Sponsor's Executive Summary

DIAM® Spinal Stabilization System

P140007

Orthopaedic and Rehabilitation Devices Panel of the Medical Devices Advisory Committee

Table of Contents

1. INTRODUCTION

The subject of this Executive Summary is the DIAM Spinal Stabilization System premarket approval (PMA) application, P140007. The DIAM implant is designed for the treatment of symptoms of moderate low back pain secondary to degenerative disc disease.

This Executive Summary outlines the clinical study data presented in support of the PMA application for the DIAM Spinal Stabilization System device. In brief, a prospective, randomized, multi-center, concurrently controlled clinical study was conducted to compare the DIAM device to the control, a defined regimen of conservative care, the standard of care for this population. The study was executed under FDA oversight with an approved Investigational Device Exemption (IDE). From the patients who met eligibility requirements, 181 subjects were treated with the investigational DIAM device, and 101 patients were treated with the conservative care control treatment. A FDA-approved interim analysis was performed with the first 150 randomized subjects (97 investigational and 53 control subjects). The primary endpoint, overall success, which included measures of both safety and effectiveness, was evaluated at 12 months, with annual follow-up continuing until at least 24 months after the initial treatment. The clinical data demonstrate that the DIAM device was statistically superior to the conservative care control treatment in the primary composite endpoint that combines safety and effectiveness outcomes. In addition to the interim analysis dataset including the first 150 subjects, all available data on the 181 subjects treated with the DIAM device and the 101 control subjects were also summarized and demonstrated similar results. The study had a crossover component that permitted control subjects to elect to receive a surgical treatment after six months of failed conservative care; results for subjects who crossed over to receive the DIAM device were also summarized and presented.

In addition to the primary outcome data, this Executive Summary presents the results of additional effectiveness endpoints, radiographic observations, and safety data. Non-clinical data in support of the device is also summarized. Further, this summary provides the results of additional exploratory analyses conducted at the request of FDA.

The Executive Summary concludes with a discussion of the benefit-to-risk comparison for the DIAM device when used to treat symptoms of moderate low back pain secondary to degenerative disc disease.

2. SUMMARY

The DIAM Spinal Stabilization System is a spinal implant designed for the treatment of moderate low back pain secondary to degenerative disease. This device is implanted by minimally invasive methods. The device is intended to alleviate pain through the reduction of stresses on a painfully overloaded posterior disc and facet joints, while the segmental stability is enhanced by re-tensioning of the supraspinous ligament and other ligamentous structures. The DIAM device does not eliminate motion at the operated segment, and it was designed to treat patients that have not progressed down the degenerative disc disease continuum sufficiently to warrant more complex

invasive procedure such as a disc replacement or fusion. Currently, the only appropriate treatment option for these patients is continued conservative care.

Study Design

This pivotal trial had a multicenter, prospective, randomized, controlled study design. Since the trial design compared a surgical treatment to a nonsurgical treatment, blinding of either subjects or investigators was impossible. Subjects were randomized at a 2:1 ratio into investigational and control groups; those randomized to control, if not improving after a minimum of six months of conservative care and otherwise meeting the criteria defined in the protocol, were permitted to undergo surgical treatment as indicated in the opinion of the investigator. Based on a slower than expected enrollment rate, an interim analysis was added during the study following discussion with and approval of the FDA. This led to an increase in the probability criterion for assessing superiority, i.e. a more stringent criterion. The primary analysis cohort which is the focus of this interim analysis includes the first 150 study subjects who had passed the12-month evaluation with at least one evaluable overall success status at or after 6 weeks.

Summary of Results

Primary Objective - Overall Success

Overall success at 12 months post-treatment in the primary analysis dataset was observed in 63.9% of subjects in the investigational group as compared to 15.1% of subjects in the control group. Bayesian analysis demonstrated that for overall success, the posterior probability of the investigational treatment being superior to the control treatment was approximately 100%. Similar results were observed in the per-protocol dataset.

Efficacy Results

In the primary analysis dataset of 150 subjects, treatment with the DIAM device was demonstrated to be, by every measure, consistently more effective than nonoperative care. At 12 months, ODI success was observed in 69.1% of subjects in the investigational group as compared to 17.0% of controls, back pain success by 89.7% of investigational subjects as compared to 45.3% of controls, and leg pain success by 72.2% and 28.3%, of investigational and control subjects, respectively. Success was observed in 87.6% of investigational subjects and 45.3% of the control group for SF-36 PCS at 12 months. Bayesian analyses additionally demonstrated that for all four of these efficacy outcomes, the posterior probability that the investigational treatment was superior to the control treatment was approximately 100%, a conclusion also reached for ODI scores, back and leg pain scores and SF-36 PCS scores (continuous measurements). Moreover, a much larger percentage of investigational subjects viewed their treatment (with the DIAM device) as successful than did the control subjects provided with conservative care, an opinion shared by investigators (who provided both treatments). Similar results were observed in the per-protocol dataset. The vantage observed by treatment with the DIAM device, moreover, was not limited to statistical superiority,

but was accompanied by substantial, clinically meaningful benefits associated with treatment with the DIAM device.

Safety Results

The percentages of subjects experiencing adverse events within 12 months were respectively 87.6% and 75.5% in the investigational group and the control group. The 95% HPD for the difference in adverse events rates between the investigational and the control group was (-3.0%, 23.9%), suggesting that the rates were not statistically different between the two groups. For adverse events that were serious, of grade 3 or 4 severity, and/or treatment related, observed rates were numerically either similar or lower in the investigational group than in the control group. While no statistical comparison was carried out between treatment groups with regard to the secondary surgery rate, the rate of additional surgery at the index level through 12 months in the investigational group was observed to be 13.4% while the treatment surgery rate at the index level in the control group was 54.7%, with 43.4% of the total number of primary analysis dataset subjects crossing over to be implanted with DIAM device. Neurological success rates at 12 months were 86.6% and 84.9% in the investigational group and control group, respectively; Bayesian analysis demonstrated that rates were not statistically different in the two treatment groups. The DIAM Spinal Stabilization System was therefore demonstrated to be comparable to the control treatment in terms of safety.

3. BACKGROUND INFORMATION

3.1 Applicant's Name and Address

Medtronic Sofamor Danek USA, Inc.
1800 Pyramid Place
Memphis, TN 38132

3.2 Device Description

The DIAM Spinal Stabilization System device consists of 3 main components: the H-shaped interspinous process spacer, the spinous process cables, and the cable crimps. The spacer is implanted between two adjacent spinous processes, each cable is looped around a spinous process, and the crimps are used to secure the ends of the cables. Each spacer is packaged with two cables and two crimps. Two channels are molded through each spacer portion to allow the two cables to be threaded through the spacer. The device is packaged with the cables preloaded into the spacer.

The cable is manufactured from a multitude of high tenacity polyester (Polyethylene Terephthalate or PET) fibers. A small open "eye" is spliced into one end of the cable, and a curved needle is swaged onto the other end. The curved needle is used for passage of the cable around the spinous process; it is then passed through the eye end of the cable to form a complete loop and to secure the construct to the spinous process.

The crimp is used to secure the cable loop. The crimp is manufactured from Type 2 commercially pure titanium. The crimp is locked in place by compressing its diameter using a crimper tool similar to a pair of pliers.

The spacer component is manufactured from a core of stiff, highly resilient Silicone (NuSil MED 4765) and is covered by a woven polyester cover of the same material as the cable. The spacer is in a generally H-shaped configuration with the legs of the "H" extending on each side of the spinous processes between which it is placed.

The implants do not contain any color additives.

The DIAM device is manufactured in 4 sizes: 8, 10, 12, and 14 mm. The cables and crimps remain the same regardless of spacer size. Unimplanted and implanted images of the DIAM device are shown in Figure 3.1.

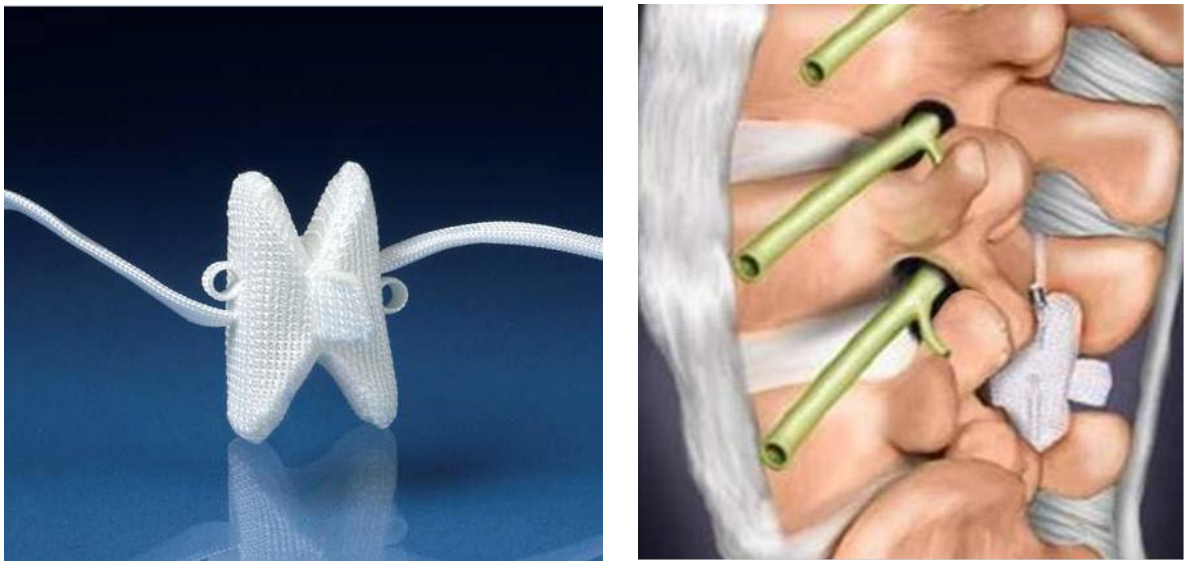

Figure 3.1: Representative images of DIAM device.

4. INDICATIONS FOR USE

The DIAM Spinal Stabilization System is indicated for skeletally mature patients that have moderate low back pain (with or without radicular pain) with current episode lasting less than one year in duration secondary to lumbar degenerative disc disease (DDD) at a single symptomatic level from L2-L5. DDD is confirmed radiologically with one or more of the following factors: 1) Patients must have greater than 2mm of decreased disc height compared to the adjacent level, 2) scarring/thickening of the ligamentum flavum, annulus fibrosis, or facet joint capsule or 3) herniated nucleus pulposus. The DIAM device is implanted via a minimally invasive posterior approach.

5. CONTRAINDICATIONS

The DIAM Spinal Stabilization system should not be implanted in patients with the following conditions:

- Congenital or iatrogenic posterior element insufficiency (e.g., facet resection, spondylolysis, pars fracture or Spinal Bifida Occulta);
- Arachnoiditis;
- Sequestered herniated nucleus pulposus;
- Motor deficit of the lower extremity;
- Cauda equina syndrome;
- Previously diagnosed with clinically significant peripheral neuropathy;
- Significant vascular disease causing vascular claudication;
- Ventral spondylolisthesis with more than 2mm of translation at the involved level;
- Evidence of prior fracture or trauma to the L1, L2, L3, L4 or L5 levels in either compression or burst;
- Lumbar scoliosis with a Cobb angle of greater than 15°;
- Lumbar kyphosis or flat back syndrome;
- Documented allergy to silicone, polyethylene, or titanium;
- Active systemic infection or infection at the operating site
- Osteoporosis defined as a DEXA bone mineral density T-scores less than -2.5;
- Osteopenia defined as a DEXA bone mineral density T-scores between -1 and -2.5; and
- Symptoms attributed to more than one lumbar level.

6. REGULATORY AND MARKETING HISTORY

In the United States, the DIAM Spinal Stabilization System device has only been used under an Investigational Device Exemption (IDE). A slightly modified design of the device has a marketing history outside the United States that began in 1997. The device is now available on six continents and in over 50 countries worldwide. The device has not been withdrawn from marketing for any reason.

Table 6.1 is a list of countries in which DIAM Spinal Stabilization System device is currently marketed.

Table 6.1: Global distribution.

Argentina	Greece	Romania
Australia	Hungary	Russia
Austria	India	Saudi Arabia
Belarus	Ireland	Serbia
Belgium	Israel	Singapore
Brazil	Italy	Slovakia
Canada	Kazakhstan	Slovenia
Chile	Latvia	South Africa
Costa Rica	Lithuania	South Korea
Croatia	Malaysia	Spain
Czech Republic	Mexico	Switzerland
Denmark	Netherlands	Taiwan
Ecuador	Panama	Thailand
Estonia	Peru	United Kingdom
France	Philippines	Venezuela
Germany	Poland	Vietnam
	Portugal	

Outside the United States, the DIAM device has a broader indications for use statement. However, two publications by Buric et al. describe the specific use of DIAM in the setting of treatment for DDD. The publications describe the 2 and 4 year follow-up results of a single-arm cohort study (N=52) using DIAM alone to treat subjects with DDD.[1,2] In the reports from Buric et al., the success was determined by clinically meaningful improvement (≥ 30%) based on the Roland Morris Disability questionnaire, and no secondary surgery; approximately 81% and 79% of DIAM subjects were considered successful at 24 and 48 months, respectively. Within the reports from Buric et al., three subjects had device migration due to inadequate securing of laces and one had damage to the implant due to a traumatic event. Two subjects had secondary surgery at other levels. The DIAM IDE study and the studies reported by Buric et al. have a similar patient population treated with DIAM alone, and provide qualitatively similar clinical evidence from greater than 2 years of follow-up that support the reasonable assurance of safety and effectiveness of the DIAM device.

7. UNDERLYING DISEASE STATE

7.1 Societal Impact

Low back pain affects nearly every population in the world.[3] Degenerative disc disease (DDD), the leading cause of low back pain,[4] is the most common cause of chronic pain in the adult population.[5] The estimate of lifetime prevalence in the US reaches as high as 90%.6 Low back pain resulting from DDD can be catastrophic to the lives of the individuals affected, creating a substantial health burden and having a profound impact on the income, social interaction, quality of life, and overall health of its sufferers.

The 2010 Global Burden of Disease study identified low back pain as the leading cause of global disability (ranked first of 291 disabling conditions).[7] Examination of results from this study shows the overwhelming impact of low back pain on affected patients. An estimated 671.1 million days are lost to bed rest in the US annually due to back pain,[8] and approximately 200 million work days are lost each year.[8] Low back pain can also dramatically affect social function,[9] interpersonal relationships9, and sexual function.[10] As the leading cause of work-related disability, the impact of low back pain on patient income and financial self-reliance can be devastating.[3]

In addition to lost time, expenditures related to low back pain are substantial. The direct care of spinal disorders cost an estimated $193.9 billion in 2004.[8] As the leading spine-associated reason for doctor's visits and second most frequent reason overall, low back pain accounted for the preponderance of these expenditures, a figure borne out by a 2006 study[11] that estimated total costs of low back pain to be between 100 and 200 billion dollars per year. In addition, costs of low back pain in the US have rapidly increased – by one estimation, 38% from 1997 to 2005.[12] Due to the increasing demand on healthcare resources throughout the world and profound consequences for those afflicted, the problem of low back pain has been deservedly called the world's most important public health problem.[3]

7.2 Low Back Pain and Degenerative Disc Disease

Back pain may originate from any number of structures in the lumbar spine and surrounding tissues. The source of low back pain, a symptom common to a multitude of pathologies, is often difficult to identify.[2] While the facet joint capsules and annulus fibrosus are likely pain generators, low back pain may be triggered by several other structures, as well as multiple structures simultaneously.[2]

Haldeman, Kirkaldy-Willis, and Bernard discuss in detail the physiology of low back pain and the spinal degenerative process. They describe the degenerative cascade as disrupting the function of the "three-joint complex," most commonly at L4/L5.[13] A common term used to describe this degenerative cascade is degenerative disc disease (DDD). The first, or inciting, event that starts the DDD cascade is often not known, but it can be caused by age-related changes, recurrent rotational strains, minor compressive injuries, or genetic predisposition. Figures 7.1 and 7.2 show a spine affected by DDD and the DDD cascade, respectively. Please note that images are for illustrative purposes only related to the DDD cascade and do not necessarily correlate to a patient's severity of symptoms.

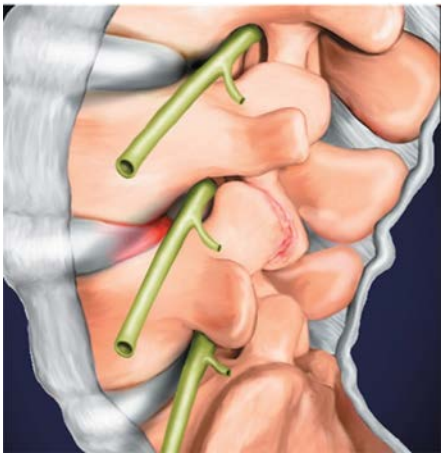

Figure 7.1: Degenerative disc disease in the spine.

Regardless of what initiates the process, what follows are degenerative events that lead to disc desiccation and circumferential or radial tears in the annulus fibrosus. Over time, these may increase in size to larger fissures that disturb the disc structure, often causing pain due to innervating nerve endings distributed throughout its surface[14]. In addition to the potential for annular pain, disruptions in the annulus may allow for the release of inflammatory proteins from the nucleus pulposus. These proteins are irritating to surrounding neural structures[15] and can be an additional source of back pain as well as leg pain due to radiculitis.

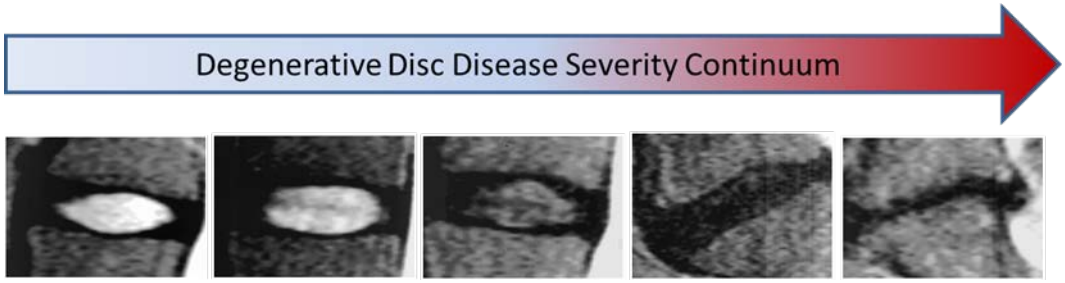

Figure 7.2: Degenerative disc disease cascade in the spine.

In response to the continued damage and tearing of the annulus, the chemical composition of the nucleus pulposus changes, resulting in a decrease in proteoglycan content and subsequent further loss of disc hydration.[1,16] As a result of these morphologic changes, chemical sequelae, and disc desiccation, the viscoelastic properties of the disc are diminished, leading to altered disc function and loss of disc height and volume.[1,2,13,17] Normal, non-degenerated discs serve the purpose of uniform load distribution across the disc and surface of the endplates.[18] However, as the degenerative cascade disrupts the biomechanics of the previously-described "three-joint complex," abnormal patterns of loading may become more focal, causing low back pain that is often aggravated by posture and spinal positioning.[1,18,19,20] The altered disc morphology (e.g., disc height loss, dehydration, and annular fissures) can lead to secondary herniated discs and mal-alignment of the facet joints, which can lead to facet joint degeneration.[18] Due to inadequate contact

between articular surfaces, facet joint degeneration also contributes to pain, and eventually, this degeneration may cause arthritic changes, osteophytes, and hypertrophy of the joints.[1,2,13,17] The loss of disc height and narrowing of the intervertebral space may also lead to a laxity of both ligaments and the annulus fibrosus, allowing anomalous, non-physiologic motion between vertebrae.[1,18] Narrowing of the disc, together with the hypertrophy of facet joints, can induce compression of neural and vascular elements.[1,2,13,17] Therefore, degenerative disc disease should be thought of as a multifactorial and often non-reversible condition with the pathologic changes within the disc resulting in abnormal load transmission patterns across multiple structures, including the posterior disc, the disc annulus, and the facet joints.[1,20]

7.3 Treatment Options

7.3.1 Conservative Care

For the majority of low back pain sufferers (i.e., those with early disease or mild symptoms), pain most often resolves spontaneously or in response to conservative care.[21] Patients with moderate symptoms that do not resolve satisfactorily on their own in a reasonable amount of time are often, but not always, treated successfully with more aggressive nonsurgical treatments. These may include physical therapy, analgesic medications, chiropractic care, and/or spinal injections.[2,22] Figure 7.3 shows conservative care treatment in the DDD care continuum.

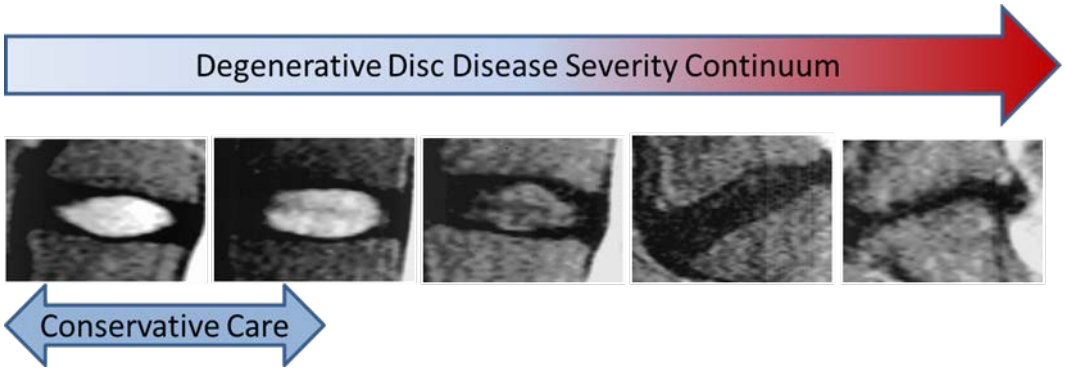

Figure 7.3: Conservative care treatment in the degenerative disc disease.

7.3.2 Currently Available Surgical Treatment Options

On the other end of the spectrum are the patients who experience continued debilitating low back pain, progress to severe symptoms, and enter into the end-stage processes of DDD. These patients often experience severe pain, with constant impact on work and activities of daily living. As a result, they often become reliant upon ever-increasing dosages of narcotics, which can lead to depression and drug dependence.

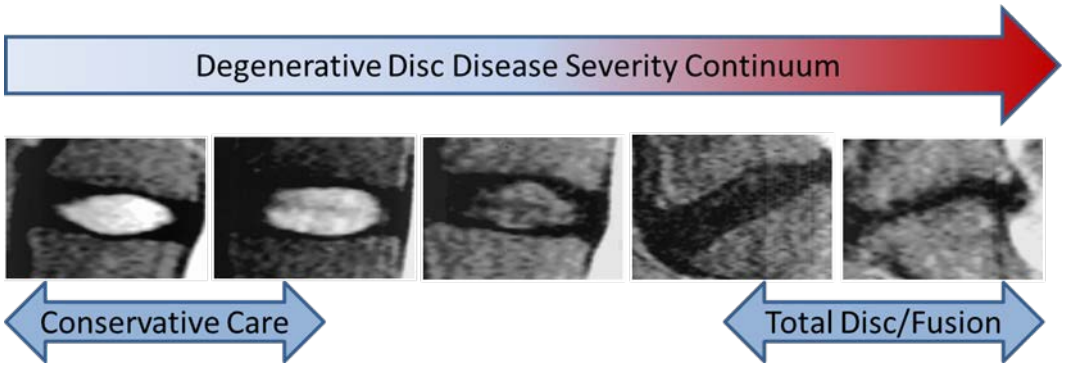

Figure 7.4: Currently available treatments for degenerative disc disease.

