
PANEL PACKET PMA SUMMARY MEMORANDUM

To: File

From: Aric Kaiser, Expert Biomedical Engineer
ODE/DGRND/REDB

Date: December 3, 2001

RE: P000058 - Medtronic Sofamor Danek's InFUSE™ Bone Graft/LT-Cage Lumbar Tapered Fusion Device

This is a summary memo which serves as an overview to the data presented in the PMA and the issues raised during the review process. The summary memos may contain excerpts from the reviews performed by others involved in this project that are not included as part of the Panel packet. These efforts by these other reviewers is acknowledged below:

device description and preclinical mechanical testing

Erin Keith, CDRH

growth factor/carrier preclinical and safety(toxicology) testing

Angel Torres-Cabassa, CDRH

Sergio Gadalca, CDRH

Kevin Lee, CDRH

Tracey Bourke, CDRH

Nirmal Mishra, CDRH

Peter Hudson, CDRH

Josie Yang, CDER (on temporary assignment to CBER during the review of this submission)

Mercedes Scrabian, CBER

Barbara Wilcox, CBER

John Hill, CBER

Gary Kikuch, CBER

clinical data

Martin Yahiro, CDRH

Barbara Buch, CDRH

statistical analysis

Telba Iron, CDRH

manufacturing/GMP compliance

Carol Arras, CDRH

Carol Rehkopf, CBER

labeling

Mary Ann Wollerton, CDRH

bioresearch monitoring (BIMO)

Pam Reynolds, CDRH

Device description

The submitted device is a three component combination product. It consists of a growth factor, a carrier and a metallic spina fusion cage.

The growth factor is rhBMP-2 manufactured by Genetics Institute (GI). They have applied for a "drug" name (dibotermun alfa) for this device component. This device component is manufactured using cloning techniques. Human BMP-2 is secreted from Chinese hamster ovary cells. The rhBMP-2 is collected, purified and processed to form the final product. This device component was provided in a single "dose" - 1.5mg/ml.

The carrier is a bovine collagen sponge known as the ACS (absorbable collagen sponge) device. It is currently marketed under a PMA (P850010) as Helistat, a hemostatic agent, by Integra LifeSciences Corporation. This device component is manufactured from bovine tendon that has been mechanically cleaned and sliced. It is then enzymatically inactivated and formed into "sponge" blocks. These blocks are crosslinked to form a matrix, cut to the desired size and sterilized with EtO.

These two device components are contained within a single carton, but are packaged separately. Each device component is contained within its own sterile packaging. The ACS component contains only the ACS sponge. The rhBMP-2 component consists of two vials and syringes. One vial contains sterile water and the other contains the dehydrated growth factor. At the time of surgery, the growth factor is rehydrated by mixing it with the provided water. Using the syringes, this solution is then applied evenly to the ACS which is then placed/molded into the fusion cage. For the clinical trial that forms the basis of the clinical data in this PMA (and as proposed for distribution in the PMA), these device components were provided as follows:

- 1 vial with rhBMP-2 ([REDACTED])
- 2 ACS, 1 x 2" ([REDACTED])
- 1 vial with sterile water ([REDACTED])
- 1 5ml syringe
- 1 20g 1½" needle
- instructions for preparing BMP solution and ACS

The metallic (Ti alloy, ASTM F136) spinal fusion cage has been referred to by a number of names, the last IDE name being the LORDOTEC Interbody Fusion Device. The name of this component of the device system has been changed to LT-Cage Lumbar Tapered Fusion Device in this PMA. This device component was originally approved for marketing in P970015/S¹¹. The only difference in intended use between the device approved in that PMA supplement and the device component in this PMA is related to the material placed into the cage for the formation of a fusion mass. The device approved in P910015/S¹⁰ is intended to be filled with autograft bone. The device component in this PMA is intended to be filled with the rhBMP-2/ACS device components. The fusion cage component is available in the following sizes:

P dia x A dia x L (x width across "flats")	part #
14 x 17 x 20 (x 12mm)	8941420
[REDACTED]	[REDACTED]
14 x 17.5 x 23 (x 12mm)	8941423
16 x 19 x 20 (x 14mm)	8941620
16 x 19.5 x 23 (x 14mm)	8941623
16 x 20 x 26 (x 14mm)	8941626
18 x 21.5 x 23 (x 16mm)	8941823
18 x 22 x 26 (x 16mm)	8941826

*The sponsor does not report this dimension in their device description.

