DIAM SPINAL STABILIZATION SYSTEM
SAFE AND EFFECTIVE

- Extensive pre-clinical testing

- DIAM device statistically superior to control in primary study endpoint that includes safety and effectiveness components, as well as in secondary endpoints

- Consistency of primary and secondary endpoint results is maintained over time and across multiple patient cohorts and subgroups
DIAM SPINAL STABILIZATION SYSTEM

- Invented by Dr. Jean Taylor
- Safely used for 16+ years outside the United States
- 140,000+ cases in more than 50 countries
PROPOSED 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.

- Proposed indication (moderate low back pain secondary to DDD) unchanged from IDE.
DIAM SPINAL STABILIZATION SYSTEM
IDE #G050025

- Prospective, randomized, controlled multicenter trial
- 282 subjects treated at 23 investigational centers
- Moderate low back pain secondary to DDD
- Single symptomatic lumbar level
- DIAM device vs. conservative care
DIAM STUDY TIMELINE

- **FDA appr. interim plan**
- **Final subj. (N=282)**
- **PMA update**
- **PMA data lock**
- **PMA sub.**
- **PMA data lock**
- **FDA mtg. interim plan**

- **# sites increased from 20 to 30**
- **1st subject**
- **Removed facet disease from incl. crit.**
  **Added disc height loss >67% as excl. crit.**
OVERVIEW

- Overview of PMA data and support for trial design

Specific FDA concerns will be addressed throughout

- Demonstrate safety, effectiveness, and positive risk-benefit profile

- DIAM has substantial, durable clinical effect
DIAM® SPINAL STABILIZATION SYSTEM
FDA PANEL PRESENTATIONS

- Treatment Rationale and Surgical Technique: Alexander Bailey, MD
  Precision Spine and Orthopaedic Specialists, Overland Park, Kansas

- Design / Preclinical Testing: Eric Lange, MS
  Medtronic Spinal and Biologics, Memphis, TN

- IDE Clinical Trial Results: Matthew Gornet, MD
  Orthopedic Center of St. Louis, St. Louis, MO

- Statistical Considerations: Donald Berry, PhD
  Berry Consultants, University of Texas MD Anderson Cancer Center, Houston, TX

- Case Presentations: Scott Kitchel, MD
  Orthopedic Spine Associates, Eugene, OR

- Summary: Kathryn Simpson, PhD
  Medtronic Spinal and Biologics, Memphis, TN
ADDITIONAL RESOURCES

- Douglas Robertson, MD, PhD
  Radiology – Emory Orthopaedics & Spine Center
- Harry Genant, MD
  Radiology – UCSF, Synarc
- Jeffrey Toth, PhD
  Histology – Medical College of Wisconsin
- Steven Kurtz, PhD
  Explant Analysis – Exponent, Inc.
- Chris Mullin, MS
  Biostatistics/Biomaterials/Pre-clinical testing - NAMSA
- Joe Carraway, DVM
  Biomaterials/Pre-clinical testing - NAMSA
- Medtronic Staff
**DEGENERATIVE CASCADE**
**NORMAL HEALTHY SPINE**

- The spinal unit
  - Vertebrae, disc, facets & ligaments
  - Dynamically stable architecture that allows complex motion
  - Load transmission
- Intervertebral disc
  - Nucleus pulposus
  - Annulus fibrosus
  - Shock absorber and spacer
- Facet joints
  - Semi-constraining synovial joints
  - Supports compressive loading
  - Supporting ligamentous structures
Low back pain (LBP) is a major societal burden
- ~85% of the US population will experience LBP
- 2nd most common reason patients seek medical attention
- 2nd most common cause for missed work after the common cold
- The most common cause of disability <45 y/o

Most LBP is short lived

The most common cause of continued LBP is lumbar Degenerative Disc Disease (DDD)
DEGENERATIVE CASCADE
ANNULUS TEARS

- Age, rotational strain, or minor compression injuries may trigger degenerative cascade
  - Loss of water content
  - Tears or fissures in the annulus
  - Innervating nerve endings cause pain
  - Secondary herniated discs

- Chemical composition changes
  - Decreased proteoglycan content
  - Further loss of hydration
  - Loss of viscoelastic properties
DEGENERATIVE CASCADE
DISC HEIGHT LOSS & FACET OVERLOADING

- Diminished disc function, loss of disc height and volume

- Altered spinal biomechanics
  - Painful load transmission
  - Instability

- Mal-alignment and over-loading of the facet joints
  - Synovial reactions
  - Cartilage destruction
  - Pain
DEGENERATIVE CASCADE
ADVANCED DEGENERATION

- Continued degeneration leads to
  - Complete disc collapse
  - Advanced arthritic changes
  - Severe joint hypertrophy
  - Large bone spurs
  - Severe stenosis
  - Symptomatic adjacent level involvement

Patients who reach advanced levels of degeneration are not DIAM candidates.
Low Back Pain

**DEGENERATIVE CASCADE**

**SUMMARY**

- Degenerative disc disease is a multifactorial and non-reversible pathologic condition
  - Degenerated disc
  - Facet joint degeneration
  - Disc herniation
  - Spinal stenosis
  - Spondylolisthesis
- Uniform transmission of load no longer possible
- Multiple structures are innervated causing pain
  - Low back pain (discogenic, facet)
  - Radicular (radiculitis, stenosis, spondylolisthesis)

*FDA concern: Adequacy of study population*
4.1 Lumbar Degenerative Disc Disease (DDD)

Many protocols involve the investigation of systems for the treatment of lumbar DDD. DDD should be based on patient history and radiographic studies. FDA suggests that the sponsor consider the following:

DDD should be defined as back and/or radicular pain with degeneration of the disc as confirmed by patient history, physical examination, and radiographic studies with 1 or more of the following factors (as measured radiographically, either by CT, MRI, plain film, myelography, discography, etc.):

- instability as defined by $\geq 3\text{mm}$ translation or $\geq 5^\circ$ angulation;
- osteophyte formation of facet joints or vertebral endplates;
- decreased disc height, on average by $\geq 2\text{mm}$, but dependent upon the spinal level;
- scarring/thickening of ligamentum flavum, annulus fibrosis, or facet joint capsule;
- herniated nucleus pulposus;
- facet joint degeneration/changes; and/or
- vacuum phenomenon.

**FDA concern: Adequacy of study population**
MODERATE LBP SECONDARY TO DDD

DIAGNOSIS

- Complicated by multi-factorial nature of LBP/DDD
- Disc degeneration without pain very common
- Multi-level radiologic degeneration with single level pain possible
- Diagnostic work-up includes
  - Patient history
    - Pain duration, location, intensity
    - Painful positions/activities
  - Physical exam
    - Palpation pain
    - Straight leg raising test
  - Radiologic confirmation
    - MRI, X-ray
    - May include provocative discography
- ODI is not a diagnostic tool

FDA concern: Adequacy of study population
MODERATE LBP SECONDARY TO DDD
OSWESTRY DISABILITY INDEX (ODI)

- **ODI** – Validated outcome measure
  - Measures a patient’s perception of their disability
  - Range 0 (no disability) to 100 (complete disability)
    - **“0% - 20%: Minimal Disability**
      This group can cope with most living activities. Usually no treatment is indicated.”
    - **“20% - 40%: Moderate Disability**
      This group experiences more pain and problems with sitting, lifting and standing. Personal care, sexual activity and sleeping are not grossly affected, and the back condition can usually be managed by conservative means.”
    - **“40% - 60%: Severe Disability**
      Pain remains the main problem in this group of patients, but travel, personal care, social life, sexual activity and sleep are also affected. These patients require detailed investigation.”
    - **“60% - 80%: Crippled**
      Back pain impinges on all aspects of these patients’ lives both at home and at work and positive intervention is required.”
    - **“80% - 100%: Other**
      These patients are either bed-bound or exaggerating their symptoms.”