At this stage of disease progression, fusion and total disc replacement are the two most common surgical therapies available.[1] However, due to the inherent costs and risks of surgical intervention, these should be considered a last resort and generally reserved only for those patients with severe degeneration, for whom a rigorous battery of non-operative therapies has failed.[2,23] Patients who receive fusion or total disc replacement surgeries have higher complication rates, longer hospital stays, and higher hospital expenses than those who undergo other less invasive types of treatment.[1] In addition, the surgical risks of these advanced procedures can include death, major blood loss, neurological injury, and the risk of the procedure failing, resulting in no improvement in or worsening of a patient's condition.

Further, fusion surgeries have specific risks that can cause additional morbidity. Fusion procedures often require the use of bone graft taken from the patient's iliac crest. This exposes the patient to additional risks from a second surgical site, as well as the potential for long-term post-operative harvest site pain.[24] Adjacent segment degeneration may also occur due to the altered biomechanics resulting from the fusion of a spinal motion segment. The symptomatic degeneration of the spinal level adjacent to a fusion results in a re-operation rate of about 36% at 10 years.[25]

Considering the increased risk, procedure irreversibility, long recovery times, and high cost of fusion or total disc replacement surgery, it is important to manage low back pain before it reaches this stage.

7.3.3 Treatment Gap

In the middle of the cascade of disease progression are the majority of patients. These patients have significant impact on their function, but do not meet the requirements to make them candidates for fusion or total disc replacements. These patients are suffering from symptoms that are moderate in severity and duration and significantly diminish their quality and enjoyment of life as well as lost work function. Patients at this point in their disease progression are stranded between the

two opposing ends of the currently existing care continuum, with little that current ethical medical science can offer. Subjecting patients in this space to total disc replacement or fusion is inappropriate and would expose them to unnecessary surgical risks, complications, and secondary effects beyond what is appropriate at this stage in their disease progression. Figure 7.5 below illustrates where the treatment gap is in the degenerative disc disease continuum.

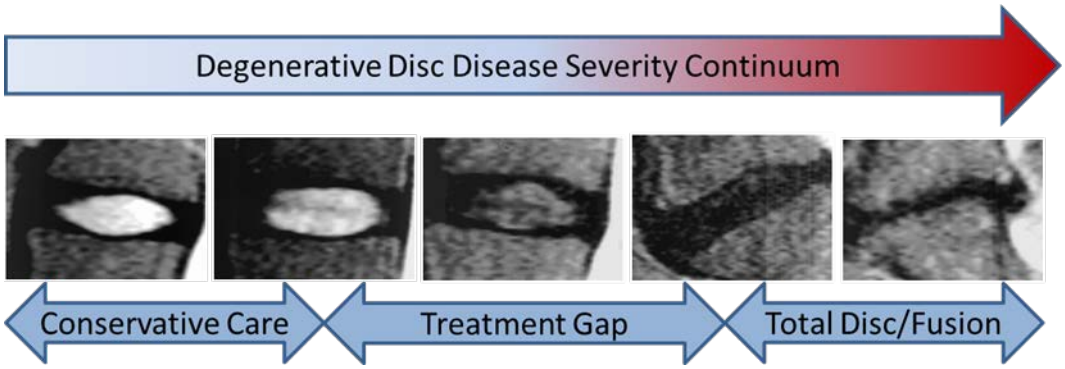

Figure 7.5: Treatment options in the degenerative disc disease cascade.

7.3.4 DIAM Spinal Stabilization System

The DIAM Spinal Stabilization System is designed to fill this treatment gap. The purpose of the DIAM device is to restore and augment the biomechanical function of the spinal unit following its compromise due to DDD. The DIAM device is implanted in a minimally invasive manner between the spinous processes of the affected spinal level. Its stiff silicone core transfers a portion of the axial spinal load through the device, thereby load sharing with the posterior disc, annulus, and facet joints.[18] It alleviates pain through the reduction of stresses on the overloaded posterior disc and facet joints.[1,18] In addition, the DIAM device re-tensions the supraspinous ligament and other ligamentous structures,[20] thereby enhancing the segmental stability of the affected level in flexion and extension without eliminating motion at that segment.[1,26] Also, unlike fusion, the DIAM device does not adversely affect the biomechanics of the adjacent segments.[18,20,26] As a consequence of its biomechanical functioning, the DIAM device is able to act on the primary pain generators associated with low back pain. Figure 7.6 shows the final placement of the DIAM device.

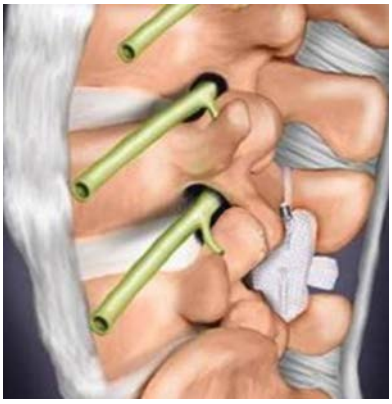

Figure 7.6: Placement of the DIAM device in the spine.

Implantation of the DIAM device is far less invasive than a fusion or total disc replacement procedure, leading to less morbidity and the avoidance of many of the risks associated with more invasive surgeries. It fits well as a treatment option earlier in the continuum of care and provides an alternative for those patients with low back pain secondary to DDD for whom conservative care is the only current treatment option and is failing to adequately meet their needs. Use of the DIAM device to manage low back pain from DDD prior to reaching the end-stage processes of the disease has the potential to dramatically benefit patients and society as a whole.

8. SUMMARY OF NON-CLINICAL DATA

A variety of mechanical and other non-clinical tests were conducted to characterize the performance of the DIAM device, including:

- Animal testing
- Biocompatibility testing
- Mechanical testing
- MRI compatibility

8.1 Animal Testing

Two DIAM biocompatibility studies have been conducted in animal models. The first study was conducted in an adult sheep model in order to analyze the long-term interactions between the implant and the interspinous process tissues. The sheep model allows for evaluation of the implant in an environment that is biomechanically similar to that of human spines. The second study, using a rabbit model, was conducted in order to evaluate potential local tissue and systemic responses to DIAM implant wear debris particulates. Summary data for the two studies are provided in the following table.

TABLE 8.1: Summary of animal testing.

Test Description	Tested Component	Methods	Acceptance Criteria	Results
Sheep Implantation Study	Standard stock DIAM devices identical to those used in the IDE study. All sheep received size 10 or 12 DIAM devices.	N = 12 sheep implanted at L3-L5. 6 sheep each euthanized at 6 and 12 months. Histological analysis was performed on major organs (kidneys, lung, spleen, heart, and liver), soft tissue and bone adjacent to the implant, and spinal cord.	This was a characterization study – therefore, no acceptance criteria were generated.	No foreign implant material was found in any tissue section. There were no tissue reactions due to the implant materials.
Rabbit Wear Particle Injection Study	4 mg total PET and silicone simulated wear particulate generated from a 14 mm DIAM implant	N = 24 total rabbits (12 treatment and 12 sham control). 12 rabbits (6 treatment and 6 control) euthanized each at 3 and 6 months. DIAM wear particulate was implanted between and around two lumbar dorsal spinous processes in the treatment animals. Clinical and neurological observations, hematology, serum chemistry, and gross and microscopic pathology used to evaluate particulate effects.	This was a characterization study – therefore no acceptance criteria were generated.	Clinical observations, body weights, necropsy observations, organ weights, organ/body weight ratios and organ/brain weight ratios were not adversely affected by implantation of the test article. There were no changes in hematology or clinical chemistry values considered related to the test article. No evidence of osteolysis was observed. Microscopic evaluation revealed no evidence of a systemic test article related response. Microscopic evaluation of the implantation sites indicated a localized inflammatory response classified as a slight irritant. There was no systemic toxicity and no systemic presence of test article wear debris.

8.2 Biocompatibility Testing

Per the requirements of ISO 10993, DIAM Spinal Stabilization System device is classified as a permanent contact, tissue/bone-contacting implant. The testing strategy was based on these requirements in addition to FDA's Program Memorandum G95-1. The following biocompatibility tests were undertaken on the complete device (or extract, as required):

- Cytotoxicity
- Genotoxicity
- Micronucleus Cytogenetic Assay in Mice
- Allowable Limits for Leachable Substances
- Maximization Sensitization
- Hemolysis
- Pyrogenicity
- Chromosomal Aberration Induction Using Human Lymphocytes
- Histopathology

All standard acceptance criteria were met. The results of the testing support the biocompatibility of the device materials. Therefore, the silicone elastomer, polyester, and CP titanium are considered to be safe for use in the lumbar spine.

8.3 Mechanical Testing

The biomechanical properties of the DIAM Spinal Stabilization System were assessed in a series of pre-clinical experiments. When applicable, all tests were performed on the worst-case size device. Finished devices were used in all tests. Summary data for the pre-clinical tests are provided in the following table.

Table 8.2: Summary of mechanical testing.

Test Description	Objective	Methods	Acceptance Criteria	Results
Static Compression	To evaluate the static compression strength of the DIAM device.	**Tested Component:** 8mm DIAM Devices **Sample Size:** N = 6 Load applied at 25 mm/min until device failure or imminent fixture-to-fixture contact (ultimate load).	The device must withstand more than 339 N of compressive force, the reported failure load of the lumbar spinous process.[27]	The mean ultimate load for the 8mm implants was 2653±380 N which exceeded the acceptance criteria of 339N.
Static Tension	To evaluate the ultimate strength and failure mode of the DIAM device under tensile load.	**Tested Component:** 8mm & 14mm DIAM Devices **Sample Size:** N = 5 (each size) The upper test fixture was displaced at a rate of	The device must withstand more than 339 N of tensile force, the reported failure load of the lumbar spinous process.	The mean failure load for the 8mm implants was 564.7±83.9 N, and the mean failure load for the 14mm implants was 519.8±45.9 N. Results for both sizes exceeded the acceptance criteria of 339 N.

Test Description	Objective	Methods	Acceptance Criteria	Results
		25mm/min until the specimen failed.		
Compression Fatigue	To evaluate the dynamic compression strength of the DIAM device.	**Tested Component:** 8mm & 14mm DIAM Devices **Sample Size:** N = 6 (8mm) N = 13 (14mm) Testing was performed in 0.9% phosphate buffered saline solution (PBS) maintained at 37°C. Cyclical compressive loads were applied at 8 Hz until 10 million cycles were reached or failure of the device occurred. The load was reduced until two runouts at one load level were achieved.	The device should survive 10 million cycles at a peak load greater than the expected peak facet loading of 360 N. The 360 N load was derived by multiplying the compressive load during activities of daily living of 1200 N[28] by 20% which represents the approximate share of axial compressive load supported by the bilateral facet joints in extension[29,30] and applying a 1.5 factor of safety.	The 8mm implants achieved runout at 480 N, and the 14mm implants achieved runout at 500 N. Results for both sizes exceeded the acceptance criteria of 360 N.
Tension Fatigue	To evaluate the strength of the DIAM device under dynamic tensile loads.	**Tested Component:** 8mm DIAM Devices **Sample Size:** N = 6 Testing was performed in 0.9% PBS maintained at 37°C. Cyclical tensile loads were applied at 8 Hz until 10 million cycles were reached or failure of the device occurred. The load was reduced until two runouts at one load level were achieved.	The device should withstand a tensile fatigue greater than 100 N for 10 million cycles. The 100N load originates from a study by Papp et al.[31] concluding that a tensile load of 50-100 N applied to a polyester braid connecting a proximal spinous process to the distal laminas of a lumbar motion segment would be required to stabilize the motion segment.	The implants achieved runout at 155 N exceeding the acceptance criteria of 100 N.

Test Description	Objective	Methods	Acceptance Criteria	Results
Torsion Fatigue	To evaluate the effects of repeated axial rotation motions on the DIAM device.	**Tested Component:** 8mm DIAM Devices **Sample Size:** N = 2 Testing was performed in 0.9% PBS maintained at 37°C. The test blocks were offset 28mm from the axis of rotation to mimic the anatomy of the spine. A 150 N compressive load was applied to each sample and the superior fixture was rotated ±3° at a rate of 8 Hz until 10 million cycles were reached or failure of the device occurred.	The device should survive 10 million cycles of worst-case axial rotation (±3°)[32,33] with a compressive load of 150N applied. The 150N compressive load represents the 20% share of the axial compressive load carried by the facet joints while standing multiplied by a 1.5 factor of safety (500 N x 20% x 1.5 = 150 N). The 500N axial compressive load is based on work by Nachemson[34] as well as ATSM F2077-03.	Two runouts were achieved at a load of 150 N and a worst-case rotation magnitude of ±3°. These results met the acceptance criteria.
Compression Creep	To determine the static compressive creep resistance of the DIAM device under a range of physiological loads.	**Tested Component:** 8mm DIAM Devices **Sample Size:** N = 3 Testing was performed in 0.9% PBS maintained at 37°C. A static load was applied to the implant. The load was applied for 1000 hours with displacement data being collected at time intervals.	For static loads of 270 N, 360 N and 450 N, the steady-state strain must be below the failure limit of 90% device compression. The 360 N load represents worst-case loading on the device with a 1.5X safety factor (see Compression Fatigue). The 270 N and 450 N values represent ±25% of this load.	At static compressive loads of 270 N, 360 N and 450 N, the implants achieved steady-state strain of 16.2%, 15.0% and 16.1% respectively. All three samples successfully met the acceptance criteria with values below the 90% strain failure limit.
Compression Fatigue (Accelerated	To evaluate the dynamic compression strength of the DIAM device	**Tested Component:** 8mm DIAM Devices	The compression fatigue runout load must be equal to or exceed a load of 360 N (source of load defined	The 8mm implants achieved two runouts at 360 N which satisfied the acceptance criteria of

Test Description	Objective	Methods	Acceptance Criteria	Results
Aged Implants)	after undergoing accelerated aging to mimic 10 years of real-time in vivo aging.	**Sample Size:** N = 7 Implants in tubes filled with 0.9% PBS were placed in a 90° C water bath for 92 days to simulate 10 years of real-time in vivo aging.[35] After aging, testing followed the previously described methods for Compression Fatigue.	in Compression Fatigue section above).	360 N.
Static Compression (Accelerated Aged Implants)	To evaluate the static compression strength of the DIAM device after undergoing accelerated aging to mimic 10 years of real-time in vivo aging.	**Tested Component:** 8mm DIAM Devices **Sample Size:** N = 5 Implants in tubes filled with 0.9% PBS were placed in a 90° C water bath for 92 days to simulate 10 years of real-time in vivo aging. After aging, testing followed the previously described methods for Static Compression.	The mean static compression stiffness must be statistically equivalent to 76.3 N/mm (mean stiffness determined for un-aged product in prior static compression testing).	The mean stiffness for the 8mm implants was 77.6±3.8 N/mm. The mean static compression stiffness was statistically equivalent to previous testing of un-aged DIAM specimens (p=0.79).
Tension Fatigue (Accelerated Aged Implants)	To evaluate the strength of the DIAM device under dynamic tensile loads after undergoing accelerated aging to mimic 10 years of real-time in vivo	**Tested Component:** 8mm DIAM Devices **Sample Size:** N = 3 Implants in tubes filled	The tensile fatigue runout load must be equal to or exceed 100 N (source of load described in Tension Fatigue section above).	The 8mm implants achieved two runouts at 100 N which satisfied the acceptance criteria of 100 N.

Test Description	Objective	Methods	Acceptance Criteria	Results
	aging.	with 0.9% PBS were placed in a 90° C water bath for 92 days to simulate 10 years of real-time in vivo aging. After aging, testing followed the previously described methods for Tension Fatigue.		
Compression Fatigue Gravimetric Wear Analysis	8mm DIAM Device 14mm DIAM Device	N = 2 N = 2	Devices were desiccated and weighed before and after fatigue testing. The weights of the 10 million cycle run out samples were recorded.	The average weight loss was 0.01136 g (range 0.00245 g - 0.02514 g)
Compression Fatigue Wear Debris Characterization	14mm DIAM Device	N = 1	Wear debris collected from one DIAM device tested to 10 million cycles at 550 N was analyzed using scanning electron microscopy (SEM) to obtain measures of particle size, shape, and composition according to ASTM F1877. Energy dispersive x-ray analysis (EDX) was used to identify the elemental composition of the particles.	The average size of particles was 1.24 µm (Equivalent Circular Diameter or ECD). The composition of the particles were polymeric-based consistent with PET and silicone. The particles were oval in shape with an aspect ratio of 1.9.
Explant Tissue Wear Debris Analysis	Tissue samples surrounding explanted DIAM devices from 3 IDE patients	N = 3	Samples of tissues surrounding the area of explanted DIAM devices were digested and then filtered to isolate any wear debris particulate. The debris was analyzed using scanning electron microscopy (SEM) to obtain measures of particle size, shape, and	The sizes of the particles ranged from 1.11 to 1.24 µm (ECD). The PET particles were smooth and spheroidal and the silicone particles were flake.

Test Description	Objective	Methods	Acceptance Criteria	Results
			composition according to ASTM F1877. Energy dispersive spectroscopy (EDS) was used to identify the elemental composition of the particles.	

8.4 MRI Compatibility

Table 8.3: Summary of MRI testing.

Test Description	Tested Component	Sample size	Methods	Results
MRI Characterization	Device Assembly	N = 1	1.) Magnetic field interactions 2.) MRI-related heating, 3.) Artifact testing.	1.) Magnetic field interactions: Implant does not present an additional risk or hazard to the patient in a 3-tesla or 1.5-tesla MRI environment with regard to translational attraction, migration, or torque. 2.) MRI-related heating: Highest temperature change recorded was not considered to be physiologically consequential for a human subject. 3.) Artifact test: Worst case artifacts that appeared on MR images were localized signal voids graded as “small” in comparison to the size and shape of the device. In non-clinical testing the DIAM Spinal Stabilization System was determined to be MR Conditional.

9. SUMMARY OF IDE STUDY

The objective of this study was to evaluate the safety and efficacy of the DIAM Spinal Stabilization System in the treatment of patients with moderate low back pain secondary to lumbar degenerative disc disease and to demonstrate superiority of the device over conservative care. Overall success,

which included measures of both safety and efficacy, was evaluated at 12 months as the primary endpoint.

The clinical study design was based on a targeted group of patients with persistent back pain who, based on the state of their disease progression, were not currently considered candidates for available surgical treatments such as fusion. Study subjects, thus selected, are representative of the majority of back pain patients, for whom the presence of persistent back pain carries significant morbidity, disability, and reduction in the of quality of life refractory to treatments currently approved for their indication.

For this study, which evaluated the safety and effectiveness of the investigational DIAM device for treatment of persistent, moderate, low back pain secondary to DDD (patients not likely to be otherwise eligible for surgical intervention), as compared to a control group treated by conservative, nonsurgical therapies was the optimal control, as conservative care represents the most likely treatment option provided to subjects with the specified diagnosis. This study therefore compared treatment with the investigational DIAM Spinal Stabilization System to nonsurgical treatment comprised of a full range of specific nonsurgical treatment options. The control group chosen, therefore, was particularly relevant in this study as it mimicked real-life practice by permitting investigators to treat control subjects individually by offering a patient-specific combination of nonsurgical treatments which, in their judgment, offered the subject the best means of providing pain relief.

9.1 Investigational Plan

9.1.1 Inclusion/Exclusion Criteria

The inclusion and exclusion criteria for the study are presented in Table 9.1.

Table 9.1: Inclusion and exclusion criteria for the DIAM IDE.

Inclusion Criteria: All subjects participating in this study were required to meet all of the following inclusion criteria, as listed in the study protocol.	**Exclusion Criteria:** A patient meeting any of the following criteria was to be excluded from this clinical trial.
1. Has moderate low back pain secondary to lumbar degenerative disc disease at a single level from L2-L5. Low back pain is defined as persistent back pain, with or without radicular pain, with current episode less than one year in duration. Degenerative disc disease is confirmed by patient history, physical examination, and radiographic studies with one or more of the following factors (as measured radiographically by MRI scans or x-rays): • decreased disc height > 2mm, compared to the disc space at the next adjacent (superior or inferior, whichever had the greatest height)	1. Has disc height loss > 67% at the involved level compared to the next adjacent (superior or inferior, which had greater disc height) spinal level 2. Has arachnoiditis 3. Has a primary diagnosis of a spinal disorder other than degenerative disc disease at the involved level 4. Requires treatment of degenerative disc disease at more than one lumbar level 5. Has had all of the following nonoperative treatments (prescribed medications, active physical therapy, spinal injections, and patient) within the past 6 weeks 6. Has a sequestered herniated nucleus pulposus 7. Has had any previous surgery at the involved or

spinal level. • scarring/thickening of the ligamentum flavum, annulus fibrosis, or facet joint capsule • herniated nucleus pulposus 2. Is 18-70 years of age, inclusive, and is skeletally mature 3. Has pre-treatment Oswestry score ≥ 30 4. Has pre-treatment back pain score ≥ 8 (based on the Pre-treatment Back and Leg Pain Questionnaire (Back pain Intensity + Back Pain frequency) 5. Has been treated nonoperatively (e.g., bed rest, physical therapy, medications, TENS, manipulation, and/or spinal injection) for a period of at least 6 weeks and not more than 6 months prior to enrollment in the clinical study 6. If of child-bearing potential, patient is not pregnant or nursing and agrees not to become pregnant during the study period 7. Willing and able to participate in either of the randomized treatments (i.e., if patient randomized to investigational treatment, he/she is willing to undergo surgery to receive the DIAM device. If patient is randomized to the control group, he/she is willing to undergo all four nonoperative treatments) 8. Is willing and able to comply with the study plan and able to understand and sign the Patient Informed Consent Form	adjacent spinal levels (including procedures such as a rhizotomy) 8. Has received any intradiskal ablation therapy such as IDET 9. Has congenital or iatrogenic posterior element insufficiency (e.g., facet resection, spondylolysis, pars fracture, or Spinal Bifida Occulta) 10. Has back pain (with or without leg, buttock, or groin pain) not alleviated in any spinal position 11. Has a motor deficit in a lower extremity 12. Has cauda equina syndrome 13. Has compression of nerve roots with neurogenic bowel dysfunction (fecal incontinence) or bladder dysfunction (urinary retention or incontinence) 14. Has been previously diagnosed with clinically significant peripheral neuropathy 15. Has significant vascular disease with vascular claudication 16. Has a medical contraindication that prevents the patient from receiving spinal injections (i.e. allergy to contrast media used to aid placement of the needle in the epidural space) 17. Has ventral spondylolisthesis with more than 2 mm of translation at the involved level 18. Has evidence of prior fracture or trauma to the L1,L2, L3, L4, or L5 levels in either compression or burst 19. Has lumbar scoliosis with a Cobb angle of greater than 15° 20. Has lumbar kyphosis or flat back syndrome 21. Has sustained a hip fracture within the last year 22. Has any of the following (if "Yes" to any of the below risk factors, a lumbar spine DEXA Scan will be require to determine eligibility): a. Previous diagnosis of osteoporosis, osteopenia, or osteomalacia b. Postmenopausal non-black female over 60 years of age and weighing less than 60 pounds c. Postmenopausal female who has sustained a non-traumatic hip, spine, or wrist fracture d. Male over 60 years of age who has sustained a non-traumatic hip, spine, or wrist fracture If the level of DEXA T-score is -1.0 or lower (i.e.,-1.5, -2.0, etc.) the patient is excluded from the study. 23. Has obesity defined by BMI greater than or equal to 40 24. Has a documented allergy to silicone, polyethylene, titanium, or latex 25. Has overt or active bacterial infection, either local or systemic, and/or potential for bacteremia

	26. Has a suppressed immune system or has taken steroids daily for more than one month within the last year (excluding low-dose inhalers for the treatment of asthma) 27. Has a history of autoimmune disease 28. Has presence of active malignancy or prior history of malignancy within the last five years (except basal cell carcinoma of the skin) 29. Has presence or prior history of a spinal malignancy 30. Has chronic or acute renal and/or hepatic failure, or history of prior renal and/or hepatic parenchymal disease 31. Has any disease (e.g. neuromuscular disease) that would preclude accurate clinical evaluation of the safety and efficacy of the treatment regimens in this study 32. Has received treatment with any other investigational therapy within 30 days prior to entering the study or such treatment is planned during the 24 months following enrollment in the study 33. Has an implantable metal device (e.g., stimulator, pacemaker) and is unable to have an MRI 34. Is an alcohol and/or drug abuser (defined by currently undergoing treatment for alcohol and/or drug abuse 35. Is mentally incompetent. If questionable, obtain psychiatric consult 36. Has a Waddell Signs of Inorganic Behavior score of 3 or greater 37. Is a prisoner.

