

**InFUSE™ Bone Graft/LT-CAGE™ Lumbar
Tapered Fusion Device**

Amendment to PMA #P000058

**REDACTED PANEL INFORMATION
FOR PUBLIC RELEASE**

**Medtronic Sofamor Danek
Memphis, Tennessee**

December 4, 2001

OPEN SURGICAL ARM

The following full pages have been redacted from II.A Open Surgical Approach Arm report:

Pages 4, 7, 13, 14, 15, 16, 17, 18, 19, 20, 21, 47

The following full pages have been redacted from II.A TABLES:

Pages 15, 16, 17, 18, 19, 20, 21, 26, 38, 39, 40, 41, 42, 43, 45, 47, 48, 49, 50, 54, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67

LAPAROSCOPIC SURGICAL ARM

The following full pages have been redacted from II.B Laparoscopic Surgical Approach Arm report:

Pages 8, 9, 10, 11, 12, 13, 14,

The following full pages have been redacted from II.B TABLES:

Pages 14, 15, 16, 17, 18, 19, 20, 25, 35, 36, 37, 38, 39, 40, 42, 44, 45, 46, 47, 51, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64

CLINICAL INFORMATION

II.A OPEN SURGICAL APPROACH ARM

II.A. Report of Pivotal Clinical Trial Results (G960065)
Open Use of InFUSE™ Bone Graft/LT-CAGE™ Device

I. Introduction

In October 1996, Medtronic Sofamor Danek filed an application for an Investigational Device Exemption (IDE) (G960065) with the FDA to study the use of rhBMP-2 with an absorbable collagen sponge (ACS) inserted into LT-CAGE™ interbody fusion devices to treat patients with symptomatic degenerative disc disease. The clinical trial design was pilot in nature and the results from it were intended to support the initiation of a larger pivotal clinical study. This IDE was conditionally approved by the FDA on November 20, 1996 and later unconditionally approved on February 10, 1997. The IDE was subsequently supplemented to allow for more patients and investigators, as well as the use of a laparoscopic surgical approach in addition to an open procedure. Fourteen (14) patients were enrolled in the pilot clinical trial – 11 receiving the rhBMP-2/ACS/LT-CAGE™ device (investigational) and 3 receiving the LT-CAGE™ device with autogenous bone (control). The results of the clinical trial were favorable for the investigational product and the 12 month results were used in support of initiation of the larger pivotal trial. This pilot trial has been completed since all patients have reached their second postoperative anniversary. The final report has been previously submitted to FDA in Module II of PMA P000058, dated December 21, 2000. Included in **Attachment II.C** is a summary of 48 month data on nine patients.

Based on the 12 month results of the pilot clinical trial, Medtronic Sofamor Danek petitioned the FDA to initiate a pivotal trial of rhBMP-2/ACS with the LT-CAGE™ device implanted with an open surgical approach. The pivotal clinical trial had a prospective, randomized control design with the control treatment being the LT-CAGE™ device filled with autogenous bone graft. Like the pilot trial, patients in the pivotal study received single level lumbar fusion procedures in the treatment of symptomatic degenerative disc disease. The pivotal clinical trial received conditional approval from the FDA on June 19, 1998 and final approval on July 31, 1998. The initial approval granted permission to enroll a total of 270 patients, 135 investigational and 135 control, at 15 institutions. FDA approved subsequent Medtronic Sofamor Danek requests to allow up to 300 total patients at 16 investigational sites. The first patient was enrolled

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on August 25, 1998 and the last study patient had surgery on July 1, 1999. A total of 143 investigational and 136 control patients received the study treatment in the clinical trial. All investigational and control patients in the clinical trial have reached their 24 month postoperative period.

Concurrent with the open surgical approach study, FDA granted permission to initiate a laparoscopic surgical approach arm to the IDE. The laparoscopic arm of this IDE (G960065) was conditionally approved by the FDA on September 11, 1998 and full approval was granted in a letter dated December 22, 1998. Except for not having a randomized control treatment, the protocol for the laparoscopic arm was identical to that of the open arm to allow for meaningful data comparisons. A total of 134 patients from 14 investigational sites received the study treatment in the study. The first surgery in the laparoscopic arm of the clinical trial occurred on November 5, 1998 and the last patient had surgery on August 25, 1999. All patients have reached their 24 month postoperative period.

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II. Methods

A. Clinical Trial Goals and Design

The goals of the IDE clinical trial of the InFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device were to evaluate the safety and effectiveness of the anterior lumbar use of the device in the treatment of patients with symptomatic degenerative disc disease. The assessments of safety and effectiveness of the InFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device (investigational) were through direct clinical data comparisons between data collected from patients implanted with the InFUSE™ Bone Graft/LT-CAGE™ device to an equivalent group of patients who received surgical treatment utilizing the LT-CAGE™ device filled with autogenous bone derived from the iliac crest (control). In the open surgical approach arm of the IDE, the investigational and control treatments were randomized in a 1:1 manner.

