# SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

## I GENERAL INFORMATION

| | |
|---|---|
| Device Generic Name: | Artificial Lumbar Disc |
| Device Trade Name: | activL® Artificial Disc (activL) |
| Device Product Code: | MJO |
| Applicant's Name and Address: | Aesculap Implant Systems, Inc.<br>3773 Corporate Parkway<br>Center Valley, PA 18034 |
| Date of Panel Recommendation: | None |
| Premarket Approval Application (PMA) Number: | P120024 |
| Date of Notice of Approval to the Applicant: | June 11, 2015 |

## II 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.

## III 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 less than or equal to -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

## IV WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the activL® Artificial Disc labeling.

## V DEVICE DESCRIPTION

The activL® Artificial Disc is a weight-bearing, modular implant which consists of two endplates and one polyethylene inlay.

Endplates:

- Materials: The activL® Artificial Disc superior and inferior endplates are manufactured from a cobalt chromium alloy which conforms to ASTM F75 and ISO 5832-12. The surfaces of both endplates are coated with a Plasmapore μ-CaP surface coating, composed of Titanium conforming to ISO 5832-2 and a microscopic Calcium Phosphate over-coating which conforms to ASTM F1609.
- Fixation: There are two versions of the activL® Artificial Disc (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® Artificial Disc to the vertebral bodies is intended to be achieved through bone growth, with initial stabilization by either the spike or keel endplate design. The choice of the spike or keel endplate version is intended to allow selection of an optimal endplate to fit the individual patient's anatomy and to accommodate physician preference.
- Sizes: The endplates are provided in four sizes (each is available in either the spike or keel design). 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.

Inlay:

- Materials: The activL® Artificial Disc inlay is manufactured from ultra-high molecular weight polyethylene (UHMWPE) which conforms to ISO 5834-2 and ASTM F648. The inlay also includes an integrated tantalum radiographic marker.

- Sizes: The UHMWPE inlays are available in four heights (8.5, 10, 12, and 14mm), and fit any of the endplates (both spike and keel designs) by seating into the grooves in the side wall of the inferior endplate.

Assembly:

- 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 Device**

Keel Design

Spike Design

**Table 1: Endplate Sizes**

| Endplate Size (Spike or Keel) | AP Dimension (mm) | Lateral Dimension (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: Polyethylene Inlay Sizes**

| Polyethylene Inlay Size | AP Dimension (mm) | Lateral Dimension (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 and inlay height as outlined in the following table. 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.

**Table 3: Maximum Device Range of Motion as Measured Through *in vitro* Testing**

| Device Size Combination (endplate size / inlay height) | Flexion Design Limit (inlay anterior)* | Flexion Design Limit (inlay posterior)* | Extension Design Limit | Lateral Bending Design Limit | Translational Design Limit (mm) |
|---|---|---|---|---|---|
| Small / 8.5mm | 11.8° | 11.5° | 11.8° | ±10.6° | 1.5 |
| Small / 10mm | 19.5° | 18.4° | 18.7° | ±15.6° | 1.5 |
| Small / 12mm | 30.5° | 26.6° | 30.2° | ±25.8° | 1.5 |
| Small / 14mm | 43.5° | 36.6° | 43.5° | ±34.1° | 1.5 |
| Medium / 8.5mm | 11.7° | 9.8° | 11.7° | ±9.2° | 2 |
| Medium / 10mm | 17.5° | 15.8° | 17.5° | ±14.3° | 2 |
| Medium / 12mm | 27.3° | 22° | 27.3° | ±25.8° | 2 |
| Medium / 14mm | 37.8° | 30.2° | 37.8° | ±32.9° | 2 |
| Large / 8.5mm | 10.5° | 9.5° | 10.7° | ±8.3° | 2 |
| Large / 10mm | 17.5° | 14.9° | 17.8° | ±12.9° | 2 |
| Large / 12mm | 26.5° | 22.9° | 26.6° | ±19.6° | 2 |
| Large / 14mm | 34.5° | 30.9° | 34.5° | ±26.1° | 2 |
| Xtra Large / 8.5mm | 9° | 8.2° | 11° | ±8° | 2 |
| Xtra Large / 10mm | 14.2° | 12.4° | 17.6° | ±12.6° | 2 |
| Xtra Large / 12mm | 21.5° | 19° | 26.4° | ±18.8° | 2 |
| Xtra Large / 14mm | 28.8° | 25.4° | 35° | ±25.4° | 2 |

* The Inlay is able to translate in the Anterior/Posterior direction 1.5 or 2.0mm based upon the endplate size. This affects the total flexion angle that can be obtained.

The activL® Artificial Disc is implanted using both implant-specific and general instrumentation.

**Table 4: activL® Artificial Disc Instruments**

| Catalog Number | Description | Device Classification |
|---|---|---|
| **Preoperative Planning** | | |
| FW921R | S1 X-ray trial plates | Class 3 |
| FW959R | X-ray templates, various scales | Class 3 |
| **Midline Marking** | | |

| Catalog Number | Description | Device Classification |
|---|---|---|
| FW938SU | Inferior midline marker tip | Class 1 |
| FW955R | Anterior midline marker | Class 1 |
| **Discectomy and Endplate preparation** | | |
| FW909R | Osteotome, angled | Class 1 |
| FW912R | Rasp, straight | Class 1 |
| FW913R | Rasp, angled | Class 1 |
| FW914R | Curette, bilateral, round, angled 10mm | Class 1 |
| **Distraction and Size Verification** | | |
| FW940R | Stem F/wedge | Class 1 |
| FW941R | Wedge F/H 6mm | Class 1 |
| FW942R | Wedge F/H 8.5mm | Class 1 |
| FW943R | Wedge F/H 10mm | Class 1 |
| FW944R | Wedge F/H 12mm | Class 1 |
| FW951R | Spacer F/H 8.5mm | Class 1 |
| FW952R | Spacer F/H 10mm | Class 1 |
| FW953R | Spacer F/H 12mm | Class 1 |
| FW954R | Spacer F/H 14mm | Class 1 |
| FW960R | Distraction forceps, angled | Class 1 |
| FW970R | Parallel distractor | Class 1 |
| FW922R | S1 Inferior trial plate, small 5° | Class 3 |
| FW923R | S1 Inferior trial plate, medium 5° | Class 3 |
| FW924R | S1 Inferior trial plate, large 5° | Class 3 |
| FW925R | S1 Inferior trial plate, x-large 5° | Class 3 |
| FW926R | Inferior trial plate, x-large 0° | Class 3 |
| FW927R | Superior trial plate, x-large 6° | Class 3 |
| FW928R | Superior trial plate, x-large 11° | Class 3 |
| FW971R | Inferior trial plate, small 0° | Class 3 |
| FW972R | Inferior trial plate, medium 0° | Class 3 |
| FW973R | Inferior trial plate, large 0° | Class 3 |
| FW974R | Superior trial plate, small 6° | Class 3 |
| FW975R | Superior trial plate, small 11° | Class 3 |
| FW976R | Superior trial plate, medium 6° | Class 3 |
| FW977R | Superior trial plate, medium 11° | Class 3 |
| FW978R | Superior trial plate, large 6° | Class 3 |
| FW979R | Superior trial plate, large 11° | Class 3 |
| **Chiseling (For Keel Device only)** | | |
| FW980R | Handle, chisel guide | Class 3 |
| FW981R | 8.5mm, 6° chisel guide | Class 3 |
| FW982R | 10mm, 6° chisel guide | Class 3 |
| FW983R | 12mm, 6° chisel guide | Class 3 |
| FW984R | 14mm, 6° chisel guide | Class 3 |
| FW985R | 8.5mm double chisel | Class 3 |
| FW986R | 10mm double chisel | Class 3 |
| FW987R | 12mm double chisel | Class 3 |
| FW988R | 14mm double chisel | Class 3 |
| FW989R | 8.5mm single chisel | Class 3 |
| FW990R | 10mm single chisel | Class 3 |
| FW991R | 12mm single chisel | Class 3 |
| FW992R | 14mm single chisel | Class 3 |
| FW993R | 8.5mm, 11° chisel guide | Class 3 |
| FW994R | 10mm, 11° chisel guide | Class 3 |
| FW995R | 12mm, 11° chisel guide | Class 3 |
| FW996R | 14mm, 11° chisel guide | Class 3 |

| Catalog Number | Description | Device Classification |
|---|---|---|
| FW579R | Miaspas TL slotted hammer | Class 1 |
| **Implantation** | | |
| FW961R | 8.5mm insertion instrument | Class 3 |
| FW962R | 10mm insertion instrument | Class 3 |
| FW963R | 12mm insertion instrument | Class 3 |
| FW964R | 14mm insertion instrument | Class 3 |
| FL045R | 30mm disc removal mallet | Class 1 |
| FW945R | Key for insertion instrument | Class 3 |
| FW999R | Impactor with Pins | Class 3 |
| FW969R | Repositioner | Class 3 |
| FW910R | activL® Impactor, straight | Class 3 |
| FW911R | activL® Impactor, angled | Class 3 |
| FW915R | activL® Implant Impactor | Class 3 |
| FW916R | Adapter for FW915R – Height 8.5/10mm | Class 3 |
| FW917R | Adapter for FW915R – Height 12/14mm | Class 3 |
| **Revision** | | |
| FW965R | Revision instrument, distraction fork | Class 1 |
| FW970R | Parallel distractor | Class 1 |
| FW997R | Osteotome | Class 1 |
| FW998R | activL revision handle | Class 1 |
| FW966R | Revision instrument S/M | Class 3 |
| FW967R | Revision instrument X/L | Class 3 |
| FW968R | Revision instrument, PE Inlay | Class 3 |

## VI ALTERNATIVE PRACTICES AND PROCEDURES

There are several alternatives for the treatment of symptomatic degenerative disc disease at a single lumbar level (L4-L5 or L5-S1):

- Non-surgical alternatives include, but are not limited to, medications, physical therapy, spinal injections, chiropractic care, braces, exercise programs, or rest.
- Surgical alternatives include, but are not limited to, surgical decompression and/or fusion using various bone grafting techniques and devices (including but not limited to interbody fusion devices and posterior pedicle screw/rod systems). Symptomatic degenerative disc disease at a single lumbar level (L4-L5 or L5-S1) may also be treated surgically using another FDA approved lumbar total disc replacement device.

Each alternative has advantages and disadvantages which should be fully discussed with the patient's physician.

## VII MARKETING HISTORY

The activL® Artificial Disc has been in commercial distribution in markets outside of the United States since 2005. The device is available in the following countries: Argentina, Austria, Belgium, Brazil, Canada, the Czech Republic, Denmark, France, Germany, Hong Kong, Italy, Malaysia, Mexico, Norway, Poland, South Africa, South Korea, Spain, Switzerland, and the United Kingdom.

The device has not been withdrawn from any market, for any reason.

## VIII POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

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. In addition to the risks listed below, there is also the risk that the procedure may not be effective and may not relieve symptoms or may cause worsening of symptoms. Additional surgery may be required to correct some of the 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 Section X (Summary of Primary 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.

# IX SUMMARY OF NONCLINICAL LABORATORY STUDIES

Several non-clinical studies were conducted to characterize the performance of the activL® Artificial Disc.

**A. Laboratory Studies**

☐Static Endplate Expulsion

☐Subsidence

☐Static and Dynamic Compression Shear

☐Creep Characterization

☐Subluxation

☐Wear/Durability

☐Impingement

**B. Animal Studies**

☐ Wear Debris Particulate

**C. Additional Studies**

☐ Retrieval Analysis

☐ Sterilization Validation

☐ Shelf Life and Packaging Validation

☐ Biocompatibility

☐ Instrument Testing

## A. Laboratory Studies

**Table 5: Summary of Laboratory Studies**

| Test Name | Purpose | Method | Acceptance Criteria | Results |
|---|---|---|---|---|
| **Static Endplate Expulsion** | To evaluate the loads required to expulse the activL® device. | Five (5) activL® spiked endplates and five (5) activL® keeled endplates were inserted onto custom grade 15 polycarbonate urethane foam blocks with a 1mm thickness of grade 80 foam on the surface to simulate the denser bone of the endplate.[1] A 450 N axial load was applied. Shear load was applied to the endplate at 5 mm/min. The force necessary to dislodge the endplates was measured. | The shear load endured by the activL® endplates and simulated bone should exceed the maximum shear forces in the lumbar spine of 400 N.[2] | The maximum shear force measured was 1258.82 ± 60.44 N in the activL® spiked endplates and 494.82 ± 13.88 N in the activL® keeled endplates. |
| **Subsidence** | To evaluate the activL® implant's resistance to subsidence into the vertebral endplate. | Five (5) activL® spiked endplates and five (5) activL® keeled endplates were compressed into custom grade 15 polycarbonate urethane foam blocks with a 1mm thickness of grade 80 | The fatigue loads endured by the activL® should exceed the maximum axial forces of 3400 N. [3] | The maximum subsidence load was 5760.57 ± 391.47 N for the spiked endplates and 5567.74 ± 458.01 N for the keeled endplates. |

| Test Name | Purpose | Method | Acceptance Criteria | Results |
|---|---|---|---|---|
| | | foam on the surface to simulate the denser bone of the endplate[4]. Load was applied at 0.1mm/min. The maximum subsidence load was measured. | | |
| **Static Compression Shear** | To evaluate the performance of the activL® under static compression-shear loading. | Five (5) activL® specimens with spiked endplates and five (5) activL® specimens with keeled endplates were tested under static compression-shear (10° angle) in saline at 37°C at a rate of 50N/sec until failure. | The loads endured by the activL® should exceed the fracture load of the L5 vertebral body (5500 N). [4] | The mean yield load of the specimens was 6625.53 ± 272.49 N for the spiked specimens and 6911.44 ± 231.13 N for the keeled design. |
| **Dynamic Compression Shear** | To evaluate the performance of the activL® under dynamic compression-shear loading. | Seven (7) activL® specimens were tested under compression shear loads (10° angle) in saline at 37°C using a sinusoidal wave form with R = 10 at 5 Hz until 10 million cycles or failure. | The fatigue loads endured by the activL® should exceed the maximum *in vivo* axial forces (3400 N).[3] | Four (4) activL® specimens ran out to 10 million cycles at 4000 N with no failure. |
| **Creep Characterization** | To evaluate the creep characteristics of the activL® device. | Six (6) specimens of each the 14 mm (tallest) and 8.5 mm (shortest) activL® UHMWPE inlay were loaded in compression shear (10° angle) in saline at 37°C as follows:<br><br>1. Static: 300 N for 4 hours<br>2. Dynamic: 300 N to 1000 N (1 Hz) for 16 hours<br>3. Static: 300 N for 8 hours (relaxation phase)<br>4. Dynamic : 300 N to 2000 N (1 Hz) for 16 hours<br>5. Static: 300 N for 8 hours (relaxation phase)<br>6. Dynamic: 300 N to 3000 N (1 Hz) for 16 hours<br>7. Static: 300 N for 8 hours (relaxation phase) | The plastic deformations should be smaller than the diurnal changes of the intervertebral disc (1.5 mm).[5] | The maximum displacements of approximately 0.5 mm observed were in the 14 mm inlay after the 3000 N cyclic loading. Maximum plastic deformations of approximately 0.16 mm were observed in the same 14 mm specimens. |
| **Subluxation** | To characterize the shear force necessary to cause subluxation of the superior endplate relative to the polyethylene core. | Twenty (20) activL® specimens were tested in the following configurations: five (5) in neutral position loaded posterior-to-anterior, five (5) in neutral position loaded medial-lateral, five (5) in maximum flexion loaded posterior-to-anterior, and five | This test was performed for characterization only. | The mean subluxation force for the various scenarios described was as follows:<br><br>0° A-P: 351.82 ± 4.65 N<br><br>0° M-L: 324.14 ± 9.66 N<br><br>29° A-P: 272.15 ± 4.11 N |

| Test Name | Purpose | Method | Acceptance Criteria | Results |
|---|---|---|---|---|
| | | (5) in maximum lateral bending loaded medial-lateral. Specimens were loaded with a 500 N axial load. Testing was conducted in ambient air. The force necessary to sublux the superior endplate from the UHMWPE inlay was measured. | | 25° M-L: 288.80 ± 12.65 N |
| **Wear/Durability** | To determine the wear and durability characteristics of the activL® device under physiologic conditions. | Six (6) activL® specimens were tested per ISO 18192-1 (2004-04-30) to 10 million cycles. A complex loading profile combining flexion/extension, lateral bending, axial rotation, and axial load was applied at a frequency of 1Hz. Specimens were tested in calf serum and deionized water solution with EDTA. Specimens were weighed prior to testing and at each 0.5 million cycle increment. | The amount of wear debris should be similar to that reported for other lumbar devices. | Average cumulative wear at 10 million cycles was 25.3mg and the mean wear rate was 2.7mg/million cycles.. The test setup was unable to create any backside wear of the polyethylene inlay. |
| **Impingement** | To determine the wear and durability characteristics of the activL® under conditions simulating device impingement. | Six (6) activL® specimens with the largest endplates (XL) and smallest height (8.5 mm) were tested under impingement conditions to 1 million cycles along with two soak controls. Specimens were cycled in flexion-extension 2° past the device range of motion limits in both flexion and extension. A cyclic axial load was applied such that the flexion and extension moments were 8 Nm. Testing was conducted in calf serum in deionized water (20 g/L) at 37°C. Weight measurements and photodocumentation was completed at 0, 0.125, 0.25, 0.5, and 1 million cycles. Particulate analysis was completed according to ASTM F1877. | This test was performed for characterization only. | Impingement behavior of the activL® included contact between the cobalt chromium endplates. Based on gravimetric measurements, the mean total material loss from both endplates was 1.5 ± 0.4 $mm^3$. The UHMWPE inlays gained mass during testing. |

## B. Animal Studies

**Table 6: Summary of Animal Studies**

| Test Name | Purpose | Method | Acceptance Criteria | Results |
|---|---|---|---|---|
| Wear Debris Particulate Animal Study | To characterize the local or systemic reactions potentially caused by UHMWPE wear debris implanted into the epidural space of New Zealand white rabbits. | Animals were injected with a control solution, low dose (10 million) particles, or high dose (25 million) particles. Animals were sacrificed at three (3) months and six (6) months. There were six (6) animals per group, for a total of 36 animals. Assessments included clinical and neurological observations, and hematological, histological, and gross pathologic methods. | There should be no evidence of neurotoxicity, systemic toxicity, or local effects associated with the UHMWPE particulate debris. | The study showed no evidence of neurotoxicity, systemic toxicity, or local effects associated with treatment with the test article wear debris. |

## C. Additional Studies

**Retrieval Analysis**

A total of three (3) activL® devices were retrieved from revision surgeries during the IDE study. Unfortunately, these three activL® explants were lost and no retrieval analysis was performed. To address this situation, the sponsor provided: (i) additional patient information on the three (3) devices that were explanted, and (ii) supplementary retrieval analysis reports of four (4) explanted activL® devices (from the Netherlands) in conjunction with a NIH Study being conducted by Drexel University.