9.1.2. Study Design

This pivotal trial had a prospective, randomized, controlled design. Since an investigational treatment consisting of a surgical procedure was compared to nonoperative care, neither subjects nor investigators could feasibly be blinded.

Patients were randomized into the two treatment groups in a ratio of two investigational subjects to every control subject. For investigational subjects, the DIAM device was implanted between adjacent spinous processes using a posterior approach. The earlier versions of the protocol required that the control group subjects received each of four components of the nonoperative regimen during the first six months of their participation in the study, which included patient education as well as physical therapy, spinal injections, and medications for their back condition. Completion of the nonoperative regimen was defined as the subject having received diagnosis-specific patient education, at least one physical therapy session, at least one spinal injection, and at least one prescription for medication. The protocol was later revised because some control patients were successfully

managed without needing all four treatment elements. With this protocol revision, control subjects were required to be treated with at least two but up to four nonoperative therapies during the first six months of their participation in the study. Investigators initiated control treatment with patient education plus one or more of the other non-operative therapies based on initial assessment of the patient's clinical condition. Completion of the nonoperative regimen was defined as the subject having received diagnosis-specific patient education plus meeting at least one or more of the following therapies: at least one physical therapy session, at least one spinal injection, or at least one prescription for medication.

Medications permitted included analgesics, NSAIDS, muscle relaxants, oral corticosteroids, neuroleptics, and antidepressants; the choice of specific medications, steroid injections and physical therapies prescribed was personalized by investigators as deemed to be in the subject's best interest. No limits were placed on the type, amount, or duration of treatments provided, with the exception that no more than 3 epidural and or facet steroid injections were allowed. Investigational subjects were also permitted to receive any of the nonoperative study treatments at the discretion of the investigator; both control and investigational subjects were also free to pursue non-prescription therapies such as massage and acupuncture in addition to the treatment provided by study therapies. All subjects in the study were to be followed until the last subject treated reached 24 months.

Control subjects were permitted to cross over to treatment with the DIAM Spinal Stabilization System as deemed indicated by the investigator, provided that the subject had completed at least six months of control therapy which had proven to be ineffective (as defined by an ODI score of at least 30 with post-treatment improvement in the ODI score of less than 15 points at the time that the subject was evaluated for crossover surgery) and completion of the nonoperative treatment regimen. Completion of the nonoperative regimen was defined, for approval of a crossover surgery, as the subject having received diagnosis-specific patient education, at least one physical therapy session, at least one spinal injection, and at least one prescription for medication. Control subjects who met the pre-defined conditions outlined in the protocol and received implantation of a DIAM device, from that point on, followed the same postoperative schedule of assessments as those originally assigned to investigational treatment. Control subjects were also permitted, under the same criteria, to undergo alternative treatment surgeries. Control subjects who did not meet any of these criteria were considered to be improving and were therefore ineligible for treatment surgeries, including crossover to treatment with the DIAM Spinal Stabilization System, unless other factors supported a medical need for operative treatment. Data collected after implantation of the DIAM device in crossover subjects provided additional information about the safety and efficacy of the DIAM device and were therefore also analyzed separately.

9.1.3. Primary Objective

The primary objective of this clinical trial was to show superiority in overall success associated with the use of the DIAM Spinal Stabilization System as compared to the control treatment. Overall success, an endpoint recommended in the FDA Guidance Document for the Preparation of IDEs for Spinal Systems, included both safety and efficacy endpoints for both treatment groups and was assessed at 12 months. Overall success was defined as 1) greater than or equal to 15 points improvement on the Oswestry Disability Index (ODI), 2) an absence of any serious adverse event classified as "implant associated," or "implant/surgical procedure associated" for the investigational group, and "nonoperative treatment associated" for the control group, and 3) the absence of necessity for an additional surgical procedure defined as a "failure."

If the overall success rate in the investigational group was found to be statistically superior to the success rate in the control group at 12 months after treatment initiation, the investigational treatment was to be considered both safe and effective.

9.1.4. Secondary Objectives

The secondary objectives of this trial were to compare the success rates of the individual endpoints at the 12-month time point. For efficacy endpoints and neurological status, comparisons were made to determine statistically if superiority of the investigational treatment, as compared to the control treatment, was demonstrated. Statistical comparisons of safety measurements were also performed. These endpoints include pain and disability success (as measured by the Oswestry Low Back Pain Disability Questionnaire) and overall neurological status, as well as the endpoints pertaining to back pain status, leg pain status, and general health as measured by the SF-36 PCS status.

9.1.5. Other Evaluations and Radiologic Observations

Other study measurements collected included radiologic evaluations of disc height, angular motion, post-treatment work status of the subject, and perceptions of both subjects and investigators with respect to treatment efficacy. In addition, although not defined as an endpoint in the study protocol, the use of supplemental medications after treatment initiation, which provides corollary information on the efficacy of study treatments, was collected. Additional radiologic evaluations related to spinous process fractures and focal bone structural changes were also conducted.

For this clinical study, radiographs were evaluated by independent radiologic reviewers at the Core Imaging Lab, Biomedical Systems, Inc. (St. Louis, Missouri). Prior to performing their study assessments, all readers were trained by an expert radiology consultant. Two primary reviewers performed all radiologic measurements and an adjudicator was used when two primary readings differed for

certain categorical data or when one yielded valid data and the other did not for continuous measures.

9.1.6. Datasets for Analysis

The protocol defined several datasets including those described below for which data are presented within this summary.

Primary Analysis Dataset

The primary analysis dataset is based on an interim analysis consisting of the first 150 subjects treated who had at least one post-baseline overall success status evaluation (i.e., at 6 weeks or after) and passed the 12-month evaluation. All subjects treated with at least one post-treatment overall success evaluation were sorted according to their treatment dates, and the first 150 subjects in the list were included in the primary analysis dataset. The analysis of the primary dataset was presented up to 12 months in accordance with the definition of the primary endpoint. For this dataset, last observation carried forward was used for all missing data as well as all post-surgical data for both investigational subjects that had a secondary surgery and control subjects that had a treatment surgery at the index level.

This interim analysis was added during the study, upon approval of the FDA, following an increase in the probability criterion for assessing superiority, a more stringent criterion to ensure control of the type I error rate.

Per-Protocol Analysis Dataset

The per-protocol analysis consisted of a subset of the primary analysis dataset (defined for this interim analysis) by excluding those subjects who had major protocol deviations. For the per-protocol analysis, last observation carried forward was only applied for post-surgical time points after an investigational subject had a secondary surgery or a control subject had a treatment surgery at the index level. It was not applied where there was missing data due to lost-to-follow-up. The per-protocol analysis was also presented up to 12 months, and was considered the secondary analysis for assessing study hypotheses.

All Available Dataset

In addition to the primary analysis dataset and the per-protocol dataset, additional analyses were presented as supplementary information, but not for statistical comparison.

The all available dataset included all available data from all study subjects with at least one post-treatment evaluation at the time of interim analysis and as well as data collected beyond 12 months. Missing values due to lost-to-follow-up for whatever

reason were not imputed in this supplementary dataset. However, for investigational subjects who had secondary surgery and control subjects who had treatment surgery, the last observation before the secondary surgery or treatment surgery was carried forward for all future visits. The intention of this dataset was to provide information on outcome results with missing data points not imputed in the event there is an interest in that evaluation.

Dataset for Crossover Subjects

Control subjects for whom six months of non-surgical conservative treatment proved ineffective were permitted to receive the DIAM Spine Stabilization System. The dataset for the crossover subjects was derived based on the all available dataset.

For this subset of control subjects, outcome measurements made after the surgical treatment were summarized and two different comparisons were made:

- Measurements after DIAM surgery were compared to measurements obtained immediately prior to the surgery, and
- Measurements immediately prior to surgery were compared with measurements obtained at baseline.

These supplemental analyses provided additional information for assessing the efficacy of the DIAM device. Note that the term ‘crossover’ only applies to control subjects who receive a treatment surgery with the investigational (DIAM) device. Once a patient received a DIAM crossover surgery, his/her follow-up schedule was reset to mirror the follow-up schedule for those originally randomized to the investigational arm. Control subjects who received a non-DIAM treatment surgery continued to be followed according to the control arm’s original follow-up schedule.

9.1.7. Sample Size Calculation and Statistical Analysis Plan

Treatment allocation in this trial was randomized on a 2:1 (investigational: control) basis to assure that an adequate number of investigational subjects were included in order to assess the safety profile. Sample size calculation was based on the primary study hypothesis, i.e., the superiority hypothesis for overall success.

In the original Statistical Considerations document, the sample size determined was based on the assumption that the overall success rate for the investigational group and the control group were, respectively, 60% and 40%. With a power of 90% and an alpha level of 0.05, the sample size desired was determined to be 173 subjects for the investigational group and 87 patients for the control group, calculated using the sample size software nQuery Advisor 4.0. With an adjustment of an estimated 15% for lost to follow-up, the study planned to enroll 204 ± 5 investigational subjects and 102 ± 5 control subjects (306 ±10 subjects in total) into the trial. These subjects

were to be enrolled at a maximum of 30 study sites and no single study site was to enroll more than 20% of the study subjects.

Frequentist methods were used to compare baseline variables between treatment groups: analysis of variance (ANOVA) for continuous variables and Fisher's exact test for categorical data. Statistical significance of post-treatment improvement within each treatment group was determined by the paired t-test.

Bayesian statistical methods were used for endpoint comparisons using non-informative priors. For binary variables such as overall success, a beta-binomial model was used to derive the posteriors distribution of the success rates on which the inference was based.

Continuous measurements used to dichotomize success/failure status (e.g., Oswestry score, back and leg pain scores, and SF-36 PCS scores) were also compared using a Bayesian normal model as supplemental/alternative analyses. Adverse event rates were compared using a Bayesian beta-binomial model as well. Due to a large number of categories of adverse events, statistical comparisons were provided only for reference purposes.

By adding the Bayesian interim analysis, the criterion for assessing superiority was increased from 95% to 97.5% based on the posterior probability of superiority.

9.2. IDE Supplements: Changes to the Investigational Plan

The request for the interim analysis was submitted to the FDA on June 27, 2013 and was approved July 30, 2013 due to the slower than expected rate of enrollment. The following list highlights changes to the investigational plan over time.

- Modified exclusion criteria to include allergy to latex
- Clarification of patient confirmation and randomization process
- The absolute requirement for each control patient to undergo each of the four nonoperative therapies was removed and replaced with the requirement that all control subjects undergo patient education and one or more of the other non-operative therapies (physical therapy, medications, spinal injection)
- Clarification to the spinal injection therapy component -wording changed from "all patients will undergo spinal steroid injections" to "Patients may receive steroid injection" based on the investigator's assessment of their pain
- Inclusion criteria regarding decreased disc height was modified to "adjacent (superior or inferior, whichever has greater disc height") spinal level"
- Removed "facet joint degeneration" from inclusion criteria as permitted confirmation of DDD
- Added "disc height loss >67% at the involved level compared to the next adjacent (superior or inferior, whichever has greater disc height) spinal level" as reason for exclusion
- Added arachnoiditis as reason for exclusion

- Clarified definitions of Revision and Reoperation
- Clarified language regarding crossover patients
- Qualifications for physical therapy providers were expanded
- Planned enrollment increased in order to build in an estimate of screen failures into the sample size to ensure the desired number of randomized and treated subjects is obtained.
- Added the ISO 14155-1 serious adverse event definition
- Clarifications to the inclusion/exclusion criteria that the use of inhaled steroids does not exclude from participation
- Clarified that a Co-Investigator may be an operating or non-operating physician to better accommodate the conservative arm of the study
- Clarified that the physical therapy portion of the control treatment can be performed by a practitioner who is qualified and licensed to perform physical therapy services in that state
- Minor changes made with respect to collection and processing of study forms

The most recent amendment to the protocol extended the required study follow-up evaluations for those study participants who have received the DIAM Spinal Stabilization System either based on being randomized and treated with the investigational treatment or being treated based on a crossover treatment surgery, but does not extend the duration of follow-up required for study participants randomized to the control therapy who have not crossed over to receive the DIAM Spinal Stabilization System.

10. SUMMARY OF CLINICAL DATA INCLUDED IN THE PMA

10.1. Patient Population

10.1.1. Patient Accounting

At the time of the data lock on February 26, 2015, enrollment for this study was completed, and post-treatment follow-up is still ongoing. The last clinical visit for all the available dataset subjects was October 31, 2014. In this study, 38 US sites were activated for participation; 28 sites had screened patients for eligibility, 25 sites had randomized subjects, and 23 sites had treated subjects. A total of 421 patients were screened against the inclusion/exclusion criteria for inclusion; 110 patients were deemed to be screen failures (determined to be ineligible). The remaining 311 subjects were randomized to treatment groups in a 2:1 ratio, yielding 207 investigational subjects and 104 controls. Among the randomized subjects, 181 investigational subjects completed the treatment surgery, and 101 control subjects had completed assigned conservative care. At the time of data lock for this interim analysis, 181 investigational and 97 control subjects had at least one post-treatment evaluation in the database and hence were included in the all available dataset.

Among the 97 control subjects, 59 of them received a crossover treatment surgery with the DIAM device.

The primary analysis dataset consisted of the first 150 treated subjects with at least one evaluable post-treatment overall success status at or after 6 weeks, as defined in the interim analysis statistical analysis plan. By these criteria, 97 investigational subjects with surgical implantation of the DIAM device and 53 subjects treated with a patient-specific conservative care regimen were included. The first subject was treated in June 2007, and the final subject was treated in January 2014.

For the 150 subjects who were included in primary analysis population, the last study enrollment occurred on June 6, 2011. There were a total of 180 subjects that had been consented on or before June 6, 2011. Thirty of these 180 subjects were counted either as disqualified or screen failure (N=13; note that these subjects were not randomized) or were without evaluable data (N=17). The 13 subjects that were disqualified/screen failures comprise the disqualified dataset. The 17 subjects without evaluable data were randomized and included in the qualified dataset along with the 150 subjects in the primary dataset (for a total of 167 subjects in the qualified dataset) for the purpose of making comparisons between 13 disqualified subjects and 167 qualified subjects. Furthermore, the comparisons were also made between 150 randomized subjects with evaluable data and 17 randomized subjects who were withdrawn before evaluable data was collected.

Of the 17 subjects without any evaluable post-treatment data (discussed above), 15/17 did not proceed to treatment and 2/17 underwent treatment but did not have evaluable post-treatment data, therefore all 17 are considered subjects without evaluable data.

Subject disposition is displayed in the form of a flow diagram in Figure 10.1 below, which depicts high level subject disposition to provide an accounting of the patients that comprise the all available, primary analysis and per-protocol datasets.

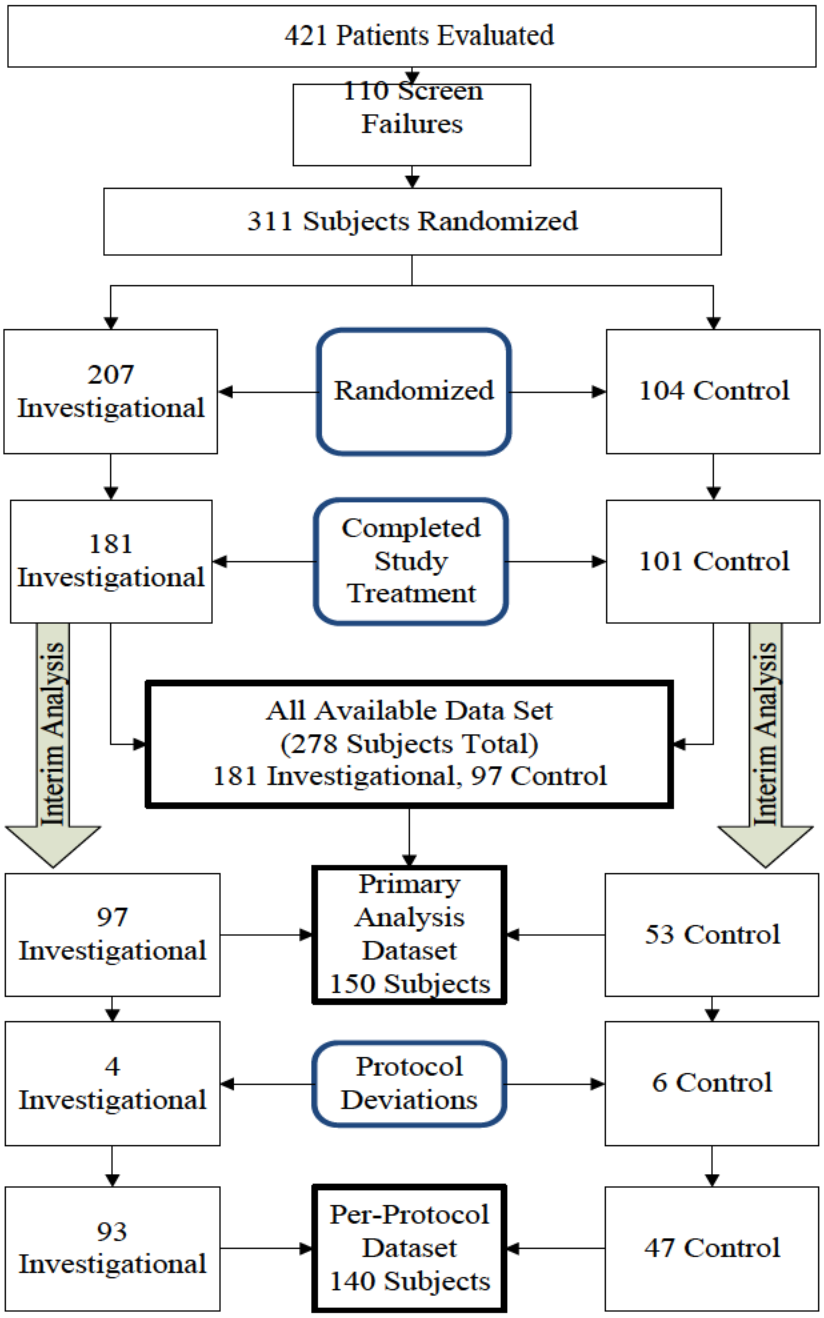

Figure 10.1: Overview of patient accounting and datasets

The following charts in Figures 10.2 and 10.2 summarize subject accountability for the investigational and control groups, respectively.

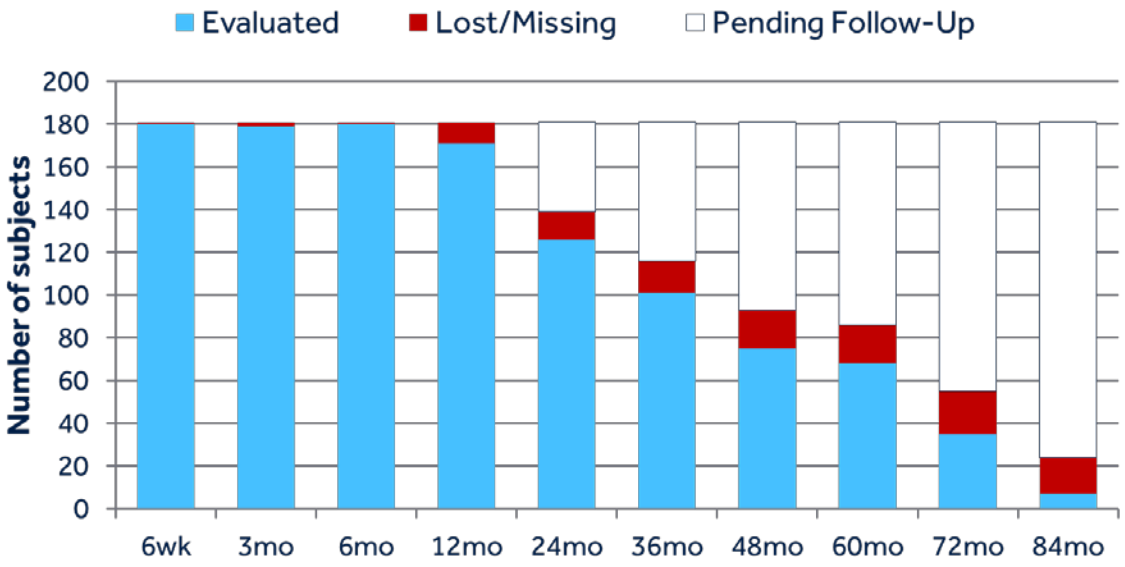

Figure 10.2: Investigational group subject accountability.