- Severe and Crippled labels are obviously over-stated
- DIAM study patients required ODI >30 (average 50)

**FDA concern: Adequacy of study population**
MODERATE LBP SECONDARY TO DDD
CURRENT TREATMENT OPTIONS

- US standard of care conservative treatments
  - Patient education
  - Activity modification
  - Analgesic medications
  - Physical therapy
  - Massage/Chiropractic
  - Acupressure/acupuncture
  - Spinal injections
- Mirza review of 4 studies
  - Extreme non-operative treatments included
    - Residence at a specialized “Back Hotel”
    - PT 25h/week for 5 weeks, OP PT, home visits
    - Cognitive behavioral treatment 5 d/wk for 3 weeks
- Fritzell study
  - PT, education, TENS, acupuncture, injections
  - Conservative care avg. ODI improvement = 5.8%
  - Results are nearly identical to the DIAM study

FDA concern: Adequacy of non-operative control
ADVANCED DISC DEGENERATION
CURRENT SURGICAL TREATMENT OPTIONS

- End-stage/advanced degeneration surgical options
  - Total disc replacement
  - Fusion

- Current surgical options are
  - Highly invasive
  - Non-reversible
  - For severe degeneration only
  - Significant surgical risks
  - Long term consequences/adjacent level fusion
    - 15-30% additional fusion at 5 years

- Direct decompression ineffective for LBP
  - Primary stenosis not our indication

- Direct decompressions not performed in this study

*FDA concern: DIAM as adjunct to direct decompression*
DEGENERATIVE DISC DISEASE CARE CONTINUUM

- **Minimal care**
- **Conservative care**
- **DIAM®**: moderate low back pain secondary to degenerative disc disease

**FDA concern**: Adequacy of non-operative control

**Disc replacement**
DIAM SPINAL STABILIZATION DEVICE
MECHANISM OF ACTION

- The DIAM device is placed between the spinous processes at the affected symptomatic level
- The DIAM device restores biomechanical integrity by
  A) Load-sharing with painfully overloaded disc & annulus
  B) Load-sharing with painfully overloaded facet joints
  C) Reestablishing ligamentous tension
**Indication:** Neurogenic Intermittent Claudication (leg/buttock/groin pain) due to stenosis (w/ or w/o back pain)

- Blocks extension/relative kyphosis
- Expands neural foramen and spinal canal via indirect decompression
- May relieve leg pain by increasing foramen/canal dimensions

**Indication:** Moderate Low Back Pain (LBP) due to DDD (w/ or w/o leg pain)

- Stabilizes but does not block extension
- Restores biomechanical integrity/load shares with facets & posterior disc
- May relieve LBP by decreasing pressure on painful structures
DIAM SPINAL STABILIZATION DEVICE
SURGICAL TECHNIQUE
DIAM SPINAL STABILIZATION DEVICE
TREATMENT INTENT

For moderate low back pain due to single level symptomatic degenerative disc disease, DIAM provides

- Safe and effective treatment option
- Less invasive/less destructive surgery
- Simple surgical technique
- Pain alleviation through reduction of stress through painful load-bearing structures
- Continuum of care gap coverage
- An option for patients not yet indicated for fusion or TDR
- Potential future surgical options (no burning of bridges)
**DIAM IMPLANT**
**DESIGN INTENT**

- DIAM has a long and very successful implantation history outside of the US
  - Simple yet robust design
  - Reestablishes biomechanical integrity

- Restores/augments the biomechanical function compromised due to degenerative disc disease
- Alleviates pain through the reduction of stress on painful load-bearing anatomic structures
- May enhance stability without eliminating motion
DIAM IMPLANT
MECHANISM OF ACTION

- Limits angulation in extension
- Load shares with posterior annulus
- Load shares with facet joints
- Stabilizes/maintains F/E motion
DIAM IMPLANT
MECHANISM OF ACTION
**DIAM IMPLANT**
**BIOMECHANICAL FUNCTION**

- Finite Element Analysis (FEA) showed:
  - 27% disc load reduction in flexion
  - 51% disc load reduction in extension
  - Significant compressive stress reduction on posterior annulus during extension

DIAM IMPLANT
BIOMECHANICAL FUNCTION

Applied Moment

L4 spinous process

DIAM Implant

L5 spinous process

Sacrum
DIAM IMPLANT
BIOMECHANICAL FUNCTION

- Biomechanical testing shows DIAM motion in flexion and extension

DIAM IMPLANT
BIOMECHANICAL FUNCTION

- Primary function = load-sharing
  - Distraction/motion reduction a secondary effect
- Ha et al. publication
  - Severe NIC w/decompressive laminotomy & foraminotomy

*FDA concern: Adequacy of timepoint for assessment of overall success*

- “DIAM can prevent further collapse”
- “No patients with recurrent stenosis”
- “Range of motion remained significantly reduced”
- “Clinical condition... was improved, and improvement was maintained”
DIAM IMPLANT
BIOMECHANICAL FUNCTION

- Extension angle decreased at all time periods
  - Stability enhancement & motion preservation
- Posterior disc height increased at all time periods
  - Posterior load-sharing function
- Coincident significant reduction in leg pain, back pain, and ODI scores
- DIAM load sharing, stabilization, and clinical effectiveness steady at 12 months and does not deteriorate over time

FDA concerns:
- Adequacy of timepoint for assessment of overall success
- Clinical significance of angular/translational motion results
DIAM MATERIALS
ANATOMY OF A DIAM DEVICE

- Spinous process spacer
  - Biocompatible materials
    - Used in implantable devices for over 20 years
  - Stiff silicone core
    - Load-bearing component
  - Polyester jacket
    - Secures implant/tissue ingrowth

- Tethers
  - Braided polyester
  - Stainless steel needle

- Titanium crimps
  - Secure tethers
MECHANICAL TESTING

- A complete battery of mechanical testing completed per ASTM F2077 (modified):
  - Axial compression (static/fatigue) (new/aged)
  - Tension (static /fatigue)
  - Torsion (fatigue)
  - Compression creep
- All testing surpassed acceptance criteria
**BIOCOMPATIBILITY TESTING**
ISO 10993

- Complete ISO 10993 series of biological testing
  - Individual components & complete device
  - Short- & long-term effects
  - Material safety and fitness
  - Chemical and toxicological characteristics
- All test results well within acceptable limits