*(i) Summary of Additional Patient Information*

The additional patient information provided on the three (3) explanted devices suggested no obvious device-related concerns, such as disassociation of components, osteolysis, gross subsidence or migration of the endplates. However, no photographs or analyses of these explants were provided.

*(ii) Summary of Supplementary Retrieval Analysis (from Drexel University)*

The Drexel study included analysis from four (4) activL explants; however, only three (3) of these explants were accompanied by clinical information. These three (3) explants were removed after 1.3 – 7.5 years due to persistent pain. In addition to pain, two (2) of these explants showed evidence of subsidence, two (2) showed evidence of facet degeneration, and one (1) explant showed evidence of possible osteolysis. Overall, the UHMWPE inserts showed typical wear features for this device class, such as polishing, scratching, pitting, and embedded particles. There was no evidence of surface delamination or cracking. Of particular note, three (3) of the four (4) explanted UHMWPE inserts showed low to

moderate oxidation levels, showing an average maximum oxidation index of 1.0 ± 0.8 (range: 0.4 – 2.2). The Drexel study did reveal some whitening and white-banding of the UHMWPE slices, which corresponded to the higher oxidation indices measured. As for the Co-Cr endplates, all articular surfaces remained highly polished. A number of small impingement wear patterns were observed implying some endplate-to-endplate contact during use, which appeared to occur in a variety of locations (i.e., in both anterior-posterior and lateral aspects of the device).

**Sterilization Validation**

Components of the activL® Artificial Disc are provided sterile. The activL® endplates are sterilized using gamma radiation and the UHMWPE inlays are sterilized using electron beam radiation. Sterilization validation according to ISO 11137-1 and -2 was conducted to confirm a sterility assurance level of $10^{-6}$.

**Shelf Life and Packaging Validation**

Shelf life and packaging validation studies, including packaging seal and integrity, accelerated aging, and real-time aging testing, were conducted to demonstrate that the device packaging can maintain a sterile barrier, with a shelf life of 5 years.

**Biocompatibility**

The materials used in the activL® Artificial Disc are standard materials commonly used in permanently implanted orthopedic devices, including cobalt-chromium-molybdenum alloy (CoCrMo per ISO 5832-12, ASTM F75), titanium plasma spray coating (per ISO 5832-2), calcium phosphate coating (per ASTM F1609) and ultra-high molecular weight polyethylene (UHMWPE per ISO 5834-2, ASTM F648). The inlays also incorporate a tantalum marker (per ASTM F560). These instruments are made of materials that have a long history of use in contact with human tissue and fluids, including surgical grade stainless steel per ISO 7153-1.

**Instrument Testing**

The instruments used to implant the activL® device are provided non-sterile for sterilization by the user. Validation testing, including cleaning and steam sterilization, was appropriately conducted and met the acceptance criteria.

# X SUMMARY OF PRIMARY CLINCIAL STUDY

The applicant performed a clinical trial within the United States to determine the safety and effectiveness of the activL® Artificial Disc (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 under IDE #G060262. Data from this clinical trial were the basis for the PMA approval decision. A summary of the clinical trial is presented below.

## A. Trial Design

Subjects were treated between January 30, 2007 and December 3, 2009. The database for this PMA reflected data collected through April 11, 2013 and included a total of 376 subjects treated (including both randomized and non-randomized subjects) at 18 investigational sites in the United States.

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 (Charité) or DePuy Synthes Spine ProDisc-L (ProDisc-L)) in reconstruction of the disc at either L4-L5 or L5-S1 following single-level discectomy for symptomatic DDD in subjects who had failed to improve with nonoperative treatment for at least six months prior to enrollment. Subjects were randomized 2:1 to the activL or one of 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 first three subjects at each investigational 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. 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.

Subjects were evaluated preoperatively, intraoperatively, immediately postoperatively, and at 6 weeks, 3 months, 6 months, 12 months, 24 months, and annually thereafter. 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 6 months post-surgery. Subjects were not specifically treated with nonsteroidal anti-inflammatory drugs (NSAIDs) postoperatively in either treatment group.

All adverse events (device-related or not) were monitored over the course of the trial, and radiographic assessments were done by an independent core laboratory. Overall success was a composite endpoint which required success in the following five elements: Oswestry Disability Index (ODI), neurological status, radiographic range of motion status, device status, and no serious device related adverse events. Overall success was determined based on data collected during the initial 24 months of follow-up. For the PMA, 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 trial was designed as a non-inferiority trial with a margin (delta) of 15%. Additional analyses using a delta of 10% as requested by FDA were also conducted. The protocol specified a sample size of 216 randomized activL subjects and 108 randomized control subjects, based on an assumed 65% success rate in both treatment groups, a 10% lost-to-follow-up rate, and 80% power for a one-sided 0.05 significance level. With the addition of up to 6 non-randomized subjects (3 activL and 3 control) per each of the planned 15-20 sites, the maximum total planned sample size was 414 (45 non-randomized activL, 216 randomized activL, 108 randomized control, and up to 45 non-randomized control).

**1. Clinical Inclusion and Exclusion 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 degenerative disc disease (DDD) with objective evidence of lumbar DDD, based on 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 fibrosus, 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 6 months of unsuccessful conservative treatment, including but not limited to physical therapy and/or medication.
- Minimum 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.

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 intradiscal electro-thermal annuloplasty (IDET), 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 < 8mm (by MRI).
- Degenerative or lytic spondylolisthesis > 3mm.
- Spondylolysis or isthmic spondylolisthesis.
- Lumbar scoliosis (> 11° sagittal plane deformity).
- Preoperative remaining disc height < 3mm.
- Facet ankylosis or severe facet degeneration.
- Active systemic infection or 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.

**2. Follow-up Schedule**

All 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) through 7 years. The following parameters were measured according to the visit schedule below:

**Table 7: Evaluation Schedule**

| Evaluation | Baseline | Intra-op | Discharge | 6 wks (±14 days) | 3 mo (±14 days) | 6 mo (±30 days) | 12 mo (±60 days) | 24 mo (±60 days) | 3-7 yrs (±60 days) |
|---|---|---|---|---|---|---|---|---|---|
| **Clinical Evaluations:** | | | | | | | | | |
| Inclusion/exclusion determination | X | | | | | | | | |
| Osteoporosis/ osteopenia screen | X | | | | | | | | |
| Medical History/ physical exam | X | | | | | | | | |
| Work status | X | | | X | X | X | X | X | X |
| Pain medications | X | | X | | | | X | X | X |
| Antibiotics | X | X* | X | | | | | | |
| VAS pain assessment | X | | | X | X | X | X | X | X |
| Neurological assessment | X | | X | X | X | X | X | X | X |
| DVT prophylaxis | | | X | | | | | | |
| Short Form 36 | X | | | X | X | X | X | X | X |
| ODI | X | | | X | X | X | X | X | X |
| Hospital stay | | | X | | | | | | |
| Subject satisfaction | | | | | | | X | X | X |
| Adverse events** | | X | X | X | X | X | X | X | X |
| **Radiographic Evaluations:** | | | | | | | | | |
| 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 |
| X-rays, A/P (R/L bending) | X | | | X | X | X | X | X | X |
| X-rays, lateral (flexion/extension) | X | | | X | X | X | X | X | X |

*Prophylactic antibiotics

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

### 3. 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.

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.

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 +2º 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. The non-inferiority hypothesis was to be evaluated according to the method of Blackwelder [6]. 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: $6 \pm 2º \leq ROM \leq 20 \pm 2º$ (device design limit) for L4-L5 and $5 \pm 2º \leq ROM \leq 20 \pm 2º$ (device design limit) for L5-S1) [7];
- 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.

For the primary and powered secondary endpoints, the protocol specified that subjects with incomplete or missing data would be classified as failures, and sensitivity analyses would be done to assess the potential impact of missing data on the trial outcomes. The specified sensitivity analyses were based on the Intent-to-Treat (ITT) population and included the following imputation methods: multiple imputation, last-observation-carried-forward, all subjects with missing data as successes, all control subjects with missing data as successes and all activL subjects with missing data as failures (worst case scenario), all control subjects with missing data as failures and all activL subjects with missing data as successes (best case scenario) and break-even analyses (tipping-point) where all missing data was counted as failures and then changed to successes one at a time to find the break-even point.

The protocol specified that missing values would be ignored for the analysis of additional secondary endpoints, other outcomes, and summaries of baseline characteristics.

## B. Accountability of PMA Cohort

Nineteen investigational sites were initiated for the activL trial. Eighteen of the 19 sites enrolled subjects. A total of 396 subjects (277 activL, 119 control) were enrolled. Of these 396 subjects, 55 subjects were non-randomized subjects (48 activL, 7 control). Three of the non-randomized subjects (2 activL, 1 control) withdrew prior to surgery. Of the remaining 341 subjects who were randomized, 17 subjects (11 activL, 6 control) withdrew prior to surgery either because the consent was withdrawn or

the subject did not meet the inclusion/exclusion criteria. Therefore, a total of 376 subjects enrolled in the trial and proceeded to surgery. Of the 376 enrolled subjects, 52 were non-randomized subjects (46 activL, 6 control) and 324 were randomized subjects after application of the ITT principle (218 activL, 106 control).

At the time of database lock (April 11, 2013), of the 324 randomized subjects enrolled in the PMA trial, all had reached the 24 month post-operative visit and 230 of the 273 expected randomized subjects (84%) had any 24 month data available for analysis.

More specifically, 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)

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 8 and a summary of data available at 24 months for specific evaluations is provided in Table 9. Limited 5-year data was also provided in the PMA, but is not included in this summary. In addition, the non-randomized control data is generally not included in the tables within this summary due to the limited sample size.

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, rather than the 67 defined by the ITT population.

**Table 8: 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.

**Table 9: 24 Month Data Accounting**

| Parameter | NR activL | R activL | R Contr |
|---|---|---|---|
| Treated | 46 | 218 | 106 |
| Expected[1] | 46 | 217 | 106 |

| Parameter | NR activL | R activL | R Contr |
|---|---|---|---|
| Primary endpoint: | | | |
| ODI (% of Expected) | 41 (89.1%) | 187 (86.2%) | 87 (82.1%) |
| Neurological assessment (% of Expected) | 41 (89.1%) | 188 (86.6%) | 87 (82.1%) |
| ROM (% of Expected) | 40 (87.0%) | 187 (86.2%) | 85 (80.2%) |
| Device failure (% of Expected) | 41 (89.1%) | 189 (87.1%) | 87 (82.1%) |
| SDAE (% of Expected) | 41 (89.1%) | 191 (88.0%) | 89 (84.0%) |
| All primary endpoint components (% of Expected) | 40 (87.0%) | 185 (85.3%) | 88 (83.0%) |
| Powered secondary endpoints: | | | |
| VAS back pain (% of Expected) | 41 (89.1%) | 185 (85.3%) | 87 (82.1%) |
| VAS leg pain (% of Expected) | 41 (89.1%) | 183 (84.3%) | 87 (82.1%) |
| Other secondary endpoints: | | | |
| SF-36 Mental Component Summary (% of Expected) | 41 (89.1%) | 185 (85.3%) | 86 (81.1%) |
| SF-36 Physical Component Summary (% of Expected) | 41 (89.1%) | 185 (85.3%) | 86 (81.1%) |
| Disc height (% of Expected) | 41 (89.1%) | 186 (85.7%) | 87 (82.1%) |
| Device subsidence (% of Expected) | 41 (89.1%) | 187 (86.2%) | 87 (82.1%) |
| Adverse events (% of Expected) | 41 (89.1%) | 189 (87.1%) | 87 (82.1%) |
| Subject Satisfaction | 41 (89.1%) | 187 (86.2%) | 87 (82.1%) |
| Device Migration | 40 (87.0%) | 187 (86.2%) | 87 (82.1%) |
| Device condition | 40 (87.0%) | 187 (86.2%) | 87 (82.1%) |
| Heterotopic Ossification Evaluation | 40 (87.0%) | 187 (86.2%) | 87 (82.1%) |

[1] Data was still collected on subjects who were already failures therefore the failures are added to the expected number from the subject accounting table to determine the number of subjects expected for data accounting.

In the tables that follow throughout this summary, primary and all secondary endpoint hypothesis testing results, safety results and all other summary data are presented for the following analysis datasets:

- Modified ITT data set (primary dataset): all randomized, implanted subjects analyzed according to their randomization assignment (218 randomized activL, 106 randomized control, 46 non-randomized activL, 6 non-randomized control)
- Complete case data set: randomized, implanted subjects with complete primary endpoint data including subjects who were already primary endpoint failures (185 randomized activL, 88 randomized control, 40 non-randomized activL, 6 non-randomized control)
- Per protocol data set: randomized, implanted subjects with complete primary endpoint data and no other major protocol deviations (153 randomized activL, 73 randomized control). The PP population definition specifies randomized subjects; therefore there are no non-randomized activL subjects or non-randomized control subjects included in the per protocol data set

For the primary endpoint analysis and analysis of the powered secondary endpoints, subjects with incomplete or missing data were imputed as failures. In addition, an observed analysis of the primary endpoint was performed for “as-treated” subjects based on all evaluable data with no imputation for missing data.

## C. 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. 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 10 and Table 11. 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. The non-randomized control data is not included due to the limited sample size.