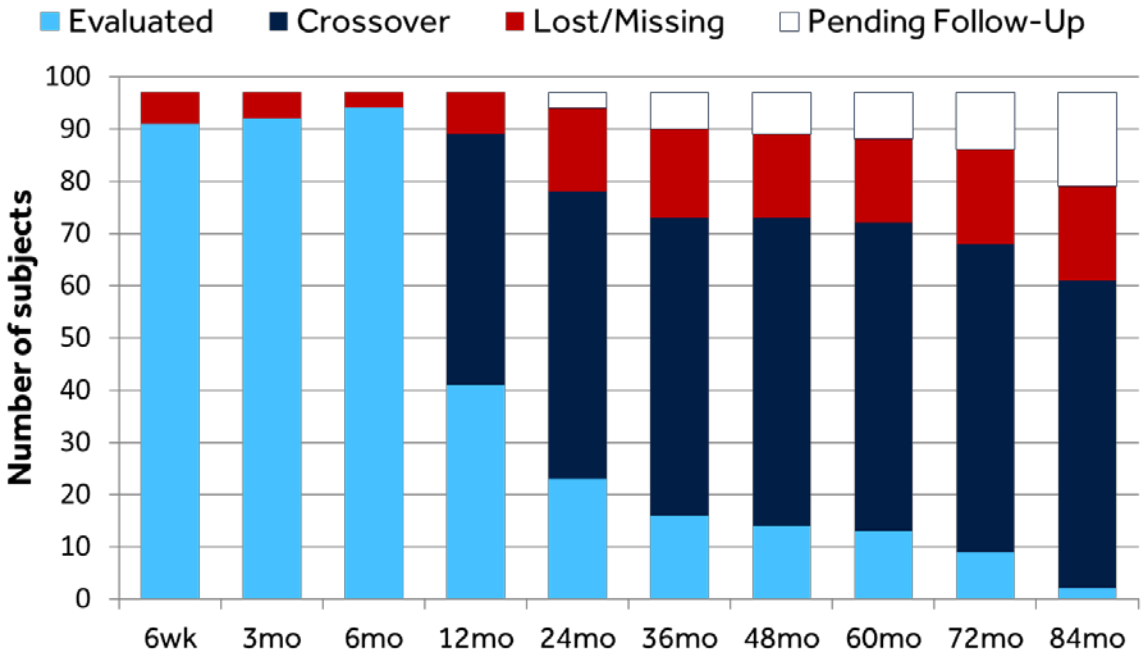

Figure 10.3: Control group subject accountability.

10.1.2. Patient Demographics

Baseline demographic information for both investigational and control subjects in the primary analysis dataset are presented in Table 10.1. Baseline demographic information for this group of subjects (the first 150 subjects treated with evaluable

post-treatment data) was also well balanced with the exception of race, for which the difference between the investigational group and the control group was observed to have a p-value of 0.033. Further examination of the distributions between the groups revealed that the percentages of Caucasians were very similar between the groups, 89.7% (87/97) and 88.7% (47/53), respectively for the investigational group and the control group; and the significant difference was, primarily, due to between-group differences in the percentages of blacks and Hispanics enrolled. Hispanics were represented disproportionately in the investigational group (8.2% of the investigational population group as compared to 1.9% of the control group), while blacks were represented at a larger percentage in the control group (7.5% of the control group versus 1.0% of the investigational group). This is most likely an occurrence by chance. As blacks and Hispanics together made up less than 10% of the primary analysis dataset, however, the impact of these differences on results is believed to be minimal. In addition, the comparison of "Caucasian" versus "Non-Caucasian" between the two groups yields a p-value of 1.000, showing no statistical significant difference between the two groups.

Table 10.1: Summary of Study Patient Demographics and Baseline Characteristics (Primary Dataset).

Variables	Investigational (N=97)	Control (N=53)	p-value
Age (years)	41.8 ± 10.8	42.5 ± 9.6	0.693
Height (inches)	67.8 ± 3.9	67.7 ± 4.4	0.905
Weight (lbs.)	184.8 ± 38.6	184.2 ± 41.3	0.928
Sex (% male)	42 (43.3%)	25 (47.2%)	0.732
Race			0.033
Caucasian	87 (89.7%)	47 (88.7%)	
Black	1 (1.0%)	4 (7.5%)	
Asian	1 (1.0%)	0 (0.0%)	
Hispanic	8 (8.2%)	1 (1.9%)	
Other	0 (0.0%)	1 (1.9%)	
Marital Status			0.444
Single	18 (18.6%)	8 (15.1%)	
Married	63 (64.9%)	37 (69.8%)	
Divorced	13 (13.4%)	4 (7.5%)	
Separated	3 (3.1%)	3 (5.7%)	
Widowed	0 (0.0%)	1 (1.9%)	
Education Level			0.965
< High School	9 (9.3%)	4 (7.5%)	
High School	28 (28.9%)	15 (28.3%)	
> High School	60 (61.9%)	34 (64.2%)	
Worker's Compensation	12 (12.4%)	7 (13.2%)	0.559
Unresolved Spinal Litigation	13 (13.4%)	6 (11.3%)	0.802
Using Tobacco at Baseline	24 (24.7%)	18 (34.0%)	0.257
Using Alcohol at Baseline	51 (52.6%)	27 (50.9%)	0.866
Working at Baseline	67 (69.1%)	38 (74.5%)	0.570

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Demographic analysis in the all available and per-protocol dataset was similar to the primary analysis dataset; only race was significant (p-value = 0.029), with a similar pattern. This statistically significant difference is not expected to influence final outcomes.

10.1.3. Baseline Characteristics

Baseline evaluation of several efficacy endpoints (ODI, back pain, leg pain, and SF-36 component scores) as well as neurological status were obtained and between-group differences were compared. The combined analyses provided a comprehensive picture of subject's pre-treatment medical condition, with no significant differences observed between the treatment groups for these potentially confounding factors. Data for these analyses are summarized in Table 10.2 below.

Table 10.2: Baseline evaluations of outcomes variables in primary analysis dataset.

Variable	Investigational N=97	Control N=53	p-value
ODI			0.702
Mean (Std)	49.1 (13.3)	49.9 (13.6)	
Median (Min-Max)	48.0 (30.0-94.0)	48.0 (30.0-80.0)	
SF-36 PCS			0.770
Mean (Std)	28.0 (6.7)	28.3 (7.1)	
Median (Min-Max)	26.8 (14.3-46.7)	26.9 (14.5-45.4)	
SF-36 MCS			0.995
Mean (Std)	46.5 (12.1)	46.4 (13.4)	
Median (Min-Max)	49.1 (20.1-67.7)	47.6 (17.7-70.1)	
Back Pain Score			0.148
Mean (Std)	16.5 (2.4)	15.9 (3.0)	
Median (Min-Max)	17.0 (9.0-20.0)	17.0 (8.0-20.0)	
Leg Pain Score			0.237
Mean (Std)	10.6 (6.1)	9.4 (6.1)	
Median (Min-Max)	12.0 (0.0-20.0)	10.0 (0.0-20.0)	
Neurological Function			
Motor n (%)			
Normal	97 (100.0)	53 (100.0)	1.000
Abnormal	0 (0.0)	0 (0.0)	
Sensory n (%)			
Normal	86 (88.7)	49 (92.5)	0.576
Abnormal	11 (11.3)	4 (7.5)	
Reflexes n (%)			
Normal	88 (90.7)	50 (94.3)	0.541
Abnormal	9 (9.3)	3 (5.7)	
Straight Leg Raise n (%)			
Normal	77 (79.4)	41 (77.4)	0.836
Abnormal	20 (20.6)	12 (22.6)	

10.2. Perioperative Outcomes

All DIAM devices were implanted using a posterior approach. Mean operative time was 1.0 hour, mean blood loss 32.0 milliliters, and mean length of hospital stay was 0.9 days. Twenty-five subjects (25.8%) were discharged from the hospital on the same day as surgery. The large majority of surgeries (83.5%) were at the L4-L5 level. Surgery and discharge data were unremarkable and are provided for informational purposes only.

10.3. Primary Endpoint (Overall Success) and Analysis

Overall success rates (defined by the criteria described in Section 9.1.3 above) at different time points for the investigational group and the control group are illustrated in Figure 10.4; the overall success rate in the investigational group was much higher than that in the control group. Bayesian analysis of overall success at 12 months demonstrated that for this primary endpoint, the posterior probability of superiority of the investigational group was approximately 100%, exceeding the threshold of 97.5% and establishing that the primary objective of the study was met. In addition, the 95% highest posterior density (HPD) Bayesian credible interval (BCI), for the difference of success rates between the investigational group and the control group was (33.5%, 60.4%), indicating that the success probability for the investigational treatment is likely at least 33.5% higher and could be as much as 60.4% higher than that for conservative car treatment at 12 months. A poolability analysis was conducted to see whether all data from all study sites could be pooled. No sites with opposite treatment effects were identified; the p-value for Breslow-Day test for homogeneity across sites was 0.471 and data was pooled.

Overall success for the primary dataset is presented in Figure 10.4 and results for the all available dataset are presented in Figure 10.5.

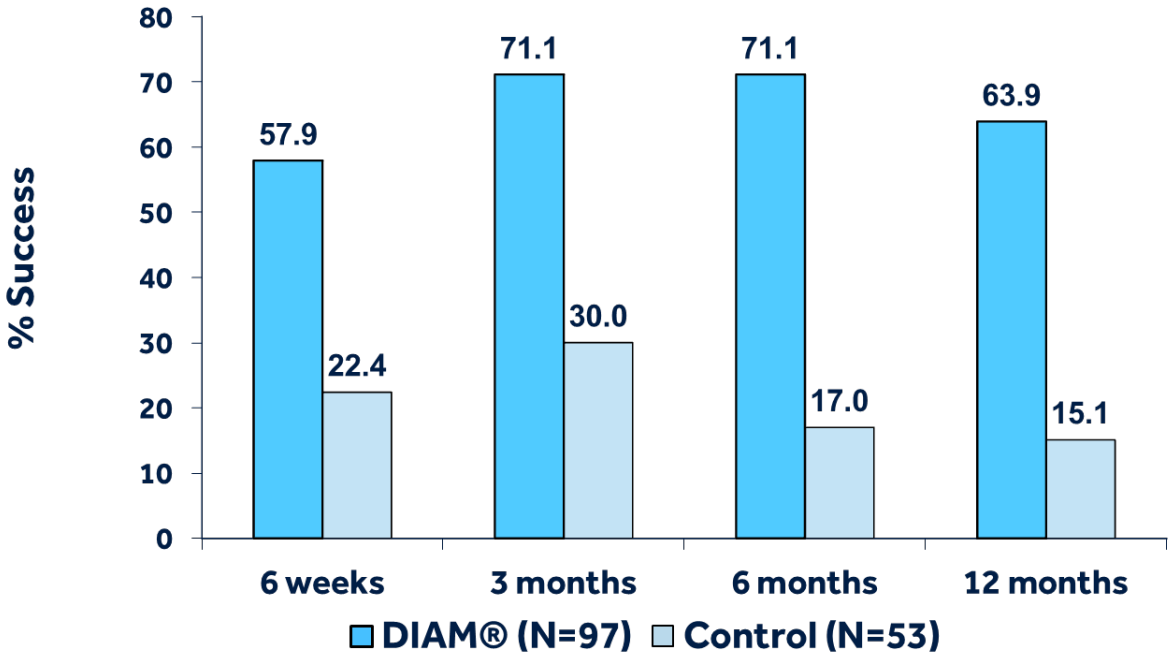
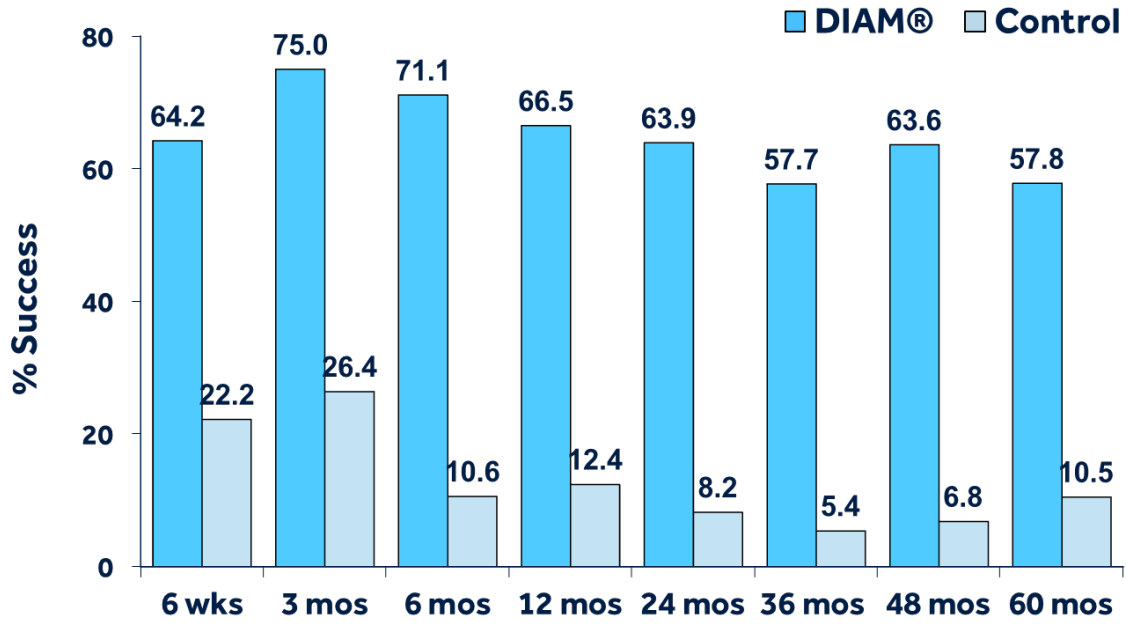


Figure 10.4: Overall success in primary dataset.



DIAM (N=)	179	176	180	164	119	97	77	64
CTRL (N=)	90	91	94	89	73	56	44	38

Figure 10.5: Overall success in all available dataset.

Results for the primary endpoint based on the per-protocol analysis data set were very similar to those based on the primary dataset. Overall success was achieved by 66.3% (59/89) of the investigational subjects versus 9.8% (4/41) of subjects in the control group at

12 months. The probability of superiority for the investigational group was also approximately 100%. In subjects who crossed over to receive the DIAM Spinal Stabilization System treatment after at least 6 months of conservative care was determined to have been ineffective, 75.0% of crossover subjects achieved overall success at 12 months after cross-over, a rate similar to that in subjects who completed investigational treatment as their original assignment.

Sensitivity Analysis (Worst-Case Scenario Analysis) for the Primary Endpoint

Additionally, a worst case scenario analysis was conducted for the primary endpoint of overall success at 12 months. In addition to the 150 subjects in the primary dataset, 17 subjects, including 14 randomized to the investigational group and 3 randomized to the control group, did not have evaluable overall success status. The worst case scenario considered these 14 subjects randomized to the investigational group to be failures and 3 subjects randomized to the control group to be successes for the overall success at 12 months. Combining the overall success result for the primary dataset: 62 out of 97 (63.9%) investigational subjects and 8 out of 53 (15.1%) control subjects have overall success at 12 months; the worst case scenario analysis yielded, respectively, 55.9% (62/111) and 19.6% (11/56) success rate for the investigational group and the control group. The Bayesian analysis shows that even for worst case scenario, the posterior probability of superiority of the investigational group is approximately 100% with 95% HPD interval for the difference of overall success rate between the investigational group and the control group being (21.2%, 48.7%).

10.4. Effectiveness Endpoints

Secondary efficacy variables consisted of:

- Oswestry Disability Index (ODI)
- back pain status
- leg pain status
- general health status (SF-36 Physical Component Summary)

As a component of overall success, ODI results were included in the computations of overall success presented above. ODI success and improvement, however, were also included as independent secondary efficacy variables. Results for ODI and other secondary efficacy variables are discussed in the following sections.

Oswestry Disability Index

The self-administered ODI was used to evaluate post-treatment levels of both pain and disability; both ODI success (defined as ≥ 15 points improvement as compared to baseline) and improvement in ODI scores were evaluated. Statistical comparison of the treatment groups was performed by Bayesian analysis.

At all post-treatment timepoints (up to 12 months), the ODI success rate in the investigational group was much higher than that in the control group: ODI success rates at 12 months were 69.1% (67/97) in the investigational group and 17.0% (9/53) for the control group. Bayesian analysis of ODI success at 12 months showed that for this endpoint, the posterior probability of superiority of the investigational group was approximately 100%. In addition, the 95% HPD interval for the difference of success rates between the investigational group and the control group was (36.8%, 63.8%).

ODI success in the per-protocol dataset was similar to that observed in the primary analysis population, 70.8% (63/89) of investigational subjects achieving success at 12 months compared to 12.8% (5/39) success in the control group. The posterior probability of superiority of the investigational group was essentially 100%. Similarly, 81.8% (36/44) of crossover subjects achieved success at 12 months.

For the investigational group, improvement in the mean ODI score at all timepoints as compared to baseline was significant (p-value < 0.001; p-value for reference only). For the control group, statistically significant improvement was only observed at 6 weeks and 3 months. At 12 months, the mean improvement in ODI score for the investigational group was 25.3 points, compared to a mean improvement of only 2.3 points in the control group.

Bayesian analyses for mean improvement of ODI scores at 12 months as compared to baseline found that the posterior probability of superiority of the investigational group was approximately 100% and the 95% HPD interval for the difference of mean improvements between the investigational group and the control group was (17.1, 28.9).

Mean ODI scores over time are shown for both treatment groups for the primary and all available datasets in Figures 10.6 and 10.7.

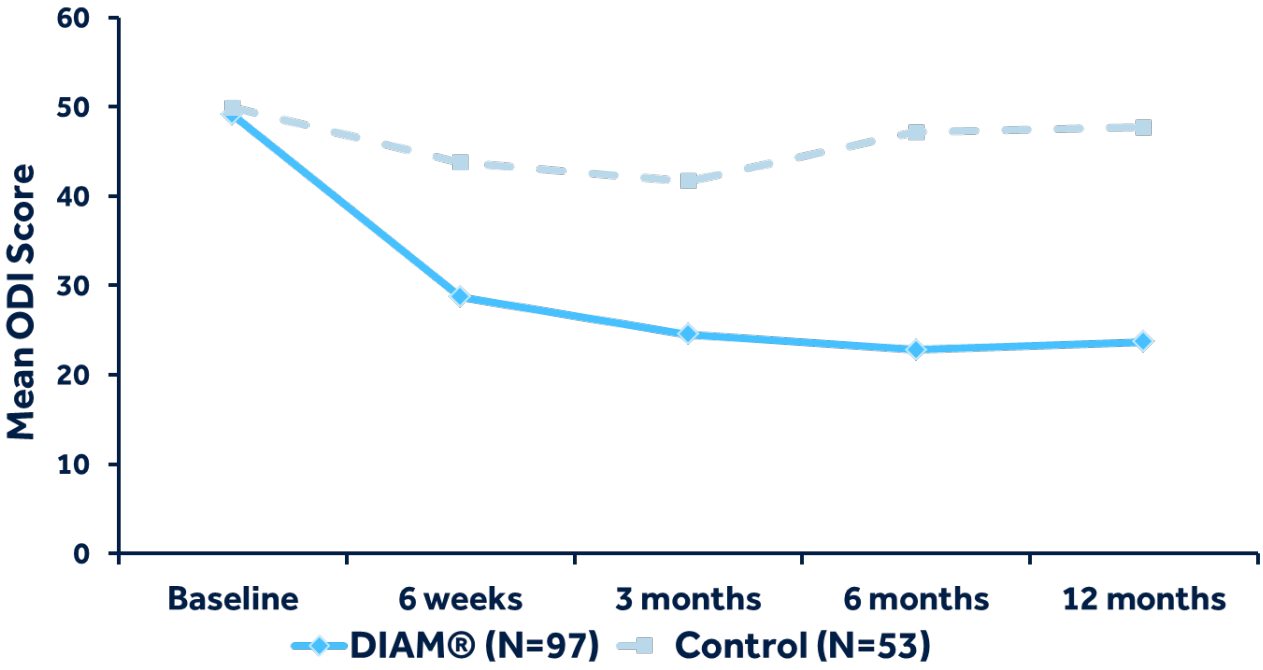
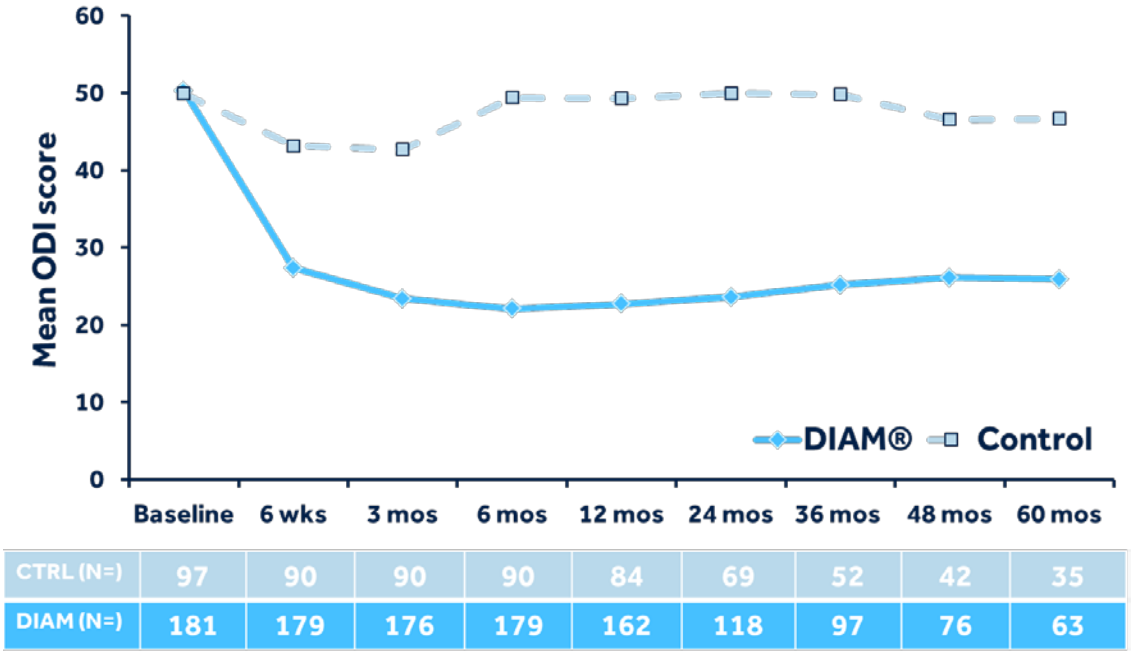


Figure 10.6: ODI scores in primary dataset.



CTRL (N=)	97	90	90	90	84	69	52	42	35
DIAM (N=)	181	179	176	179	162	118	97	76	63

Figure 10.7: ODI scores in all available dataset.

Mean ODI scores in both treatment groups in per-protocol analysis demonstrated improvements over time similar to those observed in the primary dataset. Investigational subjects had a mean baseline score of 49.3 which improved to a mean of 23.6 by 12 months,

while control subjects, with a mean of 50.1 at baseline, improved only slightly to a mean score of 48.3 at 12 months.

Back Pain

Back pain was evaluated by using a numerical rating scale which asked patients to rate both back pain intensity and frequency on a scale of 0-10, with those scores added to provide a single back pain score (out of 20 total points) as a measure of back pain status. This algorithm, which has been used in many other Medtronic-sponsored IDE studies, was developed based on the sponsor's validation research with data from more than 400 subjects in previous IDE studies, although it has not been published. Subject back pain scores were then used to calculate both back pain success (defined as any improvement over pain reported at baseline) as well as improvement in back pain scores for each subject at each visit.