[REDACTED]

The submitted combination device works through osteoinduction. The rhBMP-2 binds to the local mesenchymal cells causing them to differentiate into cartilage and bone-forming cells. As the ACS component is resorbed, trabecular bone is formed. This occurs from the outside of the sponge towards its center. During this process, the ACS component keeps the rhBMP-2 at the fracture repair site. From the preclinical evaluations, the sponsor has been able to demonstrate that the rhBMP-2 remains bioactive after it has been applied to the ACS. Through washout studies, the rhBMP-2 has been shown to remain bound to the ACS. Over a 2 week period, the BMP has also been shown to diffuse out of the ACS. During both of these evaluations, the sponsor did not note any altered bioactivity.

Review of preclinical data

See the summary memo from Peter Hudson (PLH) for a more detailed discussion of these topics. In addition, the summary memo from Barbara Buch (BDB) contains information related to the clinical aspects of antibody formation.

Because this device system contains biologically-derived components, there are numerous concerns that would not be present for the use of the fusion cage component by itself or for "typical" orthopaedic devices, e.g., immunological response, ability to signal tissue formation, dosage, etc. As a result, the sponsor was required to perform numerous tests to characterize the device system. The majority of these tests were provided as part of the IDE for this study or included as a reference to other IDEs.

Because the fusion cage component of the device system had already received PMA approval, there were no major issues that had to be addressed for this device component in the preclinical module. The few deficiencies that were submitted to the sponsor related to clarification of information or appropriate references to other submissions, e.g., P970015/S¹⁰. All of these issues were satisfactorily addressed in the preclinical module.

The primary safety concern with the device system is related to preclinical safety information and the potential for an immunological responses. This broad concern may be broken into several, more focused clinically-based concerns:

1. the potential impact of an immunological response on adverse events;
2. the potential impact of the presence of rhBMP-2 on carcinogenicity and tumorigenicity; and
3. the potential impact of the presence of rhBMP-2, rhBMP-2 antibodies and rhBMP-2 neutralizing antibodies on women of child-bearing potential, reproduction and fetal development.

It is important to note that these concerns are not based on any adverse events reported during the use of the device under review. While antibody assays were performed on all enrolled subjects, no adverse events related to these concerns were reported, e.g. birth defects or cancer. These concerns are based on the contention that such events are possible as a result of data provided by GI in their preclinical testing summary and by non-clinical studies reported in the literature that indicate the potential for these concerns exists.

The sponsor has provided a complete analysis of the adverse events seen in the clinical trial. They have evaluated the correlation between the presence of an authentic antibody response and the type and rate of adverse events. In addition, they have evaluated the correlation between the presence of an authentic antibody response and a subject's overall clinical success. From these evaluations, there did not appear to be a connection between the antibody response and the adverse events (type or rate) and the clinical success. This analysis is not definitive, however, due to the number of subjects exposed to the growth factor and the current duration of follow-up. Because of these factors, it might be reasonable to consider some type of labeling precaution related to the potential unknown impact of antibodies.

As part of their evaluation of the rhBMP-2 device component, it was necessary for the sponsor to address the carcinogenicity and tumorigenicity of this protein. Our concern was based on two factors. The first is the ability of the growth factor to induce tumors as part of its normal action of creating bone. This is related to a concern of ectopic bone formation that was expressed during the IDE reviews. The second is the ability of the growth factor to enhance the growth of pre-existing, but "dormant" tumors. The sponsor was able to address the first concern through the current set of preclinical animal tests summarized by PLH. In addition, the clinical data (IDE pilot studies, etc.) did not demonstrate the presence of bone formation away from the implantation site. While the second issue has been discussed with the sponsor and GI, this issue has not been definitively addressed. Based on input from several preclinical reviewers, we have requested that the sponsor perform some additional *in vitro* (cell and tissue) and *in vivo* (animal) studies. These studies were requested in the major deficiency letter and are discussed in PLH's summary memo. FDA believes that these studies may be performed as part of the post-approval requirements.

As part of the clinical protocols, the sponsor was required to monitor the pre- and post-op levels of antibodies to rhBMP-2, type I bovine collagen and type I human collagen. Additional information related to validation of the assays was requested as part of the major deficiency letter and submitted by the sponsor. We have also requested development of additional assays. FDA believes that these assays may be developed as part of the post-approval requirements.