**Table 10: 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<br>Range: 22 – 54 | 39.0 ± 8.7<br>Range: 19 - 60 | 40.3 ± 8.6<br>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%) |
| BMI ($kg/m^2$; mean ± standard deviation) | 26.7 ± 4.4<br>Range: 19 – 35 | 26.6 ± 4.1<br>Range: 16 – 37 | 27.1 ± 4.4<br>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%) |

| Demographic Measure/Baseline Characteristic | NR activL (N=46) | R activL (N=218) | R Contr (N=106) |
|---|---|---|---|
| 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 11: Preoperative Evaluation of Endpoints

| Variable | NR activL | R activL | R Contr |
|---|---|---|---|
| ODI<br>mean ± standard deviation | N=46<br>60.0 ±13.5<br>Range: 34 - 94 | N=218<br>57.1 ± 13.9<br>Range: 18 - 98 | N=106<br>58.6 ± 14.1<br>Range: 33.3 - 96 |
| VAS Back Pain (mm)<br>mean ± standard deviation | N=45<br>81.5 ± 13.3<br>Range: 48 - 100 | N=212<br>79.0 ± 14.9<br>Range: 46 - 100 | N=106<br>79.1 ± 14.8<br>Range: 41 - 100 |
| VAS Right Leg Pain (mm)<br>mean ± standard deviation | N=45<br>34.9 ± 31.7<br>Range: 0 - 99 | N=215<br>28.7 ± 29.8<br>Range: 0 – 96.5 | N=104<br>32.9 ± 29.6<br>Range: 0 – 89.5 |
| VAS Left Leg Pain (mm)<br>mean ± standard deviation | N=46<br>33.6 ± 31.2<br>Range: 0 – 98.5 | N=216<br>29.6 ± 29.4<br>Range: 0 - 100 | N=105<br>30.7 ± 29.5<br>Range: 0 - 98 |
| SF-36 Mental Component Summary (MCS)<br>mean ± standard deviation | N=45<br>37.6 ± 14.7<br>Range: 10.5 – 66.8 | N=213<br>39.1 ± 13.9<br>Range: 9.4 – 67.2 | N=105<br>39.6 ± 14.9<br>Range: 8.3 – 67.8 |
| SF-36 Physical Component Summary (PCS)<br>mean ± standard deviation | N=45<br>28.4 ± 7.2<br>Range: 9.3 – 43.9 | N=213<br>29.9 ± 6.2<br>Range: 14.1 – 51.4 | N=105<br>28.4 ± 6.2<br>Range: 11.2 – 49.7 |
| ROM Flexion/Extension Rotation (°)<br>mean ± standard deviation | N=46<br>7.3 ± 5.1<br>Range: -0.1 to 18.9 | N=214<br>6.6 ± 5.1<br>Range: -1.4 to 26.9 | N=105<br>6.6 ± 4.6<br>Range: -0.7 to 19.4 |
| ROM Flexion/Extension Translation (mm)<br>mean ± standard deviation | N=46<br>0.6 ± 0.7<br>Range: -0.1 to 3.2 | N=212<br>0.5 ± 0.7<br>Range: -0.4 to 3.8 | N=104<br>0.6 ± 0.6<br>Range: -1.4 to 2.8 |

| Variable | NR activL | R activL | R Contr |
|---|---|---|---|
| ROM Lateral Bending AP Rotation (°)<br>mean ± standard deviation | N=42<br>1.1 ± 1.3<br>Range: -1.3 to 5.5 | N=212<br>1.0 ± 2.0<br>Range: -2.3 to 12.5 | N=103<br>1.0 ± 1.8<br>Range: -3.3 to 10.0 |
| Normal Neurological Status (n (%)) | | | |
| Motor (Grade 5, active movement vs. full resistance) | 194 (89.0%) | 97 (91.5%) | 40 (87.0%) |
| Sensory (Grade 2, normal) | 158 (72.5%) | 78 (73.6%) | 33 (71.7%) |
| Reflexes (Grade 2, normal) | 178 (81.7%) | 91 (85.8%) | 42 (91.3%) |

The following tables provide select demographic and preoperative evaluation 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 12: Select Demographic and Baseline Characteristics - Stratified**

| Demographic Measure / Baseline 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=65) | Charité (N=41) | L4-L5 (N=34) | L5-S1 (N=72) |
| Age (years)<br>mean ± standard deviation | 37.9 ± 9.4 | 40.3 ± 7.7 | 38.9 ± 9.2 | 39.0 ± 8.5 | 40.7 ± 8.5 | 39.6 ± 8.8 | 42.6 ± 8.4 | 39.3 ± 8.5 |
| Gender (% Male) | 46.1% | 60.8% | 53.2% | 53.2% | 50.0% | 48.8% | 55.9% | 47.2% |
| BMI ($kg/m^2$)<br>mean ± standard deviation | 26.6 ± 4.2 | 26.7 ± 4.1 | 26.2 ± 4.1 | 26.7 ± 4.1 | 27.0 ± 4.8 | 27.1 ± 3.7 | 27.7 ± 4.1 | 26.8 ± 4.5 |
| Smoking Status (%) | | | | | | | | |
| Current | 17% | 25% | 19% | 22% | 27% | 12% | 18% | 22% |
| Previous | 22% | 13% | 18% | 17% | 22% | 17% | 18% | 21% |
| Never | 61% | 63% | 63% | 61% | 52% | 71% | 65% | 57% |

**Table 13: Preoperative Endpoint Evaluation Data – Stratified**

| Endpoint | 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=65) | Charité (N=41) | L4-L5 (N=34) | L5-S1 (N=72) |
| ODI mean | 55.1 | 59.1 | 58.3 | 56.6 | 57.0 | 60.9 | 15.2 | 13.5 |
| VAS Back Pain mean (mm) | 77.6 | 80.4 | 81.4 | 78.1 | 77.5 | 81.2 | 77.6 | 79.8 |
| VAS Right Leg Pain mean (mm) | 28.3 | 29.5 | 26.9 | 29.5 | 30.1 | 36.1 | 37.4 | 29.9 |
| VAS Left Leg Pain mean (mm) | 26.4 | 32.5 | 24.9 | 31.4 | 26.1 | 36.7 | 24.5 | 33.0 |
| SF-36 MCS mean | 40.0 | 38.3 | 39.5 | 38.9 | 41.2 | 36.9 | 38.4 | 40.2 |
| SF-36 PCS mean | 30.0 | 29.8 | 29.3 | 30.1 | 28.4 | 28.8 | 27.9 | 28.7 |
| ROM Flexion/Extension Rotation mean (°) | 7.1 | 5.9 | 6.8 | 6.5 | 5.8 | 7.9 | 6.4 | 6.7 |
| ROM Flexion/Extension Translation mean (mm) | 0.6 | 0.4 | 1.0 | 0.3 | 0.5 | 0.7 | 0.9 | 0.5 |

| Endpoint | 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=65) | Charité (N=41) | L4-L5 (N=34) | L5-S1 (N=72) |
| ROM Lateral Bending AP Rotation mean (°) | 1.2 | 0.9 | 2.4 | 0.5 | 0.8 | 1.4 | 1.9 | 0.7 |
| Normal Neurological Status (%) | | | | | | | | |
| Motor (Grade 5, active movement against full resistance) | 89.6% | 88.2% | 91.9% | 87.8% | 89.2% | 92.7% | 91.2% | 90.3% |
| Sensory (Grade 2, normal) | 68.7% | 76.5% | 77.4% | 70.5% | 73.8% | 70.7% | 73.5% | 72.2% |
| Reflexes (Grade 2, normal) | 80.0% | 83.3% | 90.3% | 78.2% | 89.2% | 78.0% | 94.1% | 80.6% |

## D. Safety and Effectiveness Results

### 1. Safety Results

The analysis of safety was based on the modified ITT 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) available through April 11, 2013.

***Surgery 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 14. 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. The non-randomized control data is not included due to the limited sample size. The majority of surgery was performed at the L5-S1 level.

**Table 14: Procedural Characteristics**

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

Table 15 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 15: 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 | 35 (30.4%) | 26 (25.5%) | 62 (100%) | -- | 19 (29.7%) | 15 (36.6%) | 34 (100%) | -- |
| L5-S1 | 80 (69.6%) | 76 (74.5%) | -- | 156 (100%) | 45 (70.3%) | 26 (63.4%) | -- | 72 (100%) |
| Device Design | | | | | | | | |
| Spike | 115 (100%) | -- | 35 (57.4%) | 80 (51.3%) | N/A | N/A | N/A | N/A |
| Keel | -- | 102 (100%) | 26 (42.6%) | 76 (48.7%) | | | | |
| Control Device | | | | | | | | |
| ProDisc-L | N/A | N/A | N/A | N/A | 64 (100%) | -- | 19 (55.9%) | 45 (63.4%) |
| Charité | | | | | -- | 41 (100%) | 15 (44.1%) | 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 | 112 (97.4%) | 102 (100%) | 62 (100%) | 153 (98.1%) | 62 (96.9%) | 41 (100%) | 33 (97.1%) | 71 (98.6%) |
| Transperitoneal | 3 (2.6%) | 0 | 0 | 3 (1.9%) | 2 (3.1%) | 0 | 1 (2.9%) | 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 16 provides an overview of the characteristics of activL devices implanted during the clinical trial. No subjects received the following $11^{o}$ superior endplates: small spike, extra-large spike, or small keel. No subjects received the 14mm height inlay.

**Table 16: 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 |

***Adverse Events That Occurred in the PMA Clinical Trial:***

**Adverse Event Summary**

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.

A summary of the adverse event data is presented in Table 17. 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 randomized subjects treated in the study as well as for non-randomized activL subjects. Although p-values were obtained without any adjustment for multiplicity, there were no statistically significant differences in all adverse events, subsequent surgical interventions at the index level, device-related adverse events, serious device-related adverse events, or adverse events within two days of the procedure when comparing the randomized treatment groups. Again, although p-values were obtained without any adjustment for multiplicity, there were statistically significant differences noted in procedure-related adverse events and serious adverse events in favor of the activL group when comparing the randomized treatment groups. The non-randomized control data is not included due to the limited sample size.

**Table 17: 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 18 provides data on the total number of adverse events in each randomized treatment group stratified by device design and level treated for the randomized activL and control device and level treated for the randomized control group.

**Table 18: 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%) |

**All Adverse Events**

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 19. This table includes adverse events from all subjects, randomized and non-randomized, to establish the safety profile of the device. All investigational subjects (randomized and non-randomized) are summarized together in one group, and all control subjects (randomized and non-randomized) are summarized together in one group. 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 20. Subject 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 19: Time Course of All 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 Contr (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 |

| 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 Contr (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 |
| 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 |
| 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 |

| 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 Contr (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 - 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 |
| 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

Definitions of the adverse event categories and subcategories used by the CEC are provided in the following table:

**Table 20: 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. |
| 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). |

| Adverse Event | Definition |
|---|---|
| Genitourinary<br>• Erectile or Sexual Dysfunction<br>• Retrograde Ejaculation<br>• Other | <br>• 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.<br>• Occurs when semen enters the bladder instead of emerging through the penis during orgasm.<br>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<br>• Fracture-Adjacent Vertebra<br>• Degenerative Joint Disease<br>• Joint or Muscle<br>• Spasms – Lumbar/Buttock/Leg<br>• Radiographic Observation<br>• DDD Progression Adjacent<br>• Scoliosis<br>• Spinal Stenosis - Index | <br>• Fracture of the vertebra surrounding the device location including posterior rim. Example - index procedure = L4-L5, adjacent vertebrae = L4 OR L5.<br>• Includes ankylosing spondylitis, arthropathy, facet joint deterioration – index level, inflammatory polyarthritis, rheumatoid arthritis.<br>• Includes benign mass/tumor – lumbar, joint sprain – lumbar, and pulled or strained muscle or muscle cramp – lumbar.<br>• 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.<br>• Includes disc herniation – adjacent and trabecular bone bridging or heterotopic ossification – index level<br>• Condition in which pain is caused from a damaged disc at an adjacent level.<br>• Abnormal curving of the lumbar spine.<br>• 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<br>• Motor Deficit<br>*Persistent, Unilateral*<br>*Subjective, Bilateral*<br>*Subjective, Unilateral*<br>*Transient, Bilateral*<br>*Transient, Unilateral*<br>• Nerve Root or Spinal Cord Injury<br>• Reflex Change or Abnormality<br>• Sensory Deficit<br>*Measureable, Bilateral*<br>*Measureable, Unilateral*<br>*Subjective, Bilateral*<br>*Subjective, Unilateral*<br>Straight Leg Raise + or Change | <br><br>*Measurable decrease of motor deficit unilaterally lasting > ~2 years.*<br>*Functional weakness reported in bilateral lower extremities with no score changes.*<br>*Functional weakness reported in unilateral lower extremity with no score changes.*<br>*Measurable decrease of motor deficit bilaterally lasting ≤~2 years.*<br>*Measurable decrease of motor deficit unilaterally lasting ≤~2 years.*<br>• 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.<br>• Change or abnormal reflexes (e.g., patellar and Achilles); includes both unilateral or bilateral changes and/or abnormalities.<br><br>*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.*<br>*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.*<br>*Reported sensory deficit in bilateral lower extremities with no score changes. Includes paresthesia and dysesthesia terms such as numbness, tingling, sensitivity/hypersensitivity, burning.*<br>*Reported sensory deficit in unilateral lower extremity with no score changes.*<br>• 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<br>• Lower Extremity Pain Only<br>*Bilateral Lower Leg*<br>*Bilateral Upper Leg*<br>*Unilateral Lower Leg*<br>*Unilateral Upper Leg*<br>• Lumbar Pain Only | <br><br>*Bilateral lower leg pain.*<br>*Bilateral upper leg pain.*<br>*Unilateral lower leg pain.*<br>*Unilateral upper leg pain.*<br>• 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. |

| Adverse Event | Definition |
|---|---|
| • Lumbar and Lower Extremity Pain<br>*Lumbar & Bilat. Radiation Lower Leg*<br>*Lumbar & Bilat. Radiation Upper Leg*<br>*Lumbar & Unilat. Radiation Lower Leg*<br>*Lumbar & Unilat. Radiation Upper Leg* | <br>*Pain in the lumbar area with radiation to the bilateral lower legs.*<br>*Pain in the lumbar area with radiation to the bilateral upper legs.*<br>*Pain in the lumbar area with radiation to the unilateral lower leg.*<br>*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. |
| 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

Table 21 presents a comparison of adverse event categories for randomized subjects. 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 except for lumbar pain only in which the difference favored the activL group.

**Table 21: Comparison of Adverse Events in Randomized Subjects**

| Adverse Event | R activL (N=218) | R Contr (N=106) |
|---|---|---|
| Total Adverse Events | 186 (85.3%) | 95 (89.6%) |
| Cancer | 1 (0.5%) | 3 (2.8%) |
| Cardiac and Vascular | 27 (12.4%) | 12 (11.3%) |
| Dermatologic | 6 (2.8%) | 3 (2.8%) |
| Device Deficiency Total | 7 (3.2%) | 7 (6.6%) |
| • Implant Expulsion | • 0 (0.0%) | • 1 (0.9%) |
| • Implant Malposition | • 2 (0.9%) | • 2 (1.9%) |
| • Implant Migration | • 1 (0.5%) | • 1 (0.9%) |
| • Implant Subsidence | • 4 (1.8%) | • 3 (2.8%) |
| Endocrine | 10 (4.6%) | 2 (1.9%) |
| Eyes/Ears/Nose/Throat (EENT) | 4 (1.8%) | 6 (5.7%) |
| Gastrointestinal | 44 (20.2%) | 21 (19.8%) |
| Genitourinary | 50 (22.9%) | 21 (19.8%) |
| Hepatobiliary | 6 (2.8%) | 2 (1.9%) |
| Immunological | 9 (4.1%) | 5 (4.7%) |
| Metabolic/Blood/Electrolytes | 10 (4.6%) | 9 (8.5%) |
| Musculoskeletal – Lumbar | 23 (10.6%) | 14 (13.2%) |
| Musculoskeletal - Non-Lumbar | 76 (34.9%) | 35 (33.0%) |
| Neurological Total | 35 (16.1%) | 22 (20.8%) |
| • Motor Deficit | • 10 (4.6%) | • 7 (6.6%) |
| • Nerve Root or Spinal Cord Injury | • 0 (0.0%) | • 0 (0.0%) |
| • Reflex Change or Abnormality | • 4 (1.8%) | • 1 (0.9%) |
| • Sensory Deficit | • 24 (11.0%) | • 17 (16.0%) |
| • Straight Leg Raise + or Change | • 1 (0.5%) | • 1 (0.9%) |
| Neurological - Non-lumbar/Lower Extremity | 21 (9.6%) | 14 (13.2%) |
| Pain - Lumbar and Lower Extremity Total | 116 (53.2%) | 65 (61.3%) |
| • Lower Extremity Pain Only | • 58 (26.6%) | • 22 (20.8%) |
| • Lumbar Pain Only | • 47 (21.6%) | • 35 (33.0%) |
| • Lumbar and Lower Extremity Pain | • 39 (17.9%) | • 22 (20.8%) |
| Psychosocial | 22 (10.1%) | 11 (10.4%) |
| Respiratory | 15 (6.9%) | 9 (8.5%) |
| Trauma | 42 (19.3%) | 24 (22.6%) |
| Uncoded | 0 (0.0%) | 1 (0.9%) |
| Wound Issue - Index Procedure | 24 (11.0%) | 16 (15.1%) |

SSI = subsequent surgical intervention

Table 22 provides data on the number of adverse events in each category in each randomized treatment group. Adverse events for the randomized activL group are stratified by device design and treated level. Adverse events for the randomized control group are stratified by control device type and level treated.

In the activL group, more adverse 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 adverse 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).

In the activL group, the most frequently reported adverse event, for both device designs and both treatment levels, was lower extremity pain. In the control group, the most frequently reported adverse event, for both device types and both treatment levels, was lumbar pain only.