<table>
<thead>
<tr>
<th>ISO Standard</th>
<th>Test Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>10993-3 Genotoxicity</td>
<td>Chromosomal Aberration Study</td>
</tr>
<tr>
<td>10993-4 Interactions with Blood</td>
<td>Bacterial Reverse Mutation Assay Ames Test</td>
</tr>
<tr>
<td>10993-4 Interactions with Blood</td>
<td>Micronucleus Cytogenetic Assay in Mice</td>
</tr>
<tr>
<td>10993-5 Cytotoxicity</td>
<td>In Vitro Hemolysis Test</td>
</tr>
<tr>
<td>10993-6 Local Effects after Implantation</td>
<td>ISO MEM Elution Cytotoxicity Assay</td>
</tr>
<tr>
<td>10993-6 Local Effects after Implantation</td>
<td>Short-term Implantation with Histopathology</td>
</tr>
<tr>
<td>10993-6 Local Effects after Implantation</td>
<td>Long-term Implantation with Histopathology</td>
</tr>
<tr>
<td>10993-10 Irritation and Skin Sensitization</td>
<td>Maximization Sensitization Study</td>
</tr>
<tr>
<td>10993-10 Irritation and Skin Sensitization</td>
<td>Intracutaneous Test</td>
</tr>
<tr>
<td>10993-11 Systemic Toxicity</td>
<td>Systemic Toxicity Test</td>
</tr>
<tr>
<td>10993-11 Systemic Toxicity</td>
<td>Material Mediated Pyrogenicity Test</td>
</tr>
<tr>
<td>10993-18 Chem. Char. of Materials</td>
<td>Chemical characterization</td>
</tr>
</tbody>
</table>
BIOCOMPATIBILITY TESTING
ANIMAL STUDIES

- Sheep Study
  - 12 adult sheep
  - Explanted at 6 months and 1 year
  - No adverse tissue reaction, wear debris, osteolysis, implant loosening, or migration

- Rabbit Study
  - 12 rabbits
  - 4 mg of Silicone and PET debris
    - Same size/shape as mechanical/explant debris
    - 82.4 mg scaled to 70 kg human
    - Greater than 3X wear that would be generated in 80 years
  - Sacrificed at 3 and 6 months
  - No systemic related or osteolytic response
  - Localized inflammatory response classified as a slight irritant
BIOCOMPATIBILITY TESTING
EXPLANT ANALYSIS

- Over 140,000 DIAM devices implanted worldwide
- 240 DIAM devices in IDE study
- 8 total explants, 6 analyzed
- “Fibrous & fibrofatty connective tissues surrounding implant”
- No osteolysis
- A “mild” foreign body host response consistent with Dacron™ fabrics implanted in humans
SUMMARY OF PRECLINICAL TESTING

DIAM design and function are simple:
- Load shares with posterior disc/annulus
- Load shares with facet joints
- Maintains flexion/extension motion

Preclinical testing has confirmed:

<table>
<thead>
<tr>
<th>Enhanced load sharing and stability</th>
<th>Biomechanical testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strength well in excess of physiologic loads</td>
<td>Static &amp; fatigue testing</td>
</tr>
<tr>
<td>Excellent biocompatibility</td>
<td>ISO 10993/sheep/rabbit testing/explant analysis</td>
</tr>
</tbody>
</table>
The primary study endpoint was met:
  - Composite primary study endpoint includes clinically meaningful safety and effectiveness parameters

Superior Effectiveness Over Alternative Treatment

- The primary study objective was met:
  - DIAM device statistically superior to control in Overall Success at 12 months (63.9% vs 15.1%, primary dataset)
DIAM DEVICE IDE TRIAL
KEY FINDINGS

Clinically Meaningful Results

- Consistency of primary and secondary endpoints is maintained over time and across multiple patient cohorts and subgroups

Safe Procedure

- Low rate of serious device-related adverse events
- Few secondary surgeries
STUDY DESIGN

- Prospective, randomized clinical trial
- 23 sites treated patients
- 2:1 randomization ratio
- Treatment groups
  - Investigational – DIAM device
  - Control – conservative care
- Total number of treated subjects: 282
  - 181 Investigational
  - 101 Control
PATIENT SELECTION

- Moderate low back pain (with or without radicular pain)
- Radiographic evidence of DDD
- Single symptomatic level L2-L5
- Current episode of low back pain less than 1 year duration
- Failed 6 weeks of conservative non operative care
- Patient capable of undergoing a minimally invasive posterior procedure

*FDA concern: Adequacy of study population*
CONTROL: COMPREHENSIVE CONSERVATIVE THERAPY

- Patient education
  - NASS-derived patient information regarding low back pain
  - Education on lifting techniques/back strengthening

- Medication – NSAID, muscle relaxants, non-narcotics, narcotics, neuroleptics, anti-depressants

- Physical therapy – Community standard

- Spinal injections – Epidural and/or facet joint steroidal injections

**FDA concern**: Selection and adequacy of non-operative control group/therapies
PRIMARY ENDPOINT

- Primary endpoint - Patient “OVERALL SUCCESS” at 12 months

- To Achieve “OVERALL SUCCESS”
  - ODI improvement of ≥ 15 points; AND
  - No serious adverse event related to treatment; AND
  - No additional surgical procedure (DIAM subjects) or “treatment surgery” at the involved level (Control subjects)

- Primary study objective
  - Superiority in OVERALL SUCCESS at 12 months
EFFECTIVENESS ENDPOINTS

- Effectiveness endpoints
  - ODI
  - Back pain
  - Leg pain
  - SF-36 PCS

- Secondary study objective
  - Superiority in effectiveness endpoints at 12 months
CROSSOVER REQUIREMENTS

- Study protocol allowed crossover to DIAM device or to receive other surgical treatments after 6 months given these conditions:
  - Completed all conservative care options; AND
  - ODI score ≥ 30 points; AND
  - ODI score improvement from baseline < 15 points

- Crossover subjects (who received DIAM device)
  - Followed same evaluation as subjects originally randomized to the DIAM device group
    - 6 weeks, 3, 6, 12, 24, 36, 48, and 60 months, etc.
THREE DATASETS REVIEWED

- Primary dataset
- All available dataset
- Crossover dataset

Dataset definitions will be provided in the Statistical Presentation
### PATIENT DEMOGRAPHICS/BASELINE FACTORS
#### PRIMARY DATASET

<table>
<thead>
<tr>
<th>Variable</th>
<th>DIAM (n=97)</th>
<th>Control (n=53)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age [mean (range)]</td>
<td>42 (18-67)</td>
<td>43 (23-65)</td>
</tr>
<tr>
<td>Male (%)</td>
<td>43%</td>
<td>47%</td>
</tr>
<tr>
<td>BMI [mean (range)]</td>
<td>28 (19-41)</td>
<td>28 (19-40)</td>
</tr>
<tr>
<td>Caucasian (%)</td>
<td>90%</td>
<td>89%</td>
</tr>
<tr>
<td>Tobacco Use (%)</td>
<td>25%</td>
<td>34%</td>
</tr>
<tr>
<td>Working (%)</td>
<td>69%</td>
<td>75%</td>
</tr>
<tr>
<td>Litigation (%)</td>
<td>13%</td>
<td>11%</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>4%</td>
<td>6%</td>
</tr>
<tr>
<td>Pre-op ODI Score [mean]</td>
<td>49</td>
<td>50</td>
</tr>
<tr>
<td>Pre-op Back Pain [mean]</td>
<td>17</td>
<td>16</td>
</tr>
<tr>
<td>Pre-op Leg Pain [mean]</td>
<td>11</td>
<td>9</td>
</tr>
</tbody>
</table>
## PATIENT DEMOGRAPHICS/BASELINE FACTORS
### ALL AVAILABLE DATASET