In the laparoscopic arm of the IDE, the InFUSE™ Bone Graft/LT-CAGE™ device (investigational) was the only treatment. As indicated in the protocol for this arm, the investigational treatment results are to be compared to the control group results from the open surgical approach arm. The laparoscopic InFUSE™ Bone Graft/LT-CAGE™ device data, in particular surgical parameters such as operative time and blood loss, can also be compared to the LT-CAGE™ device (filled with autogenous bone graft) data arising from the previous IDE clinical trial of the device (G950165). The data from that trial led to the previously mentioned PMA approval of the LT-CAGE™ device.

The effectiveness of the InFUSE™ Bone Graft/LT-CAGE™ device will be based primarily on a patient having radiographically demonstrated fusion, Oswestry pain/disability improvement, and maintenance or improvement in neurological status following surgery. These factors, as well as the patient not having a serious device or device/surgical procedure associated adverse event or having a second surgery classified as a "failure", will determine whether the patient is an overall success – the primary endpoint for the clinical investigation. In addition, back pain, leg pain, graft site (hip) pain, disc height, general health status, and patient satisfaction will be evaluated. Safety will be based primarily on the nature and frequency of adverse events and second surgeries.

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Antibody test results and radiographic review comments will also be considered in assessing product safety.

For additional information pertaining to the analyses of the clinical trial results, please refer to the statistical considerations provided in **II.A, Attachment A**.

The presentation of information in the following clinical summaries will focus primarily on the data arising from the investigational and control groups of the open surgical approach arm of the clinical trial. It is believed this manner of presentation has the most scientific appeal since the data arise from a randomized treatment process. In addition, this manner of data presentation is the sternest test for the investigational group since the laparoscopic arm overall success rates at both 12 and 24 month postoperative for the InFUSE™ Bone Graft/LT-CAGE™ device are higher than that for the open investigational group. If we had chosen to combine the data from open and laparoscopic arms, this would have bolstered the overall success results of the investigational group. Instead, the data from the laparoscopic arm of the clinical trial are presented separately in Section II.B and are to be used in supporting the PMA approval for this method of surgical implantation of the device.

B. Statistical Methodology

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III. Results

A. Patient Accountability

Summaries of the open investigational and control treatment groups and the accountability of patients in each group at the different clinical trial periods are provided in **Tables 1 and 1a**, respectively. A total of 143 patients received the investigational treatment and a total of 136 patients received the control treatment. In addition, three patients, two open investigational and one control, were enrolled into the study but did not receive either study treatment and are not included in the number of evaluable patients. Please refer to **II.A, Attachment H** for information on these three patients. The cut-off date for analyses was July 25, 2001.

The patient accountability rates are high at all postoperative periods and all rates exceeded FDA's target of 85%. [REDACTED]

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was statistically significant, it was not considered clinically important since the mean values differed by less than two points. The difference in mean SF-36 MCS scores was also statistically significant with the investigational group being three points higher - probably not clinically relevant. Subsequent analyses of the SF-36 data involve comparing the postoperative score to the preoperative score on a patient basis and such analyses diminish the importance of any baseline differences. Finally, SF-36 findings are not considered primary endpoints in this clinical trial.

In summary, the preoperative medical conditions were very similar for the open investigational and control patients involved in the clinical trial.

E. Surgery Information

Table 6 provides summaries of information related to the surgical procedures and postoperative hospitalizations of patients. The results of the statistical analyses between the open investigational and control groups are provided in II.A, Attachment C. The mean operative times for the open investigational and the control treatment groups are 1.6 hrs. and 2.0 hrs., respectively. These mean operative times were found to be statistically different (probability of superiority=100%) based on Bayesian analyses. Open investigational patients were found to have less blood loss than the control group patients (109.8 ml. versus 153.1 ml.), with a probability of superiority value of 99.1%.

The mean hospital stays of patients in both treatment groups were slightly more than three days. 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 the patients in the two treatment groups for the variables of treated level, operative approach, type of external orthosis, and outpatient/inpatient classification were very similar. These findings are considered beneficial for the clinical trial since they indicate that both the open investigational and control patients had similar procedures and were treated similarly postoperatively.

In summary, open investigational device patients had shorter operative times and less blood loss than control group patients. The other operative parameters yielded similar results.

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F. Safety Measurements
1. Adverse Events

The safety of the investigational device was evaluated based on the nature and frequency of adverse events compared to those occurring in the control group. 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. Information pertaining to the adverse events from each treatment group are provided in **II.A, Attachment D**.

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

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Table 7 provides a time course summary of operative and postoperative adverse events reported for open investigational and control patients as a function of adverse

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event category.² The total number of occurrences per category is also provided. There are 23 categories of adverse events. Bayesian statistical analyses comparing the adverse event rates of the open investigational and control groups for each category were performed (see II.A, **Attachment E**). The rates are based on dividing the number of patients having at least one occurrence of a particular adverse event by the total number of patients in that treatment group.