**Table 22: 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 |

| 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) |
| 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 | | | | | | | |
| • Radiographic Observation | 0 | 7 | 4 | 6 | 4 | 0 | 1 | 3 |
| • DDD Progression Adjacent | 0 | 0 | 0 | 0 | 2 | 0 | 1 | 1 |
| • Scoliosis | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 1 |
| • Spinal Stenosis - Index | 0 | 0 | 0 | 0 | 1 | 0 | 1 | 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 |
| *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 |

| 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) |
| 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

**Deaths**

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

**Index Level Subsequent Surgical Interventions**

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 are 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 23. Note that there were no subsequent surgical interventions at the index level in either of the non-randomized cohorts (activL or control).

**Table 23: 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%) |

| 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) |
| 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 24 provides data on the number of subsequent surgical interventions at the index level in each randomized treatment group. Data for the randomized activL group are stratified by device design and treated level. Data for the randomized control group are stratified by control device type and treated level .

**Table 24: 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 25 provides detailed information on each activL subsequent surgical intervention at the index level. Similarly, Table 26 provides detailed information on each control group subsequent surgical intervention at the index level.

**Table 25: 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.

**Table 26: Detailed Information on Control Group Subsequent Surgical Interventions at the Index Level***

| Surgical Intervention Type | Procedure Type | Procedure Level | Adverse Event Type | Contr Device | Days From Index Procedure | Device Removed? |
|---|---|---|---|---|---|---|
| Removal | Fusion | L5-S1 | Implant expulsion | ProDisc-L | 317 | Yes |
| Removal | Fusion | L5-S1 | Implant subsidence | Charité | 835 | Yes |
| Supplemental Fixation | Fusion | L5-S1 | Lumbar pain only | Charité | 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 | Charité | 79 | No |
| Reoperation | Foraminotomy/ decompression | L5-S1 | Pain lumbar & unilateral radiation into lower legs | ProDisc-L | 710 | No |

* As of April 11, 2013.

**Index Level Additional Procedures**

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 27. Table 28 provides similar information on index level additional procedures in the control group. The majority of procedures in both groups were rhizotomy/ablation procedures.

**Table 27: activL Index Level Additional Procedures**

| Procedure Type | Procedure Level | Adverse Event Type | activL Device Design | Days From Index Procedure |
|---|---|---|---|---|
| Rhizotomy/Ablation | L4-L5, L5-S1 | Facet joint deterioration - index level | Keel | 147 |
| Rhizotomy/Ablation | L5-S1 | Bone fracture - adjacent vertebra | Spike | 246 |
| Rhizotomy/Ablation | L4-L5, L5-S1 | Lumbar pain only | Keel | 361 |
| Rhizotomy/Ablation | L3-L4, L4-L5, L5-S1 | Pain lumbar & bilateral radiation into lower legs | Keel | 555 |
| Rhizotomy/Ablation | L3-L4, L4-L5, L5-S1 | Pain lumbar & bilateral radiation into lower legs | Keel | 576 |
| Rhizotomy/Ablation | L4-L5, L5-S1 | Pain lumbar & bilateral radiation into lower legs | Spike | 582 |
| Rhizotomy/Ablation | L4-L5, L5-S1 | Pain lumbar & unilateral radiation into upper legs | Spike | 719 |
| Rhizotomy/Ablation | L3-L4, L4-L5, L5-S1 | Pain lumbar & bilateral radiation into lower legs | Keel | 742 |
| Other (Reinsertion rod ) | L5-S1 | Implant Malposition | Spike | 156 |

**Table 28: Control Group Index Level Additional Procedures**

| Procedure Type | Procedure Level | Adverse Event Type | Contr Device | Days From Index Procedure |
|---|---|---|---|---|
| Rhizotomy/Ablation | Sacral | Lumbar pain only | ProDisc-L | 133 |
| Rhizotomy/Ablation | Sacral | Lumbar pain only | ProDisc-L | 154 |
| Rhizotomy/Ablation | Other (unknown) | Lumbar pain only | Charité | 196 |
| Rhizotomy/Ablation | L1-L2, L2-L3, L3-L4, L4-L5, L5-S1 | Pain bilateral lower leg | Charité | 488 |
| Rhizotomy/Ablation | L4-L5, L5-S1 | Pain lumbar & unilateral radiation into lower legs | Charité | 504 |
| Rhizotomy/Ablation | L4-L5, L5-S1 | Pain lumbar & unilateral radiation into lower legs | Charité | 580 |
| Fusion prior to study treatment | L5-S1 | Bone fracture - adjacent vertebra | N/A | 0 |

**Device-Related Adverse Events**

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 29. 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 29: 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 Contr (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 |

| 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 Contr (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 |
| 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

SSI = subsequent surgical intervention

Table 30 presents data for the randomized activL group stratified by device design and treated level and data for the randomized control group stratified by control device type and treated level.

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.

**Table 30: Device-Related Adverse Events - 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 a Device-Related AE (%) | 68 (59.1%) | 65 (63.7%) | 33 (53.2%) | 101 (64.7%) | 58 (90.6%) | 36 (87.8%) | 23 (67.6%) | 46 (63.9%) |
| Total Number of Device-Related AEs | 110 | 104 | 50 | 167 | 62 | 52 | 40 | 74 |
| Total Subjects with a Serious Device-Related AE (%) | 16 (13.9%) | 12 (11.8%) | 9 (14.5%) | 19 (12.2%) | 10 (15.6%) | 10 (24.4%) | 7 (20.6%) | 13 (18.1%) |
| Total Number of Serious Device-Related AEs | 16 | 15 | 10 | 21 | 10 | 10 | 7 | 13 |
| Cardiac and Vascular | 2 | 0 | 1 | 1 | 0 | 1 | 1 | 0 |
| Device Deficiency | 4 | 1 | 2 | 3 | 3 | 2 | 1 | 4 |
| • Implant Expulsion | • 0 | • 0 | • 0 | • 0 | • 1 | • 0 | • 0 | • 1 |
| • Implant Migration | • 1 | • 0 | • 0 | • 1 | • 1 | • 0 | • 0 | • 1 |
| • Implant Subsidence | • 3 | • 1 | • 2 | • 2 | • 1 | • 2 | • 1 | • 2 |
| Musculoskeletal – Lumbar | 4 | 5 | 2 | 7 | 1 | 0 | 1 | 0 |
| Neurological – Lumbar and lower extremities | 19 | 15 | 4 | 31 | 11 | 11 | 11 | 11 |
| • Motor Deficit | • 5 | • 6 | • 1 | • 10 | • 3 | • 4 | • 5 | • 2 |
| *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, Unilateral* | *1* | *5* | *1* | *5* | *3* | *4* | *5* | *2* |
| • Nerve Root or Spinal Cord Injury | • 0 | • 0 | • 0 | • 0 | • 0 | • 0 | • 0 | • 0 |
| • Sensory Deficit | • 14 | • 9 | • 2 | • 21 | • 8 | • 6 | • 5 | • 9 |
| *Measureable, Bilateral* | • 0 | *1* | *0* | *1* | *0* | *0* | *0* | *0* |
| *Measureable, Unilateral* | *7* | *3* | *1* | *9* | *4* | *3* | *5* | *2* |
| *Subjective, Bilateral* | *4* | *2* | *1* | *5* | *2* | *3* | *0* | *5* |
| *Subjective, Unilateral* | *3* | *3* | *0* | *6* | *2* | *0* | *0* | *2* |
| • Straight Leg Raise + or Change | • 0 | • 0 | • 1 | • 0 | • 0 | • 1 | • 1 | • 0 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Pain - Lumbar and Lower Extremity | 81 | 83 | 41 | 125 | 47 | 38 | 26 | 59 |
| • Lower Extremity Pain Only | • 32 | • 35 | • 17 | • 51 | • 16 | • 13 | • 6 | • 23 |
| *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* | *5* | *7* | *2* | *10* |
| *Unilateral Upper Leg* | *5* | *3* | *2* | *6* | *2* | *1* | *1* | *2* |
| • Lumbar Pain Only | • 27 | • 29 | • 8 | • 48 | • 19 | • 17 | • 11 | • 25 |
| • Lumbar and Lower Extremity Pain | • 22 | • 19 | • 16 | • 26 | • 12 | • 8 | • 9 | • 11 |
| *Lumbar & Bilat. Radiation Lower Leg* | *10* | *6* | *6* | *11* | *6* | *3* | • 5 | *4* |
| *Lumbar & Bilat. Radiation Upper Leg* | *2* | *4* | *1* | *5* | *1* | *1* | *0* | *2* |
| *Lumbar & Unilat. Radiation Lower Leg* | *7* | *8* | *8* | *7* | *5* | *4* | *4* | *5* |
| *Lumbar & Unilat. Radiation Upper Leg* | *3* | *1* | *1* | *3* | *0* | *0* | *0* | *0* |

**Procedure-Related Adverse Events**

The CEC defined procedure-related events as those having etiology, temporal association, or cause that was related to the surgical index procedure. Based on this definition, the number and percentage of subjects who experienced a procedure-related adverse event as determined by the CEC is provided in Table 31. Three hundred sixty-three (363) procedure-related events occurred in all subjects during the course of the trial (NR activL = 46; R activL = 195; R Contr = 118; NR Contr = 3). The proportion of randomized subjects with a procedure-related adverse event was higher in the control group (R activL = 53.2%; R Contr = 66.0%), and the difference was statistically significant, although p-values were obtained without any adjustment for multiplicity. The most common procedure-related adverse events were lower extremity pain, sensory deficit and lumbar pain only.

**Table 31: Total Procedure-Related Adverse Events***

| Adverse Event | All activL (N=264) | | All Contr (N=112) | |
|---|---|---|---|---|
| | Subjects n (%) | Events N | Subjects n (%) | Events N |
| Total Procedure-Related AEs | 145 (52.4%) | 241 | 73 (61.3%) | 122 |
| Total Serious Procedure-Related AEs | 33 (11.91%) | 40 | 24 (20.17%) | 27 |
| Cardiac & Vascular | 18 (6.5%) | 19 | 5 (4.2%) | 5 |
| Dermatologic | 3 (1.1%) | 3 | 1 (0.8%) | 1 |
| Device Deficiency | 6 (2.2%) | 6 | 5 (4.2%) | 5 |
| • Implant Malposition | • 2 (0.7%) | • 2 | • 2 (1.7%) | • 2 |
| • Implant Subsidence | • 4 (1.4%) | • 4 | • 3 (2.5%) | • 3 |
| Endocrine | 1 (0.4%) | 1 | 1 (0.8%) | 1 |
| Eyes/Ears/Nose/Throat | 2 (0.7%) | 2 | 1 (0.8%) | 1 |
| Gastrointestinal | 26 (9.4%) | 26 | 12 (10.1%) | 13 |
| Genitourinary | 25 (9.0%) | 27 | 11 (9.2%) | 11 |
| Hepatobiliary | 1 (0.4%) | 1 | 0 (0.0%) | 0 |
| Immunological | 3 (1.1%) | 3 | 1 (0.8%) | 1 |
| Metabolic/Blood/ Electrolytes | 4 (1.4%) | 4 | 4 (3.4%) | 4 |
| Musculoskeletal – Lumbar | 4 (1.4%) | 4 | 5 (4.2%) | 5 |
| Musculoskeletal - Non-Lumbar | 0 (0.0%) | 0 | 0 (0.0%) | 0 |
| Neurological | 25 (9.0%) | 28 | 14 (11.8%) | 17 |
| • Motor Deficit | • 6 (2.2%) | • 7 | • 5 (4.5%) | • 7 |
| *Persistent, Unilateral* | *1 (0.4%)* | *1* | *0 (0.0%)* | *0* |
| *Subjective, Unilateral* | *2 (0.7%)* | *2* | *0 (0.0%)* | *0* |
| *Transient, Unilateral* | *3 (1.1%)* | *4* | *5 (4.2%)* | *7* |
| • Nerve Root or Spinal Cord Injury | • 1 (0.4%) | • 1 | • 0 (0.0%) | • 0 |
| • Sensory Deficit | • 17 (6.1%) | • 19 | • 9 (7.6%) | • 9 |
| *Measureable, Bilateral* | *1 (0.4%)* | *1* | *0 (0.0%)* | *0* |
| *Measureable, Unilateral* | *10 (3.6%)* | *11* | *4 (3.4%)* | *4* |
| *Subjective, Bilateral* | *4 (1.4%)* | *4* | *4 (3.4%)* | *4* |
| *Subjective, Unilateral* | *2 (0.7%)* | *3* | *1 (0.8%)* | *1* |
| • Straight Leg Raise + or Change | • 1 (0.4%) | • 1 | • 1 (0.8%) | • 1 |

| Adverse Event | All activL (N=264) | | All Contr (N=112) | |
|---|---|---|---|---|
| | Subjects n (%) | Events N | Subjects n (%) | Events N |
| Neurological - Non-lumbar/ Lower Extr | 5 (1.8%) | 5 | 1 (0.8%) | 1 |
| Pain - Lumbar and Lower Extremity (LE) | 70 (25.3%) | 76 | 34 (28.6%) | 38 |
| • LE Pain Only | • 68 (25.8%) | • 47 | • 23 (20.5%) | • 14 |
| *Bilateral Lower Leg* | *11 (3.97%)* | *11* | *6 (5.04%)* | *6* |
| *Bilateral Upper Leg* | *7 (2.5%)* | *7* | *2 (1.7%)* | *2* |
| *Unilateral Lower Leg* | *25 (9.0%)* | *26* | *5 (4.2%)* | *5* |
| *Unilateral Upper Leg* | *3 (1.1%)* | 3 | *1 (0.8%)* | 1 |
| • Lumbar Pain Only | • 13 (4.7%) | • 14 | • 14 (11.8%) | • 14 |
| • Lumbar and LE Pain | • 14 (5.3%) | • 15 | • 10 (8.9%) | • 10 |
| *Lumbar & Bilat. Radiation Lower Leg* | *6 (2.2%)* | *6* | *6 (5.4%)* | *6* |
| *Lumbar & Bilat. Radiation Upper Leg* | *2 (0.7%)* | *2* | *0 (0.0%)* | *0* |
| *Lumbar & Unilat. Radiation Lower Leg* | *6 (2.2%)* | *7* | *4 (3.4%)* | *4* |
| Respiratory | 5 (1.8%) | 5 | 1 (0.8%) | 1 |
| Trauma | 4 (1.4%) | 4 | 0 (0.0%) | 0 |
| Wound Issue - Index Procedure | 25 (9.0%) | 26 | 17 (14.3%) | 18 |

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

Table 32 provides data on procedure-related adverse events for the randomized activL group stratified by device design and treated level and data for the randomized control group stratified by control device type and treated level.

