP-2 Concentration (mg/cc)	rhBMP-2 Dose (mg)	rhBMP-2 Carrier Used	Spine Region	# of Patients Who Had Any Follow-Up (Total Patient-Years of Follow-Up)	
						rhBMP-2 Group	Non-rhBMP-2 Group
G020053		1.5	8.4			30 (70)	-
G020056		1.5	12.0			25 (53)	21 (46)
G040219		2.0	40.0			29 (58)	-
G060021		1.5	0.4 or 0.7			76 (31)	-

Wyeth Clinical Studies

In addition to the Medtronic studies listed above, clinical studies of rhBMP-2 were also performed by Wyeth. The protocol numbers and titles of these 26 clinical trials are shown in the table below.

Table A1-3. Twenty-six (26) Wyeth Studies of rhBMP-2 in Orthopedic Trauma, Orthopedic Non-Trauma, and Oral Maxillofacial Indications							
Protocol #	Study Title	rhBMP-2 Concentration (mg/cc)	rhBMP-2 Dose (mg)	rhBMP-2 Carrier Used	Indication	# of Patients Who Had Any Follow-Up (Total Patient-Years of Follow-Up)	
						rhBMP-2 Group	Non-rhBMP-2 Group
108		1	5.0			11 (11)	-
109		1	9.0			21 (18)	-
110		1	1.0 2.0			6 (3)	-
114		1 2	0.5 1.0			20 (17)	20 (19)
115		1 2	5.0 10.0			30 (28)	-
210		1 2	5.0 10.0			- *	35 (18)

* No rhBMP-2 patients were included in the analysis for Study 210 because the patients were still blinded to treatment at the time of database closure; the control patients listed here received conservative care.

Table A1-3. Twenty-six (26) Wyeth Studies of rhBMP-2 in Orthopedic Trauma, Orthopedic Non-Trauma, and Oral Maxillofacial Indications (cont.)							
Protocol #	Study Title	rhBMP-2 Concentration (mg/cc)	rhBMP-2 Dose (mg)	rhBMP-2 Carrier Used	Indication	# of Patients Who Had Any Follow-Up (Total Patient-Years of Follow-Up)	
						rhBMP-2 Group	Non- rhBMP-2 Group
211		1 2	3 to 5 6 to 10			61 (32)	31 (19)
212		1 2	3 6			-	17 (10)
400		1.5 mg/cc	≤ 6 or 12mg			137 (128)	134 (127)
C9109-11		0.1	1			18 (35)	7 (13)
C9307-11		0.1	1			24 (42)	18 (25)
C9320-11		0.43 mg/cc	≤ 6.8mg			12 (8)	-
C9402-11		No info available	No info available			-	82 (37)
C9409-11**		0.43 mg/cc	≤ 3.4mg			12 (47)	-

* No rhBMP-2 patients were included in the analysis for Study 212 because the patients were still blinded to treatment at the time of database closure; the control patients listed here received conservative care.

** These clinical studies were the basis for the oromaxillofacial PMA (P050053). Wyeth transferred ownership of these data to Medtronic after completion of the clinical study, but prior to the time of PMA.

Table A1-3. Twenty-six (26) Wyeth Studies of rhBMP-2 in Orthopedic Trauma, Orthopedic Non-Trauma, and Oral Maxillofacial Indications (cont.)							
Protocol #	Study Title	rhBMP-2 Concentration (mg/cc)	rhBMP-2 Dose (mg)	rhBMP-2 Carrier Used	Indication	# of Patients Who Had Any Follow-Up (Total Patient-Years of Follow-Up)	
						rhBMP-2 Group	Non-rhBMP-2 Group
C9410-11**		0.43 mg/cc	≤ 3.4mg			12 (24)	-
C9414-11		0.75 or 1.5 mg/cc	≤ 6 or 12mg			14 (10)	8 (4)
C9514-11**		0, 0.75 or 1.5 mg/cc	≤ 6 or 12mg			43 (126)	37 (100)
C9524-11		0.43, 0.75 or 1.5 mg/cc	≤ 3.4, 6, or 12mg			24 (12)	16 (8)
C9530-11†		0.75 or 1.5 mg/cc	≤ 6 or 12mg			297 (288)	150 (143)
C9531-11**		0.75 or 1.5 mg/cc	≤ 24 or 48mg			35 (127)	13 (53)
C9612-11		0.75 or 1.5 mg/cc	≤ 6 or 12mg			40 (39)	20 (19)
C9713-11		0.43, 0.75 or 1.5 mg/cc	≤ 3.4, 6, or 12mg			12 (10)	3 (2)
C9730-11**		1.5 mg/cc	≤ 48mg			82 (264)	78 (278)

** These clinical studies were the basis for the oralmaxillofacial PMA (P050053). Wyeth transferred ownership of these data to Medtronic after completion of the clinical study, but prior to the time of PMA.

† This clinical study was the basis for the orthopedic trauma (tibia) PMA (P000054). Wyeth transferred ownership of this PMA to Medtronic after approval.

Table A1-3. Twenty-six (26) Wyeth Studies of rhBMP-2 in Orthopedic Trauma, Orthopedic Non-Trauma, and Oral Maxillofacial Indications (cont.)							
Protocol #	Study Title	rhBMP-2 Concentration (mg/cc)	rhBMP-2 Dose (mg)	rhBMP-2 Carrier Used	Indication	# of Patients Who Had Any Follow-Up (Total Patient-Years of Follow-Up)	
						rhBMP-2 Group	Non- rhBMP-2 Group
C9731-11	[REDACTED] ad	0.75 or 1.5 mg/cc	≤ 3 or 6mg	[REDACTED]	[REDACTED]	29 (84)	16 (47)
C9828-11	[REDACTED]	1.5 mg/cc	≤ 24mg	[REDACTED]	[REDACTED]	51 (48)	49 (47)
C9910-11	[REDACTED]	1.5 mg/cc	≤ 6 or 12mg	[REDACTED]	[REDACTED]	15 (18)	15 (19)

ATTACHMENT 2: SUMMARY OF WYETH PRECLINICAL STUDIES

The following preclinical studies were performed by Wyeth to assess the oncogenic potential of rhBMP-2 systematically. The last three studies were performed as FDA-mandated conditions of approval for PMA P000058 (INFUSE® Bone Graft with the LT-CAGE® Lumbar Tapered Fusion Device in the lumbar spine) and for PMA P000054 (INFUSE® Bone Graft).

In Vitro Studies

1. Inhibition of Tumor Cell Growth *In Vitro* (PB-040-91)

The potential effects of rhBMP-2 on tumor cell line growth *in vitro* were assessed at concentrations of 10, 100, and 1000 ng/mL. Human osteosarcoma cell lines (SaOS-2, U-2 OS, TE-85, and MG-63) were unaffected by treatment. The growth of human prostate carcinomas (DU-145 and PC-3), breast carcinomas (ZR-75-1 and HTD-30), tongue carcinoma (SCC-9), and lung carcinoma (HTB-58) were all inhibited by rhBMP-2. rhBMP-2 was also tested at concentrations of 10, 100, and 1000 ng/mL for the ability to potentiate growth of primary tumor isolates *in vitro* in a colony-forming assay. In this study, there were 65 evaluable specimens, representing ovarian carcinoma, breast carcinoma, non-small cell lung carcinoma, melanoma, and hepatoma. rhBMP-2 did not potentiate the growth of any isolates and showed significant growth inhibition in 16 of 65 specimens.

Overall, these studies investigating the potential effects of rhBMP-2 on tumor cell growth, including studies of osteosarcoma cell lines, showed no evidence of growth potentiation,

2. Screening of BMP-2 Receptors in Human Tumor Cells (RPT-44654)

BMP-2 receptor subunit mRNA expression was determined in tumor cell lines of various cellular origins in order to identify those tumor cell lines that may display altered proliferation in response to rhBMP-2.

The relative mRNA levels of the three BMP-2 receptor subunits BMPR-IA (Alk-3), BMPR-IB (Alk-6), and BMPR-II were profiled in 21 different human tumor cell lines using quantitative reverse transcriptase-polymerase chain reaction. The tumor cell lines were selected to contain carcinomas from a variety of tissue types and included bone, brain, breast, colon, epithelia, melanoma, ovary, pancreas, and prostate tumors. The mRNA levels of the three different BMP-2 receptor subunits in these cell lines were compared to the receptor mRNA levels in cell types that have been shown to be responsive to BMP-2 (and, therefore, presumed to contain functionally relevant levels of BMP-2 receptor). Additional comparisons of BMP-2 receptor subunit mRNA levels in these cell lines were made to cells that have been shown to be unresponsive to BMP-2 (negative control).

Based upon these comparisons, ten of the 21 cell lines expressed functionally relevant levels of BMP-2 receptor subunits (BMPR-II, and either BMPR-IA or BMPR-IB).

3. The Effect of rhBMP-2 on the *In Vitro* Proliferation of Human Cancer Cell Lines (RPT-45118)

In this study, the possible role of rhBMP-2 in human cancer cell proliferation was further investigated using the ten cell lines from the previous study (RPT-44654) that expressed BMP-2 receptors and one additional cell line (U20S) derived from an osteosarcoma. Cell lines were evaluated for their relative rate of growth in the presence and absence of increasing concentrations of BMP-2 in 10% to 20% fetal bovine serum. Each cell line was incubated with BMP-2 at concentrations of 3, 10, 30, and 100 ng/mL. The effect of rhBMP-2 on the proliferation of human cancer cell lines was assessed using a protein-binding dye assay that measured the relative amount of cellular protein present after 96 hours of cell growth. The relative amount of protein present was measured spectrophotometrically by determining the amount of protein-bound Sulforhodamine B dye.

Ten of the 11 cell lines showed no additional mitogenic activity response to rhBMP-2 when compared with cells grown in the absence of rhBMP-2. rhBMP-2 inhibited growth in the remaining cell line, LnCap, in a dose-dependent fashion. These data demonstrate that cells grown in rhBMP-2 in the presence of fetal bovine serum show no additional enhancement of growth compared to cells grown in a comparable fashion in the absence of rhBMP-2.

***In Vivo* Studies**

4. Effect of rhBMP-2 on the Growth of Human Tumor Cell Line Xenografts in Female Nude Mice (RPT-50783)

This study further assessed the effects of rhBMP-2/ACS surgical treatment on the growth of subcutaneously (SC) implanted human tumor cell lines (xenografts) in athymic nude mice. This report summarizes the results of seven independent experiments with different xenografts.

The human tumor cell lines used in this study were selected for evaluation based on expression of mRNA for either the Type I or Type II receptors of BMP-2. Two tumor cell lines (DLD-1 and SW620) were known not to express one or more of the mRNAs encoding the receptors for BMP-2. The other five tumor cell lines evaluated (A431, Lox, U87MG, LoVo, or HT29) were known to express mRNA for both the Type I and Type II BMP-2 receptors. For each xenograft tested, groups of 40 athymic nu/nu female mice were implanted with the xenograft SC in one flank. In each experiment, mice were divided into four groups of ten each. Individual groups

were surgically treated SC in the flank opposite from the xenograft as follows: sham surgery (surgery but no ACS and rhBMP-2); buffer/ACS (absorbable collagen sponge with buffer, no rhBMP-2); 0.422 mg/mL rhBMP-2/ACS; and 4.22 mg/mL rhBMP-2/ACS. Xenograft mass was determined approximately every seven days, and the xenograft growth in each of the ACS and/or BMP-2-treated groups was determined relative to the sham surgery group. Mice were necropsied at the end of each experiment, and the xenograft injection sites, surgical treatment sites, and a standard list of tissues were examined microscopically.

Surgical treatment with 0.422 or 4.22mg/mL rhBMP-2/ACS did not result in increased growth of the implanted xenograft relative to the sham surgery group in any group of mice. Indeed, surgical treatment with 0.422 or 4.22mg/mL rhBMP-2/ACS resulted in a reduction in the relative growth of the Lox, SW620, and HT29 xenografts *in vivo*. Surgical treatment with 0.422 or 4.22mg/mL rhBMP-2/ACS had no effect on the growth of the A431, DLD-1, U87MG, or LoVo xenografts *in vivo*.

Xenograft was observed microscopically at the SC tumor cell injection site in each experiment. As expected, based on the anticipated pharmacologic effect of rhBMP-2, normal bone was seen at the SC surgical site in 47% or 84% of mice surgically treated with 0.422 or 4.22 mg/mL rhBMP-2/ACS, respectively. Surgical treatment with 0.422 or 4.22 mg/mL rhBMP-2/ACS did not increase the numbers of microscopically observed xenograft cell metastases.

In conclusion, exposure of seven human tumor cell lines xenografts in nude mice to rhBMP-2/ACS (0.422 or 4.22 mg/mL) did not promote the *in vivo* growth of any of the seven human tumor cell lines tested, which included tumor cell lines that were known to express mRNA for Type I or Type II components of the BMP-2 receptor complex.

ATTACHMENT 3: STATISTICAL TABLES

Table A3-1. Summary of Follow-up Durations and Demographics
All MSD Clinical Studies Involving rhBMP-2

Variable	rhBMP-2	Non rhBMP-2
Systematic Follow-up Duration (Years)		
n	1152	1008
Patient-Years	3774	3234
Mean	3.3	3.2
Min	0.0	0.1
Q1 (25% Quantile)	2.0	2.0
Median	2.9	3.1
Q3 (75% Quantile)	4.9	4.8
Max	7.7	6.4
Systematic Follow-up Duration (Months)		
n	1152	1008
Mean	39.3	38.5
Min	0.4	1.1
Q1 (25% Quantile)	23.7	24.5
Median	34.6	36.7
Q3 (75% Quantile)	59.2	57.4
Max	92.1	77.4
Age (yrs.)		
n	1152	1008
Mean	47.0	45.2
Min	18.0	18.0
Q1 (25% Quantile)	38.0	36.3
Median	46.0	44.0
Q3 (75% Quantile)	55.0	52.5
Max	81.0	86.0
Sex [n (%)]		
Male	526 (45.7)	475 (47.1)
Female	626 (54.3)	533 (52.9)
Race [n (%)]		
White	1030 (89.6)	897 (89.5)
Black	57 (5.0)	59 (5.9)
Other	6 (0.5)	6 (0.6)
Program (Date): T_DURATION_DEMOG (09FEB09) (11:21) (PAGE 1 OF 1)		

Table A3-2. Summary of Follow-up Duration and Demographics
(All Wyeth Clinical Studies Involving rhBMP-2)

Variable	rhBMP-2	Non rhBMP-2
Systematic Follow-up Duration (Years)		
n	1006	749
Patient-Years	1417	989.1
Mean	1.4	1.3
Min	0.0	0.0
Q1 (25% Quantile)	0.9	0.9
Median	1.0	1.0
Q3 (75% Quantile)	1.2	1.1
Max	5.9	4.9
Systematic Follow-up Duration (Months)		
n	1006	749
Mean	16.9	15.8
Min	0.0	0.0
Q1 (25% Quantile)	11.3	10.2
Median	11.8	11.8
Q3 (75% Quantile)	14.5	13.0
Max	70.9	58.9
Age (yrs.)		
n	1006	749
Mean	42.6	42.3
Min	16.0	17.0
Q1 (25% Quantile)	28.0	28.0
Median	41.0	41.0
Q3 (75% Quantile)	54.0	54.0
Max	92.0	88.0
Sex [n (%)]		
F	298 (29.6)	241 (32.2)
M	708 (70.4)	508 (67.8)
Race [n (%)]		
BLACK	160 (15.9)	110 (14.7)
HISPANIC	43 (4.3)	17 (2.3)
OTHER	72 (7.2)	71 (9.5)
WHITE	731 (72.7)	551 (73.6)
Program (Date): T_DURATION_DEMOG_WYETH (12JAN09) (11:15) (PAGE 1 OF 1)		

Table A3-3. Comparison of Cancer Cases Diagnosed in Clinical Trial Patients with the U.S. Normal Population
(All MSD Clinical Studies Involving rhBMP-2)
[Pre-existing malignancy cases are included. The 95% SIR CIs are not adjusted for multiplicity.]

