activL® Artificial Disc Spike Endplate

CAUTION—Federal (USA) law restricts this device to sale by or on the order of a physician.

How Supplied –
Implants: Sterile
Surgical Instruments: Non-Sterile

The activL® Artificial Disc has not been evaluated for safety and compatibility in the MR environment. It has not been tested for heating or migration in the MR environment.

Indications for Use

The activL® Artificial Disc (activL) is indicated for reconstruction of the disc at one level (L4-L5 or L5-S1) following single-level discectomy in skeletally mature patients with symptomatic degenerative disc disease (DDD) with no more than Grade I spondylolisthesis at the involved level. DDD is defined as discogenic back pain with degeneration of the disc confirmed by patient history, physical examination, and radiographic studies. The activL® Artificial Disc is implanted using an anterior retroperitoneal approach. Patients receiving the activL® Artificial Disc should have failed at least six months of nonoperative treatment prior to implantation of the device.

Device Description

The activL® Artificial Disc is a weight-bearing, modular implant comprised of three elements: an inferior Cobalt/Chromium (CoCr) alloy endplate (which is anchored in the endplate of the caudal vertebral body), an ultra-high molecular weight polyethylene (UHMWPE) inlay (which engages with the inferior endplate), and a superior CoCr alloy endplate (which is anchored in the endplate of the cranial vertebral body). Longer-term fixation of the activL® Artificial Disc to the vertebral bodies is intended to be achieved through bone growth, with initial stabilization by spikes on the endplates.

There are four endplate sizes and four inlay heights available. The superior endplates are provided in either 6° or 11° lordotic angle options, and the inferior endplates are provided in either 0° or 5° lordotic angle options. The 5° inferior endplate is designed for cases where the sacrum has a rounded posterior edge to allow placement of the endplate closer to the posterior border of the S1 vertebra, without the edges protruding.

The activL® Artificial Disc is assembled by the surgeon in the operating room prior to implantation. Two lateral wings on the inlay engage in grooves in the lateral walls of the inferior endplate. The superior endplate is then seated on the inferior endplate. Once assembled, the activL® Artificial Disc is mounted onto the inserter and implanted as a single unit via an anterior retroperitoneal approach.

Figure 1 Assembled activL® Artificial Disc with Spike Endplates

Table 1: activL® Endplate Sizes

ActivL® ENDPLATE SIZE	AP DIMENSIONS (mm)	LATERAL DIMENSIONS (mm)	LORDOTIC ANGLE
Small - Inferior	26	31	0° or 5°
Small - Superior	26	31	6° or 11°
Medium - Inferior	28	34.5	0° or 5°
Medium - Superior	28	34.5	6° or 11°
Large - Inferior	30	39	0° or 5°
Large - Superior	30	39	6° or 11°
Xtra Large - Inferior	33	40	0° or 5°
Xtra Large - Superior	33	40	6° or 11°

Table 2: activL® Inlay Sizes

activL® POLYETHYLENE INLAY SIZE	AP DIMENSIONS (mm)	LATERAL DIMENSIONS (mm)	INLAY HEIGHT/TOTAL DEVICE HEIGHT (mm)
Small	21	21	5.3 / 8.5
Medium	21	21	6.8 / 10
Large	21	21	8.8 / 12
Xtra Large	21	21	10.8 / 14

The maximum range of motion allowed by the activL® Artificial Disc (as measured through *in vitro* testing) is dependent on the endplate size, inlay height, and inlay location within the inferior endplate:

- The maximum allowable flexion is 43.5 degrees, and the minimum allowable flexion is 8.2 degrees.
- The maximum allowable extension is 43.5 degrees, and the minimum allowable flexion is 10.7 degrees.
- The maximum allowable lateral bending is ±34.1 degrees, and the minimum allowable lateral bending is ±8.

Note that the device design limit for many configurations is not achievable *in vivo* due to anatomic constraints. The activL® Artificial Disc is unconstrained in rotation.

The activL® Artificial Disc is implanted using instruments specific to the device, as well as manual surgical instruments. Instruments specifically designed for implanting the activL® include the insertion instrument (FW961R-FW964R), Trial Endplates (FW922R – FW928R, FW971R-FW979R), Impactor (FW910R-FW911R, FW915R, FW999R), revision instruments (FW965R-FW969R), Repositioner (FW969R), and Parallel distractor (FW970R). Manual surgical instruments include the Rasp (FW912R-FW913R), Wedges (FW940R – FW944R), Spacers (FW951R-FW954R) Midline Marker (FW955R, FW938SU), Distraction forceps (FW960R), and the handle for the revision instrument (FW998R).

Materials

The activL® Artificial Disc endplates are manufactured from Cobalt Chromium Alloy (ISO 5832-12). The surfaces are coated with a Plasmapore® μ-CaP surface coating which is made out of pure titanium (ISO5832-2), with an additional microscopic calcium phosphate over-coating (ASTM F 1609).

The activL® Artificial Disc inlay is manufactured from Ultra-High Molecular Weight Polyethylene (UHMWPE) (ISO 5834-2).

Contraindications

The activL® Artificial Disc should not be implanted in patients with the following conditions:

- Active systemic infection or localized infection near the surgical site
- Osteoporosis or osteopenia defined as DEXA bone mineral density T-score ≤ -1.0
- Allergy or sensitivity to the implant materials (cobalt, chromium, polyethylene, titanium, tantalum, or calcium phosphate)
- Isolated lumbar radiculopathy, especially due to herniated disc
- Chronic radiculopathy (unremitting pain with predominance of leg pain symptoms greater than back pain symptoms extending over a period of at least a year)
- Extruded disc material with sequestrum (i.e., free disc fragment)
- Myelopathy
- Spinal stenosis
- Spinal deformity such as scoliosis
- Spondylolysis/isthmic spondylolisthesis, degenerative spondylolisthesis > Grade I, or segmental instability
- Clinically compromised vertebral bodies at the affected level due to current or past trauma (e.g., current or prior vertebral fracture) or disease (e.g., ankylosing spondylitis)
- Facet ankylosis or facet joint degeneration
- Preoperative remaining disc height < 3mm
- Symptoms attributed to more than one vertebral level
- Abdominal pathology that would preclude an anterior retroperitoneal approach
- Involved vertebral endplate that is dimensionally smaller than 31mm in the medial-lateral and/or 26mm in the anterior-posterior directions

Warnings

Use of the activL® Artificial Disc should only be undertaken after the surgeon has become thoroughly knowledgeable about spinal anatomy and biomechanics, has had experience with anterior approach spinal surgeries, and has had hands-on-training in the use of this device. Only surgeons who are familiar with the activL® implant components, instruments, procedure, clinical applications, biomechanics, and risks should use this device. A lack of adequate experience and/or training may lead to a higher incidence of adverse events, including neurological complications.

Correct selection of the appropriate implant size and correct placement of the device are essential to ensure optimal performance and function of the device. Please refer to the activL® surgical technique manual for step-by-step instructions on the required surgical technique.

Heterotopic Ossification (HO) is a potential complication associated with lumbar total disc replacement surgery, which could result in reduced motion in the lumbar spine. However, the clinical impact of the presence of HO is not clearly understood.

Precautions

The safety and effectiveness of this device has not been established in patients with the following conditions:

- More than one vertebral level with DDD
- Skeletally immature patients, children < 18 years old, or patients over the age of 60
- Prior surgery at any lumbar level other than intradiscal electro-thermal annuloplasty (IDET), percutaneous nucleoplasty, microdiscectomy, hemilaminectomy, or laminotomy
- Back or leg pain of unknown etiology
- Paget's disease, osteomalacia, or other metabolic bone disease
- Morbid obesity (BMI>35)
- Pregnancy
- Taking medications known to potentially interfere with bone/soft tissue healing (e.g, steroids)
- Rheumatoid arthritis, lupus, or other autoimmune diseases
- Systematic disease including AIDS, HIV, Hepatitis
- Active malignancy
- Any degenerative muscular or neurological condition, including but not limited to Parkinson's disease, amyotrophic lateral sclerosis (ALS), or multiple sclerosis.
- Psychiatric or cognitive impairment.
- Current or recent history of illicit drug or alcohol abuse, or dependence as defined as the continued use of alcohol despite the development of social, legal, or health problems.
- Insulin-dependent diabetes.

Preoperative:
Patient selection is extremely important. In selecting patients for a total disc replacement, the following factors can be of extreme importance to the success of the procedure: the patient's occupation or activity level, a condition of senility, mental illness, alcoholism, or drug abuse, and certain degenerative disease (e.g, degenerative scoliosis or ankylosing spondylitis) that may be so advanced at the time of implantation that the expected useful life of the device is substantially decreased.

In order to minimize the risk of atraumatic periprosthetic vertebral fractures, surgeons must consider all co-morbidities, past and present medications, previous treatments, etc. Upon reviewing all relevant information, the surgeon must determine whether a bone density scan is prudent. A screening questionnaire for osteoporosis, SCORE (Simple Calculated Osteoporosis Risk Evaluation), may be used to screen patients to determine if a DEXA bone mineral density measurement is necessary. If DEXA is performed, the patient should be excluded from receiving the device if the DEXA bone density measured T score is ≤ -1.0, as the patient may be osteopenic.

The patient should be informed of the potential adverse effects (risks/complications) included in this insert (see POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH).

Preoperative planning should be used to estimate the required implant size, and to ensure that the appropriate sizes are available for surgery. The procedure should not take place if the appropriate range of sizes will not be available.

Examine all instruments prior to surgery for wear or damage. Instruments which have been used excessively may be more likely to break. Replace any worn or damaged instruments.

Intraoperative:
Correct selection of the appropriate device is extremely important to ensure the placement and function of the disc. See the surgical technique manual for step by step instructions.

Surgical implants must never be re-used or re-implanted. Even if the device appears undamaged, it may have small defects and internal stress patterns that my lead to early breakage.

Use aseptic technique when removing the activL® Artificial Disc components from the innermost packaging. Carefully inspect each component and its packaging for signs of damage, including damage to the sterile barrier. Do not use activL® implants if the packaging is damaged or the implant shows signs of damage.

Use care when handling the activL® Artificial Disc implant to ensure that it does not come in contact with objects that could damage the implant. Exercise care to ensure that implantation instruments do not contact the highly polished articulating surfaces of the endplates. Damaged implants are no longer functionally reliable.

To ensure correct and stable joining of the modular activL® Artificial Disc components, ensure that the combination dimensions are congruent. See the surgical technique manual for step by step instructions.

To prevent damage to the bearing surfaces and ensure a solid assembly, clean each component with sterile saline before joining to ensure that tissue, blood or other debris is not trapped within the assembly.

The activL® Artificial Disc should not be used with components or instruments of spinal systems from other manufacturers.

Due to the proximity of vascular and neurological structures to the implantation site, there are risks of serious or fatal hemorrhage and risks of neurological damage with the use of this device. Serious or fatal hemorrhage may occur if the great vessels are eroded or punctured during implantation or are subsequently damaged due to breakage of implants, migration of implants, or if pulsatile erosion of the vessels occurs because of close apposition of the implants. Care should be taken to identify and protect these structures during surgery.

Postoperative:
Patients should be instructed in postoperative care procedures and should be advised of the importance of adhering to these procedures for successful treatment with the device. Following completion of the procedure, each patient should receive postoperative care customized to his/her postoperative needs and demonstrated progress. Typically, patients should be permitted to ambulate on the day of surgery, as tolerated, with an elastic bandage or lumbosacral orthosis (LSO) to provide support to the abdominal musculature. Lumbar stabilization therapy can typically be initiated 2 to 4 weeks postoperatively as tolerated. Water therapy and/or swimming can typically be encouraged starting at two weeks postoperatively. Aerobic walking should typically be stressed for the first 6 postoperative weeks with more resistive exercise using fitness machines after that time.

Patients should be instructed not to engage in activities requiring lifting, bending or twisting for six months post-surgery. Overloading of the spine by engaging in extreme activities (i.e., heavy weight lifting) may result in failure of the prosthesis.

Potential Adverse Effects of the Device on Health
As with any surgery, surgical treatment of lumbar degenerative disc disease is not without risk. A variety of complications related to the surgery or the use of the activL® Artificial Disc may occur. The following is a list of the potential adverse effects (i.e., complications, risks) associated with the use of the activL® Artificial Disc identified from the activL® Artificial Disc clinical trial results, use of the activL® Artificial Disc outside of the United States, approved device labeling for other lumbar total disc replacement devices, and published scientific literature including: (1) those associated with any surgical procedure; (2) those associated with lumbar spinal surgery using an anterior approach; and (3) those associated with a lumbar total disc replacement device (including the activL® Artificial Disc). These risks may occur singly or in combination, and may be severe and/or negatively impact patient outcomes. In addition to the risks listed below, there is also the risk that the procedure may not be effective and may not relieve or may cause worsening of symptoms. Additional surgery may be required to correct some of the potential adverse effects.

1. Risks associated with any surgical procedure:
    - Anesthesia complications including an allergic reaction or anaphylaxis;

- Infection (wound, local, and/or systemic) or abscess;
- Wound dehiscence or necrosis;
- Edema;
- Soft tissue damage or fluid collections, including hematoma or seroma;
- Pain/discomfort at the surgical incision and/or skin or muscle sensitivity over the incision which may result in skin breakdown, pain, and/or irritation;
- Heart or vascular complications including bleeding, hemorrhage or vascular damage resulting in catastrophic or potentially fatal bleeding, ischemia, myocardial infarction, abnormal blood pressure, venous thromboembolism including deep vein thrombosis and pulmonary embolism, thrombophlebitis, or stroke;
- Pulmonary complications including atelectasis or pneumonia;
- Impairment of the gastrointestinal system including ileus or bowel obstruction;
- Impairment of the genitourinary system including incontinence, bladder dysfunction, or reproductive system complications;
- Neurological complications including nerve damage, paralysis, seizures, changes to mental status, or reflex sympathetic dystrophy;
- Complications of pregnancy including miscarriage or congenital defects;
- Inability to resume activities of daily living; and
- Death.

2. Risks specifically associated with lumbar spinal surgery using an anterior approach:
    - Injury to surrounding organs and structures including the cauda equina, nerve roots, other neurologic structures adjacent to the spinal column, adjacent vertebrae, lymphatic vessels, blood vessels, soft tissue, dura, intestines, kidneys, or ureters;
    - Neurological difficulties, including trouble with bowel and/or bladder function (including incontinence), sexual dysfunction (including retrograde ejaculation in males), muscle weakness or paralysis, changes in sensation (including numbness, dysesthesias, or paresthesias), chronic reflex sympathetic dystrophy, or pain;
    - Back or leg pain;
    - Epidural or retroperitoneal hematoma or fibrosis;
    - Scarring, adhesions, or swelling including in the peritoneum;
    - Hernia; and
    - Meningitis.

3. Risks associated with a lumbar total disc replacement device (including the activL® Artificial Disc):
    - Risks directly related to the device including malposition, migration/displacement, subsidence/loss of disc height, device breakage, device disassembly, or early or late loosening of the device. Any of these issues may cause pain or injury to surrounding organs and structures including the cauda equina, nerve roots, or other neurologic structures adjacent to the spinal column (which could cause pain, paralysis, numbness, or retrograde ejaculation in males) or blood vessel damage or erosion (which could cause catastrophic or fatal bleeding even in the late postoperative period);
    - Deterioration in neurologic status;
    - Development of new pain;
    - Failure of the device to improve symptoms or function;
    - Problems during placement of the device including trouble sizing the device, anatomical or technical difficulties implanting the device, or issues with the device instruments (e.g., bending or breakage) including the possibility that a fragment of a broken instrument may remain in the patient after implantation;
    - Adverse reaction or allergy to the device materials (cobalt, chromium, polyethylene, titanium, tantalum, calcium phosphate) or device wear debris which may lead to an adverse reaction of the local tissues or chronic inflammation that may lead to implant loosening or failure of the device, osteolysis, tumor formation, autoimmune disease, metallosis, scarring, or other symptoms;
    - Change in the alignment of the spine or loss of proper anatomic curvature, correction, height or reduction of the spine including spondylolisthesis, change in lordosis, or instability of the spine;
    - Degeneration of other parts of the spine including the facet joints or adjacent discs;
    - Spinal stenosis;
    - Fracture of the surrounding vertebrae;
    - Unintended bone formation (i.e., heterotopic ossification, annular ossification) that may result in bridging trabecular bone and may reduce spinal motion or result in unintended fusion at either the treated level or adjacent levels; and
    - Device failure which may require a subsequent surgical intervention (including removal of the activL, revision, re-operation or supplemental fixation).

Some of the adverse effects listed above were observed in the activL® Artificial Disc clinical trial. For more detailed information on the specific adverse effects that occurred during the clinical trial, please refer to the Safety Results Section below (Summary of IDE Clinical Study). Some of the most common adverse effects experienced by study patients were: lower extremity pain, lumbar pain alone, and both lumbar and lower extremity pain.

Clinical Study

The clinical investigation of the activL® Artificial Disc was conducted under an approved IDE (G060262) and was intended to determine the safety and effectiveness of the activL for reconstruction of the disc at one level (L4-L5 or L5-S1) following single-level discectomy in skeletally mature subjects with symptomatic degenerative disc disease (DDD) and no more than Grade I spondylolisthesis at the involved level who had been unresponsive to at least six months of prior nonoperative treatment. The trial was a prospective, multi-center, randomized (2:1), single masked, concurrently controlled, non-inferiority clinical trial to compare the safety and effectiveness of the activL to one of two alternative lumbar total disc replacement control devices (DePuy Spine Charité or DePuy Synthes Spine ProDisc-L). Two design versions of the activL were studied as part of the clinical trial (spike version and keel version). Both have an identical articulation; the only difference is the method of initial stabilization. Longer-term fixation of the activL to the vertebral bodies is intended to be achieved through bone growth, with initial stabilization by either the spike or keel endplate design. During the IDE trial, the choice of the

spike or keel endplate version was at the discretion of the investigator to allow selection of an optimal endplate to fit each individual patient's anatomy and to accommodate physician preference.

The first three subjects at each site received the activL and were not randomized. In addition, investigators who had not performed at least three prior control device implantations were allowed to perform up to three non-randomized control procedures. Subsequent subjects were randomized 2:1 to the activL or one of the two controls (Charité or ProDisc-L). The choice of control device was at the discretion of the investigator (i.e., each investigator used one or the other for all of the subjects he or she treated), and subjects involved in the trial were specifically consented to one or the other control device prior to surgery). The randomized subjects were masked to their treatment assignment, and every effort was made to maintain the masking through 24 months of follow-up. To assess the effectiveness of the masking, subjects were asked at each follow-up visit if they had learned which device they received. The investigator was not masked to the treatment. The purpose of the trial was to determine whether the activL was non-inferior to the alternative lumbar total disc replacement control group.

Subjects were treated between January 30, 2007 and December 3, 2009. A total of 376 subjects were treated at 18 investigational sites in the United States. Of these subjects, 52 were non-randomized subjects (46 activL, 6 control) and 324 were randomized subjects after application of the Intent-to-Treat (ITT) principle (218 activL, 106 control). The final analysis was conducted after all subjects had reached the 24 month timepoint based on data collected through April 11, 2013.

Clinical Inclusion and Exclusion Criteria
Subjects were eligible for the trial if they met the following criteria:

Inclusion Criteria
Enrollment in the activL trial was limited to subjects who met the following inclusion criteria:

- Age 18 – 60 years and skeletally mature.
- Back pain at the operative level only (minimum Visual Analog Scale (VAS) back pain score of 40/100mm and greater than the higher of the two VAS leg pain scores).
- Symptomatic DDD with objective evidence of lumbar DDD, based on objective evidence of identification of any of the following characteristics by Computed Tomography (CT) or Magnetic Resonance Imaging (MRI) scan:
    - Instability as defined by ≥ 3mm translation or ≥ 5° angulation;
    - Osteophyte formation of facet joints or vertebral endplates;
    - Decreased disc height of > 2mm as compared to the adjacent level;
    - Scarring/thickening of the ligamentum flavum, annulus fibrosis, or facet joint capsule;
    - Herniated nucleus pulposus;
    - Facet joint degeneration/changes; and/or
    - Vacuum phenomenon.
- Single level symptomatic disease at L4/L5 or L5/S1.
- Minimum of six months of unsuccessful conservative treatment, including, but not limited to physical therapy and/or medication.
- Minimum Oswestry Disability Index (ODI) score of 40/100.
- Surgical candidate for an anterior approach to the lumbar spine.
- Willing and able to return for follow-up visits regularly and sign an Informed Consent and HIPAA Authorization.

Exclusion Criteria
Subjects were not permitted to enroll in the activL trial if they met any of the following exclusion criteria:

- History of allergies to any of the device components including cobalt chromium alloy, titanium, UHMWPE, and calcium phosphate.
- Evidence of significant, symptomatic disc degeneration at another lumbar level.
- Previous surgery at any lumbar level, except IDET (Intradiscal Electro-thermal Annuloplasty), percutaneous nucleoplasty, microdiscectomy, hemilaminectomy, or laminotomy.
- Chronic radiculopathy as defined by subject complaint of unremitting pain with a predominance of leg pain symptoms greater than back pain symptoms extending over a period of at least 1 year.
- Sequestered herniated nucleus pulposus with migration.
- Leg pain with migrated sequestrum fragment.
- Myelopathy.
- Previous compression or burst fracture at the affected level.
- Mid-sagittal stenosis of <8 mm (by MRI).
- Degenerative or lytic spondylolisthesis > 3mm.
- Spondylolysis or isthmic spondylolisthesis.
- Lumbar scoliosis (> 11° sagittal plan deformity).
- Preoperative remaining disc height < 3mm.
- Facet ankylosis or severe facet degeneration.
- Active systemic infection of infection at the site of surgery.
- Spinal tumor.
- Anatomic requirements incompatible with the available range of dimensions for the experimental or control devices, based on preoperative assessment using radiographic templates. Specifically, endplate dimensions smaller than 34.5 mm in the medial-lateral and/or 27 mm in the anterior-posterior directions.
- Osteoporosis or osteopenia, indicated by a lumbar spine dual-energy X-ray absorptiometry (DEXA) T-score ≤ -1.
- Metabolic bone disease.
- Continuing steroid use or prior use for more than 2 months.

- Abdominal adhesions, endometriosis, inflammatory bowel disease, Crohn's disease, diverticulitis, ulcerative colitis or other abdominal pathology that would preclude the abdominal surgical approach.
- Prior nephrectomy.
- History of Pelvic Inflammatory Disease.
- Peritonitis.
- Morbid obesity (Body Mass Index >35).
- History of rheumatoid arthritis, lupus, or other autoimmune disorder.
- Ankylosing spondylitis.
- History of human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS) or hepatitis that precludes surgery.
- History of deep vein thrombosis, symptoms of arterial insufficiency, or thromboembolytic disease.
- Insulin-dependent diabetes.
- Pregnant or planning to become pregnant within the next 2 years.
- Life expectancy less than 5 years.
- Undergone chemotherapy within 5 years, or had any cancer other than non-melanoma skin cancer treated with curative intent within 5 years.
- Current or recent history of illicit drug or alcohol abuse, or dependence as defined as the continued use of alcohol despite the development of social, legal, or health problems.
- Investigational drug or device use within 30 days.
- Any degenerative muscular or neurological condition that would interfere with evaluation of outcomes, including but not limited to Parkinson's disease, amyotrophic lateral sclerosis (ALS), or multiple sclerosis.
- Currently in active spinal litigation as a result of medical negligence.
- A prisoner.
- Psychiatric or cognitive impairment that, in the opinion of the investigator, would interfere with the subject's ability to comply with the study requirements, e.g., Alzheimer's disease.

Postoperative Care

Following completion of the procedure, subjects in both treatment groups received postoperative care customized to their postoperative needs and demonstrated progress. Typically, subjects were permitted to ambulate on the day of surgery, as tolerated, with an elastic bandage or lumbosacral orthosis (LSO) to provide support to the abdominal musculature. Lumbar stabilization therapy was initiated 2 to 4 weeks postoperatively as tolerated. Water therapy and/or swimming were encouraged and could start two weeks postoperatively. Aerobic walking was stressed for the first 6 postoperative weeks with more resistive exercise using fitness machines after that time. Subjects were also instructed not to engage in activities requiring lifting, bending or twisting for six months post-surgery. Subjects were not specifically treated with NSAIDs postoperatively in either treatment group.

Follow-up Schedule

Subjects were scheduled to return for follow-up examinations at 6 weeks (±14 days), 3 months (±14 days), 6 months (±30 days), 12 months (±60 days), 24 months (±60 days), and annually thereafter (±60 days), as shown in Table 3.

Table 3: Clinical Evaluation Schedule

Evaluation	Baseline	Intra-op	Discharge	6 wks	3 mo	6 mo	12 mo	24 mo & Annually
Medical History/ physical exam	X							
Work status	X			X	X	X	X	X
Pain medications	X		X				X	X
VAS pain assessment	X			X	X	X	X	X
Neurological assessment	X		X	X	X	X	X	X
Short Form 36	X			X	X	X	X	X
ODI	X			X	X	X	X	X
Subject satisfaction							X	X
Adverse events*		X	X	X	X	X	X	X
MRI scan	X							
DEXA scan	X (if req)							
X-rays, A/P and lateral (standing neutral)	X	X (implant position)	X (implant position)	X	X	X	X	X
X-rays, A/P (R/L bending)	X			X	X	X	X	X
X-rays, lateral (flexion/extension)	X			X	X	X	X	X

* Adverse events and complications were recorded at all visits (both scheduled and unscheduled).

Clinical Endpoints

The safety of the activL was assessed by comparing the nature and frequency of adverse events (overall and in terms of seriousness and relationship to the device and/or procedure) and subsequent surgical interventions as well as maintenance or improvement in neurological status compared to the ProDisc-L/Charité control group. All adverse events were independently adjudicated (for adverse event category, severity and relationship to the device and/or procedure) by a Clinical Events Committee (CEC) comprised of three practicing spine surgeons.

The effectiveness of the activL was assessed by evaluating improvement in ODI score, back and leg pain measured at rest using a VAS, quality of life measured using the Short-Form 36 (SF-36) questionnaire, subject satisfaction, pain medication usage, and work status compared to the ProDisc-L/Charité control group.

In addition, several radiographic endpoints were considered in evaluating both safety and effectiveness, including range of motion, disc height, device migration, device subsidence, device condition, and heterotopic ossification. Radiographic endpoints were evaluated by an independent core imaging laboratory.

Per the protocol, an individual subject was considered a success if the following criteria were met at 24 months postoperative:

- Improvement of at least 15 points in ODI score at 24 months compared to baseline;
- Maintenance or improvement in neurological status at 24 months compared to baseline as measured by motor and sensory evaluations with a decrease of one grade in either evaluation considered a failure;
- Maintenance or improvement in range of motion (ROM) at the index level, defined as: 24 month ROM – preoperative ROM ≥ 0 (with a ±2° measurement error applied) in a subject who did not meet the definition of fusion (evidence of continuous bridging bone and < 3° of angular motion from flexion to extension);
- No device failure requiring revision, re-operation, removal, or supplemental fixation at the index level; and
- Absence of serious device-related adverse events (SDAE) as adjudicated by the CEC.

In addition, because the ROM success component of the primary endpoint was such a notable driver of the difference in overall success rates in favor of activL when comparing the two randomized treatment groups, FDA requested an additional analysis of overall success without the ROM success component.

Overall study success criteria were based on a comparison of individual subject success rates, such that the subject success rate for the activL investigational group was required to be non-inferior to that of the ProDisc-L/Charité control group. The IDE was approved using a non-inferiority margin (delta) of 15% with an advisory that a non-inferiority margin of 10% would be required to demonstrate a reasonable assurance of the device's effectiveness. As outlined in the statistical analysis plan, if non-inferiority was demonstrated, then superiority would be evaluated.

The following two secondary effectiveness endpoints were designated as "powered" in the protocol for the purposes of generating potential labeling claims:

- Improvement in 24 month back pain (measured at rest) ≥ 20/100mm on a VAS compared to baseline; and
- Improvement in 24 month leg pain (measured at rest) ≥ 20/100mm on a VAS compared to baseline for the leg with the maximum pain at baseline with no worsening in the other leg.

Additional secondary effectiveness evaluations and other outcomes specified in the protocol included comparisons of:

- ODI (mean score, mean improvement from baseline, incidence of 15% improvement, incidence of 15 point improvement);
- Quality of Life, measured using the SF-36 Questionnaire with improvement of 15% compared to baseline considered clinically significant;
- Subject satisfaction;
- Device condition;
- Device migration (≥ 3 mm);
- Device subsidence (≥ 3 mm);
- Disc height (incidence of ≥ 3 mm change);
- ROM (flexion/extension, lateral bending) including comparison of 24 month ROM to baseline and to "normal" ROM at the operative level (defined as: $6 \pm 2° \leq ROM \leq 20 \pm 2°$ (device design limit) for L4-L5 and $5 \pm 2° \leq ROM \leq 20 \pm 2°$ (device design limit) for L5-S1) Reference: Huang, R.C., Girardi, F.P., Cammisa, F.P. Jr., Lim, M.R. Tropiano, P., & Mamy, T. (2005). Correlation Between Range of Motion and Outcome After Lumbar Total Disc Replacement: 8.6-Year Follow-up. Spine 30(12), 1407-1411.;
- Heterotopic ossification at the index level compared to baseline;
- Pain medication usage at 12 and 24 months compared to post injury and pre-implant usage;
- Work status/return to work (including level of activity) as compared to pre- and post- injury conditions;
- Mean operative time, duration of hospitalization, and blood loss;
- Neurological status; and
- Adverse event rates.

Accountability of PMA Cohort

A total of 376 subjects at 18 U.S. sites were treated in the IDE clinical trial. Of these subjects, 52 were non-randomized subjects (46 activL, 6 control) and 324 were randomized subjects after application of the Intent-to-Treat (ITT) principle (218 activL, 106 control). At the time of database lock, of the 324 randomized subjects enrolled in the PMA trial, all had reached the 24 month postoperative visit and 230 of the 273 expected randomized subjects (84%) had any 24 month data available for analysis. Complete 24 month primary endpoint data was available for:

- 192 activL subjects (47 treated at L4-L5, 145 treated at L5-S1)
    - 156 randomized (80 treated with the spike version of activL, 76 treated with the keel version of activL)
    - 36 non-randomized (16 treated with spike version of activL, 20 treated with keel version of activL)
- 72 control subjects (24 treated at L4-L5, 48 treated at L5-S1)
    - 67 randomized (40 treated with the ProDisc-L, 26 treated with the Charité)
    - 5 non-randomized (5 treated with the ProDisc-L, 0 treated with the Charité). Note that unless otherwise noted, data on the non-randomized control group subjects is typically not included in the tables within this clinical trial results summary due to the small sample size.

A total of 33 activL subjects (29 randomized and 4 non-randomized) and 22 control subjects (21 randomized and 1 non-randomized) were primary endpoint failures at or prior to the 24 month visit because they had a removal, revision, reoperation, or supplemental fixation surgery at the index level or experienced a SDAE. Of the 33 activL subjects who were primary endpoint failures for these reasons, 18 received the spike version of the activL and 15 received the keel version of the activL.

A summary of subject accountability data for the 12 month, 24 month, 3 year, and 4 year follow-up visits is provided in Table 4. Note that one subject was randomized to the activL group but a control device was erroneously implanted instead. This was recorded as a protocol deviation, and the subject is included as an investigational subject in the ITT analysis set throughout this summary. Note that because this subject did not receive either the spike or keel device, he/she is not counted in any of the tables stratified by device design in this summary. Another subject was randomized to the control group (ProDisc-L) but was not implanted due to a posterior inferior rim fracture which occurred intra-operatively. The subject was subsequently fused and is included as a control subject in the ITT analysis set throughout this summary. Note that because this subject did not receive either control device, he/she is not counted in any of the tables stratified by control device in this summary. This explains why there are a total of 66 control subjects when stratified by device, instead of the 67 defined by the ITT population.

Table 4: Subject Accounting

	12 Months			24 Months			3 Years			4 Years		
	NR activL	R activL	R Contr	NR activL	R activL	R Contr	NR activL	R activL	R Contr	NR activL	R activL	R Contr
Treated	46	218	106	46	218	106	46	218	106	46	218	106
Deaths (cumulative)	0	1	0	0	1	0	0	1	0	0	1	0
Failures (cumulative)[1]	4	25	18	4	29	21	4	30	22	4	30	22
Not Yet Overdue	0	0	0	0	0	0	0	0	0	12	53	22
Expected[2]	42	192	88	42	188	85	42	187	84	30	134	62
Withdrawn (cumulative)	*1*	*0*	*0*	*1*	*0*	*1*	*1*	*1*	*1*	*2*	*1*	*1*
Missed Visit	*4*	*4*	*2*	*2*	*7*	*6*	*5*	*29*	*10*	*6*	*53*	*26*
Lost to Follow-Up (LTFU)/ Presumed LTFU	*0*	*9*	*8*	*2*	*19*	*10*	*2*	*36*	*13*	*5*	*44*	*16*
Actual, primary endpoint data (% follow-up)[3]	37 (88%)	174 (91%)	78 (89%)	36 (86%)	156 (83%)	67 (79%)	34 (81%)	115 (61%)	59 (70%)	17 (57%)	34 (25%)	17 (27%)
Actual, primary endpoint data in window (% follow-up)[4]	36 (86%)	157 (82%)	73 (83%)	34 (81%)	144 (77%)	61 (72%)	31 (74%)	106 (57%)	53 (63%)	17 (57%)	33 (25%)	17 (27%)
Actual, any data (% follow-up)[5]	37 (88%)	179 (93%)	78 (89%)	37 (88%)	162 (86%)	68 (80%)	34 (81%)	121 (65%)	60 (71%)	17 (57%)	36 (27%)	19 (30%)

NR=Non-randomized; R=Randomized; Contr=Control

[1] Subjects who had a removal, revision, reoperation or supplemental fixation surgery at the index level or experienced a SDAE.

[2] Treated subjects – (Deaths + Not yet overdue + Failures).

[3] Subjects with complete data for the primary endpoint, regardless of in-window status, and not a failure.

[4] Subjects with complete data for the primary endpoint, evaluated per protocol, and in-window and not a failure.

[5] Subjects with any follow-up data reviewed or evaluated and not a failure.

The primary dataset was based on a Modified Intent-to-Treat (mITT) population which consisted of all randomized, implanted subjects analyzed according to their randomization assignment (218 randomized activL, 106 randomized control, 46 non-randomized activL, 6 non-randomized control). For the primary endpoint analysis and analysis of the powered secondary endpoints, subjects with incomplete or missing data were imputed as failures, and sensitivity analyses were done to assess the potential impact of missing data on the trial outcomes. Missing values were ignored for the analysis of additional secondary endpoints, other outcomes, and summaries of baseline characteristics.