**Table 32: Procedure-Related Adverse Events by Category - Stratified**

| Adverse Event (AE) | R activL (N=218) | | | | R Contr (N=106) | | | |
|---|---|---|---|---|---|---|---|---|
| | Device Design | | Treatment Level | | Contr 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 a Procedure-Related AE (%) | 54 (47.0%) | 61 (59.8%) | 31 (50.0%) | 85 (54.5%) | 42 (65.6%) | 27 (65.9%) | 22 (64.7%) | 48 (66.7%) |
| Total Number of Procedure-Related AEs | 90 | 103 | 51 | 144 | 67 | 50 | 37 | 81 |
| Total Subjects with a Serious Procedure-Related AE (%) | 13 (11.3%) | 14 (13.7%) | 10 (16.1%) | 17 (10.9%) | 12 (18.8%) | 10 (24.4%) | 7 (20.6%) | 16 (22.2%) |
| Total Number of Serious Procedure-Related AEs | 16 | 18 | 13 | 21 | 13 | 12 | 7 | 19 |
| Cardiac & Vascular | 10 | 5 | 7 | 8 | 2 | 3 | 1 | 4 |
| • Bleeding - index procedure | • 3 | • 0 | • 2 | • 1 | • 0 | • 0 | • 0 | • 0 |
| • DVT - index procedure | • 0 | • 2 | • 2 | • 0 | • 0 | • 0 | • 0 | • 0 |
| • Thrombosis | • 1 | • 0 | • 0 | • 1 | • 0 | • 0 | • 0 | • 0 |
| • Arterial dissection | • 0 | • 0 | • 0 | • 0 | • 0 | • 1 | • 1 | • 0 |
| • Iliac vessel tear - index procedure | • 2 | • 0 | • 0 | • 2 | • 0 | • 1 | • 0 | • 1 |
| • Iliac vessel tear – SSI procedure | • 1 | • 1 | • 0 | • 2 | • 0 | • 0 | • 0 | • 0 |
| • Other | • 3 | • 2 | • 3 | • 2 | • 2 | • 1 | • 0 | • 3 |
| Dermatologic | 0 | 3 | 0 | 3 | 1 | 0 | 0 | 1 |

| Adverse Event (AE) | R activL (N=218) | | | | R Contr (N=106) | | | |
|---|---|---|---|---|---|---|---|---|
| | Device Design | | Treatment Level | | Contr 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) |
| Device Deficiency | 4 | 2 | 2 | 4 | 3 | 2 | 2 | 3 |
| • Implant Malposition | • 1 | • 1 | • 0 | • 2 | • 2 | • 0 | • 1 | • 1 |
| • Implant Subsidence | • 3 | • 1 | • 2 | • 2 | • 1 | • 2 | • 1 | • 2 |
| Endocrine | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 1 |
| Eyes/Ears/Nose/Throat | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 1 |
| Gastrointestinal | 8 | 13 | 9 | 12 | 9 | 3 | 4 | 8 |
| Genitourinary | 9 | 15 | 5 | 19 | 6 | 5 | 1 | 10 |
| • Erectile or Sexual Dysfunction | • 2 | • 0 | • 0 | • 2 | • 1 | • 0 | • 0 | • 1 |
| • Retrograde Ejaculation | • 1 | • 2 | • 0 | • 3 | • 1 | • 2 | • 0 | • 3 |
| • Other | • 6 | • 13 | • 5 | • 14 | • 4 | • 3 | • 1 | • 6 |
| Hepatobiliary | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Immunological | 0 | 2 | 0 | 2 | 1 | 0 | 0 | 1 |
| Metabolic/Blood/ Electrolytes | 1 | 2 | 2 | 1 | 2 | 2 | 2 | 2 |
| Musculoskeletal – Lumbar | 1 | 1 | 1 | 1 | 4 | 0 | 2 | 3 |
| Musculoskeletal - Non-Lumbar | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Neurological – Lumbar and lower extremities | 10 | 9 | 4 | 16 | 6 | 10 | 10 | 6 |
| | • 3 | • 1 | • 0 | • 4 | • 3 | • 4 | • 4 | • 3 |
| • Motor Deficit | *1* | *0* | *0* | *1* | *0* | *0* | *0* | *0* |
| *Persistent, Unilateral* | *2* | *0* | *0* | *2* | *0* | *0* | *0* | *0* |
| *Subjective, Unilateral* | *0* | *1* | *0* | *1* | *3* | *4* | *4* | *3* |
| *Transient, Unilateral* | • 0 | • 0 | • 0 | • 0 | • 0 | • 0 | • 0 | • 0 |
| • Nerve Root or Spinal Cord Injury | • 7 | • 8 | • 3 | • 12 | • 3 | • 5 | • 5 | • 3 |
| • Sensory Deficit | *0* | *1* | *0* | *1* | *0* | *0* | *0* | *0* |
| *Measureable, Bilateral* | *4* | *4* | *2* | *6* | *1* | *3* | *3* | *1* |
| *Measureable, Unilateral* | *3* | *1* | *1* | *3* | *2* | *1* | *1* | *2* |
| *Subjective, Bilateral* | *0* | *2* | *0* | *2* | *0* | *1* | *1* | *0* |
| *Subjective, Unilateral* | • 0 | • 0 | • 1 | • 0 | • 0 | • 1 | • 1 | • 0 |
| • Straight Leg Raise + or Change | • 0 | • 0 | • 0 | • 0 | • 0 | • 1 | • 0 | • 0 |
| Neurological - Non-lumbar/ Lower Extremity | 1 | 2 | 1 | 2 | 1 | 0 | 0 | 1 |
| Pain - Lumbar and Lower Extremity (LE) | 30 | 31 | 15 | 47 | 18 | 19 | 11 | 26 |
| • LE Pain Only | • 16 | • 22 | • 10 | • 29 | • 7 | • 7 | • 2 | • 12 |
| *Bilateral Lower Leg* | *1* | *9* | *1* | *9* | *3* | *3* | *0* | *6* |
| *Bilateral Upper Leg* | *2* | *1* | *3* | *1* | *2* | *0* | *0* | *2* |
| *Unilateral Lower Leg* | *11* | *11* | *5* | *17* | *1* | *4* | *2* | *3* |
| *Unilateral Upper Leg* | *2* | *1* | *1* | *2* | *1* | *0* | *0* | *1* |
| • Lumbar Pain Only | • 7 | • 5 | • 1 | • 11 | • 7 | • 6 | • 3 | • 10 |
| • Lumbar and LE Pain | • 7 | • 4 | • 4 | • 7 | • 4 | • 6 | • 6 | • 4 |
| *Lumbar & Bilat. Radiation Lower Leg* | *2* | *2* | *1* | *3* | *3* | *3* | *4* | *2* |
| *Lumbar & Bilat. Radiation Upper Leg* | *1* | *1* | *0* | *2* | *0* | *0* | *0* | *0* |
| *Lumbar & Unilat. Radiation Lower Leg* | *4* | *1* | *3* | *2* | *1* | *3* | *2* | *2* |
| Respiratory | 2 | 3 | 1 | 4 | 1 | 0 | 1 | 0 |
| Trauma | 1 | 3 | 0 | 4 | 0 | 0 | 0 | 0 |

| Adverse Event (AE) | R activL (N=218) | | | | R Contr (N=106) | | | |
|---|---|---|---|---|---|---|---|---|
| | Device Design | | Treatment Level | | Contr 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) |
| 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 Injury/Tear or CSF Leak | • 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

**Serious Adverse Events**

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; and/or
- Led to a congenital anomaly in the offspring, or caused fetal distress or death.

Based on this definition, the number and percentage of subjects who experienced a serious adverse event as determined by the CEC is provided in Table 33. Two hundred fourteen (214) SAEs were reported in all subjects during the course of the trial (NR activL = 21; R activL = 121; R Contr = 68; NR Contr = 4). The proportion of randomized subjects with SAEs was higher in the control group (R activL = 33.0%; R Contr = 48.1%), and the difference was statistically significant, although p-values were obtained without adjustment for multiplicity. The most common serious adverse events in both treatment groups were lumbar and lower extremity pain and lumbar pain only.

**Table 33: Total Serious Adverse Events**

| Adverse Event | All activL (N=264) | | All Contr (N=112) | |
|---|---|---|---|---|
| | Subjects n (%) | Events N | Subjects n (%) | Events N |
| Total Serious Adverse Events | 90 (34.1%) | 142 | 53 (47.3%) | 72 |
| Cancer | 3 (1.1%) | 3 | 3 (2.7%) | 3 |
| Cardiac & Vascular | 13 (4.9%) | 14 | 4 (3.6%) | 4 |
| Dermatologic | 0 (0.0%) | 0 | 0 (0.0%) | 0 |
| Device Deficiency | 6 (2.3%) | 6 | 6 (5.4%) | 6 |
| • Implant Expulsion | • 0 (0.0%) | • 0 | • 1 (0.9%) | • 1 |
| • Implant Malposition | • 2 (0.8%) | • 2 | • 2 (1.8%) | • 2 |
| • Implant Migration | • 1 (0.4%) | • 1 | • 1 (0.9%) | • 1 |
| • Implant Subsidence | • 3 (1.1%) | • 3 | • 2 (1.8%) | • 2 |
| Endocrine | 2 (0.8%) | 2 | 1 (0.9%) | 1 |
| Eyes/Ears/Nose/Throat | 1 (0.4%) | 1 | 0 (0.0%) | 0 |
| Gastrointestinal | 12 (4.5%) | 13 | 6 (5.4%) | 6 |
| Genitourinary | 20 (7.6%) | 21 | 8 (7.1%) | 8 |
| Hepatobiliary | 5 (1.9%) | 5 | 2 (1.8%) | 2 |
| Immunological | 3 (1.1%) | 3 | 1 (0.9%) | 1 |
| Metabolic/Blood/ Electrolytes | 2 (0.8%) | 2 | 0 (0.0%) | 0 |
| Musculoskeletal – Lumbar | 9 (3.4%) | 9 | 1 (0.9%) | 1 |
| Musculoskeletal - Non-Lumbar | 18 (6.8%) | 18 | 9 (8.0%) | 9 |
| Neurological | 4 (1.5%) | 4 | 0 (0.0%) | 0 |
| • Motor Deficit | • 3 (1.1%) | • 3 | • 0 (0.0%) | • 0 |
| • Nerve Root or Spinal Cord Injury | • 0 (0.0%) | • 0 | • 0 (0.0%) | • 0 |
| • Reflex Change or Abnormality | • 0 (0.0%) | • 0 | • 0 (0.0%) | • 0 |
| • Sensory Deficit | • 1 (0.4%) | • 1 | • 0 (0.0%) | • 0 |
| • Straight Leg Raise + or Change | • 0 (0.0%) | • 0 | • 0 (0.0%) | • 0 |
| Neurological - Non-lumbar/ Lower Extr | 5 (1.9%) | 5 | 3 (2.7%) | 3 |
| Pain - Lumbar and Lower Extremity (LE) | 17 (6.4%) | 18 | 18 (16.1%) | 19 |
| • LE Pain Only | • 3 (1.1%) | • 3 | • 4 (3.6%) | • 4 |
| • Lumbar Pain Only | • 5 (1.9%) | • 5 | • 6 (5.4%) | • 6 |
| • Lumbar and LE Pain | • 9 (3.4%) | • 10 | • 8 (7.1%) | • 9 |
| Psychosocial | 6 (2.3%) | 6 | 4 (3.6%) | 4 |
| Respiratory | 2 (0.8%) | 2 | 1 (0.9%) | 1 |
| Trauma | 5 (1.9%) | 5 | 1 (0.9%) | 1 |
| Uncoded | 1 (0.4%) | 1 | 1 (0.9%) | 1 |
| Wound Issue - Index Procedure | 4 (1.5%) | 4 | 2 (1.8%) | 2 |

SSI = subsequent surgical intervention

**Serious Device-Related Adverse Events**

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. The CEC defined serious device-related adverse events as device-related adverse events that also 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; and/or
- Led to a congenital anomaly in the offspring, or caused fetal distress or death.

Based on this definition, the number and percentage of subjects who experienced a serious device-related adverse event (SDAE) as determined by the CEC is provided in Table 34. Fifty-eight (58) 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 event in both treatment groups was lumbar and lower extremity pain.

**Table 34: Total Serious Device-Related Adverse Events**

| Adverse Event | All activL (N=264) | | All Contr (N=112) | |
|---|---|---|---|---|
| | Subjects n (%) | Events N | Subjects n (%) | Events N |
| Total Serious Device-Related Adverse Events | 32 (12.1%) | 36 | 21 (18.8%) | 22 |
| Cardiac & Vascular | 2 (1.0%) | 2 | 0 (0.0%) | 0 |
| Device Deficiency | 4 (1.5%) | 4 | 4 (3.6%) | 4 |
| • Implant Expulsion | • 0 (0.0%) | • 0 | • 1 (0.9%) | • 1 |
| • Implant Migration | • 1 (0.5%) | • 1 | • 1 (0.9%) | • 1 |
| • Implant Subsidence | • 3 (1.4%) | • 3 | • 2 (1.9%) | • 2 |
| Musculoskeletal – Lumbar | 7 (3.2%) | 7 | 0 (0.0%) | 0 |
| Neurological | 3 (1.1%) | 3 | 0 (0.0%) | 0 |
| • Motor Deficit | • 3 (1.1%) | • 3 | • 0 (0.0%) | • 0 |
| • Sensory Deficit | • 0 (0.0%) | • 0 | • 0 (0.0%) | • 0 |
| • Straight Leg Raise + or Change | • 0 (0.0%) | • 0 | • 0 (0.0%) | • 0 |
| Pain - Lumbar and Lower Extremity (LE) | 18 (6.8%) | 19 | 18(16.1%) | 20 |
| • LE Pain Only | • 3 (1.1%) | • 3 | • 4 (3.6%) | • 4 |
| • Lumbar Pain Only | • 5 (1.9%) | • 5 | • 6 (5.4%) | • 6 |
| • Lumbar and LE Pain | • 9 (3.4%) | • 10 | • 7 (6.3%) | • 8 |
| Uncoded | 1 (2.2%) | 1 | 1 (0.0%) | 0 |

SSI = subsequent surgical intervention

**Neurological Status:**

The change in overall neurological status at each timepoint is provided in Table 35. 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 (motor evaluations: R activL = 97.3%, R Contr = 98.9%; sensory evaluations: R activL = 94.1%, R Contr = 93.1%), and there were no statistically significant differences although p-values were obtained without any adjustment for multiplicity.

**Table 35: 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 |

Table 36 provides data on 24-month neurological status for the randomized activL group stratified by device design and treatment level and data for the randomized control group stratified by control device type and treated level.

**Table 36: 24 Month Overall Neurological Status - Stratified**

| Neurological Status | R activL (N=218) | | | | R Contr (N=106) | | | |
|---|---|---|---|---|---|---|---|---|
| | Device Design | | Treatment Level | | Contr 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) |
| Improved | 29/99 (29.3%) | 21/89 (23.6%) | 11/49 (22.4%) | 39/139 (28.1%) | 14/51 (27.5%) | 10/36 (27.8%) | 7/27 (25.9%) | 17/60 (28.3%) |
| Stable | 62/99 (62.6%) | 63/89 (70.8%) | 36/49 (73.5%) | 89/139 (64.0%) | 35/51 (68.6%) | 22/36 (61.1%) | 17/27 (63.0%) | 40/60 (66.7%) |
| Deteriorated | 8/99 (8.1%) | 5/89 (5.6%) | 2/49 (4.1%) | 11/139 (7.9%) | 2/51 (3.9%) | 4/36 (11.1%) | 3/27 (11.1%) | 3/60 (5.0%) |

## 2. Effectiveness Results

The analysis of effectiveness was based on the modified ITT cohort of subjects evaluable at the 24-month timepoint, 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).

***Primary Effectiveness Analysis:***

**Overall Success at 24 Months (Missing Imputed as Failures)**

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. Please note that since the control group had a higher percentage of missing data, the primary imputed analysis may have been biased in favor of the activL group; therefore, observed data are also presented throughout this summary.

The success rates at 24 months postoperative for each of the individual success components and overall success are provided in Table 37 for the randomized study subjects and non-randomized activL subjects. The non-randomized control data is not included due to the limited sample size. 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 in Table 37.

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 in this summary; 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 37: 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) | 34/46 (73.9%) | 164/218 (75.2%) | 70/106 (66.0%) | |
| 95% Confidence Interval (CI) | (58.9, 85.7) | (68.9, 80.8) | (56.2, 75.0) | 0.0874 |
| Neurological success (maintenance or improvement – motor & sensory evaluations) | 38/46 (82.6%) | 175/218 (80.3%) | 81/106 (76.4%) | |
| 95% CI | (68.6, 92.2) | (74.4, 85.3) | (67.2, 84.1) | 0.4678 |
| ROM success (maintenance or improvement) | 26/46 (56.5%) | 128/218 (58.7%) | 45/106 (42.5%) | |
| 95% CI | (41.1, 71.1) | (51.9, 65.3) | (32.9, 52.4) | 0.0065 |
| Device success (no SSIs at index level) | 43/46 (93.5%) | 184/218 (84.4%) | 90/106 (84.9%) | |
| 95% CI | (82.1, 98.6) | (78.9, 89.0) | (76.6, 91.1) | 1.0000 |
| No serious device-related AEs per CEC | 39/46 (84.8%) | 167/218 (76.6%) | 75/106 (70.8%) | |
| 95% CI | (71.1, 93.7) | (70.4, 82.1) | (61.1, 79.2) | 0.2772 |
| Overall success including ROM success component | 20/46 (43.5%) | 92/218 (42.2%) | 30/106 (28.3%) | |
| 95% CI | (28.9, 58.9) | (35.6, 49.1) | (20.0, 37.9) | |
| P-value (difference between groups; delta = 10%) | | | | <0.0001 |
| P-value (superiority) | | | | 0.0200 |
| Overall success without ROM success component | 30/46 (65.2%) | 135/218 (61.9%) | 56/106 (52.8%) | |
| 95% CI | (49.8, 78.6) | (55.1, 68.4) | (42.9, 62.6) | |
| P-value (difference between groups; delta = 10%) | | | | 0.0004 |
| P-value (superiority) R activL vs. R Contr | | | | 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).

Table 38 provides data on overall success at 24 months (missing imputed as failures) in the randomized activL group stratified by device design and level treated as compared to the all activL group. In randomized activL subjects, overall success and component outcomes were qualitatively comparable when comparing 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 the effect of treatment level on outcome success parameters in activL subjects, 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. While qualitatively higher overall and component success rates were noted in activL subjects treated at L5-S1, overall success and component outcomes were more comparable in the observed analysis (Tables 40-42, see section below). However, the trial was not designed or powered to demonstrate statistical poolability for the two activL treatment levels.