Cancer Site	Number of Cancer Patients							
	rhBMP-2 Group				Non-rhBMP-2 Group			
	N	Expected*	Observed	SIR** (95% C.I.)	N	Expected*	Observed	SIR** (95% C.I.)
All Sites ***	1152	23.84	23	0.965 (0.589, 1.355)	1008	17.71	11	0.621 (0.302, 1.013)
Brain and Other Nervous System Cancer	1150	0.323	0	0.000 (0.000, 8.537)	1005	0.255	0	0.000 (0.000, 10.831)
Breast Cancer	921	4.748	3	0.632 (0.152, 1.582)	764	3.773	2	0.530 (0.091, 1.605)
Cervix Uteri Cancer	626	0.258	0	0.000 (0.000, 10.674)	533	0.219	0	0.000 (0.000, 12.592)
Colon and Rectum Cancer	1143	2.256	1	0.443 (0.035, 1.996)	999	1.717	1	0.582 (0.046, 2.624)
Corpus and Uterus, Nos Cancer	617	0.861	0	0.000 (0.000, 3.204)	528	0.665	1	1.504 (0.120, 6.774)
Esophagus Cancer	871	0.221	0	0.000 (0.000, 12.486)	723	0.151	0	0.000 (0.000, 18.244)
Hodgkin Lymphoma	1104	0.113	0	0.000 (0.000, 24.364)	968	0.101	1	9.913 (0.789, 44.653)
Kaposi's Sarcoma	525	0.036	0	0.000 (0.000, 76.170)	475	0.033	0	0.000 (0.000, 83.945)
Kidney and Renal Pelvis Cancer	1108	0.606	1	1.650 (0.131, 7.433)	956	0.441	0	0.000 (0.000, 6.255)
Larynx Cancer	892	0.214	1	4.681 (0.373, 21.083)	727	0.141	0	0.000 (0.000, 19.565)
Leukemia	1141	0.488	1	2.049 (0.163, 9.228)	1001	0.378	0	0.000 (0.000, 7.293)
Liver and Intrahepatic Bile Duct Cancer	950	0.210	1	4.756 (0.379, 21.420)	800	0.150	0	0.000 (0.000, 18.362)
Lung and Bronchus Cancer	1111	3.090	1	0.324 (0.026, 1.458)	961	2.209	0	0.000 (0.000, 1.249)
Melanoma of the Skin	1095	1.101	3	2.726 (0.658, 6.824)	949	0.868	0	0.000 (0.000, 3.179)
Myeloma	965	0.246	0	0.000 (0.000, 11.211)	816	0.181	0	0.000 (0.000, 15.240)
Non-Hodgkin Lymphoma	1152	0.937	1	1.068 (0.085, 4.810)	1008	0.730	1	1.369 (0.109, 6.167)
Oral Cavity and Pharynx Cancer	1132	0.575	0	0.000 (0.000, 4.793)	986	0.419	0	0.000 (0.000, 6.581)
Ovary Cancer	625	0.461	1	2.170 (0.173, 9.773)	533	0.368	0	0.000 (0.000, 7.498)
Pancreas Cancer	1027	0.463	3	6.485 (1.565, 16.234)	874	0.347	0	0.000 (0.000, 7.940)
Prostate Cancer	471	3.557	2	0.562 (0.097, 1.702)	407	2.166	2	0.923 (0.159, 2.795)
Stomach Cancer	1099	0.290	0	0.000 (0.000, 9.504)	951	0.217	0	0.000 (0.000, 12.726)
Testis Cancer	466	0.134	1	7.490 (0.596, 33.738)	420	0.133	0	0.000 (0.000, 20.795)
Thyroid Cancer	1121	0.431	3	6.961 (1.680, 17.426)	973	0.358	3	8.384 (2.023, 20.990)
Urinary Bladder Cancer	1096	0.905	0	0.000 (0.000, 3.047)	947	0.652	0	0.000 (0.000, 4.227)

Program (Date): A_CANCER_MSD (09FEB09) (11:33)

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- * Subjects in some age or gender groups were not expected to have cancers in certain categories.
- N is the number of the study patients who contributed to the calculation of the expected number.
- ** Based on follow-up durations and adjusted by race, gender, and age of the study patients.
- *** Standardized Incidence Ratio - calculated by Observed/Expected. C.I. was calculated by using the mid-p approximation method (Ng et al, 2008). An interval containing a value of '1' indicates that the observed incidence is not statistically different from the population.

Table A3-4. Comparison of Cancer Cases Diagnosed in Clinical Trial Patients with the U.S. Normal Population
(All MSD Clinical Studies Involving rhBMP-2)
[Pre-existing malignancy cases are excluded. The 95% SIR CIs are not adjusted for multiplicity.]

Cancer Site	Number of Cancer Patients							
	rhBMP-2 Group				Non-rhBMP-2 Group			
	N	Expected*	Observed	SIR** (95% C.I.)	N	Expected*	Observed	SIR** (95% C.I.)
All Sites ***	1152	23.84	21	0.881 (0.525, 1.257)	1008	17.71	11	0.621 (0.302, 1.013)
Brain and Other Nervous System Cancer	1150	0.323	0	0.000 (0.000, 8.537)	1005	0.255	0	0.000 (0.000, 10.831)
Breast Cancer	921	4.748	3	0.632 (0.152, 1.582)	764	3.773	2	0.530 (0.091, 1.605)
Cervix Uteri Cancer	626	0.258	0	0.000 (0.000, 10.674)	533	0.219	0	0.000 (0.000, 12.592)
Colon and Rectum Cancer	1143	2.256	1	0.443 (0.035, 1.996)	999	1.717	1	0.582 (0.046, 2.624)
Corpus and Uterus, Nos Cancer	617	0.861	0	0.000 (0.000, 3.204)	528	0.665	1	1.504 (0.120, 6.774)
Esophagus Cancer	871	0.221	0	0.000 (0.000, 12.486)	723	0.151	0	0.000 (0.000, 18.244)
Hodgkin Lymphoma	1104	0.113	0	0.000 (0.000, 24.364)	968	0.101	1	9.913 (0.789, 44.653)
Kaposi's Sarcoma	525	0.036	0	0.000 (0.000, 76.170)	475	0.033	0	0.000 (0.000, 83.945)
Kidney and Renal Pelvis Cancer	1108	0.606	0	0.000 (0.000, 4.550)	956	0.441	0	0.000 (0.000, 6.255)
Larynx Cancer	892	0.214	1	4.681 (0.373, 21.083)	727	0.141	0	0.000 (0.000, 19.565)
Leukemia	1141	0.488	1	2.049 (0.163, 9.228)	1001	0.378	0	0.000 (0.000, 7.293)
Liver and Intrahepatic Bile Duct Cancer	950	0.210	1	4.756 (0.379, 21.420)	800	0.150	0	0.000 (0.000, 18.362)
Lung and Bronchus Cancer	1111	3.090	1	0.324 (0.026, 1.458)	961	2.209	0	0.000 (0.000, 1.249)
Melanoma of the Skin	1095	1.101	3	2.726 (0.658, 6.824)	949	0.868	0	0.000 (0.000, 3.179)
Myeloma	965	0.246	0	0.000 (0.000, 11.211)	816	0.181	0	0.000 (0.000, 15.240)
Non-Hodgkin Lymphoma	1152	0.937	1	1.068 (0.085, 4.810)	1008	0.730	1	1.369 (0.109, 6.167)
Oral Cavity and Pharynx Cancer	1132	0.575	0	0.000 (0.000, 4.793)	986	0.419	0	0.000 (0.000, 6.581)
Ovary Cancer	625	0.461	1	2.170 (0.173, 9.773)	533	0.368	0	0.000 (0.000, 7.498)
Pancreas Cancer	1027	0.463	2	4.323 (0.745, 13.088)	874	0.347	0	0.000 (0.000, 7.940)
Prostate Cancer	471	3.557	2	0.562 (0.097, 1.702)	407	2.166	2	0.923 (0.159, 2.795)
Stomach Cancer	1099	0.290	0	0.000 (0.000, 9.504)	951	0.217	0	0.000 (0.000, 12.726)
Testis Cancer	466	0.134	1	7.490 (0.596, 33.738)	420	0.133	0	0.000 (0.000, 20.795)
Thyroid Cancer	1121	0.431	3	6.961 (1.680, 17.426)	973	0.358	3	8.384 (2.023, 20.990)
Urinary Bladder Cancer	1096	0.905	0	0.000 (0.000, 3.047)	947	0.652	0	0.000 (0.000, 4.227)

Program (Date): A_CANCER_MSD2 (09FEB09) (11:35)

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- * Subjects in some age or gender groups were not expected to have cancers in certain categories.
N is the number of the study patients who contributed to the calculation of the expected number.
- ** Based on follow-up durations and adjusted by race, gender, and age of the study patients.
- *** Standardized Incidence Ratio - calculated by Observed/Expected. C.I. was calculated by using the mid-p approximation method (Ng et al, 2008). An interval containing a value of '1' indicates that the observed incidence is not statistically different from the population.

Table A3-5. Comparison of Cancer Cases Diagnosed in Clinical Trial Patients with the U.S. Normal Population
(All MSD Clinical Studies Involving rhBMP-2)

[Pre-existing malignancy cases are included. The 95% SIR CIs are adjusted for multiplicity.]

Cancer Site	Number of Cancer Patients							
	rhBMP-2 Group				Non-rhBMP-2 Group			
	N	Expected*	Observed	SIR** (95% C.I.)	N	Expected*	Observed	SIR** (95% C.I.)
All Sites ***	1152	23.84	23	0.965 (0.589, 1.355)	1008	17.71	11	0.621 (0.302, 1.013)
Brain and Other Nervous System Cancer	1150	0.323	0	0.000 (0.000, 18.684)	1005	0.255	0	0.000 (0.000, 23.705)
Breast Cancer	921	4.748	3	0.632 (0.044, 2.434)	764	3.773	2	0.530 (0.015, 2.607)
Cervix Uteri Cancer	626	0.258	0	0.000 (0.000, 23.359)	533	0.219	0	0.000 (0.000, 27.558)
Colon and Rectum Cancer	1143	2.256	1	0.443 (0.000, 3.545)	999	1.717	1	0.582 (0.000, 4.659)
Corpus and Uterus, Nos Cancer	617	0.861	0	0.000 (0.000, 7.013)	528	0.665	1	1.504 (0.001, 12.029)
Esophagus Cancer	871	0.221	0	0.000 (0.000, 27.326)	723	0.151	0	0.000 (0.000, 39.927)
Hodgkin Lymphoma	1104	0.113	0	0.000 (0.000, 53.321)	968	0.101	1	9.913 (0.005, 79.289)
Kaposi's Sarcoma	525	0.036	0	0.000 (0.000, 166.700)	475	0.033	0	0.000 (0.000, 183.717)
Kidney and Renal Pelvis Cancer	1108	0.606	1	1.650 (0.001, 13.198)	956	0.441	0	0.000 (0.000, 13.689)
Larynx Cancer	892	0.214	1	4.681 (0.003, 37.437)	727	0.141	0	0.000 (0.000, 42.818)
Leukemia	1141	0.488	1	2.049 (0.001, 16.386)	1001	0.378	0	0.000 (0.000, 15.962)
Liver and Intrahepatic Bile Duct Cancer	950	0.210	1	4.756 (0.003, 38.035)	800	0.150	0	0.000 (0.000, 40.186)
Lung and Bronchus Cancer	1111	3.090	1	0.324 (0.000, 2.588)	961	2.209	0	0.000 (0.000, 2.733)
Melanoma of the Skin	1095	1.101	3	2.726 (0.192, 10.500)	949	0.868	0	0.000 (0.000, 6.957)
Myeloma	965	0.246	0	0.000 (0.000, 24.535)	816	0.181	0	0.000 (0.000, 33.354)
Non-Hodgkin Lymphoma	1152	0.937	1	1.068 (0.001, 8.540)	1008	0.730	1	1.369 (0.001, 10.950)
Oral Cavity and Pharynx Cancer	1132	0.575	0	0.000 (0.000, 10.489)	986	0.419	0	0.000 (0.000, 14.402)
Ovary Cancer	625	0.461	1	2.170 (0.001, 17.354)	533	0.368	0	0.000 (0.000, 16.409)
Pancreas Cancer	1027	0.463	3	6.485 (0.456, 24.978)	874	0.347	0	0.000 (0.000, 17.377)
Prostate Cancer	471	3.557	2	0.562 (0.016, 2.765)	407	2.166	2	0.923 (0.026, 4.540)
Stomach Cancer	1099	0.290	0	0.000 (0.000, 20.799)	951	0.217	0	0.000 (0.000, 27.851)
Testis Cancer	466	0.134	1	7.490 (0.004, 59.907)	420	0.133	0	0.000 (0.000, 45.510)
Thyroid Cancer	1121	0.431	3	6.961 (0.490, 26.813)	973	0.358	3	8.384 (0.590, 32.295)
Urinary Bladder Cancer	1096	0.905	0	0.000 (0.000, 6.668)	947	0.652	0	0.000 (0.000, 9.252)

Program (Date): A_CANCER_MSD3 (09FEB09) (11:35)

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- * Subjects in some age or gender groups were not expected to have cancers in certain categories.
N is the number of the study patients who contributed to the calculation of the expected number.
- ** Based on follow-up durations and adjusted by race, gender, and age of the study patients.
- *** Standardized Incidence Ratio - calculated by Observed/Expected. C.I. was calculated by using the mid-p approximation method (Ng et al, 2008). An interval containing a value of '1' indicates that the observed incidence is not statistically different from the population.

Table A3-6. Comparison of Cancer Cases Diagnosed in Clinical Trial Patients with the U.S. Normal Population
(All MSD Clinical Studies Involving rhBMP-2)

[Pre-existing malignancy cases are excluded. The 95% SIR CIs are adjusted for multiplicity.]

Cancer Site	Number of Cancer Patients							
	rhBMP-2 Group				Non-rhBMP-2 Group			
	N	Expected*	Observed	SIR** (95% C.I.)	N	Expected*	Observed	SIR** (95% C.I.)
All Sites ***	1152	23.84	21	0.881 (0.525, 1.257)	1008	17.71	11	0.621 (0.302, 1.013)
Brain and Other Nervous System Cancer	1150	0.323	0	0.000 (0.000, 18.684)	1005	0.255	0	0.000 (0.000, 23.705)
Breast Cancer	921	4.748	3	0.632 (0.044, 2.434)	764	3.773	2	0.530 (0.015, 2.607)
Cervix Uteri Cancer	626	0.258	0	0.000 (0.000, 23.359)	533	0.219	0	0.000 (0.000, 27.558)
Colon and Rectum Cancer	1143	2.256	1	0.443 (0.000, 3.545)	999	1.717	1	0.582 (0.000, 4.659)
Corpus and Uterus, Nos Cancer	617	0.861	0	0.000 (0.000, 7.013)	528	0.665	1	1.504 (0.001, 12.029)
Esophagus Cancer	871	0.221	0	0.000 (0.000, 27.326)	723	0.151	0	0.000 (0.000, 39.927)
Hodgkin Lymphoma	1104	0.113	0	0.000 (0.000, 53.321)	968	0.101	1	9.913 (0.005, 79.289)
Kaposi's Sarcoma	525	0.036	0	0.000 (0.000, 166.700)	475	0.033	0	0.000 (0.000, 183.717)
Kidney and Renal Pelvis Cancer	1108	0.606	0	0.000 (0.000, 9.959)	956	0.441	0	0.000 (0.000, 13.689)
Larynx Cancer	892	0.214	1	4.681 (0.003, 37.437)	727	0.141	0	0.000 (0.000, 42.818)
Leukemia	1141	0.488	1	2.049 (0.001, 16.386)	1001	0.378	0	0.000 (0.000, 15.962)
Liver and Intrahepatic Bile Duct Cancer	950	0.210	1	4.756 (0.003, 38.035)	800	0.150	0	0.000 (0.000, 40.186)
Lung and Bronchus Cancer	1111	3.090	1	0.324 (0.000, 2.588)	961	2.209	0	0.000 (0.000, 2.733)
Melanoma of the Skin	1095	1.101	3	2.726 (0.192, 10.500)	949	0.868	0	0.000 (0.000, 6.957)
Myeloma	965	0.246	0	0.000 (0.000, 24.535)	816	0.181	0	0.000 (0.000, 33.354)
Non-Hodgkin Lymphoma	1152	0.937	1	1.068 (0.001, 8.540)	1008	0.730	1	1.369 (0.001, 10.950)
Oral Cavity and Pharynx Cancer	1132	0.575	0	0.000 (0.000, 10.489)	986	0.419	0	0.000 (0.000, 14.402)
Ovary Cancer	625	0.461	1	2.170 (0.001, 17.354)	533	0.368	0	0.000 (0.000, 16.409)
Pancreas Cancer	1027	0.463	2	4.323 (0.120, 21.260)	874	0.347	0	0.000 (0.000, 17.377)
Prostate Cancer	471	3.557	2	0.562 (0.016, 2.765)	407	2.166	2	0.923 (0.026, 4.540)
Stomach Cancer	1099	0.290	0	0.000 (0.000, 20.799)	951	0.217	0	0.000 (0.000, 27.851)
Testis Cancer	466	0.134	1	7.490 (0.004, 59.907)	420	0.133	0	0.000 (0.000, 45.510)
Thyroid Cancer	1121	0.431	3	6.961 (0.490, 26.813)	973	0.358	3	8.384 (0.590, 32.295)
Urinary Bladder Cancer	1096	0.905	0	0.000 (0.000, 6.668)	947	0.652	0	0.000 (0.000, 9.252)

Program (Date): A_CANCER_MSD4 (09FEB09) (11:35)

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- * Subjects in some age or gender groups were not expected to have cancers in certain categories.
N is the number of the study patients who contributed to the calculation of the expected number.
- ** Based on follow-up durations and adjusted by race, gender, and age of the study patients.
- *** Standardized Incidence Ratio - calculated by Observed/Expected. C.I. was calculated by using the mid-p approximation method (Ng et al, 2008). An interval containing a value of '1' indicates that the observed incidence is not statistically different from the population.

Table A3-7. Comparison of Cancer Cases Diagnosed in Clinical Trial Patients with the U.S. Normal Population
(All Wyeth Clinical Studies Involving rhBMP-2)
[Pre-existing malignancy cases are included. The 95% SIR CIs are not adjusted for multiplicity.]