From **Table 7**, a total of 113 (79.0%) open investigational patients had at least one adverse event. In addition, adverse events and second surgeries such as nonunions that do not appear on the adverse event table² are evaluated for severity and possible cause. Seventeen (11.9%) patients had adverse events or nonunions which were judged to be device associated or device/surgical procedure associated. Many of these events were not considered to be serious. Of those patients having a device associated or device/surgical procedure associated adverse event or nonunion, only 11 (7.7%) patients had events rated as "serious". These three rates were similar to those rates for the control group, which were 80.1%, 13.2%, and 8.8%, respectively.

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2. Radiographic Reviewer Findings

In this clinical study, the radiographs were evaluated by two independent teams of radiographic reviewers. A third review team was used to adjudicate any differences in opinions regarding fusion and disc height between the two teams⁴. This is discussed in greater detail in the fusion and disc height sections of this report. As part of the review process, the reviewers also were asked to indicate if they believed the implant(s) had loosened, bent, broken, or migrated, and if there was evidence of a fractured fusion mass. In all reviews, there were no reports of bent or broken implants, or fractured fusion masses.

There were two observations of implant migration.

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There were eight patients who were reported to have implant loosening by Team 1.

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Review Team 1 noted implant loosening in six control group patients

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Review Team 2 noted implant loosening in twelve patients

Implant loosening was reported in seven of these patients by Team 1 as well.

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[REDACTED]
[REDACTED]

Review Team 3 noted implant loosening in five patients [REDACTED]. These patients are all control patients and all were included in the implant loosening reports of Review Teams 1 and/or 2.

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In addition, there were a few comments that pertained to other observations. Five such comments were made concerning the presence of cystic lesions: two open investigational patients [REDACTED] and [REDACTED] and three control patients [REDACTED]. For control patient [REDACTED] there were comments concerning a vacuum phenomena seen within the cystic lesions. The adverse events for the two open investigational patients [REDACTED] were respiratory, trauma, other, spinal event, back and/or leg pain, and urogenital. There was one reported adverse event for the control patients and it was neurological.

One comment was made concerning the presence of a lytic lesion [REDACTED]. There was implant subsidence reported in this patient and the patient eventually had a supplemental fixation procedure due to a nonunion.

These types of lesions have been noted in animal studies involving rhBMP-2 and autograft and do not appear to have any material affect on arthrodesis⁵.

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One additional comment made was concerning the calcification of the left primary iliac artery projecting anteriorly to the left implant [REDACTED]. This was noted on both the 6 and 12 month CT scans but not on the 24 month CT scans. [REDACTED]

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3. Secondary Surgical Procedures

Some of the adverse events led to surgical interventions subsequent to the clinical trial surgery. These additional surgical interventions can be classified as revisions, removals, supplemental fixations, reoperations, and other.

A revision is a procedure that adjusts or in any way modifies the original implant configuration. A removal is a procedure that removes one or more components of the original implant configuration without replacement with the same type of device. A supplemental fixation is a procedure in which additional spinal devices not approved as part of the protocol are placed. A reoperation is 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 are ones which may not even involve the lumbar spine.

Table 8 summarizes the secondary surgical interventions in the open investigational and control treatment groups and II.A, Attachment F provides case histories of all revision, removal, or supplemental fixation procedures in both

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treatment groups. The statistical analyses of the rates of secondary surgical procedures between the two treatment groups are provided in II.A, Attachment G.

The various rates for the two treatment groups were comparable and there were no statistical differences for any of the comparisons. No revision procedures occurred in either treatment group.

There were two implant removal procedures in the investigational group and none in the control group. Both of these removals occurred early in the postoperative phase of the study. One removal [REDACTED] happened five days postoperative due to a vertebral bone fracture and displacement of the cages. [REDACTED]

The other removal (603) occurred at approximately four months following surgery due to implant displacement and a possible failed fusion. [REDACTED]

Supplemental fixations occurred at a rate of 7.0% in the open investigational group (this rate included one patient [REDACTED] who received supplemental fixation after having the devices removed five days following surgery due to a vertebral bone fracture and displacement of the cages) as compared to a 10.3% rate in the control group. Most were due to the investigators' diagnoses of a possible pseudarthrosis, with the exception of one open investigational patient which was documented as being due to radiculopathy and two control patients who were both documented as being due to discogenic pain.

In accordance with the protocol, if a study patient had a revision, removal, or supplemental fixation procedure, the

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patient was then classified as a second surgery "failure". These events are considered in the calculations of "overall success" rate for the study. The open investigational group had eleven second surgery "failures" as compared to fourteen for the control group.

For more information concerning the nature of the reoperation and other second surgery procedures, please refer to II.A, Attachment D.

4. **Antibody Testing**

The development of antibodies to protein components of a medical device is a potential safety concern which could affect the effectiveness of the product. Therefore, because of the proteinaceous nature of both the rhBMP-2 and the absorbable collagen sponge (ACS), the development of antibodies was assessed as part of the IDE protocol. Serum samples were taken from each patient preoperatively, to establish their baseline condition, and at three months following surgery. The samples were analyzed for the presence of antibodies specific to rhBMP-2 and bovine Type I collagen (the ACS is derived from bovine collagen). If a patient had a positive response to bovine Type I collagen, the serum was also tested for antibodies to human Type I collagen.