Study Population Demographics and Baseline Parameters

The demographics of the study population are typical for a lumbar artificial disc study conducted in the United States. Select demographic data and preoperative evaluations for the randomized subjects treated in the study as well as the non-randomized activL subjects are included in Table 5 and Table 6. Although p-values were obtained without any adjustment for multiplicity, there were no statistically significant differences in demographics, baseline characteristics, or preoperative evaluations when comparing the randomized treatment groups.

Table 5: Subject Demographics and Baseline Characteristics

Demographic Measure/Baseline Characteristic	NR activL (N=46)	R activL (N=218)	R Contr (N=106)
Age (years; mean ± standard deviation)	39.5 ± 8.3 Range: 22 – 54	39.0 ± 8.7 Range: 19 - 60	40.3 ± 8.6 Range: 19 – 56
Gender (n (%))			
Male	24 (52.2%)	116 (53.2%)	53 (50.0%)
Female	22 (47.8%)	102 (46.8%)	53 (50.0%)
Race (n (%))			
White	43 (93.5%)	190 (87.2%)	100 (94.3%)
Asian	1 (2.2%)	2 (0.9%)	0
Black	1 (2.2%)	17 (7.8%)	5 (4.7%)
American Indian or Alaska Native	0	3 (1.4%)	0
Native Hawaiian or Other Pacific Islander	0	0	0
Other	1 (2.2%)	6 (2.8%)	1 (0.9%)

Demographic Measure/Baseline Characteristic	NR activL (N=46)	R activL (N=218)	R Contr (N=106)
BMI (kg/m^2; mean ± standard deviation)	26.7 ± 4.4 Range: 19 – 35	26.6 ± 4.1 Range: 16 – 37	27.1 ± 4.4 Range: 16 – 34
Smoking Status* (n (%))			
Current	13 (28.3%)	46 (21.1%)	22 (20.8%)
Previous	9 (19.6%)	38 (17.4%)	21 (19.8%)
Never	24 (52.2%)	134 (61.5%)	63 (59.4%)
Duration of Back Pain Symptoms (n (%))			
< 6 mo	2 (4.3%)	1 (0.5%)	2 (1.9%)
6 mo – 1 year	6 (13.0%)	30 (13.8%)	13 (12.3%)
≥1 year	38 (82.6%)	187 (85.8%)	91 (85.8%)
Duration of Leg Pain Symptoms (n (%))			
< 6 mo	4 (9.8%)	15 (7.8%)	10 (10.4%)
6 mo – 1 year	9 (22.0%)	46 (24.0%)	19 (19.8%)
≥ 1 year	28 (68.3%)	131 (68.2%)	67 (69.8%)
Current or Previous Non-operative Spinal Therapies (n (%))			
Physical Therapy	44 (95.7%)	195 (89.4%)	97 (91.5%)
Chiropractic or Osteopathic Treatment	33 (71.7%)	120 (55.0%)	51 (48.1%)
Pain Medication	46 (100%)	212 (97.2%)	103 (97.2%)
Epidural Injections	38 (82.6%)	174 (79.8%)	87 (82.1%)
Previous Operative Spinal Therapies (n (%))			
Lumbar Spinal Surgery	9 (19.6%)	52 (23.9%)	30 (28.3%)
Non-Lumbar Spinal Surgery	2 (4.3%)	10 (4.6%)	12 (11.3%)
Pain Medication Use (n (%))			
Narcotic/Narcotic Combination Analgesics	34 (73.9%)	141 (64.7%)	65 (61.3%)
Other Controlled Analgesic Medication	10 (21.7%)	30 (13.8%)	17 (16.0%)
NSAID/Combination NSAID	21 (45.7%)	96 (44.0%)	40 (37.7%)
Salicylate/Combination Salicylate	1 (2.2%)	4 (1.8%)	2 (1.9%)
Acetaminophen/Combination Acetaminophen	6 (13.0%)	22 (10.1%)	4 (3.8%)
Steroid	1 (2.2%)	0	1 (0.9%)
Muscle Relaxant	15 (32.6%)	61 (28.0%)	34 (32.1%)
Agonist/Antagonist	0	0	0
Preoperative Spine Characteristics on MRI (n (%))			
Instability (≥ 3mm translation or ≥ 5° angulation)	5 (10.9%)	16 (7.3%)	10 (9.4%)
Osteophyte formation facets or vertebral endplates	15 (32.6%)	44 (20.2%)	17 (16.0%)
Decreased disc height (> 2mm versus adjacent level)	35 (76.1%)	159 (72.9%)	71 (67.0%)
Scarring/thickening ligamentum flavum, annulus fibrosus, or facet joint capsule	9 (19.6%)	40 (18.3%)	18 (17.0%)
Herniated nucleus pulposus	31 (67.4%)	152 (69.7%)	83 (78.3%)
Facet joint degeneration/changes	11 (23.9%)	52 (23.9%)	30 (28.3%)
Vacuum phenomenon	6 (13.0%)	13 (6.0%)	12 (11.3%)

* Data on amount and length of tobacco use was not captured.

Table 6: Preoperative Evaluation of Endpoints

Variable	NR activL	R activL	R Contr
ODI mean ± standard deviation	N=46 60.0 ±13.5 Range: 34 - 94	N=218 57.1 ± 13.9 Range: 18 - 98	N=106 58.6 ± 14.1 Range: 33.3 – 96
VAS Back Pain (mm) mean ± standard deviation	N=45 81.5 ± 13.3 Range: 48 - 100	N=212 79.0 ± 14.9 Range: 46 - 100	N=106 79.1 ± 14.8 Range: 41 – 100
VAS Right Leg Pain (mm) mean ± standard deviation	N=45 34.9 ± 31.7 Range: 0 - 99	N=215 28.7 ± 29.8 Range: 0 – 96.5	N=104 32.9 ± 29.6 Range: 0 – 89.5
VAS Left Leg Pain (mm) mean ± standard deviation	N=46 33.6 ± 31.2 Range: 0 – 98.5	N=216 29.6 ± 29.4 Range: 0 - 100	N=105 30.7 ± 29.5 Range: 0 – 98
SF-36 Mental Component Summary (MCS) mean ± standard deviation	N=45 37.6 ± 14.7 Range: 10.5 – 66.8	N=213 39.1 ± 13.9 Range: 9.4 – 67.2	N=105 39.6 ± 14.9 Range: 8.3 – 67.8
SF-36 Physical Component Summary (PCS) mean ± standard deviation	N=45 28.4 ± 7.2 Range: 9.3 – 43.9	N=213 29.9 ± 6.2 Range: 14.1 – 51.4	N=105 28.4 ± 6.2 Range: 11.2 – 49.7
ROM Flexion/Extension Rotation (°) mean ± standard deviation	N=46 7.3 ± 5.1 Range: -0.1 to 18.9	N=214 6.6 ± 5.1 Range: -1.4 to 26.9	N=105 6.6 ± 4.6 Range: -0.7 to 19.4

Variable	NR activL	R activL	R Contr
ROM Flexion/Extension Translation (mm) mean ± standard deviation	N=46 0.6 ± 0.7 Range: -0.1 to 3.2	N=212 0.5 ± 0.7 Range: -0.4 to 3.8	N=104 0.6 ± 0.6 Range: -1.4 to 2.8
ROM Lateral Bending AP Rotation (°) mean ± standard deviation	N=42 1.1 ± 1.3 Range: -1.3 to 5.5	N=212 1.0 ± 2.0 Range: -2.3 to 12.5	N=103 1.0 ± 1.8 Range: -3.3 to 10.0
Normal Neurological Status (n (%)) Motor (Grade 5, active movement vs. full resistance) Sensory (Grade 2, normal) Reflexes (Grade 2, normal)	 194 (89.0%) 158 (72.5%) 178 (81.7%)	 97 (91.5%) 78 (73.6%) 91 (85.8%)	 40 (87.0%) 33 (71.7%) 42 (91.3%)

Surgical and Hospitalization Data

Surgical data for the randomized subjects treated in the study as well as the non-randomized activL subjects are included in Table 7. Although p-values were obtained without any adjustment for multiplicity, there were no statistically significant differences in procedural characteristics when comparing the randomized treatment groups.

Table 7: Procedural Characteristics

Procedural Characteristic	NR activL (N=46)	R activL (N=218)	R Contr (N=106)
Treated Level (n (%)) L4-L5 L5-S1	 11 (23.9%) 35 (76.1%)	 62 (28.4%) 156 (71.6%)	 34 (32.1%) 72 (67.9%)
Operative Time (min) mean ± standard deviation	129.5 ± 48.7 Range: 40 - 243	109.8 ± 43.3 Range: 30 – 233	119.0 ± 52.1 Range: 35 - 373
Access Surgeon Used (n (%))	46 (100%)	218 (100%)	106 (100%)
Surgical Approach (n (%)) Retroperitoneal Transperitoneal	 44 (95.7%) 2 (4.3%)	 215 (98.6%) 3 (1.4%)	 104 (98.1%) 2 (1.9%)
Blood loss (cc) mean ± standard deviation	194.6 ± 220.6 Range: 25 - 1050	135.2 ± 126.1 Range: 10 - 900	161.2 ± 200.0 Range: 5 - 1800
Length of stay (days) mean ± standard deviation	2.7 ± 1.1 Range: 1 - 6	2.3 ± 1.3 Range: 1 - 11	2.3 ± 1.3 Range: 1 – 8
Return to Work Time (days) mean ± standard deviation	260.6 ± 410.7 Range: 6 - 1772	262.5 ± 411.9 Range: 2 - 1815	349.7 ± 491.7 Range: 6 – 1886

Table 8 provides select procedural characteristic data stratified by device design (spike or keel) in the randomized activL group and by specific control device (ProDisc-L or Charité) in the randomized control group as well as by treatment level (L4-L5 or L5-S1) in both randomized groups.

Table 8: Select Procedural Characteristics - Stratified

Procedural Characteristic	R activL (N=218)				R Contr (N=106)			
	Spike (N=115)	Keel (N=102)	L4-L5 (N=62)	L5-S1 (N=156)	ProDisc-L (N=64)	Charité (N=41)	L4-L5 (N=34)	L5-S1 (N=72)
Treated Level (n (%)) L4-L5 L5-S1	 35 (30.4%) 80 (69.6%)	 26 (25.5%) 76 (74.5%)	 62 (100%) --	 -- 156 (100%)	 19 (29.7%) 45 (70.3%)	 15 (36.6%) 26 (63.4%)	 34 (100%) --	 -- 72 (100%)
Device Design Spike Keel	 115 (100%) --	 -- 102 (100%)	 35 (57.4%) 26 (42.6%)	 80 (51.3%) 76 (48.7%)	N/A	N/A	N/A	N/A
Control Device ProDisc-L Charité	N/A	N/A	N/A	N/A	64 (100%) --	 -- 41 (100%)	19 (55.9%) 15 (44.1%)	45 (63.4%) 26 (36.6%)
Operative Time (min) mean ± standard deviation	115.7 ± 43.8	102.9 ± 42.1	123.9 ± 41.5	104.2 ± 42.9	119.8 ± 58.9	118.3 ± 40.4	125.9 ± 52.4	115.7 ± 52.0
Approach (n (%)) Retroperitoneal Transperitoneal	 112 (97.4%) 3 (2.6%)	 102 (100%) 0	 62 (100%) 0	 153 (98.1%) 3 (1.9%)	 62 (96.9%) 2 (3.1%)	 41 (100%) 0	 33 (97.1%) 1 (2.9%)	 71 (98.6%) 1 (1.4%)
Blood loss (cc) mean ± standard deviation	138.5 ± 127.2	131.9 ± 125.9	154.1 ± 146.7	127.7 ± 116.5	135.9 ± 98.4	200.1 ± 292.3	153.5 ± 138.8	164.9 ± 224.7
Length of stay (days) mean ± standard deviation	2.4 ± 1.0	2.3 ± 1.6	2.6 ± 1.4	2.2 ± 1.3	2.0 ± 1.1	2.9 ± 1.5	2.2 ± 1.1	2.4 ± 1.4

Table 9 provides an overview of the characteristics of activL devices implanted during the clinical trial. No subjects received the following 11° superior endplates: small spike, extra-large spike, or small keel. No subjects received the 14mm height inlay.

Table 9: activL Implants Used

Size/Option	NR activL (N=46)	R activL (N=217)
Endplate Design (n (%))		
Spike	21 (45.7%)	115 (53.0%)
Keel	25 (54.3%)	102 (47.0%)
Superior Endplate Angle (n (%))		
6°	44 (95.7%)	203 (93.5%)
11°	2 (4.3%)	14 (6.5%)
Inferior Endplate (n (%))		
Small	11 (23.91%)	37 (17.05%)
Medium	9 (19.57%)	50 (23.04%)
Large	13 (28.26%)	48 (22.12%)
Extra-large	1 (2.17%)	8 (3.69%)
S1	12 (26.09%)	74 (34.10%)
Superior Endplate (n (%))		
Small	14 (30.43%)	59 (27.19%)
Medium	12 (26.09%)	77 (35.48%)
Large	19 (41.30%)	72 (33.18%)
Extra-large	1 (2.17%)	9 (4.15%)
Inlay Height (n (%))		
8.5 mm	40 (87.0%)	189 (87.1%)
10 mm	6 (13.0%)	25 (11.5%)
12 mm	0	3 (1.4%)
14 mm	0	0
Endplate/Inlay Combinations (n (%))		
Spike 6° Superior Endplate / 8.5 mm Inlay	18 (39.1%)	94 (43.3%)
Spike 6° Superior Endplate / 10 mm Inlay	2 (4.3%)	12 (5.5%)
Spike 6° Superior Endplate / 12 mm Inlay	0	2 (0.9%)
Spike 6° Superior Endplate / 14 mm Inlay	0	0
Spike 11° Superior Endplate / 8.5 mm Inlay	1 (2.2%)	7 (3.2%)
Spike 11° Superior Endplate / 10 mm Inlay	0	0
Spike 11° Superior Endplate / 12 mm Inlay	0	0
Spike 11° Superior Endplate / 14 mm Inlay	0	0
Keel 6° Superior Endplate / 8.5 mm Inlay	20 (43.5%)	83 (38.2%)
Keel 6° Superior Endplate / 10 mm Inlay	4 (8.7%)	12 (5.5%)
Keel 6° Superior Endplate / 12 mm Inlay	0	0
Keel 6° Superior Endplate / 14 mm Inlay	0	0
Keel 11° Superior Endplate / 8.5 mm Inlay	1 (2.2%)	5 (2.3%)
Keel 11° Superior Endplate / 10 mm Inlay	0	1 (0.5%)
Keel 11° Superior Endplate / 12 mm Inlay	0	1 (0.5%)
Keel 11° Superior Endplate / 14 mm Inlay	0	0

Safety and Effectiveness Results

Safety Results

The CEC defined serious adverse events as events that met any of the following criteria:

- Potentially life-threatening or resulted in death;
- Required in-subject hospitalization (hospital stay > 24 hours) or prolongation of hospitalization;
- Resulted in permanent impairment of body structure or a body function;
- Gave rise to a malignant tumor; or
- Led to a congenital anomaly in the offspring, or caused fetal distress or death.

In addition, the CEC defined device-related events as those with an etiology, temporal association, or cause related to the device. Procedure-related events were defined as those with an etiology, temporal association, or cause related to the surgical index procedure.

The analysis of safety was based on the mITT cohort of subjects which consisted of all randomized, implanted subjects analyzed according to their randomization assignment (218 randomized activL, 106 randomized control, 46 non-randomized activL, 6 non-randomized control). A summary of the adverse event data is presented in Table 10. The total number of adverse events, subsequent surgical interventions at the index level, adverse events classified by the CEC as device-related, procedure-related, serious, and serious device-related, as well as

adverse events occurring within 2 days of the index procedure are shown for the randomized subjects treated in the study as well as for the non-randomized activL subjects.

Table 10: Summary of Adverse Events

Adverse Event Category	NR activL (N=46)		R activL (N=218)		R Contr (N=106)	
	Subjects n (%)	Events N	Subjects n (%)	Events N	Subjects n (%)	Events N
All Adverse Events	40 (87.0%)	145	186 (85.3%)	701	95 (89.6%)	366
Subsequent Surgical Interventions at the Index Level	0 (0.0%)	0	12 (5.5%)	15	6 (5.7%)	6
Device-Related Adverse Events	30 (65.2%)	45	134 (61.5%)	217	69 (65.1%)	114
Procedure-Related Adverse Events	29 (63.0%)	46	116 (53.2%)	195	70 (66.0%)	118
Serious Adverse Events	18 (39.1%)	21	72 (33.0%)	121	51 (48.1%)	68
Serious Device-Related Adverse Events	6 (13.0%)	6	28 (12.8%)	31	20 (18.9%)	20
Adverse Events within 2 days of Procedure	7 (15.2%)	8	39 (17.9%)	49	23 (21.7%)	33

Note: This table includes data collected beyond 24 months.

Table 11 provides adverse event summary data stratified by device design and level treated for the randomized activL and control device and level treated for the randomized control group.

Table 11: Summary of Adverse Events - Stratified

Adverse Event (AE) Category	R activL (N=218)				R Contr (N=106)			
	Device Design		Treatment Level		Control Device		Treatment Level	
	Spike (N=115)	Keel (N=102)	L4-L5 (N=62)	L5-S1 (N=156)	ProDisc-L (N=65)	Charité (N=41)	L4-L5 (N=34)	L5-S1 (N=72)
All AEs	96 (83.5%)	89 (87.3%)	51 (82.3%)	135 (86.5%)	58 (90.6)	36 (87.8%)	34 (100%)	61 (84.7%)
Subsequent Surgical Interventions at the Index Level	3 (2.6%)	0 (0.0%)	1 (1.6%)	2 (1.3%)	1 (1.5%)	0 (0.0%)	0 (0.0%)	1 (1.4%)
Device-Related AEs	68 (59.1%)	65 (63.7%)	33 (53.2%)	101 (64.7%	40 (62.5)	29 (70.7%)	23 (67.6%)	46 (63.9%)
Procedure-Related AEs	54 (47.0%)	61 (59.8%)	31 (50.0%)	85 (54.5%)	42 (65.6)	27 (65.9%)	22 (64.7%)	48 (66.7%)
Serious AEs	34 (29.6%)	37 (36.3%)	19 (30.6%)	53 (34.0%)	31 (48.4)	19 (46.3%)	16 (47.1%)	35 (48.6%)
Serious Device-Related AEs	16 (13.9%)	15 (14.7%)	10 (16.1%)	21 (13.5%)	10 (15.4%)	10 (24.4%)	7 (20.6%)	13 (18.1%)

The time course of adverse events reported in the PMA clinical trial from all 264 activL subjects (randomized and non-randomized) and 112 control subjects (randomized and non-randomized) are shown in Table 12. This table includes adverse events from all subjects, randomized and non-randomized, to establish the safety profile of the device. Adverse events are listed in alphabetical order by main category with clinically relevant subcategories also detailed. Definitions of the adverse event categories and subcategories are provided in Table 13. Adverse event rates are based on the number of subjects having at least one occurrence of an adverse event divided by the number of subjects in that treatment group. Note that subjects with the same event reported within a window are counted once but may appear in multiple timepoints for the same event.

The percentage of subjects experiencing at least one adverse event is comparable in the “all activL” group and the “all Control” group. In the activL group, the most common reported adverse events were lower extremity pain, lumbar pain and lumbar and lower extremity pain.

Table 12: Time Course of All Adverse Events in the US IDE Trial (All Subjects)*

Adverse Event	Intra-Op**		Peri-Op (up to 6wks)		Short Term (>6wks-12mo)		Long Term (>12mo-24mo)		Longer Term (>24mo)		All activL (N=264)		All Control (N=112)	
	All activL	All Contr	All activL	All Contr	All activL	All Contr	All activL	All Contr	All activL	All Contr	Subjects n (%)	Events N	Subjects n (%)	Events N
Total Adverse Events	69	46	178	77	303	150	145	52	151	73	226 (85.6%)	846	100 (89.3%)	398
Cancer	0	0	0	0	2	0	1	2	0	1	3 (1.1%)	3	3 (2.7%)	3
Cardiac and Vascular Total	14	4	3	1	7	3	5	2	9	2	27 (9.8%)	38	12 (10.7%)	12
• Bleeding - index procedure	• 3	• 0	• 0	• 0	• 0	• 0	• 0	• 0	• 0	• 0	• 3 (1.1%)	• 3	• 0 (0.0%)	• 0
• DVT - index procedure	• 1	• 0	• 2	• 0	• 0	• 0	• 0	• 0	• 0	• 0	• 3 (1.1%)	• 3	• 0 (0.0%)	• 0
• Thrombosis	• 0	• 0	• 1	• 0	• 1	• 0	• 0	• 0	• 0	• 0	• 2 (0.8%)	• 2	• 0 (0.0%)	• 0
• Arterial dissection	• 0	• 0	• 0	• 1	• 0	• 0	• 0	• 0	• 0	• 0	• 0 (0.0%)	• 0	• 1 (0.9%)	• 1
• Iliac vessel tear - index procedure	• 4	• 1	• 0	• 0	• 0	• 0	• 0	• 0	• 0	• 0	• 4(1.5%)	• 4	• 1 (0.9%)	• 1
• Iliac vessel tear – SSI procedure	• 0	• 0	• 0	• 0	• 0	• 0	• 1	• 0	• 1	• 0	• 2 (0.8%)	• 2	• 0 (0.0%)	• 0
• Other	• 6	• 3	• 0	• 0	• 6	• 3	• 4	• 2	• 8	• 2	• 13 (4.9%)	• 24	• 10 (8.9%)	• 10
Dermatologic	1	1	2	0	1	1	2	1	1	0	7 (2.7%)	7	3 (2.7%)	3
Device Deficiency Total	1	2	3	2	3	2	0	0	0	1	7 (2.7%)	7	7 (6.3%)	7
• Implant Expulsion	• 0	• 0	• 0	• 0	• 0	• 1	• 0	• 0	• 0	• 0	• 0 (0.0%)	• 0	• 1 (0.9%)	• 1
• Implant Malposition	• 1	• 1	• 0	• 1	• 1	• 0	• 0	• 0	• 0	• 0	• 2 (0.8%)	• 2	• 2 (1.8%)	• 2
• Implant Migration	• 0	• 0	• 0	• 0	• 1	• 0	• 0	• 0	• 0	• 1	• 1 (0.4%)	• 1	• 1 (0.9%)	• 1
• Implant Subsidence	• 0	• 1	• 3	• 1	• 1	• 1	• 0	• 0	• 0	• 0	• 4 (1.5%)	• 4	• 3 (2.7%)	• 3
Endocrine	0	1	1	0	2	0	3	0	6	1	12 (4.5%)	12	2 (1.8%)	2
Eyes/Ears/Nose/Throat (EENT)	0	1	2	0	3	2	0	1	2	2	7 (2.7%)	7	6 (5.4%)	6
Gastrointestinal	8	5	16	8	13	6	20	4	9	6	51 (19.3%)	66	23 (20.5%)	29
Genitourinary Total	12	7	16	5	14	9	10	3	19	4	59 (22.3%)	71	24 (21.4)	28
• Erectile or Sexual Dysfunction	• 2	• 1	• 0	• 0	• 2	• 1	• 0	• 0	• 1	• 0	• 5 (1.9%)	• 5	• 2 (1.8%)	• 2
• Retrograde Ejaculation	• 1	• 1	• 2	• 2	• 2	• 0	• 1	• 0	• 0	• 0	• 6 (2.3%)	• 6	• 3 (2.7%)	• 3
• Other	• 9	• 5	• 14	• 3	• 10	• 8	• 9	• 3	• 18	• 4	• 48 (18.2%)	• 60	• 19 (17.0%)	• 23
Hepatobiliary	0	0	1	0	2	1	3	0	1	1	7 (2.7%)	7	2 (1.8%)	2
Immunological	1	1	4	0	4	2	3	2	5	4	16 (6.1%)	17	6 (5.4%)	9
Metabolic/Blood/Electrolytes	2	2	3	2	4	4	2	1	3	2	14 (5.3%)	14	10 (8.9%)	11
Musculoskeletal – Lumbar Total	0	3	5	2	16	4	6	1	6	4	30 (11.4%)	33	14 (12.5%)	14
• Bone Fracture-Adjacent Vertebra	• 0	• 1	• 0	• 0	• 1	• 0	• 0	• 0	• 0	• 0	• 1 (0.4%)	• 1	• 1 (0.9%)	• 1
• Degenerative Joint Disease	• 0	• 0	• 1	• 0	• 3	• 0	• 1	• 0	• 2	• 0	• 7 (2.7%)	• 7	• 0 (0.0%)	• 0
• Joint or Muscle	• 0	• 0	• 1	• 0	• 3	• 3	• 0	• 1	• 2	• 0	• 6 (2.3%)	• 6	• 4 (3.6%)	• 4
• Spasms – Lumbar/Buttock/Leg	• 0	• 2	• 2	• 2	• 8	• 0	• 3	• 0	• 1	• 0	• 14 (5.3%)	• 14	• 4 (3.6%)	• 4
• Radiographic Observation	• 0	• 0	• 0	• 0	• 0	• 0	• 0	• 0	• 1	• 2	• 1 (0.4%)	• 1	• 2 (1.8%)	• 2
• DDD Progression Adjacent	• 0	• 0	• 0	• 0	• 0	• 1	• 1	• 0	• 0	• 1	• 1 (0.4%)	• 1	• 2 (1.8%)	• 2
• Scoliosis	• 0	• 0	• 0	• 0	• 0	• 0	• 0	• 0	• 0	• 1	• 0 (0.0%)	• 0	• 1 (0.9%)	• 1
• Spinal Stenosis - Index	• 0	• 0	• 1	• 0	• 1	• 0	• 1	• 0	• 0	• 0	• 3 (1.1%)	• 3	• 0 (0.0%)	• 0
Musculoskeletal - Non-Lumbar	3	4	12	7	52	20	26	6	30	11	92 (34.8%)	124	39 (34.8%)	48

Adverse Event	Intra-Op**		Peri-Op (up to 6wks)		Short Term (>6wks-12mo)		Long Term (>12mo-24mo)		Longer Term (>24mo)		All activL (N=264)		All Control (N=112)	
	All activL	All Contr	All activL	All Contr	All activL	All Contr	All activL	All Contr	All activL	All Contr	Subjects n (%)	Events N	Subjects n (%)	Events N
Neurological - lumbar/lower extremity	7	1	18	13	31	14	4	2	2	3	44 (16.7%)	62	23 (20.5%)	33
• Motor Deficit	• 3	• 0	• 3	• 6	• 9	• 4	• 1	• 0	• 0	• 0	• 12 (4.5%)	• 16	• 7 (6.3%)	• 10
Persistent, Unilateral	*0*	*0*	*1*	*0*	*1*	*0*	*0*	*0*	*0*	*0*	*2 (0.8%)*	*2*	*0 (0.0%)*	*0*
Subjective, Bilateral	*0*	*0*	*0*	*0*	*1*	*0*	*0*	*0*	*0*	*0*	*1 (0.4%)*	*1*	*0 (0.0%)*	*0*
Subjective, Unilateral	*2*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*2 (0.8%)*	*2*	*0 (0.0%)*	*0*
Transient, Bilateral	*0*	*0*	*0*	*0*	*1*	*0*	*0*	*0*	*0*	*0*	*1 (0.4%)*	*1*	*0 (0.0%)*	*0*
Transient, Unilateral	*1*	*0*	*2*	*6*	*6*	*4*	*1*	*0*	*0*	*0*	*6 (2.3%)*	*10*	*7 (6.3%)*	*10*
• Nerve Root or Spinal Cord Injury	• 1	• 0	• 0	• 0	• 0	• 0	• 0	• 0	• 0	• 0	• 1 (0.4%)	• 1	• 0 (0.0%)	• 0
• Reflex Change or Abnormality	• 0	• 0	• 1	• 0	• 4	• 1	• 0	• 0	• 1	• 0	• 5 (1.9%)	• 6	• 1 (0.9%)	• 1
• Sensory Deficit	• 2	• 1	• 14	• 7	• 18	• 8	• 3	• 2	• 1	• 3	• 30 (11.4%)	• 38	• 18 (16.1%)	• 21
Measureable, Bilateral	*0*	*0*	*1*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*1 (0.4%)*	*1*	*0 (0.0%)*	*0*
Measureable, Unilateral	*1*	*0*	*8*	*3*	*12*	*5*	*0*	*0*	*0*	*1*	*16 (6.1%)*	*21*	*8 (7.1%)*	*9*
Subjective, Bilateral	*0*	*0*	*3*	*4*	*3*	*1*	*1*	*2*	*0*	*0*	*7 (2.7%)*	*7*	*7 (6.3%)*	*7*
Subjective, Unilateral	*1*	*1*	*2*	*0*	*3*	*2*	*2*	*0*	*1*	*2*	*8 (3.0%)*	*9*	*4 (3.6%)*	*5*
• Straight Leg Raise + or Change	• 1	• 0	• 0	• 0	• 0	• 1	• 0	• 0	• 0	• 0	• 1 (0.4%)	• 1	• 1 (0.9%)	• 1
Neurological - Non-lumbar/Lower Extremity	2	1	4	0	11	7	7	2	4	6	27 (10.2%)	28	15 (13.4%)	16
Pain - Lumbar & Lower Extremity Total	11	8	55	21	76	42	29	12	29	13	142 (53.8%)	200	68 (60.7%)	96
• Lower Extremity Pain Only	• 6	• 3	• 36	• 9	• 21	• 11	• 11	• 5	• 5	• 4	• 68 (25.8%)	• 79	• 24 (21.4%)	• 32
Bilateral Lower Leg	*1*	*2*	*9*	*3*	*6*	*3*	*3*	*1*	*2*	*1*	*18 (6.8%)*	*21*	*10 (8.9%)*	*10*
Bilateral Upper Leg	*0*	*0*	*4*	*2*	*5*	*1*	*3*	*1*	*1*	*2*	*13 (4.9%)*	*13*	*5 (4.5%)*	*6*
Unilateral Lower Leg	*5*	*1*	*21*	*4*	*4*	*5*	*4*	*2*	*2*	*1*	*35 (13.3%)*	*36*	*11 (9.8%)*	*13*
Unilateral Upper Leg	*0*	*0*	*2*	*0*	*6*	*2*	*1*	*1*	*0*	*0*	*9 (3.4%)*	*9*	*3 (2.7%)*	*3*
• Lumbar Pain Only	• 4	• 2	• 7	• 5	• 32	• 19	• 12	• 6	• 14	• 6	• 59 (22.3%)	• 69	• 37 (33.0%)	• 38
• Lumbar and Lower Extremity Pain	• 1	• 3	• 12	• 7	• 23	• 12	• 6	• 1	• 10	• 3	• 48 (18.2%)	• 52	• 24 (21.4%)	• 26
Lumbar & Bilat. Radiation Lower Leg	*1*	*1*	*5*	*3*	*10*	*7*	*0*	*0*	*6*	*1*	*21 (8.0%)*	*22*	*10 (8.9%)*	*12*
Lumbar & Bilat. Radiation Upper Leg	*0*	*1*	*1*	*0*	*4*	*2*	*1*	*0*	*0*	*0*	*5 (1.9%)*	*6*	*3 (2.7%)*	*3*
Lumbar & Unilat. Radiation Lower Leg	*0*	*1*	*6*	*4*	*8*	*3*	*3*	*1*	*3*	*2*	*18 (6.8%)*	*20*	*11 (9.8%)*	*11*
Lumbar & Unilat. Radiation Upper Leg	*0*	*0*	*0*	*0*	*1*	*0*	2	*0*	*1*	*0*	*4 (1.5%)*	*4*	*0 (0.0%)*	*0*
Psychosocial	2	1	3	0	12	9	7	1	3	1	23 (8.7%)	27	12 (10.7%)	12
Respiratory	1	1	3	1	6	2	5	4	4	4	17 (6.4%)	19	10 (8.9%)	12
Trauma	0	1	10	2	38	19	12	7	17	7	53 (20.1%)	77	27 (24.1%)	36
Uncoded	1	1	0	0	0	0	0	0	0	0	1 (0.4%)	1	1 (0.9%)	1

Adverse Event	Intra-Op**		Peri-Op (up to 6wks)		Short Term (>6wks-12mo)		Long Term (>12mo-24mo)		Longer Term (>24mo)		All activL (N=264)		All Control (N=112)	
	All activL	All Contr	All activL	All Contr	All activL	All Contr	All activL	All Contr	All activL	All Contr	Subjects n (%)	Events N	Subjects n (%)	Events N
Wound Issue - Index Procedure Total	3	1	17	13	5	3	0	1	1	0	25 (9.5%)	26	17 (15.2%)	18
• Abscess	• 0	• 0	• 3	• 2	• 2	• 0	• 0	• 0	• 0	• 0	• 5 (1.9%)	• 5	• 2 (1.8%)	• 2
• Deep	• 0	• 0	• 1	• 0	• 0	• 0	• 0	• 0	• 0	• 0	• 1 (0.4%)	• 1	• 0 (0.0%)	• 0
• Dehiscence	• 0	• 0	• 2	• 3	• 0	• 0	• 0	• 0	• 0	• 0	• 2 (0.8%)	• 2	• 3 (2.7%)	• 3
• Dural Injury/Tears/CSF Leaks	• 2	• 0	• 0	• 0	• 0	• 0	• 0	• 0	• 0	• 0	• 2 (0.8%)	• 2	• 0 (0.0%)	• 0
• Erythema/Drainage/Inflammation	• 0	• 0	• 2	• 3	• 0	• 1	• 0	• 0	• 0	• 0	• 2 (0.8%)	• 2	• 4 (3.6%)	• 4
• Incisional Hernia	• 0	• 0	• 0	• 1	• 0	• 0	• 0	• 1	• 1	• 0	• 1 (0.4%)	• 1	• 2 (1.8%)	• 2
• Incisional Cellulitis	• 0	• 0	• 2	• 0	• 1	• 0	• 0	• 0	• 0	• 0	• 3 (1.1%)	• 3	• 0 (0.0%)	• 0
• Pain at Incision Site	• 1	• 1	• 1	• 2	• 1	• 1	• 0	• 0	• 0	• 0	• 3 (1.1%)	• 3	• 4 (3.6%)	• 4
• Suture Reaction	• 0	• 0	• 1	• 1	• 1	• 0	• 0	• 0	• 0	• 0	• 2 (0.8%)	• 2	• 1 (0.9%)	• 1
• Wound Infection	• 0	• 0	• 5	• 1	• 0	• 1	• 0	• 0	• 0	• 0	• 5 (1.9%)	• 5	• 1 (0.9%)	• 2

* This table includes all monitored adverse events for all subjects (randomized and non-randomized investigational and control) as of April 11, 2013.

**The Intra-Op timepoint includes all adverse events which occurred through the discharge date. This includes 18 events (5 activL, 13 Control) which occurred prior to surgery or have an unknown onset date.