Cancer Site	Number of Cancer Patients							
	rhBMP-2 Group				Non-rhBMP-2 Group			
	N	Expected*	Observed	SIR** (95% C.I.)	N	Expected*	Observed	SIR** (95% C.I.)
All Sites ***	1006	8.781	9	1.025 (0.460, 1.759)	749	5.815	6	1.032 (0.384, 1.993)
Brain and Other Nervous System Cancer	945	0.117	0	0.000 (0.000, 23.609)	709	0.080	1	12.511 (0.996, 56.355)
Breast Cancer	511	1.379	2	1.451 (0.250, 4.392)	399	1.026	3	2.923 (0.705, 7.317)
Cervix Uteri Cancer	289	0.066	0	0.000 (0.000, 41.915)	237	0.048	0	0.000 (0.000, 57.889)
Colon and Rectum Cancer	883	0.910	1	1.098 (0.087, 4.947)	668	0.577	0	0.000 (0.000, 4.778)
Corpus and Uterus, Nos Cancer	269	0.262	0	0.000 (0.000, 10.526)	212	0.195	0	0.000 (0.000, 14.129)
Esophagus Cancer	554	0.090	0	0.000 (0.000, 30.579)	404	0.058	0	0.000 (0.000, 47.879)
Hodgkin Lymphoma	894	0.046	0	0.000 (0.000, 60.545)	668	0.031	0	0.000 (0.000, 89.623)
Kaposi's Sarcoma	681	0.019	0	0.000 (0.000, 148.739)	484	0.012	0	0.000 (0.000, 227.328)
Kidney and Renal Pelvis Cancer	700	0.226	0	0.000 (0.000, 12.215)	525	0.152	0	0.000 (0.000, 18.152)
Larynx Cancer	531	0.083	0	0.000 (0.000, 33.170)	386	0.055	0	0.000 (0.000, 50.242)
Leukemia	933	0.195	0	0.000 (0.000, 14.111)	699	0.125	0	0.000 (0.000, 22.095)
Liver and Intrahepatic Bile Duct Cancer	587	0.083	0	0.000 (0.000, 33.028)	432	0.054	0	0.000 (0.000, 50.756)
Lung and Bronchus Cancer	713	1.216	0	0.000 (0.000, 2.269)	541	0.779	0	0.000 (0.000, 3.538)
Melanoma of the Skin	846	0.356	0	0.000 (0.000, 7.745)	639	0.246	1	4.067 (0.324, 18.319)
Myeloma	587	0.098	1	10.165 (0.810, 45.787)	431	0.062	0	0.000 (0.000, 44.159)
Non-Hodgkin Lymphoma	974	0.356	0	0.000 (0.000, 7.743)	720	0.237	0	0.000 (0.000, 11.622)
Oral Cavity and Pharynx Cancer	763	0.216	0	0.000 (0.000, 12.792)	581	0.147	1	6.792 (0.541, 30.594)
Ovary Cancer	285	0.137	0	0.000 (0.000, 20.182)	230	0.102	0	0.000 (0.000, 27.125)
Pancreas Cancer	596	0.187	0	0.000 (0.000, 14.768)	435	0.118	0	0.000 (0.000, 23.277)
Prostate Cancer	369	1.529	4	2.617 (0.770, 5.828)	261	0.926	0	0.000 (0.000, 2.977)
Stomach Cancer	692	0.120	0	0.000 (0.000, 22.918)	518	0.075	0	0.000 (0.000, 36.932)
Testis Cancer	548	0.064	0	0.000 (0.000, 42.773)	423	0.044	0	0.000 (0.000, 63.200)
Thyroid Cancer	856	0.116	0	0.000 (0.000, 23.672)	657	0.086	0	0.000 (0.000, 32.140)
Urinary Bladder Cancer	732	0.377	0	0.000 (0.000, 7.308)	546	0.229	0	0.000 (0.000, 12.024)

Program (Date): A_CANCER_WYETH (09FEB09) (08:25)

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* Subjects in some age or gender groups were not expected to have cancers in certain categories.

N is the number of the study patients who contributed to the calculation of the expected number.

** Based on follow-up durations and adjusted by race, gender, and age of the study patients.

*** Standardized Incidence Ratio - calculated by Observed/Expected. C.I. was calculated by using the mid-p approximation method (Ng et al, 2008). An interval containing a value of '1' indicates that the observed incidence is not statistically different from the population. One cancer of 'abdominal lining' in the BMP group was counted in 'All Sites', but the individual SIR analysis was not done because the SEER Statistics do not include information for this category.

Table A3-8. Comparison of Cancer Cases Diagnosed in Clinical Trial Patients with the U.S. Normal Population
(All Wyeth Clinical Studies Involving rhBMP-2)
[Pre-existing malignancy cases are excluded. The 95% SIR CIs are not adjusted for multiplicity.]

Cancer Site	Number of Cancer Patients							
	rhBMP-2 Group				Non-rhBMP-2 Group			
	N	Expected*	Observed	SIR** (95% C.I.)	N	Expected*	Observed	SIR** (95% C.I.)
All Sites ***	1006	8.781	9	1.025 (0.460, 1.759)	749	5.815	5	0.860 (0.290, 1.765)
Brain and Other Nervous System Cancer	945	0.117	0	0.000 (0.000, 23.609)	709	0.080	1	12.511 (0.996, 56.355)
Breast Cancer	511	1.379	2	1.451 (0.250, 4.392)	399	1.026	2	1.948 (0.336, 5.899)
Cervix Uteri Cancer	289	0.066	0	0.000 (0.000, 41.915)	237	0.048	0	0.000 (0.000, 57.889)
Colon and Rectum Cancer	883	0.910	1	1.098 (0.087, 4.947)	668	0.577	0	0.000 (0.000, 4.778)
Corpus and Uterus, Nos Cancer	269	0.262	0	0.000 (0.000, 10.526)	212	0.195	0	0.000 (0.000, 14.129)
Esophagus Cancer	554	0.090	0	0.000 (0.000, 30.579)	404	0.058	0	0.000 (0.000, 47.879)
Hodgkin Lymphoma	894	0.046	0	0.000 (0.000, 60.545)	668	0.031	0	0.000 (0.000, 89.623)
Kaposi's Sarcoma	681	0.019	0	0.000 (0.000, 148.739)	484	0.012	0	0.000 (0.000, 227.328)
Kidney and Renal Pelvis Cancer	700	0.226	0	0.000 (0.000, 12.215)	525	0.152	0	0.000 (0.000, 18.152)
Larynx Cancer	531	0.083	0	0.000 (0.000, 33.170)	386	0.055	0	0.000 (0.000, 50.242)
Leukemia	933	0.195	0	0.000 (0.000, 14.111)	699	0.125	0	0.000 (0.000, 22.095)
Liver and Intrahepatic Bile Duct Cancer	587	0.083	0	0.000 (0.000, 33.028)	432	0.054	0	0.000 (0.000, 50.756)
Lung and Bronchus Cancer	713	1.216	0	0.000 (0.000, 2.269)	541	0.779	0	0.000 (0.000, 3.538)
Melanoma of the Skin	846	0.356	0	0.000 (0.000, 7.745)	639	0.246	1	4.067 (0.324, 18.319)
Myeloma	587	0.098	1	10.165 (0.810, 45.787)	431	0.062	0	0.000 (0.000, 44.159)
Non-Hodgkin Lymphoma	974	0.356	0	0.000 (0.000, 7.743)	720	0.237	0	0.000 (0.000, 11.622)
Oral Cavity and Pharynx Cancer	763	0.216	0	0.000 (0.000, 12.792)	581	0.147	1	6.792 (0.541, 30.594)
Ovary Cancer	285	0.137	0	0.000 (0.000, 20.182)	230	0.102	0	0.000 (0.000, 27.125)
Pancreas Cancer	596	0.187	0	0.000 (0.000, 14.768)	435	0.118	0	0.000 (0.000, 23.277)
Prostate Cancer	369	1.529	4	2.617 (0.770, 5.828)	261	0.926	0	0.000 (0.000, 2.977)
Stomach Cancer	692	0.120	0	0.000 (0.000, 22.918)	518	0.075	0	0.000 (0.000, 36.932)
Testis Cancer	548	0.064	0	0.000 (0.000, 42.773)	423	0.044	0	0.000 (0.000, 63.200)
Thyroid Cancer	856	0.116	0	0.000 (0.000, 23.672)	657	0.086	0	0.000 (0.000, 32.140)
Urinary Bladder Cancer	732	0.377	0	0.000 (0.000, 7.308)	546	0.229	0	0.000 (0.000, 12.024)

Program (Date): A_CANCER_WYETH2 (09FEB09) (08:30)

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- * Subjects in some age or gender groups were not expected to have cancers in certain categories.
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- ** Based on follow-up durations and adjusted by race, gender, and age of the study patients.
- *** Standardized Incidence Ratio - calculated by Observed/Expected. C.I. was calculated by using the mid-p approximation method (Ng et al, 2008). An interval containing a value of '1' indicates that the observed incidence is not statistically different from the population.
One cancer of 'abdominal lining' in the BMP group was counted in 'All Sites', but the individual SIR analysis was not done because the SEER Statistics do not include information for this category.

Table A3-9. Comparison of Cancer Cases Diagnosed in Clinical Trial Patients with the U.S. Normal Population
(All Wyeth Clinical Studies Involving rhBMP-2)
[Pre-existing malignancy cases are included. The 95% SIR CIs are adjusted for multiplicity.]

Cancer Site	Number of Cancer Patients							
	rhBMP-2 Group				Non-rhBMP-2 Group			
	N	Expected*	Observed	SIR** (95% C.I.)	N	Expected*	Observed	SIR** (95% C.I.)
All Sites ***	1006	8.781	9	1.025 (0.460, 1.759)	749	5.815	6	1.032 (0.384, 1.993)
Brain and Other Nervous System Cancer	945	0.117	0	0.000 (0.000, 51.669)	709	0.080	1	12.511 (0.007, 100.068)
Breast Cancer	511	1.379	2	1.451 (0.040, 7.135)	399	1.026	3	2.923 (0.206, 11.257)
Cervix Uteri Cancer	289	0.066	0	0.000 (0.000, 91.733)	237	0.048	0	0.000 (0.000, 126.693)
Colon and Rectum Cancer	883	0.910	1	1.098 (0.001, 8.784)	668	0.577	0	0.000 (0.000, 10.457)
Corpus and Uterus, Nos Cancer	269	0.262	0	0.000 (0.000, 23.037)	212	0.195	0	0.000 (0.000, 30.922)
Esophagus Cancer	554	0.090	0	0.000 (0.000, 66.923)	404	0.058	0	0.000 (0.000, 104.784)
Hodgkin Lymphoma	894	0.046	0	0.000 (0.000, 132.505)	668	0.031	0	0.000 (0.000, 196.143)
Kaposi's Sarcoma	681	0.019	0	0.000 (0.000, 325.521)	484	0.012	0	0.000 (0.000, 497.517)
Kidney and Renal Pelvis Cancer	700	0.226	0	0.000 (0.000, 26.733)	525	0.152	0	0.000 (0.000, 39.727)
Larynx Cancer	531	0.083	0	0.000 (0.000, 72.594)	386	0.055	0	0.000 (0.000, 109.956)
Leukemia	933	0.195	0	0.000 (0.000, 30.883)	699	0.125	0	0.000 (0.000, 48.355)
Liver and Intrahepatic Bile Duct Cancer	587	0.083	0	0.000 (0.000, 72.282)	432	0.054	0	0.000 (0.000, 111.083)
Lung and Bronchus Cancer	713	1.216	0	0.000 (0.000, 4.965)	541	0.779	0	0.000 (0.000, 7.743)
Melanoma of the Skin	846	0.356	0	0.000 (0.000, 16.950)	639	0.246	1	4.067 (0.002, 32.528)
Myeloma	587	0.098	1	10.165 (0.006, 81.302)	431	0.062	0	0.000 (0.000, 96.644)
Non-Hodgkin Lymphoma	974	0.356	0	0.000 (0.000, 16.946)	720	0.237	0	0.000 (0.000, 25.435)
Oral Cavity and Pharynx Cancer	763	0.216	0	0.000 (0.000, 27.995)	581	0.147	1	6.792 (0.004, 54.325)
Ovary Cancer	285	0.137	0	0.000 (0.000, 44.169)	230	0.102	0	0.000 (0.000, 59.365)
Pancreas Cancer	596	0.187	0	0.000 (0.000, 32.321)	435	0.118	0	0.000 (0.000, 50.942)
Prostate Cancer	369	1.529	4	2.617 (0.294, 8.632)	261	0.926	0	0.000 (0.000, 6.515)
Stomach Cancer	692	0.120	0	0.000 (0.000, 50.158)	518	0.075	0	0.000 (0.000, 80.826)
Testis Cancer	548	0.064	0	0.000 (0.000, 93.610)	423	0.044	0	0.000 (0.000, 138.316)
Thyroid Cancer	856	0.116	0	0.000 (0.000, 51.807)	657	0.086	0	0.000 (0.000, 70.339)
Urinary Bladder Cancer	732	0.377	0	0.000 (0.000, 15.994)	546	0.229	0	0.000 (0.000, 26.316)

Program (Date): A_CANCER_WYETH3 (09FEB09) (08:31)

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- *** Standardized Incidence Ratio - calculated by Observed/Expected. C.I. was calculated by using the mid-p approximation method (Ng et al, 2008). An interval containing a value of '1' indicates that the observed incidence is not statistically different from the population.
One cancer of 'abdominal lining' in the BMP group was counted in 'All Sites', but the individual SIR analysis was not done because the SEER Statistics do not include information for this category.

Table A3-10. Comparison of Cancer Cases Diagnosed in Clinical Trial Patients with the U.S. Normal Population
(All Wyeth Clinical Studies Involving rhBMP-2)
[Pre-existing malignancy cases are excluded. The 95% SIR CIs are adjusted for multiplicity.]

Cancer Site	Number of Cancer Patients							
	rhBMP-2 Group				Non-rhBMP-2 Group			
	N	Expected*	Observed	SIR** (95% C.I.)	N	Expected*	Observed	SIR** (95% C.I.)
All Sites ***	1006	8.781	9	1.025 (0.460, 1.759)	749	5.815	5	0.860 (0.290, 1.765)
Brain and Other Nervous System Cancer	945	0.117	0	0.000 (0.000, 51.669)	709	0.080	1	12.511 (0.007, 100.068)
Breast Cancer	511	1.379	2	1.451 (0.040, 7.135)	399	1.026	2	1.948 (0.054, 9.582)
Cervix Uteri Cancer	289	0.066	0	0.000 (0.000, 91.733)	237	0.048	0	0.000 (0.000, 126.693)
Colon and Rectum Cancer	883	0.910	1	1.098 (0.001, 8.784)	668	0.577	0	0.000 (0.000, 10.457)
Corpus and Uterus, Nos Cancer	269	0.262	0	0.000 (0.000, 23.037)	212	0.195	0	0.000 (0.000, 30.922)
Esophagus Cancer	554	0.090	0	0.000 (0.000, 66.923)	404	0.058	0	0.000 (0.000, 104.784)
Hodgkin Lymphoma	894	0.046	0	0.000 (0.000, 132.505)	668	0.031	0	0.000 (0.000, 196.143)
Kaposi's Sarcoma	681	0.019	0	0.000 (0.000, 325.521)	484	0.012	0	0.000 (0.000, 497.517)
Kidney and Renal Pelvis Cancer	700	0.226	0	0.000 (0.000, 26.733)	525	0.152	0	0.000 (0.000, 39.727)
Larynx Cancer	531	0.083	0	0.000 (0.000, 72.594)	386	0.055	0	0.000 (0.000, 109.956)
Leukemia	933	0.195	0	0.000 (0.000, 30.883)	699	0.125	0	0.000 (0.000, 48.355)
Liver and Intrahepatic Bile Duct Cancer	587	0.083	0	0.000 (0.000, 72.282)	432	0.054	0	0.000 (0.000, 111.083)
Lung and Bronchus Cancer	713	1.216	0	0.000 (0.000, 4.965)	541	0.779	0	0.000 (0.000, 7.743)
Melanoma of the Skin	846	0.356	0	0.000 (0.000, 16.950)	639	0.246	1	4.067 (0.002, 32.528)
Myeloma	587	0.098	1	10.165 (0.006, 81.302)	431	0.062	0	0.000 (0.000, 96.644)
Non-Hodgkin Lymphoma	974	0.356	0	0.000 (0.000, 16.946)	720	0.237	0	0.000 (0.000, 25.435)
Oral Cavity and Pharynx Cancer	763	0.216	0	0.000 (0.000, 27.995)	581	0.147	1	6.792 (0.004, 54.325)
Ovary Cancer	285	0.137	0	0.000 (0.000, 44.169)	230	0.102	0	0.000 (0.000, 59.365)
Pancreas Cancer	596	0.187	0	0.000 (0.000, 32.321)	435	0.118	0	0.000 (0.000, 50.942)
Prostate Cancer	369	1.529	4	2.617 (0.294, 8.632)	261	0.926	0	0.000 (0.000, 6.515)
Stomach Cancer	692	0.120	0	0.000 (0.000, 50.158)	518	0.075	0	0.000 (0.000, 80.826)
Testis Cancer	548	0.064	0	0.000 (0.000, 93.610)	423	0.044	0	0.000 (0.000, 138.316)
Thyroid Cancer	856	0.116	0	0.000 (0.000, 51.807)	657	0.086	0	0.000 (0.000, 70.339)
Urinary Bladder Cancer	732	0.377	0	0.000 (0.000, 15.994)	546	0.229	0	0.000 (0.000, 26.316)

Program (Date): A_CANCER_WYETH4 (09FEB09) (08:31)

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- * Subjects in some age or gender groups were not expected to have cancers in certain categories.
N is the number of the study patients who contributed to the calculation of the expected number.
- ** Based on follow-up durations and adjusted by race, gender, and age of the study patients.
- *** Standardized Incidence Ratio - calculated by Observed/Expected. C.I. was calculated by using the mid-p approximation method (Ng et al, 2008). An interval containing a value of '1' indicates that the observed incidence is not statistically different from the population.
One cancer of 'abdominal lining' in the BMP group was counted in 'All Sites', but the individual SIR analysis was not done because the SEER Statistics do not include information for this category.

Table A3-11. Comparison of Cancer Cases Diagnosed in Clinical Trial Patients with the U.S. Normal Population
(All Medtronic and Wyeth Clinical Studies Involving rhBMP-2)
[Pre-existing malignancy cases are included. The 95% SIR CIs are not adjusted for multiplicity.]