<table>
<thead>
<tr>
<th>Variable</th>
<th>DIAM™ (n=181)</th>
<th>Control (n=97)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age [mean (range)]</td>
<td>43 (18-69)</td>
<td>45 (23-70)</td>
</tr>
<tr>
<td>Male (%)</td>
<td>43%</td>
<td>51%</td>
</tr>
<tr>
<td>BMI [mean (range)]</td>
<td>28 (19-41)</td>
<td>28 (17-40)</td>
</tr>
<tr>
<td>Caucasian (%)</td>
<td>92%</td>
<td>91%</td>
</tr>
<tr>
<td>Tobacco Use (%)</td>
<td>25%</td>
<td>34%</td>
</tr>
<tr>
<td>Working (%)</td>
<td>67%</td>
<td>69%</td>
</tr>
<tr>
<td>Litigation (%)</td>
<td>14%</td>
<td>11%</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>6%</td>
<td>5%</td>
</tr>
<tr>
<td>Pre-op ODI Score [mean]</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>Pre-op Back Pain [mean]</td>
<td>17</td>
<td>16</td>
</tr>
<tr>
<td>Pre-op Leg Pain [mean]</td>
<td>10</td>
<td>9</td>
</tr>
</tbody>
</table>
PRIMARY ENDPOINT

- Primary endpoint - Patient “OVERALL SUCCESS” at 12 months

- To Achieve “OVERALL SUCCESS”
  - ODI improvement of ≥ 15 points; AND
  - No serious adverse event related to treatment; AND
  - No additional surgical procedure (DIAM subjects) or “treatment surgery” at the involved level

- Primary study objective
  - Superiority in OVERALL SUCCESS at 12 months
DIAM PATIENTS HAVE GREATER OVERALL SUCCESS
PRIMARY DATASET

Probability of superiority >99.9%

% Success

<table>
<thead>
<tr>
<th>Time</th>
<th>DIAM® (N=97)</th>
<th>Control (N=53)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 weeks</td>
<td>57.9</td>
<td>22.4</td>
</tr>
<tr>
<td>3 months</td>
<td>71.1</td>
<td>30.0</td>
</tr>
<tr>
<td>6 months</td>
<td>71.1</td>
<td>17.0</td>
</tr>
<tr>
<td>12 months</td>
<td>63.9</td>
<td>15.1</td>
</tr>
</tbody>
</table>

DIAM® (N=97)
SUPPORTING DATASETS

- Consistency of results with the primary dataset
- The treatment effect with DIAM device maintained over time
- Crossover cohort results consistent with DIAM subjects in primary dataset
DIAM SUBJECTS HAVE GREATER OVERALL SUCCESS
ALL AVAILABLE DATASET

% Success

<table>
<thead>
<tr>
<th></th>
<th>6 wks</th>
<th>3 mos</th>
<th>6 mos</th>
<th>12 mos</th>
<th>24 mos</th>
<th>36 mos</th>
<th>48 mos</th>
<th>60 mos</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTRL (N=)</td>
<td>90</td>
<td>91</td>
<td>94</td>
<td>89</td>
<td>73</td>
<td>56</td>
<td>44</td>
<td>38</td>
</tr>
<tr>
<td>DIAM (N=)</td>
<td>179</td>
<td>176</td>
<td>180</td>
<td>164</td>
<td>119</td>
<td>97</td>
<td>77</td>
<td>64</td>
</tr>
</tbody>
</table>
SIMILAR OVERALL SUCCESS RATES OVER TIME
CROSSOVER DATASET

<table>
<thead>
<tr>
<th></th>
<th>DIAM (N=)</th>
<th>Cross (N=)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 weeks</td>
<td>179</td>
<td>58</td>
</tr>
<tr>
<td>3 months</td>
<td>176</td>
<td>57</td>
</tr>
<tr>
<td>6 months</td>
<td>180</td>
<td>56</td>
</tr>
<tr>
<td>12 months</td>
<td>164</td>
<td>44</td>
</tr>
<tr>
<td>24 months</td>
<td>119</td>
<td>35</td>
</tr>
</tbody>
</table>

% Success

- 6 weeks: DIAM® 64.2%, Crossover 60.3%
- 3 months: DIAM® 75.0%, Crossover 66.7%
- 6 months: DIAM® 71.1%, Crossover 73.2%
- 12 months: DIAM® 66.5%, Crossover 75.0%
- 24 months: DIAM® 63.9%, Crossover 65.7%

Medtronic
EFFECTIVENESS ENDPOINTS
PRIMARY DATASET
DIAM SUBJECTS HAVE LOWER MEAN POSTOPERATIVE ODI SCORES

PRIMARY DATASET

Probability of superiority >99.9%
DIAM SUBJECTS HAVE LOWER MEAN POSTOPERATIVE BACK PAIN SCORES
PRIMARY DATASET

Probability of superiority >99.9%

DIAM® (N=97)
Control (N=53)
DIAM SUBJECTS HAVE LOWER MEAN POSTOPERATIVE LEG PAIN SCORES

PRIMARY DATASET

Probability of superiority >99.9%
DIAM SUBJECTS HAVE HIGHER SF-36 PCS GENERAL HEALTH STATUS
PRIMARY DATASET

Probability of superiority >99.9%
EFFECTIVENESS ENDPOINTS
ALL AVAILABLE DATASET
DIAM SUBJECTS HAVE LOWER MEAN POSTOPERATIVE ODI SCORES
ALL AVAILABLE DATASET

<table>
<thead>
<tr>
<th>Months</th>
<th>CTRL (N=)</th>
<th>DIAM (N=)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>97</td>
<td>181</td>
</tr>
<tr>
<td>12</td>
<td>90</td>
<td>179</td>
</tr>
<tr>
<td>24</td>
<td>84</td>
<td>162</td>
</tr>
<tr>
<td>36</td>
<td>69</td>
<td>118</td>
</tr>
<tr>
<td>48</td>
<td>52</td>
<td>97</td>
</tr>
<tr>
<td>60</td>
<td>42</td>
<td>76</td>
</tr>
<tr>
<td>63</td>
<td>35</td>
<td>63</td>
</tr>
</tbody>
</table>
DIAM SUBJECTS HAVE LOWER MEAN POSTOPERATIVE BACK PAIN SCORES
ALL AVAILABLE DATASET

<table>
<thead>
<tr>
<th>Months</th>
<th>CTRL (N=)</th>
<th>DIAM (N=)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>97</td>
<td>181</td>
</tr>
<tr>
<td>12</td>
<td>93</td>
<td>178</td>
</tr>
<tr>
<td>24</td>
<td>84</td>
<td>161</td>
</tr>
<tr>
<td>36</td>
<td>69</td>
<td>118</td>
</tr>
<tr>
<td>48</td>
<td>52</td>
<td>96</td>
</tr>
<tr>
<td>60</td>
<td>42</td>
<td>76</td>
</tr>
</tbody>
</table>

**Mean Back Pain Score**

- **DIAM®**
- **Control**
DIAM SUBJECTS HAVE LOWER MEAN POSTOPERATIVE LEG PAIN SCORES
ALL AVAILABLE DATASET

![Graph showing mean leg pain scores over months for DIAM and control groups.]