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Assay results are available for 261 patients, 137 open investigational and 124 control, involved in this clinical trial. Preoperative and/or postoperative samples were not available for 18 patients (6 open investigational and 12

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control).⁶



rhBMP-2 Antibody Results

Three patients (two open investigational and one control) had postoperative samples that were positive for antibodies to rhBMP-2 but only two (one open investigational and one control) were considered to be an authentic elevated response. One investigational patient was not considered to have an authentic elevated response since the patient had a positive preoperative antibody and the postoperative sample did not yield a 3-fold increase.

Of the two authentic elevated responses, one occurred in the investigational group (0.7%) and one occurred in the control group (0.8%).

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Bovine Type I Collagen Antibody Results

Antibodies to bovine Type I collagen were detected in the postoperative serum samples of 74 patients.

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34 patients were considered to have an authentic elevated antibody response. The remaining 40 patients had a positive preoperative result without a substantial increase in postoperative titer. Of the 34 patients with an authentic elevated finding, 18 patients (13.1%) were in the open investigational group and 16 patients (12.9%) were in the control group. The rates of occurrence were similar

It is interesting to note that one of the patients who had a positive result had a second postoperative serum sample drawn at approximately one year postoperative. This sample was negative, thus indicating a transient antibody response to the bovine Type I collagen.

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[REDACTED]

None of the patients who tested positive for bovine Type I collagen antibodies had a positive result for human Type I collagen.

Summary

The rates of authentic antibody responses to rhBMP-2 were very low and were very similar for the two treatment groups. In addition, the rates of authentic positive antibody responses to bovine Type I collagen were very similar and not statistically different 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. 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.

5. Integrated Safety Profile

As previously mentioned, there have been three clinical trials involving the use of the InFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device – the pilot trial and the open and laparoscopic pivotal trials. In total, there were 288 investigational patients and 139 control patients who received treatment in these three studies. In order to provide a broader perspective on the use of the investigational device, the adverse event and second surgery information from these studies have been combined and are presented in II.A, Attachment K.

Further, the antibody test results for these three clinical trials have also been integrated to obtain an overall view of the rates. The incidence rates of authentic positive responses to rhBMP-2 antibodies were 0.7% (2/277) and 0.8% (1/127) for the investigational and control groups, respectively. The authentic positive bovine Type I collagen antibody response rates for the investigational group were 18.8% (52/277) and 12.6% (16/127) for the control group [REDACTED]

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It is evident that the combined safety results resemble the information from the pivotal open and laparoscopic arms. It is anticipated that this information will be used in the commercial labeling of the device since approval is being sought for both surgical approach methods of implantation.

As referenced in the introduction of this report, there are other IDE clinical trials which are considered supportive. These trials involve the use of InFUSE™ Bone Graft with other lumbar interbody fusion methodologies, [REDACTED]

[REDACTED] The adverse event and second surgery information pertaining to patients who received InFUSE™ Bone Graft (investigational) from these studies has been combined to provide an even broader perspective. A total of [REDACTED] investigational patients are represented in this summary of supporting clinical trials. These summary tables, which are provided in II.A, Attachment K, show similar results to those from the InFUSE™ Bone Graft/LT-CAGE™ device studies. Further, Attachment K provides additional adverse event and second surgery tables in which the data from the supportive studies have been combined with that from the composite investigational InFUSE™ Bone Graft/LT-CAGE™ device studies. These tables represent information from a total of [REDACTED] patients who were in the InFUSE™ Bone Graft treatment group.

Combining the antibody test results from these supportive studies with the InFUSE™ Bone Graft/LT-CAGE™ device composite results provides an even broader perspective on this issue. The incidence rate of authentic positive responses to rhBMP-2 antibodies was 0.6% [REDACTED] and 0.5% [REDACTED] for the lumbar interbody InFUSE™ Bone Graft and control groups, respectively. The authentic positive bovine Type I collagen antibody response rate for the InFUSE™ Bone Graft was 17.8% [REDACTED] and 14.2% [REDACTED] for the control group [REDACTED]

Antibody results are currently available for [REDACTED] other clinical trials involving rhBMP-2 [REDACTED] in [REDACTED] procedures. In a total of [REDACTED] rhBMP-2 patients tested, there has been an authentic positive rhBMP-

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2 antibody response in one patient and two patients exhibited authentic positive antibody responses to bovine Type I collagen. There have been no authentic positive responses to rhBMP-2 or bovine Type 1 collagen in the control group for these clinical trials.

In addition, antibody results are also available for a clinical trial involving [REDACTED]. The authentic positive bovine Type 1 collagen antibody response rate for the InFUSE™ Bone Graft was 5.6% [REDACTED] and 7.7% [REDACTED] for the control group. There were no authentic positive responses to rhBMP-2 antibodies for either treatment group in this trial.

In all of the clinical trials sponsored by Medtronic Sofamor Danek involving rhBMP-2, none of the patients have had a positive antibody test result for human Type I collagen.