Cancer Site	Number of Cancer Patients							
	rhBMP-2 Group				Non-rhBMP-2 Group			
	N	Expected*	Observed	SIR** (95% C.I.)	N	Expected*	Observed	SIR** (95% C.I.)
All Sites ***	2158	32.62	32	0.981 (0.647, 1.308)	1757	23.53	17	0.723 (0.406, 1.072)
Brain and Other Nervous System Cancer	2095	0.440	0	0.000 (0.000, 6.270)	1714	0.335	1	2.989 (0.238, 13.465)
Breast Cancer	1432	6.127	5	0.816 (0.275, 1.675)	1163	4.800	5	1.042 (0.351, 2.139)
Cervix Uteri Cancer	915	0.324	0	0.000 (0.000, 8.507)	770	0.267	0	0.000 (0.000, 10.342)
Colon and Rectum Cancer	2026	3.167	2	0.632 (0.109, 1.912)	1667	2.294	1	0.436 (0.035, 1.964)
Corpus and Uterus, Nos Cancer	886	1.123	0	0.000 (0.000, 2.457)	740	0.860	1	1.163 (0.093, 5.237)
Esophagus Cancer	1425	0.311	0	0.000 (0.000, 8.866)	1127	0.209	0	0.000 (0.000, 13.210)
Hodgkin Lymphoma	1998	0.159	0	0.000 (0.000, 17.373)	1636	0.132	1	7.596 (0.605, 34.216)
Kaposi's Sarcoma	1206	0.055	0	0.000 (0.000, 50.373)	959	0.045	0	0.000 (0.000, 61.307)
Kidney and Renal Pelvis Cancer	1808	0.832	1	1.202 (0.096, 5.415)	1481	0.593	0	0.000 (0.000, 4.652)
Larynx Cancer	1423	0.297	1	3.369 (0.268, 15.177)	1113	0.196	0	0.000 (0.000, 14.081)
Leukemia	2074	0.684	1	1.463 (0.117, 6.590)	1700	0.503	0	0.000 (0.000, 5.483)
Liver and Intrahepatic Bile Duct Cancer	1537	0.294	1	3.404 (0.271, 15.333)	1232	0.205	0	0.000 (0.000, 13.484)
Lung and Bronchus Cancer	1824	4.306	1	0.232 (0.018, 1.046)	1502	2.988	0	0.000 (0.000, 0.923)
Melanoma of the Skin	1941	1.457	3	2.060 (0.497, 5.156)	1588	1.113	1	0.898 (0.072, 4.046)
Myeloma	1552	0.344	1	2.904 (0.231, 13.080)	1247	0.243	0	0.000 (0.000, 11.330)
Non-Hodgkin Lymphoma	2126	1.293	1	0.774 (0.062, 3.485)	1728	0.968	1	1.033 (0.082, 4.655)
Oral Cavity and Pharynx Cancer	1895	0.791	0	0.000 (0.000, 3.486)	1567	0.566	1	1.766 (0.141, 7.954)
Ovary Cancer	910	0.598	1	1.674 (0.133, 7.538)	763	0.469	0	0.000 (0.000, 5.874)
Pancreas Cancer	1623	0.649	3	4.620 (1.115, 11.566)	1309	0.466	0	0.000 (0.000, 5.920)
Prostate Cancer	840	5.086	6	1.180 (0.439, 2.279)	668	3.093	2	0.647 (0.111, 1.958)
Stomach Cancer	1791	0.410	0	0.000 (0.000, 6.718)	1469	0.291	0	0.000 (0.000, 9.464)
Testis Cancer	1014	0.198	1	5.051 (0.402, 22.751)	843	0.176	0	0.000 (0.000, 15.647)
Thyroid Cancer	1977	0.547	3	5.480 (1.322, 13.718)	1630	0.444	3	6.763 (1.632, 16.930)
Urinary Bladder Cancer	1828	1.282	0	0.000 (0.000, 2.150)	1493	0.882	0	0.000 (0.000, 3.128)

Program (Date): A_CANCER_POOLED (09FEB09) (11:35)

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* Subjects in some age or gender groups were not expected to have cancers in certain categories.

N is the number of the study patients who contributed to the calculation of the expected number.

** Based on follow-up durations and adjusted by race, gender, and age of the study patients.

*** Standardized Incidence Ratio - calculated by Observed/Expected. C.I. was calculated by using the mid-p approximation method (Ng et al, 2008). An interval containing a value of '1' indicates that the observed incidence is not statistically different from the population.
One cancer of 'abdominal lining' in the BMP group was counted in 'All Sites', but the individual SIR analysis was not done because the SEER Statistics do not include information for this category.

Table A3-12. Comparison of Cancer Cases Diagnosed in Clinical Trial Patients with the U.S. Normal Population
(All Medtronic and Wyeth Clinical Studies Involving rhBMP-2)
[Pre-existing malignancy cases are excluded. The 95% SIR CIs are not adjusted for multiplicity.]

Cancer Site	Number of Cancer Patients							
	rhBMP-2 Group				Non-rhBMP-2 Group			
	N	Expected*	Observed	SIR** (95% C.I.)	N	Expected*	Observed	SIR** (95% C.I.)
All Sites ***	2158	32.62	30	0.920 (0.598, 1.238)	1757	23.53	16	0.680 (0.375, 1.021)
Brain and Other Nervous System Cancer	2095	0.440	0	0.000 (0.000, 6.270)	1714	0.335	1	2.989 (0.238, 13.465)
Breast Cancer	1432	6.127	5	0.816 (0.275, 1.675)	1163	4.800	4	0.833 (0.245, 1.856)
Cervix Uteri Cancer	915	0.324	0	0.000 (0.000, 8.507)	770	0.267	0	0.000 (0.000, 10.342)
Colon and Rectum Cancer	2026	3.167	2	0.632 (0.109, 1.912)	1667	2.294	1	0.436 (0.035, 1.964)
Corpus and Uterus, Nos Cancer	886	1.123	0	0.000 (0.000, 2.457)	740	0.860	1	1.163 (0.093, 5.237)
Esophagus Cancer	1425	0.311	0	0.000 (0.000, 8.866)	1127	0.209	0	0.000 (0.000, 13.210)
Hodgkin Lymphoma	1998	0.159	0	0.000 (0.000, 17.373)	1636	0.132	1	7.596 (0.605, 34.216)
Kaposi's Sarcoma	1206	0.055	0	0.000 (0.000, 50.373)	959	0.045	0	0.000 (0.000, 61.307)
Kidney and Renal Pelvis Cancer	1808	0.832	0	0.000 (0.000, 3.315)	1481	0.593	0	0.000 (0.000, 4.652)
Larynx Cancer	1423	0.297	1	3.369 (0.268, 15.177)	1113	0.196	0	0.000 (0.000, 14.081)
Leukemia	2074	0.684	1	1.463 (0.117, 6.590)	1700	0.503	0	0.000 (0.000, 5.483)
Liver and Intrahepatic Bile Duct Cancer	1537	0.294	1	3.404 (0.271, 15.333)	1232	0.205	0	0.000 (0.000, 13.484)
Lung and Bronchus Cancer	1824	4.306	1	0.232 (0.018, 1.046)	1502	2.988	0	0.000 (0.000, 0.923)
Melanoma of the Skin	1941	1.457	3	2.060 (0.497, 5.156)	1588	1.113	1	0.898 (0.072, 4.046)
Myeloma	1552	0.344	1	2.904 (0.231, 13.080)	1247	0.243	0	0.000 (0.000, 11.330)
Non-Hodgkin Lymphoma	2126	1.293	1	0.774 (0.062, 3.485)	1728	0.968	1	1.033 (0.082, 4.655)
Oral Cavity and Pharynx Cancer	1895	0.791	0	0.000 (0.000, 3.486)	1567	0.566	1	1.766 (0.141, 7.954)
Ovary Cancer	910	0.598	1	1.674 (0.133, 7.538)	763	0.469	0	0.000 (0.000, 5.874)
Pancreas Cancer	1623	0.649	2	3.080 (0.531, 9.324)	1309	0.466	0	0.000 (0.000, 5.920)
Prostate Cancer	840	5.086	6	1.180 (0.439, 2.279)	668	3.093	2	0.647 (0.111, 1.958)
Stomach Cancer	1791	0.410	0	0.000 (0.000, 6.718)	1469	0.291	0	0.000 (0.000, 9.464)
Testis Cancer	1014	0.198	1	5.051 (0.402, 22.751)	843	0.176	0	0.000 (0.000, 15.647)
Thyroid Cancer	1977	0.547	3	5.480 (1.322, 13.718)	1630	0.444	3	6.763 (1.632, 16.930)
Urinary Bladder Cancer	1828	1.282	0	0.000 (0.000, 2.150)	1493	0.882	0	0.000 (0.000, 3.128)

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- * Subjects in some age or gender groups were not expected to have cancers in certain categories.
N is the number of the study patients who contributed to the calculation of the expected number.
- ** Based on follow-up durations and adjusted by race, gender, and age of the study patients.
- *** Standardized Incidence Ratio - calculated by Observed/Expected. C.I. was calculated by using the mid-p approximation method (Ng et al, 2008). An interval containing a value of '1' indicates that the observed incidence is not statistically different from the population.
One cancer of 'abdominal lining' in the BMP group was counted in 'All Sites', but the individual SIR analysis was not done because the SEER Statistics do not include information for this category.

Table A3-13. Comparison of Cancer Cases Diagnosed in Clinical Trial Patients with the U.S. Normal Population
(All Medtronic and Wyeth Clinical Studies Involving rhBMP-2)
[Pre-existing malignancy cases are included. The 95% SIR CIs are adjusted for multiplicity.]

Cancer Site	Number of Cancer Patients							
	rhBMP-2 Group				Non-rhBMP-2 Group			
	N	Expected*	Observed	SIR** (95% C.I.)	N	Expected*	Observed	SIR** (95% C.I.)
All Sites ***	2158	32.62	32	0.981 (0.647, 1.308)	1757	23.53	17	0.723 (0.406, 1.072)
Brain and Other Nervous System Cancer	2095	0.440	0	0.000 (0.000, 13.722)	1714	0.335	1	2.989 (0.002, 23.909)
Breast Cancer	1432	6.127	5	0.816 (0.123, 2.412)	1163	4.800	5	1.042 (0.157, 3.078)
Cervix Uteri Cancer	915	0.324	0	0.000 (0.000, 18.618)	770	0.267	0	0.000 (0.000, 22.634)
Colon and Rectum Cancer	2026	3.167	2	0.632 (0.017, 3.106)	1667	2.294	1	0.436 (0.000, 3.487)
Corpus and Uterus, Nos Cancer	886	1.123	0	0.000 (0.000, 5.376)	740	0.860	1	1.163 (0.001, 9.299)
Esophagus Cancer	1425	0.311	0	0.000 (0.000, 19.403)	1127	0.209	0	0.000 (0.000, 28.911)
Hodgkin Lymphoma	1998	0.159	0	0.000 (0.000, 38.021)	1636	0.132	1	7.596 (0.004, 60.757)
Kaposi's Sarcoma	1206	0.055	0	0.000 (0.000, 110.244)	959	0.045	0	0.000 (0.000, 134.172)
Kidney and Renal Pelvis Cancer	1808	0.832	1	1.202 (0.001, 9.616)	1481	0.593	0	0.000 (0.000, 10.181)
Larynx Cancer	1423	0.297	1	3.369 (0.002, 26.950)	1113	0.196	0	0.000 (0.000, 30.818)
Leukemia	2074	0.684	1	1.463 (0.001, 11.702)	1700	0.503	0	0.000 (0.000, 12.001)
Liver and Intrahepatic Bile Duct Cancer	1537	0.294	1	3.404 (0.002, 27.225)	1232	0.205	0	0.000 (0.000, 29.510)
Lung and Bronchus Cancer	1824	4.306	1	0.232 (0.000, 1.858)	1502	2.988	0	0.000 (0.000, 2.020)
Melanoma of the Skin	1941	1.457	3	2.060 (0.145, 7.933)	1588	1.113	1	0.898 (0.000, 7.184)
Myeloma	1552	0.344	1	2.904 (0.002, 23.226)	1247	0.243	0	0.000 (0.000, 24.796)
Non-Hodgkin Lymphoma	2126	1.293	1	0.774 (0.000, 6.187)	1728	0.968	1	1.033 (0.001, 8.265)
Oral Cavity and Pharynx Cancer	1895	0.791	0	0.000 (0.000, 7.630)	1567	0.566	1	1.766 (0.001, 14.124)
Ovary Cancer	910	0.598	1	1.674 (0.001, 13.385)	763	0.469	0	0.000 (0.000, 12.856)
Pancreas Cancer	1623	0.649	3	4.620 (0.325, 17.795)	1309	0.466	0	0.000 (0.000, 12.957)
Prostate Cancer	840	5.086	6	1.180 (0.217, 3.207)	668	3.093	2	0.647 (0.018, 3.180)
Stomach Cancer	1791	0.410	0	0.000 (0.000, 14.702)	1469	0.291	0	0.000 (0.000, 20.713)
Testis Cancer	1014	0.198	1	5.051 (0.003, 40.399)	843	0.176	0	0.000 (0.000, 34.243)
Thyroid Cancer	1977	0.547	3	5.480 (0.386, 21.107)	1630	0.444	3	6.763 (0.476, 26.049)
Urinary Bladder Cancer	1828	1.282	0	0.000 (0.000, 4.706)	1493	0.882	0	0.000 (0.000, 6.845)

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(PAGE 1 OF 1)

- * Subjects in some age or gender groups were not expected to have cancers in certain categories.
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- *** Standardized Incidence Ratio - calculated by Observed/Expected. C.I. was calculated by using the mid-p approximation method (Ng et al, 2008). An interval containing a value of '1' indicates that the observed incidence is not statistically different from the population.
One cancer of 'abdominal lining' in the BMP group was counted in 'All Sites', but the individual SIR analysis was not done because the SEER Statistics do not include information for this category.

Table A3-14. Comparison of Cancer Cases Diagnosed in Clinical Trial Patients with the U.S. Normal Population
(All Medtronic and Wyeth Clinical Studies Involving rhBMP-2)
[Pre-existing malignancy cases are excluded. The 95% SIR CIs are adjusted for multiplicity.]

Cancer Site	Number of Cancer Patients							
	rhBMP-2 Group				Non-rhBMP-2 Group			
	N	Expected*	Observed	SIR** (95% C.I.)	N	Expected*	Observed	SIR** (95% C.I.)
All Sites ***	2158	32.62	30	0.920 (0.598, 1.238)	1757	23.53	16	0.680 (0.375, 1.021)
Brain and Other Nervous System Cancer	2095	0.440	0	0.000 (0.000, 13.722)	1714	0.335	1	2.989 (0.002, 23.909)
Breast Cancer	1432	6.127	5	0.816 (0.123, 2.412)	1163	4.800	4	0.833 (0.094, 2.749)
Cervix Uteri Cancer	915	0.324	0	0.000 (0.000, 18.618)	770	0.267	0	0.000 (0.000, 22.634)
Colon and Rectum Cancer	2026	3.167	2	0.632 (0.017, 3.106)	1667	2.294	1	0.436 (0.000, 3.487)
Corpus and Uterus, Nos Cancer	886	1.123	0	0.000 (0.000, 5.376)	740	0.860	1	1.163 (0.001, 9.299)
Esophagus Cancer	1425	0.311	0	0.000 (0.000, 19.403)	1127	0.209	0	0.000 (0.000, 28.911)
Hodgkin Lymphoma	1998	0.159	0	0.000 (0.000, 38.021)	1636	0.132	1	7.596 (0.004, 60.757)
Kaposi's Sarcoma	1206	0.055	0	0.000 (0.000, 110.244)	959	0.045	0	0.000 (0.000, 134.172)
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Larynx Cancer	1423	0.297	1	3.369 (0.002, 26.950)	1113	0.196	0	0.000 (0.000, 30.818)
Leukemia	2074	0.684	1	1.463 (0.001, 11.702)	1700	0.503	0	0.000 (0.000, 12.001)
Liver and Intrahepatic Bile Duct Cancer	1537	0.294	1	3.404 (0.002, 27.225)	1232	0.205	0	0.000 (0.000, 29.510)
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Pancreas Cancer	1623	0.649	2	3.080 (0.085, 15.146)	1309	0.466	0	0.000 (0.000, 12.957)
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Testis Cancer	1014	0.198	1	5.051 (0.003, 40.399)	843	0.176	0	0.000 (0.000, 34.243)
Thyroid Cancer	1977	0.547	3	5.480 (0.386, 21.107)	1630	0.444	3	6.763 (0.476, 26.049)
Urinary Bladder Cancer	1828	1.282	0	0.000 (0.000, 4.706)	1493	0.882	0	0.000 (0.000, 6.845)

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- *** Standardized Incidence Ratio - calculated by Observed/Expected. C.I. was calculated by using the mid-p approximation method (Ng et al, 2008). An interval containing a value of '1' indicates that the observed incidence is not statistically different from the population.
One cancer of 'abdominal lining' in the BMP group was counted in 'All Sites', but the individual SIR analysis was not done because the SEER Statistics do not include information for this category.

Wyeth Report

WYETH EPIDEMIOLOGY MEDICARE STUDY

Further research on the specific issue of pancreatic cancer in rhBMP-2 patients has been performed by Wyeth's Epidemiology Group. Wyeth undertook these epidemiological investigations to evaluate a signal that rhBMP-2 use was associated with an increased risk of pancreatic cancer, based on a post hoc analysis of clinical trials that involved multiple comparisons. In this study, Wyeth investigated the potential association between rhBMP-2 exposure and risk of pancreatic cancer, using a retrospective cohort of Medicare patients who underwent lumbar spinal fusion surgery between October 2003 and December 2005. Based on their analysis, they found that, patients exposed to rhBMP-2 were not at an increased risk of pancreatic cancer, as compared to patients who did not receive rhBMP-2. The report of their work, titled "Diboterminal alfa [recombinant human Bone Morphogenetic Protein-2; rhBMP-2] (InductOs) and Pancreatic Cancer: A Retrospective Cohort Study," is provided here.

**Diboterminal alfa [recombinant human Bone Morphogenetic Protein-2; rhBMP-2]
(InductOs) and Pancreatic Cancer: A Retrospective Cohort Study**

Report Prepared by:

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18 June 2007

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1.0 EXECUTIVE SUMMARY

Bone Morphogenetic Protein-2 (rhBMP-2) is licensed in Europe and the US for two orthopedic indications, anterior lumbar spinal fusion and acute tibial fracture. In the fall of 2004, a potential signal of pancreatic cancer emerged from an analysis of rhBMP-2 randomized clinical trials for lumbar spinal fusion. During the 18 months following surgery, three cases of pancreatic cancers were observed among 1008 patients who received rhBMP-2, while no pancreatic cancer was observed in the 1007 patients who received placebo. Wyeth subsequently performed a standardized incidence ratio (SIR) analysis, using reference cancer incidence rates based on US population-based statistics. The SIR was 16 [95% confidence interval (CI): 3.33 – 46.75] in patients in the rhBMP-2 arm. Across randomized clinical trials for all rhBMP-2 indications, the SIR for rhBMP-2 - treated patients was 8.81 (95% CI: 1.82 – 25.75).

To further evaluate this issue, Wyeth designed a retrospective cohort study using Medicare data. The EMEA approved the study proposal April 2006. Wyeth commissioned Gregory S. Cooper, MD, Professor of Medicine at the Case Western Reserve University, to conduct this study. The study report appears in [section 2.0](#) of this document. To facilitate the interpretation of the Medicare study, Wyeth conducted a separate chart review substudy using information from the HealthCore Integrated Research Database. The final report from this chart review study appears in [section 3.0](#) of this document.