SSI = subsequent surgical intervention

Table 13: Adverse Event Categories and Subcategories Used by the CEC

Adverse Event	Definition
Cancer	Includes cases of Breast Cancer, Colon Cancer, Hodgkin's Lymphoma, Prostate Cancer, and Vulvar Cancer.
Cardiac and Vascular	
• Bleeding - index procedure	• Blood loss requiring intervention due to index study procedure.
• DVT - index procedure	• Blood clot formation in one or more vein, usually in the legs, causing pain, swelling, warmth, or changes in skin color due to the index study procedure.
• Thrombosis	• Blood clot in a vein or artery which can partially or completely block the flow of blood in a vessel.
• Arterial dissection	• Tear within the wall of a blood vessel, which allows blood to separate the wall layers.
• Iliac vessel tear - index procedure	• Tear or rupture of the iliac vessel due to the index procedure.
• Iliac vessel tear – SSI procedure	• Tear or rupture of the iliac vessel due to an SSI procedure.
• Other	The cardiac and vascular total also includes the following subcategories which are not listed in detail: bleeding requiring intervention - other (not due to the index or a SSI procedure), hypertension, hypotension, syncope/fainting, arrhythmia/irregularities, cardiac chest pain, coronary artery/heart disease, myocardial infarct/heart attack, pulmonary embolism (non-index procedure or spontaneous), aneurysm, atherosclerosis, and ecchymosis.
Dermatologic	Any condition of the skin (e.g., skin problems -rash, wart, skin virus/infection -shingles, Lyme disease). If condition is around surgical site, code to Wound Issue.
Device Deficiency	
• Implant Expulsion	• Occurs when the device is expelled from the original location.
• Implant Malposition	• Malposition of the device after implant.
• Implant Migration	• Evaluated as AP slippage of the device component(s) parallel to the vertebral endplates (movement of implanted device from original position). Includes Subluxation at Index level.
• Implant Subsidence	• Evaluated as sinking of the device component(s) into the cranial or caudal vertebral endplates.

Adverse Event	Definition
Endocrine	Includes adrenal gland disorders, decreased levels of testosterone in the blood, diabetes mellitus (types I, II, and unknown), gestational diabetes, and thyroid disorders (goiter, hyperthyroidism, and hypothyroidism).
Eyes/Ears /Nose/Throat (EENT)	Any condition of the ears, eyes, nose, throat, or mouth (e.g., ear infection, corneal abrasion, cataracts, eye infection, blurry vision, eyelid blepharoplasty, epistaxis, strep throat, oral herpes, oral candidiasis, nose bleed, oral thrush).
Gastrointestinal	Includes abdominal adhesions, abdominal pain, acid reflux, Barrett's Esophagus, decreased appetite/weight loss, dyspepsia/indigestion, esophageal bleeding, esophagitis, food poisoning, GERD, gastric lesions, gastritis, gastroenteritis/stomach flu, gastrointestinal infection, narcotic bowel syndrome, peptic ulcer, peritonitis, weight gain, appendicitis, bowel irregularity, bowel obstruction/ileus, constipation, diverticulitis, hiatal hernia, inflammatory bowel syndrome, nausea/vomiting/diarrhea, and gastrointestinal procedures (colonoscopy and hernia repair).
Genitourinary • Erectile or Sexual Dysfunction • Retrograde Ejaculation • Other	 • Occurs when a man can no longer get or keep an erection firm enough for sexual intercourse and/or persistent, recurrent problems with sexual response or desire in both males and females. • Occurs when semen enters the bladder instead of emerging through the penis during orgasm. • The genitourinary total also includes the following subcategories which are not listed in detail: decreased urine output/oliguria, kidney problems – other (including renal failure), kidney stone, benign prostatic hypertrophy, prostatitis, abnormal pap smear results, breast cyst/mass/tumor not indicated as cancerous, breast implant leakage, cystocele/prolapsed bladder, epididymitis, inguinal or testicular pain, irregular menstrual bleeding, menopause, nipple discharge, ovarian or uterine cyst/mass/tumor not indicated as cancerous, pregnancy/delivery, rectocele/posterior prolapse, vaginal or yeast infection, bladder infection, hematuria, urinary incontinence, painful urination/dysuria, pelvic pain, urinary hesitance, urinary retention, urinary tract infection, urinary urgency, and genitourinary procedures (breast reduction or enhancement, hysterectomy, and lumpectomy).
Hepatobiliary	Includes cholecystectomy, cholecystitis, cholelithiasis/gallstones, cirrhosis, liver fibrosis, and liver lesion.
Immunological	Includes systemic allergic reaction (both index or SSI procedure and non-index or SSI procedure), seasonal allergies, suture reaction (non-index or SSI procedure), Sjogren's syndrome, chills or night sweats, fever or pyrexia (index or SSI procedure), abscess (non-index or SSI procedure), cellulitis (non-index or SSI procedure), musculoskeletal wound infection (not at site of index level procedure or SSI), and Raynaud's Phenomenon.
Metabolic/Blood /Electrolytes	Includes abnormal blood chemistry, anemia, hypoxemia, dehydration, lower extremity edema, other edema, hypercholesterolemia, lymphadenopathy, and vitamin deficiency.
Musculoskeletal – Lumbar • Fracture-Adjacent Vertebra • Degenerative Joint Disease • Joint or Muscle • Spasms – Lumbar/Buttock/Leg • Radiographic Observation • DDD Progression Adjacent • Scoliosis • Spinal Stenosis - Index	 • Fracture of the vertebra surrounding the device location including posterior rim. Example - index procedure = L4-L5, adjacent vertebrae = L4 OR L5. • Includes ankylosing spondylitis, arthropathy, facet joint deterioration – index level, inflammatory polyarthritis, rheumatoid arthritis. • Includes benign mass/tumor – lumbar, joint sprain – lumbar, and pulled or strained muscle or muscle cramp – lumbar. • Persistent increased tension and shortness in a muscle or group of muscles in the lumbar back, buttock or leg that cannot be released voluntarily. Code to muscle spasm if noted as any combination of muscle spasm and pain; only exception is if described as radicular pain - code to pain. If only back spasm is specified, conservatively code to lumbar. • Includes disc herniation – adjacent and trabecular bone bridging or heterotopic ossification – index level • Condition in which pain is caused from a damaged disc at an adjacent level. • Abnormal curving of the lumbar spine. • Narrowing of the spinal column that causes pressure on the spinal cord at the index level.
Musculoskeletal - Non-Lumbar	Includes medullary canal erosion, bone fracture, arthritis, arthropathy, plantar fasciitis, foot problem – other, benign mass/tumor – non-lumbar, bursitis, ganglion cyst, gout, hallux rigidus, hiccups, hip joint pain/discomfort, inflammation of muscle, joint sprain – non-lumbar, leg length discrepancy, piriformis syndrome, pulled or strained muscle or muscle cramp – non-lumbar, restless leg syndrome, SI joint pain and discomfort, surgical procedure of a joint (e.g., shoulder/rotator cuff, hip, knee surgery and/or repair),

Adverse Event	Definition
	torn meniscus or hip labral tear, trigger finger or stenosing tenosynovitis, muscle spasms non-lumbar, pain or discomfort non-lumbar or leg (ankle only, back and upper extremities, fibromyalgia, foot only, knee only, neck or cervical, thoracic upper and mid back only, upper extremities), radiographic observation non-lumbar (disc bulge or protrusion non-lumbar or disc herniation non-lumbar), and degenerative disc disease progression non-lumbar.
Neurological • Motor Deficit *Persistent, Unilateral* *Subjective, Bilateral* *Subjective, Unilateral* *Transient, Bilateral* *Transient, Unilateral* • Nerve Root or Spinal Cord Injury • Reflex Change or Abnormality • Sensory Deficit *Measureable, Bilateral* *Measureable, Unilateral* *Subjective, Bilateral* *Subjective, Unilateral* • Straight Leg Raise + or Change	 *Measurable decrease of motor deficit unilaterally lasting > ~2 years.* *Functional weakness reported in bilateral lower extremities with no score changes.* *Functional weakness reported in unilateral lower extremity with no score changes.* *Measurable decrease of motor deficit bilaterally lasting ≤~2 years.* *Measurable decrease of motor deficit unilaterally lasting ≤~2 years.* • Damage to any part of the spinal cord or nerves at the end of the spinal canal, often causing permanent changes in strength, sensation and other body functions below the site of the injury. • Change or abnormal reflexes (e.g., patellar and Achilles); includes both unilateral or bilateral changes and/or abnormalities. *Paresthesia and dysesthesia descriptors of tingling, numbness, burning, sensitivity/hypersensitivity. Measurable decrease of sensory deficit in bilateral lower extremities. Test scores-pin test (e.g., L5/S1 dermatome) indicate measurable deficit.* *Paresthesia and dysesthesia descriptors of tingling, numbness, burning, sensitivity/hypersensitivity. Measurable decrease of sensory deficit in unilateral lower extremity. Test scores-pin test (e.g., L5/S1 dermatome) indicate measurable deficit.* *Reported sensory deficit in bilateral lower extremities with no score changes. Includes paresthesia and dysesthesia terms such as numbness, tingling, sensitivity/ hypersensitivity, burning.* *Reported sensory deficit in unilateral lower extremity with no score changes.* • Positive measurement or change in straight leg raise, includes both unilateral and bilateral changes.
Neurological - Non-lumbar/Lower Extremity	Includes Bell's Palsy, brain tumor, dysphagia/difficulty swallowing, forgetfulness/memory loss, headache, loss of consciousness, migraine, multiple sclerosis, nerve entrapment, numbness or tingling, restlessness or agitation, seizure, tremor, vertigo or dizziness, carpal tunnel syndrome, peripheral neuropathy, upper extremity motor deficit, upper extremity sensory deficit.
Pain - Lumbar and Lower Extremity • Lower Extremity Pain Only *Bilateral Lower Leg* *Bilateral Upper Leg* *Unilateral Lower Leg* *Unilateral Upper Leg* • Lumbar Pain Only • Lumbar and Lower Extremity Pain *Lumbar & Bilat. Radiation Lower Leg* *Lumbar & Bilat. Radiation Upper Leg* *Lumbar & Unilat. Radiation Lower Leg* *Lumbar & Unilat. Radiation Upper Leg*	 *Bilateral lower leg pain.* *Bilateral upper leg pain.* *Unilateral lower leg pain.* *Unilateral upper leg pain.* • Includes low back, lumbar or non-specified back pain. Also includes post-procedural pain unless incisional site is specifically indicated. Thoracic pain is coded to musculoskeletal non-lumbar. Mid and upper back pain only are coded to Thoracic pain in Musculoskeletal Non-Lumbar. *Pain in the lumbar area with radiation to the bilateral lower legs.* *Pain in the lumbar area with radiation to the bilateral upper legs.* *Pain in the lumbar area with radiation to the unilateral lower leg.* *Pain in the lumbar area with radiation to the unilateral upper leg.*
Psychosocial	Includes anxiety disorders, bipolar disorder or manic episode, conversion disorder, depressive disorders, suicidal ideation or attempt, suicide, fatigue or sleepiness or somnolence, insomnia, and substance dependence or withdrawal.
Respiratory	Includes shortness of breath/dyspnea, sleep apnea, cough, bronchitis, COPD, hemoptysis, lung problems – other, pneumonia, reactive airway disease, respiratory infection, sinus infection/sinusitis, and sinus problems – other.

Adverse Event	Definition
Trauma	Includes fall/trip/slip/twist, injury other, and motor vehicle accident.
Wound Issue - Index Procedure Total	
• Abscess	• Painful mass (collection of pus) causing swelling and inflammation, often adjacent to the surgical incision of the index procedure; including stitch abscesses.
• Deep	• Seroma, fluid packet, hematoma (localized collection of blood outside the blood vessels), with or without bleeding intervention.
• Dehiscence	• Rupture along the incision line of the index procedure wound; including major or minor dehiscence.
• Dural Injury/Tear or CSF Leak	• Any injury tear, or leak of the dura caused by or occurring during the index procedure.
• Erythema/Drainage/Inflammation	• Adverse events that have a combination of two or three of the following criteria (erythema, drainage, inflammation), or just one criterion if the adverse event involves the index procedure wound.
• Incisional Hernia	• Hernia caused by an incompletely-healed index procedure wound.
• Incisional Cellulitis	• Common, potentially serious bacterial skin infection along the index procedure incision appearing as swollen, red skin that is hot or tender.
• Pain at Incision Site	• Also includes terms such as irritation. Note for pain with drainage, code to drainage. Pain also includes term such as irritation.
• Suture Reaction	• Any reaction to the suture used during the index procedure.
• Wound Infection	• Any wound infection, with the wound identified being the index study procedure wound that gets infected. All other infections get coded within specific body system.

SSI = subsequent surgical intervention

When adverse events in the randomized treatment groups were compared, although p-values were obtained without any adjustment for multiplicity, there were no statistically significant differences between the two randomized treatment groups in the total number of adverse events or the number of adverse events in any category other than lumbar pain only in which the difference favored the activL group.

Table 15 provides data on the number of adverse events in each category in each randomized treatment group stratified by device design and level treated for the randomized activL group, and by control device and level treated for the randomized control group. In the activL group, more events occurred in subjects treated with the keel device than the spike device. In the control group, more events occurred in subjects treated with ProDisc-L than with the Charité device. In both treatment groups, more events occurred at the L5-S1 level than the L4-L5 though the difference was greater in the randomized activL group (activL: 526 vs 175; control: 250 vs 116).

Table 15: Adverse Events by Category - Stratified

Adverse Event (AE)	R activL (N=218)				R Contr (N=106)			
	Device Design		Treatment Level		Control Device		Treatment Level	
	Spike (N=115)	Keel (N=102)	L4-L5 (N=62)	L5-S1 (N=156)	ProDisc-L (N=65)	Charité (N=41)	L4-L5 (N=34)	L5-S1 (N=72)
Total Subjects with an AE (%)	96 (83.5%)	89 (87.3%)	51 (82.3%)	135 (86.5%)	58 (90.6%)	36 (87.8%)	34 (100%)	61 (84.7%)
Total Number of AEs	305	391	175	526	235	129	116	250
Cancer	1	0	0	1	3	0	0	3
Cardiac & Vascular	14	15	9	20	7	5	4	8
• Bleeding requiring intervention - index procedure	• 3	• 0	• 2	• 1	• 0	• 0	• 0	• 0
• DVT - index study procedure	• 0	• 2	• 2	• 0	• 0	• 0	• 0	• 0
• Thrombosis	• 2	• 0	• 0	• 2	• 0	• 0	• 0	• 0
• Arterial dissection	• 0	• 0	• 0	• 0	• 0	• 1	• 1	• 0
• Iliac vessel tear - index study procedure	• 2	• 0	• 0	• 2	• 0	• 1	• 0	• 1
• Iliac vessel tear – SSI procedure	• 1	• 1	• 0	• 2	• 0	• 0	• 0	• 0
• Other	• 6	• 12	• 5	• 13	• 7	• 3	• 3	• 7
Dermatologic	2	4	1	5	3	0	1	2
Device Deficiency	5	2	2	5	5	2	2	5
• Implant Expulsion	• 0	• 0	• 0	• 0	• 1	• 0	• 0	• 1
• Implant Malposition	• 1	• 1	• 0	• 2	• 2	• 0	• 1	• 1
• Implant Migration	• 1	• 0	• 0	• 1	• 1	• 0	• 0	• 1
• Implant Subsidence	• 3	• 1	• 2	• 2	• 1	• 2	• 1	• 2
Endocrine	3	7	3	7	1	1	0	2
Eyes/Ears/Nose/Throat	2	2	1	3	5	1	2	4
Gastrointestinal	25	33	17	41	18	9	6	21
Genitourinary	26	36	14	48	12	12	5	19
• Erectile/Sexual Dysfunction	• 2	• 1	• 0	• 3	• 1	• 1	• 0	• 2
• Retrograde Ejaculation	• 3	• 2	• 0	• 5	• 1	• 2	• 0	• 3
• Other	• 21	• 33	• 14	• 40	• 10	• 9	• 5	• 14
Hepatobiliary	3	3	0	6	2	0	1	1
Immunological	4	6	2	8	4	2	1	5
Metabolic/Blood/ Electrolytes	2	8	4	6	6	4	6	4
Musculoskeletal – Lumbar	9	16	6	19	11	2	6	8
• Bone Fracture-Adjacent Vertebra	• 1	• 0	• 0	• 1	• 0	• 0	• 0	• 1
• Degenerative Joint Disease	• 3	• 4	• 1	• 6	• 0	• 0	• 0	• 0
• Joint or Muscle	• 2	• 2	• 0	• 4	• 3	• 1	• 2	• 2
• Muscle spasms – Lumbar/Buttock/Leg	• 3	• 7	• 4	• 6	• 4	• 0	• 1	• 3
• Radiographic Observation	• 0	• 0	• 0	• 0	• 2	• 0	• 1	• 1
• DDD Progression Adjacent	• 0	• 0	• 0	• 0	• 1	• 1	• 1	• 1
• Scoliosis	• 0	• 0	• 0	• 0	• 1	• 0	• 1	• 0
• Spinal Stenosis - Index	• 0	• 3	• 1	• 2	• 0	• 0	• 0	• 0
Musculoskeletal - Non-Lumbar	46	59	30	75	26	17	13	30
Neurological – Lumbar and Lower Extremities	27	22	13	38	17	15	14	18
• Motor Deficit	• 6	• 7	• 2	• 11	• 5	• 5	• 5	• 5
Persistent, Unilateral	*1*	*1*	*0*	*2*	*0*	*0*	*0*	*0*
Subjective, Bilateral	*1*	*0*	*0*	*1*	*0*	*0*	*0*	*0*
Subjective, Unilateral	*2*	*0*	*0*	*2*	*0*	*0*	*0*	*0*
Transient, Bilateral	*1*	*0*	*1*	*0*	*0*	*0*	*0*	*0*
Transient, Unilateral	*1*	*6*	*1*	*6*	*5*	*5*	*5*	*5*
• Nerve Root or Spinal Cord Injury	• 0	• 0	• 0	• 0	• 0	• 0	• 0	• 0
• Reflex Change or Abnormality	• 3	• 2	• 3	• 2	• 1	• 0	• 0	• 1
• Sensory Deficit	• 18	• 13	• 7	• 25	• 11	• 9	• 8	• 12
Measureable, Bilateral	*0*	*1*	*0*	*1*	*0*	*0*	*0*	*0*
Measureable, Unilateral	*11*	*6*	*6*	*12*	*4*	*5*	*6*	*3*
Subjective, Bilateral	*4*	*2*	*1*	*5*	*3*	*3*	*1*	*5*

Adverse Event (AE)	R activL (N=218)				R Contr (N=106)			
	Device Design		Treatment Level		Control Device		Treatment Level	
	Spike (N=115)	Keel (N=102)	L4-L5 (N=62)	L5-S1 (N=156)	ProDisc-L (N=65)	Charité (N=41)	L4-L5 (N=34)	L5-S1 (N=72)
Subjective, Unilateral	*3*	*4*	*0*	*7*	*4*	*1*	*1*	*4*
• Straight Leg Raise Test Positive or Change	0	0	1	0	0	1	1	0
Neurological - Non-lumbar and Lower Extremities	7	15	6	16	12	2	5	10
Pain - Lumbar and Lower Extremity (LE)	81	83	41	125	51	38	26	63
• LE Pain Only	• 32	• 35	• 17	• 51	• 17	• 13	• 6	• 24
Bilateral Lower Leg	*5*	*14*	*3*	*16*	*5*	*4*	*2*	*7*
Bilateral Upper Leg	*4*	*5*	*5*	*5*	*4*	*1*	*1*	*4*
Unilateral Lower Leg	*18*	*13*	*7*	*24*	*6*	*7*	*2*	*11*
Unilateral Upper Leg	*5*	*3*	*2*	*6*	*2*	*1*	*1*	*2*
• Lumbar Pain Only	• 27	• 29	• 8	• 48	• 19	• 17	• 11	• 25
• Lumbar and LE Pain	• 22	• 19	• 16	• 26	• 15	• 8	• 9	• 14
Lumbar & Bilat. Radiation Lower Leg	*10*	*6*	*6*	*11*	*7*	*3*	*5*	*5*
Lumbar & Bilat. Radiation Upper Leg	*2*	*4*	*1*	*5*	*2*	*1*	*0*	*3*
Lumbar & Unilat. Radiation Lower Leg	*7*	*8*	*8*	*7*	*6*	*4*	*4*	*6*
Lumbar & Unilat. Radiation Upper Leg	*3*	*1*	*1*	*3*	*0*	*0*	*0*	*0*
Psychosocial	7	18	4	22	9	2	4	7
Respiratory	8	8	2	14	7	3	4	6
Trauma	20	42	16	46	24	8	13	19
Uncoded	0	0	0	0	0	1	0	1
Wound Issue - Index Procedure	13	12	4	21	12	5	3	14
• Abscess	• 3	• 2	• 1	• 4	• 2	• 0	• 0	• 2
• Deep	• 0	• 1	• 0	• 1	• 0	• 0	• 0	• 0
• Dehiscence	• 1	• 1	• 0	• 2	• 2	• 1	• 1	• 2
• Dural Injuries/Tears/CSF Leaks	• 1	• 1	• 0	• 2	• 0	• 0	• 0	• 0
• Erythema/Drainage/Inflammation	• 0	• 2	• 0	• 2	• 3	• 1	• 1	• 3
• Incisional Hernia	• 1	• 0	• 1	• 0	• 1	• 1	• 0	• 2
• Incisional Cellulitis	• 2	• 1	• 1	• 2	• 0	• 0	• 0	• 0
• Pain at Incision Site	• 2	• 0	• 1	• 1	• 3	• 0	• 1	• 2
• Suture Reaction	• 1	• 1	• 0	• 2	• 1	• 0	• 0	• 1
• Wound Infection	• 2	• 3	• 0	• 5	• 0	• 2	• 0	• 2

SSI=subsequent surgical intervention

One randomized activL subject died 146 days after surgery of hypertrophic heart disease with the effects of multiple drugs as contributing factors. The CEC adjudicated the event as death from suicide, and they determined it was not related to the activL device.

Some adverse events resulted in surgical intervention at the index level, subsequent to the initial surgery. Subsequent surgical interventions (SSIs), classified as revisions, removals, reoperations, or supplemental fixation procedures at the index level were study failures. There were 21 subsequent surgical interventions at the index level defined as revisions, removals, reoperations, or supplemental fixation procedures (activL = 15, control = 6) in 18 randomized subjects (activL = 12, control = 6); one subject had multiple interventions. The time course of the subsequent surgical procedures is summarized in Table 16. Note that there were no subsequent surgical interventions at the index level in either of the non-randomized cohorts (activL or control).

Table 16: Subsequent Surgical interventions at the Index Level

Type	Intra-Op**		Peri-Op (up to 6wks)		Short Term (>6wks-12mo)		Long Term (>12-24mo)		Longer Term (>24mo)		Total Events		Total Subjects	
	R activL	R Contr	R activL	R Contr	R activL	R Contr	R activL	R Contr	R activL	R Contr	R activL	R Contr	R activL (N=264)	R Contr (N=112)
Removal	0	0	0	0	0	1	2	0	1	1	3	2	3 (1.1%)	2 (1.8%)
Supplemental Fixation	0	0	0	0	1	0	1	0	3	1	5	1	5 (1.9%)	1 (0.9%)
Revision	0	1	0	0	0	0	0	0	0	0	0	1	0 (0%)	1 (0.9%)
Reoperation	2	0	1	0	3	1	0	1	1	0	7	2	5 (1.9%)	2 (1.8%)
Total	2	1	1	0	4	2	3	1	5	2	15	6	12 (4.5%)*	6 (5.4%)

*The total reported in the table is the sum of each of the rows; however, there are subjects who had multiple intervention types at the index level (i.e., the rows are not mutually exclusive). Therefore, there are actually 12 activL subjects and 6 control subjects who had a removal, reoperation, revision and/or supplemental fixation at the index level; one of these subjects had multiple interventions so is noted twice in the "total" row.

** The intra-op timepoint includes all subsequent surgical interventions which occurred through the discharge date.

Table 17 provides data on the number of subsequent surgical interventions at the index level in each randomized treatment group stratified by device design and level treated for the randomized activL group and control device and level treated for the randomized control group.

Table 17: Subsequent Surgical interventions at the Index Level – Stratified

Type	R activL (N=218)				R Contr (N=106)			
	Device Design		Treatment Level		Control Device		Treatment Level	
	Spike (N=115)	Keel (N=102)	L4-L5 (N=62)	L5-S1 (N=156)	ProDisc-L (N=65*)	Charité (N=41)	L4-L5 (N=34)	L5-S1 (N=72)
Removal	2 events (2 subjects)	1 event (1 subject)	0	3 events (3 subjects)	1 event (1 subject)	1 event (1 subject)	0	0
Supplemental Fixation	4 events (4 subjects)	1 event (1 subject)	3 events (3 subjects)	2 events (2 subjects)	0	1 event (1 subject)	0	1 event (1 subject)
Revision	0	0	0	0	1 event (1 subject)	0	1 event (1 subject)	0
Reoperation	1 event (1 subject)	6 events (4 subjects)	3 events 2 subjects)	4 events (3 subjects)	1 event (1 subject)	1 event (1 subject)	1 event (1 subject)	1 event (1 subject)
Total	7 events (7 subjects)	8 events (6 subjects)	6 events (5 subjects)	9 events (8 subjects)	3 events (3 subjects)	3 events (3 subjects)	2 events (2 subjects)	4 events (4 subjects)

Table 18 provides detailed information on each activL subsequent surgical intervention at the index level.

Table 18: Detailed Information on activL Subsequent Surgical interventions at the Index Level*

Surgical Intervention Type	Procedure Type	Procedure Level	Adverse Event Type	activL Device Design	Days From Index Procedure	Device Removed?
Removal	Fusion	L5-S1	Pain lumbar + bilateral radiation into lower legs	Spike	608	Yes
Removal	Fusion	L5-S1	Bone fracture - adjacent vertebra	Spike	668	Yes
Removal	Fusion	L5-S1	Lumbar pain only	Keel	883	Yes
Supplemental Fixation	Fusion	L5-S1	Implant malposition	Spike	101	No
Supplemental Fixation	Fusion	L4-L5	Pain lumbar & bilateral radiation into lower legs	Spike	611	No
Supplemental Fixation	Fusion	L4-L5, L5-S1	Pain lumbar & bilateral radiation into lower legs	Spike	799	No
Supplemental Fixation	Fusion	L4-L5, L5-S1	Pain lumbar & unilateral radiation into lower legs	Keel	882	No
Supplemental Fixation	Fusion	L5-S1	Implant subsidence	Spike	1243	No
Reoperation	Foraminotomy/ decompression	L5-S1	Implant malposition	Keel	4	No
Reoperation	Other Procedure (Dural Repair)	L5-S1	Dural injury or tear or CSF leak	Keel	4	No
Reoperation	Foraminotomy/ decompression	L5-S1	Pain bilateral lower legs	Keel	55	No
Reoperation	Fusion	L5-S1	Implant malposition	Spike	101	No
Reoperation	Foraminotomy/ decompression	L4-L5	Spinal stenosis - index	Keel	112	No
Reoperation	Foraminotomy/ decompression	L4-L5	Pain unilateral lower leg	Keel	340	No
Reoperation	Foraminotomy/ decompression	Listed as L5	Pain unilateral lower leg	Keel	970	No

* As of April 11, 2013.

Detailed information regarding subsequent procedures at the index level not associated with revision, removal, reoperation, or supplemental fixation in the activL group are provided in Table 19. The majority of procedures were rhizotomy/ablation procedures.

Table 19: Detailed Information on Control Group Subsequent Surgical Interventions at the Index Level*

Surgical Intervention Type	Procedure Type	Procedure Level	Adverse Event Type	Control Device	Days From Index Procedure	Device Removed?
Removal	Fusion	L5-S1	Implant expulsion	ProDisc-L	317	Yes
Removal	Fusion	L5-S1	Implant subsidence	Charite	835	Yes
Supplemental Fixation	Fusion	L5-S1	Lumbar pain only	Charite	846	No
Revision	Reposition (study device)	L4-L5	Implant malposition	ProDisc-L	3	No
Reoperation	Foraminotomy/ decompression	L4-L5, L5-S1	Pain lumbar & bilateral radiation into lower legs	Charite	79	No
Reoperation	Foraminotomy/ decompression	L5-S1	Pain lumbar & unilateral radiation into lower legs	ProDisc-L	710	No

* As of April 11, 2013.

Per the CEC Definitions and Guidelines, device-related events were defined as those events having an etiology, temporal association, or cause that was related to the device. Based on this definition, the timecourse and total number and percentage of subjects who experienced a device-related adverse event as determined by the CEC is provided in Table 20. Three hundred eighty four (384) device-related events occurred in all subjects during the course of the trial (NR activL = 45; R activL = 217; R Contr = 114; NR Contr = 8). The proportion of randomized subjects with a device-related adverse event was slightly higher in the control group (R activL = 61.5%; R Contr = 65.1%). The difference was not statistically significant although p-values were obtained without adjustment for multiplicity. The most common device-related adverse events in both treatment groups were lower extremity pain, lumbar pain only and lumbar and lower extremity pain. Fifty seven (57) SDAEs were reported in all subjects during the course of the trial (NR activL = 4; R activL = 31; R Contr = 20; NR Contr = 2). The proportion of randomized subjects with SDAEs was higher in the control group (R activL = 12.8%; R Contr = 18.9%). The most common serious device-related adverse events in both treatment groups were lumbar and lower extremity pain.

Table 20: Time Course of Device-Related Adverse Events*

Adverse Event	Intra-Op**		Peri-Op (up to 6wks)		Short Term (>6wks-12mo)		Long Term (>12mo-24mo)		Longer Term (>24mo)		All activL (N=264)		All Control (N=112)	
	All activL	All Contr	All activL	All Contr	All activL	All Contr	All activL	All Contr	All activL	All Contr	Subjects n (%)	Events N	Subjects n (%)	Events N
Total Device-Related AEs	21	5	71	34	104	53	34	14	32	16	164 (59.21%)	262	73 (61.34%)	122
Total Serious Device-Related AEs‡											32 (11.55%)	35	21 (17.65%)	22
Cardiac and Vascular Total	5	0	0	1	0	0	0	0	0	0	5 (1.9%)	5	1 (0.8%)	1
Device Deficiency Total	0	1	3	1	2	2	0	0	0	1	5 (1.8%)	5	5 (4.2%)	5
• Implant Expulsion	• 0	• 0	• 0	• 0	• 0	• 1	• 0	• 0	• 0	• 0	• 0 (0.0%)	• 0	• 1 (0.8%)	• 1
• Implant Migration	• 0	• 0	• 0	• 0	• 1	• 0	• 0	• 0	• 0	• 1	• 1 (0.4%)	• 1	• 1 (0.8%)	• 1
• Implant Subsidence	• 0	• 1	• 3	• 1	• 1	• 1	• 0	• 0	• 0	• 0	• 4 (1.4%)	• 4	• 3 (2.5%)	• 3
Musculoskeletal – Lumbar Total	• 0	0	2	0	4	0	1	0	2	1	9 (3.3%)	9	1 (0.8%)	1
• Fracture-Adjacent Vertebra	• 0	• 0	• 0	• 0	• 1	• 0	• 0	• 0	• 0	• 0	• 1 (0.4%)	• 1	• 0 (0.0%)	• 0
• Degenerative Joint Disease	• 0	• 0	• 1	• 0	• 3	• 0	• 1	• 0	• 2	• 0	• 7 (2.7%)	• 7	• 0 (0.0%)	• 0
• Radiographic Observation	• 0	• 0	• 0	• 0	• 0	• 0	• 0	• 0	• 0	• 1	• 0 (0.0%)	• 0	• 0 (0%)	• 0
• Spinal Stenosis - Index	• 0	• 0	• 1	• 0	• 0	• 0	• 0	• 0	• 0	• 0	• 1 (0.4%)	• 1	• 0 (0.0%)	• 0
Neurological Total	4	0	11	11	22	9	4	2	1	1	33 (11.9%)	42	16 (13.5%)	23
• Motor Deficit	• 2	• 0	• 3	• 6	• 8	• 1	• 1	• 0	• 0	• 0	• 11 (3.97%)	• 14	• 4 (3.4%)	• 7
Persistent, Unilateral	*0*	*0*	*1*	*0*	*1*	*0*	*0*	*0*	*0*	*0*	*2 (0.7%)*	*2*	*0 (0.0%)*	*0*
Subjective, Bilateral	*0*	*0*	*0*	*0*	*1*	*0*	*0*	*0*	*0*	*0*	*1 (0.4%)*	*1*	*0 (0.0%)*	*0*
Subjective, Unilateral	*2*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*2 (0.7%)*	*2*	*0 (0.0%)*	*0*
Transient, Unilateral	*0*	*0*	*2*	*6*	*6*	*1*	*1*	*0*	*0*	*0*	*6 (2.2%)*	*9*	*4 (3.4%)*	*7*
• Nerve Root or Spinal Cord Injury	• 1	• 0	• 0	• 0	• 0	• 0	• 0	• 0	• 0	• 0	• 1 (0.4%)	• *1*	• 0 (0.0%)	• 0
• Sensory Deficit	• 0	• 0	• 8	• 5	• 14	• 7	• 3	• 2	• 1	• 1	• 22 (7.9%)	• 26	• 14 (11.8%)	• 15
Measureable, Bilateral	*0*	*0*	*1*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*1 (0.4%)*	*1*	*0 (0.0%)*	*0*
Measureable, Unilateral	*0*	*0*	*3*	*2*	*8*	*4*	*0*	*0*	*0*	*1*	*9 (3.3%)*	*11*	*6 (5.0%)*	*7*
Subjective, Bilateral	*0*	*0*	*3*	*3*	*3*	*1*	*1*	*2*	*0*	*0*	*7 (2.5%)*	*7*	*6 (5.0%)*	*6*
Subjective, Unilateral	*0*	*0*	*1*	*0*	*3*	*2*	*2*	*0*	*1*	*0*	*7 (2.57%)*	*7*	*2 (1.7%)*	*2*
• Straight Leg Raise + or Change	• 1	• 0	• 0	• 0	• 0	• 1	• 0	• 0	• 0	• 0	• 1 (0.4%)	• 1	• 1 (0.8%)	• 1
Pain - Lumbar and Lower Extremity Total	11	4	55	21	76	42	29	12	29	13	142 (51.3%)	200	65 (54.62%)	92
• Lower Extremity Pain Only	• 6	• 2	• 36	• 9	• 21	• 11	• 11	• 5	• 5	• 4	• 68 (25.8%)	• 79	• 23 (20.5%)	• 31
Bilateral Lower Leg	*1*	*2*	*9*	*3*	*6*	*3*	*3*	*1*	*2*	*1*	*18 (6.5%)*	*21*	*10 (8.4%)*	*10*
Bilateral Upper Leg	*0*	*0*	*4*	*2*	*5*	*1*	*3*	*1*	*1*	*2*	*13 (4.7%)*	*13*	*5 (4.2%)*	*6*
Unilateral Lower Leg	*5*	*0*	*21*	*4*	*4*	*5*	*4*	*2*	*2*	*1*	*35 (12.6%)*	*36*	*10 (8.4%)*	*12*
Unilateral Upper Leg	*0*	*0*	*2*	*0*	*6*	*2*	*1*	*1*	*0*	*0*	*9 (3.3%)*	*9*	*3 (2.5%)*	*3*
• Lumbar Pain Only	• 4	• 2	• 7	• 5	• 32	• 19	• 12	• 6	• 14	• 6	• 59 (22.3%)	• 69	• 37 (33.0%)	• 38
• Lumbar and Lower Extremity Pain	• 1	• 0	• 12	• 7	• 23	• 12	• 6	• 1	• 10	• 3	• 48 (18.2%)	• 52	• 22 (19.6%)	• 23
Lumbar & Bilat. Radiation Lower Leg	*1*	*0*	*5*	*3*	*10*	*7*	*0*	*0*	*6*	*1*	*21 (7.8%)*	*22*	*10 (8.4%)*	*11*
Lumbar & Bilat. Radiation Upper Leg	*0*	*0*	*1*	*0*	*4*	*2*	*1*	*0*	*0*	*0*	*5 (1.8%)*	*6*	*2 (1.7%)*	*2*
Lumbar & Unilat. Radiation Lower Leg	*0*	*0*	*6*	*4*	*8*	*3*	*3*	*1*	*3*	*2*	*18 (6.5%)*	*20*	*10 (8.4%)*	*10*
Lumbar & Unilat. Radiation Upper Leg	*0*	*0*	*0*	*0*	*1*	*0*	*2*	*0*	*1*	*0*	*4 (1.4%)*	*4*	*0 (0.0%)*	*0*

* This table includes all monitored adverse events for all subjects (randomized and nonrandomized investigational and control) as of April 11, 2013.