The remaining issue is related to the impact of antibodies on women of child-bearing potential and a developing fetus. This issue has been raised as a result of reports in the literature related to teratogenicity in the absence of various growth factors. While no birth defects or pregnancy problems have been reported specifically with the submitted device, this remains a concern with the general class of growth factor-containing devices. The agency has discussed and suggested the use of a pregnancy registry with the sponsor as an aid to monitoring this. Additional measure, such as labeling might also be appropriate. The specific format of this labeling will need to be discussed as part of the Panel deliberations. For example, would warnings and/or precautions be sufficient or would a contraindication against women of child-bearing potential potentially be necessary.

Review of clinical data

See the summary memos from Barbara Buch (BDB) for a more detailed discussion of the clinical data and from Telba Irany (TZI) for a more detailed discussion of the statistical analyses.

General IDE and IP info

The clinical data for this PMA were collected under an FDA-approved IDE. The IDE contained a feasibility phase and a pivotal phase. The pivotal trial contained 2 arms – an open approach ALIF arm and a laparoscopic approach arm. The open

arm was randomized and used the tapered cage filled with iliac crest allograft as the control. The scope arm was not randomized and did not have its own control. The data from this arm were compared to the open control data. The limits were 16 open sites with 135 subjects per group (270 total open subjects) and 15 scope sites with 135 total subjects. This was subsequently modified to allow a termination of open enrollment when 300 total subjects or 135 per group were reached. No changes were made to the scope group limits.

Neither the investigators nor the subjects were blinded to the treatment. Subject blinding was not possible due to the second surgical site resulting from the need to collect iliac crest grafts. Subject outcome was assessed through objective self-assessments, thereby removing the potential for investigator bias. The independent radiologists were blinded to treatment. Only their radiographic evaluations were used for determining radiographic success.

The nominal indication was ddd (degenerative disc disease) at L₄-S₁ with the following inclusion/exclusion criteria:

inclusion

- ddd with one or more of the following:
 - instability (angle [redacted] and/or translation [redacted] on F/E radiographs)
 - osteophyte formation
 - decreased disc height
 - ligamentous thickening
 - disc degeneration/herniation
 - facet joint degeneration
- pre-op Oswestry \geq 35
- spondylolisthesis no more than grade I
- single level disease between L₄ and S₁
- non-responsive to non-operative treatment for at least 4 months

exclusion

- previous anterior fusion at involved level
- posterior instrumentation at involved level

clinical and radiographic outcome parameters that were evaluated

The sponsor evaluated numerous primary and secondary clinical and radiographic outcome parameters:

- | | |
|---------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| primary clinical outcome parameters | <ul style="list-style-type: none"> • Oswestry Low Back Pain Questionnaire for pain and function • neuro • overall success |
| primary radiographic parameter | <ul style="list-style-type: none"> • fusion (plain films and CT) |
| secondary clinical outcome parameters | <ul style="list-style-type: none"> • antibody testing (rhBMP-2, bovine type I collagen and human type I collagen) <p>All subjects had serum evaluations [redacted]. If the evaluation for bovine type I collagen was positive, an assay for human type I collagen was also performed. An authentic antibody response was said to exist if:</p> <ol style="list-style-type: none"> 1. [redacted] 2. [redacted] <ul style="list-style-type: none"> • back pain (composite of intensity and duration) • leg pain (composite of intensity and duration) • donor site pain/appearance (for control subjects only) • SF-36 PCS • SF-36 MCS • subject satisfaction with procedure/outcome <ul style="list-style-type: none"> Q1 - are you satisfied with outcome?, Q2 - were you helped by procedure?, Q3 - would you do it again? • subject global perceived effect ("completely recovered" vs. levels of improvement or no improvement) |
| secondary radiographic parameter | <ul style="list-style-type: none"> • disc height |

Incidences of second surgical interventions and serious adverse events were also included as part of the evaluation of individual subject success. The sponsor also evaluated the investigator's perception of success ("excellent", "good", "fair", "poor") and the subject's post-op work status (if previously employed - ability to return to work and time until return to work).

success/failure definitions

The original PMA submission proposed to base safety and effectiveness primarily on evaluations of 12 month data and used Bayesian statistical models to predict the 24 month clinical outcome. Ultimately, the final dataset submitted for review (and discussed by BDB and TZI) bases its demonstration of safety and effectiveness on 24 month clinical outcome data.