At all post-treatment timepoints (up to 12 months), the back pain success rate in the investigational group was much higher than that in the control group. Back pain success rates at 12 months were 89.7% (87/97) in investigational subjects and 45.3% (24/53) in controls. Bayesian analysis of back pain success at 12 months shows that for this endpoint, the posterior probability of superiority of the investigational group was approximately 100%. In addition, the 95% HPD interval for the difference of success rates between the investigational group and the control group was (29.0%, 57.7%).

For the investigational group, improvement in mean back pain score at all timepoints as compared to baseline was significant (p-value < 0.001; p-value for reference only), while in the control group, significant improvement was not observed at 12 months. At 12 months, the mean improvement in back pain score was 8.7 points in the investigational group as compared to only 0.8 points in the control group.

Bayesian analyses for mean improvement of back pain scores at 12 months from baseline illustrated that the posterior probability of superiority of the investigational group was approximately 100% and the 95% HPD interval for the difference of mean improvement between the investigational group and the control group was (6.3, 9.5).

Mean back pain scores over time are shown for both treatment groups for the primary and all available datasets in Figures 10.8 and 10.9.

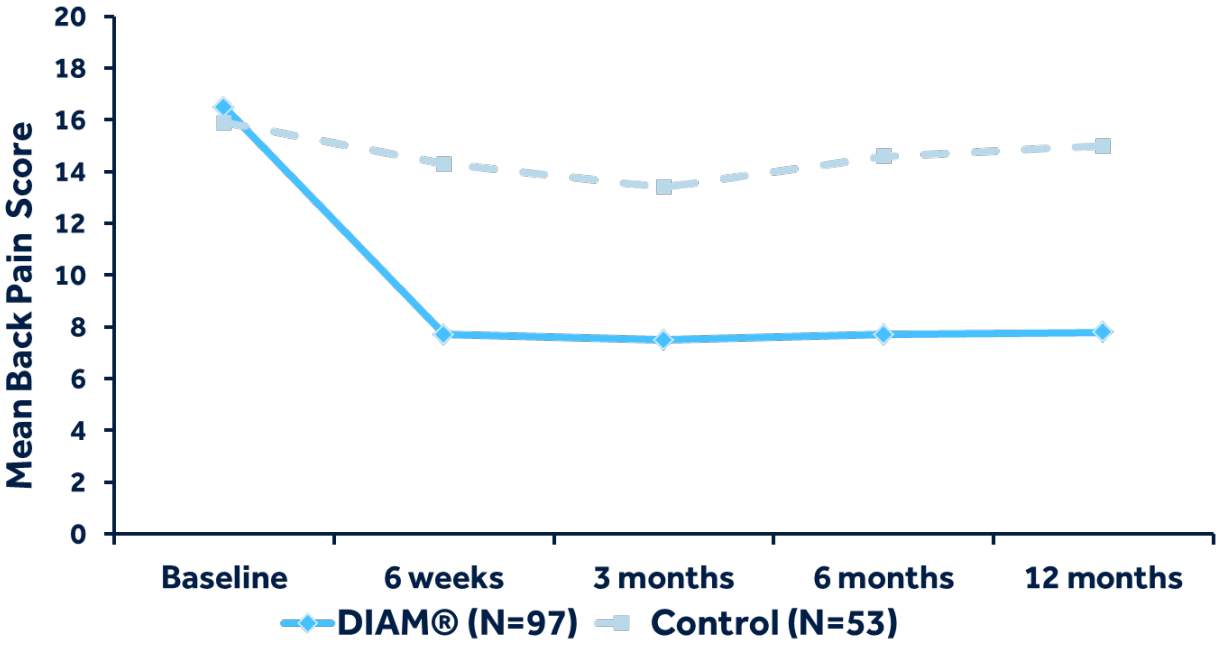
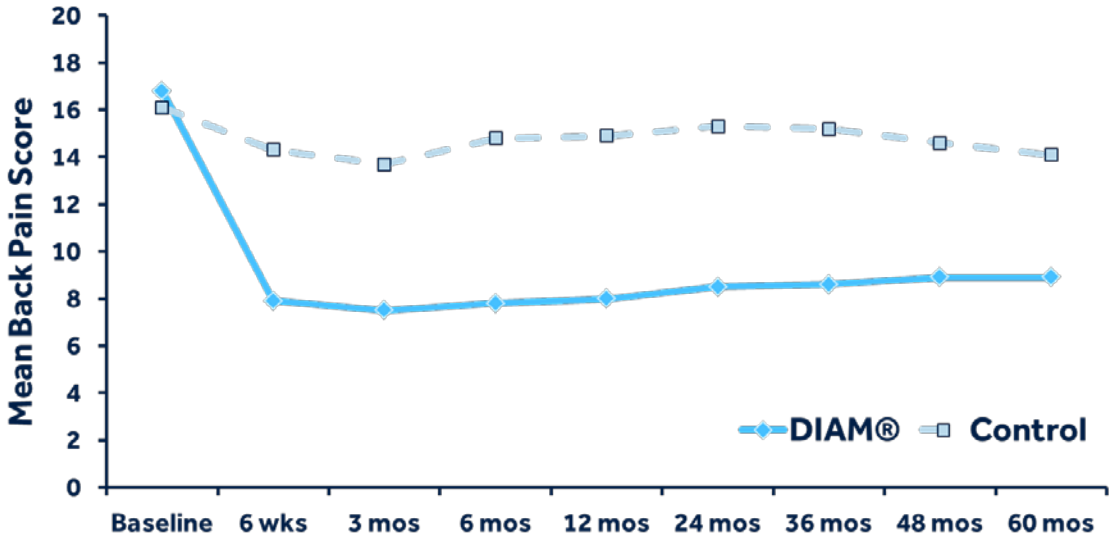


Figure 10.8: Back pain scores in primary dataset.



CTRL(N=)	97	90	90	93	84	69	52	42	35
DIAM (N=)	181	179	176	178	161	118	96	76	63

Figure 10.9: Back pain scores in all available dataset.

Leg Pain Score

Leg pain was evaluated by using a numerical rating scale, which asked subjects to rate both intensity and frequency of leg pain separately, each on a 10 point scale. A total leg pain score (scale of 20 total points) was then calculated by adding the scores for frequency and intensity, and the total leg pain score was used to calculate leg pain success (defined as any

improvement over pain reported at baseline) as well as improvement in leg pain scores for each subject at each visit. This algorithm, which has been used in many other Medtronic-sponsored IDE studies, was developed based on the sponsor's validation research with data from more than 400 subjects in previous IDE studies, although it has not been published.

At all post-treatment timepoints (up to 12 months), the leg pain success rate in the investigational group was much higher than that in the control. Leg pain success rates at 12 months were 72.2% (70/97) for the investigational group and 28.3% (15/53) for the control group. Bayesian analysis for leg pain success at 12 months shows that for this endpoint, the posterior probability of superiority of the investigational group was approximately 100%. In addition, the 95% HPD interval for the difference of success rate between the investigational group and the control group was (27.7%, 57.1%).

For the investigational group, improvement in mean leg pain score at all timepoints as compared to baseline was significant (p-value < 0.001; p-value for reference only). In contrast, no significant improvement at any time point was observed in the control group; in fact, the mean leg pain score at 12-months in the control group was significantly worse than the mean score at baseline. Mean improvement at 12 months was 5.9 points in the investigational group as compared to a mean worsening of 2.1 points in the control group.

Bayesian analyses for mean improvement of leg pain scores at 12 months from baseline illustrated that the posterior probability of superiority of the investigational group was approximately 100% and the 95% HPD interval for the difference in mean improvement between the investigational group and the control group was (5.9, 10.1).

Mean leg pain scores over time are shown for both treatment groups for the primary and all available datasets in Figures 10.10 and 10.11.

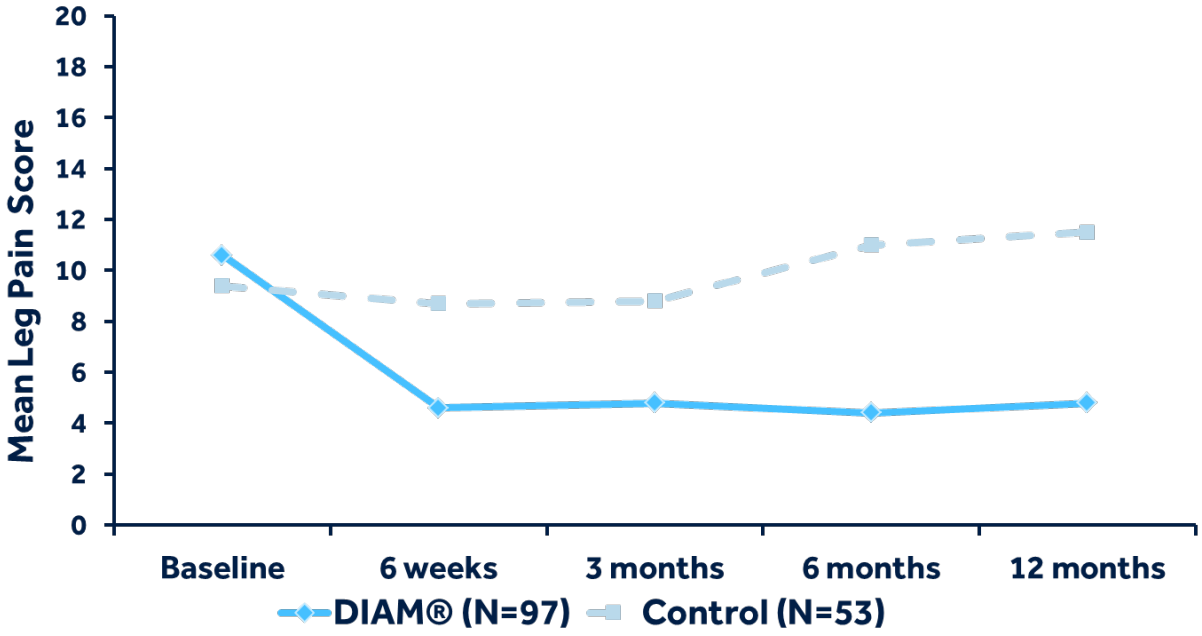
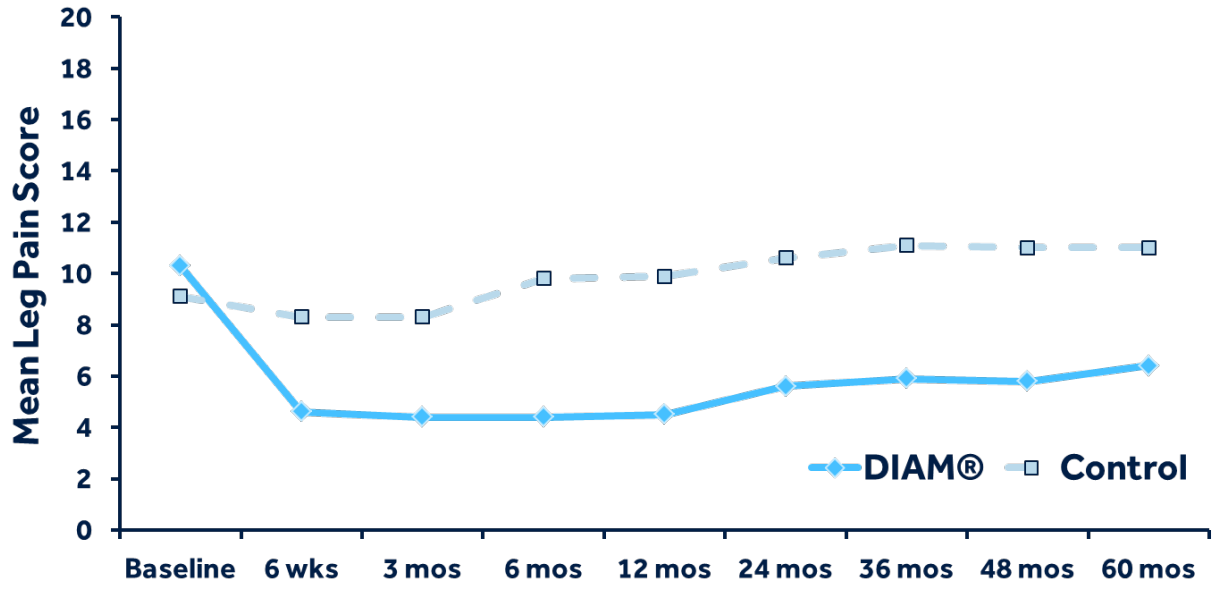


Figure 10.10: Leg pain scores in primary dataset.



CTRL(N=)	97	90	90	93	84	68	52	42	35
DIAM (N=)	181	179	176	178	162	118	97	76	63

Figure 10.11: Leg pain scores in all available dataset.

SF-36 PCS General Health Status

General health status was evaluated by the use of a validated and commonly employed instrument, SF-36, which includes both physical component summary and mental

component summary assessments. Self-reported SF-36 data were collected at baseline and at each post-treatment visit, and the rates of SF-36 PCS success (pre-specified as any improvement from baseline in SF-36 physical health component summary scores) were determined.

At all post-treatment timepoints (up to 12 months), the SF-36 PCS success rate in the investigational group was much higher than that in the control. SF-36 PCS success rates at 12 months were 87.6% (85/97) in the investigational group and 45.3% (24/53) in controls. Bayesian analysis for SF-36 PCS success at 12 months showed that for this endpoint, the posterior probability of superiority of the investigational group was approximately 100%. In addition, the 95% HPD interval for the difference in success rates between the investigational group and the control group was (26.7%, 55.9%).

For the investigational group, improvement in mean SF-36 PCS scores at all timepoints (compared to baseline) was significant (p-value < 0.001; p-value for reference only). For the control group, significant improvement was observed only at 6 weeks. At 12 months, improvement in mean SF-36 PCS score was 14.0 points in the investigational group as compared to only 0.4 point in the control group.

Bayesian analyses for mean improvement of SF-36 PCS scores at 12 months from baseline illustrated that the posterior probability of superiority of the investigational group was approximately 100% and the 95% HPD interval for the difference of mean improvement between the investigational group and the control group was (10.4, 16.8).

Mean SF-36 PCS scores over time are shown for both treatment groups for the primary and all available datasets in Figures 10.12 and 10.13

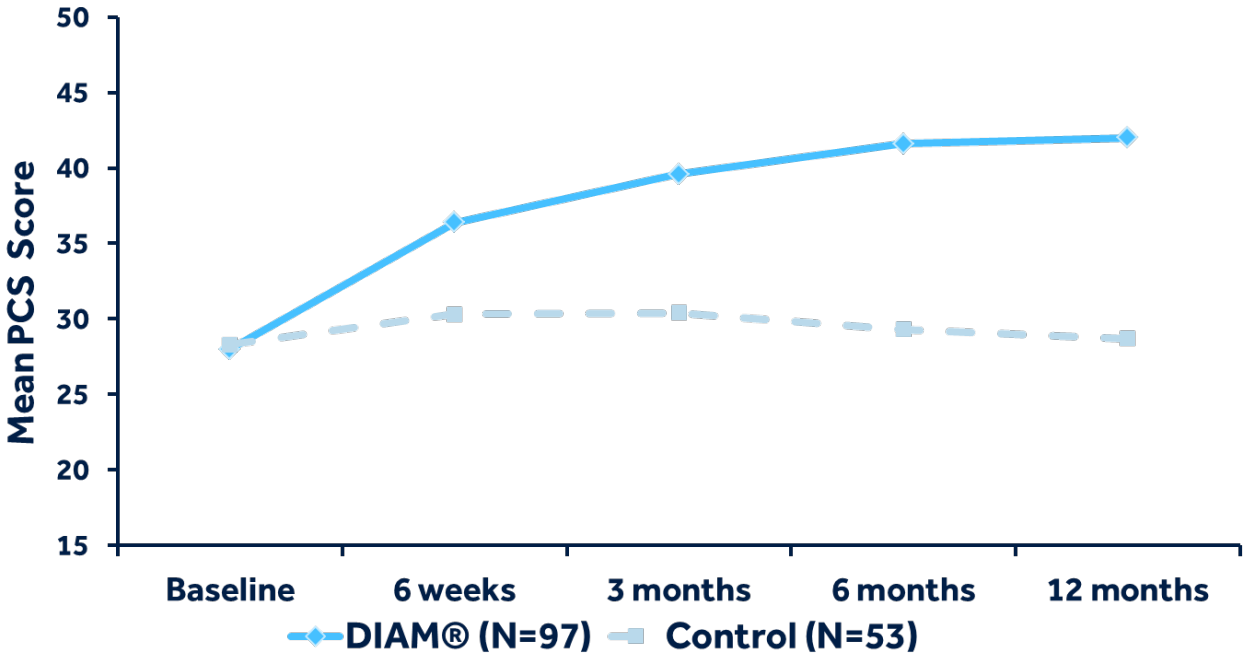
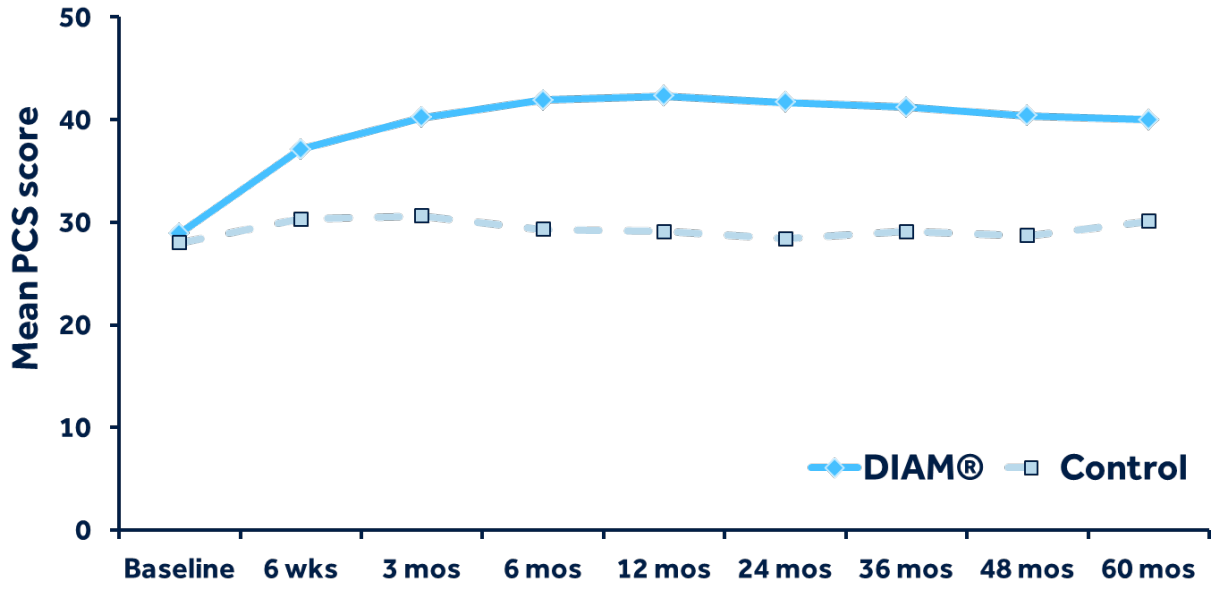


Figure 10.12: SF-36 PCS scores in primary dataset.



CTRL(N=)	97	90	89	93	84	69	52	42	35
DIAM (N=)	180	175	175	178	162	117	96	76	63

Figure 10.13: SF-36 PCS scores in all available dataset.

10.5. Other Evaluations

Patient Satisfaction

Subjects were asked to evaluate their satisfaction with their study treatment at each visit (beginning 6 weeks after treatment initiation). Subjects were asked to define their level of agreement with three different statements:

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

Subjects were asked to respond to those questions by choosing from the following list of predetermined responses:

- Definitely true
- Mostly true
- Do not know
- Mostly false
- Definitely false

Each question was evaluated separately. Success for each question was defined as "definitely true" or "mostly true" in response. For each time point in the primary dataset, DIAM subjects were more satisfied with treatment. The results of patient satisfaction for each time point are presented in Figure 10.14 below.

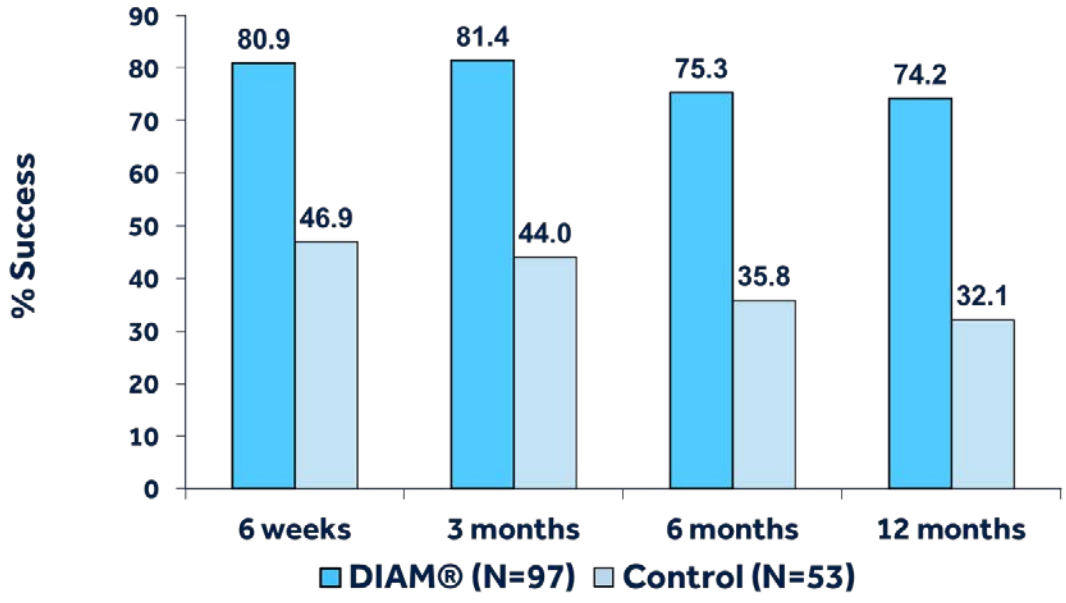


Figure 10.14: Percentage of subjects satisfied with treatment.

Medication Usage and Injections

Although no statistical analysis was performed, use of pain medications (narcotic and non-narcotic), NSAIDS and muscle relaxants was recorded for all study subjects; and similarly various spinal injections were also recorded. At follow-up, use of pain medications and injection therapy was consistently higher in the control group than in the investigational group; use of antidepressants and neuroleptics in the two treatment groups tended to be more similar.

For example, in the primary dataset, at baseline, the percentages of subjects using narcotic pain medications are similar in the investigational group (46 of 73 or 63.0%) and the control (26 of 42 or 61.9%). In the control group, the percentages of subjects taking narcotics are consistent over time (e.g., 32 of 52 or 61.5% at 12 months) whereas the number of investigational subjects who were taking narcotics substantially decreased (e.g., 34 of 97 or 35.1% at 12 months). The results for subjects using narcotics in the primary dataset are presented in the Figure 10.15 below.