**Table 38: Overall Success at 24 Months Randomized activL (Missing Imputed as Failures) - Stratified**

| Primary Endpoint Component | R activL (N=218) | | | | | |
|---|---|---|---|---|---|---|
| | Device Design | | | Treatment Level | | |
| | All activL (N=218) | Spike (N=115) | Keel (N=102) | All activL (N=218) | L4-L5 (N=62) | L5-S1 (N=156) |
| ODI success (≥15 point improvement) | 164/218 (75.2%) | 87/115 (75.7%) | 77/102 (75.5%) | 164/218 (75.2%) | 45/62 (72.6%) | 119/156 (76.3%) |
| 95% CI | (68.9, 80.8) | (66.8, 83.2) | (66.0, 83.5) | (68.9, 80.8) | (59.8, 83.1) | (68.8, 82.7) |
| Neurological success (maintenance or improvement – motor & sensory evaluations) | 175/218 (80.3%) | 91/115 (79.1%) | 84/102 (82.4%) | 175/218 (80.3%) | 47/62 (75.8%) | 128/156 (82.1%) |
| 95% CI | (74.4, 85.3) | (70.6, 86.1) | (73.6, 89.2) | (74.4, 85.3) | (63.3, 85.8) | (75.1, 87.7) |
| ROM success (maintenance or improvement) | 128/218 (58.7%) | 68/115 (59.1%) | 60/102 (58.8%) | 128/218 (58.7%) | 32/62 (51.6%) | 96/156 (61.5%) |
| 95% CI | (51.9, 65.3) | (49.6, 68.2) | (48.6, 68.5) | (51.9, 65.3) | (38.6, 64.5) | (53.4, 69.2) |
| Device success (no SSIs at index level) | 184/218 (84.4%) | 98/115 (85.2%) | 86/102 (84.3%) | 184/218 (84.4%) | 48/62 (77.4%) | 136/156 (87.2%) |
| 95% CI | (78.9, 89.0) | (77.4, 91.1) | (75.8, 90.8) | (78.9, 89.0) | (65.0, 87.1) | (80.9, 92.0) |
| No serious device-related AEs per CEC | 167/218 (76.6%) | 87/115 (75.7%) | 80/102 (78.4%) | 167/218 (76.6%) | 43/62 (69.4%) | 124/156 (79.5%) |
| 95% CI | (70.4, 82.1) | (66.8, 83.2) | (69.2, 86.0) | (70.4, 82.1) | (56.3, 80.4) | (72.3, 85.5) |
| Overall success including ROM success component | 92/218 (42.2%) | 48/115 (41.7%) | 44/102 (43.1%) | 92/218 (42.2%) | 22/62 (35.5%) | 70/156 (44.9%) |
| 95% CI | (35.6, 49.1) | (32.6, 51.3) | (33.4, 53.3) | (35.6, 49.1) | (23.7, 48.7) | (36.9, 53.0) |
| Overall success without ROM success component | 135/218 (61.9%) | 69/115 (60.0%) | 66/102 (64.7%) | 135/218 (61.9%) | 36/62 (58.1%) | 99/156 (63.5%) |
| 95% CI | (55.1, 68.4) | (50.4, 69.0) | (54.6, 73.9) | (55.1, 68.4) | (44.8, 70.5) | (55.4, 71.0) |

SSI = subsequent surgical intervention

Table 39 provides data on overall success at 24 months (missing imputed as failures) in the randomized control group stratified by control device and level treated as compared to the all control group. In randomized control subjects, overall success and component success rates (both missing imputed as failures and observed) were generally qualitatively higher in the subjects treated with the ProDisc-L as compared to those treated with the Charité. However, the trial was not designed or powered to demonstrate statistical poolability of the two control devices. When considering treatment level in control subjects, qualitative differences were evident in both the missing imputed as failures and observed analyses comparing control subjects treated at L4-L5 with control subjects treated at L5-S1. In general, qualitatively higher overall and component success rates were noted in control subjects treated at L5-S1. The trial was not designed or powered to demonstrate statistical poolability for the two control group treatment levels.

**Table 39: Overall Success at 24 Months Randomized Control (Missing Imputed as Failures) - Stratified**

| Primary Endpoint Component | R Contr (N=106) | | | | | |
|---|---|---|---|---|---|---|
| | Contr Device | | | Treatment Level | | |
| | All Contr (N=106) | ProDisc-L (N=64) | Charité (N=41) | All Contr (N=106) | L4-L5 (N=34) | L5-S1 (N=72) |
| ODI success (≥15 point improvement) | 70/106 (66.0%) | 43/64 (67.2%) | 26/41 (63.4%) | 70/106 (66.0%) | 23/34 (67.6%) | 47/72 (65.3%) |
| 95% CI | (56.2, 75.0) | (54.3, 78.4) | (46.9, 77.9) | (56.2, 75.0) | (49.5, 82.6) | (53.1, 76.1) |
| Neurological success (maintenance or improvement – motor & sensory evaluations) | 81/106 (76.4%) | 48/64 (75.0%) | 32/41 (78.0%) | 81/106 (76.4%) | 24/34 (70.6%) | 57/72 (79.2%) |
| 95% CI | (67.2, 84.1) | (62.6, 85.0) | (62.4, 89.4) | (67.2, 84.1) | (52.5, 84.9) | (68.0, 87.8) |
| ROM success (maintenance or improvement) | 45/106 (42.5%) | 28/64 (43.8%) | 16/41 (39.0%) | 45/106 (42.5%) | 14/34 (41.2%) | 31/72 (43.1%) |
| 95% CI | (32.9, 52.4) | (31.4, 56.7) | (24.2, 55.5) | (32.9, 52.4) | (24.6, 59.3) | (31.4, 55.3) |
| Device success (no SSIs at index level) | 90/106 (84.9%) | 54/64 (84.4%) | 35/41 (85.4%) | 90/106 (84.9%) | 26/34 (76.5%) | 64/72 (88.9%) |
| 95% CI | (76.6, 91.1) | (73.1, 92.2) | (70.8, 94.4) | (76.6, 91.1) | (58.8, 89.3) | (79.3, 95.1) |
| No serious device-related AEs per CEC | 75/106 (70.8%) | 48/64 (75.0%) | 26/41 (63.4%) | 75/106 (70.8%) | 22/34 (64.7%) | 53/72 (73.6%) |
| 95% CI | (61.1, 79.2) | (62.6, 85.0) | (46.9, 77.9) | (61.1, 79.2) | (46.5, 80.3) | (61.9, 83.3) |
| Overall success including ROM success component | 30/106 (28.3%) | 20/64 (31.3%) | 9/41 (22.0%) | 30/106 (28.3%) | 8/34 (23.5%) | 22/72 (30.6%) |
| 95% CI | (20.0, 37.9) | (20.2, 44.1) | (10.6, 37.6) | (20.0, 37.9) | (10.7, 41.2) | (20.2, 42.5) |
| Overall success without ROM success component | 56/106 (52.8%) | 36/64 (56.3%) | 19/41 (46.3%) | 56/106 (52.8%) | 16/34 (47.1%) | 40/72 (55.6%) |
| 95% CI | (42.9, 62.6) | (43.3, 68.6) | (30.7, 62.6) | (42.9, 62.6) | (29.8, 64.9) | (43.4, 67.3) |

SSI = subsequent surgical intervention

**Overall Success at 24 Months (Observed)**

Analysis of overall success was also performed based on observed data (missing data not included as failures) as presented in Table 40 for the randomized subjects treated in the study as well as the non-randomized activL subjects both with and without the ROM success component. The non-randomized control data is not included due to the limited sample size.

**Table 40: Overall Success at 24 Months (Observed)**

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

* Difference between randomized groups
SSI = subsequent surgical intervention

Regarding the overall success rate at 24 months (observed), 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 component (p value <0.0001 for both 15% and 10% margins). Statistical superiority was demonstrated for overall success including ROM (p=0.0129), but not for overall success without ROM.

Table 41 provides data on overall success at 24 months (observed) in the randomized activL group stratified by device design and level treated as compared to the all activL group. 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, qualitative differences were evident in the missing imputed as failures analysis (Table 38) comparing activL subjects treated at L4-L5 and L5-S1, with qualitatively higher overall and component success rates in activL subjects treated at L5-S1. However, overall success and component outcomes were more comparable for subjects treated with activL at L4-L5 and L5-S1 in the observed analysis (Table 41). The trial was not designed or powered to demonstrate statistical poolability for the two activL treatment levels.

**Table 41: Overall Success at 24 Months Randomized activL (Observed) - Stratified**

| Primary Endpoint Component | R activL (N=218) | | | | | |
|---|---|---|---|---|---|---|
| | Device Design | | | Treatment Level | | |
| | All activL (N=218) | Spike (N=115) | Keel (N=102) | All activL (N=218) | L4-L5 (N=62) | L5-S1 (N=156) |
| ODI success (≥15 point improvement) | 164/187 (87.7%) | 87/98 (88.8%) | 77/89 (86.5%) | 164/187 (87.7%) | 45/49 (91.8%) | 119/138 (86.2%) |
| 95% CI | (82.1, 92.0) | (80.8, 94.3) | (77.6, 92.8) | (82.1, 92.0) | (80.4, 97.7) | (79.3, 91.5) |
| Neurological success (maintenance or improvement – motor & sensory evaluations) | 175/188 (93.1%) | 91/99 (91.9%) | 84/89 (94.4%) | 175/188 (93.1%) | 47/49 (95.9%) | 128/139 (92.1%) |
| 95% CI | (88.5, 96.3) | (84.7, 96.4) | (87.4, 98.2) | (88.5, 96.3) | (86.0, 99.5) | (86.3, 96.0) |
| ROM success (maintenance or improvement) | 128/184 (69.6%) | 68/98 (69.4%) | 60/86 (69.8%) | 128/184 (69.6%) | 32/47 (68.1%) | 96/137 (70.1%) |
| 95% CI | (62.4, 76.1) | (59.3, 78.3) | (58.9, 79.2) | (62.4, 76.1) | (52.9, 80.9) | (61.7, 77.6) |
| Device success (no SSIs at index level) | 184/192 (95.8%) | 98/102 (96.1%) | 86/90 (95.6%) | 184/192 (95.8%) | 48/51 (94.1%) | 136/141 (96.5%) |
| 95% CI | (92.0, 98.2) | (90.3, 98.9) | (89.0, 98.8) | (92.0, 98.2) | (83.8, 98.8) | (91.9, 98.8) |
| No serious device-related AEs per CEC | 167/194 (86.1%) | 87/102 (85.3%) | 80/92 (87.0%) | 167/194 (86.1%) | 43/51 (84.3%) | 124/143 (86.7%) |
| 95% CI | (80.4, 90.6) | (76.9, 91.5) | (78.3, 93.1) | (80.4, 90.6) | (71.4, 93.0) | (80.0, 91.8) |
| Overall success including ROM success component | 92/185 (49.7%) | 48/96 (50.0%) | 44/89 (49.4%) | 92/185 (49.7%) | 22/46 (47.8%) | 70/139 (50.4%) |
| 95% CI | (42.3, 57.2) | (39.6, 60.4) | (38.7, 60.2) | (42.3, 57.2) | (32.9, 63.1) | (41.8, 58.9) |
| Overall success without ROM success component | 135/189 (71.4%) | 69/98 (70.4%) | 66/91 (72.5%) | 135/189 (71.4%) | 36/49 (73.5%) | 99/140 (70.7%) |
| 95% CI | (64.4, 77.8) | (60.3, 79.2) | (62.2, 81.4) | (64.4, 77.8) | (58.9, 85.1) | (62.4, 78.1) |

SSI = subsequent surgical intervention

Table 42 provides data on overall success at 24 months (observed) in the randomized control group stratified by control device and level treated as compared to the all control group. In randomized control subjects, overall success and component success rates (both missing imputed as failures and observed) were generally qualitatively higher in the subjects treated with the ProDisc-L as compared to those treated with the Charité. However, the trial was not designed or powered to demonstrate statistical poolability of the two control devices. When considering treatment level in control subjects, qualitative differences were evident in both the missing imputed as failures and observed analyses comparing control subjects treated at L4-L5 with control subjects treated at L5-S1, with generally qualitatively higher success rates in control subjects treated at L5-S1. The trial was not designed or powered to demonstrate statistical poolability for the two control group treatment levels.

**Table 42: Overall Success at 24 Months Randomized Control (Observed) - Stratified**

| Primary Endpoint Component | R Contr (N=106) | | | | | |
|---|---|---|---|---|---|---|
| | Contr Device | | | Treatment Level | | |
| | All Contr (N=106) | ProDisc-L (N=64) | Charité (N=41) | All Contr (N=106) | L4-L5 (N=34) | L5-S1 (N=72) |
| ODI success (≥15 point improvement) | 69/86 (80.2%) | 43/50 (86.0%) | 26/36 (72.2%) | 69/86 (80.2%) | 23/27 (85.2%) | 46/59 (78.0%) |
| 95% CI | (70.2, 88.0) | (73.3, 94.2) | (54.8, 85.8) | (70.2, 88.0) | (66.3, 95.8) | (65.3, 87.7) |
| Neurological success (maintenance or improvement – motor & sensory evaluations) | 80/86 (93.0%) | 48/50 (96.0%) | 32/36 (88.9%) | 80/86 (93.0%) | 24/27 (88.9%) | 56/59 (94.9%) |
| 95% CI | (85.4, 97.4) | (86.3, 99.5) | (73.9, 96.9) | (85.4, 97.4) | (70.8, 97.6) | (85.9, 98.9) |
| ROM success (maintenance or improvement) | 44/84 (52.4%) | 28/49 (57.1%) | 16/35 (45.7%) | 44/84 (52.4%) | 14/27 (51.9%) | 30/57 (52.6%) |
| 95% CI | (41.2, 63.4) | (42.2, 71.2) | (28.8, 63.4) | (41.2, 63.4) | (31.9, 71.3) | (39.0, 66.0) |
| Device success (no SSIs at index level) | 89/92 (96.7%) | 54/56 (96.4%) | 35/36 (97.2%) | 89/92 (96.7%) | 26/28 (92.9%) | 63/34 (98.4%) |
| 95% CI | (90.8, 99.3) | (87.7, 99.6) | (85.5, 99.9) | (90.8, 99.3) | (76.5, 99.1) | (91.6, 100.0) |
| No serious device-related AEs per CEC | 74/94 (78.7%) | 48/58 (82.8%) | 26/36 (72.2%) | 74/94 (78.7%) | 22/29 (75.9%) | 52/65 (80.0%) |
| 95% CI | (69.1, 86.5) | (70.6, 91.4) | (54.8, 85.8) | (69.1, 86.5) | (56.5, 89.7) | (68.2, 88.9) |
| Overall success including ROM success component | 29/87 (33.3%) | 20/51 (39.2%) | 9/36 (25.0%) | 29/87 (33.3%) | 8/28 (28.6%) | 21/59 (35.6%) |
| 95% CI | (23.6, 44.3) | (25.8, 53.9) | (12.1, 42.2) | (23.6, 44.3) | (13.2, 48.7) | (23.6, 49.1) |
| Overall success without ROM success component | 55/88 (62.5%) | 36/52 (69.2%) | 19/36 (52.8%) | 55/88 (62.5%) | 16/28 (57.1%) | 39/60 (65.0%) |
| 95% CI | (51.5, 72.6) | (54.9, 81.3) | (35.5, 69.6) | (51.5, 72.6) | (37.2, 75.5) | (51.6, 76.9) |

SSI = subsequent surgical intervention

**Time course of Overall Success**

Table 43 provides data on the time course of overall success (missing imputed as failures) for the randomized subjects treated in the study as well as the non-randomized activL subjects. The non-randomized control data is not included due to the limited sample size. Again, 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 requested an analysis of overall success without the ROM success component. The time course data for overall success (missing imputed as failures) with and without the ROM success component is also presented in Table 43.

**Table 43: 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 44 provides the 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. Again, the non-randomized control data is not included due to the limited sample size.