**The Intra-Op timepoint includes all device-related adverse events which occurred through the discharge date. This includes 3 events (2 activL, 1 control) which have an unknown onset date.

‡ Time point break downs for Total Serious Device-Related AEs are not available

There were 68 activL spike subjects (59.1% of subjects treated with the spike device design) who experienced a device-related adverse event as determined by the CEC as compared to 65 activL keel subjects (63.7% of subjects treated with the keel device design) who experienced a device-related adverse event as determined by the CEC. There were 16 activL spike subjects (13.9% of subject treated with the spike device design) who experienced a serious device-related adverse event as determined by the CEC as compared to 12 activL keel subject (11.8% of subjects treated with the keel device design) who experienced a serious device-related adverse event as determined by the CEC.

Considering treatment level, there were 33 activL subjects treated at L4-L5 (53.2% of activL subjects treated at L4-L5) who experienced a device-related adverse event as determined by the CEC as compared to 101 activL subjects treated at L5-S1 (64.7% of activL subjects treated at L5-S1) who experienced a device-related adverse event as determined by the CEC. There were 9 activL subjects treated at L4-L5 (14.5% of activL subjects treated at L4-L5) who experienced a serious device-related adverse event as determined by the CEC as compared to 19 activL subjects treated at L5-S1 (12.2% of activL subjects treated at L5-S1) who experienced a device-related adverse event as determined by the CEC.

The change in overall neurological status at each timepoint is provided in Table 21. If any of the motor or sensory neurological assessments deteriorated, then the overall neurological status was considered deteriorated. At 24 months, the proportion of subjects with no decline in either motor or sensory evaluations was comparable between treatment groups, and there were no statistically significant differences

although p-values were obtained without any adjustment for multiplicity (motor evaluations: R activL = 97.3%, R Contr = 98.9%; sensory evaluations: R activL = 94.1%, R Contr = 93.1%).

Table 21: Time Course of Overall Neurological Status

Timepoint	Neurological Status	NR activL (N=46)	R activL (N=218)	R Contr (N=106)
6 weeks	Improved	11/45 (24.4%)	59/213 (27.7%)	31/105 (29.5%)
	Stable	29/45 (64.4%)	139/213 (65.3%)	64/105 (61.0%)
	Deteriorated	5/45 (11.1%)	15/213 (7.0%)	10/105 (9.5%)
3 months	Improved	12/45 (26.7%)	56/208 (26.9%)	29/101 (28.7%)
	Stable	27/45 (60.0%)	134/208 (64.4%)	59/101 (58.4%)
	Deteriorated	6/45 (13.3%)	18/208 (8.7%)	13/101 (12.9%)
6 months	Improved	11/45 (24.4%)	53/202 (26.2%)	26/96 (27.1%)
	Stable	31/45 (68.9%)	131/202 (64.9%)	61/96 (63.5%)
	Deteriorated	3/45 (6.7%)	18/202 (8.9%)	9/96 (9.4%)
12 months	Improved	11/41 (26.8%)	60/201 (29.9%)	27/96 (28.1%)
	Stable	27/41 (65.9%)	128/201 (63.7%)	63/96 (65.6%)
	Deteriorated	3/41 (7.3%)	13/201 (6.5%)	6/96 (6.3%)
24 months	Improved	10/41 (24.4%)	50/188 (26.6%)	24/87 (27.6%)
	Stable	28/41 (68.3%)	125/188 (66.5%)	57/87 (65.5%)
	Deteriorated	3/41 (7.3%)	13/188 (6.9%)	6/87 (6.9%)
3 years	Improved	7/37 (18.9%)	35/140 (25.0%)	22/72 (30.6%)
	Stable	26/37 (70.3%)	96/140 (68.6%)	46/72 (63.9%)
	Deteriorated	4/37 (10.8%)	9/140 (6.4%)	4/72 (5.6%)
4 years	Improved	5/19 (26.3%)	12/41 (29.3%)	5/24 (20.8%)
	Stable	11/19 (57.9%)	27/41 (65.9%)	19/24 (79.2%)
	Deteriorated	3/19 (15.8%)	2/41 (4.9%)	0/24 (0.0%)

Primary Effectiveness Results

The analysis of effectiveness was based on the mITT cohort of subjects, which consisted of all randomized, implanted subjects analyzed according to their randomization assignment (218 randomized activL, 106 randomized control, 46 non-randomized activL, 6 non-randomized control).

The individual subject success rate was defined in the IDE protocol as the number of subjects classified as a success at 24 months divided by the number of subjects treated with missing 24 month outcomes imputed as failures. Overall study success criteria were based on a comparison of individual subject success rates, such that the subject success rate for the activL investigational group was required to be non-inferior to that of the ProDisc-L/Charité control group.

The success rates at 24 months postoperative for each of the individual success components and overall success are provided in Table 22 for the randomized subjects treated in the study as well as the non-randomized activL subjects. Because the ROM success component of the primary endpoint was such a notable driver of the difference in overall success rates when comparing the two treatment groups, FDA also requested an analysis of overall success without the ROM success component. This analysis is also included. The trial was designed as a non-inferiority trial with a margin (delta) of 15%; however, additional analyses using a delta of 10% were requested by FDA. Only the 10% delta analyses are included here; 15% non-inferiority is always met for all variables demonstrating non-inferiority at 10%. According to the statistical analysis plan, if non-inferiority was demonstrated, then superiority was to be evaluated. These results are also presented.

Table 22: Overall Success at 24 Months (Missing Imputed as Failures)

Primary Endpoint Component	NR activL	R activL	R Contr	p-value*
ODI success (≥15 point improvement) 95% Confidence Interval (CI)	34/46 (73.9%) (58.9, 85.7)	164/218 (75.2%) (68.9, 80.8)	70/106 (66.0%) (56.2, 75.0)	 0.0874
Neurological success (maintenance or improvement – motor & sensory evaluations) 95% CI	38/46 (82.6%) (68.6, 92.2)	175/218 (80.3%) (74.4, 85.3)	81/106 (76.4%) (67.2, 84.1)	 0.4678
ROM success (maintenance or improvement) 95% CI	26/46 (56.5%) (41.1, 71.1)	128/218 (58.7%) (51.9, 65.3)	45/106 (42.5%) (32.9, 52.4)	 0.0065
Device success (no SSIs at index level) 95% CI	43/46 (93.5%) (82.1, 98.6)	184/218 (84.4%) (78.9, 89.0)	90/106 (84.9%) (76.6, 91.1)	 1.0000
No serious device-related AEs per CEC 95% CI	39/46 (84.8%) (71.1, 93.7)	167/218 (76.6%) (70.4, 82.1)	75/106 (70.8%) (61.1, 79.2)	 0.2772
Overall success including ROM success component 95% CI P-value (difference between groups; delta = 10%) P-value (superiority)	20/46 (43.5%) (28.9, 58.9)	92/218 (42.2%) (35.6, 49.1)	30/106 (28.3%) (20.0, 37.9)	 <0.0001 0.0200
Overall success without ROM success component 95% CI P-value (difference between groups; delta = 10%) P-value (superiority) R activL vs. R Contr	30/46 (65.2%) (49.8, 78.6)	135/218 (61.9%) (55.1, 68.4)	56/106 (52.8%) (42.9, 62.6)	 0.0004 0.1485

* Difference between randomized groups

SSI = subsequent surgical intervention

Regarding the overall success rate at 24 months (missing imputed as failures), in randomized subjects, activL was found to be non-inferior to control for the analysis of overall success both with and without the ROM success component (p value <0.0001 for both 15% and 10% margins).

Analysis of overall success was also performed based on observed data (missing data not included as failures) as presented in Table 23 for the randomized subjects treated in the study as well as the non-randomized activL subjects both with and without the ROM success component. Similar to the missing imputed as failures analysis, in randomized subjects, activL was found to be non-inferior to the control for the analysis of overall success both with and without the ROM success components based on observed data (p value <0.0001 for both 15% and 10% margins).

Table 23: Overall Success at 24 Months (Observed)

Primary Endpoint Component	NR activL	R activL	R Contr	p-value*
ODI success (≥15 point improvement) 95% CI	34/41 (82.9%) (67.9, 92.8)	164/187 (87.7%) (82.1, 92.0)	69/86 (80.2%) (70.2, 88.0)	 0.1394
Neurological success (maintenance or improvement – motor & sensory evaluations) 95% CI	38/41 (92.7%) (80.1, 98.5)	175/188 (93.1%) (88.5, 96.3)	80/86 (93.0%) (85.4, 97.4)	 1.0000
ROM success (maintenance or improvement) 95% CI	26/40 (65.0%) (48.3, 79.4%)	128/184 (69.6%) (62.4, 76.1)	44/84 (52.4%) (41.2, 63.4)	 0.0089
Device success (no SSIs at index level) 95% CI	43/43 (100.0%) (91.8, 100.0)	184/192 (95.8%) (92.0, 98.2)	89/92 (96.7%) (90.8, 99.3)	 1.0000
No serious device-related AEs per CEC 95% CI	39/43 (90.7%) (77.9, 97.4)	167/194 (86.1%) (80.4, 90.6)	74/94 (78.7%) (69.1, 86.5)	 0.1271
Overall success including ROM success component 95% CI P-value (difference between groups; delta = 10%) P-value (superiority)	20/40 (50.0%) (33.8, 66.2)	92/185 (49.7%) (42.3, 57.2)	29/87 (33.3%) (23.6, 44.3)	 <0.0001 0.0129
Overall success without ROM success component 95% CI P-value (difference between groups; delta = 10%) P-value (superiority)	30/41 (73.2%) (57.1, 85.8)	135/189 (71.4%) (64.4, 77.8)	55/88 (62.5%) (51.5, 72.6)	 0.0005 0.1644

* Difference between randomized groups
SSI = subsequent surgical intervention

In randomized activL subjects, overall success and component outcomes were qualitatively comparable when comparing observed data for the spike and keel device designs; however, the trial was not designed or powered to demonstrate statistical poolability of the two device designs. When considering treatment level in activL subjects, while qualitative differences were evident in the missing imputed as failures analysis comparing activL subjects treated at L4-L5 with activL subjects treated at L5-S1, with qualitatively higher overall and component success rates in activL subjects treated at L5-S1, overall success and component outcomes were more comparable in the observed analysis. The trial was not designed or powered to demonstrate statistical poolability for the two activL treatment levels.

Table 24 provides observed time course data (missing data not included as failures) for overall success for the randomized subjects treated in the study as well as the non-randomized activL subjects, with and without the ROM success component.

Table 24: Time Course of Overall Success (Missing Imputed as Failures)

Treatment Group	6 Months n/N (%)	12 Months n/N (%)	24 Months n/N (%)	3 Years n/N (%)	4 Years n/N (%)
Overall success (imputed) including ROM success component:					
NR activL (N=46)	19/46 (41.3%)	20/46 (43.5%)	20/46 (43.5%)	19/46 (41.3%)	11/46 (23.9%)
R activL (N=218)	99/218 (45.4%)	88/218 (40.4%)	92/218 (42.2%)	62/218 (28.4%)	14/218 (6.4%)
R Contr (N=106)	35/106 (33.0%)	40/106 (37.7%)	30/106 (28.3%)	33/106 (31.1%)	9/106 (8.5%)
Overall success (imputed) without ROM success component:					
NR activL (N=46)	33/46 (71.7%)	33/46 (71.7%)	30/46 (65.2%)	28/46 (60.9%)	14/46 (30.4%)
R activL(N=218)	147/218 (67.4%)	148/218 (67.9%)	135/218 (61.9%)	97/218 (44.5%)	30/218 (13.8%)
R Contr(N=106)	59/106 (55.7%)	66/106 (62. 3%)	56/106 (52.8%)	49/106 (46.2%)	13/106 (12.3%)

Table 25 provides time course data on overall success (observed only, without the ROM success component) for the randomized activL group stratified by device design and level treated.

Table 25: Time Course of Overall Success (Observed)

Treatment Group	6 Months n/N (%)	12 Months n/N (%)	24 Months n/N (%)	3 Years n/N (%)	4 Years n/N (%)
Overall success (observed) without ROM success component:					
R activL, spike (N=115)	75/106 (70.8%)	79/107 (73.8%)	69/98 (70.4%)	42/71 (59.2%)	5/25 (20.0%)
R activL, keel (N=102)	71/95 (74.7%)	69/96 (71.9%)	66/91 (72.5%)	55/79 (69.6%)	25/41 (61.0%)
R activL, L4-L5 (N=62)	43/56 (76.8%)	45/58 (77.6%)	36/49 (73.5%)	30/42 (71.4%)	12/21 (57.1%)
R activL, L5-S1 (N=156)	103/145 (71.0%)	103/145 (71.0%)	99/140 (70.7%)	67/108 (62.0%)	18/45 (40.0%)

Various post-hoc sensitivity analyses were conducted to assess the robustness of the study conclusions. Specifically, the following analyses were provided:

- Overall success with and without the ROM component of overall success as well as with different ROM success definitions.
- Overall success stratified by activL device design, control device, and treatment level as well as by surgical approach (retroperitoneal versus the 5 subjects (3 activL, 2 control) treated via a transperitoneal approach).
- Overall success with and without the ROM component of overall success with various imputations for missing 24 month values including multiple imputation, last observation carried forward, all missing as failures, all missing as successes, best case analysis (missing activL as successes and missing control as failures), worst case analysis (missing activL as failures and missing control as successes), and tipping point (break-even) analysis.
- Sensitivity analyses comparing overall success in the randomized activL group to each control device separately (both missing imputed as failures and observed).
- Overall success for complete cases as well as complete cases excluding subjects with major protocol violations.

Non-inferiority was established for nearly all of these scenarios both with and without the ROM component of overall success except the most extreme case in which all missing activL outcomes were considered failures and all missing control outcomes were considered successes where non-inferiority with a 10% margin was not established (either with or without the ROM component of overall success). Non-inferiority was further evidenced in the tipping point (break-even) analysis where 98% of combinations of missing data favored activL versus only 2% that favored control, utilizing a delta of 10%.

Additional data was provided which stratified overall success by 24 month ODI status (≥ 15 point improvement, unchanged, ≥ 15 point worsening), 24 month neurological status (improved, unchanged, deteriorated), 24 month ROM status (≥ 2° improvement, unchanged, ≥ 2° worsening), 24 month VAS status (≥ 20mm improvement, unchanged, ≥ 20mm worsening), duration of symptoms (< 1 year, ≥ 1 year), and gender.

Additional data was provided which stratified outcomes by subject race as shown in Table 26. For subjects randomized to activL, the Caucasian group had higher success rates than the non-Caucasian group for both overall success definitions and several overall success components whereas for subjects randomized to the control group, the non-Caucasian group generally had higher success rates. Among the Caucasian subject population, those treated with the activL had higher success rates than those in the control group whereas among the non-Caucasian group, the reverse was true. It is important to note that the non-Caucasian subject population was relatively small (2 NR activL, 22 R activL, 6 R Contr). Due to the relatively small numbers of non-Caucasians treated in the IDE study, this potential variability in outcomes based on race will be evaluated further as part of an Enhanced Surveillance Study the applicant will conduct for ten years postmarket.

Table 26: Overall Success at 24 Months Stratified by Subject Race (Observed)

	R activL		R Contr	
Primary Endpoint Component	**Caucasian (N=163)**	**Non-Caucasian (N=22)**	**Caucasian (N=81)**	**Non-Caucasian (N=6)**
Overall success including ROM success component 95% CI	85/163 (52.1%) (44.2, 60.0)	7/22 (31.8%) (13.9, 54.9)	26/81 (32.1%) (22.2, 43.4)	3/6 (50.0%) (11.8, 88.2)
Overall success without ROM success component 95% CI	122/166 (73.5%) (66.1, 80.0)	13/23 (56.5%) (34.5, 76.8)	50/82 (61.0%) (49.6, 71.6)	5/6 (83.3%) 35.9, 99.6)

SSI = subsequent surgical intervention

Secondary Effectiveness Analysis

In addition to the components of the primary endpoint presented above, secondary effectiveness variables were also assessed. The following secondary endpoint success definitions were specified in the protocol:

- VAS back, left leg, and right leg pain success: improvement of ≥ 20mm from baseline
- ODI success: improvement of both ≥ 15 points and ≥ 15% from baseline
- SF-36 success: improvement of ≥ 15% from baseline

Observed success rates at 24 months in the randomized treatment groups based on these definitions are presented in Table 27. The results were comparable.

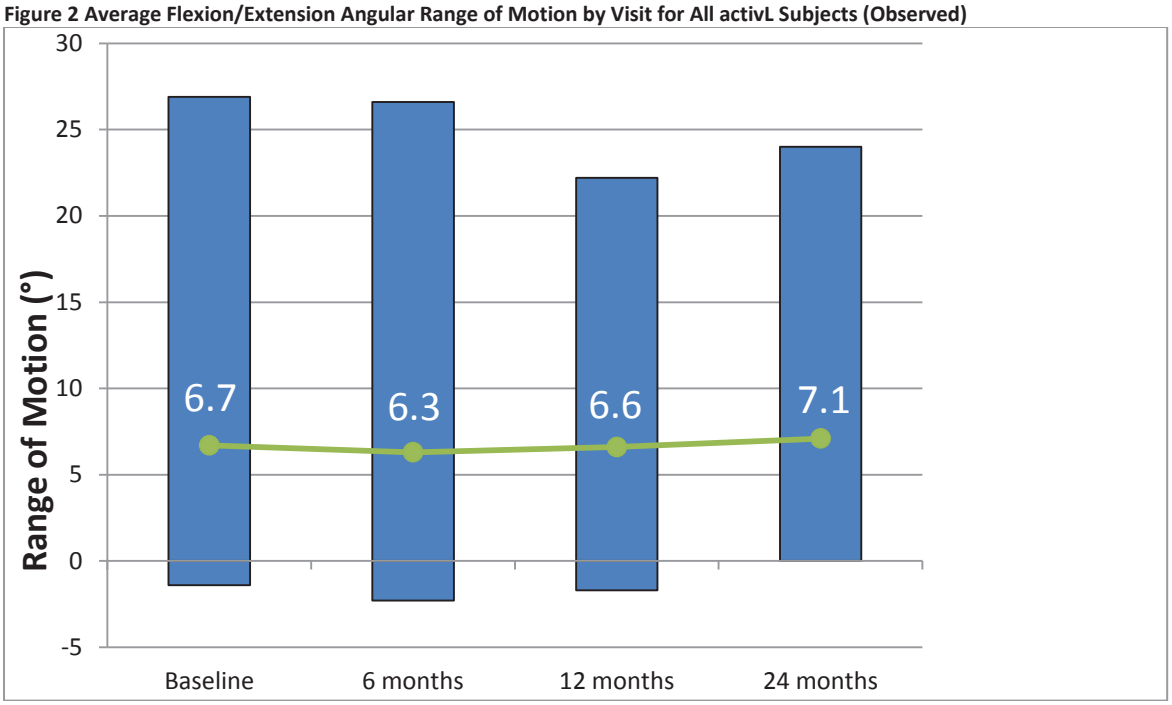
Table 27: Secondary Effectiveness Endpoints - Subject Reported Outcomes at 24 Months (Observed)

Outcome Measure	R activL n/N (%)	R Contr n/N (%)	p-value
VAS Back Pain ≥ 20 mm Improvement	162/180 (90.0%)	72/87 (82.8%)	0.1124*
VAS Left Leg Pain ≥ 20 mm Improvement	72/182 (39.6%)	35/86 (40.7%)	0.8941*
VAS Right Leg Pain ≥ 20 mm Improvement	73/182 (40.1%)	36/84 (42.9%)	0.6892*
ODI ≥ 15 point Improvement	164/187 (87.7%)	70/87 (80.5%)	N/A
ODI ≥ 15% Improvement	170/187 (90.9%)	77/87 (88.5%)	N/A
SF-36 MCS ≥ 15% Improvement	101/180 (56.1%)	48/86 (55.8%)	N/A
SF-36 PCS ≥ 15% Improvement	156/180 (86.7%)	69/86 (80.2%)	N/A

* Difference between randomized groups for pre-specified powered secondary endpoints

For all subjects receiving the activL (randomized plus non-randomized), the mean flexion/extension angular range of motion values at 12 months and 24 months postoperative were 6.6° and 7.1°, respectively, compared to 6.7° at the preoperative evaluation. The average angulation range of motion (flexion/extension) and range of results for all activL subjects (randomized plus non-randomized) at the preoperative, 6 month, 12 month, and 24 month visits are shown in Figure 2.

Figure 2 Average Flexion/Extension Angular Range of Motion by Visit for All activL Subjects (Observed)



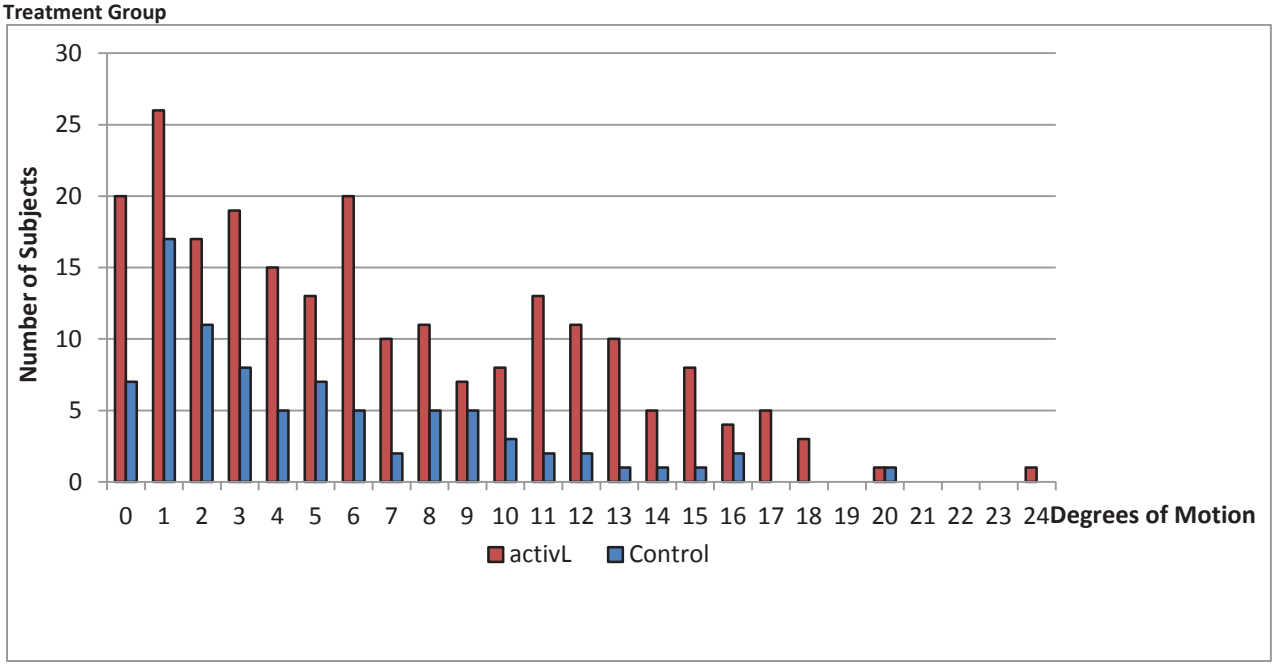
Range of motion success for both treatment groups was defined as maintenance or improvement in flexion/extension angular range of motion relative to preoperative baseline. Table 28 presents data on change in range of motion from preoperative baseline for each timepoint by treatment group for the randomized subjects treated in the trial as well as the non-randomized activL subjects at 6, 12 and 24 months follow-up.

Table 28: Time Course of Flexion/Extension Angular Range of Motion Improvement (Observed)

	6 mo			12 mo			24 mo		
	NR activL	R activL	R Contr	NR activL	R activL	R Contr	NR activL	R activL	R Contr
ROM, N	42	198	94	41	197	95	40	184	85
Improved (>0°)	45.2%	42.9%	40.4%	43.9%	41.6%	45.3%	52.5%	52.2%	36.5%
Stable (≥-2° but ≤0°)	9.5%	25.3%	14.9%	17.1%	20.8%	14.7%	12.5%	17.4%	16.5%
Deteriorated (<-2°)	45.2%	31.8%	44.7%	39.0%	37.6%	40.0%	35.0%	30.4%	47.1%

A histogram of angular range of motion on flexion/extension radiographs at 24 months for all subjects treated with the activL (randomized plus non-randomized) as compared to all subjects treated with the control devices (randomized plus non-randomized) is provided in Figure 3 (values are rounded to the nearest integer).

Figure 3: Histogram of Flexion/Extension Angular Range of Motion at 24 Months for All Subjects (Randomized Plus Non-randomized) by Treatment Group



The applicant evaluated the correlation between 24 month range of motion in rotation as well as translation and 24 month pain and function outcomes. In both randomized treatment groups, there was an inverse correlation between angular range of motion and back pain and angular range of motion and function. The clinical significance of these results is not clear.

Radiographic evaluation of mean disc height for the treated level at the preoperative and 24 month time points are shown in Table 29 by treatment group for the randomized subjects treated in the study as well as the non-randomized activL subjects. Data on the number of subjects with >3mm change in disc height compared to preoperative at 24 months by treatment group is also provided.

Table 29: Time Course of Observed Angular Range of Motion Compared to "Normal" Angular Range of Motion

	Baseline			24 mo		
	NR activL	R activL	R Contr	NR activL	R activL	R Contr
L4-L5 "Normal" ROM	7/11 (63.6%)	35/61 (57.4%)	22/33 (66.7%)	6/9 (66.7%)	33/48 (68.8%)	9/27 (33.3%)
L5-S1 "Normal" ROM	27/35 (77.1%)	109/153 (71.2%)	52/72 (72.2%)	20/31 (64.5%)	102/139 (73.4%)	40/58 (69.0%)

"Normal" ROM definitions:
L4-L5: ROM ≥ 5 degrees and ≤ 20 degrees, ± 2 degrees
L5-S1: ROM ≥ 6 degrees and ≤ 20 degrees, ± 2 degrees

Table 30 provides a summary of radiographic safety data at 24 months for all of the study treatment groups which shows few instances of subsidence (≥ 3mm), migration (≥ 3mm), or poor device condition (disassembly, loosening, or device fracture).

Table 30: Summary of Radiographic Safety Data at 24 Months (Observed)

Radiographic Measure	NR activL n/N (%)	R activL n/N (%)	R Contr n/N (%)	NR Contr n/N (%)
Subsidence (≥ 3mm)	0/41 (0%)	0/185 (0%)	2/85 (2.4%)	1/6 (16.7%)
Migration (≥ 3mm)	0/41 (0%)	0/185 (0%)	1/85 (1.2%)	0/6 (0%)
Device Condition (disassembled, loose, or fractured)	0/41 (0%)	1/185 (0.5%)	2/86 (2.3%)	0/6 (0%)

Available radiographs for all treated subjects were assessed by an independent radiographic evaluator to determine heterotopic ossification (HO) class, based on a scale from 0 to 4 (shown below), as well as to determine the number of subjects with stable or "worsening" (progressing by at least one grade) HO from visit to visit.

HO Scale:

- None: No evidence of HO or osteophyte formation.
- Class 1: HO present in islands of bone within soft tissue but not influencing the range of motion of the vertebral motion segment (i.e., bone was not between the planes formed by the two vertebral endplates).
- Class 2: HO present between the two planes formed by the vertebral endplates but not blocking or articulating between adjacent vertebral endplates or osteophytes.
- Class 3: Range of motion of the vertebral endplates blocked by the formation of HO and/or postoperative osteophytes on flexion-extension or lateral bending radiographs.

- Class 4: Radiographic evidence of a continuous bony connection from the superior vertebral body to the inferior vertebral body caused by osteophyte formation or HO

In some cases, the rating could not be determined ("Indeterminate") because the subject had undergone a fusion procedure.

Table 31 presents 24 month data on HO by treatment group for the randomized subjects as well as the non-randomized activL subjects. Incidence and severity of HO increased over time, but was lower in both investigational groups than in the control group. HO will be studied further as part of both a seven year post-approval study and a ten year Enhanced Surveillance Postmarket Study that will be conducted by the applicant. Demographic and baseline characteristics and clinical outcomes were evaluated for potential correlation with HO class. There was no clear correlation between demographics or baseline characteristics and HO. There was a correlation between clinical outcome and severe HO (Class III and IV). All subjects with severe HO (Class III and IV) were primary endpoint failures, regardless of treatment group; only 1 subject (activL) was a radiographic success.

Table 31: Heterotopic Ossification at 24 Months

Time Period / HO Class	NR activL	R activL	R Contr
24-Month Follow-Up			
None	34/41 (82.9%)	156/187 (83.4%)	61/87 (70.1%)
Class I	5/41 (12.2%)	14/187 (7.5%)	17/87 (19.5%)
Class II	1/41 (2.4%)	12/187 (6.4%)	6/87 (6.9%)
Class III	1/41 (2.4%)	3/187 (1.6%)	1/87 (1.1%)
Class IV	0/41 (0.0%)	0/187 (0.0%)	0/87 (0.0%)
Indeterminate	0/41 (0.0%)	2/187 (1.1%)	2/87 (2.3%)
Not Assessed	0/41 (0.0%)	0/187 (0.0%)	0/87 (0.0%)
Stable vs. Baseline	*38/41 (92.7%)*	*167/187 (89.3%)*	*74/87 (85.1%)*
Progressive vs. Baseline	*3/41 (7.3%)*	*20/187 (10.7%)*	*13/87 (14.9%)*

Clinical Trial Conclusions

The clinical data support the reasonable assurance of safety and effectiveness of the activL® Artificial Disc when used in accordance with the indications for use. Based on the clinical trial results, it is reasonable to conclude that a significant portion of the indicated patient population will achieve clinically significant results and that the clinical benefits of the use of the activL in terms of improvement in pain and function, and the potential for motion preservation, outweigh the risks associated with the device and surgical procedure through 24-months follow-up when used in the indicated population in accordance with the directions for use.

How Supplied

- The activL® Artificial Disc implant components are supplied pre-packaged and sterile.
- The components are provided in protective packaging that is labeled to indicate its contents.
- The implant components are provided sterile using beta and gamma irradiation
- Implant components may not be resterilized
- Components are to be kept in their original packaging until just prior to use.
- Prior to use, check the expiration date and assure the integrity of the packaging. Do not use components if they are past their expiration date or if the packaging has been damaged. Damaged packages /devices should be returned to Aesculap Implant System, LLC. at 615 Lambert Pointe Drive, Hazelwood, MO 63042.
- Instruments are provided non-sterile. For more information on the sterilization and cleaning of the Instruments, please visit www.aesculapimplantsystems.com/products/instructions-for-use and reference IFU TA014275.

MRI Information

The activL® Artificial Disc has not been evaluated for safety and compatibility in the MR environment. It has not been tested for heating or migration in the MR environment.

Product Complaints

Any health care professional (e.g., customer or user of this system), who has complaints or who has experienced any dissatisfaction in the product quality, identity, durability, reliability, safety, effective-ness and/or performance, should notify Aesculap Implant Systems.

Further, if any of the implanted system component(s) ever "malfunctions,"(i.e. does not meet any of its performance specifications or otherwise does not perform as intended), or
may have caused or contributed to the death or serious injury of a patient, Aesculap Implant Systems should be notified immediately by telephone, fax or written correspondence. When filing a complaint, please provide the component(s) name and number, lot number(s), your name and address, and the nature of the complaint. Complaints may also be reported directly to Medwatch at http://www.fda.gov/medwatch. You will be contacted by Aesculap Implant Systems to provide specific information for an Enhanced Surveillance Study, for specific information regarding your clinical experience, regarding the complaint and overall experience with the device. In the event that the activL® Artificial Disc requires removal for any reason, follow the instructions provided below in the DEVICE RETRIEVAL section.

Device Retrieval

Should it be necessary to remove the activL® Artificial Disc, please contact Aesculap Implant Systems (Spine) to receive instructions regarding the data collection, including histopathological, mechanical, patient and adverse event information. Please refer to the activL® Artificial Disc Surgical Technique for step-by-step instructions on the required surgical technique for device retrieval.

All explanted devices must be returned to Aesculap for analysis per the detailed instructions in the surgical technique.

Please note that the activL® Artificial Disc should be removed as carefully as possible in order to keep the implant and surrounding tissue intact. In addition, descriptive information about the gross appearance of the device in situ, as well as descriptions of the removal

methods, i.e. intact or in pieces, should also be provided as outlined in detail in the surgical technique. Aesculap will also request additional information regarding the reason for removal, patient information, and associated clinical outcomes.

Limited warranty and disclaimer: Aesculap Implant Systems' products are sold with a limited warranty to the original purchaser against defects in workmanship and materials. Any other express or implied warranties, including warranties of merchantability or fitness, are hereby disclaimed.

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(IFU-864)

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activL® Artificial Disc Keel Endplate

CAUTION—Federal (USA) law restricts this device to sale by or on the order of a physician.