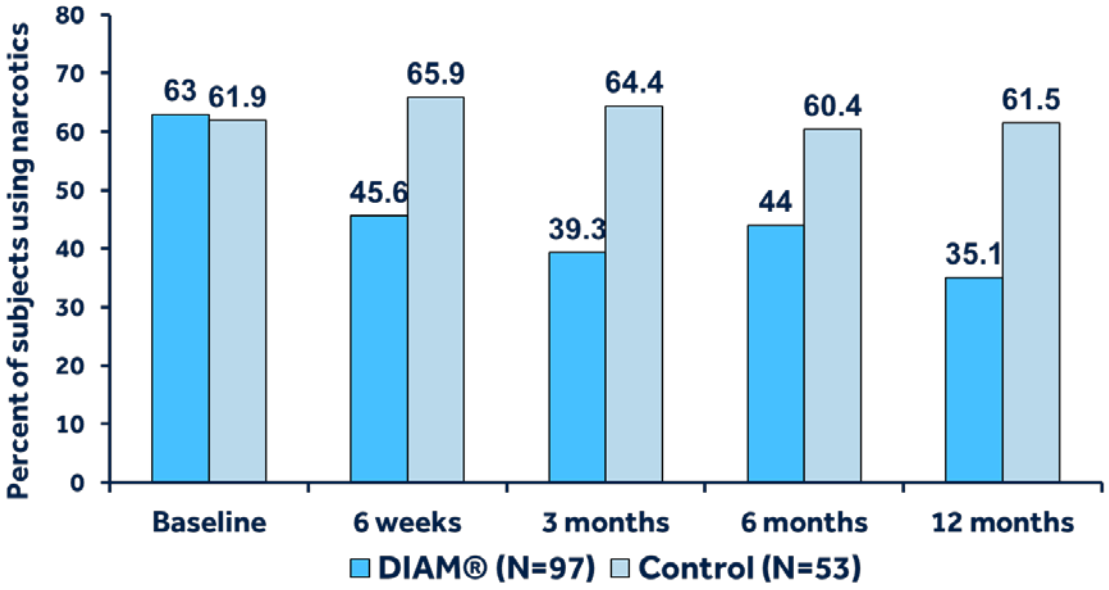


Figure 10.15: Percentage of subjects using narcotics in the primary dataset.

Similarly for spinal injections, in the primary dataset, up to 12 months, 13 (13.4%) of 97 investigational subjects had cumulatively 47 injections, compared to 24 (45.3%) of 53 control subjects with 66 injections. The results for subjects that received spinal injections at the target level in the primary dataset are presented in the Figure 10.16 below.

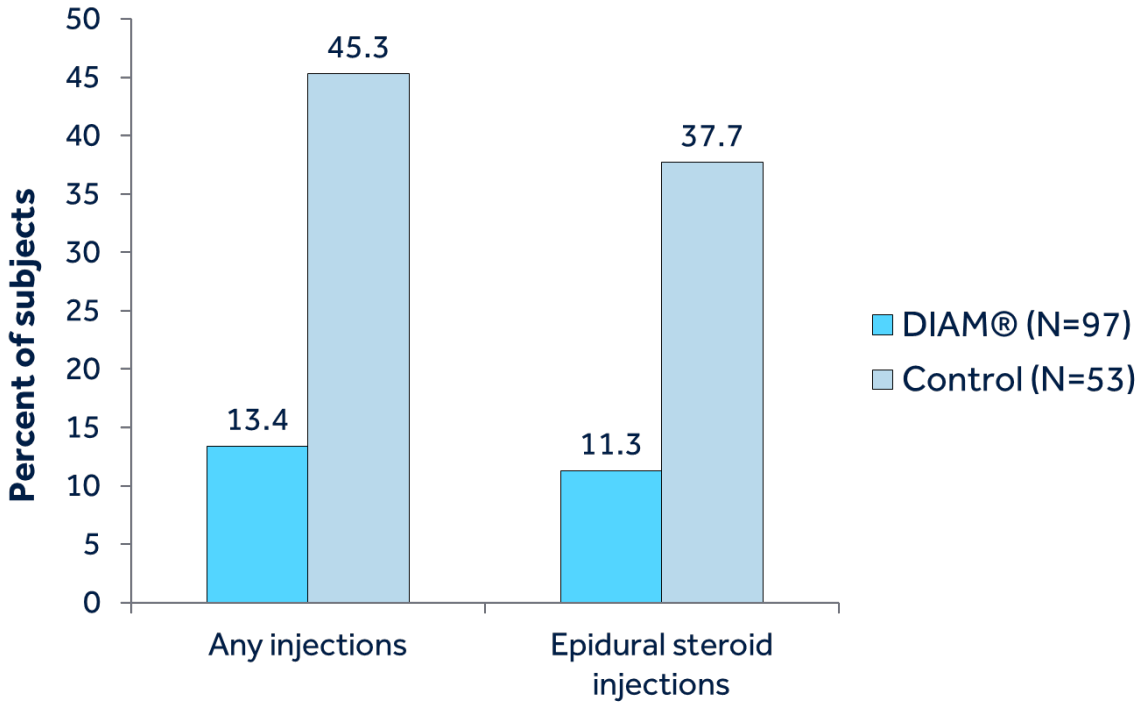


Figure 10.16: Percentage of subjects using narcotics in the primary dataset.

10.6. Radiologic Observations

10.6.1. Spinous Process Fractures

According to the imaging review protocol, independent reviewers from the core laboratory assessed the presence of spinous process fractures at each time point; from these original core laboratory data, the occurrence, timing and healing could be derived. However the readers from the core laboratory were not specifically directed to assess the anatomical location of a fracture or the status of fracture displacement or healing. In response to an FDA question, Medtronic conducted an internal review of images with a radiologist consultant for the few subjects with an adjudicated positive outcome for the presence of spinous process fractures since the imaging review protocol did not indicate for independent reviewers to assess anatomical fracture location, displacement status and healing status; in these additional methods used, healing status was driven by the original prospectively defined core laboratory findings of spinous process fracture and in no case did the retrospective review indicate healing when the core lab results indicated presence of a fracture at the last available time point (though there was a case where the additional review found a spinous process fracture present at the last time point where the core lab indicated no fracture and this was considered unhealed). Finally, to be transparent and as accurate as possible with regard to the total number of spinous process fractures observed in the trial, all spinous process fractures including those that were reported

clinically (and not necessarily radiographically) via adverse event case report forms are included; typically information was not available about fracture location, displacement or healing in these cases. The following observations were noted from these reviews:

1) The overall spinous process fracture rate for investigational and crossover DIAM subjects (from radiographs and AE reports; approximately 7.9%, or 19/240) is low. In comparison to other interspinous process devices studied in randomized IDE clinical trials; the overall rate found for DIAM is lower than that reported for both Coflex (18.0%) [36] and Superion (12.1%)[37] and is similar to that reported for X-STOP (6.5%).[27]
2) Occur primarily at the spinous process tip and posterior to the device core. For unique subjects where an anatomic location was able to be determined, 12/14, or 85.7%, had the primary fracture line posterior to the spinous processes bone/investigational device core interface.
3) Most spinous process fractures are detected relatively early (i.e., 16/19, or 84.2%, were detected within 6 months post-operative).
4) Most occurrences of spinous process fractures are asymptomatic. Only 6 of 19, or 31.6%, came to clinical attention; 10 of 19 subjects had a positive overall success outcome at the last available visit.
5) Occurrences of fracture often spontaneously heal. For unique subjects where a healing status was able to be determined, 10/15, or 66.7%, had a spinous process fracture that healed.

10.6.2. Mechanical Contour Changes

As the DIAM Spinal Stabilization System obligatorily contacts bone, radiologic reviewers at the core laboratory independently identified possible radiologic changes to areas of bone in contact with the DIAM device at every post-surgery visit; this assessment included the presence or absence of bony erosion. If the opinions of two independent radiologic reviewers with respect to the presence of or absence of changes to bone were in conflict, a third independent reader was employed to adjudicate the result. The context of this data discussion is the all available dataset since the focus of the analyses is to explore the relationship between focal bone structural changes and study outcomes, not to compare treatment groups.

The original imaging review protocol called for assessment of presence or absence of bony erosion but did not provide a definition regarding what constitutes bony erosion. Therefore, FDA requested an additional evaluation. To accomplish this, a separate group of independent imaging core lab radiologists performed a supplementary review of positive erosion cases (based upon adjudicated results from the original independent radiologic reviewers) in order to sub-classify the bony

changes of spinous processes in those cases after implantation. In accordance with a medical image data review protocol supplement, changes to bone observed were categorized by these readers as either mechanical contour change or inflammatory erosion, according to the definitions in Table 10.3. The location and extent of the changes were also defined according to the criteria in Table 10.4.

Table 10.3: Characterization of focal bone structural changes observed by independent radiologic reviewers.

Mechanical Contour Change	Change consistent with remodeling within the spinous process due to removal of some bone at surgery and/or altered mechanical loading/pressure with visual maintenance of or increased density of cortical bone at the device/bone interface or other locations within the spinous process.
Inflammatory Erosion	Change characterized as bony foci changes manifested by resorption/osteolysis at the spinous process bone cortex or device/bone interface and visually decreased deep bone density.

Table 10.4: Sub-localization of focal bone structural changes observed by independent radiologic reviewers.

Location of focal bone structural change and/or inflammatory erosion	• at DIAM core/spinous process interface • at DIAM tether/spinous process interface • Other location (specified)
Extent of focal bone structural change and/or inflammatory erosion	• ≤ 15% of the spinous process area • > 15% but ≤ 30% of the spinous process area • > 30% of the spinous process area

Based upon the supplemental review at all follow-up time points, focal bone structural changes were determined to be mechanical contour changes, consistent with pressure/mechanical loading with maintenance of or increased cortication at the implant/bone interface as may be anticipated by Wolff's law. Importantly, none of the focal bone structural changes were classified as inflammatory erosions associated with decreased bone density that may be manifested by resorption/osteolysis. Mechanical contour changes noted were more frequent at the implant core/bone interface and more frequent at the superior spinous process with the overall rate reaching a peak at approximately 50% of subjects at 36 months.

The results from a stepwise logistic regression analysis suggested that there was not a reliable predictor among the 36 demographic and baseline factors considered for focal bone structural change. In addition, a large number of subgroup analyses comparing the presence and absence of mechanical contour change subgroups

revealed no consistent relationship between mechanical contour changes with overall success, ODI, back pain, leg pain, and SF-36 scores or adverse event profiles, secondary surgeries, or neurological success.

Overall, noted focal bone structural changes are not likely to represent a pathologic response because all were found to be mechanical contour changes consistent with Wolff's law and do not appear to be associated with an inflammatory erosion process. Additionally, because there were no consistent relationships between mechanical contour changes and baseline factors, or key efficacy or safety variables at 12, 24 or 36 months, these data suggest that the mechanical contour changes observed do not have a clinically meaningful impact on efficacy or safety outcomes.

10.6.3. Disc Height Measurements

Disc height was measured at the target level in the lateral neutral position at the most anterior and posterior margin of the disc space. Disc height was read independently by two radiologic reviewers.

Disc height success status was determined in order to assess whether disc height had been maintained post-treatment, and posterior and anterior measurements at every follow-up visit were compared to those obtained at 6 weeks. Disc height success was defined as having less than or equal to 2 mm decrease in either the anterior or posterior disc height as compared to that at the 6-week visit. If a discrepancy existed between the two primary readers, a third reader would provide adjudication; if the third reader failed to resolve, disc height status was considered missing.

In the primary analysis dataset, disc height success was observed in 100% of subjects in both the investigational and control groups, at every postoperative measurement (3, 6, and 12 months).

In addition to disc height success as defined in the protocol as the decrease of less than or equal to 2 mm from the measurement at 6 weeks, an additional examination of disc height data was presented. The DIAM device may act on the posterior part of the functional spinal unit and disc by load sharing via its placement between spinous processes. Therefore, the mean posterior disc heights over time from the pre-treatment baseline to post-treatment time points for both treatment groups in the primary dataset are presented in Figure 10.17 below.

Together with the angular motion information presented in the next section, these data suggest a contribution of DIAM in posterior load sharing while preserving motion and providing index-level stability in flexion/extension that is maintained over time.

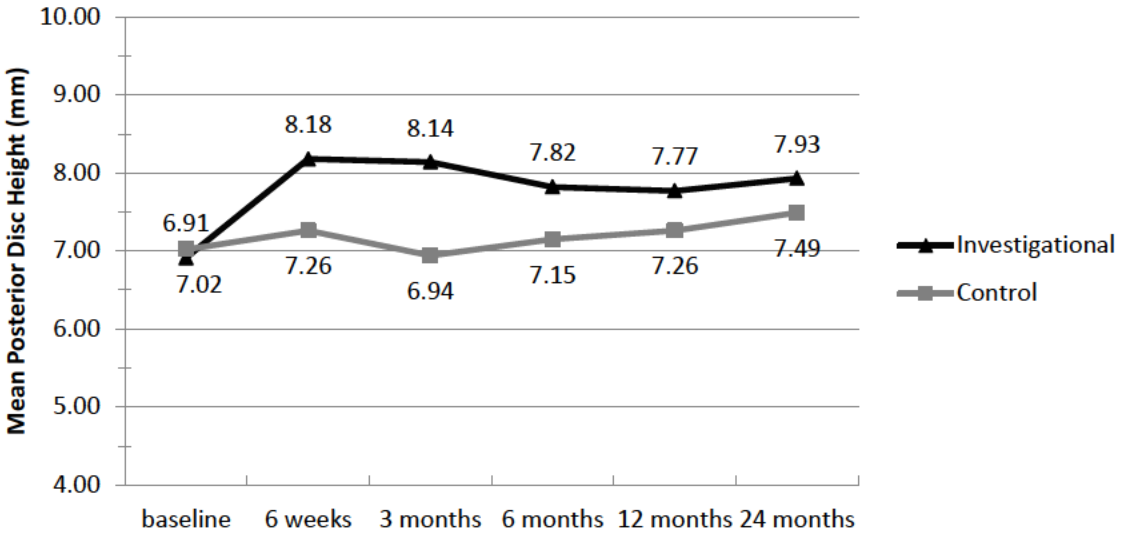


Figure 10.17: Mean posterior disc height over time in primary dataset.

The mean posterior disc height at the target level for the investigational group increased, on average, from 6.91 mm at baseline to 8.18 mm at 6 weeks, 8.14 mm at 3 months, 7.82 mm at 6 months, and 7.77 mm at 12 months. Although the primary endpoint for this study is 12 months, the posterior disc height was even maintained through 24 months in primary dataset analysis. These postoperative increases from baseline were all statistically significant ($p<0.001$; p-value for reference only). As a comparison, the mean posterior disc height change from the baseline for the control group was not statistically significant at any of those post-treatment time points, other than 24 months.

Furthermore, all available data analysis showed the mean posterior disc heights in investigational subjects were significantly increased ($p<0.001$; p-value for reference only) from baseline at all the postoperative time points from 6 weeks and maintained through 60 months post-operation, the latest time point when a meaningful number of patients have been evaluated.

10.6.4. Angular Motion Measurements

Using lateral flexion and extension radiographs at each evaluation time point, angular ROM (defined as absolute value of flexion – extension) was measured and then averaged for both the index and adjacent levels by two independent radiographic reviewers. At the target level, average angulation was comparable between the investigational and control groups at baseline, 6 months, and 12 months post treatment. Within the investigational group, on average, angulation was significantly reduced (-2.28 degrees) at 6 weeks postoperative ($p<0.001$; p-values in this section are for reference only) and -1.49 degrees at 3 months postoperative ($p=0.003$). Change from baseline in angulation was no longer statistically different

at 6 months postoperative (-0.58 degrees; p=0.228) and 12 months postoperative (0.10 degrees; p=0.834) in the investigational group. For the immediate superior and inferior adjacent levels, average angulation was also comparable between the investigational and control groups at all follow-up time points.

Intervertebral angle at the extension position at the target level may reveal a clearer impact of the implantation of the DIAM device. Figures 10.18 and 10.19 below present mean intervertebral angles at the target level over time for both treatment groups, respectively for those at the extension and flexion positions.

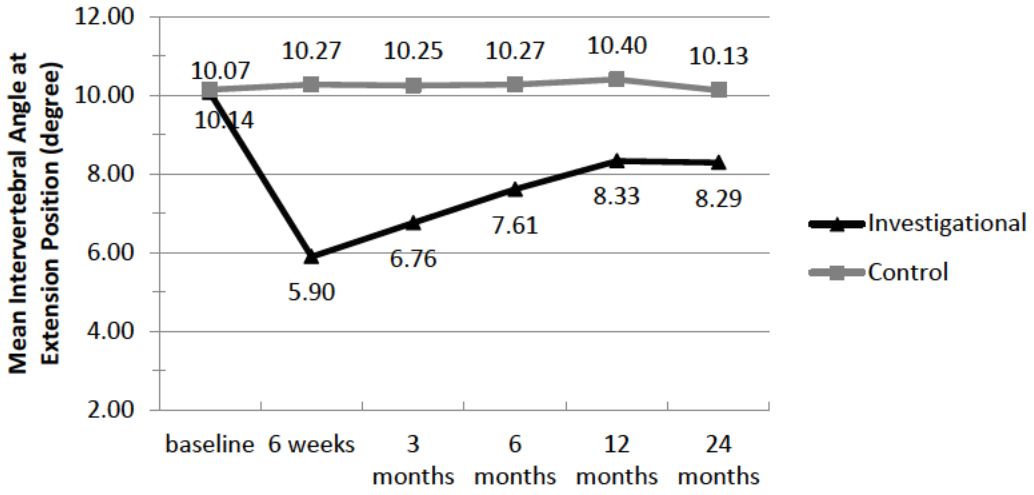


Figure 10.18: Mean intervertebral angle at extension position in primary dataset.

The mean intervertebral angle at extension position at target level for the investigational group decreased from 10.07 degrees at baseline to 5.90 degrees at 6 weeks, 6.76 degrees at 3 months, 7.61 degrees at 6 months, 8.33 degrees at 12 months, and 8.29 degrees at 24 month. These postoperative decreases from the baseline were all statistically significant ($p<0.001$; p-value for reference only). As a comparison, the mean intervertebral angle at the extension position for the control group did not significantly change at any of those post-treatment time points from baseline.

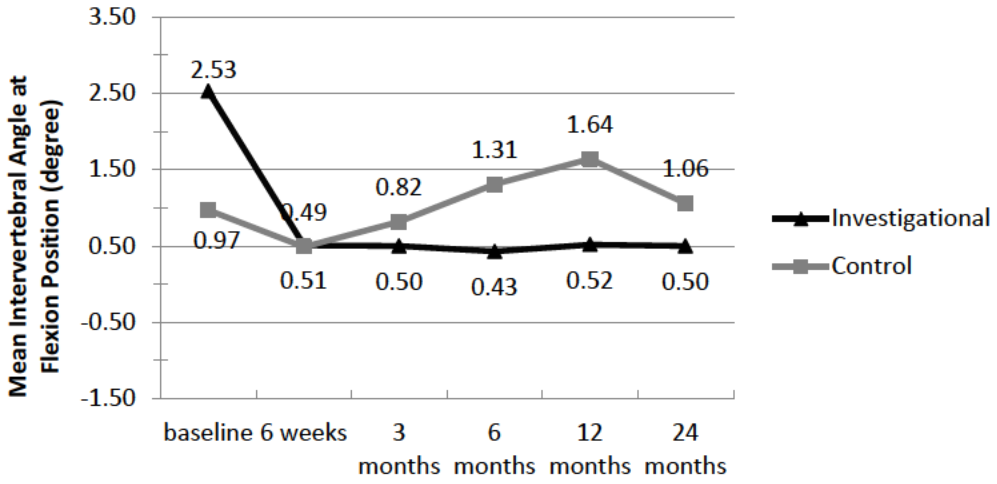


Figure 10.19: Mean intervertebral angle at flexion position over time in primary dataset.

Similarly, the mean intervertebral angle at flexion position at the target level for the investigational group decreased from 2.53 degrees at baseline to 0.51 degrees at 6 weeks, 0.50 degree at 3 months, 0.43 degree at 6 months, 0.52 degree at 12 months, and 0.50 degrees at 24 months. These postoperative decreases from baseline were all statistically significant ($p<0.001$; p-value for reference only). As a comparison, the mean intervertebral angle at flexion position for the control group did not significantly change at any of those post-treatment time points from baseline.

Furthermore, all available data analysis showed the mean intervertebral angle at the extension position in investigational subjects were significantly increased ($p<0.001$; p-value for reference only) from baseline at all the postoperative time points from 6 weeks and maintained through 60 months post-operation, the latest time point when a meaningful number of patients have been evaluated.

Together with the disc height information presented in the prior section, these data suggest a contribution of DIAM in posterior load sharing while preserving motion and providing index-level stability in flexion/extension that is maintained over time.

10.7. Safety

10.7.1. Neurological Status

Neurological status included evaluations of motor, sensory, and reflex function as well as straight leg raise. Neurological status of the patients participating in the clinical study was assessed at baseline and at every post-treatment follow-up visit. (Motor, sensory and reflex status was also evaluated at surgery discharge for investigational subjects). Each assessment defined neurological function as "normal" or "abnormal"; if a function was deemed to be abnormal, documentation

of the abnormal findings for each element of the functional category assessed was required. Neurological success for each functional category was defined as post-treatment maintenance or improvement of each assessed element in that category, as compared to pre-treatment status for each element. Overall neurological success required success for all four functions. If any specific elements worsened compared to its pre-treatment value, the corresponding function and overall neurological status was deemed a failure, regardless of whether or not the other elements were maintained or improved.

Neurological status was evaluated as a safety measure at every study time point. In the primary analysis dataset, neurological success rates were, in general, numerically higher in the investigational group than in the control group at all-time points as shown in Figure 22. In particular, at 12 months, 86.6% (84/97) of the investigational subjects and 84.9% (45/53) of the control subjects achieved neurological success.

The Bayesian analyses for neurological success at 12 months illustrated that the posterior probability of superiority of the investigational group is 63.4%, which is below the threshold of 97.5% for superiority. However, the 95% HPD for the difference in the neurological success rates between the investigational group and the control group is (-9.3%, 14.4%) with “0” being contained in the interval, suggesting that the rates are not statistically different between the two groups. This is expected, since this moderate low back pain population does not typically present with neurological deficits.

10.7.2. Adverse Events

For this study, an adverse event was defined as any clinically adverse sign, symptom, syndrome, or illness (not already being measured in the trial) that had onset or that worsened during the treatment period of the trial, regardless of causality.

Expected sequelae, related to recent surgery in the investigational group were excluded and, according to the protocol, were not required to be reported as adverse events unless the investigator deemed otherwise.

The 95% highest posterior density (HPD) interval was used for assessing between-group differences by using Bayesian methods. The statistical comparison of each category of adverse events based on the 95% HPD interval is for reference only. Caution should be observed when making any statistical inference for each adverse event category due to multiple comparisons performed.