<table>
<thead>
<tr>
<th>Months</th>
<th>DIAM (N=)</th>
<th>Control (N=)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>181</td>
<td>97</td>
</tr>
<tr>
<td>12</td>
<td>178</td>
<td>93</td>
</tr>
<tr>
<td>24</td>
<td>162</td>
<td>84</td>
</tr>
<tr>
<td>36</td>
<td>118</td>
<td>68</td>
</tr>
<tr>
<td>48</td>
<td>97</td>
<td>52</td>
</tr>
<tr>
<td>60</td>
<td>76</td>
<td>42</td>
</tr>
<tr>
<td></td>
<td></td>
<td>35</td>
</tr>
</tbody>
</table>

CTRL (N=) 97 93 84 68 52 42 35
DIAM (N=) 181 178 162 118 97 76 63
DIAM SUBJECTS HAVE HIGHER SF-36 PCS GENERAL HEALTH STATUS SCORES
ALL AVAILABLE DATASET

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

Mean PCS score

Months

DIAM®

Control
EFFECTIVENESS ENDPOINTS
CROSSOVER DATASET
SIMILAR RESULTS OVER TIME
CROSSOVER DATASET

Mean ODI score

Mean back pain score

Mean leg pain score

Mean SF-36 PCS score
ADDITIONAL SUPPORTIVE INFORMATION
PRIMARY DATASET
DIAM SUBJECTS MORE SATISFIED WITH TREATMENT

PRIMARY DATASET

* Subjects responding with “definitely true” or “mostly true” for being “satisfied with the results of treatment.”
LOWER PERCENTAGE OF SUBJECTS USED NARCOTICS IN DIAM DEVICE GROUP
PRIMARY DATASET

Percent of subjects using narcotics:

- Baseline: DIAM® (N=97) 63, Control (N=53) 61.9
- 6 weeks: DIAM® 45.6, Control 65.9
- 3 months: DIAM® 39.3, Control 64.4
- 6 months: DIAM® 44, Control 60.4
- 12 months: DIAM® 35.1, Control 61.5
FEWER DIAM SUBJECTS REQUIRED POST-OPERATIVE INJECTIONS AT INDEX LEVEL

PRIMARY DATASET

<table>
<thead>
<tr>
<th>Time Period</th>
<th>DIAM® (N=97)</th>
<th>Control (N=53)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Up to 12 months</td>
<td>13.4%</td>
<td>18.6%</td>
</tr>
<tr>
<td>Up to 24 months</td>
<td>45.3%</td>
<td>47.2%</td>
</tr>
</tbody>
</table>
SAFETY RESULTS
# SUMMARY OF ADVERSE EVENTS
## UP TO 12 MONTHS (PRIMARY DATASET)

<table>
<thead>
<tr>
<th>Type of Event</th>
<th>Number of Events</th>
<th>Number of Subjects Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DIAM® (N=97)</td>
<td>Control (N=53)</td>
</tr>
<tr>
<td>Any Event</td>
<td>408</td>
<td>109</td>
</tr>
<tr>
<td>Study Treatment Related Event</td>
<td>28</td>
<td>42</td>
</tr>
<tr>
<td>Serious Event</td>
<td>340</td>
<td>87</td>
</tr>
<tr>
<td>Serious, Study Treatment Related Event</td>
<td>25</td>
<td>38</td>
</tr>
</tbody>
</table>
SERIOUS, STUDY TREATMENT RELATED EVENTS
CONTROL GROUP

- Driven by worsening or increased low back pain
- 17 subjects had no improvement with continued conservative treatment and eventually received operative treatment
- 2 subjects stabilized and continued non-operative treatment
- All events deemed by CAC as serious due to medical or surgical intervention to prevent permanent impairment, and non-operative treatment associated

FDA concern: Higher than expected frequency of serious, study treatment related adverse events in the non-operative treatment group as compared to the DIAM group
ADDITIONAL OR TREATMENT SURGERIES
UP TO 12 MONTHS (PRIMARY DATASET)

- Additional Surgical Procedures: DIAM
  - Revision: A procedure that adjusts or in any way modifies the original implant configuration (e.g., adjusting position of the original configuration).
  - Removal: removal of one or more components of the original implant configuration
  - Reoperation: any procedure at the involved level not classified as a revision or removal. May include decompression (e.g., laminectomy or foraminotomy); discectomy; fusion; or other procedures to alleviate the symptoms of DDD.
  - Other: Any additional surgical procedure not classified as a revision, removal or reoperation. (Includes lumbar surgery not at index level, non-lumbar spinal surgery, and non-spinal surgery)

- Additional Surgical Procedures: Control
  - Other index level surgery: a surgical procedure to treat DDD. May include fusion, spinal decompression (e.g., laminectomy or foraminotomy), discectomy, or other procedures
### ADDITIONAL OR TREATMENT SURGERIES
ALL AVAILABLE DATA

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Surgery Type</th>
<th>Number (% of patients reporting)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td><strong>Up to 12 months</strong></td>
</tr>
<tr>
<td>DIAM Group (n=181)</td>
<td>Revisions</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td></td>
<td>Removals</td>
<td>4 (2.2%)</td>
</tr>
<tr>
<td></td>
<td>Reoperations</td>
<td>14 (7.7%)</td>
</tr>
<tr>
<td>Control Group (n=97)</td>
<td>Crossovers (to DIAM only)</td>
<td>54 (55.7%)</td>
</tr>
<tr>
<td></td>
<td>Other index-level surgeries</td>
<td>9 (9.3%)</td>
</tr>
</tbody>
</table>
RADIOGRAPHIC OBSERVATIONS
SPINOUS PROCESS EROSIONS (CONTOURING)

Background
- Core lab originally assessed presence or absence of “bony erosion”
- FDA requested additional evaluation
- Submitted revised Medical Data Image Review Protocol to FDA
- Supplementary review of positive erosion cases to sub-classify bony changes
  - Mechanical contour changes or inflammatory erosion?

Findings
- Consistent with spinous process remodeling due to altered mechanical loading/pressure (Wolff’s Law)
- All of the spinous process erosions were determined to be mechanical and non-inflammatory
- No meaningful impact of radiographic changes on any clinical outcome measures
- No reliable patient demographic and preoperative predictors identified for occurrence of contour change

FDA concern: Clinical significance of erosions
RADIOGRAPHIC OBSERVATIONS
SPINOUS PROCESS FRACTURES

Background
- Core lab originally assessed location, occurrence and timing
- FDA requested additional evaluation
- Supplementary review of positive spinous process fractures to assess anatomical location, displacement, and healing status

Findings
- Occurred in 19 (7.9%) subjects based on radiographic readings and adverse event reports
- Observed early and most were asymptomatic
- Mostly posterior to interface between spinous process and device (core or tether)
- Majority healed without intervention
- Lower spinous process fracture rate than other interspinous process devices studied in trials

FDA concern: Clinical significance of spinous process fractures
SIGNIFICANT REDUCTION IN INTERVERTEBRAL ANGLE EXTENSION RADIOGRAPH – ALL AVAILABLE DATASET

<table>
<thead>
<tr>
<th>Months</th>
<th>CTRL (N=)</th>
<th>DIAM (N=)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>94</td>
<td>177</td>
</tr>
<tr>
<td>6</td>
<td>87</td>
<td>172</td>
</tr>
<tr>
<td>12</td>
<td>90</td>
<td>170</td>
</tr>
<tr>
<td>18</td>
<td>84</td>
<td>162</td>
</tr>
<tr>
<td>24</td>
<td>81</td>
<td>155</td>
</tr>
</tbody>
</table>