The Medicare Study

To investigate the potential association between rhBMP-2 exposure and risk of pancreatic cancer, Wyeth performed a retrospective cohort study among Medicare patients who underwent lumbar spinal fusion surgery between October 2003 and December 2005. Medicare is a health insurance system funded by the US federal government. It provides health care coverage for nearly all patients aged 65 years and older. Medicare data include information about patient demographics, enrollment, and billing claims for hospital care (diagnoses and procedures) and physician care (procedures with diagnoses).

Patients were identified based on the procedure codes (ICD-9-CM or CPT-4) for a lumbar spinal fusion. A claim for bone morphogenetic protein (BMP) (ICD-9-CM 84.52) on the same day as

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surgery was used as a surrogate for rhBMP-2 exposure. Patients were followed in the database from the date of lumbar fusion surgery until the diagnosis of pancreatic cancer, death, disenrollment, or end of the study period. A diagnosis of pancreatic cancer (ICD-9-CM code: 157.xx) was the major outcome of interest. We used three different case definitions of pancreatic cancer, which ranged from highly sensitive to highly specific. The primary case definition was the most restrictive one, which required at least two diagnosis codes for pancreatic cancer on different dates of service and at least one procedure code consistent with therapy specific for cancer.

93,654 patients met study inclusion criteria. The mean age of the study population was 75 years, and 16.5% had claims indicating BMP exposure. Baseline characteristics of the BMP and non-BMP cohorts were generally similar. During an average 1.4 years of follow up, 91 patients (8 cases with BMP and 83 cases without BMP, based on the primary case definition) developed pancreatic cancer. Consistent with previously published studies, increased risk of pancreatic cancer was associated with older age, male gender, black race and history of diabetes. Based on multivariate Cox regression analysis, compared to patient who did not receive BMP, patients exposed to BMP were not at increased risk of pancreatic cancer (Hazard Ratio (HR)=0.70, 95% CI: 0.34 – 1.45). Results were substantially unchanged using alternative case definitions and in a sensitivity analysis that adjusted for smoking differences across treatment groups, as ascertained from the chart review substudy. A separate analysis, using reference cancer rates for the general US population, also demonstrated no association between BMP use and pancreatic cancer risk (SIR = 0.85, 95% CI: 0.26 – 1.44).

HealthCore Chart Review Substudy

To facilitate interpretation of the Medicare study, Wyeth also conducted a chart review substudy among Medicare-aged US patients undergoing spinal fusion surgery. The principal motivation for this was that smoking, which is not captured in Medicare, could confound results of the Medicare study. Smoking is a strong risk factor for both pancreatic cancer and poor bone healing, and concerns about poor bone healing might lead to selective use of BMP in smokers. While the primary aim of this study was to estimate the prevalence of smoking by BMP use, it also sought to assess the positive predictive value of BMP claims and the proportion of BMP-2 use among patients who had claims for BMP. Using claims data from the HealthCore Integrated

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Research Database, we identified 1543 patients who met the study entry criteria and underwent lumbar spinal fusion surgery between October 2003 and December 2005. Chart review was completed for 158 patients. The prevalence of ever smoking at the time of surgery was 27% and 32% for patients with and without BMP, respectively. While data on smoking history was missing in about 14% of the charts reviewed, the anticipated association between BMP use and smoking was not observed.

Using medical chart information as the gold standard for BMP exposure, the positive predictive value of BMP claims was 100%. While the type of BMP could not be characterized about 40% of the time, among patients for whom the type of BMP was specified, nearly all (94.5%) of the patients exposed to BMP received rhBMP-2. These results support the validity of the BMP exposure measure used in the Medicare study.

The potential limitations of the two studies deserve mention. In the Medicare study, exposure misclassification is a theoretical concern since we used the ICD-9-CM code 84.52 as a proxy for exposure to rhBMP-2. However, the HealthCore substudy demonstrated that this code had a perfect positive predictive value for BMP use, and to the degree that BMP type could be characterized, nearly all the BMP used was rhBMP-2. As Medicare researchers do not have access to patients' medical records, we did not confirm each pancreatic cancer diagnosis. Nonetheless, we believe that our primary case definition (at least 2 claims for pancreatic cancer associated with cancer-specific therapy) has strong clinical face validity. The fact that the SIR for BMP use was so close to 1 further supports our case definition. Even if there were some outcome misclassification, there is no reason to suspect that it would have varied by exposure status. The concern that BMP could have been preferentially selected for smokers was not borne out in the chart review substudy, and adjustment for the small difference in smoking prevalence across exposure groups did not change the results.

Wyeth undertook these epidemiological investigations to evaluate a signal that rhBMP-2 use was associated with an increased risk of pancreatic cancer, based on a post-hoc analysis of clinical trials that involved multiple comparisons. This hypothesis was not confirmed in our Medicare study of more than 93,000 elderly patients who underwent lumbar spinal fusion surgery, more than 15,000 of whom received BMP (HR=0.70, 95% CI: 0.34 – 1.45). Wyeth believes that the

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results of the epidemiological studies presented here provide reasonable assurance that rhBMP-2 does not increase the risk of pancreatic cancer.

2.0 MEDICARE STUDY

18 June 2007

**Recombinant Human Bone Morphogenetic Protein-2 (rhBMP-2) and Pancreatic Cancer:
A Retrospective Cohort Study**

Principal Investigator:

**Gregory S. Cooper, MD
Professor of Medicine and Epidemiology
Division of Gastroenterology
Case Western Reserve University
11100 Euclid Avenue, Wearn 247
Cleveland, OH 44106-5066**

Sponsored by:

**Wyeth Research
500 Arcola Road
Collegeville, PA 19426
USA**

Date completed:

01 June 2007

2.1 Study Aim

To assess whether the risk of pancreatic cancer is increased among patients exposed to rhBMP-2 compared to those without this exposure during lumbar spinal fusion surgery.

2.2 Background And Rationale

The Bone Morphogenic Proteins are a member of a large family of growth factors collectively known as the Transforming Growth Factor- β (TGF- β) superfamily.¹ This large group of signaling polypeptides plays a key role in cell differentiation and growth and BMP-2 is expressed in a variety of tissues/cell types, including malignant cells. One of these proteins, recombinant human Bone Morphogenetic Protein-2 (rhBMP-2) is licensed in Europe and the US for two orthopedic indications, anterior lumbar spinal fusion and acute tibial fracture. Lumbar spinal fusion surgery is a commonly performed procedure, with estimates of between 150,000 to 250,000 patients operated on annually in the US.^{2,3} Although the actual procedure volume in Medicare beneficiaries is not known, for the years 1999-2000, the US National Hospital Discharge Survey (NHDS) indicated that about 22% of patients were aged 65 years and older.⁴ The exact number of Medicare beneficiaries treated with rhBMP-2 at the time of surgery is also not known, but market estimates indicate that about 15% of lumbar fusion operations in the US involved the use of rhBMP-2 between the market introduction in July 2002 and the end of 2004. Whether the product is used uniformly in Medicare beneficiaries compared to other patient subgroups is not known.

In the fall of 2004, a potential signal of pancreatic cancer emerged from an analysis of rhBMP-2 randomized clinical trials for lumbar spinal fusion. During the 18 months following surgery, three cases of pancreatic cancers were observed among 1008 patients who received rhBMP-2, while no pancreatic cancer was observed in the 1007 patients who received placebo. To determine whether the frequency of pancreatic cancers in the rhBMP-2 arm was within expectations, standardized incidence ratio (SIR) analysis was performed, using reference cancer incidence rates based on US population-based statistics.⁵ The SIR was 16 [95% CI: 3.33 – 46.75]. Across randomized clinical trials for all rhBMP-2 indications, the SIR for rhBMP-2 treated patients was 8.81 (95% CI: 1.82 – 25.75). The Wyeth Drug Safety and Metabolism

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group conducted a series of experiments to test the potential of rhBMP-2 to enhance tumor growth *in vitro* and *in vivo*. These studies did not demonstrate a pro-oncogenic effect of rhBMP-2.

Although the pancreatic cancer incidence in spinal fusion trials may represent a chance finding due to multiple testing, given the magnitude of the relative risk observed in the clinical trials, further epidemiological evaluation is prudent. A retrospective analysis of Medicare claims data would provide an opportunity to expeditiously determine whether an increased rate of pancreatic cancer can be replicated in an independent sample of patients treated with rhBMP-2.

2.3 Research Design And Methods

2.3.1 Patients

We conducted a retrospective cohort study among Medicare patients who underwent lumbar fusion surgery between October 2003 and December 2005. The relevant files included the Medicare Provider Analysis and Review (MEDPAR) file, which includes services provided in Medicare certified inpatient hospitals, the Carrier file, which includes claims from physicians and free standing ambulatory surgical centers, and the Outpatient file, which includes claims from institutional outpatient providers, including hospital outpatient providers. Patients were identified if they had a procedure code for a lumbar fusion operation by one of the following International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) or Current Procedural Terminology 4th Edition (CPT-4) codes: ICD-9-CM 81.06, 81.07, 81.08, 81.36, 81.37, 81.38, CPT-4 22558, 22630, 22612. The MEDPAR, Physician/Supplier and Outpatient files were combined and records unduplicated by the encrypted beneficiary identification code, procedure, and date of service, such that a procedure documented in more than one file for the same individual and date of service within two weeks of each other was counted only once.

In order to obtain complete claims history on the entire cohort, patients were excluded if they were not continuously enrolled in fee-for-service Medicare for at least 2 years prior to the index surgery date. Patients who did not continuously participate in Medicare Part B, which provides coverage for physician charges and outpatient services, were also excluded because their claims

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histories may have been incomplete. In addition, patients younger than 67 years were excluded – those younger than 65 were not representative of the general population, and those aged 65 or 66 had less than two years of enrollment data prior to the spinal surgery. In order to exclude prevalent cases of pancreatic cancer, any patients with a claim indicating a pancreatic cancer diagnosis (ICD-9-CM 157.xx) during the two-year period prior to the date of fusion surgery were excluded from the study. A two-year cut off was used to maximize the sensitivity of capturing and excluding patients who were long-term cancer survivors.

2.3.2 Measures

A claim for bone morphogenetic protein (ICD-9-CM 84.52) on the same day as fusion surgery was used as a surrogate for rhBMP-2 exposure, which cannot be ascertained directly using Medicare data. This code covers use of both bone morphogenetic proteins involved during the study period, BMP-2 and BMP-7. Sales of rhBMP-2 have been substantially greater than for BMP-7. While the code 84.52 (for BMP) was introduced in October 2002, Medicare did not provide additional reimbursement for these products until October 2003; therefore, to reduce exposure misclassification, we limited our study to patients who underwent fusion surgery from this date onward.

A diagnosis of pancreatic cancer was the major outcome of interest for this study and was identified by ICD-9-CM code 157.xx. Because a single code may not be valid and may reflect “rule out” diagnoses and other suspected cancer diagnoses that were ultimately found to represent benign diseases, we used three different definitions of pancreatic cancer that are ordered from highest sensitivity to highest specificity:

1. Any ICD-9-CM diagnosis code for pancreatic cancer in any file type beginning at the date of index surgery through the end of follow up.
2. An ICD-9-CM diagnosis code for pancreatic cancer on more than one date of service.
3. Two or more diagnosis codes for pancreatic cancer on different dates of service *and* at least one procedure code consistent with cancer therapy. Procedure codes include gastrointestinal bypass surgery (ICD-9-CM: 44.39, 51.36, 51.39, 51.42. CPT-4: 43820, 43825, 47720 - 47790), pancreatectomy (ICD-9-CM: 52.50 – 52.79. CPT-4: 48140 – 48144, 48146, 48147, 48149 - 48155), radiation therapy (CPT-4: 77401 - 77799) and

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chemotherapy (CPT-4: 77305 – 77334, 77401 – 77417, 77750 – 77799, 96400, 96408 – 96414, 96440, 96445, 96545, 96549. HCPCS: J9000 – J9999).

After an extensive discussion with clinical experts, we concluded that the third (most specific) definition would serve as the primary outcome for the analyses.

In addition to data about exposure and outcomes, we included data on potential confounders such as age (at time of index surgery), gender, race (white, black, other), length of follow up, and specific diagnoses and procedures that are known to increase the risk of pancreatic cancer and may potentially be associated with the likelihood of BMP administration. The diagnoses or procedures associated with pancreatic cancer were searched for in the MEDPAR, Outpatient, and Carrier files and included diabetes mellitus (ICD-9-CM 250.xx, 790.2), alcohol abuse (ICD-9-CM 291.xx, 303.0, 303.9, 425.5, 571.0, 571.1, 571.2, 571.3, V11.3), chronic pancreatitis (ICD-9-CM 577.1, 577.2, 577.8), gastrectomy (ICD-9-CM 43.5, 43.6, 43.7, 43.8, 43.9; CPT-4 43620, 43622, 43631, 43632, 43633, 43634, 43638, 43639, 43640), and cholecystectomy (ICD-9-CM 51.2x; CPT-4 47562, 47563, 47564, 47600, 47605, 47610, 47612, 47620).

Medicare does not include systematic information on smoking, obesity, and family history of pancreatic cancer, and thus we were unable to capture these data. However, because smoking is a strong risk factor for pancreatic cancer as well as potentially bone nonunion (and thus BMP administration), an independent medical record review of Medicare eligible patients was conducted. A separate substudy used medical chart review to estimate the prevalence of smoking among patients who underwent lumbar spine fusion surgery by BMP use.

2.3.3 Analysis

Patients were followed in the database from the date of index lumbar fusion surgery until the diagnosis of pancreatic cancer, death, disenrollment, or end of the study period (December 2005). Individuals who underwent an initial operation without BMP and a subsequent procedure with BMP were followed in the nonexposed group to the date of the second surgery and thereafter in the exposed group.

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The association of demographic variables, comorbid conditions and BMP administration with pancreatic cancer was examined using each of the three cancer definitions described above. Chi-square analysis was used to determine the statistical significance of the associations, and odds ratios (OR) with corresponding 95% confidence intervals estimated.

We also estimated the standardized incidence ratio (SIR) along with 95% confidence intervals for risk of pancreatic cancer in the BMP exposed and unexposed patients. To measure the SIR we used age and gender specific incidence rates for pancreatic cancer in the general U.S. population as measured by the Surveillance Epidemiology and End Results (SEER) Program.⁶

The independent association of factors with pancreatic cancer was determined in multivariable analyses. The primary analysis used Cox proportional hazard regression to determine the hazard ratios (HR) along with 95% confidence intervals for time to development of cancer among those who received BMP compared to those who did not. As a secondary analysis, Poisson regression was used to determine the relative risk of BMP with pancreatic cancer. In both models, covariates included all factors that were associated with pancreatic cancer in unadjusted analyses as well as factors that were thought to be clinically meaningful.

Based on the data from medical record review on the prevalence of smoking in patients administered BMP and those who did not, the hazard ratio for pancreatic cancer associated with BMP exposure was recalculated.⁷

2.3.4 Role of the Sponsor

This study was supported by Wyeth Research, and two Wyeth epidemiologists contributed to the study design, analysis and reporting. However, all final decisions about design, analysis, reporting and interpretation rested with Dr. Gregory S. Cooper, the principal investigator.

2.4 Results

Using MEDPAR, Carrier and Outpatient files from October 2003 through December 2005, we identified 154,689 beneficiaries with one or more procedure codes for lumbar fusion surgery. Among this cohort, we excluded 28,151 patients who qualified for Medicare because of end

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stage renal disease or chronic disability (as opposed to advanced age), 25,048 individuals who were members of Medicare sponsored HMO's, 39,927 patients who were aged less than 67 at the time of surgery and 74 patients with a prior diagnosis code for pancreatic cancer. Patients may have been excluded for more than one indication. The remaining 93,654 patients who met none of the above exclusion criteria were the subject of this analysis.

Descriptive statistics for the study population are shown in Table 2-1. The mean age of the cohort was 74.7 ± 5.1 years, and most patients were female and Caucasian. For the BMP cohort the average duration of follow-up was 1.04 ± 0.73 years (range: 1-1094 days) and for the non-BMP cohort, it was 1.46 ± 0.86 years (range: 1-1095 days). The most common documented comorbid condition was diabetes mellitus, with much smaller proportions of patients having codes for chronic pancreatitis, alcoholism, or a previous cholecystectomy. Because codes for gastrectomy were present in only 0.08% of the cohort, this variable was not included in further analyses. Codes consistent with BMP administration were present in 16.5% of spine fusion operations. Although some patients who did not receive BMP initially were administered BMP during a second surgical procedure, this only represented 1% of the total cohort.

Several factors were found to be associated with BMP administration (Table 2-1). These included younger age, black race, female gender, diabetes, and prior cholecystectomy. Of note, there was no association of BMP administration with chronic pancreatitis, or alcoholism. Survival in the entire cohort through the end of the follow up period was documented in 95.2% and was greater in patients administered BMP (96.9%) than in others (94.9%) ($p < 0.001$ by log-rank test).

Table 2-1: Demographic and Clinical Characteristics of the Study Cohort

Variable	Non-BMP Group (%)	BMP Group (%)	P Value
Patients	78,194 (83.5)	15,460 (16.5)	
Patient-years	114,498	16,018	
Mean age \pm SD	74.6 ± 5.2	74.2 ± 5.1	
Age Group			
67-69	16,554 (21.2)	3,660 (23.7)	
70-74	26,955 (34.5)	5,455 (35.3)	
75-79	21,742 (27.8)	4,058 (26.3)	
80-84	10,254 (13.1)	1,828 (11.8)	
≥ 85	2,688 (3.4)	459 (3.0)	< 0.001

Table 2-1: Demographic and Clinical Characteristics of the Study Cohort (Cont'd)

Variable	Non-BMP Group (%)	BMP Group (%)	P Value
Gender			
Male	27,071 (34.6)	5,102 (33.0)	< 0.001
Female	51,123 (65.4)	10,358 (67.0)	
Race			
White	73,537 (94.0)	14,567 (94.2)	0.029
Black	2,899 (3.7)	596 (3.9)	
Other	1,758 (2.3)	297 (1.9)	
Comorbid Conditions			
Diabetes	28,265 (35.4)	5,618 (36.3)	0.018
Chronic Pancreatitis	739 (1.0)	140 (0.9)	0.641
Alcoholism	1,061 (1.4)	226 (1.5)	0.306
Cholecystectomy	2,308 (3.0)	539 (3.5)	< 0.001

One or more diagnosis codes consistent with pancreatic cancer were documented in follow up in 182 patients (definition 1), two or more codes were present in 129 patients (definition 2) and two or more diagnosis codes plus one or more treatment codes were recorded in 91 patients (definition 3). As discussed above, the most specific cancer definition (definition 3) was the primary outcome of interest.