To date, over [REDACTED] patients have received rhBMP-2 in clinical trials sponsored by Medtronic Sofamor Danek. In addition, over [REDACTED] control patients have been enrolled in these studies. In assessing the safety of rhBMP-2, FDA has been particularly interested in adverse events related to cancer and heterotopic bone formation. In all of these study patients, there have been two reports of cancer; one patient in the rhBMP-2 treatment group and one control patient (both in open G960065 trial). The investigational patient is a 79 year old male who was diagnosed with pancreatic cancer eleven months postoperatively. The control patient is a 67 year old female who was diagnosed with breast cancer five months postoperatively. Medtronic Sofamor Danek does not believe either of these events are related to the treatment, either investigational or control.

[REDACTED] there have been several patients reported to potentially have a noticeable amount of posterior bone formation seen on CT scans. However, there does not seem to be a clear correlation between the amount of posterior bone formation and any clinical symptoms. Overall, the control and investigational groups have similar clinical outcomes. Please refer to Attachment II.D.1.b for information

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rhBMP-2 or ACS. Patients who had authentic 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 consequence to positive antibody test results.

Finally, the integrated safety profile information shows that the InFUSE™ Bone Graft/LT-CAGE™ device results are consistent with the safety information arising from the other clinical trials involving rhBMP-2 being sponsored by Medtronic Sofamor Danek.

G. Effectiveness Measurements

The effectiveness variables included assessment of fusion at the involved level, Oswestry pain/disability status, neurological status, back pain, leg pain, graft site pain, general health status, and disc height status. [REDACTED]

[REDACTED]

The results of statistical analyses of the effectiveness outcomes, as well as overall success, between the InFUSE™ Bone Graft/LT-CAGE™ device (open investigational) group and the control treatment group are provided in II.A, Attachment L.

1. Fusion

Fusion of the surgically treated vertebral bodies was determined using CT scans, and A/P, lateral, and flexion/extension radiographs. [REDACTED]

[REDACTED]

At [REDACTED], there were two teams of reviewers assessing the radiographs for fusion. Each team worked independently of the other. If their overall conclusions differed, a third independent reviewer at [REDACTED] was used to adjudicate the findings (break the tie). All reviewers were blinded to treatment group. Information pertaining to the radiographic review procedures was provided in the December 21, 2000 clinical module of the PMA submission.

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The fusion status of study patients was assessed at 6, 12, and 24 months following surgery. To be considered fused, there had to be evidence of bridging trabecular bone spanning the two vertebral bodies in the treated segment. This determination was made with CT scans and radiographs. Additional criteria for fusion utilized radiographs and these included angular motion stability (), translation stability (), and no radiolucent lines covering more than 50% of the implant surface. Also, patients having secondary surgeries due to nonunions were considered as having failed fusions and were included in the fusion calculations.⁷

Table 9 presents the fusion results for the patients in the investigational and control groups at 6, 12, and 24 months following surgery. The fusion rates at all time periods were high for both treatment groups. At 12 months following surgery, the fusion rate of the open investigational group was 96.9% as compared to a 92.6% rate for the control group. At 24 months postoperative, the open investigational group fusion rate was still higher than the control group rate – 94.5% vs. 88.7%. Bayesian statistical analyses showed that the posterior probability of equivalence of the open investigational group to the control group was 100%. The posterior probability of superiority for the open investigational group was 90.2%. Based on these probabilities, the open investigational treatment is substantially equivalent to the control treatment in terms of fusion. Statistical superiority cannot be claimed even though the open investigational group fusion rate is nearly six percentage points higher than the control group rate.

There was extremely good agreement between the two primary radiographic review teams at () in terms of assessing fusion. At 6, 12, and 24 months following surgery, the percent agreement between the two teams all exceeded 98% for both treatment groups. (II.A, Additional Analyses, Appendix A).

⁷ Copies of CT scans and radiographs are included in this submission for a sample of the patients. These copies will include films for several patients who were deemed fusion failures, as well as those for several patients who were fusion successes.

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2. Pain/Disability

The Oswestry Low Back Pain Disability Questionnaire 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 which 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 summing the scores of the individual questions and dividing that total by the maximum possible total score (50 if all questions are answered). This yields 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 open investigational and control patients at the different clinical trial periods are provided in Table 10. At all postoperative time periods for both treatment groups, the mean overall Oswestry scores improved as compared to the preoperative scores. The mean improvement in Oswestry scores were similar at the time periods for both treatment groups. For example, the Oswestry scores for open investigational patients improved from surgery to 24 months by an average 29.0 points as compared to a 29.5 point value for the control group.

Table 11 shows the distributions of patients demonstrating preoperative to postoperative improvements in Oswestry scores of at least 15 points. Similar to the mean improvement scores, the Oswestry success rates were very similar for the investigational and control groups. At 12 months following surgery, the Oswestry success rate for the investigational group was 76.9% as compared to a 75.2% rate for the control group. These success rates were maintained at the 24 month postoperative period. The open investigational group success rate was 73.0% and the control group rate was 73.1%.