Primary effectiveness included an evaluation of radiographic fusion, the Oswestry pain/disability questionnaire and neurological status. In order for a subject to be considered a success, fusion had to be present, Oswestry score had to be maintained and neuro status had to be maintained or improved. Subjects also had to not experience adverse events or second surgeries that had been defined as failures. Safety was evaluated by an analysis of the rate and type of adverse events and second surgeries. The presence of antibody and radiographic comments, e.g., the presence of heterotopic bone formation, were also taken into consideration. Secondary parameters included back pain, leg pain, donor site pain, disc height, general health status and patient satisfaction.

The sponsor performed a statistical analysis which evaluated equivalence and superiority of various variables. The primary assessment was an equivalence analysis of the proportion of subjects who were considered as overall successes. Non-informative, uniform priors were used to obtain the posterior probabilities for equivalence and superiority. For the evaluation of Oswestry pain/function data and overall success, [REDACTED] for the evaluation of all other endpoints.

fusion success presence of all of the following:

1. evidence of trabecular bridging in at least one area [REDACTED]. If not visible on plain films, CT scans were used to assess this parameter.
2. no motion, as defined by [REDACTED] translation on flex/ex films and [REDACTED] angulation on flex/ex films
3. no radiolucencies around more than 50% of either cage

Oswestry success improvement by at least 15 points from baseline (pre-op)

neuro success maintenance or improvement compared to baseline (pre-op)

disc height success maintenance or improvement in height compared to baseline (6 week radiographs)

SF-36 success $PCS_{post-op} - PCS_{pre-op} \geq 0$
 $MCS_{post-op} - MCS_{pre-op} \geq 0$

back pain success [REDACTED]

leg pain success [REDACTED]

subject satisfaction success

only those responses rated as "definitely true", "mostly true" or "yes"

subject global perceived effect success

only those responses rated as "completely recovered", "much improved" or "slightly improved"

investigator's perception of results success

responses of excellent or good

site/investigator and financial disclosure info

The open study was performed at 16 sites with 36 investigators. The lap study was performed at 14 sites with 24 investigators. The sponsor provided an analysis which compared the success rates of investigators who had a financial interest in the sponsor to those who did not. The investigators with financial interests did have a higher success rate. This may not be as important as it first appears because many of the clinical outcome parameters involved subject self-assessments and all of the radiographic assessments were performed by an independent examiner.

Antibody evaluations

A certain number of subjects in all groups had authentic positive responses to both rhBMP-2 and bovine type I collagen antibodies. No subjects had authentic positive responses to human type I collagen antibodies. There did not appear to be a correlation between positive antibody response and successful clinical/radiographic outcome. At this point it is difficult to state this definitively because of the relatively small populations and "short" follow-up duration.

Reference to other studies for additional safety info

In addition to the safety data generated from the IDE used to support this PMA, the sponsor has also provided safety information from other studies that they are currently running that utilize the rhBMP-2 device component. These other studies are of various types, [REDACTED]

Because of the differences in the device systems being studied, direct comparisons cannot be made. [REDACTED]

The provided data can only be used to increase the scope of the type and rate of adverse events reported for device systems which contain the rhBMP-2 device component.

Use of plain films and CT scans in the assessment of fusion

In previous studies of spinal fusion cages, determinations of radiographic success, e.g., the presence of bridging trabecular bone, have been based solely on an evaluation of plain films. In this study, the sponsor added the use of CT scans at the 6, 12 and 24 month follow-up evaluations. Their belief was that it might be possible to detect fusion on CT scans in the absence of signs of fusion on plain films. [REDACTED]

FDA believes that this study was able to demonstrate that in the presence of autograft bone, the CT scans provided a useful set of supplementary information to that provided by plain films. The sponsor has not provided a similar analysis when the rhBMP-2/ACS device components were present. We believe that this type of complementary analysis is necessary due to the possible behavior differences between the investigational and control graft materials.

It is our belief that the changes that occur in autograft bone during the fusion mass "solidification" process were sufficiently understood by the investigators and independent radiologist to allow for accurate fusion assessments. The basis for this belief is that they have the most experience interpreting the radiodensity changes that are expected to occur for autograft bone over time. In the case of the investigational groups, however, the radiodensity changes as the rhBMP-2/ACS is converted to bone may be very different. The progress of fusion, i.e., the rate and characteristics of the radiodensity changes, in the initial absence of bone are probably not fully understood and may be very different from those expected in the presence of autograft bone. This lack of understanding could have an impact on the correct interpretation of fusion from the plain films and CT scans in the investigational subjects (See the summary memo from BDB for a discussion of this issue.)