Among the 91 cases of pancreatic cancer (definition 3), the median time to event was 0.86 years. Risk factors for pancreatic cancer are shown in [Table 2-2](#). There was an association of pancreatic cancer with age 70-74 and 75-79, but no significant association with age 80 and older. Pancreatic cancer was also less commonly noted in women and more common in black patients. Among comorbid conditions, the only association that achieved statistical significance was diabetes, though the magnitude of the association was highest for chronic pancreatitis. Importantly, there was no association and a borderline reduced risk of BMP administration with cancer (OR = 0.49, 95% CI: 0.24-1.02). When the other cancer definitions (definition 1 and 2) were considered ([Table 2-2](#)), the results were similar to those with definition 3. Again, no association of BMP administration and cancer risk was identified, and for definition 1, BMP was actually associated with a reduced cancer risk (OR = 0.56, 95% CI: 0.35-0.92).

Table 2-2: Demographic and Clinical Factors Associated with Pancreatic Cancer in Univariate Analysis

Cancer Case Definition^a	1 (n=182)		2 (n = 129)		3 (n=91)	
	%	OR (95% CI)	%	OR (95% CI)	%	OR (95% CI)
Mean Age (SD)	75.5 (4.5)		75.2 (4.5)		74.9 (4.1)	
67-69	12.6	1.00	13.2	1.00	12.1	1.00
70-74	34.6	1.71 (1.06, 2.76)	40.3	1.91 (1.10, 3.30)	40.7	2.10 (1.07, 4.11)
75-79	35.2	2.18 (1.36, 3.52)	32.6	1.94 (1.10, 3.40)	37.4	2.42 (1.23, 4.78)
80-84	15.9	2.11 (1.22, 3.65)	11.6	1.48 (0.74, 2.96)	7.7	1.06 (0.41, 2.75)
≥ 85	1.7	0.84 (0.25, 2.79)	2.3	1.13 (0.33, 3.87)	2.2	1.17 (0.26, 5.27)
Gender						
Male	37.9	1.00	41.1	1.00	45.1	1.00
Female	62.1	0.86 (0.64, 1.16)	58.9	0.75 (0.53, 1.07)	54.9	0.64 (0.42, 0.96)
Race						
White	90.1	1.00	89.9	1.00	89.0	1.00
Black	6.0	1.68 (0.91, 3.10)	7.8	2.16 (1.13, 4.12)	7.7	2.18 (1.00, 4.72)
Other	3.9	1.82 (0.85, 3.88)	2.3	1.10 (0.35, 3.47)	3.3	1.59 (0.50, 5.03)
Comorbid Conditions						
Diabetes	43.4	1.42 (1.06, 1.91)	44.2	1.47 (1.04, 2.08)	46.2	1.56 (1.03, 2.35)
Chronic Pancreatitis	5.5	6.28 (3.31, 11.92)	3.1	3.44 (1.27, 9.32)	2.2	2.37 (0.58, 9.66)
Alcoholism	2.2	1.64 (0.61, 4.41)	2.3	1.73 (0.55, 5.46)	1.1	0.80 (0.11, 5.73)
Cholecystectomy	3.9	1.29 (0.61, 2.76)	3.9	1.30 (0.53, 3.19)	4.4	1.46 (0.54, 4.00)
BMP Use, % (N)	9.9 (18)	0.56 (0.35, 0.92)	10.9 (14)	0.63 (0.36, 1.09)	8.8 (8)	0.49 (0.24, 1.02)

a. Case Definition 1=Any ICD-9-CM diagnosis code for pancreatic cancer in any file type beginning at the date of index surgery through the end of follow up.
Case Definition 2=An ICD-9-CM diagnosis code for pancreatic cancer on more than one date of service.
Case Definition 3=Two or more diagnosis codes for pancreatic cancer on different dates of service and at least one procedure code consistent with cancer therapy.

Among patients who received BMP, a total of 8 cases of pancreatic cancer were identified through definition 3. Based on age and gender specific SEER data, 9.4 cases were expected which corresponded to an SIR of 0.85 (95% CI: 0.26 – 1.44). Among patients who did not receive BMP, a total of 83 cancer were identified (definition 3), compared to an expected number of 48.5. This corresponded to an SIR of 1.71 (95% CI: 1.34 to 2.08) in the non-BMP group.

In a multivariate Cox proportional hazards model (Table 2-3), we studied the independent associations with time to cancer diagnosis. For definition 3, there was an increased risk

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associated with age 70-74 or 75-79, male gender, black race and diabetes. No significant associations were found with “other” race, chronic pancreatitis, alcoholism or cholecystectomy. Consistent with the univariate analyses, there was no association of BMP administration with pancreatic cancer (HR = 0.70, 95% CI: 0.34-1.45). Similar findings were observed for definitions 1 and 2 (Table 2-3), with no significant association between BMP and pancreatic cancer observed.

Table 2-3: Factors Associated with Pancreatic Cancer in Multivariate Cox Regression Analysis^a

Variable	HR (95% CI)		
	Case Definition 1 ^b	Case Definition 2 ^c	Case Definition 3 ^d
Age			
67-69	1.00	1.00	1.00
70-74	1.70 (1.05, 2.74)	1.91 (1.10, 3.29)	2.08 (1.06, 4.08)
75-79	2.17 (1.35, 3.50)	1.96 (1.11, 3.45)	2.42 (1.23, 4.78)
80-84	2.23 (1.29, 3.86)	1.58 (0.79, 3.18)	1.12 (0.44, 2.91)
≥ 85	0.95 (0.29, 3.17)	1.31 (0.38, 4.49)	1.33 (0.29, 6.01)
Gender			
Male	1.00	1.00	1.00
Female	0.82 (0.61, 1.11)	0.72 (0.51, 1.03)	0.61 (0.41, 0.93)
Race			
White	1.00	1.00	1.00
Black	1.76 (0.95, 3.25)	2.24 (1.17, 4.29)	2.24 (1.03, 4.89)
Other	1.73 (0.81, 3.68)	1.05 (0.33, 3.32)	1.48 (0.47, 4.68)
Comorbid Conditions			
Diabetes	1.44 (0.71, 1.94)	1.48 (1.04, 2.10)	1.58 (1.04, 2.40)
Chronic Pancreatitis	6.75 (3.53, 12.90)	3.74 (1.37, 10.22)	2.53 (0.62, 10.38)
Alcoholism	1.77 (0.66, 4.79)	1.80 (0.57, 5.67)	0.79 (0.11, 5.71)
Cholecystectomy	1.26 (0.59, 2.71)	1.39 (0.56, 3.43)	1.66 (0.60, 4.55)
BMP Use	0.82 (0.50, 1.33)	0.90 (0.51, 1.57)	0.70 (0.34, 1.45)

a. Models include each of the variables listed in the table. HR=Hazard Ratio.

b. Case Definition 1=Any ICD-9-CM diagnosis code for pancreatic cancer in any file type beginning at the date of index surgery through the end of follow up.

c. Case Definition 2=An ICD-9-CM diagnosis code for pancreatic cancer on more than one date of service.

d. Case Definition 3=Two or more diagnosis codes for pancreatic cancer on different dates of service and at least one procedure code consistent with cancer therapy.

In multivariate Poisson regression analysis (Table 2-4), factors associated with an increased risk of pancreatic cancer for definition 3 were similar to the Cox model and included age 70-79, and

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male gender. BMP use was again not a risk factor for cancer risk and consistent with the univariate analyses, actually had a borderline reduced association (Relative Risk (RR) = 0.49, 95% CI: 0.24-1.02). Consistent results were also observed for the other two case definitions (Table 2-4).

Table 2-4: Factors Associated with Pancreatic Cancer in Multivariate Poisson Regression Analysis^a

Variable	RR (95% CI)		
	Case Definition 1 ^b	Case Definition 2 ^c	Case Definition 3 ^d
Age			
67-69	1.00	1.00	1.00
70-74	1.70 (1.05, 2.74)	1.90 (1.10, 3.29)	2.08 (1.06, 4.07)
75-79	2.16 (1.34, 3.48)	1.94 (1.11, 3.41)	2.40 (1.21, 4.74)
80-84	2.11 (1.22, 3.65)	1.50 (0.75, 3.01)	1.07 (0.42, 2.77)
≥ 85	0.85 (0.26, 3.84)	1.17 (0.34, 4.01)	1.19 (0.26, 5.37)
Gender			
Male	1.00	1.00	1.00
Female	0.86 (0.64, 1.16)	0.76 (0.53, 1.08)	0.64 (0.42, 0.97)
Race			
White	1.00	1.00	1.00
Black	1.70 (0.92, 3.15)	2.15 (1.12, 4.13)	2.16 (0.99, 4.69)
Other	1.69 (0.79, 3.60)	1.04 (0.33, 3.26)	1.47 (0.46, 4.65)
Comorbid Conditions			
Diabetes	1.32 (0.98, 1.77)	1.36 (0.96, 1.93)	1.46 (0.96, 2.21)
Chronic Pancreatitis	5.75 (3.02, 10.98)	3.20 (1.17, 8.74)	2.23 (0.54, 9.14)
Alcoholism	1.50 (0.56, 4.07)	1.56 (0.49, 4.83)	0.70 (0.10, 5.03)
Cholecystectomy	1.10 (0.51, 2.36)	2.20 (0.48, 2.95)	1.42 (0.52, 3.89)
BMP Use	0.57 (0.35, 0.92)	0.62 (0.36, 1.08)	0.49 (0.24, 1.02)

a. Models include each of the variables listed in the table. RR=Relative Risk.

b. Case Definition 1=Any ICD-9-CM diagnosis code for pancreatic cancer in any file type beginning at the date of index surgery through the end of follow up.

c. Case Definition 2=An ICD-9-CM diagnosis code for pancreatic cancer on more than one date of service.

d. Case Definition 3=Two or more diagnosis codes for pancreatic cancer on different dates of service and at least one procedure code consistent with cancer therapy.

An independent medical record review of 158 patients who underwent spinal fusion surgery between October 2003 and August 2006 was performed, including 96 patients who received BMP and 62 patients who did not. Among the patients who received BMP, the prevalence of ever smoking at the time of surgery was 27% (3.1% were current smokers and 24.0% were

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former smokers). Among patients who did not receive BMP, the prevalence of ever smoking was 32% (8.1% and 24.2% were current and former smokers, respectively). If we assume that the relative risk of pancreatic cancer among ever smokers is 2.0^{8,9,10}, the adjusted hazard ratio for BMP administration (case definition 3) was 0.73.

2.5 Discussion

In this large retrospective cohort study of Medicare patients who underwent lumbar fusion surgery, we found no association between BMP use and increased risk for pancreatic cancer. However, consistent with the previously described epidemiology of pancreatic cancer, we found an increased risk associated with older age, male gender, history of diabetes mellitus, and African American race.

In a separate SIR analysis, we found that the observed frequency of pancreatic cancer among patients who received BMP was consistent with that in the general population. However, we observed an elevated risk (SIR 1.71) among those patients who did not receive BMP. This finding may be due to an overly sensitive case definition or indicate that the background risk in the unexposed study population is actually elevated.

Although this study was limited to patients at least 67 years old, we believe that Medicare was the most appropriate data source to address the research question. Between 1998 and 2002, almost 70% of new pancreatic cancer cases occurred among those 65 years or older^{5,6}, and pancreatic cancer represented the fourth leading cause of cancer death in men and women aged 60-79.¹¹

Since we used the ICD-9-CM code 84.52 as a proxy for exposure to rhBMP-2, misclassification could be a concern. The code 84.52 was not specific for rhBMP-2, as it is also used for BMP-7. Wyeth commissioned a chart review study to evaluate this issue. Reported separately, that study found that among 55 patients in whom the type of BMP could be characterized, 94.5% (52/55) received rhBMP-2. That study also found that the positive predictive value for the ICD-9-CM code 84.52 was 100%, based on validating 57 claims of BMP use against the medical record.

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Although there was potential for underreporting of BMP utilization, we believe that given the cost of rhBMP, the likelihood of underreporting of its administration was low.

We expect that most patients with diabetes were identified on the basis of relevant codes associated with outpatient care or inpatient care at the time of fusion surgery, and in fact, the prevalence of diabetes in both the BMP and non-BMP groups was higher than we anticipated from the general Medicare population. This may be due to the association of obesity and diabetes, with obesity an established risk factor for lumbar spine disease; alternatively some diagnoses of diabetes could be false positives if diabetes was listed as an indication for laboratory testing but was not confirmed. Other potential confounders may have been under-ascertained, including history of cholecystectomy, gastrectomy, or chronic pancreatitis. Because of lack of specific diagnosis codes, family history of pancreatic cancer was not ascertained at all. We expect that the true prevalence of these factors were low and that they are unlikely to be associated with BMP use.

Another potential limitation of this study was the possibility of unmeasured confounding by smoking, which is not captured in Medicare claims. Smoking is a risk factor for both pancreatic cancer and poor bone healing, and in turn, may be a selection factor for BMP use. The chart review study, however, found that the prevalence of smoking was slightly higher in the non-BMP group. Adjustment for these smoking data did not materially affect our results.

2.6 Conclusion

In this study of more than 90,000 elderly patients who underwent lumbar fusion surgery, the risk of pancreatic cancer among patients exposed to BMP was not increased compared to the risk among those who were not exposed.

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2.7 References

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3.0 HEALTHCORE STUDY

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**Identification of Risk Factors for Pancreatic Cancer in Elderly Patients
Undergoing Lumbar Spinal Fusion Surgery**

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Date completed:

30 May 2007

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3.1 Rationale For Study

Recombinant human bone morphogenetic protein-2 (rhBMP-2) is licensed in the United States and Europe to promote bone union in two orthopedic indications: anterior lumbar spinal fusion and acute tibial fracture. Current estimates are that lumbar spinal fusion surgery is performed in as many as 60,000 Medicare beneficiaries annually. In 2005, an estimated 20-25% of these procedures in the Medicare population involved the use of a BMP. A post-hoc analysis of data from randomized clinical trials of rhBMP-2 indicated a possible association of rhBMP-2 and development of pancreatic cancer.

To test this hypothesis, Wyeth commissioned a retrospective cohort study using Medicare claims data. That study relied on an ICD-9 procedure code for BMP use to identify patients exposed to rhBMP-2, but this approach was not validated against medical records. Additionally, it was not clear what proportion of total BMP use in spinal fusion surgery among the elderly was due to rhBMP-2, as opposed to recombinant human bone morphogenetic protein-7 (rhBMP-7). The Medicare study measured and adjusted for a number of factors that could confound a BMP-pancreatic cancer association, but smoking, an established risk factor for pancreatic cancer, was not recorded in those data.

It is possible that among patients undergoing spinal fusion, BMP may be used preferentially for smokers, who are at increased risk of poor bone healing. To address these issues, Wyeth commissioned HealthCore, Inc. to conduct chart review study of Medicare-aged US patients undergoing spinal fusion surgery, as identified via administrative claims data from commercial health plans.

3.2 Study Objectives

1. To describe the prevalence of smoking by BMP use in a population of patients older than 65 years who have undergone lumbar spinal fusion surgery.
2. To determine the positive predictive value of BMP claims by validating against medical records.

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3. To determine what proportion of BMP use in the study population extracted from medical charts is from rhBMP-2.

3.3 Study Methodology

3.3.1 Data Source

The HealthCore Integrated Research Database contains a broad, clinically rich and geographically diverse spectrum of longitudinal claims data from health plans in the southeastern, mid-Atlantic, central, and western regions of the United States, dating back to 01 January 2000. The lines of business within the managed care database include health maintenance and preferred provider organizations, including commercial Medicare, as well as Medicaid.

Nearly all US residents aged 65 years and older are eligible for Medicare, a federally-funded health insurance program that provides benefits for physician care and hospital services. Despite this benefit, patients may be personally responsible for up to 20% of these healthcare costs, and many purchase supplemental commercial health insurance to cover what Medicare does not. In patients with supplemental insurance through the health plans, the HealthCore database will only include information on claims paid by the health plan, not those paid for by federally-funded Medicare.

3.3.2 Patients

Patients were identified from a review of medical claims between 01 October 2003 and 31 December 2005. The date of the first medical claim for a lumbar spinal fusion surgery (ICD-9-CM procedure codes: 81.06, 81.07, 81.08, 81.36, 81.37, 81.38; CPT codes: 22558, 22630, 22612) within the intake period was defined as the index date. Patients needed to be at least 65 years of age at index date. Patients with a diagnosis of pancreatic cancer (ICD-9-CM code 157.xx) before the index date were excluded.

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3.3.3 Exposure

To identify patients who received BMP in the automated data, we used a medical claim containing the ICD-9-CM procedure code for bone morphogenetic protein (84.52) on the same day as lumbar spinal fusion. While the ICD-9-CM code for BMP was introduced in October 2002, Medicare did not provide additional reimbursement for these products until October 2003. To reduce exposure misclassification, we limited our study to patients who underwent lumbar spinal fusion surgery from this date onward. Exposure to BMP was also ascertained through human review of medical charts, as explained in the section that follows.

3.3.4 Data Collection

Data for this project included automated claims data and actual medical records of the spine fusion surgeries. Using claims data we identified patients who underwent lumbar spinal fusion, and extracted information about patient characteristics, including age at time of surgery, gender, year of surgery, duration of enrollment in the health plan, and history of diabetes, chronic pancreatitis, gastrectomy and cholecystectomy.

From this source population, a total of 200 patients were targeted for medical chart abstraction (100 each with and without documented BMP in the medical claims). We requested medical records from the surgeon and hospitals associated with the index spinal surgery.