How Supplied –
Implants: Sterile
Surgical Instruments: Non-Sterile

The activL® Artificial Disc has not been evaluated for safety and compatibility in the MR environment. It has not been tested for heating or migration in the MR environment.

Indications for Use

The activL® Artificial Disc (activL) is indicated for reconstruction of the disc at one level (L4-L5 or L5-S1) following single-level discectomy in skeletally mature patients with symptomatic degenerative disc disease (DDD) with no more than Grade I spondylolisthesis at the involved level. DDD is defined as discogenic back pain with degeneration of the disc confirmed by patient history, physical examination, and radiographic studies. The activL® Artificial Disc is implanted using an anterior retroperitoneal approach. Patients receiving the activL® Artificial Disc should have failed at least six months of nonoperative treatment prior to implantation of the device.

Device Description

The activL® Artificial Disc is a weight-bearing, modular implant comprised of three elements: an inferior Cobalt/Chromium (CoCr) alloy endplate (which is anchored in the endplate of the caudal vertebral body), an ultra-high molecular weight polyethylene (UHMWPE) inlay (which engages with the inferior endplate), and a superior CoCr alloy endplate (which is anchored in the endplate of the cranial vertebral body). Longer-term fixation of the activL® Artificial Disc to the vertebral bodies is intended to be achieved through bone growth, with initial stabilization by keels on the endplates.

There are four endplate sizes and four inlay heights available. The superior endplates are provided in either 6° or 11° lordotic angle options, and the inferior endplates are provided in either 0° or 5° lordotic angle options. The 5° inferior endplate is designed for cases where the sacrum has a rounded posterior edge to allow placement of the endplate closer to the posterior border of the S1 vertebra, without the edges protruding.

The activL® Artificial Disc is assembled by the surgeon in the operating room prior to implantation. Two lateral wings on the inlay engage in grooves in the lateral walls of the inferior endplate. The superior endplate is then seated on the inferior endplate. Once assembled, the activL® Artificial Disc is mounted onto the inserter and implanted as a single unit via an anterior retroperitoneal approach.

Figure 1 Assembled activL® Artificial Disc with Keel Endplates

Table 1: activL® Endplate Sizes

ActivL® ENDPLATE SIZE	AP DIMENSIONS (mm)	LATERAL DIMENSIONS (mm)	LORDOTIC ANGLE
Small - Inferior	26	31	0° or 5°
Small - Superior	26	31	6° or 11°
Medium - Inferior	28	34.5	0° or 5°
Medium - Superior	28	34.5	6° or 11°
Large - Inferior	30	39	0° or 5°
Large - Superior	30	39	6° or 11°
Xtra Large - Inferior	33	40	0° or 5°
Xtra Large - Superior	33	40	6° or 11°

Table 2: activL® Inlay Sizes

activL® POLYETHYLENE INLAY SIZE	AP DIMENSIONS (mm)	LATERAL DIMENSIONS (mm)	INLAY HEIGHT/TOTAL DEVICE HEIGHT (mm)
Small	21	21	5.3 / 8.5
Medium	21	21	6.8 / 10
Large	21	21	8.8 / 12
Xtra Large	21	21	10.8 / 14

The maximum range of motion allowed by the activL® Artificial Disc (as measured through *in vitro* testing) is dependent on the endplate size, inlay height, and inlay location within the inferior endplate:

- The maximum allowable flexion is 43.5 degrees, and the minimum allowable flexion is 8.2 degrees.
- The maximum allowable extension is 43.5 degrees, and the minimum allowable flexion is 10.7 degrees.
- The maximum allowable lateral bending is ±34.1 degrees, and the minimum allowable lateral bending is ±8.

Note that the device design limit for many configurations is not achievable *in vivo* due to anatomic constraints. The activL® Artificial Disc is unconstrained in rotation.

The activL® Artificial Disc is implanted using instruments specific to the device, as well as manual surgical instruments. Instruments specifically designed for implanting the activL® include the insertion instrument (FW961R-FW964R), Trial Endplates (FW922R – FW928R, FW971R-FW979R), Impactor (FW910R-FW911R, FW915R, FW999R), revision instruments (FW965R-FW969R), Chisel Guides (FW980R – FW984R, FW993R-FW996R), Chisels (FW981R-FW992R), Repositioner (FW969R), and Parallel distractor (FW970R). Manual surgical instruments include the Mallets (FW579R, FL045R) Osteotomes (FW909R, FW997R), Rasp (FW912R-FW913R), Wedges (FW940R – FW944R), Spacers (FW951R-FW954R) Midline Marker (FW955R, FW938SU), Distraction forceps (FW960R), and the handle for the revision instrument (FW998R).

Materials

The activL® Artificial Disc endplates are manufactured from Cobalt Chromium Alloy (ISO 5832-12). The surfaces are coated with a Plasmapore® μ-CaP surface coating which is made out of pure titanium (ISO5832-2), with an additional microscopic calcium phosphate over-coating (ASTM F 1609).

The activL® Artificial Disc inlay is manufactured from Ultra-High Molecular Weight Polyethylene (UHMWPE) (ISO 5834-2).

Contraindications

The activL® Artificial Disc should not be implanted in patients with the following conditions:

- Active systemic infection or localized infection near the surgical site
- Osteoporosis or osteopenia defined as DEXA bone mineral density T-score ≤ -1.0
- Allergy or sensitivity to the implant materials (cobalt, chromium, polyethylene, titanium, tantalum, or calcium phosphate)
- Isolated lumbar radiculopathy, especially due to herniated disc
- Chronic radiculopathy (unremitting pain with predominance of leg pain symptoms greater than back pain symptoms extending over a period of at least a year)
- Extruded disc material with sequestrum (i.e., free disc fragment)
- Myelopathy
- Spinal stenosis
- Spinal deformity such as scoliosis
- Spondylolysis/isthmic spondylolisthesis, degenerative spondylolisthesis > Grade I, or segmental instability
- Clinically compromised vertebral bodies at the affected level due to current or past trauma (e.g., current or prior vertebral fracture) or disease (e.g., ankylosing spondylitis)
- Facet ankylosis or facet joint degeneration
- Preoperative remaining disc height < 3mm
- Symptoms attributed to more than one vertebral level
- Abdominal pathology that would preclude an anterior retroperitoneal approach
- Involved vertebral endplate that is dimensionally smaller than 31mm in the medial-lateral and/or 26mm in the anterior-posterior directions

Warnings

Use of the activL® Artificial Disc should only be undertaken after the surgeon has become thoroughly knowledgeable about spinal anatomy and biomechanics, has had experience with anterior approach spinal surgeries, and has had hands-on-training in the use of this device. Only surgeons who are familiar with the activL® implant components, instruments, procedure, clinical applications, biomechanics, and risks should use this device. A lack of adequate experience and/or training may lead to a higher incidence of adverse events, including neurological complications.

Correct selection of the appropriate implant size and correct placement of the device are essential to ensure optimal performance and function of the device. Please refer to the activL® surgical technique manual for step-by-step instructions on the required surgical technique.

Heterotopic Ossification (HO) is a potential complication associated with lumbar total disc replacement surgery, which could result in reduced motion in the lumbar spine. However, the clinical impact of the presence of HO is not clearly understood.

Precautions

The safety and effectiveness of this device has not been established in patients with the following conditions:

- More than one vertebral level with DDD
- Skeletally immature patients, children < 18 years old, or patients over the age of 60
- Prior surgery at any lumbar level other than intradiscal electro-thermal annuloplasty (IDET), percutaneous nucleoplasty, microdiscectomy, hemilaminectomy, or laminotomy
- Back or leg pain of unknown etiology
- Paget's disease, osteomalacia, or other metabolic bone disease
- Morbid obesity (BMI>35)
- Pregnancy
- Taking medications known to potentially interfere with bone/soft tissue healing (e.g, steroids)
- Rheumatoid arthritis, lupus, or other autoimmune diseases
- Systematic disease including AIDS, HIV, Hepatitis
- Active malignancy
- Any degenerative muscular or neurological condition, including but not limited to Parkinson's disease, amyotrophic lateral sclerosis (ALS), or multiple sclerosis.
- Psychiatric or cognitive impairment.
- Current or recent history of illicit drug or alcohol abuse, or dependence as defined as the continued use of alcohol despite the development of social, legal, or health problems.

- Insulin-dependent diabetes.

Preoperative:
Patient selection is extremely important. In selecting patients for a total disc replacement, the following factors can be of extreme importance to the success of the procedure: the patient's occupation or activity level, a condition of senility, mental illness, alcoholism, or drug abuse, and certain degenerative disease (e.g, degenerative scoliosis or ankylosing spondylitis) that may be so advanced at the time of implantation that the expected useful life of the device is substantially decreased.

In order to minimize the risk of atraumatic periprosthetic vertebral fractures, surgeons must consider all co-morbidities, past and present medications, previous treatments, etc. Upon reviewing all relevant information, the surgeon must determine whether a bone density scan is prudent. A screening questionnaire for osteoporosis, SCORE (Simple Calculated Osteoporosis Risk Evaluation), may be used to screen patients to determine if a DEXA bone mineral density measurement is necessary. If DEXA is performed, the patient should be excluded from receiving the device if the DEXA bone density measured T score is ≤ -1.0, as the patient may be osteopenic.

The patient should be informed of the potential adverse effects (risks/complications) included in this insert (see POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH).

Preoperative planning should be used to estimate the required implant size, and to ensure that the appropriate sizes are available for surgery. The procedure should not take place if the appropriate range of sizes will not be available.

Examine all instruments prior to surgery for wear or damage. Instruments which have been used excessively may be more likely to break. Replace any worn or damaged instruments.

Intraoperative:
Correct selection of the appropriate device is extremely important to ensure the placement and function of the disc. See the surgical technique manual for step by step instructions.

Surgical implants must never be re-used or re-implanted. Even if the device appears undamaged, it may have small defects and internal stress patterns that my lead to early breakage.

Use aseptic technique when removing the activL® Artificial Disc components from the innermost packaging. Carefully inspect each component and its packaging for signs of damage, including damage to the sterile barrier. Do not use activL® implants if the packaging is damaged or the implant shows signs of damage.

Use care when handling the activL® Artificial Disc implant to ensure that it does not come in contact with objects that could damage the implant. Exercise care to ensure that implantation instruments do not contact the highly polished articulating surfaces of the endplates. Damaged implants are no longer functionally reliable.

To ensure correct and stable joining of the modular activL® Artificial Disc components, ensure that the combination dimensions are congruent. See the surgical technique manual for step by step instructions.

To prevent damage to the bearing surfaces and ensure a solid assembly, clean each component with sterile saline before joining to ensure that tissue, blood or other debris is not trapped within the assembly.

The activL® Artificial Disc should not be used with components or instruments of spinal systems from other manufacturers.

Due to the proximity of vascular and neurological structures to the implantation site, there are risks of serious or fatal hemorrhage and risks of neurological damage with the use of this device. Serious or fatal hemorrhage may occur if the great vessels are eroded or punctured during implantation or are subsequently damaged due to breakage of implants, migration of implants, or if pulsatile erosion of the vessels occurs because of close apposition of the implants. Care should be taken to identify and protect these structures during surgery.

Postoperative:
Patients should be instructed in postoperative care procedures and should be advised of the importance of adhering to these procedures for successful treatment with the device. Following completion of the procedure, each patient should receive postoperative care customized to his/her postoperative needs and demonstrated progress. Typically, patients should be permitted to ambulate on the day of surgery, as tolerated, with an elastic bandage or lumbosacral orthosis (LSO) to provide support to the abdominal musculature. Lumbar stabilization therapy can typically be initiated 2 to 4 weeks postoperatively as tolerated. Water therapy and/or swimming can typically be encouraged starting at two weeks postoperatively. Aerobic walking should typically be stressed for the first 6 postoperative weeks with more resistive exercise using fitness machines after that time.

Patients should be instructed not to engage in activities requiring lifting, bending or twisting for six months post-surgery. Overloading of the spine by engaging in extreme activities (i.e., heavy weight lifting) may result in failure of the prosthesis.

Potential Adverse Effects of the Device on Health
As with any surgery, surgical treatment of lumbar degenerative disc disease is not without risk. A variety of complications related to the surgery or the use of the activL® Artificial Disc may occur. The following is a list of the potential adverse effects (i.e., complications, risks) associated with the use of the activL® Artificial Disc identified from the activL® Artificial Disc clinical trial results, use of the activL® Artificial Disc outside of the United States, approved device labeling for other lumbar total disc replacement devices, and published scientific literature including: (1) those associated with any surgical procedure; (2) those associated with lumbar spinal surgery using an anterior approach; and (3) those associated with a lumbar total disc replacement device (including the activL® Artificial Disc). These risks may occur singly or in combination, and may be severe and/or negatively impact patient outcomes. In addition to the risks listed below, there is also the risk that the procedure may not be effective and may not relieve or may cause worsening of symptoms. Additional surgery may be required to correct some of the potential adverse effects.

1. Risks associated with any surgical procedure:
    - Anesthesia complications including an allergic reaction or anaphylaxis;
    - Infection (wound, local, and/or systemic) or abscess;
    - Wound dehiscence or necrosis;
    - Edema;
    - Soft tissue damage or fluid collections, including hematoma or seroma;
    - Pain/discomfort at the surgical incision and/or skin or muscle sensitivity over the incision which may result in skin breakdown, pain, and/or irritation;
    - Heart or vascular complications including bleeding, hemorrhage or vascular damage resulting in catastrophic or potentially fatal bleeding, ischemia, myocardial infarction, abnormal blood pressure, venous thromboembolism including deep vein thrombosis and pulmonary embolism, thrombophlebitis, or stroke;
    - Pulmonary complications including atelectasis or pneumonia;
    - Impairment of the gastrointestinal system including ileus or bowel obstruction;
    - Impairment of the genitourinary system including incontinence, bladder dysfunction, or reproductive system complications;
    - Neurological complications including nerve damage, paralysis, seizures, changes to mental status, or reflex sympathetic dystrophy;
    - Complications of pregnancy including miscarriage or congenital defects;
    - Inability to resume activities of daily living; and
    - Death.

2. Risks specifically associated with lumbar spinal surgery using an anterior approach:
    - Injury to surrounding organs and structures including the cauda equina, nerve roots, other neurologic structures adjacent to the spinal column, adjacent vertebrae, lymphatic vessels, blood vessels, soft tissue, dura, intestines, kidneys, or ureters;
    - Neurological difficulties, including trouble with bowel and/or bladder function (including incontinence), sexual dysfunction (including retrograde ejaculation in males), muscle weakness or paralysis, changes in sensation (including numbness, dysesthesias, or paresthesias), chronic reflex sympathetic dystrophy, or pain;
    - Back or leg pain;
    - Epidural or retroperitoneal hematoma or fibrosis;
    - Scarring, adhesions, or swelling including in the peritoneum;
    - Hernia; and
    - Meningitis.

3. Risks associated with a lumbar total disc replacement device (including the activL® Artificial Disc):
    - Risks directly related to the device including malposition, migration/displacement, subsidence/loss of disc height, device breakage, device disassembly, or early or late loosening of the device. Any of these issues may cause pain or injury to surrounding organs and structures including the cauda equina, nerve roots, or other neurologic structures adjacent to the spinal column (which could cause pain, paralysis, numbness, or retrograde ejaculation in males) or blood vessel damage or erosion (which could cause catastrophic or fatal bleeding even in the late postoperative period);
    - Deterioration in neurologic status;
    - Development of new pain;
    - Failure of the device to improve symptoms or function;
    - Problems during placement of the device including trouble sizing the device, anatomical or technical difficulties implanting the device, or issues with the device instruments (e.g., bending or breakage) including the possibility that a fragment of a broken instrument may remain in the patient after implantation;
    - Adverse reaction or allergy to the device materials (cobalt, chromium, polyethylene, titanium, tantalum, calcium phosphate) or device wear debris which may lead to an adverse reaction of the local tissues or chronic inflammation that may lead to implant loosening or failure of the device, osteolysis, tumor formation, autoimmune disease, metallosis, scarring, or other symptoms;
    - Change in the alignment of the spine or loss of proper anatomic curvature, correction, height or reduction of the spine including spondylolisthesis, change in lordosis, or instability of the spine;
    - Degeneration of other parts of the spine including the facet joints or adjacent discs;
    - Spinal stenosis;
    - Fracture of the surrounding vertebrae;
    - Unintended bone formation (i.e., heterotopic ossification, annular ossification) that may result in bridging trabecular bone and may reduce spinal motion or result in unintended fusion at either the treated level or adjacent levels; and
    - Device failure which may require a subsequent surgical intervention (including removal of the activL, revision, re-operation or supplemental fixation).

Some of the adverse effects listed above were observed in the activL® Artificial Disc clinical trial. For more detailed information on the specific adverse effects that occurred during the clinical trial, please refer to the Safety Results Section below (Summary of IDE Clinical Study). Some of the most common adverse effects experienced by study patients were: lower extremity pain, lumbar pain alone, and both lumbar and lower extremity pain.

Clinical Study

The clinical investigation of the activL® Artificial Disc was conducted under an approved IDE (G060262) and was intended to determine the safety and effectiveness of the activL for reconstruction of the disc at one level (L4-L5 or L5-S1) following single-level discectomy in skeletally mature subjects with symptomatic degenerative disc disease (DDD) and no more than Grade I spondylolisthesis at the involved level who had been unresponsive to at least six months of prior nonoperative treatment. The trial was a prospective, multi-center, randomized (2:1), single masked, concurrently controlled, non-inferiority clinical trial to compare the safety and effectiveness of the activL

to one of two alternative lumbar total disc replacement control devices (DePuy Spine Charité or DePuy Synthes Spine ProDisc-L). Two design versions of the activL were studied as part of the clinical trial (spike version and keel version). Both have an identical articulation; the only difference is the method of initial stabilization. Longer-term fixation of the activL to the vertebral bodies is intended to be achieved through bone growth, with initial stabilization by either the spike or keel endplate design. During the IDE trial, the choice of the spike or keel endplate version was at the discretion of the investigator to allow selection of an optimal endplate to fit each individual patient's anatomy and to accommodate physician preference.

The first three subjects at each site received the activL and were not randomized. In addition, investigators who had not performed at least three prior control device implantations were allowed to perform up to three non-randomized control procedures. Subsequent subjects were randomized 2:1 to the activL or one of the two controls (Charité or ProDisc-L). The choice of control device was at the discretion of the investigator (i.e., each investigator used one or the other for all of the subjects he or she treated), and subjects involved in the trial were specifically consented to one or the other control device prior to surgery). The randomized subjects were masked to their treatment assignment, and every effort was made to maintain the masking through 24 months of follow-up. To assess the effectiveness of the masking, subjects were asked at each follow-up visit if they had learned which device they received. The investigator was not masked to the treatment. The purpose of the trial was to determine whether the activL was non-inferior to the alternative lumbar total disc replacement control group.

Subjects were treated between January 30, 2007 and December 3, 2009. A total of 376 subjects were treated at 18 investigational sites in the United States. Of these subjects, 52 were non-randomized subjects (46 activL, 6 control) and 324 were randomized subjects after application of the Intent-to-Treat (ITT) principle (218 activL, 106 control). The final analysis was conducted after all subjects had reached the 24 month timepoint based on data collected through April 11, 2013.

Clinical Inclusion and Exclusion Criteria
Subjects were eligible for the trial if they met the following criteria:

Inclusion Criteria
Enrollment in the activL trial was limited to subjects who met the following inclusion criteria:

- Age 18 – 60 years and skeletally mature.
- Back pain at the operative level only (minimum Visual Analog Scale (VAS) back pain score of 40/100mm and greater than the higher of the two VAS leg pain scores).
- Symptomatic DDD with objective evidence of lumbar DDD, based on objective evidence of identification of any of the following characteristics by Computed Tomography (CT) or Magnetic Resonance Imaging (MRI) scan:
    - Instability as defined by ≥ 3mm translation or ≥ 5° angulation;
    - Osteophyte formation of facet joints or vertebral endplates;
    - Decreased disc height of > 2mm as compared to the adjacent level;
    - Scarring/thickening of the ligamentum flavum, annulus fibrosis, or facet joint capsule;
    - Herniated nucleus pulposus;
    - Facet joint degeneration/changes; and/or
    - Vacuum phenomenon.
- Single level symptomatic disease at L4/L5 or L5/S1.
- Minimum of six months of unsuccessful conservative treatment, including, but not limited to physical therapy and/or medication.
- Minimum Oswestry Disability Index (ODI) score of 40/100.
- Surgical candidate for an anterior approach to the lumbar spine.
- Willing and able to return for follow-up visits regularly and sign an Informed Consent and HIPAA Authorization.

Exclusion Criteria
Subjects were not permitted to enroll in the activL trial if they met any of the following exclusion criteria:

- History of allergies to any of the device components including cobalt chromium alloy, titanium, UHMWPE, and calcium phosphate.
- Evidence of significant, symptomatic disc degeneration at another lumbar level.
- Previous surgery at any lumbar level, except IDET (Intradiscal Electro-thermal Annuloplasty), percutaneous nucleoplasty, microdiscectomy, hemilaminectomy, or laminotomy.
- Chronic radiculopathy as defined by subject complaint of unremitting pain with a predominance of leg pain symptoms greater than back pain symptoms extending over a period of at least 1 year.
- Sequestered herniated nucleus pulposus with migration.
- Leg pain with migrated sequestrum fragment.
- Myelopathy.
- Previous compression or burst fracture at the affected level.
- Mid-sagittal stenosis of <8 mm (by MRI).
- Degenerative or lytic spondylolisthesis > 3mm.
- Spondylolysis or isthmic spondylolisthesis.
- Lumbar scoliosis (> 11° sagittal plan deformity).
- Preoperative remaining disc height < 3mm.
- Facet ankylosis or severe facet degeneration.
- Active systemic infection of infection at the site of surgery.
- Spinal tumor.
- Anatomic requirements incompatible with the available range of dimensions for the experimental or control devices, based on preoperative assessment using radiographic templates. Specifically, endplate dimensions smaller than 34.5 mm in the medial-lateral and/or 27 mm in the anterior-posterior directions.

- Osteoporosis or osteopenia, indicated by a lumbar spine dual-energy X-ray absorptiometry (DEXA) T-score ≤ -1.
- Metabolic bone disease.
- Continuing steroid use or prior use for more than 2 months.
- Abdominal adhesions, endometriosis, inflammatory bowel disease, Crohn's disease, diverticulitis, ulcerative colitis or other abdominal pathology that would preclude the abdominal surgical approach.
- Prior nephrectomy.
- History of Pelvic Inflammatory Disease.
- Peritonitis.
- Morbid obesity (Body Mass Index >35).
- History of rheumatoid arthritis, lupus, or other autoimmune disorder.
- Ankylosing spondylitis.
- History of human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS) or hepatitis that precludes surgery.
- History of deep vein thrombosis, symptoms of arterial insufficiency, or thromboembolytic disease.
- Insulin-dependent diabetes.
- Pregnant or planning to become pregnant within the next 2 years.
- Life expectancy less than 5 years.
- Undergone chemotherapy within 5 years, or had any cancer other than non-melanoma skin cancer treated with curative intent within 5 years.
- Current or recent history of illicit drug or alcohol abuse, or dependence as defined as the continued use of alcohol despite the development of social, legal, or health problems.
- Investigational drug or device use within 30 days.
- Any degenerative muscular or neurological condition that would interfere with evaluation of outcomes, including but not limited to Parkinson's disease, amyotrophic lateral sclerosis (ALS), or multiple sclerosis.
- Currently in active spinal litigation as a result of medical negligence.
- A prisoner.
- Psychiatric or cognitive impairment that, in the opinion of the investigator, would interfere with the subject's ability to comply with the study requirements, e.g., Alzheimer's disease.

Postoperative Care

Following completion of the procedure, subjects in both treatment groups received postoperative care customized to their postoperative needs and demonstrated progress. Typically, subjects were permitted to ambulate on the day of surgery, as tolerated, with an elastic bandage or lumbosacral orthosis (LSO) to provide support to the abdominal musculature. Lumbar stabilization therapy was initiated 2 to 4 weeks postoperatively as tolerated. Water therapy and/or swimming were encouraged and could start two weeks postoperatively. Aerobic walking was stressed for the first 6 postoperative weeks with more resistive exercise using fitness machines after that time. Subjects were also instructed not to engage in activities requiring lifting, bending or twisting for six months post-surgery. Subjects were not specifically treated with NSAIDs postoperatively in either treatment group.

Follow-up Schedule

Subjects were scheduled to return for follow-up examinations at 6 weeks (±14 days), 3 months (±14 days), 6 months (±30 days), 12 months (±60 days), 24 months (±60 days), and annually thereafter (±60 days), as shown in Table 3.

Table 3: Clinical Evaluation Schedule

Evaluation	Baseline	Intra-op	Discharge	6 wks	3 mo	6 mo	12 mo	24 mo & Annually
Medical History/ physical exam	X							
Work status	X			X	X	X	X	X
Pain medications	X		X				X	X
VAS pain assessment	X			X	X	X	X	X
Neurological assessment	X		X	X	X	X	X	X
Short Form 36	X			X	X	X	X	X
ODI	X			X	X	X	X	X
Subject satisfaction							X	X
Adverse events*		X	X	X	X	X	X	X
MRI scan	X							
DEXA scan	X (if req)							
X-rays, A/P and lateral (standing neutral)	X	X (implant position)	X (implant position)	X	X	X	X	X
X-rays, A/P (R/L bending)	X			X	X	X	X	X
X-rays, lateral (flexion/extension)	X			X	X	X	X	X

* Adverse events and complications were recorded at all visits (both scheduled and unscheduled).

Clinical Endpoints

The safety of the activL was assessed by comparing the nature and frequency of adverse events (overall and in terms of seriousness and relationship to the device and/or procedure) and subsequent surgical interventions as well as maintenance or improvement in neurological

status compared to the ProDisc-L/Charité control group. All adverse events were independently adjudicated (for adverse event category, severity and relationship to the device and/or procedure) by a Clinical Events Committee (CEC) comprised of three practicing spine surgeons.

The effectiveness of the activL was assessed by evaluating improvement in ODI score, back and leg pain measured at rest using a VAS, quality of life measured using the Short-Form 36 (SF-36) questionnaire, subject satisfaction, pain medication usage, and work status compared to the ProDisc-L/Charité control group.

In addition, several radiographic endpoints were considered in evaluating both safety and effectiveness, including range of motion, disc height, device migration, device subsidence, device condition, and heterotopic ossification. Radiographic endpoints were evaluated by an independent core imaging laboratory.

Per the protocol, an individual subject was considered a success if the following criteria were met at 24 months postoperative:

- Improvement of at least 15 points in ODI score at 24 months compared to baseline;
- Maintenance or improvement in neurological status at 24 months compared to baseline as measured by motor and sensory evaluations with a decrease of one grade in either evaluation considered a failure;
- Maintenance or improvement in range of motion (ROM) at the index level, defined as: 24 month ROM – preoperative ROM ≥ 0 (with a ±2° measurement error applied) in a subject who did not meet the definition of fusion (evidence of continuous bridging bone and < 3° of angular motion from flexion to extension);
- No device failure requiring revision, re-operation, removal, or supplemental fixation at the index level; and
- Absence of serious device-related adverse events (SDAE) as adjudicated by the CEC.

In addition, because the ROM success component of the primary endpoint was such a notable driver of the difference in overall success rates in favor of activL when comparing the two randomized treatment groups, FDA requested an additional analysis of overall success without the ROM success component.

Overall study success criteria were based on a comparison of individual subject success rates, such that the subject success rate for the activL investigational group was required to be non-inferior to that of the ProDisc-L/Charité control group. The IDE was approved using a non-inferiority margin (delta) of 15% with an advisory that a non-inferiority margin of 10% would be required to demonstrate a reasonable assurance of the device's effectiveness. As outlined in the statistical analysis plan, if non-inferiority was demonstrated, then superiority would be evaluated.

The following two secondary effectiveness endpoints were designated as "powered" in the protocol for the purposes of generating potential labeling claims:

- Improvement in 24 month back pain (measured at rest) ≥ 20/100mm on a VAS compared to baseline; and
- Improvement in 24 month leg pain (measured at rest) ≥ 20/100mm on a VAS compared to baseline for the leg with the maximum pain at baseline with no worsening in the other leg.

Additional secondary effectiveness evaluations and other outcomes specified in the protocol included comparisons of:

- ODI (mean score, mean improvement from baseline, incidence of 15% improvement, incidence of 15 point improvement);
- Quality of Life, measured using the SF-36 Questionnaire with improvement of 15% compared to baseline considered clinically significant;
- Subject satisfaction;
- Device condition;
- Device migration (≥ 3 mm);
- Device subsidence (≥ 3 mm);
- Disc height (incidence of ≥ 3 mm change);
- ROM (flexion/extension, lateral bending) including comparison of 24 month ROM to baseline and to "normal" ROM at the operative level (defined as: $6 \pm 2° \leq ROM \leq 20 \pm 2°$ (device design limit) for L4-L5 and $5 \pm 2° \leq ROM \leq 20 \pm 2°$ (device design limit) for L5-S1) Reference: Huang, R.C., Girardi, F.P., Cammisa, F.P. Jr., Lim, M.R. Tropiano, P., & Mamy, T. (2005). Correlation Between Range of Motion and Outcome After Lumbar Total Disc Replacement: 8.6-Year Follow-up. Spine 30(12), 1407-1411.;
- Heterotopic ossification at the index level compared to baseline;
- Pain medication usage at 12 and 24 months compared to post injury and pre-implant usage;
- Work status/return to work (including level of activity) as compared to pre- and post- injury conditions;
- Mean operative time, duration of hospitalization, and blood loss;
- Neurological status; and
- Adverse event rates.

Accountability of PMA Cohort

A total of 376 subjects at 18 U.S. sites were treated in the IDE clinical trial. Of these subjects, 52 were non-randomized subjects (46 activL, 6 control) and 324 were randomized subjects after application of the Intent-to-Treat (ITT) principle (218 activL, 106 control). At the time of database lock, of the 324 randomized subjects enrolled in the PMA trial, all had reached the 24 month postoperative visit and 230 of the 273 expected randomized subjects (84%) had any 24 month data available for analysis. Complete 24 month primary endpoint data was available for:

- 192 activL subjects (47 treated at L4-L5, 145 treated at L5-S1)
    - 156 randomized (80 treated with the spike version of activL, 76 treated with the keel version of activL)
    - 36 non-randomized (16 treated with spike version of activL, 20 treated with keel version of activL)
- 72 control subjects (24 treated at L4-L5, 48 treated at L5-S1)
    - 67 randomized (40 treated with the ProDisc-L, 26 treated with the Charité)

- 5 non-randomized (5 treated with the ProDisc-L, 0 treated with the Charité). Note that unless otherwise noted, data on the non-randomized control group subjects is typically not included in the tables within this clinical trial results summary due to the small sample size.

A total of 33 activL subjects (29 randomized and 4 non-randomized) and 22 control subjects (21 randomized and 1 non-randomized) were primary endpoint failures at or prior to the 24 month visit because they had a removal, revision, reoperation, or supplemental fixation surgery at the index level or experienced a SDAE. Of the 33 activL subjects who were primary endpoint failures for these reasons, 18 received the spike version of the activL and 15 received the keel version of the activL.

A summary of subject accountability data for the 12 month, 24 month, 3 year, and 4 year follow-up visits is provided in Table 4. Note that one subject was randomized to the activL group but a control device was erroneously implanted instead. This was recorded as a protocol deviation, and the subject is included as an investigational subject in the ITT analysis set throughout this summary. Note that because this subject did not receive either the spike or keel device, he/she is not counted in any of the tables stratified by device design in this summary. Another subject was randomized to the control group (ProDisc-L) but was not implanted due to a posterior inferior rim fracture which occurred intra-operatively. The subject was subsequently fused and is included as a control subject in the ITT analysis set throughout this summary. Note that because this subject did not receive either control device, he/she is not counted in any of the tables stratified by control device in this summary. This explains why there are a total of 66 control subjects when stratified by device, instead of the 67 defined by the ITT population.

Table 4: Subject Accounting

	12 Months			24 Months			3 Years			4 Years		
	NR activL	R activL	R Contr	NR activL	R activL	R Contr	NR activL	R activL	R Contr	NR activL	R activL	R Contr
Treated	46	218	106	46	218	106	46	218	106	46	218	106
Deaths (cumulative)	0	1	0	0	1	0	0	1	0	0	1	0
Failures (cumulative)[1]	4	25	18	4	29	21	4	30	22	4	30	22
Not Yet Overdue	0	0	0	0	0	0	0	0	0	12	53	22
Expected[2]	42	192	88	42	188	85	42	187	84	30	134	62
Withdrawn (cumulative)	*1*	*0*	*0*	*1*	*0*	*1*	*1*	*1*	*1*	*2*	*1*	*1*
Missed Visit	*4*	*4*	*2*	*2*	*7*	*6*	*5*	*29*	*10*	*6*	*53*	*26*
Lost to Follow-Up (LTFU)/ Presumed LTFU	*0*	*9*	*8*	*2*	*19*	*10*	*2*	*36*	*13*	*5*	*44*	*16*
Actual, primary endpoint data (% follow-up)[3]	37 (88%)	174 (91%)	78 (89%)	36 (86%)	156 (83%)	67 (79%)	34 (81%)	115 (61%)	59 (70%)	17 (57%)	34 (25%)	17 (27%)
Actual, primary endpoint data in window (% follow-up)[4]	36 (86%)	157 (82%)	73 (83%)	34 (81%)	144 (77%)	61 (72%)	31 (74%)	106 (57%)	53 (63%)	17 (57%)	33 (25%)	17 (27%)
Actual, any data (% follow-up)[5]	37 (88%)	179 (93%)	78 (89%)	37 (88%)	162 (86%)	68 (80%)	34 (81%)	121 (65%)	60 (71%)	17 (57%)	36 (27%)	19 (30%)

NR=Non-randomized; R=Randomized; Contr=Control

[1] Subjects who had a removal, revision, reoperation or supplemental fixation surgery at the index level or experienced a SDAE.

[2] Treated subjects – (Deaths + Not yet overdue + Failures).

[3] Subjects with complete data for the primary endpoint, regardless of in-window status, and not a failure.

[4] Subjects with complete data for the primary endpoint, evaluated per protocol, and in-window and not a failure.

[5] Subjects with any follow-up data reviewed or evaluated and not a failure.

The primary dataset was based on a Modified Intent-to-Treat (mITT) population which consisted of all randomized, implanted subjects analyzed according to their randomization assignment (218 randomized activL, 106 randomized control, 46 non-randomized activL, 6 non-randomized control). For the primary endpoint analysis and analysis of the powered secondary endpoints, subjects with incomplete or missing data were imputed as failures, and sensitivity analyses were done to assess the potential impact of missing data on the trial outcomes. Missing values were ignored for the analysis of additional secondary endpoints, other outcomes, and summaries of baseline characteristics.