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Bayesian statistical analyses for comparing 24 month responses showed that the posterior probability of equivalence of the investigational device to the control was 99.6% and the posterior probability of superiority of the open investigational group to the control group was 51.3%. Based on these probabilities, the open investigational device was shown to be as good as the control in terms of Oswestry pain/disability improvement.

3. Neurological

The neurological status of the patients participating in the clinical trial was assessed preoperatively and postoperatively at every follow-up visit. The neurological status assessment tool addressed motor function, sensory, reflexes, and straight leg raise reproducing pain. An

[REDACTED]

The means of these subsection scores for the treatments groups at the various clinical trial periods are presented in Table 12.

[REDACTED] the postoperative subsection scores were then compared to the preoperative scores and a successful outcome was declared if the postoperative score was greater than or equal to the preoperative score, i.e. maintenance or improvement in condition. Overall neurological measure was the mean score for all four parameters. Overall neurological success

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was based on demonstrating maintenance or improvement, i.e., success, in all four neurological parameters.⁸

Table 13 shows the distributions of patients in the two treatment groups having a maintenance or improvement in conditions following surgery for the various neurological parameters. The overall neurological success rates at all postoperative time periods for both treatment groups were similar.

At 12 months following surgery, the overall neurological success rate for the investigational group was 81.8% as compared to a 84.7% rate for the control group. The 24 month success rates were 82.8% and 83.3%, respectively. Bayesian analyses for comparing the 24 month responses yielded a posterior probability equivalence value of 96.7%. These results indicated that the overall neurological success rate for the investigational group was equivalent to that for the control group.

4. Back Pain

Numerical rating scales were used to specifically evaluate back pain intensity and duration. [REDACTED]

[REDACTED]. A summary of back pain scores is provided in Table 14. The mean back pain scores at all postoperative time periods were less than the preoperative mean values for both treatment groups thus indicating significant status improvement following surgery. In addition, the mean score and mean improvement scores were similar for the two treatment groups.

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Back pain success was determined by comparing the postoperative overall back pain score to the preoperative score on a patient basis. [REDACTED]

[REDACTED]. The distributions of patients with successful outcomes are provided in **Table 15**. At 12 and 24 months postoperative, the investigational group had back pain success rates of 79.1% and 74.6%, respectively. These rates are similar to the respective 72.8% and 78.7% control group rates.

The Bayesian statistical analyses showed that the posterior probability of equivalence of the investigational device to the control at 24 months was 87.8%. Based on this, the back pain success rate associated with the use of the investigational device approached equivalence to that for the control device at 24 months following surgery. Even though equivalence in success rates could not be claimed, the mean improvements in back pain scores from preoperative at both 12 and 24 months were greater for the open investigational group as compared to the control group (**Table 14**).

5. Leg Pain

Leg pain was assessed in a similar manner to back pain using numerical rating scales for pain intensity and duration. A summary of leg pain scores is provided in **Table 16**. The mean leg pain scores for each treatment group were similar and there were significant improvements in condition following surgery.

Leg pain success was evaluated as a function of the preoperative condition of the patient. [REDACTED]

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The distributions of patients with successful outcomes are provided in **Table 17**. At 12 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 72.1% and the control group had a success rate of 72.8%. The leg pain success rate for the open investigational group at 24 months postoperative improved to 80.3% and it was considerably higher than the 74.1% rate for the control group.

The Bayesian statistical analyses showed that the posterior probability of equivalence of the investigational device to the control at 24 months was 99.8% and the posterior probability of superiority was 84.1%. Based on this, the leg pain results associated with the use of the investigational device are equivalent to those of the control device.

6. Graft Site Pain

Control patients had bone graft harvested from their iliac crests for insertion into the LT-CAGE™ 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 hip graft site pain scores is provided in **Table 18**. As expected, the highest level of hip pain was noted by patients shortly after surgery, 12.7 points out of a maximum of 20 points. The pain scores improved over time following surgery. At 24 months postoperative, the mean hip graft site pain score was 1.8.

In addition to graft site pain, the control patients were also asked to evaluate the appearance of the graft site. At the surgery/discharge period, over 56% of the patients indicated that the appearance of the graft-site bothered them some or very much. Over time, the patients became less bothered with the graft site appearance, and at 24 months following surgery, nearly 84% of the patients indicated that the graft

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site appearance did not bother them at all or very little. This finding is expected considering the healing process.

7. General Health

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 to be 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, as well as 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 19** presents the mean scores of the eight SF-36 scales, as well as the PCS and MCS, at various study periods. Higher scores represent higher levels of health.

In terms of the mean PCS and MCS results, all postoperative scores were higher than preoperative scores for both treatment groups. The mean improvements in PCS and MCS scores from preoperative to 12 months following surgery for the investigational group (13.7 and 5.4 points, respectively) were comparable to the values for the control group (11.1 and 8.1, respectively). At 24 months postoperative, the mean improvements in PCS scores for the open investigational and control groups were 14.7 and 12.2, respectively. The respective mean improvements in MCS scores at 24 months were 5.6 and 7.5.