Because the study required use of protected health information (PHI), including patient names and dates of birth to identify medical charts for abstraction, an Institutional Review Board (IRB) Waiver of Authorization for patient consent was obtained. No individuals on the research team had access to any PHI prior to approval of this waiver.

HealthCore contracted a vendor to locate, collect, and abstract the relevant health records. Staff from the contracted vendor were educated on areas of the medical chart to review and information to collect. As part of this education, a pilot phase was conducted to review a sample of charts (i.e., 5-10 charts) to ensure that the abstractors were accurately collecting the data. Abstracted data were recorded on standardized case report forms, which were then entered into an Access database created for this project.

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We gathered the following information from the medical charts: date of birth, date of lumbar spinal fusion surgery, use of BMP, type of BMP (BMP-2 or BMP-7), height and weight at index date, smoking status at index date, duration and intensity of smoking, and history of diabetes, chronic pancreatitis, gastrectomy and cholecystectomy.

3.3.5 Data Analysis

Descriptive statistics included means (\pm standard deviation) and relative frequencies for continuous and categorical data, respectively. We also calculated the positive predictive value and sensitivity of a claim for BMP, using chart data as the gold standard.

3.3.6 Role of the Sponsor

This study was supported by Wyeth Research, and two Wyeth epidemiologists contributed to the study design, analysis and reporting. However, all final decisions about design, analysis, reporting and interpretation rested with Dr. John Barron, the principal investigator.

3.4 Results

From medical claims data, we identified 1543 patients who met the study entry criteria and underwent lumbar spinal fusion surgery between 01 October 2003 and 31 December 2005. Based on the ICD-9-CM code (84.52) from the claims data, 80 (5.2%; 95% CI: 4.1-6.4%) patients were identified as having received BMP during the surgery.

Table 3-1 shows the characteristics of these patients by BMP use ascertained through claims.

Table 3-1: Summary of Claims Data from October 2003 through December 2005

Variable ^a	BMP use	
	No N (%) ^b	Yes N (%) ^b
Number of patients	1,463	80
Female	916 (62.6)	52 (65.0)
Age at surgery		
Mean \pm SD	71.7 \pm 5.3	72.5 \pm 5.9
Median (Range)	71 (65 - 93)	71 (65 - 85)
65 - 74	1059 (72.4)	55 (68.8)

Table 3-1: Summary of Claims Data from October 2003 through December 2005 (Cont'd)

Variable ^a	BMP use	
	No N (%) ^b	Yes N (%) ^b
Age at surgery (Cont'd)		
75 – 84	379 (25.9)	24 (30.0)
85 +	25 (1.7)	1 (1.3)
Prior diabetes mellitus by diagnosis	326 (22.3)	17 (21.3)
Prior diabetes mellitus by diagnosis or treatment	337 (23.0)	18 (22.5)
Year of surgery		
2003	142 (9.7)	10 (12.5)
2004	618 (42.2)	41 (51.3)
2005	703 (48.1)	29 (36.3)
Cumulative duration of health plan enrollment		
Less than 1 year	420 (28.7)	22 (27.5)
1-2 years	280 (19.1)	17 (21.3)
2-3 years	256 (17.5)	15 (18.8)
3-4 years	89 (6.1)	6 (7.5)
4 or more years	418 (28.6)	20 (25.0)
History of chronic pancreatitis	1 (0.1)	0 (0.0)
History of gastrectomy	10 (0.7)	0 (0.0)
History of cholecystectomy	26 (1.8)	0 (0.0)

a. All data elements were obtained for each patient during the time period prior to and including the Index Surgery Date

b. All percentages are column percentages

We identified 116 patients for medical chart review during the study period. Of these, 36 patients had a claim for BMP, and 80 patients did not. [Table 3-2](#) describes the characteristics of these patients by BMP use ascertained through claims. Based on chart review, all 36 patients who were claim-positive for BMP did receive BMP. Therefore, the positive predictive value for BMP through claims is 100% (97.5% one-tailed CI: 90.2-100%). However, 30 (38%) of 80 patients without a claim for BMP actually received BMP according to the medical record. Based on this sample, the sensitivity of claims to detect BMP use is 55% (36/66; 95% CI: 41.8-66.9%). As we discuss in the limitations section below, there are methodological reasons to believe that the sensitivity estimate is artificially low.

Compared to patients with no claim for BMP, claim-positive patients had similar prevalence of current smoking (6% vs. 5%), lower prevalence of former smoking (25% vs. 29%) and lower

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prevalence of never smoking (50% vs. 55%). Smoking status was not recorded for 19% and 11% of the BMP claim-positive and -negative patients, respectively.

**Table 3-2: Summary of Abstracted Data by BMP Status Determined from Claims,
October 2003 - December 2005**

Variable ^a	BMP use-Claims	
	No (n=80) N (%) ^b	Yes (n=36) N (%) ^b
Use of BMP, claims	0 (0.0)	36 (100.0)
Use of BMP, charts	30 (37.5)	36 (100.0)
BMP-2	18 (60.)	19 (52.8)
BMP-7	0 (0.0)	1 (2.8)
BMP type unknown	12 (40.)	16 (44.4)
Female	47 (58.8)	22 (61.1)
Age at surgery		
Mean ± SD	71.2 ± 4.9	72.7 ± 5.9
Median (Range)	70 (65 - 83)	71 (65 - 85)
65 - 74	59 (73.8)	25 (69.4)
75 - 84	21 (26.3)	10 (27.8)
85 +	0 (0.0)	1 (2.8)
Patients with BMI data	77 (96.3)	26 (72.2)
Mean ± SD	30.0 ± 6.3	28.6 ± 5.2
Median BMI (range)	29.7 (19.5-60.4)	27.5 (20.7-41.9)
Smoking status (at time of surgery)		
Current smoker	4 (5.0)	2 (5.6)
Former smoker	23 (28.8)	9 (25.)
Never smoked	44 (55.0)	18 (50.)
Unknown	9 (11.3)	7 (19.4)
Diabetes mellitus		
Yes	19 (23.8)	4 (11.1)
No	47 (58.8)	23 (63.9)
Unknown	14 (17.5)	9 (25.)
Duration of diabetes, Mean (N)	13.3 (7)	10. (1)
Cumulative duration of health plan enrollment		
Less than 1 year	18 (22.5)	13 (36.1)
1-2 years	26 (32.5)	5 (13.9)
2-3 years	21 (26.3)	8 (22.2)
3-4 years	5 (6.3)	3 (8.3)
4 or more years	10 (12.5)	7 (19.4)
History of chronic pancreatitis		
Yes	0 (0.0)	0 (0.0)
No	15 (18.8)	8 (22.2)
Unknown	65 (81.3)	28 (77.8)
History of gastrectomy		
Yes	0 (0.0)	0 (0.0)
No	18 (22.5)	11 (30.6)
Unknown	62 (77.5)	25 (69.4)

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**Table 3-2: Summary of Abstracted Data by BMP Status Determined from Claims,
October 2003 - December 2005 (Cont'd)**

Variable ^a	BMP use-Claims	
	No (n=80) N (%) ^b	Yes (n=36) N (%) ^b
History of cholecystectomy		
Yes	11 (13.8)	3 (8.3)
No	19 (23.8)	9 (25.)
Unknown	50 (62.5)	24 (66.7)

a. All data elements were obtained for each patient during the time period prior to and including the Index Surgery Date

b. All percentages are column percentages

In addition to the records of 116 patients who underwent surgery during the study period, we were able to complete chart review for an additional 42 patients who had lumbar fusion surgery in 2006, for a total of 158 patients' medical records. [Table 3-3](#) describes the characteristics of these patients by BMP use as determined by chart review. Of the 57 patients who were claim positive for BMP, all had chart confirmation of BMP use ([Table 3-3](#), positive predictive value = 100%, 97.5% one-tailed CI, CI: 93.7-100%). Given that Medicare no longer reimbursed for BMP after 2005 and, in turn, hospitals would no longer have incentive to code for it, we believe that it is not reasonable to calculate sensitivity of claims using data beyond that date. Among 96 patients with chart evidence of BMP use, the specific BMP could not be identified in 42.7% (n=42); however, among the 55 patients in whom BMP could be characterized, 94.5% (52/55) received rhBMP-2. Compared to those without BMP according to the charts, patients with BMP had a lower prevalence of current smoking (3.1% vs. 8.1%) and a similar prevalence of former smoking (24.0% vs. 24.2%) and never smoking (56.3% vs. 56.5%), while smoking status was not recorded for 16.7% and 11.3% of patients with and without BMP, respectively.

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**Table 3-3: Summary of Abstracted Data by BMP Status Determined from Charts,
October 2003 - August 2006**

Variable ^a	BMP use-Charts	
	No (n=62) N (%) ^b	Yes (n=96) N (%) ^b
Use of BMP, claims	0 (0.0)	57 (59.4)
Use of BMP, charts	0 (0.0)	96 (100.0)
BMP-2	0 (0.0)	52 (54.2)
BMP-7	0 (0.0)	3 (3.1)
BMP type unknown	0 (0.0)	41 (42.7)
Female	37 (59.7)	57 (59.4)
Age at surgery		
Mean \pm SD	71.7 \pm 4.9	71.7 \pm 5.5
Median (Range)	70.5 (65 - 86)	70.5 (65 - 89)
65 - 74	45 (72.6)	71 (74.0)
75 - 84	16 (25.8)	23 (24.0)
85 +	1 (1.6)	2 (2.1)
Patients with BMI data	58 (93.6)	75 (78.1)
Mean \pm SD	29.2 \pm 5.0	29.5 \pm 6.3
Median BMI (range)	29.2 (19.5 - 37.3)	28.5 (20.7 - 60.4)
Smoking status (at time of surgery)		
Current smoker	5 (8.1)	3 (3.1)
Former smoker	15 (24.2)	23 (24.0)
Never smoked	35 (56.5)	54 (56.3)
Unknown	7 (11.3)	16 (16.7)
Diabetes mellitus		
Yes	16 (25.8)	18 (18.8)
No	32 (51.6)	59 (61.5)
Unknown	14 (22.6)	19 (19.8)
Duration of diabetes, Mean, (N)	10.7 (7)	14.4 (5)
Cumulative duration of health plan enrollment		
Less than 1 year	16 (25.8)	23 (24.0)
1-2 years	23 (37.1)	14 (14.6)
2-3 years	15 (24.2)	23 (24.0)
3-4 years	3 (4.8)	13 (13.5)
4 or more years	5 (8.1)	23 (24.0)
History of chronic pancreatitis		
Yes	0 (0.0)	0 (0.0)
No	0 (0.0)	28 (29.2)
Unknown	62 (100.0)	68 (70.8)
History of gastrectomy		
Yes	0 (0.0)	0 (0.0)
No	7 (11.3)	33 (34.4)
Unknown	55 (88.7)	63 (65.6)

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**Table 3-3: Summary of Abstracted Data by BMP Status Determined from Charts,
October 2003 - August 2006 (Cont'd)**

Variable ^a	BMP use-Charts	
	No (n=62) N (%) ^b	Yes (n=96) N (%) ^b
History of cholecystectomy		
Yes	11 (17.7)	12 (12.5)
No	7 (11.3)	30 (31.3)
Unknown	44 (71.)	54 (56.3)

a. All data elements were obtained for each patient during the time period prior to and including the Index Surgery Date

b. All percentages are column percentages

Table 3-4 describes the characteristics of patients by BMP use as determined by chart review through the end of 2005, when Medicare stopped reimbursement for BMP. Results were largely similar to those in [Table 3-3](#), which included patients who underwent surgery in 2006 as well.

**Table 3-4: Summary of Abstracted Data by BMP Status Determined from Charts,
October 2003 - December 2005**

Variable ^a	BMP use-Charts	
	No (n=50) N (%) ^b	Yes (n=66) N (%) ^b
Use of BMP, claims	0 (0.0)	36 (54.6)
Use of BMP, charts	0 (0.0)	66 (100.0)
BMP-2	0 (0.0)	37 (56.1)
BMP-7	0 (0.0)	1 (1.5)
BMP type unknown	0 (0.0)	28 (42.4)
Female	28 (56.0)	41 (62.1)
Age at surgery		
Mean ± SD	71.5 ± 4.8	71.8 ± 5.7
Median (Range)	70 (65 - 83)	71 (65 - 85)
65 - 74	36 (72.0)	48 (72.7)
75 - 84	14 (28.0)	17 (25.8)
85 +	0 (0.0)	1 (1.5)
Patients with BMI data	49 (98.0)	54 (81.8)
Mean ± SD	29.2 ± 4.9	30. ± 6.9
Median BMI (range)	29.7 (19.5-37.3)	28.5 (20.7-60.4)
Smoking status (at time of surgery)		
Current smoker	4 (8.0)	2 (3.0)
Former smoker	15 (30.0)	17 (25.8)
Never smoked	25 (50.0)	37 (56.1)
Unknown	6 (12.0)	10 (15.2)

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**Table 3-4: Summary of Abstracted Data by BMP Status Determined from Charts,
October 2003 - December 2005 (Cont'd)**

Variable ^a	BMP use-Charts	
	No (n=50) N (%) ^b	Yes (n=66) N (%) ^b
Diabetes mellitus		
Yes	13 (26.0)	10 (15.2)
No	27 (54.0)	43 (65.2)
Unknown	10 (20.0)	13 (19.7)
Duration of diabetes, Mean, (N)	10.0 (6)	21.5 (2)
Cumulative duration of health plan enrollment		
Less than 1 year	14 (23.0)	17 (27.9)
1-2 years	20 (32.8)	11 (18.0)
2-3 years	10 (16.4)	19 (31.1)
3-4 years	2 (3.3)	6 (9.8)
4 or more years	4 (6.6)	13 (21.3)
History of chronic pancreatitis		
Yes	0 (0.0)	0 (0.0)
No	0 (0.0)	23 (34.9)
Unknown	50 (100.0)	43 (65.2)
History of gastrectomy		
Yes	0 (0.0)	0 (0.0)
No	6 (12.0)	23 (34.9)
Unknown	44 (88.0)	43 (65.2)
History of cholecystectomy		
Yes	8 (16.0)	6 (9.1)
No	6 (12.0)	22 (33.3)
Unknown	36 (72.0)	38 (57.6)

a. All data elements were obtained for each patient during the time period prior to and including the Index Surgery Date

b. All percentages are column percentages

3.5 Discussion

Compared to the main Medicare study, in which the prevalence of BMP use during fusion surgery was 16.5% (15,460/93,654), the corresponding prevalence in the HealthCore claims data was only 5.2% (80/1543). We believe that it is unlikely that this discrepancy can be attributed to true differences in BMP use between the HealthCore sample and the overall Medicare population of elderly patients who underwent lumbar fusion. Methodological issues in ascertaining the ICD-9 procedure code for BMP seem more likely. The UB92 form used for Medicare claims submissions includes six fields for potential ICD-9 procedure codes, but the HealthCore data set includes only the first three. That 70% (21/30) of the patients who were claim-negative but chart-positive for BMP had all three ICD-9 procedure codes fields populated suggests that a

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‘crowding-out’ phenomenon may well account for under-ascertainment of BMP use in HealthCore claims data. An additional two patients who were chart-positive but claim-negative for BMP had no ICD-9 procedure code recorded at all, suggesting that there were problems in data completeness for some patients. (The fusion surgeries for such patients would have been identified through CPT-procedure codes, and in the CPT schema no code for BMP exists.)

Based on these methodological considerations, we believe that our study underestimated the sensitivity of BMP detection by claims. In view of these findings, for the planned sensitivity analysis of smoking as a potential confounder in the main Medicare study, we suggest using the prevalence of smoking based on BMP use as characterized by chart review rather than claims ([Table 3-3](#)).

Other limitations of the current study should be acknowledged. Because of difficulties accessing patients’ medical records, we did not meet our target to review 100 charts from patients in each exposure group. In the end, we reviewed only 96 for patients who received BMP (according to the charts) and 62 for patients who did not. Uncertainty surrounds prevalence estimates of smoking because (1) not all records included information about smoking and (2) a limited number of charts were reviewed. Nonetheless, available information does not suggest substantial differences in smoking patterns between patients who did and did not receive BMP. Finally, estimates of smoking prevalence and other comorbidities from the HealthCore population may not be completely representative of the general Medicare population. HealthCore data largely reflect the experience of patients with commercial insurance, and these patients likely have a higher education status and social economic status than the general Medicare population. Since these factors tend to be associated with lower frequency of smoking, our study may have underestimated the smoking prevalence among patients from the general Medicare population who underwent lumbar fusion.

3.6 Conclusions

This chart review sub-study provides important information for the interpretation of the main Medicare study. We did not find substantial differences in the prevalence of smoking by BMP use. Using chart review as the gold standard, we found that the positive predictive value for BMP through claims was 100%, thus validating our exposure measure. Among the 55 patients

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in whom BMP could be characterized, 94.5% (52/55) received rhBMP-2. This information provides additional evidence of the validity of the exposure measure in the Medicare study.

RELEVANT RESPONSES TO FDA QUESTIONS

The following section contains information that has been requested by FDA for inclusion in the Panel Pack.

RESPONSE TO FDA QUESTION, SUBMITTED MAY 14, 2010

1. In your reply to our previous Deficiency 5, you have provided a table with p-values and risk ratios for a Cox proportional hazards regression comparing rhBMP-2 and non-rhBMP-2 patients in the time to malignancy diagnosis. We are concerned that these risk ratios and confidence intervals may have been inverted, as these results show a greater and protective effect of the Investigational treatment in the “Medtronic” data. Please provide programming code showing how the variable “TRT” was coded in each of these regressions. This information is necessary to validate the risk ratios and confidence intervals in your results. Please provide it to FDA.

MEDTRONIC RESPONSE:

As indicated in the dataset explanation Medtronic provided in February 2010, the investigational treatment was coded as “1,” while the control was coded as “2” in the original datasets. Medtronic recognizes that because of that, the risk (hazard) ratios generated from SAS PROC PHREG were for the control, rather than the rhBMP-2 treatment.