Study Population Demographics and Baseline Parameters

The demographics of the study population are typical for a lumbar artificial disc study conducted in the United States. Select demographic data and preoperative evaluations for the randomized subjects treated in the study as well as the non-randomized activL subjects are included in Table 5 and Table 6. Although p-values were obtained without any adjustment for multiplicity, there were no statistically significant differences in demographics, baseline characteristics, or preoperative evaluations when comparing the randomized treatment groups.

Table 5: Subject Demographics and Baseline Characteristics

Demographic Measure/Baseline Characteristic	NR activL (N=46)	R activL (N=218)	R Contr (N=106)
Age (years; mean ± standard deviation)	39.5 ± 8.3 Range: 22 – 54	39.0 ± 8.7 Range: 19 - 60	40.3 ± 8.6 Range: 19 – 56
Gender (n (%)) Male Female	 24 (52.2%) 22 (47.8%)	 116 (53.2%) 102 (46.8%)	 53 (50.0%) 53 (50.0%)

Demographic Measure/Baseline Characteristic	NR activL (N=46)	R activL (N=218)	R Contr (N=106)
Race (n (%))			
White	43 (93.5%)	190 (87.2%)	100 (94.3%)
Asian	1 (2.2%)	2 (0.9%)	0
Black	1 (2.2%)	17 (7.8%)	5 (4.7%)
American Indian or Alaska Native	0	3 (1.4%)	0
Native Hawaiian or Other Pacific Islander	0	0	0
Other	1 (2.2%)	6 (2.8%)	1 (0.9%)
BMI (kg/m^2; mean ± standard deviation)	26.7 ± 4.4 Range: 19 – 35	26.6 ± 4.1 Range: 16 – 37	27.1 ± 4.4 Range: 16 – 34
Smoking Status* (n (%))			
Current	13 (28.3%)	46 (21.1%)	22 (20.8%)
Previous	9 (19.6%)	38 (17.4%)	21 (19.8%)
Never	24 (52.2%)	134 (61.5%)	63 (59.4%)
Duration of Back Pain Symptoms (n (%))			
< 6 mo	2 (4.3%)	1 (0.5%)	2 (1.9%)
6 mo – 1 year	6 (13.0%)	30 (13.8%)	13 (12.3%)
≥1 year	38 (82.6%)	187 (85.8%)	91 (85.8%)
Duration of Leg Pain Symptoms (n (%))			
< 6 mo	4 (9.8%)	15 (7.8%)	10 (10.4%)
6 mo – 1 year	9 (22.0%)	46 (24.0%)	19 (19.8%)
≥ 1 year	28 (68.3%)	131 (68.2%)	67 (69.8%)
Current or Previous Non-operative Spinal Therapies (n (%))			
Physical Therapy	44 (95.7%)	195 (89.4%)	97 (91.5%)
Chiropractic or Osteopathic Treatment	33 (71.7%)	120 (55.0%)	51 (48.1%)
Pain Medication	46 (100%)	212 (97.2%)	103 (97.2%)
Epidural Injections	38 (82.6%)	174 (79.8%)	87 (82.1%)
Previous Operative Spinal Therapies (n (%))			
Lumbar Spinal Surgery	9 (19.6%)	52 (23.9%)	30 (28.3%)
Non-Lumbar Spinal Surgery	2 (4.3%)	10 (4.6%)	12 (11.3%)
Pain Medication Use (n (%))			
Narcotic/Narcotic Combination Analgesics	34 (73.9%)	141 (64.7%)	65 (61.3%)
Other Controlled Analgesic Medication	10 (21.7%)	30 (13.8%)	17 (16.0%)
NSAID/Combination NSAID	21 (45.7%)	96 (44.0%)	40 (37.7%)
Salicylate/Combination Salicylate	1 (2.2%)	4 (1.8%)	2 (1.9%)
Acetaminophen/Combination Acetaminophen	6 (13.0%)	22 (10.1%)	4 (3.8%)
Steroid	1 (2.2%)	0	1 (0.9%)
Muscle Relaxant	15 (32.6%)	61 (28.0%)	34 (32.1%)
Agonist/Antagonist	0	0	0
Preoperative Spine Characteristics on MRI (n (%))			
Instability (≥ 3mm translation or ≥ 5° angulation)	5 (10.9%)	16 (7.3%)	10 (9.4%)
Osteophyte formation facets or vertebral endplates	15 (32.6%)	44 (20.2%)	17 (16.0%)
Decreased disc height (> 2mm versus adjacent level)	35 (76.1%)	159 (72.9%)	71 (67.0%)
Scarring/thickening ligamentum flavum, annulus fibrosus, or facet joint capsule	9 (19.6%)	40 (18.3%)	18 (17.0%)
Herniated nucleus pulposus	31 (67.4%)	152 (69.7%)	83 (78.3%)
Facet joint degeneration/changes	11 (23.9%)	52 (23.9%)	30 (28.3%)
Vacuum phenomenon	6 (13.0%)	13 (6.0%)	12 (11.3%)

* Data on amount and length of tobacco use was not captured.

Table 6: Preoperative Evaluation of Endpoints

Variable	NR activL	R activL	R Contr
ODI mean ± standard deviation	N=46 60.0 ±13.5 Range: 34 - 94	N=218 57.1 ± 13.9 Range: 18 - 98	N=106 58.6 ± 14.1 Range: 33.3 – 96
VAS Back Pain (mm) mean ± standard deviation	N=45 81.5 ± 13.3 Range: 48 - 100	N=212 79.0 ± 14.9 Range: 46 - 100	N=106 79.1 ± 14.8 Range: 41 – 100
VAS Right Leg Pain (mm) mean ± standard deviation	N=45 34.9 ± 31.7 Range: 0 - 99	N=215 28.7 ± 29.8 Range: 0 – 96.5	N=104 32.9 ± 29.6 Range: 0 – 89.5
VAS Left Leg Pain (mm) mean ± standard deviation	N=46 33.6 ± 31.2 Range: 0 – 98.5	N=216 29.6 ± 29.4 Range: 0 - 100	N=105 30.7 ± 29.5 Range: 0 – 98
SF-36 Mental Component Summary (MCS) mean ± standard deviation	N=45 37.6 ± 14.7 Range: 10.5 – 66.8	N=213 39.1 ± 13.9 Range: 9.4 – 67.2	N=105 39.6 ± 14.9 Range: 8.3 – 67.8

Variable	NR activL	R activL	R Contr
SF-36 Physical Component Summary (PCS) mean ± standard deviation	N=45 28.4 ± 7.2 Range: 9.3 – 43.9	N=213 29.9 ± 6.2 Range: 14.1 – 51.4	N=105 28.4 ± 6.2 Range: 11.2 – 49.7
ROM Flexion/Extension Rotation (°) mean ± standard deviation	N=46 7.3 ± 5.1 Range: -0.1 to 18.9	N=214 6.6 ± 5.1 Range: -1.4 to 26.9	N=105 6.6 ± 4.6 Range: -0.7 to 19.4
ROM Flexion/Extension Translation (mm) mean ± standard deviation	N=46 0.6 ± 0.7 Range: -0.1 to 3.2	N=212 0.5 ± 0.7 Range: -0.4 to 3.8	N=104 0.6 ± 0.6 Range: -1.4 to 2.8
ROM Lateral Bending AP Rotation (°) mean ± standard deviation	N=42 1.1 ± 1.3 Range: -1.3 to 5.5	N=212 1.0 ± 2.0 Range: -2.3 to 12.5	N=103 1.0 ± 1.8 Range: -3.3 to 10.0
Normal Neurological Status (n (%)) Motor (Grade 5, active movement vs. full resistance) Sensory (Grade 2, normal) Reflexes (Grade 2, normal)	 194 (89.0%) 158 (72.5%) 178 (81.7%)	 97 (91.5%) 78 (73.6%) 91 (85.8%)	 40 (87.0%) 33 (71.7%) 42 (91.3%)

Surgical and Hospitalization Data

Surgical data for the randomized subjects treated in the study as well as the non-randomized activL subjects are included in Table 7. Although p-values were obtained without any adjustment for multiplicity, there were no statistically significant differences in procedural characteristics when comparing the randomized treatment groups.

Table 7: Procedural Characteristics

Procedural Characteristic	NR activL (N=46)	R activL (N=218)	R Contr (N=106)
Treated Level (n (%)) L4-L5 L5-S1	 11 (23.9%) 35 (76.1%)	 62 (28.4%) 156 (71.6%)	 34 (32.1%) 72 (67.9%)
Operative Time (min) mean ± standard deviation	129.5 ± 48.7 Range: 40 - 243	109.8 ± 43.3 Range: 30 – 233	119.0 ± 52.1 Range: 35 - 373
Access Surgeon Used (n (%))	46 (100%)	218 (100%)	106 (100%)
Surgical Approach (n (%)) Retroperitoneal Transperitoneal	 44 (95.7%) 2 (4.3%)	 215 (98.6%) 3 (1.4%)	 104 (98.1%) 2 (1.9%)
Blood loss (cc) mean ± standard deviation	194.6 ± 220.6 Range: 25 - 1050	135.2 ± 126.1 Range: 10 - 900	161.2 ± 200.0 Range: 5 - 1800
Length of stay (days) mean ± standard deviation	2.7 ± 1.1 Range: 1 - 6	2.3 ± 1.3 Range: 1 - 11	2.3 ± 1.3 Range: 1 – 8
Return to Work Time (days) mean ± standard deviation	260.6 ± 410.7 Range: 6 - 1772	262.5 ± 411.9 Range: 2 - 1815	349.7 ± 491.7 Range: 6 – 1886

Table 8 provides select procedural characteristic data stratified by device design (spike or keel) in the randomized activL group and by specific control device (ProDisc-L or Charité) in the randomized control group as well as by treatment level (L4-L5 or L5-S1) in both randomized groups.

Table 8: Select Procedural Characteristics - Stratified

Procedural Characteristic	R activL (N=218)				R Contr (N=106)			
	Spike (N=115)	Keel (N=102)	L4-L5 (N=62)	L5-S1 (N=156)	ProDisc-L (N=64)	Charité (N=41)	L4-L5 (N=34)	L5-S1 (N=72)
Treated Level (n (%)) L4-L5 L5-S1	 35 (30.4%) 80 (69.6%)	 26 (25.5%) 76 (74.5%)	 62 (100%) --	 -- 156 (100%)	 19 (29.7%) 45 (70.3%)	 15 (36.6%) 26 (63.4%)	 34 (100%) --	 -- 72 (100%)
Device Design Spike Keel	 115 (100%) --	 -- 102 (100%)	 35 (57.4%) 26 (42.6%)	 80 (51.3%) 76 (48.7%)	N/A	N/A	N/A	N/A
Control Device ProDisc-L Charité	N/A	N/A	N/A	N/A	64 (100%) --	-- 41 (100%)	19 (55.9%) 15 (44.1%)	45 (63.4%) 26 (36.6%)
Operative Time (min) mean ± standard deviation	115.7 ± 43.8	102.9 ± 42.1	123.9 ± 41.5	104.2 ± 42.9	119.8 ± 58.9	118.3 ± 40.4	125.9 ± 52.4	115.7 ± 52.0
Approach (n (%)) Retroperitoneal Transperitoneal	 112 (97.4%) 3 (2.6%)	 102 (100%) 0	 62 (100%) 0	 153 (98.1%) 3 (1.9%)	 62 (96.9%) 2 (3.1%)	 41 (100%) 0	 33 (97.1%) 1 (2.9%)	 71 (98.6%) 1 (1.4%)

Procedural Characteristic	R activL (N=218)				R Contr (N=106)			
	Spike (N=115)	Keel (N=102)	L4-L5 (N=62)	L5-S1 (N=156)	ProDisc-L (N=64)	Charité (N=41)	L4-L5 (N=34)	L5-S1 (N=72)
Blood loss (cc) mean ± standard deviation	138.5 ± 127.2	131.9 ± 125.9	154.1 ± 146.7	127.7 ± 116.5	135.9 ± 98.4	200.1 ± 292.3	153.5 ± 138.8	164.9 ± 224.7
Length of stay (days) mean ± standard deviation	2.4 ± 1.0	2.3 ± 1.6	2.6 ± 1.4	2.2 ± 1.3	2.0 ± 1.1	2.9 ± 1.5	2.2 ± 1.1	2.4 ± 1.4

Table 9 provides an overview of the characteristics of activL devices implanted during the clinical trial. No subjects received the following 11° superior endplates: small spike, extra-large spike, or small keel. No subjects received the 14mm height inlay.

Table 9: activL Implants Used

Size/Option	NR activL (N=46)	R activL (N=217)
Endplate Design (n (%))		
Spike	21 (45.7%)	115 (53.0%)
Keel	25 (54.3%)	102 (47.0%)
Superior Endplate Angle (n (%))		
6°	44 (95.7%)	203 (93.5%)
11°	2 (4.3%)	14 (6.5%)
Inferior Endplate (n (%))		
Small	11 (23.91%)	37 (17.05%)
Medium	9 (19.57%)	50 (23.04%)
Large	13 (28.26%)	48 (22.12%)
Extra-large	1 (2.17%)	8 (3.69%)
S1	12 (26.09%)	74 (34.10%)
Superior Endplate (n (%))		
Small	14 (30.43%)	59 (27.19%)
Medium	12 (26.09%)	77 (35.48%)
Large	19 (41.30%)	72 (33.18%)
Extra-large	1 (2.17%)	9 (4.15%)
Inlay Height (n (%))		
8.5 mm	40 (87.0%)	189 (87.1%)
10 mm	6 (13.0%)	25 (11.5%)
12 mm	0	3 (1.4%)
14 mm	0	0
Endplate/Inlay Combinations (n (%))		
Spike 6° Superior Endplate / 8.5 mm Inlay	18 (39.1%)	94 (43.3%)
Spike 6° Superior Endplate / 10 mm Inlay	2 (4.3%)	12 (5.5%)
Spike 6° Superior Endplate / 12 mm Inlay	0	2 (0.9%)
Spike 6° Superior Endplate / 14 mm Inlay	0	0
Spike 11° Superior Endplate / 8.5 mm Inlay	1 (2.2%)	7 (3.2%)
Spike 11° Superior Endplate / 10 mm Inlay	0	0
Spike 11° Superior Endplate / 12 mm Inlay	0	0
Spike 11° Superior Endplate / 14 mm Inlay	0	0
Keel 6° Superior Endplate / 8.5 mm Inlay	20 (43.5%)	83 (38.2%)
Keel 6° Superior Endplate / 10 mm Inlay	4 (8.7%)	12 (5.5%)
Keel 6° Superior Endplate / 12 mm Inlay	0	0
Keel 6° Superior Endplate / 14 mm Inlay	0	0
Keel 11° Superior Endplate / 8.5 mm Inlay	1 (2.2%)	5 (2.3%)
Keel 11° Superior Endplate / 10 mm Inlay	0	1 (0.5%)
Keel 11° Superior Endplate / 12 mm Inlay	0	1 (0.5%)
Keel 11° Superior Endplate / 14 mm Inlay	0	0

Safety and Effectiveness Results

Safety Results

The CEC defined serious adverse events as events that met any of the following criteria:

- Potentially life-threatening or resulted in death;
- Required in-subject hospitalization (hospital stay > 24 hours) or prolongation of hospitalization;
- Resulted in permanent impairment of body structure or a body function;
- Gave rise to a malignant tumor; or
- Led to a congenital anomaly in the offspring, or caused fetal distress or death.

In addition, the CEC defined device-related events as those with an etiology, temporal association, or cause related to the device. Procedure-related events were defined as those with an etiology, temporal association, or cause related to the surgical index procedure.

The analysis of safety was based on the mITT cohort of subjects which consisted of all randomized, implanted subjects analyzed according to their randomization assignment (218 randomized activL, 106 randomized control, 46 non-randomized activL, 6 non-randomized control). A summary of the adverse event data is presented in Table 10. The total number of adverse events, subsequent surgical interventions at the index level, adverse events classified by the CEC as device-related, procedure-related, serious, and serious device-related, as well as adverse events occurring within 2 days of the index procedure are shown for the randomized subjects treated in the study as well as for the non-randomized activL subjects.

Table 10: Summary of Adverse Events

Adverse Event Category	NR activL (N=46)		R activL (N=218)		R Contr (N=106)	
	Subjects n (%)	Events N	Subjects n (%)	Events N	Subjects n (%)	Events N
All Adverse Events	40 (87.0%)	145	186 (85.3%)	701	95 (89.6%)	366
Subsequent Surgical Interventions at the Index Level	0 (0.0%)	0	12 (5.5%)	15	6 (5.7%)	6
Device-Related Adverse Events	30 (65.2%)	45	134 (61.5%)	217	69 (65.1%)	114
Procedure-Related Adverse Events	29 (63.0%)	46	116 (53.2%)	195	70 (66.0%)	118
Serious Adverse Events	18 (39.1%)	21	72 (33.0%)	121	51 (48.1%)	68
Serious Device-Related Adverse Events	6 (13.0%)	6	28 (12.8%)	31	20 (18.9%)	20
Adverse Events within 2 days of Procedure	7 (15.2%)	8	39 (17.9%)	49	23 (21.7%)	33

Note: This table includes data collected beyond 24 months.

Table 11 provides adverse event summary data stratified by device design and level treated for the randomized activL and control device and level treated for the randomized control group.

Table 11: Summary of Adverse Events - Stratified

Adverse Event (AE) Category	R activL (N=218)				R Contr (N=106)			
	Device Design		Treatment Level		Control Device		Treatment Level	
	Spike (N=115)	Keel (N=102)	L4-L5 (N=62)	L5-S1 (N=156)	ProDisc-L (N=65)	Charité (N=41)	L4-L5 (N=34)	L5-S1 (N=72)
All AEs	96 (83.5%)	89 (87.3%)	51 (82.3%)	135 (86.5%)	58 (90.6)	36 (87.8%)	34 (100%)	61 (84.7%)
Subsequent Surgical Interventions at the Index Level	3 (2.6%)	0 (0.0%)	1 (1.6%)	2 (1.3%)	1 (1.5%)	0 (0.0%)	0 (0.0%)	1 (1.4%)
Device-Related AEs	68 (59.1%)	65 (63.7%)	33 (53.2%)	101 (64.7%	40 (62.5)	29 (70.7%)	23 (67.6%)	46 (63.9%)
Procedure-Related AEs	54 (47.0%)	61 (59.8%)	31 (50.0%)	85 (54.5%)	42 (65.6)	27 (65.9%)	22 (64.7%)	48 (66.7%)
Serious AEs	34 (29.6%)	37 (36.3%)	19 (30.6%)	53 (34.0%)	31 (48.4)	19 (46.3%)	16 (47.1%)	35 (48.6%)
Serious Device-Related AEs	16 (13.9%)	15 (14.7%)	10 (16.1%)	21 (13.5%)	10 (15.4%)	10 (24.4%)	7 (20.6%)	13 (18.1%)

The time course of adverse events reported in the PMA clinical trial from all 264 activL subjects (randomized and non-randomized) and 112 control subjects (randomized and non-randomized) are shown in Table 12. This table includes adverse events from all subjects, randomized and non-randomized, to establish the safety profile of the device. Adverse events are listed in alphabetical order by main category with clinically relevant subcategories also detailed. Definitions of the adverse event categories and subcategories are provided in Table 13. Adverse event rates are based on the number of subjects having at least one occurrence of an adverse event divided by the number of subjects in that treatment group. Note that subjects with the same event reported within a window are counted once but may appear in multiple timepoints for the same event.

The percentage of subjects experiencing at least one adverse event is comparable in the “all activL” group and the “all Control” group. In the activL group, the most common reported adverse events were lower extremity pain, lumbar pain and lumbar and lower extremity pain.

Table 12: Time Course of All Adverse Events in the US IDE Trial (All Subjects)*

Adverse Event	Intra-Op**		Peri-Op (up to 6wks)		Short Term (>6wks-12mo)		Long Term (>12mo-24mo)		Longer Term (>24mo)		All activL (N=264)		All Control (N=112)	
	All activL	All Contr	All activL	All Contr	All activL	All Contr	All activL	All Contr	All activL	All Contr	Subjects n (%)	Events N	Subjects n (%)	Events N
Total Adverse Events	69	46	178	77	303	150	145	52	151	73	226 (85.6%)	846	100 (89.3%)	398
Cancer	0	0	0	0	2	0	1	2	0	1	3 (1.1%)	3	3 (2.7%)	3
Cardiac and Vascular Total	14	4	3	1	7	3	5	2	9	2	27 (9.8%)	38	12 (10.7%)	12
• Bleeding - index procedure	• 3	• 0	• 0	• 0	• 0	• 0	• 0	• 0	• 0	• 0	• 3 (1.1%)	• 3	• 0 (0.0%)	• 0
• DVT - index procedure	• 1	• 0	• 2	• 0	• 0	• 0	• 0	• 0	• 0	• 0	• 3 (1.1%)	• 3	• 0 (0.0%)	• 0
• Thrombosis	• 0	• 0	• 1	• 0	• 1	• 0	• 0	• 0	• 0	• 0	• 2 (0.8%)	• 2	• 0 (0.0%)	• 0
• Arterial dissection	• 0	• 0	• 0	• 1	• 0	• 0	• 0	• 0	• 0	• 0	• 0 (0.0%)	• 0	• 1 (0.9%)	• 1
• Iliac vessel tear - index procedure	• 4	• 1	• 0	• 0	• 0	• 0	• 0	• 0	• 0	• 0	• 4(1.5%)	• 4	• 1 (0.9%)	• 1
• Iliac vessel tear – SSI procedure	• 0	• 0	• 0	• 0	• 0	• 0	• 1	• 0	• 1	• 0	• 2 (0.8%)	• 2	• 0 (0.0%)	• 0
• Other	• 6	• 3	• 0	• 0	• 6	• 3	• 4	• 2	• 8	• 2	• 13 (4.9%)	• 24	• 10 (8.9%)	• 10
Dermatologic	1	1	2	0	1	1	2	1	1	0	7 (2.7%)	7	3 (2.7%)	3
Device Deficiency Total	1	2	3	2	3	2	0	0	0	1	7 (2.7%)	7	7 (6.3%)	7
• Implant Expulsion	• 0	• 0	• 0	• 0	• 0	• 1	• 0	• 0	• 0	• 0	• 0 (0.0%)	• 0	• 1 (0.9%)	• 1
• Implant Malposition	• 1	• 1	• 0	• 1	• 1	• 0	• 0	• 0	• 0	• 0	• 2 (0.8%)	• 2	• 2 (1.8%)	• 2
• Implant Migration	• 0	• 0	• 0	• 0	• 1	• 0	• 0	• 0	• 0	• 1	• 1 (0.4%)	• 1	• 1 (0.9%)	• 1
• Implant Subsidence	• 0	• 1	• 3	• 1	• 1	• 1	• 0	• 0	• 0	• 0	• 4 (1.5%)	• 4	• 3 (2.7%)	• 3
Endocrine	0	1	1	0	2	0	3	0	6	1	12 (4.5%)	12	2 (1.8%)	2
Eyes/Ears/Nose/Throat (EENT)	0	1	2	0	3	2	0	1	2	2	7 (2.7%)	7	6 (5.4%)	6
Gastrointestinal	8	5	16	8	13	6	20	4	9	6	51 (19.3%)	66	23 (20.5%)	29
Genitourinary Total	12	7	16	5	14	9	10	3	19	4	59 (22.3%)	71	24 (21.4)	28
• Erectile or Sexual Dysfunction	• 2	• 1	• 0	• 0	• 2	• 1	• 0	• 0	• 1	• 0	• 5 (1.9%)	• 5	• 2 (1.8%)	• 2
• Retrograde Ejaculation	• 1	• 1	• 2	• 2	• 2	• 0	• 1	• 0	• 0	• 0	• 6 (2.3%)	• 6	• 3 (2.7%)	• 3
• Other	• 9	• 5	• 14	• 3	• 10	• 8	• 9	• 3	• 18	• 4	• 48 (18.2%)	• 60	• 19 (17.0%)	• 23
Hepatobiliary	0	0	1	0	2	1	3	0	1	1	7 (2.7%)	7	2 (1.8%)	2
Immunological	1	1	4	0	4	2	3	2	5	4	16 (6.1%)	17	6 (5.4%)	9
Metabolic/Blood/Electrolytes	2	2	3	2	4	4	2	1	3	2	14 (5.3%)	14	10 (8.9%)	11
Musculoskeletal – Lumbar Total	0	3	5	2	16	4	6	1	6	4	30 (11.4%)	33	14 (12.5%)	14
• Bone Fracture-Adjacent Vertebra	• 0	• 1	• 0	• 0	• 1	• 0	• 0	• 0	• 0	• 0	• 1 (0.4%)	• 1	• 1 (0.9%)	• 1
• Degenerative Joint Disease	• 0	• 0	• 1	• 0	• 3	• 0	• 1	• 0	• 2	• 0	• 7 (2.7%)	• 7	• 0 (0.0%)	• 0
• Joint or Muscle	• 0	• 0	• 1	• 0	• 3	• 3	• 0	• 1	• 2	• 0	• 6 (2.3%)	• 6	• 4 (3.6%)	• 4
• Spasms – Lumbar/Buttock/Leg	• 0	• 2	• 2	• 2	• 8	• 0	• 3	• 0	• 1	• 0	• 14 (5.3%)	• 14	• 4 (3.6%)	• 4
• Radiographic Observation	• 0	• 0	• 0	• 0	• 0	• 0	• 0	• 0	• 1	• 2	• 1 (0.4%)	• 1	• 2 (1.8%)	• 2
• DDD Progression Adjacent	• 0	• 0	• 0	• 0	• 0	• 1	• 1	• 0	• 0	• 1	• 1 (0.4%)	• 1	• 2 (1.8%)	• 2
• Scoliosis	• 0	• 0	• 0	• 0	• 0	• 0	• 0	• 0	• 0	• 1	• 0 (0.0%)	• 0	• 1 (0.9%)	• 1
• Spinal Stenosis - Index	• 0	• 0	• 1	• 0	• 1	• 0	• 1	• 0	• 0	• 0	• 3 (1.1%)	• 3	• 0 (0.0%)	• 0
Musculoskeletal - Non-Lumbar	3	4	12	7	52	20	26	6	30	11	92 (34.8%)	124	39 (34.8%)	48

Adverse Event	Intra-Op**		Peri-Op (up to 6wks)		Short Term (>6wks-12mo)		Long Term (>12mo-24mo)		Longer Term (>24mo)		All activL (N=264)		All Control (N=112)	
	All activL	All Contr	All activL	All Contr	All activL	All Contr	All activL	All Contr	All activL	All Contr	Subjects n (%)	Events N	Subjects n (%)	Events N
Neurological - lumbar/lower extremity	7	1	18	13	31	14	4	2	2	3	44 (16.7%)	62	23 (20.5%)	33
• Motor Deficit	• 3	• 0	• 3	• 6	• 9	• 4	• 1	• 0	• 0	• 0	• 12 (4.5%)	• 16	• 7 (6.3%)	• 10
Persistent, Unilateral	*0*	*0*	*1*	*0*	*1*	*0*	*0*	*0*	*0*	*0*	*2 (0.8%)*	*2*	*0 (0.0%)*	*0*
Subjective, Bilateral	*0*	*0*	*0*	*0*	*1*	*0*	*0*	*0*	*0*	*0*	*1 (0.4%)*	*1*	*0 (0.0%)*	*0*
Subjective, Unilateral	*2*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*2 (0.8%)*	*2*	*0 (0.0%)*	*0*
Transient, Bilateral	*0*	*0*	*0*	*0*	*1*	*0*	*0*	*0*	*0*	*0*	*1 (0.4%)*	*1*	*0 (0.0%)*	*0*
Transient, Unilateral	*1*	*0*	*2*	*6*	*6*	*4*	*1*	*0*	*0*	*0*	*6 (2.3%)*	*10*	*7 (6.3%)*	*10*
• Nerve Root or Spinal Cord Injury	• 1	• 0	• 0	• 0	• 0	• 0	• 0	• 0	• 0	• 0	• 1 (0.4%)	• 1	• 0 (0.0%)	• 0
• Reflex Change or Abnormality	• 0	• 0	• 1	• 0	• 4	• 1	• 0	• 0	• 1	• 0	• 5 (1.9%)	• 6	• 1 (0.9%)	• 1
• Sensory Deficit	• 2	• 1	• 14	• 7	• 18	• 8	• 3	• 2	• 1	• 3	• 30 (11.4%)	• 38	• 18 (16.1%)	• 21
Measureable, Bilateral	*0*	*0*	*1*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*1 (0.4%)*	*1*	*0 (0.0%)*	*0*
Measureable, Unilateral	*1*	*0*	*8*	*3*	*12*	*5*	*0*	*0*	*0*	*1*	*16 (6.1%)*	*21*	*8 (7.1%)*	*9*
Subjective, Bilateral	*0*	*0*	*3*	*4*	*3*	*1*	*1*	*2*	*0*	*0*	*7 (2.7%)*	*7*	*7 (6.3%)*	*7*
Subjective, Unilateral	*1*	*1*	*2*	*0*	*3*	*2*	*2*	*0*	*1*	*2*	*8 (3.0%)*	*9*	*4 (3.6%)*	*5*
• Straight Leg Raise + or Change	• 1	• 0	• 0	• 0	• 0	• 1	• 0	• 0	• 0	• 0	• 1 (0.4%)	• 1	• 1 (0.9%)	• 1
Neurological - Non-lumbar/Lower Extremity	2	1	4	0	11	7	7	2	4	6	27 (10.2%)	28	15 (13.4%)	16
Pain - Lumbar & Lower Extremity Total	11	8	55	21	76	42	29	12	29	13	142 (53.8%)	200	68 (60.7%)	96
• Lower Extremity Pain Only	• 6	• 3	• 36	• 9	• 21	• 11	• 11	• 5	• 5	• 4	• 68 (25.8%)	• 79	• 24 (21.4%)	• 32
Bilateral Lower Leg	*1*	*2*	*9*	*3*	*6*	*3*	*3*	*1*	*2*	*1*	*18 (6.8%)*	*21*	*10 (8.9%)*	*10*
Bilateral Upper Leg	*0*	*0*	*4*	*2*	*5*	*1*	*3*	*1*	*1*	*2*	*13 (4.9%)*	*13*	*5 (4.5%)*	*6*
Unilateral Lower Leg	*5*	*1*	*21*	*4*	*4*	*5*	*4*	*2*	*2*	*1*	*35 (13.3%)*	*36*	*11 (9.8%)*	*13*
Unilateral Upper Leg	*0*	*0*	*2*	*0*	*6*	*2*	*1*	*1*	*0*	*0*	*9 (3.4%)*	*9*	*3 (2.7%)*	*3*
• Lumbar Pain Only	• 4	• 2	• 7	• 5	• 32	• 19	• 12	• 6	• 14	• 6	• 59 (22.3%)	• 69	• 37 (33.0%)	• 38
• Lumbar and Lower Extremity Pain	• 1	• 3	• 12	• 7	• 23	• 12	• 6	• 1	• 10	• 3	• 48 (18.2%)	• 52	• 24 (21.4%)	• 26
Lumbar & Bilat. Radiation Lower Leg	*1*	*1*	*5*	*3*	*10*	*7*	*0*	*0*	*6*	*1*	*21 (8.0%)*	*22*	*10 (8.9%)*	*12*
Lumbar & Bilat. Radiation Upper Leg	*0*	*1*	*1*	*0*	*4*	*2*	*1*	*0*	*0*	*0*	*5 (1.9%)*	*6*	*3 (2.7%)*	*3*
Lumbar & Unilat. Radiation Lower Leg	*0*	*1*	*6*	*4*	*8*	*3*	*3*	*1*	*3*	*2*	*18 (6.8%)*	*20*	*11 (9.8%)*	*11*
Lumbar & Unilat. Radiation Upper Leg	*0*	*0*	*0*	*0*	*1*	*0*	2	*0*	*1*	*0*	*4 (1.5%)*	*4*	*0 (0.0%)*	*0*
Psychosocial	2	1	3	0	12	9	7	1	3	1	23 (8.7%)	27	12 (10.7%)	12
Respiratory	1	1	3	1	6	2	5	4	4	4	17 (6.4%)	19	10 (8.9%)	12
Trauma	0	1	10	2	38	19	12	7	17	7	53 (20.1%)	77	27 (24.1%)	36
Uncoded	1	1	0	0	0	0	0	0	0	0	1 (0.4%)	1	1 (0.9%)	1

Adverse Event	Intra-Op**		Peri-Op (up to 6wks)		Short Term (>6wks-12mo)		Long Term (>12mo-24mo)		Longer Term (>24mo)		All activL (N=264)		All Control (N=112)	
	All activL	All Contr	All activL	All Contr	All activL	All Contr	All activL	All Contr	All activL	All Contr	Subjects n (%)	Events N	Subjects n (%)	Events N
Wound Issue - Index Procedure Total	3	1	17	13	5	3	0	1	1	0	25 (9.5%)	26	17 (15.2%)	18
• Abscess	• 0	• 0	• 3	• 2	• 2	• 0	• 0	• 0	• 0	• 0	• 5 (1.9%)	• 5	• 2 (1.8%)	• 2
• Deep	• 0	• 0	• 1	• 0	• 0	• 0	• 0	• 0	• 0	• 0	• 1 (0.4%)	• 1	• 0 (0.0%)	• 0
• Dehiscence	• 0	• 0	• 2	• 3	• 0	• 0	• 0	• 0	• 0	• 0	• 2 (0.8%)	• 2	• 3 (2.7%)	• 3
• Dural Injury/Tears/CSF Leaks	• 2	• 0	• 0	• 0	• 0	• 0	• 0	• 0	• 0	• 0	• 2 (0.8%)	• 2	• 0 (0.0%)	• 0
• Erythema/Drainage/Inflammation	• 0	• 0	• 2	• 3	• 0	• 1	• 0	• 0	• 0	• 0	• 2 (0.8%)	• 2	• 4 (3.6%)	• 4
• Incisional Hernia	• 0	• 0	• 0	• 1	• 0	• 0	• 0	• 1	• 1	• 0	• 1 (0.4%)	• 1	• 2 (1.8%)	• 2
• Incisional Cellulitis	• 0	• 0	• 2	• 0	• 1	• 0	• 0	• 0	• 0	• 0	• 3 (1.1%)	• 3	• 0 (0.0%)	• 0
• Pain at Incision Site	• 1	• 1	• 1	• 2	• 1	• 1	• 0	• 0	• 0	• 0	• 3 (1.1%)	• 3	• 4 (3.6%)	• 4
• Suture Reaction	• 0	• 0	• 1	• 1	• 1	• 0	• 0	• 0	• 0	• 0	• 2 (0.8%)	• 2	• 1 (0.9%)	• 1
• Wound Infection	• 0	• 0	• 5	• 1	• 0	• 1	• 0	• 0	• 0	• 0	• 5 (1.9%)	• 5	• 1 (0.9%)	• 2

* This table includes all monitored adverse events for all subjects (randomized and non-randomized investigational and control) as of April 11, 2013.