The safety of the investigational device was evaluated based on the nature and frequency of AEs in the investigational group as compared to those experienced by control group who received conservative care treatment. Adverse event

categorization was based on the description of the adverse event as reported by the investigator. For example, if a diagnosis was provided, the event was placed in a class of event appropriate to the diagnosis (e.g., diagnosis of diabetes was categorized an endocrine event). If signs or symptoms were reported, then the adverse event was assigned a category most appropriate for the signs and symptoms and a diagnosis was not assumed (e.g., foot pain was categorized as a lower extremity pain event).

In addition, each adverse event was assessed for its severity, seriousness, and association with treatment by an independent Clinical Adjudication Committee (CAC).

Severity of adverse events were rated as mild, moderate, severe, or life-threatening (Grades 1-4), according to a modified version of the World Health Organization (WHO) Recommendations. Any adverse event rated Grade 4 was automatically considered a serious adverse event.

All serious adverse event determinations, regardless of association with the study treatment, were assessed according to the ISO 14155-1 Serious Adverse Event (SAE) definition.

Table 10.5 summarizes the total number of adverse events for the primary data set and the number of subjects who reported an adverse event segmented by cohort with a comparison of adverse event type based on association with study treatment, severity determination, and seriousness determination. The rates of subjects in the primary dataset experiencing any adverse event(s) were, respectively, 87.6% (85/97) in the investigational group and 75.5% (40/53) in the control group.

Table 10.5: Summary of all adverse events in the primary dataset.

	Number of Events		**Number of Subjects** Number (%)	
Type of Event	Investigational	Control	Investigational N=97	Control N=53
Any events	408	109	85 (87.6)	40 (75.5)
Any events associated with study treatment	28	42	11 (11.3)	23 (43.4)
Any Grade 3 or 4 severity events [38]	114	29	38 (39.2)	13 (24.5)
Grade 3 or 4 severity events associated with treatment	10	17	4 (4.1)	6 (11.3)
Any serious events	340	87	80 (82.5)	34 (64.2)
Serious events associated with treatment	25	38	8 (8.2)	19 (35.8)

Table 10.6 displays the posterior mean difference (95% HPD) between the investigational group and the control group for all adverse events and per type of adverse event for subjects in the primary data set. The posterior mean difference (95% HPD) between the investigational group and the control group was 12.3% (-0.6%, 25.7%) with 0 being contained in the interval, demonstrating that there is no significant difference between the two groups with regard to the rate of any adverse events.

Table 10.6: Posterior mean difference for all adverse events in the primary analysis dataset.

Type of Event	Investigational (N=97)	Control (N=53)	Investigational-Control
	Number of Subjects (%)	Number of Subjects (%)	Posterior Mean Difference (95% HPD)
Any event	85 (87.6%)	40 (75.5%)	12.3% (-0.6%, 25.7%)
Accidental injury/muscle strain	13 (13.4)	4 (7.5)	5.1% (-5.4%, 15.1%)
Anatomical/technical difficulty	2 (2.1)	0 (0.0)	1.2% (-3.9%, 6.2%)
Cardiac disorders	1 (1.0)	1 (1.9)	-1.6% (-7.8%, 3.7%)
Congenital/familial/genetic disorders	1 (1.0)	0 (0.0)	0.2% (-4.7%, 4.7%)
Ear/labyrinth disorders	2 (2.1)	0 (0.0)	1.2% (-4.0%, 6.2%)
Endocrine disorders	0 (0.0)	1 (1.9)	-2.6% (-8.5%, 2.0%)
Eye Disorders	2 (2.1)	0 (0.0)	1.2% (-4.0%, 6.2%)
Gastrointestinal disorders	12 (12.4)	4 (7.5)	4.0% (-6.1%, 14.0%)
General Disorders/administration site conditions	6 (6.2)	1 (1.9)	3.4% (-3.9%, 10.5%)
Hematological	2 (2.1)	0 (0.0)	1.2% (-4.0%, 6.2%)
Immune system disorders	3 (3.1)	0 (0.0)	2.2% (-3.1%, 7.7%)
Implant event	5 (5.2)	0 (0.0)	4.2% (-1.7%, 10.4%)
Incision related (non-infectious)	13 (13.4)	0 (0.0)	12.3% (4.8%, 20.2%)
Infection	16 (16.5)	3 (5.7)	9.9% (-0.2%, 20.1%)
Investigations	6 (6.2)	2 (3.8)	1.6% (-6.5%, 9.4%)
Metabolism/nutrition disorders	6 (6.2)	0 (0.0)	5.2% (-0.9%, 11.6%)
Musculoskeletal/pain events (possible spine etiology)	31 (32.0)	17 (32.1)	-0.4% (-15.8%, 14.8%)
Neurological	20 (20.6)	7 (13.2)	6.7% (-5.7%, 18.8%)
Other	3 (3.1)	0 (0.0)	2.2% (-3.3%, 7.6%)
Other musculoskeletal/pain events (non-spinal)	20 (20.6)	4 (7.5)	12.1% (1.0%, 23.0%)
Psychiatric disorders	10 (10.3)	2 (3.8)	5.7% (-3.1%, 14.3%)
Renal/urinary disorders	5 (5.2)	0 (0.0)	4.2% (-1.7%, 10.3%)
Reproductive system/breast disorders	7 (7.2)	1 (1.9)	4.4% (-2.9%, 11.9%)

Type of Event	Investigational (N=97)	Control (N=53)	Investigational-Control
	Number of Subjects (%)	Number of Subjects (%)	Posterior Mean Difference (95% HPD)
Respiratory disorders	6 (6.2)	1 (1.9)	3.4% (-3.8%, 10.5%)
Skin disorders	4 (4.1)	0 (0.0)	3.2% (-2.4%, 9.0%)
Spine event	33 (34.0)	18 (34.0)	-0.2% (-15.9%, 15.2%)
Surgical/medical procedure	6 (6.2)	1 (1.9)	3.4% (-3.8%, 10.5%)
Trauma	14 (14.4)	4 (7.5)	6.1% (-4.4%, 16.3%)
Vascular disorders	8 (8.2)	1 (1.9)	5.5% (-2.2%, 13.1%)

Detailed summary tables for all adverse events over time are provided in Appendix 1 and 2 for the primary and all available datasets, respectively.

Serious Adverse Events

Adverse event seriousness was assessed by a Clinical Adjudication Committee (CAC) according to the definition in the protocol. Serious adverse events were defined as events occurring after treatment initiation that led to a death or resulted in substantial physical harm which led to the serious deterioration in the health of the subject or led to fetal distress, death, or congenital abnormality to a fetus carried by the subject. A total of 340 serious adverse events occurred in 80/97 (82.5%) investigational subjects while 34/53 (64.2%) control subjects reported a total of 87 serious adverse events. The number of subjects in the primary dataset experiencing serious adverse events by category are shown in Table 10.7.

Table 10.7: Summary of serious adverse events through 12 months in the primary analysis dataset.

Type of Event	Investigational (N = 97)	Control (N = 53)
	Number of Subjects (%)	Number of Subjects (%)
Any Serious Adverse Events	80 (82.5)	34 (64.2)
Accidental Injury/Muscle Strain	12 (12.4)	4 (7.5)
Anatomical/Technical Difficulty	2 (2.1)	0 (0.0)
Cardiac Disorders	1 (1.0)	1 (1.9)
Congenital/Familial/Genetic Disorders	1 (1.0)	0 (0.0)
Ear/Labyrinth Disorders	1 (1.0)	0 (0.0)
Endocrine Disorders	0 (0.0)	1 (1.9)
Eye Disorders	2 (2.1)	0 (0.0)
Gastrointestinal Disorders	8 (8.2)	3 (5.7)

Type of Event	Investigational (N = 97)	Control (N = 53)
	Number of Subjects (%)	Number of Subjects (%)
General Disorders/Administration Site Conditions	5 (5.2)	1 (1.9)
Immune System Disorders	1 (1.0)	0 (0.0)
Implant Event	3 (3.1)	0 (0.0)
Incision Related (Non-Infectious)	9 (9.3)	0 (0.0)
Infection	12 (12.4)	2 (3.8)
Investigations	4 (4.1)	2 (3.8)
Metabolism/Nutrition Disorders	6 (6.2)	0 (0.0)
Musculoskeletal/Pain Events (Possible Spine Etiology)	25 (25.8)	14 (26.4)
Neurological	17 (17.5)	2 (3.8)
Other	3 (3.1)	0 (0.0)
Other Musculoskeletal/Pain Events (Non-Spinal)	18 (18.6)	3 (5.7)
Psychiatric Disorders	10 (10.3)	2 (3.8)
Renal/Urinary Disorders	4 (4.1)	0 (0.0)
Reproductive System/Breast Disorders	7 (7.2)	0 (0.0)
Respiratory Disorders	5 (5.2)	1 (1.9)
Skin Disorders	3 (3.1)	0 (0.0)
Spine Event	31 (32.0)	17 (32.1)
Surgical/Medical Procedure	5 (5.2)	1 (1.9)
Trauma	11 (11.3)	3 (5.7)
Vascular Disorders	8 (8.2)	1 (1.9)

Adverse Events Associated with Treatment

Adverse event association with study treatment was assessed by Clinical Adjudication Committee (CAC) according to the definitions as defined in the protocol.

- **Implant Associated**: Adverse event for which there is a reasonable possibility that the event may have been primarily caused by the implant/implant component.
- **Implant/Surgical Procedure Associated**: Adverse event for which there is a reasonable possibility that the event may have been caused both by the implant/implant component and the surgical procedure.

- **Surgical Procedure Associated**: Adverse event for which there is a reasonable possibility that the event may have been caused primarily by the surgical procedure.
- **Nonoperative Treatment Associated**: Adverse event for which there is a reasonable possibility that the event may have been caused primarily by the nonoperative treatment.
- **Undetermined:** Adverse event for which sufficient information is not available at the time of the event to determine its causality.
- **Not Related**: Adverse event for which sufficient information exists to indicate that the etiology is unrelated to the implant or surgical procedure.

Any event categorized as Implant Associated or Implant/Surgical Procedure Associated was considered to be "associated with treatment" for the investigational group in the analyses. Any event categorized as Nonoperative Treatment Associated was considered to be "associated with treatment" for the control group in the analyses.

A summary of adverse events in the primary data set considered to be associated with treatment is shown in Table 10.8. Eleven (11.3%) investigational group subjects reported 28 adverse events considered to be associated with treatment, while 23 (43.4%) control subjects reported 42 adverse events considered to be associated with treatment.

Table 10.8: Summary of adverse events associated with treatment through 12 months in the primary analysis dataset.

Type of Adverse Events	Investigational (N = 97)	Control (N = 53)
	Number of Subjects (%)	Number of Subjects (%)
Any Related Event	11 (11.3)	23 (43.4)
Anatomical/Technical Difficulty	1 (1.0)	0 (0.0)
Implant Event	3 (3.1)	0 (0.0)
Investigations	0 (0.0)	1 (1.9)
Musculoskeletal/Pain Events (Possible Spine Etiology)	1 (1.0)	14 (26.4)
Neurological	1 (1.0)	1 (1.9)
Spine Event	7 (7.2)	11 (20.8)
Trauma	1 (1.0)	0 (0.0)

Table 10.9 summarizes the serious adverse events in the primary dataset considered to be associated with treatment. Eight (8.2%) investigational group subjects reported 25 adverse events considered to be associated with treatment, while 19

(35.8%) control subjects reported 38 adverse events considered to be associated with treatment.

Table 10.9: Summary of serious, associated with treatment adverse events through 12 months in the primary analysis dataset.

Type of Event	Investigational (N = 97)	Control (N = 53)
	Number of Subjects (%)	Number of Subjects (%)
Any Serious Related Event	8 (8.2)	19 (35.8)
Anatomical/Technical Difficulty	1 (1.0)	0 (0.0)
Implant Event	1 (1.0)	0 (0.0)
Investigations	0 (0.0)	1 (1.9)
Musculoskeletal/Pain Events (Possible Spine Etiology)	1 (1.0)	11 (20.8)
Neurological	1 (1.0)	0 (0.0)
Spine Event	6 (6.2)	11 (20.8)
Trauma	1 (1.0)	0 (0.0)

Table 10.10 below provides additional detail on the specifics of the 8 subjects within the investigational group experiencing a serious, treatment related adverse event.

Table 10.10: Investigational subjects with serious, treatment related adverse event.

Subject	DIAM Group (N=97)
	Event Detail
(b) (6)	Spinous process erosion
	Posterior migration DIAM secondary to MVA
	L4-L5 spondylolisthesis DIAM device may not be positioned properly
	L4-L5 bone spurs L4-L5 loss of distraction
	L4-L5 DDD L4-L5 herniated nucleus pulposus impinging on thecal sac
	Postoperative back spasms

Subject	DIAM Group (N=97)
	Event Detail
(b) (6)	L4-L5 bilateral facet narrowing L4-L5 DDD
	Tether broke; caught on distractor Postoperative leg weakness; decreased sensation in foot prior to discharge (resolved at discharge)
	L4-L5 facet arthropathy L4-L5 Stenosis L4-L5 disc bulge (lumbar pain; limited range of motion)
	L2-L3 DDD with disc bulges, facet hypertrophy, canal Stenosis (numbness, pain in legs)

Detailed summary tables for all serious, treatment related adverse events over time are provided in Appendix 3 and 4 for the primary and all available datasets, respectively.

10.7.3. Additional Surgical Procedures and Surgical Interventions

Additional surgical procedures can occur in both treatment groups. To assist in analyzing the relationship of additional surgical procedures to study treatment and/or designated outcomes, additional surgical procedures were classified into distinct categories, specific to treatment group, as described below. All subjects who had either an additional surgical procedure or a surgical intervention after study treatment initiation were to be followed for the duration of the study.

Table 10.11: Classifications of additional surgical procedures and surgical interventions.

Term	Definition
Additional Surgical Procedures in Investigational Group (i.e., any surgery that occurred after the study surgery)	
Revision	A procedure that adjusts or in any way modifies the original implant configuration (e.g., adjusting position of the original configuration).
Removal	Any procedure that removed one or more components of the original implant configuration
Reoperation	Any surgical procedure at the involved level that is not classified as a revision or removal. This includes decompression (such as laminectomy or foraminotomy); discectomy; fusion procedures, such as anterior or posterior lumbar interbody fusion or posterolateral fusion, with or without instrumentation; or other procedures to alleviate the symptoms of DDD.
Other	Any additional surgical procedure not classified as a revision, removal or reoperation
Surgical Intervention in Control Group	
Treatment Surgery	A surgical procedure at the involved level to treat the patient's degenerative disc disease. This may include anterior or posterior lumbar interbody fusion or posterolateral fusion, with or without instrumentation. It may also include a spinal decompression (such as laminectomy or foraminotomy), discectomy, or other procedures to alleviate the symptoms of DDD.
Crossover (Treatment Surgery)	A control group patient may also be treated with the DIAM Spinal Stabilization System at the involved level.
Other	Any surgical procedure performed at a location other than the involved level (i.e., not a "treatment surgery").

The designation of an additional surgery (after initial treatment) as a "failure" had very specific criteria that differed between treatment groups. Failure for the investigational group was defined as any revision procedure necessary to adjust or in any way modify the original implant configuration, any removal procedure intended to replace migrated, broken, or erroneously positioned device components, and any removal procedure intended to explant components believed to have resulted in infection. Any reoperations at the involved level for an indication related to the original diagnosis, or any surgery indicated for pain relief (e.g., denervation procedures or rhizotomies) related to the original diagnosis were also counted as a failure in the investigational group.

For the control group, a surgical failure was defined as receiving a surgery (subsequent to poor response to the conservative care provided) which was considered necessary to effectively treat the subject's originally diagnosed DDD at the target level. Such surgeries were termed "treatment surgeries." Six months of conservative care were required before control subjects could receive a "treatment surgery"; any "treatment surgeries" before six months of conservative treatment was completed (including implantation of a DIAM device) were considered protocol deviations.

Investigational subjects who received additional surgical procedures or interventions that were classified as "failures" were deemed failures with respect to overall success. Control subjects who received a "treatment surgery" were not automatically deemed "failures" for overall success; rather, outcomes before the treatment surgery were carried forward in order to determine overall success status.

For the investigational subjects in the primary dataset, there were 3 (3.1%) removals and no subjects required revision of the DIAM device. Ten (10.3%) investigational subjects required a reoperation.

For control subjects in the primary dataset, there were 29 (54.7%) subjects who received a treatment surgery. Treatment surgeries included 23 (43.4%) subjects who crossed over to receive the DIAM device.

For both cohorts, surgical procedures performed at other lumbar spine levels, all non-lumbar spinal surgeries and all non-spinal surgeries were classified as "Other". For more details, see Table 10.12.

Table 10.12: Summary of additional surgical procedures and treatment surgeries up to 12 months in primary dataset.

Investigational (N = 97)			**Control (N = 53)**		
	Number of Events	**Number (%) of Subjects**		**Number of Events**	**Number (%) of Subjects**
Second Surgery*[39] (Index Level)	**14**	**13 (13.4)**	**Treatment Surgery*[40] (Index Level)**	29	29 (54.7)
Revision	0	0 (0.0)	Crossover (Received DIAM device; Index Level Only)	23	23 (43.4)
Removal	3	3 (3.1)	Other Index Surgeries	6	6 (11.3)
Reoperation	11	10 (10.3)			

Investigational (N = 97)			Control (N = 53)		
	Number of Events	Number (%) of Subjects		Number of Events	Number (%) of Subjects
Other Second Surgery	**26**	**23 (23.7)**	**Other Surgery**	**10**	**7 (13.2)**
Lumbar Surgery (Other Than Index Only)	11	9 (9.3)	Lumbar Surgery (Other Than Index Only)	3	3 (5.7)
Adjacent Level Only	2	2 (2.1)	Adjacent Level Only	0	0 (0.0)
Other Lumbar (Non-Adjacent, Non-Index)	3	3 (3.1)	Other Lumbar (Non-Adjacent, Non-Index)	0	0 (0.0)
Adjacent Level Surgery Involved at Both Index and Adjacent Levels*	6	5 (5.2)	Adjacent Level Surgery Involved at Both Index and Adjacent Levels*	3	3 (5.7)
Non-Lumbar Spinal Surgery	2	2 (2.1)	Non-Lumbar Spinal Surgery	0	0 (0.0)
Non-Spinal Surgery	19	16 (16.5)	Non-Spinal Surgery	10	7 (13.2)

10.8. Additional Data Analyses Requested by FDA

10.8.1. DDD diagnostic sub-group analysis

FDA asked Medtronic to provide an analysis for the primary study outcome for overall success, individual success components of the primary study outcome, and all secondary effectiveness outcomes stratified into subgroups based on clinical syndrome.

In order to provide the largest sample within the sub-groups, Medtronic initially conducted the analysis using the all available dataset. Descriptions of the characteristics of each sub-group are listed below. In order to provide a patient-level analysis, the groups below were defined sequentially.

Disc Herniation

We collected data on leg pain symptoms and not specifically on radicular leg symptoms or disc bulges. Therefore, we stratified patients into a 'disc herniation' sub-group using the following criteria: with protrusion or extrusion (with or

without sequestration) from the MRI dataset at the index level with any back pain present and either leg pain ≥ 8 or a positive straight leg raising test (left or right leg).

Disc Degeneration without Disc Herniation

We have sub-grouped 'disc degeneration' patients using the following criteria: patients with any back or leg pain, without 'disc herniation' (excluded any subject from 1.a.i.), with either disc height loss (> 2 mm loss of the average of anterior and posterior height compared to the average of anterior and posterior height at either the superior or inferior adjacent level on x-ray) or disc desiccation (Pfirrmann grade ≥ 4 on MRI) at the index level. Please note we did not specifically collect data on sclerosis of the vertebral endplates, or osteophytes at the vertebral apophyses within our pre-specified imaging protocol.

Spinal Stenosis

Based on the original study protocol, we collected leg pain and back pain symptoms but did not collect any radiologic data on lumbar spinal stenosis nor did we collect any information regarding neurogenic claudication, buttock pain or radicular leg symptoms. Upon FDA's request, pre-treatment MRIs were read to collect data related to lumbar spinal stenosis. Two independent radiologists (and a third adjudicator) from the core laboratory assessed location (central canal, left and right subarticular zones and left and right foraminal zones) and severity of spinal stenosis (none, mild, moderate or severe) at the target level and the adjacent superior and inferior levels according to the methods of Lurie et al.[41] The anatomical structures involved in the stenosis locations were also recorded.

We initially defined the 'spinal stenosis' sub-group as subjects with any back pain, leg pain ≥ 8, and with any severe stenosis within any anatomic location (but without being disc herniation or disc degeneration subjects as defined in parts i and ii above). This sub-grouping yielded a total of only 8 subjects which would not be a large enough to provide a meaningful assessment of the intended question. Therefore, we expanded this 'spinal stenosis' sub-group using the following criteria: patients with any back pain, leg pain ≥ 8, with any moderate or severe stenosis (central canal, left or right subarticular or left or right foraminal) but not in the sub-groups defined in parts i and ii above. This yielded a total of 24 subjects.

This information also indicated that there were very few subjects that would be considered as having typical stenosis in the patient population studied.

Facet Joint Degeneration

Similar to part iii above, we initially sub-grouped ‘facet joint degeneration’ subjects using the following criteria: patients with any back or leg pain, having facet joint osteoarthritis of grade III on either side and excluding subjects defined as disc herniation, disc degeneration or spinal stenosis subjects as defined in parts i, ii and iii above. However, this sub-grouping yielded only a total of 5 subjects, a size which is too small to yield any meaningful analysis results. Therefore we expanded the ‘facet joint degeneration’ group of subjects using the following criteria: patients with any back or leg pain and having facet joint osteoarthritis of grade II or III on either side (excluding subjects defined as disc herniation, disc degeneration or spinal stenosis subjects as defined in parts i, ii and iii above) which yielded 45 subjects.

Other

All subjects classified as 'other' were those that were not included in disc herniation, disc degeneration, spinal stenosis or facet joint degeneration sub-groups as defined in parts i, ii, iii and iv above.

Overall Summary

For the five cohorts described above, Medtronic summarized clinical results including 12-month ODI and overall success for each cohort as shown in the graph below for the all available dataset. Within each treatment group for the investigational subjects, there is no meaningful difference between sub-groups in overall or ODI success and each investigational sub-group had greater success than the comparative control sub-group. Results for sub-groups within each treatment arm were qualitatively similar to overall success of the pooled population that was analyzed according to the statistical analysis plan. Similarly, there was no meaningful difference between sub-groups in the other parameters (neurologic success, back pain scores/success, leg pain scores/success, and SF-36 scores) evaluated. There is some fluctuation of success rates, likely due to comparison of non-randomized sub-groups and the relatively small sample size in some of the sub-groups.