Mean Intervertebral Angle in Extension (Degrees)
SIGNIFICANT CHANGE FROM BASELINE IN POSTERIOR DISC HEIGHT
NEUTRAL POSITION – ALL AVAILABLE DATASET

<table>
<thead>
<tr>
<th>Months</th>
<th>CTRL (N=)</th>
<th>DIAM (N=)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>87</td>
<td>171</td>
</tr>
<tr>
<td>6</td>
<td>91</td>
<td>171</td>
</tr>
<tr>
<td>12</td>
<td>86</td>
<td>157</td>
</tr>
<tr>
<td>18</td>
<td>81</td>
<td>152</td>
</tr>
<tr>
<td>24</td>
<td>66</td>
<td>109</td>
</tr>
</tbody>
</table>
CONCLUSIONS FROM CLINICAL STUDY

- Superior clinical performance of DIAM when compared to alternative treatment for this population
  - Overall success
  - ODI
  - Back pain
  - Leg pain
  - SF-36 PCS

- Other endpoints also show advantage of DIAM over control
  - Patient satisfaction
  - Decreased narcotic usage
  - Decreased need for injections
CONCLUSIONS FROM CLINICAL STUDY

- Consistency of clinical results for different patient cohorts
- Evidence of duration of effect
- Low rate of serious device-related adverse events
- Few secondary surgeries
CLINICAL RELEVANCE

- Substantial clinical evidence in support of DIAM as a treatment for subjects with moderate back pain, with or without leg pain, secondary to DDD
  - As measured by objective endpoints
  - As measured by patient general health status endpoints
  - As measured by incidence of adverse events

- Risks are minimal and manageable

- Treatment effect is significant and consistent despite weaknesses pointed out by FDA
Overall results support a reasonable assurance of safety and effectiveness of the DIAM device.
DIAM® SPINAL STABILIZATION SYSTEM
IDE CLINICAL TRIAL RESULTS - G050025
STATISTICAL CONSIDERATIONS

PRESENTED BY
DONALD BERRY, PHD
BERRY CONSULTANTS, UNIVERSITY OF TEXAS MD ANDERSON CANCER CENTER
HOUSTON, TX

Medtronic
Further, Together
OVERVIEW

- Study design and interim analysis
- Study endpoint and timepoint for assessment
- Analysis populations
- Additional statistical considerations
  - Crossovers
  - Intention to treat
  - Subgroups
STUDY DESIGN

- Randomized controlled trial, 2:1 (DIAM : Control) allocation

- Primary endpoint: Overall success at 12 months

- Bayesian model for proportions
  - Consistent with FDA Bayesian guidance
  - Analysis model pre-specified
  - Non-informative prior
INTERIM ANALYSIS

- Original planned sample size = 306
  - 90% power for hypothesized success rates 60% versus 40%
  - Power higher for larger difference (e.g. lower control success rate)

- Plans for interim analysis discussed and agreed with FDA
  - Superiority criterion set to 97.5% to control type I error rate < 5%
  - Approval of 150 subjects = primary analysis set
ANALYSIS POPULATIONS DEFINITIONS

Primary analysis set (n=150)
- Comparisons by randomized assignment
- First 150 treated subjects with ≥ 1 post-baseline (6 weeks or after) overall success status evaluation and passed 12-month evaluation

Per-protocol (n=140)

All available (n=278)
- All treated subjects with ≥ 1 post-baseline evaluation
- All follow-up timepoints
STUDY ENDPOINT AND TIMEPOINT FOR ASSESSMENT

PRIMARY ANALYSIS: IMPROVED SUCCESS RATE AT MONTH 12

- Subject success if
  - ODI improvement ≥ 15 points
  - No treatment-related serious adverse event
  - No additional surgery at involved level
### CONSISTENT SUPERIORITY ACROSS DATASETS

**PRIMARY ANALYSIS: IMPROVED OVERALL SUCCESS AT MONTH 12**

<table>
<thead>
<tr>
<th>Dataset</th>
<th>DIAM</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td>62/97</td>
<td>8/53</td>
</tr>
<tr>
<td>Per Protocol</td>
<td>59/89</td>
<td>4/41</td>
</tr>
<tr>
<td>All Available</td>
<td>109/164</td>
<td>11/89</td>
</tr>
</tbody>
</table>

- **DIAM Control**
  - 47.3% advantage
  - 54.3% advantage
  - 53.1% advantage

---

**Advantage in DIAM Success Rate at Month 12**
STUDY ENDPOINT AND TIMEPOINT FOR ASSESSMENT
PRIMARY ANALYSIS: IMPROVED SUCCESS RATE AT MONTH 12

- Subject success if
  - ODI improvement ≥ 15 points
  - No treatment-related serious adverse event
  - No additional surgery at involved level

FDA concern: Adequacy of study endpoint and timepoint for assessment of overall success

- I will address both
FDA CONCERNS REGARDING BIAS, CROSSTERS IN CONTROL GROUP, TIME FOR ENDPOINT ASSESSMENT

“The proportion of crossover subjects in the nonoperative control group makes the proper interpretation of study results difficult”

“In addition, the last observation carried forward approach for the determination of overall success at 12 months is biased”

“Consequently, the treatment difference is unclear, and should be interpreted with caution”

- We agree
- I will describe the biases and address them ...
- Concluding that although the treatment difference is unclear, the superiority of DIAM is clear
Crossovers in Pre-Specified Design & Analysis

- Controls could cross over to DIAM at or after 6 months if ODI ≥ 30 and ODI improvement < 15.
- Analysis: last observation carried forward (LOCF), so crossover before month 12 is failure at month 12.

- Why crossovers allowed, and even necessary
  - Practical & ethical concern: not withhold potentially effective treatment if control therapy is failing for 12 months.
  - Regarded by opinion leaders as essential for enrollment and adherence to follow-up.

What happened in the trial?
TIME TO CROSSOVER IN CONTROL SUBJECTS

PRIMARY DATASET (N=53)

20 subjects crossed over to DIAM between month 6 and 12 visits
CROSSOVER FROM CONTROL
PRIMARY DATASET (N=53 CONTROLS)

No Xover before 6-mo visit

Randomized to control (n=53)
- Eval. at 6 wks
- Eval. at 3 mos
- Eval. at 6 mos

Candidate for surgery (n=41)
- Xover to DIAM (n=20)
  - 6-mo ODI carried to 12 mos
- Other surgery (n=4)
  - 6-mo ODI carried to 12 mos
- No surgery (n=17)
  - Eval. at 12 mos

Not candidate for surgery (n=12)
- No surgery (n=12)
  - Eval. at 12 mos
**MEAN ODI SCORES FOR CONTROLS**

**PRIMARY ANALYSIS OF PRIMARY DATASET (N=53)**

Summary not previously provided to FDA

![Graph showing mean ODI scores over months for different groups: Crossovers (n=20), Qualified but Not Crossover (n=17), Other Surgeries (n=4), and Not Qualified for Crossover (n=12).]
MEAN ODI SCORES FOR CONTROLS
PRIMARY ANALYSIS OF PRIMARY DATASET (N=53)

Summary not previously provided to FDA
MEAN ODI SCORES FOR CONTROLS

PRIMARY ANALYSIS OF PRIMARY DATASET (N=53)