**The Intra-Op timepoint includes all adverse events which occurred through the discharge date. This includes 18 events (5 activL, 13 Control) which occurred prior to surgery or have an unknown onset date.

SSI = subsequent surgical intervention

Table 13: Adverse Event Categories and Subcategories Used by the CEC

Adverse Event	Definition
Cancer	Includes cases of Breast Cancer, Colon Cancer, Hodgkin's Lymphoma, Prostate Cancer, and Vulvar Cancer.
Cardiac and Vascular	
• Bleeding - index procedure	• Blood loss requiring intervention due to index study procedure.
• DVT - index procedure	• Blood clot formation in one or more vein, usually in the legs, causing pain, swelling, warmth, or changes in skin color due to the index study procedure.
• Thrombosis	• Blood clot in a vein or artery which can partially or completely block the flow of blood in a vessel.
• Arterial dissection	• Tear within the wall of a blood vessel, which allows blood to separate the wall layers.
• Iliac vessel tear - index procedure	• Tear or rupture of the iliac vessel due to the index procedure.
• Iliac vessel tear – SSI procedure	• Tear or rupture of the iliac vessel due to an SSI procedure.
• Other	The cardiac and vascular total also includes the following subcategories which are not listed in detail: bleeding requiring intervention - other (not due to the index or a SSI procedure), hypertension, hypotension, syncope/fainting, arrhythmia/irregularities, cardiac chest pain, coronary artery/heart disease, myocardial infarct/heart attack, pulmonary embolism (non-index procedure or spontaneous), aneurysm, atherosclerosis, and ecchymosis.
Dermatologic	Any condition of the skin (e.g., skin problems -rash, wart, skin virus/infection -shingles, Lyme disease). If condition is around surgical site, code to Wound Issue.
Device Deficiency	
• Implant Expulsion	• Occurs when the device is expelled from the original location.
• Implant Malposition	• Malposition of the device after implant.
• Implant Migration	• Evaluated as AP slippage of the device component(s) parallel to the vertebral endplates (movement of implanted device from original position). Includes Subluxation at Index level.
• Implant Subsidence	• Evaluated as sinking of the device component(s) into the cranial or caudal vertebral endplates.

Adverse Event	Definition
Endocrine	Includes adrenal gland disorders, decreased levels of testosterone in the blood, diabetes mellitus (types I, II, and unknown), gestational diabetes, and thyroid disorders (goiter, hyperthyroidism, and hypothyroidism).
Eyes/Ears /Nose/Throat (EENT)	Any condition of the ears, eyes, nose, throat, or mouth (e.g., ear infection, corneal abrasion, cataracts, eye infection, blurry vision, eyelid blepharoplasty, epistaxis, strep throat, oral herpes, oral candidiasis, nose bleed, oral thrush).
Gastrointestinal	Includes abdominal adhesions, abdominal pain, acid reflux, Barrett's Esophagus, decreased appetite/weight loss, dyspepsia/indigestion, esophageal bleeding, esophagitis, food poisoning, GERD, gastric lesions, gastritis, gastroenteritis/stomach flu, gastrointestinal infection, narcotic bowel syndrome, peptic ulcer, peritonitis, weight gain, appendicitis, bowel irregularity, bowel obstruction/ileus, constipation, diverticulitis, hiatal hernia, inflammatory bowel syndrome, nausea/vomiting/diarrhea, and gastrointestinal procedures (colonoscopy and hernia repair).
Genitourinary • Erectile or Sexual Dysfunction • Retrograde Ejaculation • Other	 • Occurs when a man can no longer get or keep an erection firm enough for sexual intercourse and/or persistent, recurrent problems with sexual response or desire in both males and females. • Occurs when semen enters the bladder instead of emerging through the penis during orgasm. • The genitourinary total also includes the following subcategories which are not listed in detail: decreased urine output/oliguria, kidney problems – other (including renal failure), kidney stone, benign prostatic hypertrophy, prostatitis, abnormal pap smear results, breast cyst/mass/tumor not indicated as cancerous, breast implant leakage, cystocele/prolapsed bladder, epididymitis, inguinal or testicular pain, irregular menstrual bleeding, menopause, nipple discharge, ovarian or uterine cyst/mass/tumor not indicated as cancerous, pregnancy/delivery, rectocele/posterior prolapse, vaginal or yeast infection, bladder infection, hematuria, urinary incontinence, painful urination/dysuria, pelvic pain, urinary hesitance, urinary retention, urinary tract infection, urinary urgency, and genitourinary procedures (breast reduction or enhancement, hysterectomy, and lumpectomy).
Hepatobiliary	Includes cholecystectomy, cholecystitis, cholelithiasis/gallstones, cirrhosis, liver fibrosis, and liver lesion.
Immunological	Includes systemic allergic reaction (both index or SSI procedure and non-index or SSI procedure), seasonal allergies, suture reaction (non-index or SSI procedure), Sjogren's syndrome, chills or night sweats, fever or pyrexia (index or SSI procedure), abscess (non-index or SSI procedure), cellulitis (non-index or SSI procedure), musculoskeletal wound infection (not at site of index level procedure or SSI), and Raynaud's Phenomenon.
Metabolic/Blood /Electrolytes	Includes abnormal blood chemistry, anemia, hypoxemia, dehydration, lower extremity edema, other edema, hypercholesterolemia, lymphadenopathy, and vitamin deficiency.
Musculoskeletal – Lumbar • Fracture-Adjacent Vertebra • Degenerative Joint Disease • Joint or Muscle • Spasms – Lumbar/Buttock/Leg • Radiographic Observation • DDD Progression Adjacent • Scoliosis • Spinal Stenosis - Index	 • Fracture of the vertebra surrounding the device location including posterior rim. Example - index procedure = L4-L5, adjacent vertebrae = L4 OR L5. • Includes ankylosing spondylitis, arthropathy, facet joint deterioration – index level, inflammatory polyarthritis, rheumatoid arthritis. • Includes benign mass/tumor – lumbar, joint sprain – lumbar, and pulled or strained muscle or muscle cramp – lumbar. • Persistent increased tension and shortness in a muscle or group of muscles in the lumbar back, buttock or leg that cannot be released voluntarily. Code to muscle spasm if noted as any combination of muscle spasm and pain; only exception is if described as radicular pain - code to pain. If only back spasm is specified, conservatively code to lumbar. • Includes disc herniation – adjacent and trabecular bone bridging or heterotopic ossification – index level • Condition in which pain is caused from a damaged disc at an adjacent level. • Abnormal curving of the lumbar spine. • Narrowing of the spinal column that causes pressure on the spinal cord at the index level.
Musculoskeletal - Non-Lumbar	Includes medullary canal erosion, bone fracture, arthritis, arthropathy, plantar fasciitis, foot problem – other, benign mass/tumor – non-lumbar, bursitis, ganglion cyst, gout, hallux rigidus, hiccups, hip joint pain/discomfort, inflammation of muscle, joint sprain – non-lumbar, leg length discrepancy, piriformis syndrome, pulled or strained muscle or muscle cramp – non-lumbar, restless leg syndrome, SI joint pain and discomfort, surgical procedure of a joint (e.g., shoulder/rotator cuff, hip, knee surgery and/or repair),

Adverse Event	Definition
	torn meniscus or hip labral tear, trigger finger or stenosing tenosynovitis, muscle spasms non-lumbar, pain or discomfort non-lumbar or leg (ankle only, back and upper extremities, fibromyalgia, foot only, knee only, neck or cervical, thoracic upper and mid back only, upper extremities), radiographic observation non-lumbar (disc bulge or protrusion non-lumbar or disc herniation non-lumbar), and degenerative disc disease progression non-lumbar.
Neurological • Motor Deficit *Persistent, Unilateral* *Subjective, Bilateral* *Subjective, Unilateral* *Transient, Bilateral* *Transient, Unilateral* • Nerve Root or Spinal Cord Injury • Reflex Change or Abnormality • Sensory Deficit *Measureable, Bilateral* *Measureable, Unilateral* *Subjective, Bilateral* *Subjective, Unilateral* • Straight Leg Raise + or Change	 *Measurable decrease of motor deficit unilaterally lasting > ~2 years.* *Functional weakness reported in bilateral lower extremities with no score changes.* *Functional weakness reported in unilateral lower extremity with no score changes.* *Measurable decrease of motor deficit bilaterally lasting ≤~2 years.* *Measurable decrease of motor deficit unilaterally lasting ≤~2 years.* • Damage to any part of the spinal cord or nerves at the end of the spinal canal, often causing permanent changes in strength, sensation and other body functions below the site of the injury. • Change or abnormal reflexes (e.g., patellar and Achilles); includes both unilateral or bilateral changes and/or abnormalities. *Paresthesia and dysesthesia descriptors of tingling, numbness, burning, sensitivity/hypersensitivity. Measurable decrease of sensory deficit in bilateral lower extremities. Test scores-pin test (e.g., L5/S1 dermatome) indicate measurable deficit.* *Paresthesia and dysesthesia descriptors of tingling, numbness, burning, sensitivity/hypersensitivity. Measurable decrease of sensory deficit in unilateral lower extremity. Test scores-pin test (e.g., L5/S1 dermatome) indicate measurable deficit.* *Reported sensory deficit in bilateral lower extremities with no score changes. Includes paresthesia and dysesthesia terms such as numbness, tingling, sensitivity/ hypersensitivity, burning.* *Reported sensory deficit in unilateral lower extremity with no score changes.* • Positive measurement or change in straight leg raise, includes both unilateral and bilateral changes.
Neurological - Non-lumbar/Lower Extremity	Includes Bell's Palsy, brain tumor, dysphagia/difficulty swallowing, forgetfulness/memory loss, headache, loss of consciousness, migraine, multiple sclerosis, nerve entrapment, numbness or tingling, restlessness or agitation, seizure, tremor, vertigo or dizziness, carpal tunnel syndrome, peripheral neuropathy, upper extremity motor deficit, upper extremity sensory deficit.
Pain - Lumbar and Lower Extremity • Lower Extremity Pain Only *Bilateral Lower Leg* *Bilateral Upper Leg* *Unilateral Lower Leg* *Unilateral Upper Leg* • Lumbar Pain Only • Lumbar and Lower Extremity Pain *Lumbar & Bilat. Radiation Lower Leg* *Lumbar & Bilat. Radiation Upper Leg* *Lumbar & Unilat. Radiation Lower Leg* *Lumbar & Unilat. Radiation Upper Leg*	 *Bilateral lower leg pain.* *Bilateral upper leg pain.* *Unilateral lower leg pain.* *Unilateral upper leg pain.* • Includes low back, lumbar or non-specified back pain. Also includes post-procedural pain unless incisional site is specifically indicated. Thoracic pain is coded to musculoskeletal non-lumbar. Mid and upper back pain only are coded to Thoracic pain in Musculoskeletal Non-Lumbar. *Pain in the lumbar area with radiation to the bilateral lower legs.* *Pain in the lumbar area with radiation to the bilateral upper legs.* *Pain in the lumbar area with radiation to the unilateral lower leg.* *Pain in the lumbar area with radiation to the unilateral upper leg.*
Psychosocial	Includes anxiety disorders, bipolar disorder or manic episode, conversion disorder, depressive disorders, suicidal ideation or attempt, suicide, fatigue or sleepiness or somnolence, insomnia, and substance dependence or withdrawal.
Respiratory	Includes shortness of breath/dyspnea, sleep apnea, cough, bronchitis, COPD, hemoptysis, lung problems – other, pneumonia, reactive airway disease, respiratory infection, sinus infection/sinusitis, and sinus problems – other.

Adverse Event	Definition
Trauma	Includes fall/trip/slip/twist, injury other, and motor vehicle accident.
Wound Issue - Index Procedure Total	
• Abscess	• Painful mass (collection of pus) causing swelling and inflammation, often adjacent to the surgical incision of the index procedure; including stitch abscesses.
• Deep	• Seroma, fluid packet, hematoma (localized collection of blood outside the blood vessels), with or without bleeding intervention.
• Dehiscence	• Rupture along the incision line of the index procedure wound; including major or minor dehiscence.
• Dural Injury/Tear or CSF Leak	• Any injury tear, or leak of the dura caused by or occurring during the index procedure.
• Erythema/Drainage/Inflammation	• Adverse events that have a combination of two or three of the following criteria (erythema, drainage, inflammation), or just one criterion if the adverse event involves the index procedure wound.
• Incisional Hernia	• Hernia caused by an incompletely-healed index procedure wound.
• Incisional Cellulitis	• Common, potentially serious bacterial skin infection along the index procedure incision appearing as swollen, red skin that is hot or tender.
• Pain at Incision Site	• Also includes terms such as irritation. Note for pain with drainage, code to drainage. Pain also includes term such as irritation.
• Suture Reaction	• Any reaction to the suture used during the index procedure.
• Wound Infection	• Any wound infection, with the wound identified being the index study procedure wound that gets infected. All other infections get coded within specific body system.

SSI = subsequent surgical intervention

When adverse events in the randomized treatment groups were compared, although p-values were obtained without any adjustment for multiplicity, there were no statistically significant differences between the two randomized treatment groups in the total number of adverse events or the number of adverse events in any category other than lumbar pain only in which the difference favored the activL group.

Table 15 provides data on the number of adverse events in each category in each randomized treatment group stratified by device design and level treated for the randomized activL group, and by control device and level treated for the randomized control group. In the activL group, more events occurred in subjects treated with the keel device than the spike device. In the control group, more events occurred in subjects treated with ProDisc-L than with the Charité device. In both treatment groups, more events occurred at the L5-S1 level than the L4-L5 though the difference was greater in the randomized activL group (activL: 526 vs 175; control: 250 vs 116).

Table 15: Adverse Events by Category - Stratified

Adverse Event (AE)	R activL (N=218)				R Contr (N=106)			
	Device Design		Treatment Level		Control Device		Treatment Level	
	Spike (N=115)	Keel (N=102)	L4-L5 (N=62)	L5-S1 (N=156)	ProDisc-L (N=65)	Charité (N=41)	L4-L5 (N=34)	L5-S1 (N=72)
Total Subjects with an AE (%)	96 (83.5%)	89 (87.3%)	51 (82.3%)	135 (86.5%)	58 (90.6%)	36 (87.8%)	34 (100%)	61 (84.7%)
Total Number of AEs	305	391	175	526	235	129	116	250
Cancer	1	0	0	1	3	0	0	3
Cardiac & Vascular	14	15	9	20	7	5	4	8
• Bleeding requiring intervention - index procedure	• 3	• 0	• 2	• 1	• 0	• 0	• 0	• 0
• DVT - index study procedure	• 0	• 2	• 2	• 0	• 0	• 0	• 0	• 0
• Thrombosis	• 2	• 0	• 0	• 2	• 0	• 0	• 0	• 0
• Arterial dissection	• 0	• 0	• 0	• 0	• 0	• 1	• 1	• 0
• Iliac vessel tear - index study procedure	• 2	• 0	• 0	• 2	• 0	• 1	• 0	• 1
• Iliac vessel tear – SSI procedure	• 1	• 1	• 0	• 2	• 0	• 0	• 0	• 0
• Other	• 6	• 12	• 5	• 13	• 7	• 3	• 3	• 7
Dermatologic	2	4	1	5	3	0	1	2
Device Deficiency	5	2	2	5	5	2	2	5
• Implant Expulsion	• 0	• 0	• 0	• 0	• 1	• 0	• 0	• 1
• Implant Malposition	• 1	• 1	• 0	• 2	• 2	• 0	• 1	• 1
• Implant Migration	• 1	• 0	• 0	• 1	• 1	• 0	• 0	• 1
• Implant Subsidence	• 3	• 1	• 2	• 2	• 1	• 2	• 1	• 2
Endocrine	3	7	3	7	1	1	0	2
Eyes/Ears/Nose/Throat	2	2	1	3	5	1	2	4
Gastrointestinal	25	33	17	41	18	9	6	21
Genitourinary	26	36	14	48	12	12	5	19
• Erectile/Sexual Dysfunction	• 2	• 1	• 0	• 3	• 1	• 1	• 0	• 2
• Retrograde Ejaculation	• 3	• 2	• 0	• 5	• 1	• 2	• 0	• 3
• Other	• 21	• 33	• 14	• 40	• 10	• 9	• 5	• 14
Hepatobiliary	3	3	0	6	2	0	1	1
Immunological	4	6	2	8	4	2	1	5
Metabolic/Blood/ Electrolytes	2	8	4	6	6	4	6	4
Musculoskeletal – Lumbar	9	16	6	19	11	2	6	8
• Bone Fracture-Adjacent Vertebra	• 1	• 0	• 0	• 1	• 0	• 0	• 0	• 1
• Degenerative Joint Disease	• 3	• 4	• 1	• 6	• 0	• 0	• 0	• 0
• Joint or Muscle	• 2	• 2	• 0	• 4	• 3	• 1	• 2	• 2
• Muscle spasms – Lumbar/Buttock/Leg	• 3	• 7	• 4	• 6	• 4	• 0	• 1	• 3
• Radiographic Observation	• 0	• 0	• 0	• 0	• 2	• 0	• 1	• 1
• DDD Progression Adjacent	• 0	• 0	• 0	• 0	• 1	• 1	• 1	• 1
• Scoliosis	• 0	• 0	• 0	• 0	• 1	• 0	• 1	• 0
• Spinal Stenosis - Index	• 0	• 3	• 1	• 2	• 0	• 0	• 0	• 0
Musculoskeletal - Non-Lumbar	46	59	30	75	26	17	13	30
Neurological – Lumbar and Lower Extremities	27	22	13	38	17	15	14	18
• Motor Deficit	• 6	• 7	• 2	• 11	• 5	• 5	• 5	• 5
Persistent, Unilateral	*1*	*1*	*0*	*2*	*0*	*0*	*0*	*0*
Subjective, Bilateral	*1*	*0*	*0*	*1*	*0*	*0*	*0*	*0*
Subjective, Unilateral	*2*	*0*	*0*	*2*	*0*	*0*	*0*	*0*
Transient, Bilateral	*1*	*0*	*1*	*0*	*0*	*0*	*0*	*0*
Transient, Unilateral	*1*	*6*	*1*	*6*	*5*	*5*	*5*	*5*
• Nerve Root or Spinal Cord Injury	• 0	• 0	• 0	• 0	• 0	• 0	• 0	• 0
• Reflex Change or Abnormality	• 3	• 2	• 3	• 2	• 1	• 0	• 0	• 1
• Sensory Deficit	• 18	• 13	• 7	• 25	• 11	• 9	• 8	• 12
Measureable, Bilateral	*0*	*1*	*0*	*1*	*0*	*0*	*0*	*0*
Measureable, Unilateral	*11*	*6*	*6*	*12*	*4*	*5*	*6*	*3*
Subjective, Bilateral	*4*	*2*	*1*	*5*	*3*	*3*	*1*	*5*

Adverse Event (AE)	R activL (N=218)				R Contr (N=106)			
	Device Design		Treatment Level		Control Device		Treatment Level	
	Spike (N=115)	Keel (N=102)	L4-L5 (N=62)	L5-S1 (N=156)	ProDisc-L (N=65)	Charité (N=41)	L4-L5 (N=34)	L5-S1 (N=72)
Subjective, Unilateral	*3*	*4*	*0*	*7*	*4*	*1*	*1*	*4*
• Straight Leg Raise Test Positive or Change	0	0	1	0	0	1	1	0
Neurological - Non-lumbar and Lower Extremities	7	15	6	16	12	2	5	10
Pain - Lumbar and Lower Extremity (LE)	81	83	41	125	51	38	26	63
• LE Pain Only	• 32	• 35	• 17	• 51	• 17	• 13	• 6	• 24
Bilateral Lower Leg	*5*	*14*	*3*	*16*	*5*	*4*	*2*	*7*
Bilateral Upper Leg	*4*	*5*	*5*	*5*	*4*	*1*	*1*	*4*
Unilateral Lower Leg	*18*	*13*	*7*	*24*	*6*	*7*	*2*	*11*
Unilateral Upper Leg	*5*	*3*	*2*	*6*	*2*	*1*	*1*	*2*
• Lumbar Pain Only	• 27	• 29	• 8	• 48	• 19	• 17	• 11	• 25
• Lumbar and LE Pain	• 22	• 19	• 16	• 26	• 15	• 8	• 9	• 14
Lumbar & Bilat. Radiation Lower Leg	*10*	*6*	*6*	*11*	*7*	*3*	*5*	*5*
Lumbar & Bilat. Radiation Upper Leg	*2*	*4*	*1*	*5*	*2*	*1*	*0*	*3*
Lumbar & Unilat. Radiation Lower Leg	*7*	*8*	*8*	*7*	*6*	*4*	*4*	*6*
Lumbar & Unilat. Radiation Upper Leg	*3*	*1*	*1*	*3*	*0*	*0*	*0*	*0*
Psychosocial	7	18	4	22	9	2	4	7
Respiratory	8	8	2	14	7	3	4	6
Trauma	20	42	16	46	24	8	13	19
Uncoded	0	0	0	0	0	1	0	1
Wound Issue - Index Procedure	13	12	4	21	12	5	3	14
• Abscess	• 3	• 2	• 1	• 4	• 2	• 0	• 0	• 2
• Deep	• 0	• 1	• 0	• 1	• 0	• 0	• 0	• 0
• Dehiscence	• 1	• 1	• 0	• 2	• 2	• 1	• 1	• 2
• Dural Injuries/Tears/CSF Leaks	• 1	• 1	• 0	• 2	• 0	• 0	• 0	• 0
• Erythema/Drainage/Inflammation	• 0	• 2	• 0	• 2	• 3	• 1	• 1	• 3
• Incisional Hernia	• 1	• 0	• 1	• 0	• 1	• 1	• 0	• 2
• Incisional Cellulitis	• 2	• 1	• 1	• 2	• 0	• 0	• 0	• 0
• Pain at Incision Site	• 2	• 0	• 1	• 1	• 3	• 0	• 1	• 2
• Suture Reaction	• 1	• 1	• 0	• 2	• 1	• 0	• 0	• 1
• Wound Infection	• 2	• 3	• 0	• 5	• 0	• 2	• 0	• 2

SSI=subsequent surgical intervention

One randomized activL subject died 146 days after surgery of hypertrophic heart disease with the effects of multiple drugs as contributing factors. The CEC adjudicated the event as death from suicide, and they determined it was not related to the activL device.

Some adverse events resulted in surgical intervention at the index level, subsequent to the initial surgery. Subsequent surgical interventions (SSIs), classified as revisions, removals, reoperations, or supplemental fixation procedures at the index level were study failures. There were 21 subsequent surgical interventions at the index level defined as revisions, removals, reoperations, or supplemental fixation procedures (activL = 15, control = 6) in 18 randomized subjects (activL = 12, control = 6); one subject had multiple interventions. The time course of the subsequent surgical procedures is summarized in Table 16. Note that there were no subsequent surgical interventions at the index level in either of the non-randomized cohorts (activL or control).

Table 16: Subsequent Surgical interventions at the Index Level

Type	Intra-Op**		Peri-Op (up to 6wks)		Short Term (>6wks-12mo)		Long Term (>12-24mo)		Longer Term (>24mo)		Total Events		Total Subjects	
	R activL	R Contr	R activL	R Contr	R activL	R Contr	R activL	R Contr	R activL	R Contr	R activL	R Contr	R activL (N=264)	R Contr (N=112)
Removal	0	0	0	0	0	1	2	0	1	1	3	2	3 (1.1%)	2 (1.8%)
Supplemental Fixation	0	0	0	0	1	0	1	0	3	1	5	1	5 (1.9%)	1 (0.9%)
Revision	0	1	0	0	0	0	0	0	0	0	0	1	0 (0%)	1 (0.9%)
Reoperation	2	0	1	0	3	1	0	1	1	0	7	2	5 (1.9%)	2 (1.8%)
Total	2	1	1	0	4	2	3	1	5	2	15	6	12 (4.5%)*	6 (5.4%)

*The total reported in the table is the sum of each of the rows; however, there are subjects who had multiple intervention types at the index level (i.e., the rows are not mutually exclusive). Therefore, there are actually 12 activL subjects and 6 control subjects who had a removal, reoperation, revision and/or supplemental fixation at the index level; one of these subjects had multiple interventions so is noted twice in the "total" row.

** The intra-op timepoint includes all subsequent surgical interventions which occurred through the discharge date.

Table 17 provides data on the number of subsequent surgical interventions at the index level in each randomized treatment group stratified by device design and level treated for the randomized activL group and control device and level treated for the randomized control group.

Table 17: Subsequent Surgical interventions at the Index Level – Stratified

Type	R activL (N=218)				R Contr (N=106)			
	Device Design		Treatment Level		Control Device		Treatment Level	
	Spike (N=115)	Keel (N=102)	L4-L5 (N=62)	L5-S1 (N=156)	ProDisc-L (N=65*)	Charité (N=41)	L4-L5 (N=34)	L5-S1 (N=72)
Removal	2 events (2 subjects)	1 event (1 subject)	0	3 events (3 subjects)	1 event (1 subject)	1 event (1 subject)	0	0
Supplemental Fixation	4 events (4 subjects)	1 event (1 subject)	3 events (3 subjects)	2 events (2 subjects)	0	1 event (1 subject)	0	1 event (1 subject)
Revision	0	0	0	0	1 event (1 subject)	0	1 event (1 subject)	0
Reoperation	1 event (1 subject)	6 events (4 subjects)	3 events 2 subjects)	4 events (3 subjects)	1 event (1 subject)	1 event (1 subject)	1 event (1 subject)	1 event (1 subject)
Total	7 events (7 subjects)	8 events (6 subjects)	6 events (5 subjects)	9 events (8 subjects)	3 events (3 subjects)	3 events (3 subjects)	2 events (2 subjects)	4 events (4 subjects)

Table 18 provides detailed information on each activL subsequent surgical intervention at the index level.

Table 18: Detailed Information on activL Subsequent Surgical interventions at the Index Level*

Surgical Intervention Type	Procedure Type	Procedure Level	Adverse Event Type	activL Device Design	Days From Index Procedure	Device Removed?
Removal	Fusion	L5-S1	Pain lumbar + bilateral radiation into lower legs	Spike	608	Yes
Removal	Fusion	L5-S1	Bone fracture - adjacent vertebra	Spike	668	Yes
Removal	Fusion	L5-S1	Lumbar pain only	Keel	883	Yes
Supplemental Fixation	Fusion	L5-S1	Implant malposition	Spike	101	No
Supplemental Fixation	Fusion	L4-L5	Pain lumbar & bilateral radiation into lower legs	Spike	611	No
Supplemental Fixation	Fusion	L4-L5, L5-S1	Pain lumbar & bilateral radiation into lower legs	Spike	799	No
Supplemental Fixation	Fusion	L4-L5, L5-S1	Pain lumbar & unilateral radiation into lower legs	Keel	882	No
Supplemental Fixation	Fusion	L5-S1	Implant subsidence	Spike	1243	No
Reoperation	Foraminotomy/ decompression	L5-S1	Implant malposition	Keel	4	No
Reoperation	Other Procedure (Dural Repair)	L5-S1	Dural injury or tear or CSF leak	Keel	4	No
Reoperation	Foraminotomy/ decompression	L5-S1	Pain bilateral lower legs	Keel	55	No
Reoperation	Fusion	L5-S1	Implant malposition	Spike	101	No
Reoperation	Foraminotomy/ decompression	L4-L5	Spinal stenosis - index	Keel	112	No
Reoperation	Foraminotomy/ decompression	L4-L5	Pain unilateral lower leg	Keel	340	No
Reoperation	Foraminotomy/ decompression	Listed as L5	Pain unilateral lower leg	Keel	970	No

* As of April 11, 2013.

Detailed information regarding subsequent procedures at the index level not associated with revision, removal, reoperation, or supplemental fixation in the activL group are provided in Table 19. The majority of procedures were rhizotomy/ablation procedures.

Table 19: Detailed Information on Control Group Subsequent Surgical Interventions at the Index Level*

Surgical Intervention Type	Procedure Type	Procedure Level	Adverse Event Type	Control Device	Days From Index Procedure	Device Removed?
Removal	Fusion	L5-S1	Implant expulsion	ProDisc-L	317	Yes
Removal	Fusion	L5-S1	Implant subsidence	Charite	835	Yes
Supplemental Fixation	Fusion	L5-S1	Lumbar pain only	Charite	846	No
Revision	Reposition (study device)	L4-L5	Implant malposition	ProDisc-L	3	No
Reoperation	Foraminotomy/ decompression	L4-L5, L5-S1	Pain lumbar & bilateral radiation into lower legs	Charite	79	No
Reoperation	Foraminotomy/ decompression	L5-S1	Pain lumbar & unilateral radiation into lower legs	ProDisc-L	710	No

* As of April 11, 2013.

Per the CEC Definitions and Guidelines, device-related events were defined as those events having an etiology, temporal association, or cause that was related to the device. Based on this definition, the timecourse and total number and percentage of subjects who experienced a device-related adverse event as determined by the CEC is provided in Table 20. Three hundred eighty four (384) device-related events occurred in all subjects during the course of the trial (NR activL = 45; R activL = 217; R Contr = 114; NR Contr = 8). The proportion of randomized subjects with a device-related adverse event was slightly higher in the control group (R activL = 61.5%; R Contr = 65.1%). The difference was not statistically significant although p-values were obtained without adjustment for multiplicity. The most common device-related adverse events in both treatment groups were lower extremity pain, lumbar pain only and lumbar and lower extremity pain. Fifty seven (57) SDAEs were reported in all subjects during the course of the trial (NR activL = 4; R activL = 31; R Contr = 20; NR Contr = 2). The proportion of randomized subjects with SDAEs was higher in the control group (R activL = 12.8%; R Contr = 18.9%). The most common serious device-related adverse events in both treatment groups were lumbar and lower extremity pain.

Table 20: Time Course of Device-Related Adverse Events*

Adverse Event	Intra-Op**		Peri-Op (up to 6wks)		Short Term (>6wks-12mo)		Long Term (>12mo-24mo)		Longer Term (>24mo)		All activL (N=264)		All Control (N=112)	
	All activL	All Contr	All activL	All Contr	All activL	All Contr	All activL	All Contr	All activL	All Contr	Subjects n (%)	Events N	Subjects n (%)	Events N
Total Device-Related AEs	21	5	71	34	104	53	34	14	32	16	164 (59.21%)	262	73 (61.34%)	122
Total Serious Device-Related AEs‡											32 (11.55%)	35	21 (17.65%)	22
Cardiac and Vascular Total	5	0	0	1	0	0	0	0	0	0	5 (1.9%)	5	1 (0.8%)	1
Device Deficiency Total	0	1	3	1	2	2	0	0	0	1	5 (1.8%)	5	5 (4.2%)	5
• Implant Expulsion	• 0	• 0	• 0	• 0	• 0	• 1	• 0	• 0	• 0	• 0	• 0 (0.0%)	• 0	• 1 (0.8%)	• 1
• Implant Migration	• 0	• 0	• 0	• 0	• 1	• 0	• 0	• 0	• 0	• 1	• 1 (0.4%)	• 1	• 1 (0.8%)	• 1
• Implant Subsidence	• 0	• 1	• 3	• 1	• 1	• 1	• 0	• 0	• 0	• 0	• 4 (1.4%)	• 4	• 3 (2.5%)	• 3
Musculoskeletal – Lumbar Total	• 0	0	2	0	4	0	1	0	2	1	9 (3.3%)	9	1 (0.8%)	1
• Fracture-Adjacent Vertebra	• 0	• 0	• 0	• 0	• 1	• 0	• 0	• 0	• 0	• 0	• 1 (0.4%)	• 1	• 0 (0.0%)	• 0
• Degenerative Joint Disease	• 0	• 0	• 1	• 0	• 3	• 0	• 1	• 0	• 2	• 0	• 7 (2.7%)	• 7	• 0 (0.0%)	• 0
• Radiographic Observation	• 0	• 0	• 0	• 0	• 0	• 0	• 0	• 0	• 0	• 1	• 0 (0.0%)	• 0	• 0 (0%)	• 0
• Spinal Stenosis - Index	• 0	• 0	• 1	• 0	• 0	• 0	• 0	• 0	• 0	• 0	• 1 (0.4%)	• 1	• 0 (0.0%)	• 0
Neurological Total	4	0	11	11	22	9	4	2	1	1	33 (11.9%)	42	16 (13.5%)	23
• Motor Deficit	• 2	• 0	• 3	• 6	• 8	• 1	• 1	• 0	• 0	• 0	• 11 (3.97%)	• 14	• 4 (3.4%)	• 7
Persistent, Unilateral	*0*	*0*	*1*	*0*	*1*	*0*	*0*	*0*	*0*	*0*	*2 (0.7%)*	*2*	*0 (0.0%)*	*0*
Subjective, Bilateral	*0*	*0*	*0*	*0*	*1*	*0*	*0*	*0*	*0*	*0*	*1 (0.4%)*	*1*	*0 (0.0%)*	*0*
Subjective, Unilateral	*2*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*2 (0.7%)*	*2*	*0 (0.0%)*	*0*
Transient, Unilateral	*0*	*0*	*2*	*6*	*6*	*1*	*1*	*0*	*0*	*0*	*6 (2.2%)*	*9*	*4 (3.4%)*	*7*
• Nerve Root or Spinal Cord Injury	• 1	• 0	• 0	• 0	• 0	• 0	• 0	• 0	• 0	• 0	• 1 (0.4%)	• *1*	• 0 (0.0%)	• 0
• Sensory Deficit	• 0	• 0	• 8	• 5	• 14	• 7	• 3	• 2	• 1	• 1	• 22 (7.9%)	• 26	• 14 (11.8%)	• 15
Measureable, Bilateral	*0*	*0*	*1*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*1 (0.4%)*	*1*	*0 (0.0%)*	*0*
Measureable, Unilateral	*0*	*0*	*3*	*2*	*8*	*4*	*0*	*0*	*0*	*1*	*9 (3.3%)*	*11*	*6 (5.0%)*	*7*
Subjective, Bilateral	*0*	*0*	*3*	*3*	*3*	*1*	*1*	*2*	*0*	*0*	*7 (2.5%)*	*7*	*6 (5.0%)*	*6*
Subjective, Unilateral	*0*	*0*	*1*	*0*	*3*	*2*	*2*	*0*	*1*	*0*	*7 (2.57%)*	*7*	*2 (1.7%)*	*2*
• Straight Leg Raise + or Change	• 1	• 0	• 0	• 0	• 0	• 1	• 0	• 0	• 0	• 0	• 1 (0.4%)	• 1	• 1 (0.8%)	• 1
Pain - Lumbar and Lower Extremity Total	11	4	55	21	76	42	29	12	29	13	142 (51.3%)	200	65 (54.62%)	92
• Lower Extremity Pain Only	• 6	• 2	• 36	• 9	• 21	• 11	• 11	• 5	• 5	• 4	• 68 (25.8%)	• 79	• 23 (20.5%)	• 31
Bilateral Lower Leg	*1*	*2*	*9*	*3*	*6*	*3*	*3*	*1*	*2*	*1*	*18 (6.5%)*	*21*	*10 (8.4%)*	*10*
Bilateral Upper Leg	*0*	*0*	*4*	*2*	*5*	*1*	*3*	*1*	*1*	*2*	*13 (4.7%)*	*13*	*5 (4.2%)*	*6*
Unilateral Lower Leg	*5*	*0*	*21*	*4*	*4*	*5*	*4*	*2*	*2*	*1*	*35 (12.6%)*	*36*	*10 (8.4%)*	*12*
Unilateral Upper Leg	*0*	*0*	*2*	*0*	*6*	*2*	*1*	*1*	*0*	*0*	*9 (3.3%)*	*9*	*3 (2.5%)*	*3*
• Lumbar Pain Only	• 4	• 2	• 7	• 5	• 32	• 19	• 12	• 6	• 14	• 6	• 59 (22.3%)	• 69	• 37 (33.0%)	• 38
• Lumbar and Lower Extremity Pain	• 1	• 0	• 12	• 7	• 23	• 12	• 6	• 1	• 10	• 3	• 48 (18.2%)	• 52	• 22 (19.6%)	• 23
Lumbar & Bilat. Radiation Lower Leg	*1*	*0*	*5*	*3*	*10*	*7*	*0*	*0*	*6*	*1*	*21 (7.8%)*	*22*	*10 (8.4%)*	*11*
Lumbar & Bilat. Radiation Upper Leg	*0*	*0*	*1*	*0*	*4*	*2*	*1*	*0*	*0*	*0*	*5 (1.8%)*	*6*	*2 (1.7%)*	*2*
Lumbar & Unilat. Radiation Lower Leg	*0*	*0*	*6*	*4*	*8*	*3*	*3*	*1*	*3*	*2*	*18 (6.5%)*	*20*	*10 (8.4%)*	*10*
Lumbar & Unilat. Radiation Upper Leg	*0*	*0*	*0*	*0*	*1*	*0*	*2*	*0*	*1*	*0*	*4 (1.4%)*	*4*	*0 (0.0%)*	*0*

* This table includes all monitored adverse events for all subjects (randomized and nonrandomized investigational and control) as of April 11, 2013.