The risk ratios for the rhBMP-2 treatment should be the reciprocals of those for the control. For the convenience of the presentation, the control treatment was re-coded as “0,” and the rhBMP-2 treatment was kept as “1”. Please see the attachments for three SAS programs and their outputs, respectively for Medtronic, Wyeth, and pooled data.

The following table is an updated version of Table 7 in the original report, with risk ratios and confidence intervals for the rhBMP-2 treatment, while the p-values are unchanged.

Time-to-Event Analyses of Time from Treatment to Malignancy Diagnosis Between rhBMP-2/non-rhBMP-2 Patients					
Source	Malignancy Type	p-value from Kaplan-Meier Analysis		Cox PHREG Analysis	
		<i>Log-Rank Test</i>	<i>Wilcoxon Test</i>	p-value	Risk Ratio (95%CI)
Medtronic	SEER malignancies	0.204	0.234	0.297	1.481 (0.708, 3.096)
	Total malignancies	0.169	0.136	0.258	1.502 (0.742, 3.040)
Wyeth	SEER malignancies	0.788	0.702	0.636	1.307 (0.431, 3.969)
	Total malignancies	0.635	0.414	0.779	0.880 (0.360, 2.150)
Pooled	SEER malignancies	0.182	0.441	0.236	1.449 (0.785, 2.674)
	Total malignancies	0.333	0.558	0.423	1.252 (0.723, 2.168)

RESPONSE TO FDA QUESTIONS, SUBMITTED FEBRUARY 10, 2010

7. In the explanation for the primary outcome of the Wyeth Medicare study, you state “after an extensive discussion with clinical experts, we concluded that the third (most specific) definition [of pancreatic cancer] would serve as the primary outcome for the analyses (P050035-A11, p.1722).” No discussion of the experts’ opinions was provided. The measure chosen as the primary outcome required two diagnosis codes and at least one procedure code, so there was the potential for outcome misclassification based on patients having fewer encounters with their providers.

a. Please provide the following information for the number of people in the BMP and non-BMP groups:

i. Number of people in each group

PFIZER (WYETH) RESPONSE:

There were 93,654 patients who met the inclusion criteria of the study, including 15,460 (16.5%) patients in the BMP group and 78,194 (83.5%) patients in the non-BMP group.

ii. Number with at least one ICD-9-CM diagnosis code for pancreatic cancer

PFIZER (WYETH) RESPONSE:

The number of patients with at least one ICD-9-CM diagnosis code for pancreatic cancer was 18 patients in the BMP group and 164 patients in the non-BMP group.

iii. Number with at least two ICD-9-CM diagnosis codes for pancreatic cancer

PFIZER (WYETH) RESPONSE:

The number of patients with at least two ICD-9-CM diagnosis codes for pancreatic cancer was 14 patients in the BMP group and 115 patients in the non-BMP group.

iv. Number with at least one ICD-9-CM diagnosis code for pancreatic cancer AND at least one procedure code consistent with cancer therapy

PFIZER (WYETH) RESPONSE:

The number of patients with at least one ICD-9-CM diagnosis code for pancreatic cancer AND at least one procedure code consistent with cancer therapy was 15 patients in the BMP group and 134 patients in the non-BMP group.

v. Number with either at least two ICD-9-CM diagnosis codes for pancreatic cancer OR at least one ICD-9-CM diagnosis code for pancreatic cancer and at least one procedure code consistent with cancer therapy

PFIZER (WYETH) RESPONSE:

There were 17 patients in the BMP group and 153 patients in the non-BMP group who had either at least two ICD-9-CM diagnosis codes for pancreatic cancer OR at least one ICD-9-CM diagnosis code for pancreatic cancer and at least one procedure code consistent with cancer therapy.

vi. Number with at least two ICD-9-CM diagnosis codes for pancreatic cancer AND at least one procedure code consistent with cancer therapy

PFIZER (WYETH) RESPONSE:

The number of patients with at least two ICD-9-CM diagnosis codes for pancreatic cancer AND at least one procedure code consistent with cancer therapy was eight patients in the BMP group and 83 patients in the non-BMP group.

b. Please provide a rationale for choosing option vi. above as your primary outcome rather than other options. Please address concerns that patients with pancreatic cancer may choose to have treatment after their initial diagnosis or may choose not to have treatment.

PFIZER (WYETH) RESPONSE:

Our study relied on Medicare claims as proxies for both exposure and outcomes. The advantage of using such a large dataset is that one can achieve large numbers needed for the study of rare outcomes, such as pancreatic cancer. However, a potential limitation is that the diagnosis codes represent administrative, rather than clinical, information. In our study we were unable to verify the outcome against actual medical charts. We evaluated a variety of case definitions, ranging from most sensitive (a single claim with a pancreatic cancer diagnosis) to more specific (at least two ICD-9-CM diagnosis codes for pancreatic cancer AND at least one procedure code consistent with cancer

therapy). We chose the most specific definition for the primary outcome data because of concerns about outcome misclassification. We suspected that some of the single-diagnosis-only cases might represent 'rule-out' diagnoses, rather than true disease. Random outcome misclassification tends to bias toward null results; in other words, it can mask true associations. We believed that, if there was a true association between rhBMP-2 use and pancreatic cancer, the association would be strongest using the most specific case definition.

Nonetheless, we performed sensitivity analyses that relied on more sensitive case definitions as well. Certainly not all patients diagnosed with pancreatic cancer receive disease-specific treatments. We believe that such patients would have been captured in the case definitions that required only one or two diagnosis codes (study case definitions 1 and 2). As one would expect, the number of outcomes increased as the case definition became less restrictive. Based on the information available, we cannot judge what proportion of this increase represents patients who chose not to receive disease-specific treatment versus false-positives.

Ultimately, results did not change substantially with case definition (Table 2-3 of the study report). Hazard ratios were consistently below one, a finding that argues against the hypothesis that rhBMP-2 use is associated with an excess risk of pancreatic cancer.

Analyses we conducted using the FDA's alternative case definitions yielded results quite similar to those from the original study. BMP use was not associated with pancreatic cancer when using FDA's alternative case definition (iv) (OR=0.81, 95% CI: 0.48-1.39) and case definition (v) (OR=0.80, 95% CI: 0.48-1.32), as compared to the results based on our primary case definition (OR=0.49, 95% CI: 0.24-1.02) in the original study report (Table 2-2).

- 8. In the explanation for the time in Medicare required prior to surgery, you state, "a two year cut off was used to maximize the sensitivity of capturing and excluding patients who were long-term cancer survivors (P050036-A11, p1721)." The long period of time patients were required to be in the Medicare data prior to surgery excludes a potentially large number of people. It is unclear how many pancreatic cancer cases occurred in patients that were excluded from this study due to this criterion and whether the excluded patients differed from patients who were eligible. Please provide either:**
 - a. An electronic dataset encompassing all patients considered for inclusion in the Medicare analysis with documentation on how exclusion criteria were applied. Please include data for exposure, all covariates in analyses, and outcomes assessed. OR**
 - b. Demographic, clinical, BMP, and pancreatic cancer information on Medicare patients who met other inclusion criteria and were captured in**

the data for one year prior to surgery. Include a comparison between this group and patients who were included in the study.

PFIZER (WYETH) RESPONSE:

Please see Table 8-1 below, which compares the demographic, clinical, BMP use, and pancreatic cancer information on Medicare patients who met other inclusion criteria and were captured in the data for at least one year but less than two years prior to surgery to those patients included in the analysis. Patients in the new cohort were very similar to the study cohort, including BMP use and occurrences of pancreatic cancer, except that they were younger and with fewer comorbidities.

Table 8-1. Demographic and Clinical Characteristics of the Original Study Cohort and the Cohort Who Met Other Inclusion Criteria and Were Captured in the Data for at Least One Year but Less than Two Years Prior to Surgery

Variable	Original Study Cohort	Cohort with 1-2 Year Prior Data Before Surgery	P-value
Patients (N)	93,654	9,425	
Patient-years	130,516	14,022	
Mean age \pm SD	74.7 \pm 5.1	68.4 \pm 3.9	
	N (%)	N (%)	
Age Group			
67-69	20,214 (21.6)	7,657 (81.2)	<0.0001
70-74	32,410 (34.6)	968 (10.3)	
75-79	25,800 (27.5)	530 (5.6)	
80-84	12,082 (12.9)	216 (2.3)	
\geq 85	3,147 (3.4)	54 ((0.6)	
Gender			
Male	32,173 (34.4)	3,190 (33.8)	0.324
Female	61,481 (65.6)	6,235 (66.2)	
Race			
White	88,104 (94.1)	8,652 (91.8)	<0.0001
Black	3,495 (3.7)	496 (5.3)	
Other	2,055 (2.2)	277 (2.9)	
Comorbid Conditions			
Diabetes	33,883 (36.2)	2,969 (31.5)	<0.0001
Chronic Pancreatitis	879 (0.9)	42 (0.4)	<0.0001
Alcoholism	1,287 (1.4)	124 (1.3)	0.6049
Cholecystectomy	2,847 (3.0)	175 (1.9)	<0.0001
BMP treatment	15,460 (16.5)	1,618 (17.2)	0.101
Pancreatic cancer			
Case definition 1	182 (0.2)	43 (0.5)	<0.0001
Case definition 2	129 (0.1)	14 (0.2)	0.77
Case definition 3	91 (0.1)	10 (0.1)	0.73

To further confirm our study results, we redid the analyses in a larger cohort, which included the original study cohort plus those patients with at least one year but less than two years data prior to surgery. Again, results were substantially unchanged (HR=0.92, 95% CI: 0.60-1.41 for case definition 1 and HR=0.74, 95% CI: 0.38-1.41 for case definition 3) (as shown in Table 8-2) as compared to the results from the original study report (Table 2-3).

Table 8-2. Factors Associated with Pancreatic Cancer in Multivariate Cox Regression Analysis among the Cohort that Included the Original Study Cohort Plus Patients with at Least One Year but Less Than Two Years Data Prior to Surgery

Variable	Hazard Ratio (95% CI)		
	Case Definition 1* (n=225)	Case Definition 2* (n = 143)	Case Definition 3* (n=101)
Age Group			
67-69	1	1	1
70-74	1.84 (1.22 - 2.76)	1.87 (1.19 - 2.94)	1.93 (1.09 - 3.40)
75-79	2.13 (1.41 - 3.21)	1.81 (1.12 - 2.91)	2.34 (1.32 - 4.16)
80-84	2.24 (1.38 - 3.63)	1.42 (0.76 - 2.64)	1.25 (0.56 - 2.81)
≥ 85	1.16 (0.41 - 3.28)	1.11 (0.33 - 3.65)	1.73 (0.51 - 5.90)
Gender			
Male	1	1	1
Female	0.78 (0.59 - 1.03)	0.74 (0.53 - 1.02)	0.53 (0.36 - 0.78)
Race			
White	1	1	1
Black	1.67 (0.95 - 2.94)	1.96 (1.05 - 3.63)	1.82 (0.84 - 3.94)
Other	1.62 (0.80 - 3.28)	1.15 (0.42 - 3.10)	1.20 (0.38 - 3.79)
Comorbid Conditions			
Diabetes	1.54 (1.17 - 2.02)	1.50 (1.09 - 2.07)	1.70 (1.16 - 2.49)
Chronic Pancreatitis	8.43 (4.93 - 14.4)	5.48 (2.54 - 11.8)	3.16 (0.99 - 10.1)
Alcoholism	1.41 (0.52 - 3.82)	1.45 (0.46 - 4.58)	0.64 (0.09 - 4.61)
Cholecystectomy	1.64 (0.88 - 3.04)	1.58 (0.73 - 3.41)	2.14 (0.93 - 4.92)
BMP treatment	0.92 (0.60 - 1.41)	0.96 (0.59 - 1.57)	0.74 (0.38 - 1.41)

* **Case Definition 1** = Any ICD-9-CM diagnosis code for pancreatic cancer in any file type beginning at the date of index surgery through the end of follow up.

Case Definition 2 = An ICD-9-CM diagnosis code for pancreatic cancer on more than one date of service.

Case Definition 3 = Two or more diagnosis codes for pancreatic cancer on different dates of service and at least one procedure code consistent with cancer therapy.

RESPONSE TO FDA QUESTION, SUBMITTED FEBRUARY 10, 2010

1. With reference to Tables 1 and 2 that you provided in your April 1, 2009 submission, please resubmit this information using the format of Table 2 from the FDA Guidance Document for Clinical Data Presentations for Orthopedic Device Applications (<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm072263.htm#4>).

MEDTRONIC RESPONSE:

FDA requested that Tables 1 and 2 from the clinical report in the April 2009 AMPLIFY™ rhBMP-2 Matrix submission be updated to match the guidance document referenced above. Medtronic believes the accountability tables we presented are more conservative and appropriate, while the format in the guidance document reflects what we used to do. Our current accounting methodology has also been utilized in our other spinal PMAs, including the PRESTIGE and BRYAN Cervical Discs, which were approved in 2007 and 2009, respectively.

As described in the Statistical Considerations and in the Statistical Methodology section of the study report, patients who had additional surgical procedures/interventions that were classified as “failures” were deemed as failures for overall success, the primary endpoint. For other individual variables, the last observations taken before the additional surgical procedures/interventions were carried forward for all future evaluation periods.

After a patient had a second surgery failure or a serious related adverse event, the patient was considered a failure for overall success status and thus was included in both the numerator and denominator for summarizing the data and statistical comparisons, even if the patient did or did not actually have a visit for evaluation. These patients were asked to continue having follow-up visits for evaluations. It is only reasonable to count those patients as “expected.” Otherwise, many of these patients who had evaluations would be included as “evaluated,” but not “expected.” Follow-up rates could potentially exceed 100%, especially at some early periods. Including them as “expected” is a reasonable, logical, and conservative approach and also maintains consistency with data summaries and analyses. The cumulative numbers of patients with second surgery failures and serious, possibly device-related adverse events were presented in the overall success summary table by period.

Nevertheless, to satisfy FDA’s requirement, we are resubmitting our original Tables 1 and 2, using the format from the FDA Guidance Document. These tables can be found in **Attachment 1**.

Table 1. STUDY PROGRESS SUMMARY
 BASED ON HAVING ANY DATA ON A PATIENT AT A GIVEN STUDY PERIOD

(Database Closure: 03FEB2009)

Variable	Preoperative		Surgery		6 Weeks		3 Months		6 Months		12 Months		24 Months		36 Months		48 Months *		60 Months	
	INV	Control	INV	Control	INV	Control	INV	Control	INV	Control	INV	Control	INV	Control	INV	Control	INV	Control	INV	Control
Number of Patients Enrolled	239	224	239	224	239	224	239	224	239	224	239	224	239	224	239	224	239	224	239	224
Theoretical Follow-up	239	224	239	224	239	224	239	224	239	224	239	224	239	224	239	224	239	224	239	224
Cumulative Deaths			0	0	1	0	1	0	1	1	2	2	3	4	3	5	4	6	5	7
Failures (Cumulative) ‡			0 (0)	0 (0)	3 (3)	2 (2)	1 (4)	2 (4)	1 (5)	1 (5)	1 (6)	9 (14)	10 (16)	15 (29)	7 (23)	6 (35)	3 (26)	2 (37)	1 (26)	3 (39)
Patients Not Yet Over Due			0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	9	15
Failure(s) Was not Counted in the Denominator																				
Expected #	239	224	239	224	239	222	234	220	233	218	231	208	220	191	213	184	209	181	199	163
Evaluated of Expected	239	224	239	224	233	217	230	214	227	204	222	191	195	157	152	132	83	61	130	99
Percent Follow-up (%)	100.0	100.0	100.0	100.0	99.1	97.7	98.3	97.3	97.4	93.6	96.1	91.8	88.6	82.2	71.4	71.7	39.7	33.7	65.3	60.7

Program: T_ACCOUNTABILITY_ANYDATA_EXCLUDE_AE Date: 03FEB10

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* Note: Even though data was available for some patients at 48 months postoperative, this was not a protocol-specified time point. As such, the follow-up rates are much lower for this time period.
 ‡ Patient who had a failure defined as an additional surgery with a supplemental fixation, non-elective implant removal, or revision or defined as a serious device- or device/surgical-related adverse event not leading to a second surgery.
 # Expected = Theoretical - Cumulative Deaths - Cumulative Failures - Additional Patients to be Evaluated (i.e., Patients Not Yet Overdue).

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Table 2. PATIENT ACCOUNTABILITY
BASED ON AVAILABILITY OF OVERALL SUCCESS OUTCOMES

(Database Closure: 03FEB2009)

Variable	6 Months		12 Months		24 Months		36 Months		48 Months *		60 Months	
	INV	Control	INV	Control	INV	Control	INV	Control	INV	Control	INV	Control
Number of Patients Enrolled	239	224	239	224	239	224	239	224	239	224	239	224
Theoretical Follow-up	239	224	239	224	239	224	239	224	239	224	239	224
Cumulative Deaths	1	1	2	2	3	4	3	5	4	6	5	7
Failures (Cumulative) \$	1 (5)	1 (5)	1 (6)	9 (14)	10 (16)	15 (29)	7 (23)	6 (35)	3 (26)	2 (37)	1 (26)	3 (39)
Patients Not Yet Over Due	0	0	0	0	0	0	0	0	0	0	9	15
Failure(s) Was not Counted in the Denominator												
Expected #	233	218	231	208	220	191	213	184	209	181	199	163
Number of Patients Who Had Overall Success Outcomes	199	184	208	183	184	153	127	105	76	45	97	72
Percent of Patients Who Had Overall Success Outcomes (%)	85.4	84.4	90.0	88.0	83.6	80.1	59.6	57.1	36.4	24.9	48.7	44.2

Program: T_ACCOUNTABILITY_ALLSUC Date: 05FEB10

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* Note: Even though data was available for some patients at 48 months postoperative, this was not a protocol-specified time point. As such, the follow-up rates are much lower for this time period.

\$ Patient who had a failure defined as an additional surgery with a supplemental fixation, non-elective implant removal, or revision or defined as a serious device- or device/surgical-related adverse event not leading to a second surgery.

Expected = Theoretical - Cumulative Deaths - Cumulative Failures - Additional Patients to be Evaluated (i.e., Patients Not Yet Overdue).

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