**Table 44: 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) including ROM success component:** | | | | | |
| NR activL (N=46) | 19/44 (43.2%) | 20/41 (48.8%) | 20/40 (50.0%) | 19/38 (50.0%) | 11/21 (52.4%) |
| R activL (N=218) | 99/198 (50.0%) | 88/199 (44.2%) | 92/185 (49.7%) | 62/145 (42.8%) | 14/64 (21.9%) |
| R Contr (N=106) | 34/96 (35.4%) | 39/95 (41.1%) | 29/87 (33.3%) | 32/80 (40.0%) | 9/39 (23.1%) |
| **Overall success (observed) without ROM success component:** | | | | | |
| NR activL (N=46) | 33/44 (75.0%) | 33/41 (80.5%) | 30/41 (73.2%) | 28/38 (73.7%) | 14/21 (66.7%) |
| R activL(N=218) | 146/201 (72.6%) | 148/203 (72.9%) | 135/189 (71.4%) | 97/150 (64.7%) | 30/66 (45.5%) |
| R Contr(N=106) | 59/96 (61.5%) | 65/95 (68.4%) | 55/88 (62. 5%) | 48/80 (60.0%) | 14/39 (35.9%) |

Table 45 provides time course data on overall success (observed only, with and without the ROM success component) 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 45: Time Course of Overall Success (Observed) - Stratified**

| 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) including ROM success component:** | | | | | |
| R activL, spike (N=115) | 50/106 (47.2%) | 49/104 (47.1%) | 48/96 (50.0% | 29/70 (41.4%) | 3/25 (12.0%) |
| R activL, keel (N=102) | 49/92 (53.3%) | 39/95 (41.1%) | 44/89 (49.4%) | 33/75 (44.0%) | 11/39 (28.2%) |
| R activL, L4-L5 (N=62) | 29/56 (51.8%) | 29/57 (50.9%) | 22/46 (47.8%) | 17/41 (41.5%) | 6/21 (28.6%) |
| R activL, L5-S1 (N=156) | 70/142 (49.3%) | 59/142 (41.5%) | 70/139 (50.4%) | 45/104 (43.3%) | 8/43 (18.6%) |
| R Contr, ProDisc-L (N=64) | 26/57 (45.6%) | 26/58 (44.8%) | 20/51 (39.2%) | 21/48 (43.8%) | 7/25 (28.0%) |
| R Contr, Charité (N=41) | 8/38 (21.1%) | 13/37 (35.1%) | 9/36 (25.0%) | 11/32 (34.4%) | 2/14 (14.3%) |
| R Contr, L4-L5 (N=34) | 11/33 (33.3%) | 10/31 (32.3%) | 8/28 (28.6%) | 10/25 (40.0%) | 2/14 (14.3%) |
| R Contr, L5-S1 (N=72) | 23/63 (36.5%) | 29/64 (45.3%) | 21/59 (35.6%) | 22/55 (40.0%) | 7/25 (28.0%) |
| **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%) |
| R Contr, ProDisc-L (N=64) | 36/57 (63.2%) | 41/58 (70.7%) | 36/52 (69.2%) | 30/48 (62.5%) | 11/25 (44.0%) |
| R Contr, Charité (N=41) | 22/38 (57.9%) | 24/37 (64.9%) | 19/36 (52.8%) | 18/32 (56.3%) | 3/14 (21.4%) |
| R Contr, L4-L5 (N=34) | 22/33 (66.7%) | 19/31 (61.3%) | 16/28 (57.1%) | 13/25 (52.0%) | 5/14 (35.7%) |
| R Contr, L5-S1 (N=72) | 37/63 (58.7%) | 46/64 (71.9%) | 39/60 (65.0%) | 35/55 (63.6%) | 9/25 (36.0%) |

**Sensitivity Analyses:**

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 (as detailed above) as well as with different ROM success definitions
- Overall success stratified by activL device design, control device, and treatment level (as detailed above) 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 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. An exception was noted in 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), 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 46:

**Table 46: 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)** |
| ODI success (≥15 point improvement)<br>95% CI | 144/165 (87.3%)<br>(81.2, 91.9) | 20/22 (90.9%)<br>(70.8, 98.9) | 64/80 (80.0%)<br>(69.6, 88.1) | 5/6 (83.3%)<br>(35.9, 99.6) |
| Neurological success (maintenance or improvement – motor & sensory evaluations)<br>95% CI | 155/165 (93.9%)<br>(89.1, 97.1) | 20/23 (87.0%)<br>(66.4, 97.2) | 74/80 (92.5%)<br>(84.4, 97.2) | 6/6 (100.0%)<br>(54.1, 100.0) |
| ROM success (maintenance or improvement)<br>95% CI | 116/162 (71.6%)<br>(64.0, 78.4) | 12/22 (54.5%)<br>(32.2, 75.6) | 41/78 (52.6%)<br>(40.9, 64.0) | 3/6 (50.0%)<br>(11.8, 88.2) |
| Device success (no SSIs at index level)<br>95% CI | 162/189 (85.7%)<br>(79.9, 90.4) | 22/28 (78.6%)<br>(59.0, 91.7) | 83/100 (83.0%)<br>(74.2, 89.8) | 6/6 (100.0%)<br>(54.1, 100.0) |
| No serious device-related AEs per CEC<br>95% CI | 151/189 (79.9%)<br>(73.5, 85.4) | 16/28 (57.1%)<br>(37.2, 75.5) | 69/100 (69.0%)<br>(59.0, 77.9) | 5/6 (83.3%)<br>(35.9, 99.6) |
| Overall success including ROM success component<br>95% CI | 85/163 (52.1%)<br>(44.2, 60.0) | 7/22 (31.8%)<br>(13.9, 54.9) | 26/81 (32.1%)<br>(22.2, 43.4) | 3/6 (50.0%)<br>(11.8, 88.2) |
| Overall success without ROM success component<br>95% CI | 122/166 (73.5%)<br>(66.1, 80.0) | 13/23 (56.5%)<br>(34.5, 76.8) | 50/82 (61.0%)<br>(49.6, 71.6) | 5/6 (83.3%)<br>(35.9, 99.6) |

SSI = subsequent surgical intervention

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. 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.

**Financial Disclosure Analysis:**
The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit marketing applications to include certain information concerning the compensation to, and financial interests and arrangements of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study of the activL included 18 principal investigators of which none were full-time or part-time employees of the applicant and 3 disclosed financial interests/arrangements as defined in 21 CFR 54.2(a), (b), (c) and (f) as described below:

- Financial arrangement between the applicant and the investigator, whereby the value of the compensation to the investigator for conducting the study could be influenced by the outcome of the study: 3 investigators;
- Any significant payment of other sorts from the applicant, such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria: 3 investigators;
- Any proprietary interest in the activL held by the investigator: 2 investigators;
- Any significant equity interest in the applicant held by the investigator: 0 investigators.

The applicant has adequately disclosed the financial interest/arrangements they have with the investigators who participated in the activL trial. Three sites disclosed financial relationships with the applicant. Statistical analyses were requested by FDA to determine whether the financial interests/arrangements had any impact on the clinical study outcome. FDA determined the information provided did raise questions about the reliability of the data due to the observation of a modest positive association between financial interest and the treatment difference in the primary endpoint in favor of activL. The following additional actions were taken and deemed necessary to ensure the reliability of the data (21 CFR 54.5(c)). Sensitivity analyses were performed to determine the robustness of the trial outcomes after excluding subjects treated at those three sites. The analyses, done for the primary endpoint, with and without the radiographic ROM component (both missing imputed as failures and observed), showed that non-inferiority was still met after exclusion of subjects from the three sites with a disclosed financial interest.

**Site Poolability Analysis:**
Statistical poolability assessments across sites were performed for the primary endpoint of overall success (both with and without the ROM success component) using the logistic regression model with treatment group, site (small sites combined following pre-defined procedures) and treatment-by-site interaction. The poolability test across sites for overall success was not significant (treatment-by-site interaction p-value = 0.7121), indicating no particular evidence of a differential treatment effect among sites. These assessments provided additional confidence that data across the investigational sites.

At FDA's request, the applicant also provided several sensitivity analyses where specific sites were excluded for various reasons (e.g., primary endpoint success outcomes opposite the overall study findings, large difference in primary endpoint success outcomes in favor of the activL group, disclosed financial relationships between specific investigators and the study sponsor as outlined in the prior

section, etc.). The sensitivity analysis results demonstrated that the study conclusion of non-inferiority of activL as compared to the control was robust.

**Comparison of Randomized and Non-Randomized activL Outcomes:**

Table 47 provides a comparison of primary endpoint and component outcomes, secondary endpoint outcomes, and adverse event data for the randomized and non-randomized activL subjects. The only potentially noteworthy difference is the shorter operative time in the randomized activL group (109.8 minutes) as compared to the non-randomized activL group (129.5 minutes).

**Table 47: Comparison of Randomized and Nonrandomized activL Subject Outcomes at 24 Months (Observed)**

| Outcome Measure | NR activL | R activL |
|---|---|---|
| **Primary Endpoint and Components** | | |
| ODI ≥ 15 Point Improvement (n/N (%)) | 34/41 (82.9%) | 164/187 (87.7%) |
| Neurological Success (maintenance or Improvement – motor & sensory evaluations)(n/N (%)) | 38/41 (92.7%) | 175/188 (93.1%) |
| ROM Success (maintenance or improvement)(n/N (%)) | 26/40 (65.0%) | 128/184 (69.6%) |
| Device Success (no SSIs at index level)(n/N (%)) | 43/43 (100%) | 184/192 (95.8%) |
| No serious device-related AEs per CEC (n/N (%)) | 39/43 (90.7%) | 167/194 (86.1%) |
| Overall success including ROM success component | 20/40 (50.0%) | 92/185 (49.7%) |
| Overall success without ROM success component | 30/41 (73.2%) | 135/189 (71.4%) |
| **Powered Secondary Endpoints** | | |
| VAS Back Pain ≥ 20 mm Improvement (n/N (%)) | 35/40 (87.5%) | 162/180 (90.0%) |
| VAS Leg Pain ≥ 20 mm Improvement (n/N (%)) | 25/40 (62.5%) | 93/180 (51.7%) |
| **Unpowered Secondary Endpoints** | | |
| ODI (Mean ± SD); N= | 20.4 ± 20.3; N=41 | 19.0 ± 17.7; N=187 |
| Change from Baseline ODI (Mean ± SD); N= | 38.9 ± 24.6; N=41 | 38.4 ± 19.9; N=187 |
| ODI ≥ 15% Improvement (n/N (%)) | 36/41 (87.8%) | 170/187 (90.9%) |
| SF-36 MCS ≥ 15% Improvement (n/N (%)) | 25/40 (62.5%) | 101/180 (56.1%) |
| SF-36 PCS ≥ 15% Improvement (n/N (%)) | 34/40 (85.0%) | 156/180 (86.7%) |
| Incidence of >3 mm Change in Average Disc Height from Baseline (n/N (%)) | 37/41 (90.2%) | 173/184 (94.0%) |
| Change from 6-week Disc Height (Mean(mm) ± SD); N= | -0.4 ± 0.4; N=41 | -0.4 ± 0.5; N=182 |
| Incidence of >3 mm Subsidence (n/N (%)) | 0/41 (0.0%) | 0/185 (0.0%) |
| Operative Time (Mean (min.) ± SD); N= | 129.5 ± 48.7; N=46 | 109.8 ± 43.3; N=218 |
| **Subjects with any AE (n/N (%))** | 40/46 (87.0%) | 184/218 (84.4%) |
| **Subjects with any Device Related AE (n/N (%))** | 24/46 (52.2%) | 129/218 (59.2%) |

SSI=subsequent surgical intervention

**Integrity of Mask:**

The IDE trial was a single-blind trial in that the subjects were masked to their treatment assignment. Every effort was made to maintain masking through the 24-month follow-up visit, at which time the sites were instructed to inform the subjects of their treatment assignment. To assess the effectiveness

of the masking, subjects were asked at each follow-up visit if they had learned which device was implanted. If the subject indicated that he/she had learned which device was implanted, he/she was then asked to identify the name of the implanted device.

Table 48 presents a summary of the subjects' responses to these questions through the 12- and 24-month follow-up visits by treatment group. By 12 months, 47.2% of activL subjects knew their assignment versus 42.9% of control subjects. By 24 months, this increased to 67.0% versus 67.4%.

**Table 48: Summary of Maintenance of Masking (ITT)**

| Visit Interval | R activL | R Contr |
|---|---|---|
| **Did subject learn through 12 months which device was implanted?** | | |
| Yes<br>• Correct<br>• Incorrect | 103/218 (47.2%)<br>• 101/103 (98.1%)<br>• 2/103 (1.9%) | 45/105 (42.9%)<br>• 43/45 (95.6%)<br>• 2/45 (4.4%) |
| No | 115/218 (52.8%) | 60/105 (57.1%) |
| **Did subject learn through 24 months which device was implanted?** | | |
| Yes<br>• Correct<br>• Incorrect | 136/203 (67.0%)<br>• 135/136 (99.3%)<br>• 1/136 (0.7%) | 62/92 (67.4%)<br>• 59/62 (95.2%)<br>• 3/62 (4.8%) |
| No | 67/203 (33.0%) | 30/92 (32.6%) |

***Secondary Effectiveness Analysis:***

**Secondary Endpoints Overview**

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 49. The results were comparable.

**Table 49: 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

**VAS Back and Leg Pain**

The time course of VAS back and leg pain improvement for the randomized subjects treated in the trial as well as the non-randomized activL subjects are shown in Table 50 through 24-month follow-up. The non-randomized control data is not included due to the limited sample size. Both randomized groups demonstrated similar postoperative improvement in VAS back and leg pain.

**Table 50: Time Course of VAS Back and Leg Pain Improvement (Observed)**

| Evaluation | 6 wks | | | 3 mo | | | 6 mo | | | 12 mo | | | 24 mo | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | NR activL | R activL | R Contr | NR activL | R activL | R Contr | NR activL | R activL | R Contr | NR activL | R activL | R Contr | NR activL | R activL | R Contr |
| **VAS Back Pain, N** | 42 | 206 | 105 | 44 | 202 | 101 | 43 | 195 | 96 | 39 | 197 | 96 | 40 | 180 | 87 |
| CS Improvement | 95.2% | 86.4% | 84.8% | 90.9% | 86.1% | 84.2% | 97.7% | 86.7% | 87.5% | 94.9% | 87.8% | 85.4% | 87.5% | 90.0% | 82.8% |
| NCS Improvement | 4.8% | 8.7% | 13.3% | 9.1% | 9.9% | 9.9% | 2.3% | 10.3% | 8.3% | 5.1% | 7.6% | 11.5% | 10.0% | 7.2% | 11.5% |
| Stable | 0% | 0% | 0% | 0% | 0% | 0% | 0% | 0% | 0% | 0% | 0.5% | 0% | 2.5% | 0% | 0% |
| Deteriorated | 0% | 4.9% | 1.9% | 0% | 4.0% | 5.9% | 0% | 3.1% | 4.2% | 0% | 4.1% | 3.1% | 0% | 2.8% | 5.7% |
| **VAS Left Leg Pain, N** | 45 | 209 | 103 | 45 | 203 | 98 | 43 | 197 | 95 | 40 | 196 | 95 | 41 | 182 | 86 |
| CS Improvement | 48.9% | 37.3% | 35.9% | 48.9% | 36.0% | 35.7% | 46.5% | 39.1% | 44.2% | 52.5% | 38.8% | 42.1% | 48.8% | 39.6% | 40.7% |
| NCS Improvement | 8.9% | 22.0% | 29.1% | 15.6% | 26.1% | 30.6% | 18.6% | 26.9% | 25.3% | 17.5% | 26.5% | 29.5% | 22.0% | 27.5% | 29.1% |
| Stable | 13.3% | 14.4% | 9.7% | 17.8% | 13.8% | 10.2% | 9.3% | 14.2% | 11.6% | 10.0% | 16.8% | 11.6% | 17.1% | 12.6% | 15.1% |
| Deteriorated | 28.9% | 26.3% | 25.2% | 17.8% | 24.1% | 23.5% | 25.6% | 19.8% | 18.9% | 20.0% | 17.9% | 16.8% | 12.2% | 20.3% | 15.1% |
| **VAS Right Leg Pain, N** | 44 | 202 | 101 | 44 | 204 | 97 | 43 | 194 | 94 | 39 | 197 | 92 | 40 | 182 | 84 |
| CS Improvement | 45.5% | 36.6% | 40.6% | 52.3% | 36.8% | 40.2% | 46.5% | 38.1% | 47.9% | 48.7% | 39.1% | 47.8% | 50.0% | 40.1% | 42.9% |
| NCS Improvement | 18.2% | 27.2% | 28.7% | 18.2% | 25.0% | 28.9% | 30.2% | 25.3% | 26.6% | 28.2% | 28.9% | 26.1% | 25.0% | 29.1% | 31.0% |
| Stable | 15.9% | 9.9% | 8.9% | 15.9% | 12.3% | 9.3% | 14.0% | 13.9% | 12.8% | 10.3% | 14.7% | 9.8% | 10.0% | 15.4% | 10.7% |
| Deteriorated | 20.5% | 26.2% | 21.8% | 13.6% | 26.0% | 21.6% | 9.3% | 22.7% | 12.8% | 12.8% | 17.3% | 16.3% | 15.0% | 15.4% | 15.5% |

CS = Clinically Significant (≥ 20mm); NCS = Non-Clinically Significant (0 - 20mm)

Table 51 provides data on 24-month VAS back and leg pain improvement (observed) in each randomized treatment group stratified by device design and level treated for the randomized activL group and control device type and level treated for the randomized control group.