Table 20 presents the proportions 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 rates at 12 and 24 months following surgery for the

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open investigational group were higher than those for the control group (90.8% vs. 80.0% at 12 months and 85.1% vs. 84.3% at 24 months). The Bayesian analyses showed that the posterior probability of equivalence was 98.9%. Based on these probabilities, the PCS results were found to be equivalent for the two treatment groups.

The control group had higher MCS success rates than the open investigational group at both 12 and 24 months postoperative (75.2% vs. 65.4% at 12 months and 70.4% vs. 66.9% at 24 months). The posterior probability of equivalence was 87.3% at 24 months. Therefore, statistical equivalence between the two groups was not demonstrated. The implications of this finding are not disconcerting since many factors other than the treatment contribute to the mental components of the SF-36.

8. Disc Height

Disc height measurements were made from the radiographs.

[REDACTED]
[REDACTED]
[REDACTED] Like fusion assessments, disc height measurements were performed by two review teams at [REDACTED]. If their determinations of disc height success differed, a third reviewer was used to break the tie.

The rates of disc height maintenance or improvement at 3, 6, 12 and 24 months following surgery are presented in Table 21. The disc height success rates at 12 months following surgery were 94.4% and 95.7% for the open investigational and control groups, respectively. These rates were maintained at 24 months postoperative (94.1% and 96.2%, respectively).

Bayesian analyses comparing the open investigational to the control group at 24 months demonstrated posterior probability of equivalence of 99.3%. Therefore, the two treatment groups were found to be statistically equivalent in terms of disc height maintenance following surgery.

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H. Overall Success

Overall success is the primary endpoint for the clinical trial and it is 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, and neurological status maintenance or improvement. Also, to be considered an overall success, a patient cannot have had a serious device associated or device/surgical procedure related adverse event or have undergone a second surgery classified as a "failure". Therefore, this parameter encompasses important safety and effectiveness aspects of the treatment. Table 22 provides this information for the two treatment groups at 6, 12, and 24 months following surgery.

The overall success rates for the open investigational group were virtually identical to those of the control group at all three postoperative periods. At 12 months postoperative the open investigational group and control group overall success rates were 59.7% and 60.8%, respectively. At 24 months postoperative, the overall success rate for the open investigational group was 58.8% as compared to a 56.3% rate for the control group. Bayesian statistical analyses yielded a posterior probability of equivalence at 24 months of 99.4%. [REDACTED]

[REDACTED] The posterior probability of superiority was found to be 51.6%.

Therefore based on these results, the overall success rate at 24 months for the open INFUSE™ Bone Graft/LT-CAGE™ device treatment group was found to be statistically equivalent to the control group rate which indicated the clinical trial objective was met.

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.

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Each question had a series of possible responses ranging from “definitely true” to “definitely false”.

Summaries of the responses to the questions are provided in **Table 23**. At 12 and 24 months following surgery, the results were fairly similar for both the open investigational and control groups, and the 24 month results were at least as good as, if not better than, the 12 month postoperative results for both treatment groups. At 24 months postoperative for the first question, 81.2% of the open investigational patients and 80.4% of the control patients responded either “definitely true” or “mostly true”. For the second question, 74.6% of the investigational and 76.6% of the control patients thought that they were helped as much as expected from their surgeries. Finally, 82.0% of the open investigational patients said that they would have the surgery again as opposed to a 76.7% rate for the control group.

Based on these results, the open investigational patients appear to be at least as satisfied with their procedures as the control group patients.

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 of responses to this question are provided in **Table 24**. At 12 and 24 months following surgery, 67.9% and 70.5%, respectively, of the open investigational patients indicated that they had either “completely recovered” or were “much improved”. These rates were very similar to the 69.3% and 70.1% rates, respectively, for the control group.

3. Doctor’s Perception of Results

At each postoperative visit, the doctors were asked to provide their perceptions of the patients’ conditions. The responses were either “excellent”, “good”, “fair”, or “poor”. The results to this question are provided in **Table 25**. At 12 months following surgery, 82.6% of the doctors responded that the open investigational patients were in “excellent” or “good” condition. This rate is similar to the 86.4% value for

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the control group. At 24 months postoperative, 87.6% of the open investigational and 85.0% of the control responses were either "excellent" or "good". 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 26 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. From Table 26, it is evident that the work status of the open investigational patients appeared to be better than the control patients at most postoperative time periods. Open investigational patients often had higher rates of returning to work, working full time, and working full duty than control patients.

Perhaps, a better way to examine work status is to analyze the number of days from surgery to work return using Kaplan-Meier life table methods. Please refer to II.A, Additional Analyses, Appendix B for the results of such analyses comparing the open investigational and control group. The analyses are presented as a function of preoperative work status. For those patients working prior to surgery, the median return to work time was 63.5 days for the open investigational group as compared to 64.5 days for the control group. These times were not statistically different [REDACTED].

5. Medication Summaries

Summaries of the medications taken by open investigational and control patients at the various study periods are summarized in II.A, Additional Analyses, Appendix C.