Summary not previously provided to FDA
MEAN ODI SCORES FOR CONTROLS
PRIMARY ANALYSIS OF PRIMARY DATASET (N=53)

Summary not previously provided to FDA
DIAM PATIENTS HAVE GREATER OVERALL SUCCESS
PRIMARY DATASET

Mean Diff: 54.1%
Probability of superiority: >99.9%

Mean Diff: 48.8%
Probability of superiority: >99.9%

6 Months

DIAM® (n=97)

69/97

63.9%

Control (n=53)

9/53

17.0%

12 Months

DIAM® (n=97)

62/97

8/53

15.1%
DIAM PATIENTS HAVE GREATER OVERALL SUCCESS
PRIMARY DATASET

Mean Diff: 54.1%
Probability of superiority: >99.9%

Mean Diff: 48.8%
Probability of superiority: >99.9%

Protected by Randomization

Not Protected by Randomization
DIAM MAINTAINS SUPERIORITY AT 12 MONTHS ASSUMING INTENTION TO TREAT (CROSSOVER IGNORED; NO LOCF) PRIMARY DATASET

Mean Diff: 36.8%
Probability of superiority: >99.9%

Observed Data

% Overall Success

DIAM® 64.5
Control 27.7

60/93 13/47 N=97 N=53 N=111 N=56
DIAM MAINTAINS SUPERIORITY AT 12 MONTHS ASSUMING INTENTION TO TREAT (CROSSOVER IGNORED; NO LOCF) PRIMARY DATASET

Mean Diff: 36.8%
Probability of superiority: >99.9%

Mean Diff: 37.4%
Probability of superiority: >99.9%

Observed Data
- DIAM®: 64.5%
- Control: 27.7%

Missing Data=Failure
- DIAM®: 61.9%
- Control: 24.5%

N=111
N=56
DIAM MAINTAINS SUPERIORITY AT 12 MONTHS ASSUMING INTENTION TO TREAT (CROSSOVER IGNORED; NO LOCF) PRIMARY DATASET

Mean Diff: 36.8%
Probability of superiority: >99.9%

Mean Diff: 37.4%
Probability of superiority: >99.9%

Mean Diff: 30.9%
Probability of superiority: >99.9%

64.5

61.9

54.1

60/93 13/47

60/97 13/53

60/111 13/56
DIAM MAINTAINS SUPERIORITY AT 12 MONTHS ASSUMING INTENTION TO TREAT (CROSSOVER IGNORED; NO LOCF) ALL AVAILABLE DATASET

Mean Diff: 25.6%
Probability of superiority: >99.9%

Mean Diff: 23.1%
Probability of superiority: >99.9%

Mean Diff: 18.1%
Probability of superiority: =99.9%
DIAM RESULTS ARE DURABLE OVER TIME
PRIMARY DATASET

Mean ODI Score

<table>
<thead>
<tr>
<th>Months</th>
<th>DIAM (n=)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>97</td>
</tr>
<tr>
<td>6</td>
<td>95</td>
</tr>
<tr>
<td>12</td>
<td>97</td>
</tr>
<tr>
<td>18</td>
<td>97</td>
</tr>
<tr>
<td>24</td>
<td>97</td>
</tr>
</tbody>
</table>
SIMILAR MEAN ODI AFTER CROSSING OVER
PRIMARY DATASET

<table>
<thead>
<tr>
<th>Months</th>
<th>DIAM (n=)</th>
<th>Xover (n=)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>97</td>
<td>59</td>
</tr>
<tr>
<td>6</td>
<td>97</td>
<td>58</td>
</tr>
<tr>
<td>12</td>
<td>97</td>
<td>57</td>
</tr>
<tr>
<td>18</td>
<td>97</td>
<td>55</td>
</tr>
<tr>
<td>24</td>
<td>97</td>
<td>35</td>
</tr>
</tbody>
</table>
SIMILAR MEAN ODI AFTER CROSSING OVER
ALL AVAILABLE SUBJECTS

DIAM (n=) 181 179 176 179 162 118
Xover (n=) 59 58 57 55 44 35
HETEROGENEITY OF DEGENERATIVE DISC SUBGROUPS

FDA concern: Adequacy of study population and impact on interpretation of safety and effectiveness results

- We agree that the population is heterogeneous. This heterogeneity reflects degenerative disc disease that presents in clinical practice.

- Results are robust showing consistent superiority of DIAM.

- DIAM shows efficacy despite heterogeneity.
POST-HOC ANALYSIS: CONSISTENT SUPERIORITY IN SEQUENTIALLY DEFINED DEGENERATIVE DISC SUBGROUPS
ALL AVAILABLE DATASET (N = 278)

<table>
<thead>
<tr>
<th>Sequential Category</th>
<th>DIAM</th>
<th>Control</th>
<th>Advantage in DIAM Overall Success Rate at Month 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Disc Herniation</td>
<td>37/55</td>
<td>2/25</td>
<td>55.6%</td>
</tr>
<tr>
<td>2. Disc Degen.</td>
<td>20/27</td>
<td>4/20</td>
<td>49.7%</td>
</tr>
<tr>
<td>3. Spinal Stenosis</td>
<td>13/16</td>
<td>1/6</td>
<td>52.8%</td>
</tr>
<tr>
<td>4. Facet Joint Deg.</td>
<td>16/26</td>
<td>0/15</td>
<td>54.8%</td>
</tr>
<tr>
<td>5. Remaining</td>
<td>23/40</td>
<td>4/23</td>
<td>37.1%</td>
</tr>
<tr>
<td>Overall</td>
<td>109/164</td>
<td>11/89</td>
<td>53.1%</td>
</tr>
</tbody>
</table>
POST-HOC ANALYSIS: CONSISTENT SUPERIORITY BY NUMBER OF LEVELS DETERMINED RADIOLOGICALLY AFTER TRIAL

ALL AVAILABLE DATASET (N = 278)

<table>
<thead>
<tr>
<th></th>
<th>DIAM</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiologically Single-Level</td>
<td>52/74</td>
<td>6/36</td>
</tr>
<tr>
<td>Radiologically Multi-Level</td>
<td>39/60</td>
<td>3/31</td>
</tr>
<tr>
<td>Missing Imaging</td>
<td>18/30</td>
<td>2/22</td>
</tr>
<tr>
<td>Overall</td>
<td>109/164</td>
<td>11/89</td>
</tr>
</tbody>
</table>

Advantage in DIAM Overall Success Rate at Month 12
STATISTICAL CONCLUSIONS

- All primary analyses show substantial DIAM effect
- LOCF for crossovers at 12 months is biased against control ... although non-crossover outcomes consistent with LOCF
- Primary analyses at 6 months is not biased by crossovers
- ITT analyses at 12 months show DIAM superiority, with somewhat lower estimated benefit
- Subject population is heterogeneous but DIAM effect is consistent across all subsets
- DIAM efficacy is durable over long term
DIAM® SPINAL STABILIZATION SYSTEM

CASE PRESENTATIONS

PRESENTED BY
SCOTT H. KITCHEL, MD
ORTHOPEDIC SPINE ASSOCIATES
EUGENE, OREGON
DIAM CASE STUDY # 1
INVESTIGATIONAL SUBJECT
DIAM CASE STUDY # 1
INVESTIGATIONAL SUBJECT