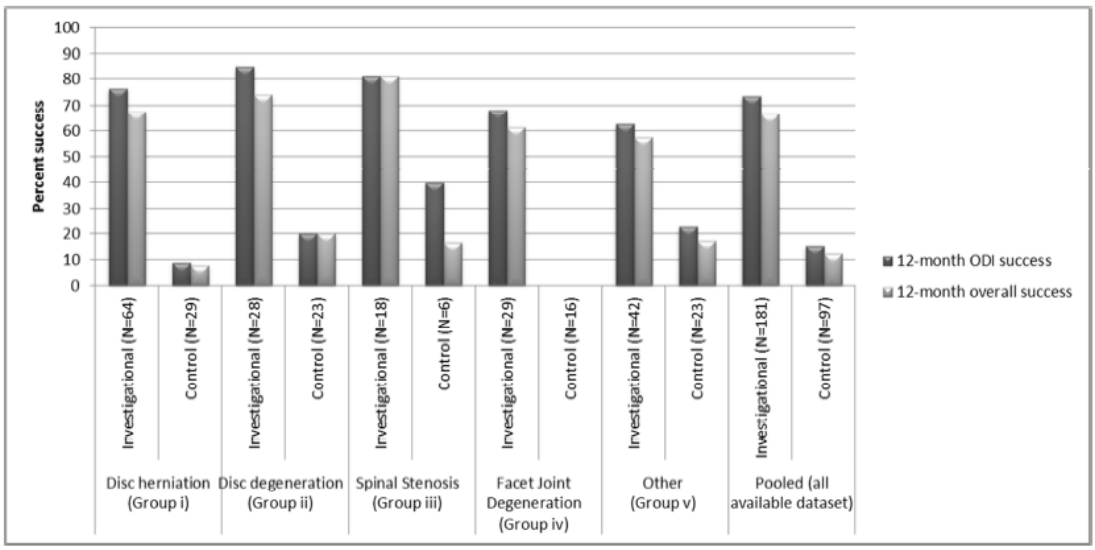


Figure 10.20: ODI and overall success in degenerative sub-populations for all available dataset.

In addition to the all available dataset analysis, FDA asked Medtronic to perform the analysis using only the primary dataset.

Medtronic summarized 12-month ODI success and overall success for each subgroup in the primary dataset in the graph below. Some of the subgroups have a small sample size, especially the control group in the stenosis subgroup, which has only one subject. Within each treatment group (investigational versus control) there is no meaningful difference between sub-groups in overall or ODI success. With the exception of the spinal stenosis subgroup (again only one subject in the control subgroup), each investigational sub-group had greater success than the comparative control sub-group. Results for sub-groups within each treatment arm were qualitatively similar to overall success of the pooled population that was analyzed according to the statistical analysis plan. There is some fluctuation of success rates (for example somewhat diminished response in the facet joint degeneration subgroup) but this is likely due to multiple comparisons of non-randomized sub-groups and the small sample size in some of the sub-groups. Similar conclusions can be drawn when evaluating data from other parameters analyzed.

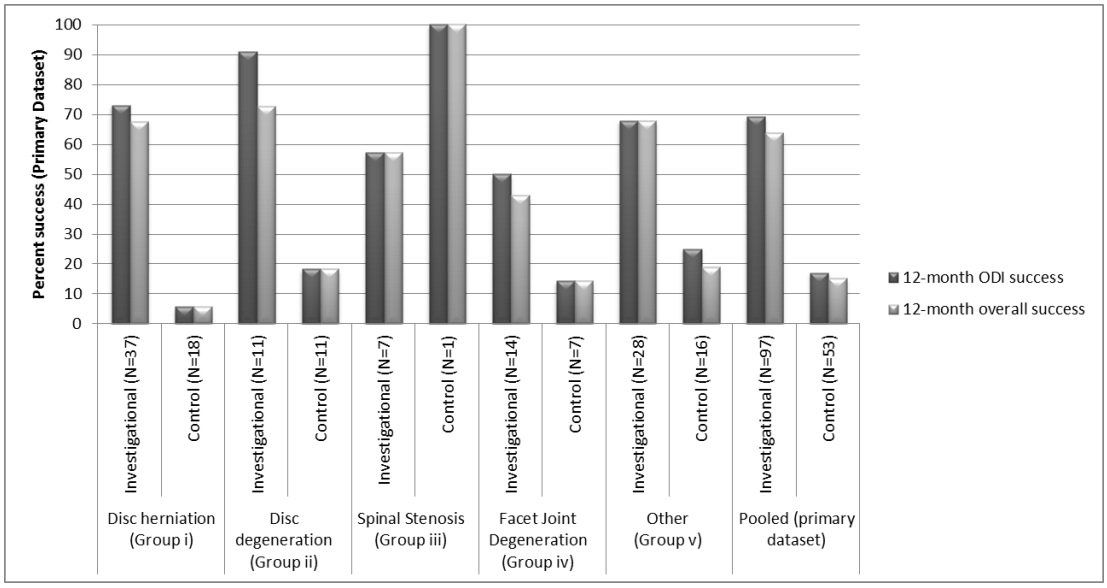


Figure 10.21: ODI and overall success in degenerative sub-populations for primary dataset.

In summary, with the exception of the primary dataset spinal stenosis sub-population with only n=1, the analyses performed yielded no clear difference in the parameters analyzed (e.g, overall success, ODI, back or leg pain) within each sub-group identified (disc herniation, disc degeneration, spinal stenosis, facet joint degeneration, or other, mixed syndromes). Each investigational sub-group had greater success than the comparative control sub-group; results for sub-groups within each treatment arm were qualitatively similar to success found within that parameter for the pooled population. These results support the concept that moderate low back pain within the setting of degenerative disc disease is a sum of various pain generators being triggered together at the level of the degenerating functional spinal unit and support the pooled population defined by the investigational protocol. It is important to note that the *post hoc* nature of this patient stratification into sub-groups, based primarily on the limited radiologic and CRF data, may not represent a true clinical diagnosis, and therefore results must be interpreted with caution. However, we believe that the results of the analyses reveal consistency of results across all of these sub-groups.

10.8.2. Single- vs. multi-level disease subgroups

Subjects in the IDE study were symptomatic at a single level per the enrollment criteria but were not excluded based on radiologic findings at other levels. FDA asked Medtronic to stratify subjects who may have had radiologic signs of degeneration at multiple levels.

As requested by the FDA, and similar to the approach used in defining degenerative sub-group populations, Medtronic used radiologic criteria in an attempt to identify sub-populations with single-level versus multiple-level pathologies. Please note, there are challenges in attempting to define subgroups post-hoc as they may not represent a true clinical diagnosis, radiological data were limited, and subgroup comparisons do not represent randomized comparisons. Medtronic summarized 12-month overall overall success and ODI scores for each subgroup in the primary dataset in the figures below.

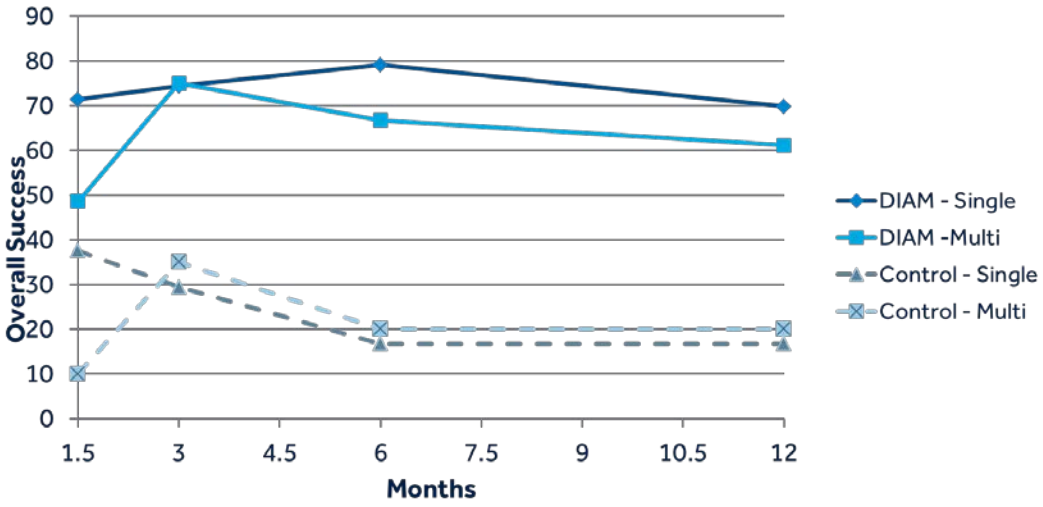


Figure 10.22: Comparison of overall success between DIAM and control subjects with single-level vs. multi-level radiologic findings.

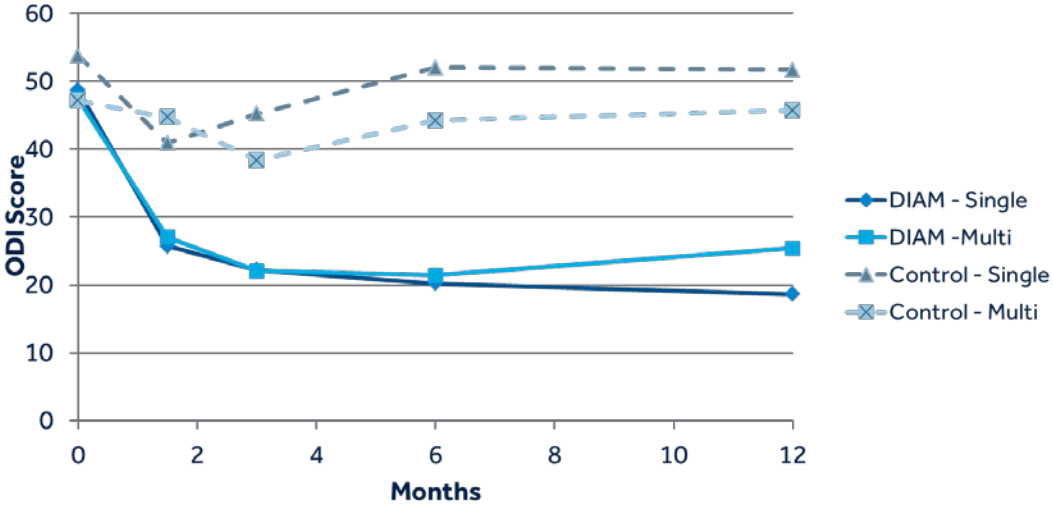


Figure 10.23: Comparison of ODI scores between DIAM and control subjects with single-level vs. multi-level radiologic findings.

Consistent with overall success and ODI success results, ODI, back pain, leg pain and SF-36 scores reveal greater improvement in the DIAM group compared to the control in both the single-level and multi-level subgroups at all time points.

Though interpretation must be made with caution given that subgroups were defined *post-hoc* and are non-randomized comparisons, results suggest that DIAM provides a substantial benefit compared to the control even in the setting of multi-level radiologic pathology findings with persistent long-term effects. Furthermore, outcomes in the longer term (24 months and beyond) trended to be even better in DIAM subjects with minimal baseline adjacent level degeneration than those with multi-level radiologic pathology findings. These findings are consistent with what is expected given the natural history of the disease that adjacent levels are at increased risk of degeneration and may progress over time.

10.9. Safety and Effectiveness Conclusion

10.9.1. Safety

Neurological success rates at 12 months were 86.6% and 84.9%, respectively for the investigational group and the control group, and Bayesian analysis demonstrated that the rates were not statistically different between the two groups.

The percentages of subjects experiencing adverse events up to the 12-month interval months were 87.6% and 75.5% in the investigational group and the control group, respectively. The 95% HPD for the difference of adverse event rates between the investigational and the control group is 12.3% (-0.6%, 25.7%), indicating that the rates were not statistically different between the two groups. For adverse events that were treatment-associated, serious adverse events that were treatment-associated and severe (Grade 3) or life threatening (Grade 4) adverse events that were treatment-associated, rates in the investigational group were numerically lower in the investigational group than in the control group.

While no statistical comparison was carried out with regard to the additional surgical procedure rate in the investigational group versus the treatment surgery rate in the control group, the additional surgical procedure rate through 12 months in the investigational group was 13.4%, while the treatment surgery rate in the control group was 54.7% in total with 43.4% of control subjects having crossed over to be implanted with the DIAM device as their treatment surgery.

The DIAM Spinal Stabilization System was demonstrated to be at least as safe as the control treatment.

10.9.2. Effectiveness

Treatment with the DIAM Spinal Stabilization System was demonstrated to be substantially more effective than non-operative care for patients with moderate low back pain secondary to DDD. By every measure, investigational subjects reported more improvement in both pain and disability and more satisfaction with their treatment than did controls. A summary of overall success and successes in efficacy variables is shown in Table 10.13.

Table 10.13: Summary of overall success and successes in efficacy variable in the primary dataset at 12 months.

Variable	Observed Success Rate (Investigational)	Observed Success Rate (Control)	Posterior Probability of Superiority
Overall Success	63.9%	15.1%	~100%
ODI Success	69.1%	17.0%	~100%
Back Pain Success	89.7%	45.3%	~100%
Leg Pain Success	72.2%	28.3%	~100%
SF36 PCS Success	87.6%	45.3%	~100%
Subject Perception of Results Success[42]	77.3%	35.8%	Not available[43]
Investigator Perception of Results Success	71.1%	15.1%	Not available

In the primary dataset, improvement in ODI score, back pain score, leg pain score and SF-36 PCS score in investigational subjects was also demonstrated by Bayesian analysis to have an approximately 100% probability of superiority as compared to the improvement in the control group.

10.9.3. Risk-Benefit Ratio

Based on the data, the DIAM Spinal Stabilization System was shown to be superior to nonoperative treatment with respect to decreasing the pain and ameliorating the disability associated with moderate low back pain due to lumbar DDD at the L2-L5 levels. Additionally, it is as safe as nonoperative care and offers an effective, minimally invasive, and anatomy-preserving surgical option for a population whose treatment is currently limited to nonoperative care.

Although DIAM implantation involves a surgical procedure, and with that are inherent surgical risks, the available data shows that the benefits of treatment with the DIAM device are significant, and DIAM was statistically superior to the

conservative care control in every effectiveness endpoint. The safety profile of the DIAM device is favorable, with a low rate of serious, treatment-related adverse events. Some radiological findings from the clinical study warranted additional review, but a thorough analysis did not have a clinically meaningful effect on outcomes and did not raise safety concerns. Overwhelmingly, the clinical study data showed meaningful improvements that were consistent and sustained over the course of the study.

Therefore, the DIAM device not only demonstrates a reasonable assurance of safety and effectiveness, but also shows additional benefits as compared to the current standard of care. The available data show that the probable benefits outweigh the probable risks of the DIAM device for moderate low back pain secondary to DDD.

11. Conclusion

The DIAM Spinal Stabilization System was shown in this interim analysis to be statistically superior to nonoperative care by overall success and every secondary efficacy measure evaluated, with a safety profile at least as good as nonoperative care as well. Of particular note, overall success reflects a clinically significant improvement in ODI scores. Additionally, investigators in this study, who treated both investigational and control subjects, viewed DIAM Spinal Stabilization System as much more effective than conservative care. The DIAM Spinal Stabilization System, shown in this study to provide greater relief for back and leg pain, greater improvement in disability, and greater satisfaction with treatment results in patient and doctor alike, and is reversible. As such, it represents a promising new treatment option for patients with persistent moderate low back pain related to clinically symptomatic single-level DDD, a population currently without other surgical options.

[1] Buric J, Pulidori M, Sinan T, Mehraj S. DIAM device for low back pain in degenerative disc disease: 24 months follow-up. *Acta Neurochir Suppl.* 2011;108:177-82.

[2] Buric J and Pulidori M. Long-term reduction in pain and disability after surgery with the interspinous device for intervertebral assisted motion (DIAM) spinal stabilization system in patients with low back pain: 4-year follow-up from a longitudinal prospective case series. *Eur Spine J*. 2011: 20(8): 1304-11.

[3] Manchikanti L, Singh V, Datta S, Cohen SP, Hirsch JA. Comprehensive review of epidemiology, scope, and impact of spinal pain. *Pain Physician.* 2009; 12(4): E35-70.

[4] Galbusera F, van Rijsbergen M, Ito K, Huyghe JM, Brayda-Bruno M, Wilke HJ. Ageing and degenerative changes of the intervertebral disc and their impact on spinal flexibility. *Eur Spine J*. 2014; 23 Suppl 3: S324-32.

[5] Dawson-Hughes B, Looker AC, Tosteson AN, Johansson H, Kanis JA, Melton LJ 3rd. The potential impact of the National Osteoporosis Foundation guidance on treatment eligibility in the USA: an update in NHANES 2005-2008. *Osteoporos Int*. 2012; 23(3): 811-20.

[6] Balague F, Mannion AF, Pellisé F, Cedraschi C. Non-specific low back pain. *Lancet*. 2012; 379(9814): 482-91.

[7] Buchbinder R, Blyth FM, March LM, Brooks P, Woolf AD, Hoy DG. Placing the global burden of low back pain in context. *Best Pract Res Clin Rheumatol*. 2013; 27(5): 575-89.

[8] The Burden of Musculoskeletal Diseases. 2010, United States Bone and Joint Initiative Rosemont, IL.

[9] Hilfiker R, Bachmann LM, Heitz CA, Lorenz T, Joronen H, Klipstein A. Value of predictive instruments to determine persisting restriction of function in patients with subacute non-specific low back pain. Systematic review. *Eur Spine J*. 2007; 16(11): 1755-75.

[10] Bahouq H, Allali F, Rkain H, Hajjaj-Hassouni N. Discussing sexual concerns with chronic low back pain patients: barriers and patients' expectations. *Clin Rheumatol*. 2013; 32(10): 1487-92.

[11] Katz, JN. Lumbar disc disorders and low-back pain: socioeconomic factors and consequences. *J Bone Joint Surg Am*. 2006; 88 Suppl 2: 21-4.

[12] Martin, BI, Deyo RA, Mirza SK, et al. Expenditures and health status among adults with back and neck problems. *JAMA*. 2008; 299(6): 656-64.

[13] Haldeman SD, Kirkaldy-Willis WH, Bernard TN. *An Atlas of Back Pain*. London, UK: The Parthenon Publishing Group; 2002: p. 27-36.

[14] Hirsch C, Ingelmark B, Miller M. The anatomical basis for low back pain. *Acta Orthop Scand*. 1963; 33: 1-17.

[15] Olmarker K, Brisby H, Yabuki S, Nordborg C, Rydevik B. The effects of normal, frozen, and hyaluronidase-digested nucleus pulposus on nerve root structure and function. *Spine*. 1997; 22:471-475.

[16] Lipson SJ, Muir H. Proteoglycans in experimental intervertebral disc degeneration. *Spine*. 1984; 6: 194-210.

[17] Kirkaldy-Willis WH, Wedge JH, Yong-Hing K and Reilly J. Pathology and pathogenesis of lumbar spondylosis and stenosis. *Spine*. 1978; 3(4): 319-328.

[18] Bellini CM. Biomechanics of the lumbar spine after dynamic stabilization. *J Spinal Disord Tech*. 2007; 20(6): 423-429.

[19] Mullholland RC, Sengupta DK. Rationale, principles and experimental evaluation of the concept of soft stabilization. *Eur Spine J*. 200;, 11(Suppl. 2): S198-S205.

[20] Nockels RP. Dynamic stabilization in the surgical management of painful lumbar spinal disorders. *Spine*. 2005; 30(16S): S68-S72.

[21] Axen I, Leboeuf-Yde C. Trajectories of low back pain. *Best Pract Res Clin Rheumatol*. 2013; 27(5): 601-12.

[22] Chou R, Qaseem A, Snow V, et al. Diagnosis and treatment of low back pain: a joint clinical practice guideline from the American College of Physicians and the American Pain Society. *Ann Intern Med*. 2007; 147(7): 478-491.

[23] Chou R, Baisden J, Carragee EJ, Resnick DK, Shaffer WO, Loeser JD. Surgery for low back pain: a review of the evidence for an American Pain Society Clinical Practice Guideline. *Spine*. 2009; 34(10): 1094-109.

[24] Sasso RC, LeHuec JC, Shaffrey C. Iliac crest bone graft donor site pain after anterior lumbar interbody fusion: a prospective patient satisfaction outcome assessment. *J Spinal Disord Tech*. 2005; 18 Suppl: S77-81.

[25] Ghiselli G, Wang JC, Bhatia NN, Hsu WK, Dawson EG. Adjacent segment degeneration in the lumbar spine. *J Bone Joint Surg Am*. 2004; 86-A(7):1497-1503.

[26] Phillips FM, Voronov LI, Gaitanis IN, Carandang G, Havey RM, Patwardhan AG. Biomechanics of posterior dynamic stabilization device (DIAM) after facetectomy and discectomy. *Spine J*. 2006; 6: 714-722.

[27] Shepherd D, Leahy J, Mahias K, Wilkinson S, Hukins D. Spinous process strength. *Spine*. 2000; 25(3): 319-323.

[28] White A, Panjabi M. *Clinical Biomechanics of the Spine*, 2nd ed. Philadelphia: J.B. Lippincott; 1990: 461.

[29] Lorenz M, Patwardhan A, Vanderby R. Load-bearing characteristics of lumbar facets in normal and surgically altered spinal segments. *Spine.* 1983; 8:122.

[30] Haher TR, O'Brien M, Dryer JW, Nucci R, Zipnick R, Leone DJ. The role of lumbar facet joints in spinal stability. *Spine*. 1994; 9:23.

[31] Papp T, Porter RW, Aspden RM, Shepperd JA. An in vitro study of the biomechanical effects of flexible stabilization on the lumbar spine. *Spine*. 1997; 22(2):151-5.

[32] Steffen T, Rubin R, Baramki H, Antoniou J, Marchesi D, Aebi M. A new technique for measuring lumbar segmental motion in vivo. *Spine.* 1997; 22(2):156-166.

[33] Pearcy MJ, Tibrewal SB. Axial rotation and lateral bending in the normal lumbar spine. *Spine*.1984; 582-587.

[34] Nachemson A. Disc pressure measurements. *Spine*. 1981; 6(1):93-97.

[35] Szycher M and Robinson WJ, eds. *Synthetic Biomedical Polymers: Concepts and Applications*. Westport, CT: Technomic Publishing; 180: 4-5.

[36] Davis R, Auerbach JD, Bae H, Errico TJ. Can low-grade spondylolisthesis be effectively treated by either coflex interlaminar stabilization or laminectomy and posterior spinal fusion? Two-year clinical and radiographic results from the randomized, prospective, multicenter US investigational device exemption trial. *J Neurosurg Spine.* 2013;19:174-84.

[37] Patel VV, Whang PG, Haley TR, et al. Superion interspinous process spacer for intermittent neurogenic claudication secondary to moderate lumbar spinal stenosis. *Spine.* 2015; 40(5):275-282.

[38] Life-threatening (Grade 4) adverse events were always assessed to be serious.

[39] A second surgical procedure which included the involved level and may have included an adjacent level and which was included in the total count for removals/reoperations for the investigational group.

[40] A surgical procedure which included the involved level and may have included an adjacent level and which was included in the total count for treatment surgeries for the control group. In the control group, crossover surgeries only included the involved level.

[41] Lurie JD, Tosteson AN, Tosteson TD, et al. Reliability of readings of magnetic resonance imaging features of lumbar spinal stenosis. *Spine*. 2008; 33(14):1605-10.

[42] Based on question "all things considered I would have the same treatment again for the same condition". Results for other subject satisfaction questions were similar.

[43] Bayesian statistics were not performed for success determinations for either subject or investigator perception of results.