6. Intent to Treat

An "intent-to treat" analysis was performed and the results are presented in Table 27. For this analysis, secondary surgery failures, deaths, patients lost-to-follow-up, and missing observations due to other causes resulted in missing observations for the outcome variables and therefore were included in the denominators of the

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calculated rates, i.e., considered as “failures”. By treating these patients as treatment failures, the clinical outcome rates in the intent-to-treat analysis were lower than those observed in the clinical data. Notwithstanding, since the follow-up rates are high at both 12 and 24 months following surgery, the intent-to-treat rates are comparable to the real rates. The open investigational group overall success rate at 12 months is the same as the control group rate. At 24 months postoperative, the open investigational group “intent-to-treat” overall success rate is higher than that for the control group.

7. **Examination of Effectiveness Variables by Investigator**
Information pertaining to the effectiveness results at 12 and 24 months by investigational site is presented in II.A, **Additional Analyses, Appendix D** for the open investigational and control treatment groups. Based on the Breslow-Day results, the results appear to be homogenous across investigational sites.
8. **Financial Disclosure of Clinical Investigators**

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9. Data Listings

Data listings for the open investigational and control patients are provided in II.A, Attachment O.

IV. Conclusions

The goal of the InfUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device IDE clinical trial (G960065) was to evaluate the safety and effectiveness of the open anterior spinal use of the device in the treatment of patients with symptomatic degenerative disc disease as compared to a control implant, the LT-CAGE™ device filled with iliac crest-derived autogenous bone. As demonstrated in this report, the clinical results of the use of the InfUSE™ Bone Graft/LT-CAGE™ device were comparable to the control group results.

The cohorts of patients in the InfUSE™ Bone Graft/LT-CAGE™ device and control treatment groups were similar demographically and medically on a preoperative basis. This enhances one's ability to interpret the effects associated with the different treatments since potentially confounding factors are similar for the two groups.

Patients receiving the open surgical implantation of the InfUSE™ Bone Graft/LT-CAGE™ device experienced shorter operative times and less blood loss during surgery than patients in the control group. These findings for the open investigational treatment group have positive safety implications and are believed to result from not having to harvest bone graft in patients receiving the InfUSE™ Bone Graft.

The InfUSE™ Bone Graft/LT-CAGE™ device was found to be at least as safe as the control treatment. The adverse event rates were comparable to those in the control treatment utilizing the approved LT-CAGE™ device filled with autogenous bone graft. The only adverse event categories in which statistical differences were noted pertained to urogenital and graft site. The rate of urogenital adverse events was higher in the investigational group. The difference in rates is mainly attributable to reports of urinary retention. There is not obvious reasons for this difference, however, the urinary retention events readily resolved and created no long-term medical issues.

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The incidence of graft site adverse events favored the investigational group. This is considered a very positive result since one of the aspects of using InFUSE™ Bone Graft is that it precludes the harvesting of bone graft and, in this case, reduces or eliminates a number of related adverse events.

In addition to comparable adverse event rates, there were no statistical differences between treatment groups for any of the second surgery categories.

The rates of authentic antibody responses to rhBMP-2 and bovine collagen were comparable between the two treatment groups. The authentic antibody response rates to rhBMP-2 for the open investigational and control groups were equal at 0.7%. The antibody response rates to bovine Type 1 collagen were similar for both treatment groups. Patients who had positive antibody responses to bovine collagen were not found to have positive antibody responses to human Type I collagen. Please note, the control treatment did not expose patients to rhBMP-2 or to the ACS. There appeared to be no negative clinical consequences to positive antibody test results.

The integrated safety profile information shows that the InFUSE™ Bone Graft/LT-CAGE™ device results are consistent with the safety information arising from the other clinical trials involving rhBMP-2 being sponsored by Medtronic Sofamor Danek.

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The following table summarizes the effectiveness results from the clinical trial of the InFUSE™ Bone Graft/LT-CAGE™ device.

InFUSE™ Bone Graft/LT-CAGE™ Device	24 Month Results
	Versus Control
Endpoint	Equivalence
Overall Success	✓
Fusion	✓
Oswestry Success	✓
Neurological Success	✓
Back Pain	
Leg Pain	✓
SF-36 Success	
PCS	✓
MCS	
Disc Height Success	✓

As readily evident from the above table, the InFUSE™ Bone Graft/LT-CAGE™ device results at 24 months postoperative were statistically equivalent to the control group results for all effectiveness parameters except for back pain and SF-36 MCS, neither of which are primary effectiveness endpoints. The open investigational group was found to be statistically equivalent for the primary effectiveness endpoints, i.e., fusion and Oswestry success, as well as neurological success, [REDACTED]. The open investigational group fusion rate was nearly six percentage points greater than the control group rate at 24 months and the rate approached statistical superiority at 90.2%. More importantly, the overall success rate for the open investigational group was statistically equivalent to the control group rate, thus satisfying the primary study objective. [REDACTED]

Therefore, based on these results, it can be concluded that the InFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device is safe and effective in the surgical treatment of symptomatic degenerative disc disease of the lumbar spine, and that the data and information presented in this PMA application provide a reasonable assurance of the safety and effectiveness of the device.