- Patient: 58 year old male
- History
  - Presented with low back pain to both sides, both buttocks, hips and tingling in both feet, left greater than right
  - Episodic back pain, no specific injury
  - Prior conservative care including physical therapy, chiropractic care, injections, and medications
- Diagnosis: central disc protrusion/annular tear; Grade 3 Pfirrmann; Grade 1 facet joint osteoarthritis at L4-5
- Treatment: DIAM device placement at L4-5
PREOPERATIVE X-RAY
CASE STUDY #1
PREOPERATIVE MRI
CASE STUDY #1
ODI SCORE OVER TIME
CASE STUDY #1

Months
0 10 20 30 40 50 60
01 0 2 0 3 0

DIAM Group Mean
Subject Score
BACK PAIN SCORE OVER TIME
CASE STUDY #1

Months

0 2 4 6 8
10 12 14 16 18

DIAM Group Mean

Subject Score

Back Pain Score

0 2 4 6 8 10 12 14 16 18

0 10 20 30

Months

Medtronic
SAFETY
CASE STUDY #1

- Baseline: neurological functions all normal except abnormal straight leg raising
- Postoperative: neurological functions all normal
- Adverse events:
  - None
- Core imaging laboratory assessment was negative for migration and spinous process fracture; Superior spinous process erosion noted at 36 months postoperative only
36-MONTH X-RAY
CASE STUDY #1
24-MONTH MRI
CASE STUDY #1
DIAM CASE STUDY # 2
CROSSOVER
SUBJECT
DIAM CASE STUDY # 2
CROSSOVER SUBJECT

- Patient: 48-year old female
- History
  - Presented with low back, bilateral buttock and posterior thigh pain
  - Began with bending event in exercise class
  - Prior conservative care including medications, independent exercises, chiropractic care, and massage
- Diagnosis: Grade 4 Pfirrmann, Grade 2 facet joint osteoarthritis and disc height loss at L4-5
- Initial treatment: Randomized to conservative care control group
  - Received patient education, 8 sessions of physical therapy, heat/ice therapy and taking daily non-narcotic medications and NSAIDS more than once a week. Received an intramuscular injection at L4-L5 at 3 months of follow-up
- Crossed over to DIAM device at approximately 6 months of follow-up
PREOPERATIVE X-RAY
CASE STUDY #2
PREOPERATIVE MRI
CASE STUDY #2
ODI SCORE OVER TIME
CASE STUDY #2

(Crossover ~6 months)

- Control Group Mean
- Subject as Control
- Crossover Group Mean
- Subject as Crossover

ODI Score (12 Months Post-op)
BACK PAIN SCORE OVER TIME
CASE STUDY #2

Back Pain Score Over Time
(Crossover ~6 months)

Months

(12 Months Post-op)

Control Group Mean

Subject as Control

Crossover Group Mean

Subject as Crossover

(12 Months Post-op)
LEG PAIN SCORE OVER TIME
CASE STUDY #2

(Crossover ~6 months)

LEG PAIN SCORE OVER TIME
CASE STUDY #2

(Crossover ~6 months)
SAFETY
CASE STUDY #2

- Baseline and Preoperative: neurological functions all normal
- Postoperative: neurological functions all normal
- No relevant adverse events reported
  - Hypothyroidism at surgery and labral tear at 11 months postoperative
- Core imaging laboratory assessment was negative for migration, focal bone structural changes, and spinous process fracture
12-MONTH X-RAY
CASE STUDY #2
12-MONTH MRI
CASE STUDY #2
CONCLUSIONS

- Multiple findings/structures involved in diagnosis of DDD
- Successful clinical outcome measures despite focal bone structural changes
- Selection criteria successfully target patients with moderate low back pain that may benefit from this therapy
DIAM® SPINAL STABILIZATION SYSTEM

SUMMARY

PRESENTED BY
KATHRYN SIMPSON, PHD
DIRECTOR, REGULATORY AFFAIRS, MEDTRONIC
IDE CLINICAL STUDY (G050025)

- Met **pre-specified** study success endpoint
- Followed **pre-specified** protocol and statistical analysis plan
- Excellent safety profile
- High level of patient satisfaction
- Longer-term consistent and positive results for DIAM patients
SPECIFIC FDA CONCERNS ADDRESSED BY SPONSOR

- Adequacy of study population
- Selection and adequacy of non-operative control group/therapies
- Adequacy of study endpoint and timepoint for assessment
- Impact of soft tissue/bone resections performed during DIAM surgical procedure
- Clinical significance of radiographic findings: bony erosion, spinous process fracture, sagittal plane motion measurements
EVIDENCE IN SUPPORT OF SAFETY AND EFFECTIVENESS

- Comprehensive pre-clinical tests
  - Mechanical testing
  - Biocompatibility testing
  - Animal testing
  - MRI compatibility

- FDA-approved IDE clinical study
  - Randomized controlled trial, 2:1 allocation
  - Primary endpoint: overall success at 12 months
  - FDA-approved interim analysis
  - Long-term data available
DIAM DEVICE AT LEAST AS SAFE AS CONTROL

- Percentages of subjects experiencing adverse events up to 12 months
  - Not statistically different between treatment groups

- Treatment-associated adverse events, treatment-associated serious adverse events, and treatment-associated severe (Grade 3) or life threatening (Grade 4) adverse events
  - Numerically lower for the DIAM group

- Additional surgical procedure rate through 12 months in the investigational group
  - Numerically lower for the DIAM group

- Safety trends continue at later follow-up intervals
## DIAM MORE EFFECTIVE THAN NON-OPERATIVE CONTROL

<table>
<thead>
<tr>
<th>Variable (Primary Dataset)</th>
<th>Observed Success Rate (Investigational)</th>
<th>Observed Success Rate (Control)</th>
<th>Posterior Probability of Superiority</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Success</td>
<td>63.9%</td>
<td>15.1%</td>
<td>&gt;99.9%</td>
</tr>
<tr>
<td>ODI Success</td>
<td>69.1%</td>
<td>17.0%</td>
<td>&gt;99.9%</td>
</tr>
<tr>
<td>Back Pain Success</td>
<td>89.7%</td>
<td>45.3%</td>
<td>&gt;99.9%</td>
</tr>
<tr>
<td>Leg Pain Success</td>
<td>72.2%</td>
<td>28.3%</td>
<td>&gt;99.9%</td>
</tr>
<tr>
<td>SF-36 PCS Success</td>
<td>87.6%</td>
<td>45.3%</td>
<td>&gt;99.9%</td>
</tr>
<tr>
<td>Patient Satisfaction</td>
<td>74.2%</td>
<td>32.1%</td>
<td>--</td>
</tr>
</tbody>
</table>
BENEFITS OF DIAM DEVICE OUTWEIGH RISKS

- Clinically significant reduction in pain and disability
- High patient satisfaction
- Decreased narcotic usage
- Decreased need for injections
- Favorable safety profile with low rate of serious, treatment-related adverse events
- No clinically meaningful radiologic findings
- Minimally invasive and anatomy-preserving
  - Preserves future surgical options, should they be needed
POST-APPROVAL STUDY
CONCLUSION

- Met pre-specified and approved study endpoint
- Followed pre-specified protocol and statistical analysis plan
- Properly defined patient population
- Appropriate control treatment
- Appropriate timepoint for assessment
- Favorable safety profile
- Superior effectiveness
- Results confirmed by longer-term data
- DIAM effective and safe as primary therapy