**The Intra-Op timepoint includes all device-related adverse events which occurred through the discharge date. This includes 3 events (2 activL, 1 control) which have an unknown onset date.

‡ Time point break downs for Total Serious Device-Related AEs are not available

There were 68 activL spike subjects (59.1% of subjects treated with the spike device design) who experienced a device-related adverse event as determined by the CEC as compared to 65 activL keel subjects (63.7% of subjects treated with the keel device design) who experienced a device-related adverse event as determined by the CEC. There were 16 activL spike subjects (13.9% of subject treated with the spike device design) who experienced a serious device-related adverse event as determined by the CEC as compared to 12 activL keel subject (11.8% of subjects treated with the keel device design) who experienced a serious device-related adverse event as determined by the CEC.

Considering treatment level, there were 33 activL subjects treated at L4-L5 (53.2% of activL subjects treated at L4-L5) who experienced a device-related adverse event as determined by the CEC as compared to 101 activL subjects treated at L5-S1 (64.7% of activL subjects treated at L5-S1) who experienced a device-related adverse event as determined by the CEC. There were 9 activL subjects treated at L4-L5 (14.5% of activL subjects treated at L4-L5) who experienced a serious device-related adverse event as determined by the CEC as compared to 19 activL subjects treated at L5-S1 (12.2% of activL subjects treated at L5-S1) who experienced a device-related adverse event as determined by the CEC.

The change in overall neurological status at each timepoint is provided in Table 21. If any of the motor or sensory neurological assessments deteriorated, then the overall neurological status was considered deteriorated. At 24 months, the proportion of subjects with no decline in either motor or sensory evaluations was comparable between treatment groups, and there were no statistically significant differences although p-values were obtained without any adjustment for multiplicity (motor evaluations: R activL = 97.3%, R Contr = 98.9%; sensory evaluations: R activL = 94.1%, R Contr = 93.1%).

Table 21: Time Course of Overall Neurological Status

Timepoint	Neurological Status	NR activL (N=46)	R activL (N=218)	R Contr (N=106)
6 weeks	Improved	11/45 (24.4%)	59/213 (27.7%)	31/105 (29.5%)
	Stable	29/45 (64.4%)	139/213 (65.3%)	64/105 (61.0%)
	Deteriorated	5/45 (11.1%)	15/213 (7.0%)	10/105 (9.5%)
3 months	Improved	12/45 (26.7%)	56/208 (26.9%)	29/101 (28.7%)
	Stable	27/45 (60.0%)	134/208 (64.4%)	59/101 (58.4%)
	Deteriorated	6/45 (13.3%)	18/208 (8.7%)	13/101 (12.9%)
6 months	Improved	11/45 (24.4%)	53/202 (26.2%)	26/96 (27.1%)
	Stable	31/45 (68.9%)	131/202 (64.9%)	61/96 (63.5%)
	Deteriorated	3/45 (6.7%)	18/202 (8.9%)	9/96 (9.4%)
12 months	Improved	11/41 (26.8%)	60/201 (29.9%)	27/96 (28.1%)
	Stable	27/41 (65.9%)	128/201 (63.7%)	63/96 (65.6%)
	Deteriorated	3/41 (7.3%)	13/201 (6.5%)	6/96 (6.3%)
24 months	Improved	10/41 (24.4%)	50/188 (26.6%)	24/87 (27.6%)
	Stable	28/41 (68.3%)	125/188 (66.5%)	57/87 (65.5%)
	Deteriorated	3/41 (7.3%)	13/188 (6.9%)	6/87 (6.9%)
3 years	Improved	7/37 (18.9%)	35/140 (25.0%)	22/72 (30.6%)
	Stable	26/37 (70.3%)	96/140 (68.6%)	46/72 (63.9%)
	Deteriorated	4/37 (10.8%)	9/140 (6.4%)	4/72 (5.6%)
4 years	Improved	5/19 (26.3%)	12/41 (29.3%)	5/24 (20.8%)
	Stable	11/19 (57.9%)	27/41 (65.9%)	19/24 (79.2%)
	Deteriorated	3/19 (15.8%)	2/41 (4.9%)	0/24 (0.0%)

Primary Effectiveness Results

The analysis of effectiveness was based on the mITT cohort of subjects, which consisted of all randomized, implanted subjects analyzed according to their randomization assignment (218 randomized activL, 106 randomized control, 46 non-randomized activL, 6 non-randomized control).

The individual subject success rate was defined in the IDE protocol as the number of subjects classified as a success at 24 months divided by the number of subjects treated with missing 24 month outcomes imputed as failures. Overall study success criteria were based on a comparison of individual subject success rates, such that the subject success rate for the activL investigational group was required to be non-inferior to that of the ProDisc-L/Charité control group.

The success rates at 24 months postoperative for each of the individual success components and overall success are provided in Table 22 for the randomized subjects treated in the study as well as the non-randomized activL subjects. Because the ROM success component of the primary endpoint was such a notable driver of the difference in overall success rates when comparing the two treatment groups, FDA also requested an analysis of overall success without the ROM success component. This analysis is also included. The trial was designed as a non-inferiority trial with a margin (delta) of 15%; however, additional analyses using a delta of 10% were requested by FDA. Only the 10% delta analyses are included here; 15% non-inferiority is always met for all variables demonstrating non-inferiority at 10%. According to the statistical analysis plan, if non-inferiority was demonstrated, then superiority was to be evaluated. These results are also presented.

Table 22: Overall Success at 24 Months (Missing Imputed as Failures)

Primary Endpoint Component	NR activL	R activL	R Contr	p-value*
ODI success (≥15 point improvement) 95% Confidence Interval (CI)	34/46 (73.9%) (58.9, 85.7)	164/218 (75.2%) (68.9, 80.8)	70/106 (66.0%) (56.2, 75.0)	0.0874
Neurological success (maintenance or improvement – motor & sensory evaluations) 95% CI	38/46 (82.6%) (68.6, 92.2)	175/218 (80.3%) (74.4, 85.3)	81/106 (76.4%) (67.2, 84.1)	0.4678
ROM success (maintenance or improvement) 95% CI	26/46 (56.5%) (41.1, 71.1)	128/218 (58.7%) (51.9, 65.3)	45/106 (42.5%) (32.9, 52.4)	0.0065
Device success (no SSIs at index level) 95% CI	43/46 (93.5%) (82.1, 98.6)	184/218 (84.4%) (78.9, 89.0)	90/106 (84.9%) (76.6, 91.1)	1.0000
No serious device-related AEs per CEC 95% CI	39/46 (84.8%) (71.1, 93.7)	167/218 (76.6%) (70.4, 82.1)	75/106 (70.8%) (61.1, 79.2)	0.2772
Overall success including ROM success component 95% CI P-value (difference between groups; delta = 10%) P-value (superiority)	20/46 (43.5%) (28.9, 58.9)	92/218 (42.2%) (35.6, 49.1)	30/106 (28.3%) (20.0, 37.9)	 <0.0001 0.0200
Overall success without ROM success component 95% CI P-value (difference between groups; delta = 10%) P-value (superiority) R activL vs. R Contr	30/46 (65.2%) (49.8, 78.6)	135/218 (61.9%) (55.1, 68.4)	56/106 (52.8%) (42.9, 62.6)	 0.0004 0.1485

* Difference between randomized groups
SSI = subsequent surgical intervention

Regarding the overall success rate at 24 months (missing imputed as failures), in randomized subjects, activL was found to be non-inferior to control for the analysis of overall success both with and without the ROM success component (p value <0.0001 for both 15% and 10% margins).

Analysis of overall success was also performed based on observed data (missing data not included as failures) as presented in Table 23 for the randomized subjects treated in the study as well as the non-randomized activL subjects both with and without the ROM success component. Similar to the missing imputed as failures analysis, in randomized subjects, activL was found to be non-inferior to the control for the analysis of overall success both with and without the ROM success components based on observed data (p value <0.0001 for both 15% and 10% margins).

Table 23: Overall Success at 24 Months (Observed)

Primary Endpoint Component	NR activL	R activL	R Contr	p-value*
ODI success (≥15 point improvement) 95% CI	34/41 (82.9%) (67.9, 92.8)	164/187 (87.7%) (82.1, 92.0)	69/86 (80.2%) (70.2, 88.0)	0.1394
Neurological success (maintenance or improvement – motor & sensory evaluations) 95% CI	38/41 (92.7%) (80.1, 98.5)	175/188 (93.1%) (88.5, 96.3)	80/86 (93.0%) (85.4, 97.4)	1.0000
ROM success (maintenance or improvement) 95% CI	26/40 (65.0%) (48.3, 79.4%)	128/184 (69.6%) (62.4, 76.1)	44/84 (52.4%) (41.2, 63.4)	0.0089
Device success (no SSIs at index level) 95% CI	43/43 (100.0%) (91.8, 100.0)	184/192 (95.8%) (92.0, 98.2)	89/92 (96.7%) (90.8, 99.3)	1.0000
No serious device-related AEs per CEC 95% CI	39/43 (90.7%) (77.9, 97.4)	167/194 (86.1%) (80.4, 90.6)	74/94 (78.7%) (69.1, 86.5)	0.1271
Overall success including ROM success component 95% CI P-value (difference between groups; delta = 10%) P-value (superiority)	20/40 (50.0%) (33.8, 66.2)	92/185 (49.7%) (42.3, 57.2)	29/87 (33.3%) (23.6, 44.3)	 <0.0001 0.0129
Overall success without ROM success component 95% CI P-value (difference between groups; delta = 10%) P-value (superiority)	30/41 (73.2%) (57.1, 85.8)	135/189 (71.4%) (64.4, 77.8)	55/88 (62.5%) (51.5, 72.6)	 0.0005 0.1644

* Difference between randomized groups
SSI = subsequent surgical intervention

In randomized activL subjects, overall success and component outcomes were qualitatively comparable when comparing observed data for the spike and keel device designs; however, the trial was not designed or powered to demonstrate statistical poolability of the two device designs. When considering treatment level in activL subjects, while qualitative differences were evident in the missing imputed as failures analysis comparing activL subjects treated at L4-L5 with activL subjects treated at L5-S1, with qualitatively higher overall and component success rates in activL subjects treated at L5-S1, overall success and component outcomes were more comparable in the observed analysis. The trial was not designed or powered to demonstrate statistical poolability for the two activL treatment levels.

Table 24 provides observed time course data (missing data not included as failures) for overall success for the randomized subjects treated in the study as well as the non-randomized activL subjects, with and without the ROM success component.

Table 24: Time Course of Overall Success (Missing Imputed as Failures)

Treatment Group	6 Months n/N (%)	12 Months n/N (%)	24 Months n/N (%)	3 Years n/N (%)	4 Years n/N (%)
Overall success (imputed) including ROM success component:					
NR activL (N=46)	19/46 (41.3%)	20/46 (43.5%)	20/46 (43.5%)	19/46 (41.3%)	11/46 (23.9%)
R activL (N=218)	99/218 (45.4%)	88/218 (40.4%)	92/218 (42.2%)	62/218 (28.4%)	14/218 (6.4%)
R Contr (N=106)	35/106 (33.0%)	40/106 (37.7%)	30/106 (28.3%)	33/106 (31.1%)	9/106 (8.5%)
Overall success (imputed) without ROM success component:					
NR activL (N=46)	33/46 (71.7%)	33/46 (71.7%)	30/46 (65.2%)	28/46 (60.9%)	14/46 (30.4%)
R activL(N=218)	147/218 (67.4%)	148/218 (67.9%)	135/218 (61.9%)	97/218 (44.5%)	30/218 (13.8%)
R Contr(N=106)	59/106 (55.7%)	66/106 (62. 3%)	56/106 (52.8%)	49/106 (46.2%)	13/106 (12.3%)

Table 25 provides time course data on overall success (observed only, without the ROM success component) for the randomized activL group stratified by device design and level treated.

Table 25: Time Course of Overall Success (Observed)

Treatment Group	6 Months n/N (%)	12 Months n/N (%)	24 Months n/N (%)	3 Years n/N (%)	4 Years n/N (%)
Overall success (observed) without ROM success component:					
R activL, spike (N=115)	75/106 (70.8%)	79/107 (73.8%)	69/98 (70.4%)	42/71 (59.2%)	5/25 (20.0%)
R activL, keel (N=102)	71/95 (74.7%)	69/96 (71.9%)	66/91 (72.5%)	55/79 (69.6%)	25/41 (61.0%)
R activL, L4-L5 (N=62)	43/56 (76.8%)	45/58 (77.6%)	36/49 (73.5%)	30/42 (71.4%)	12/21 (57.1%)
R activL, L5-S1 (N=156)	103/145 (71.0%)	103/145 (71.0%)	99/140 (70.7%)	67/108 (62.0%)	18/45 (40.0%)

Various post-hoc sensitivity analyses were conducted to assess the robustness of the study conclusions. Specifically, the following analyses were provided:

- Overall success with and without the ROM component of overall success as well as with different ROM success definitions.
- Overall success stratified by activL device design, control device, and treatment level as well as by surgical approach (retroperitoneal versus the 5 subjects (3 activL, 2 control) treated via a transperitoneal approach).
- Overall success with and without the ROM component of overall success with various imputations for missing 24 month values including multiple imputation, last observation carried forward, all missing as failures, all missing as successes, best case analysis (missing activL as successes and missing control as failures), worst case analysis (missing activL as failures and missing control as successes), and tipping point (break-even) analysis.
- Sensitivity analyses comparing overall success in the randomized activL group to each control device separately (both missing imputed as failures and observed).
- Overall success for complete cases as well as complete cases excluding subjects with major protocol violations.

Non-inferiority was established for nearly all of these scenarios both with and without the ROM component of overall success except the most extreme case in which all missing activL outcomes were considered failures and all missing control outcomes were considered successes where non-inferiority with a 10% margin was not established (either with or without the ROM component of overall success). Non-inferiority was further evidenced in the tipping point (break-even) analysis where 98% of combinations of missing data favored activL versus only 2% that favored control, utilizing a delta of 10%.

Additional data was provided which stratified overall success by 24 month ODI status (≥ 15 point improvement, unchanged, ≥ 15 point worsening), 24 month neurological status (improved, unchanged, deteriorated), 24 month ROM status (≥ 2° improvement, unchanged, ≥ 2° worsening), 24 month VAS status (≥ 20mm improvement, unchanged, ≥ 20mm worsening), duration of symptoms (< 1 year, ≥ 1 year), and gender.

Additional data was provided which stratified outcomes by subject race as shown in Table 26. For subjects randomized to activL, the Caucasian group had higher success rates than the non-Caucasian group for both overall success definitions and several overall success components whereas for subjects randomized to the control group, the non-Caucasian group generally had higher success rates. Among the Caucasian subject population, those treated with the activL had higher success rates than those in the control group whereas among the non-Caucasian group, the reverse was true. It is important to note that the non-Caucasian subject population was relatively small (2 NR activL, 22 R activL, 6 R Contr). Due to the relatively small numbers of non-Caucasians treated in the IDE study, this potential variability in outcomes based on race will be evaluated further as part of an Enhanced Surveillance Study the applicant will conduct for ten years postmarket.

Table 26: Overall Success at 24 Months Stratified by Subject Race (Observed)

	R activL		R Contr	
Primary Endpoint Component	**Caucasian (N=163)**	**Non-Caucasian (N=22)**	**Caucasian (N=81)**	**Non-Caucasian (N=6)**
Overall success including ROM success component 95% CI	85/163 (52.1%) (44.2, 60.0)	7/22 (31.8%) (13.9, 54.9)	26/81 (32.1%) (22.2, 43.4)	3/6 (50.0%) (11.8, 88.2)
Overall success without ROM success component 95% CI	122/166 (73.5%) (66.1, 80.0)	13/23 (56.5%) (34.5, 76.8)	50/82 (61.0%) (49.6, 71.6)	5/6 (83.3%) (35.9, 99.6)

SSI = subsequent surgical intervention

Secondary Effectiveness Analysis

In addition to the components of the primary endpoint presented above, secondary effectiveness variables were also assessed. The following secondary endpoint success definitions were specified in the protocol:

- VAS back, left leg, and right leg pain success: improvement of ≥ 20mm from baseline
- ODI success: improvement of both ≥ 15 points and ≥ 15% from baseline
- SF-36 success: improvement of ≥ 15% from baseline

Observed success rates at 24 months in the randomized treatment groups based on these definitions are presented in Table 27. The results were comparable.

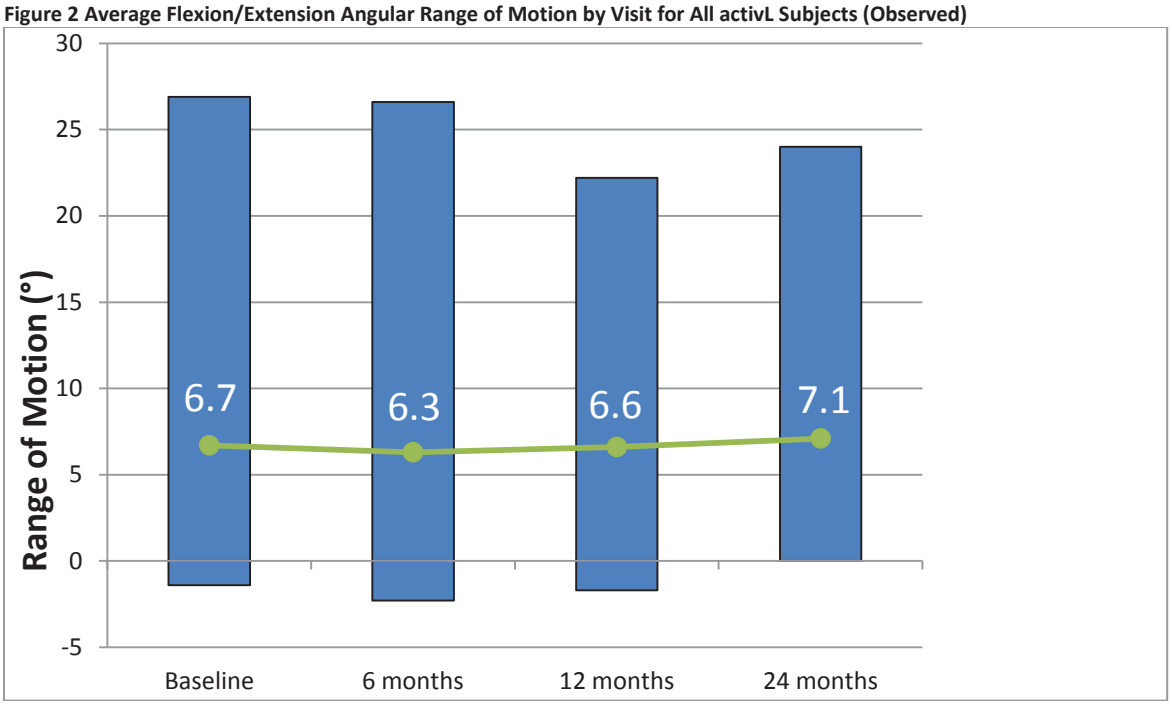
Table 27: Secondary Effectiveness Endpoints - Subject Reported Outcomes at 24 Months (Observed)

Outcome Measure	R activL n/N (%)	R Contr n/N (%)	p-value
VAS Back Pain ≥ 20 mm Improvement	162/180 (90.0%)	72/87 (82.8%)	0.1124*
VAS Left Leg Pain ≥ 20 mm Improvement	72/182 (39.6%)	35/86 (40.7%)	0.8941*
VAS Right Leg Pain ≥ 20 mm Improvement	73/182 (40.1%)	36/84 (42.9%)	0.6892*
ODI ≥ 15 point Improvement	164/187 (87.7%)	70/87 (80.5%)	N/A
ODI ≥ 15% Improvement	170/187 (90.9%)	77/87 (88.5%)	N/A
SF-36 MCS ≥ 15% Improvement	101/180 (56.1%)	48/86 (55.8%)	N/A
SF-36 PCS ≥ 15% Improvement	156/180 (86.7%)	69/86 (80.2%)	N/A

* Difference between randomized groups for pre-specified powered secondary endpoints

For all subjects receiving the activL (randomized plus non-randomized), the mean flexion/extension angular range of motion values at 12 months and 24 months postoperative were 6.6° and 7.1°, respectively, compared to 6.7° at the preoperative evaluation. The average angulation range of motion (flexion/extension) and range of results for all activL subjects (randomized plus non-randomized) at the preoperative, 6 month, 12 month, and 24 month visits are shown in Figure 2.

Figure 2 Average Flexion/Extension Angular Range of Motion by Visit for All activL Subjects (Observed)



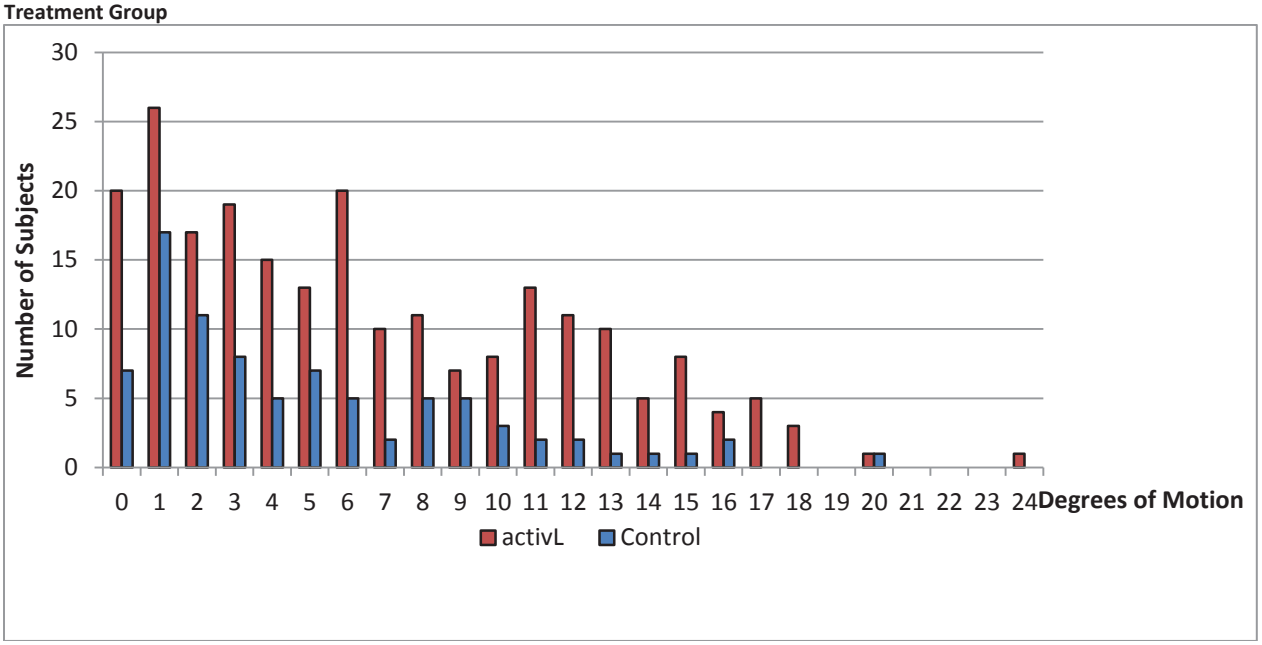
Range of motion success for both treatment groups was defined as maintenance or improvement in flexion/extension angular range of motion relative to preoperative baseline. Table 28 presents data on change in range of motion from preoperative baseline for each timepoint by treatment group for the randomized subjects treated in the trial as well as the non-randomized activL subjects at 6, 12 and 24 months follow-up.

Table 28: Time Course of Flexion/Extension Angular Range of Motion Improvement (Observed)

	6 mo			12 mo			24 mo		
	NR activL	R activL	R Contr	NR activL	R activL	R Contr	NR activL	R activL	R Contr
ROM, N	42	198	94	41	197	95	40	184	85
Improved (>0°)	45.2%	42.9%	40.4%	43.9%	41.6%	45.3%	52.5%	52.2%	36.5%
Stable (≥-2° but ≤0°)	9.5%	25.3%	14.9%	17.1%	20.8%	14.7%	12.5%	17.4%	16.5%
Deteriorated (<-2°)	45.2%	31.8%	44.7%	39.0%	37.6%	40.0%	35.0%	30.4%	47.1%

A histogram of angular range of motion on flexion/extension radiographs at 24 months for all subjects treated with the activL (randomized plus non-randomized) as compared to all subjects treated with the control devices (randomized plus non-randomized) is provided in Figure 3 (values are rounded to the nearest integer).

Figure 3: Histogram of Flexion/Extension Angular Range of Motion at 24 Months for All Subjects (Randomized Plus Non-randomized) by Treatment Group



The applicant evaluated the correlation between 24 month range of motion in rotation as well as translation and 24 month pain and function outcomes. In both randomized treatment groups, there was an inverse correlation between angular range of motion and back pain and angular range of motion and function. The clinical significance of these results is not clear.

Radiographic evaluation of mean disc height for the treated level at the preoperative and 24 month time points are shown in Table 29 by treatment group for the randomized subjects treated in the study as well as the non-randomized activL subjects. Data on the number of subjects with >3mm change in disc height compared to preoperative at 24 months by treatment group is also provided.

Table 29: Time Course of Observed Angular Range of Motion Compared to "Normal" Angular Range of Motion

	Baseline			24 mo		
	NR activL	R activL	R Contr	NR activL	R activL	R Contr
L4-L5 "Normal" ROM	7/11 (63.6%)	35/61 (57.4%)	22/33 (66.7%)	6/9 (66.7%)	33/48 (68.8%)	9/27 (33.3%)
L5-S1 "Normal" ROM	27/35 (77.1%)	109/153 (71.2%)	52/72 (72.2%)	20/31 (64.5%)	102/139 (73.4%)	40/58 (69.0%)

"Normal" ROM definitions:
L4-L5: ROM ≥ 5 degrees and ≤ 20 degrees, ± 2 degrees
L5-S1: ROM ≥ 6 degrees and ≤ 20 degrees, ± 2 degrees

Table 30 provides a summary of radiographic safety data at 24 months for all of the study treatment groups which shows few instances of subsidence (≥ 3mm), migration (≥ 3mm), or poor device condition (disassembly, loosening, or device fracture).

Table 30: Summary of Radiographic Safety Data at 24 Months (Observed)

Radiographic Measure	NR activL n/N (%)	R activL n/N (%)	R Contr n/N (%)	NR Contr n/N (%)
Subsidence (≥ 3mm)	0/41 (0%)	0/185 (0%)	2/85 (2.4%)	1/6 (16.7%)
Migration (≥ 3mm)	0/41 (0%)	0/185 (0%)	1/85 (1.2%)	0/6 (0%)
Device Condition (disassembled, loose, or fractured)	0/41 (0%)	1/185 (0.5%)	2/86 (2.3%)	0/6 (0%)

Available radiographs for all treated subjects were assessed by an independent radiographic evaluator to determine heterotopic ossification (HO) class, based on a scale from 0 to 4 (shown below), as well as to determine the number of subjects with stable or "worsening" (progressing by at least one grade) HO from visit to visit.

HO Scale:

- None: No evidence of HO or osteophyte formation.
- Class 1: HO present in islands of bone within soft tissue but not influencing the range of motion of the vertebral motion segment (i.e., bone was not between the planes formed by the two vertebral endplates).
- Class 2: HO present between the two planes formed by the vertebral endplates but not blocking or articulating between adjacent vertebral endplates or osteophytes.
- Class 3: Range of motion of the vertebral endplates blocked by the formation of HO and/or postoperative osteophytes on flexion-extension or lateral bending radiographs.
- Class 4: Radiographic evidence of a continuous bony connection from the superior vertebral body to the inferior vertebral body caused by osteophyte formation or HO

In some cases, the rating could not be determined ("Indeterminate") because the subject had undergone a fusion procedure.

Table 31 presents 24 month data on HO by treatment group for the randomized subjects as well as the non-randomized activL subjects. Incidence and severity of HO increased over time, but was lower in both investigational groups than in the control group. HO will be studied further as part of both a seven year post-approval study and a ten year Enhanced Surveillance Postmarket Study that will be conducted by the applicant. Demographic and baseline characteristics and clinical outcomes were evaluated for potential correlation with HO class. There was no clear correlation between demographics or baseline characteristics and HO. There was a correlation between clinical outcome and severe HO (Class III and IV). All subjects with severe HO (Class III and IV) were primary endpoint failures, regardless of treatment group; only 1 subject (activL) was a radiographic success.

Table 31: Heterotopic Ossification at 24 Months

Time Period / HO Class	NR activL	R activL	R Contr
24-Month Follow-Up			
None	34/41 (82.9%)	156/187 (83.4%)	61/87 (70.1%)
Class I	5/41 (12.2%)	14/187 (7.5%)	17/87 (19.5%)
Class II	1/41 (2.4%)	12/187 (6.4%)	6/87 (6.9%)
Class III	1/41 (2.4%)	3/187 (1.6%)	1/87 (1.1%)
Class IV	0/41 (0.0%)	0/187 (0.0%)	0/87 (0.0%)
Indeterminate	0/41 (0.0%)	2/187 (1.1%)	2/87 (2.3%)
Not Assessed	0/41 (0.0%)	0/187 (0.0%)	0/87 (0.0%)
Stable vs. Baseline	*38/41 (92.7%)*	*167/187 (89.3%)*	*74/87 (85.1%)*
Progressive vs. Baseline	*3/41 (7.3%)*	*20/187 (10.7%)*	*13/87 (14.9%)*

Clinical Trial Conclusions

The clinical data support the reasonable assurance of safety and effectiveness of the activL® Artificial Disc when used in accordance with the indications for use. Based on the clinical trial results, it is reasonable to conclude that a significant portion of the indicated patient population will achieve clinically significant results and that the clinical benefits of the use of the activL in terms of improvement in pain and function, and the potential for motion preservation, outweigh the risks associated with the device and surgical procedure through 24-months follow-up when used in the indicated population in accordance with the directions for use.

How Supplied

- The activL® Artificial Disc implant components are supplied pre-packaged and sterile.
- The components are provided in protective packaging that is labeled to indicate its contents.
- The implant components are provided sterile using beta and gamma irradiation
- Implant components may not be resterilized
- Components are to be kept in their original packaging until just prior to use.
- Prior to use, check the expiration date and assure the integrity of the packaging. Do not use components if they are past their expiration date or if the packaging has been damaged. Damaged packages /devices should be returned to Aesculap Implant System, LLC. at 615 Lambert Pointe Drive, Hazelwood, MO 63042.
- Instruments are provided non-sterile. For more information on the sterilization and cleaning of the Instruments, please visit www.aesculapimplantsystems.com/products/instructions-for-use and reference IFU TA014275.

MRI Information

The activL® Artificial Disc has not been evaluated for safety and compatibility in the MR environment. It has not been tested for heating or migration in the MR environment.

Product Complaints

Any health care professional (e.g., customer or user of this system), who has complaints or who has experienced any dissatisfaction in the product quality, identity, durability, reliability, safety, effective-ness and/or performance, should notify Aesculap Implant Systems.

Further, if any of the implanted system component(s) ever "malfunctions,"(i.e. does not meet any of its performance specifications or otherwise does not perform as intended), or
may have caused or contributed to the death or serious injury of a patient, Aesculap Implant Systems should be notified immediately by telephone, fax or written correspondence. When filing a complaint, please provide the component(s) name and number, lot number(s), your name and address, and the nature of the complaint. Complaints may also be reported directly to Medwatch at http://www.fda.gov/medwatch. You will be contacted by Aesculap Implant Systems to provide specific information for an Enhanced Surveillance Study, for specific information regarding your clinical experience, regarding the complaint and overall experience with the device. In the event that the activL® Artificial Disc requires removal for any reason, follow the instructions provided below in the DEVICE RETRIEVAL section**.**

Device Retrieval

Should it be necessary to remove the activL® Artificial Disc, please contact Aesculap Implant Systems (Spine) to receive instructions regarding the data collection, including histopathological, mechanical, patient and adverse event information. Please refer to the activL® Artificial Disc Surgical Technique for step-by-step instructions on the required surgical technique for device retrieval.

All explanted devices must be returned to Aesculap for analysis per the detailed instructions in the surgical technique.

Please note that the activL® Artificial Disc should be removed as carefully as possible in order to keep the implant and surrounding tissue intact. In addition, descriptive information about the gross appearance of the device in situ, as well as descriptions of the removal methods, i.e. intact or in pieces, should also be provided as outlined in detail in the surgical technique. Aesculap will also request additional information regarding the reason for removal, patient information, and associated clinical outcomes.

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