**Table 51: 24 Month VAS Back and Leg Pain Improvement (Observed) – Stratified**

| Evaluation | R activL (N=218) | | | | R Contr (N=106) | | | |
|---|---|---|---|---|---|---|---|---|
| | Device Design | | Treatment Level | | Contr 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) |
| **VAS Back Pain, N** | 95 | 85 | 48 | 132 | 51 | 36 | 27 | 60 |
| CS Improvement | 88.4% | 91.8% | 95.8% | 87.9% | 88.2% | 75.0% | 85.2% | 81.7% |
| NCS Improvement | 6.3% | 8.2% | 4.2% | 8.3% | 5.9% | 19.4% | 11.1% | 11.7% |
| Stable | 0% | 0% | 0% | 0% | 0% | 0% | 0% | 0% |
| Deteriorated | 5.3% | 0% | 0% | 3.8% | 5.9% | 5.6% | 3.7% | 6.7% |
| **VAS Left Leg Pain, N** | 95 | 87 | 48 | 134 | 50 | 36 | 26 | 60 |
| CS Improvement | 35.8% | 43.7% | 29.2% | 43.3% | 34.0% | 50.0% | 34.6% | 43.3% |
| NCS Improvement | 27.4% | 27.6% | 47.9% | 20.1% | 34.0% | 22.2% | 23.1% | 31.7% |
| Stable | 15.8% | 9.2% | 4.2% | 15.7% | 18.0% | 11.1% | 30.8% | 8.3% |
| Deteriorated | 21.1% | 19.5% | 18.8% | 20.9% | 14.0% | 16.7% | 11.5% | 16.7% |
| **VAS Right Leg Pain, N** | 95 | 87 | 49 | 133 | 49 | 35 | 27 | 57 |
| CS Improvement | 43.2% | 36.8% | 40.8% | 39.8% | 34.7% | 54.3% | 51.9% | 38.6% |
| NCS Improvement | 25.3% | 33.3% | 30.6% | 28.6% | 36.7% | 22.9% | 25.9% | 33.3% |
| Stable | 18.9% | 11.5% | 16.3% | 15.0% | 12.2% | 8.6% | 11.1% | 10.5% |
| Deteriorated | 12.6% | 18.4% | 12.2% | 16.5% | 16.3% | 14.3% | 11.1% | 17.5% |

CS = Clinically Significant (≥ 20mm); NCS = Non-Clinically Significant (0 - 20mm)

### Oswestry Disability Index

The time course of ODI improvement for the randomized subjects treated in the trial as well as the non-randomized activL subjects are shown in Table 52 through 24-month follow-up. The non-randomized control data is not included due to the limited sample size. Both randomized groups demonstrated similar postoperative improvement in ODI.

**Table 52: Time Course of ODI Improvement (Observed)**

| Evaluation | 6 wks | | | 3 mo | | | 6 mo | | | 12 mo | | | 24 mo | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | NR activL | R activL | R Contr | NR activL | R activL | R Contr | NR activL | R activL | R Contr | NR activL | R activL | R Contr | NR activL | R activL | R Contr |
| **ODI (points), N** | 45 | 213 | 105 | 45 | 208 | 101 | 44 | 202 | 97 | 41 | 202 | 96 | 41 | 187 | 87 |
| CS Improvement* | 64.4% | 68.1% | 61.0% | 82.2% | 77.4% | 80.2% | 86.4% | 83.7% | 81.4% | 92.7% | 84.7% | 86.5% | 82.9% | 87.7% | 80.5% |
| NCS Improvement† | 22.2% | 18.8% | 26.7% | 8.9% | 13.0% | 10.9% | 13.6% | 10.9% | 14.4% | 7.3% | 13.4% | 11.5% | 12.2% | 8.6% | 10.3% |
| Stable | 4.4% | 1.9% | 1.0% | 4.4% | 1.4% | 1.0% | 0% | 0.5% | 0% | 0% | 0% | 0% | 0% | 1.6% | 2.3% |
| Deteriorated | 8.9% | 11.3% | 11.4% | 4.4% | 8.2% | 7.9% | 0% | 5.0% | 4.1% | 0% | 2.0% | 2.1% | 4.9% | 2.1% | 6.9% |
| **ODI (%), N** | 45 | 213 | 105 | 45 | 208 | 101 | 44 | 202 | 97 | 41 | 202 | 96 | 41 | 187 | 87 |
| CS Improvement** | 73.3% | 74.6% | 78.1% | 88.9% | 86.1% | 89.1% | 88.6% | 90.6% | 91.8% | 97.6% | 91.1% | 89.6% | 87.8% | 90.9% | 88.5% |
| NCS Improvement‡ | 13.3% | 12.2% | 9.5% | 2.2% | 4.3% | 2.0% | 11.4% | 4.0% | 4.1% | 2.4% | 6.9% | 8.3% | 7.3% | 5.3% | 2.3% |
| Stable | 4.4% | 1.9% | 1.0% | 4.4% | 1.4% | 1.0% | 0% | 0.5% | 0% | 0% | 0% | 0% | 0% | 1.6% | 2.3% |
| Deteriorated | 8.9% | 11.3% | 11.4% | 4.4% | 8.2% | 7.9% | 0% | 5.0% | 4.1% | 0% | 2.0% | 2.1% | 4.9% | 2.1% | 6.9% |

CS = Clinically Significant (* ≥ 15 points ; ** ≥ 15%); NCS = Non-Clinically Significant († 0 – 15 points; ‡ 0 – 15%)

Table 53 provides data on 24-month ODI improvement (observed) 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 53: 24 Month ODI Improvement (Observed) – Stratified**

| Evaluation | 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) |
| **ODI (points), N** | 98 | 89 | 49 | 138 | 51 | 36 | 27 | 60 |
| CS Improvement | 88.8% | 86.5% | 91.8% | 86.2% | 86.3% | 72.2% | 85.2% | 78.3% |
| NCS Improvement | 6.1% | 11.2% | 4.1% | 10.1% | 5.9% | 16.7% | 7.4% | 11.7% |
| Stable | 2.0% | 1.1% | 0% | 2.2% | 0% | 5.6% | 0% | 3.3% |
| Deteriorated | 3.1% | 1.1% | 4.1% | 1.4% | 7.8% | 5.6% | 7.4% | 6.7% |

CS = Clinically Significant (≥ 15 points); NCS = Non-Clinically Significant (0 – 15 points)

### Short-Form 36 (SF-36)

The time course of SF-36 improvement for the randomized subjects treated in the study as well as the non-randomized activL subjects are shown in Table 54 through 24-month follow-up. The non-randomized control data is not included due to the limited sample size. Both randomized groups demonstrated similar postoperative improvement in SF-36.

**Table 54: Time Course of SF-36 Improvement (Observed)**

| Evaluation | 3 mo | | | 6 mo | | | 12 mo | | | 24 mo | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | NR activL | R activL | R Contr | NR activL | R activL | R Contr | NR activL | R activL | R Contr | NR activL | R activL | R Contr |
| **SF-36 MCS (%), N** | 43 | 203 | 98 | 42 | 196 | 96 | 40 | 197 | 95 | 40 | 180 | 86 |
| CS Improvement | 53.5% | 52.2% | 51.0% | 69.0% | 54.1% | 54.2% | 62.5% | 56.3% | 56.8% | 62.5% | 56.1% | 55.8% |
| NCS Improvement | 18.6% | 19.7% | 20.4% | 7.1% | 19.9% | 14.6% | 12.5% | 18.3% | 15.8% | 15.0% | 18.9% | 15.1% |
| Stable | 0% | 0% | 1.0% | 0% | 0% | 0% | 0% | 0% | 0% | 0% | -% | 0% |
| Deteriorated | 27.9% | 28.1% | 27.6% | 23.8% | 26.0% | 31.3% | 25.0% | 25.4% | 27.4% | 22.5% | 25.0% | 29.1% |
| **SF-36 PCS (%), N** | 43 | 203 | 98 | 42 | 196 | 96 | 40 | 197 | 95 | 40 | 180 | 86 |
| CS Improvement | 81.4% | 79.8% | 76.5% | 88.1% | 82.1% | 85.4% | 85.0% | 82.2% | 76.8% | 85.0% | 86.7% | 80.2% |
| NCS Improvement | 7.0% | 9.4% | 13.3% | 7.1% | 7.7% | 7.3% | 7.5% | 8.1% | 13.7% | 10.0% | 6.1% | 10.5% |
| Stable | 0% | 0% | 0% | 0% | 0% | 0% | 0% | 0% | 0% | 0% | 0% | 0% |
| Deteriorated | 11.6% | 10.8% | 10.2% | 4.8% | 10.2% | 7.3% | 7.5% | 9.6% | 9.5% | 5.0% | 7.2% | 9.3% |

CS = Clinically Significant (≥15%); NCS = Non-Clinically Significant (0 – 15%)

### Subject Satisfaction

Subject satisfaction data for the randomized subjects treated in the study as well as the non-randomized activL subjects are shown in Table 55 at 12 and 24 months follow-up. The non-randomized control data is not included due to the limited sample size. Both randomized groups demonstrated similar satisfaction at 24 months.

**Table 55: Subject Satisfaction (Observed)**

| Question | 12 mo | | | 24 mo | | |
|---|---|---|---|---|---|---|
| | NR activL | R activL | R contr | NR activL | R activL | R contr |
| **How satisfied are you with the treatment you received?, N** | 40 | 202 | 96 | 41 | 187 | 87 |
| Very satisfied | 90.0% | 77.7% | 71.9% | 92.7% | 82.4% | 78.2% |
| Somewhat satisfied | 7.5% | 14.9% | 22.9% | 4.9% | 11.8% | 14.9% |
| Somewhat dissatisfied | 0% | 4.5% | 3.1% | 0% | 4.3% | 4.6% |
| Very dissatisfied | 2.5% | 3.0% | 2.1% | 2.4% | 1.6% | 2.3% |
| **Would you have this surgery again for the same condition?, N** | 40 | 202 | 96 | 41 | 187 | 87 |
| Definitely yes | 87.5% | 72.3% | 69.8% | 78.0% | 77.0% | 73.6% |
| Probably yes | 10.0% | 18.8% | 22.9% | 22.0% | 14.4% | 20.7% |
| Probably not | 0% | 4.5% | 5.2% | 0% | 5.9% | 2.3% |
| Definitely not | 2.5% | 4.5% | 2.1% | 0% | 2.7% | 3.4% |
| **How effective was the treatment in eliminating your symptoms?, N** | 40 | 202 | 96 | 41 | 187 | 87 |
| Very effective | 72.5% | 65.8% | 56.3% | 65.9% | 63.6% | 57.5% |
| Moderately effective | 12.5% | 15.3% | 16.7% | 26.8% | 20.3% | 21.8% |
| Somewhat effective | 10.0% | 10.4% | 17.7% | 7.3% | 9.1% | 13.8% |
| Somewhat ineffective | 2.5% | 2.0% | 4.2% | 0% | 1.6% | 1.1% |
| Moderately ineffective | 0% | 2.0% | 1.0% | 0% | 2.7% | 2.3% |
| Very ineffective | 2.5% | 4.5% | 4.2% | 0% | 2.7% | 3.4% |

**Radiographic Assessments**

The applicant utilized an independent Imaging Core Laboratory. The Imaging Core Lab employed an independent, board-certified, fellowship-trained, practicing radiologist to conduct the radiographic assessments.

*Range of Motion*

Radiographic evaluations of mean range of motion, including angulation and translation (during flexion and extension) as well as lateral bending range of motion for the treated level at the preoperative, 12-month and 24-month time points are shown in Table 56 for the randomized subjects treated in the study as well as the non-randomized activL subjects. The non-randomized control data is not included due to the limited sample size.

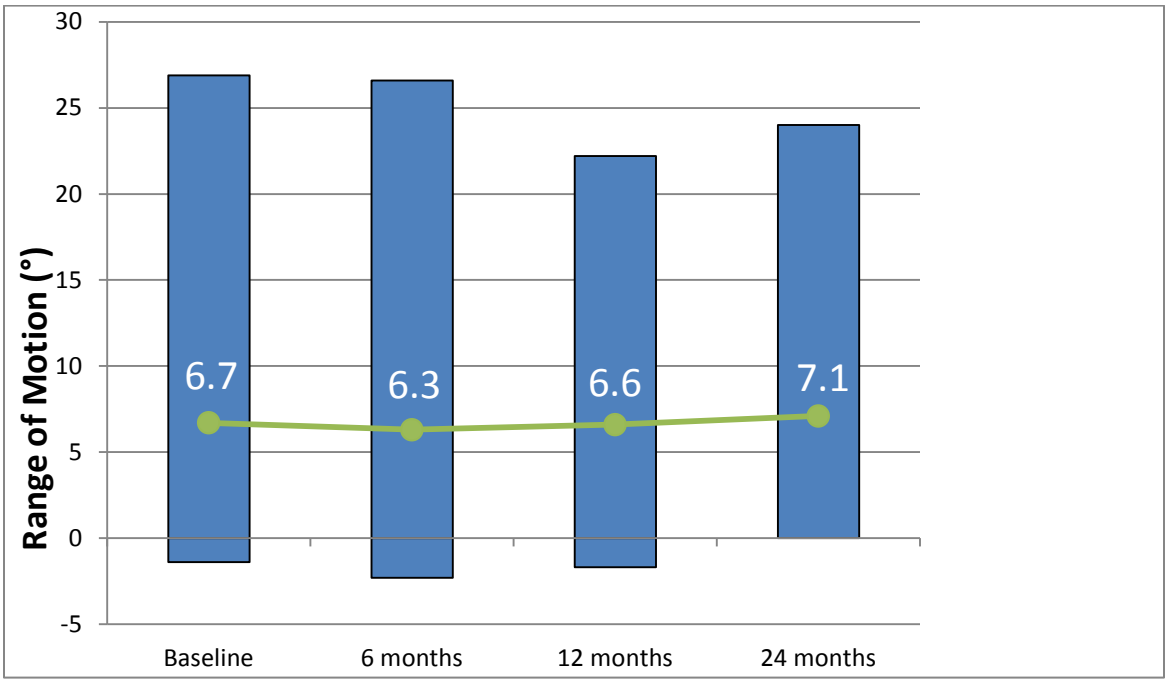
**Table 56: Time Course of Mean Range of Motion (Observed)**

| Evaluation | Baseline | | | 12 mo | | | 24 mo | | |
|---|---|---|---|---|---|---|---|---|---|
| | NR activL | R activL | R Contr | NR activL | R activL | R Contr | NR activL | R activL | R Contr |
| Flexion/ extension rotation (°) | 7.3 ± 5.1 (-0.1 to 18.9) N=46 | 6.6 ± 5.1 (-1.4 to 26.9) N=214 | 6.6 ± 4.6 (-0.7 to 19.4) N=105 | 6.7 ± 5.6 (-1.7 to 22.2) N=41 | 6.5 ± 4.8 (-0.3 to 20.2) N=200 | 5.9 ± 4.6 (0 to 21.2) N=96 | 6.9 ±5.8 (0.2 to 20.3) N=40 | 7.1 ± 5.1 (0 to 24.0) N=187 | 5.4 ± 4.5 (0.3 to 20.9) N=85 |
| Flexion/ extension translation (mm) | 0.6 ± 0.7 (-0.1 to 3.2) N=46 | 0.5 ± 0.7 (-0.4 to 3.8) N=212 | 0.6 ± 0.6 (-1.4 to 2.8) N=104 | 1.0 ±1.0 (-0.3 to 4.3) N=41 | 1.0 ± 0.9 (-0.5 to 5.0) N=198 | 0.8 ± 0.9 (-0.4 to 4.0) N=95 | 1.1 ±1.1 (0 to 4.2) N=40 | 1.0 ± 1.0 (-0.3 to 7.3) N=186 | 0.8 ± 0.8 (-0.5 to 4.1) N=85 |
| Lateral bending (°) | 1.1 ± 1.3 (-1.3 to 5.5) N=42 | 1.0 ± 2.0 (-2.3 to 12.5) N=212 | 1.0 ± 1.8 (-3.3 to 10.0) N=103 | 0.8 ± 2.4 (-4.3 to 6.4) N=41 | 1.5 ± 3.1 (-4.4 to 12.1) N=192 | 2.0 ± 3.0 (-5.4 to 16.9) N=96 | 1.3 ± 2.6 (-3.5 to 7.3) N=40 | 1.5 ± 2.8 (-5.0 to 12.8) N=179 | 1.8 ± 3.5 (-3.9 to 22.4) N=84 |

Note: Data presented as mean ±standard deviation, (min to max)

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. The points represent the averages, while the bars represent the range between maximum and minimum at each time point.

**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 57 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. The non-randomized control data is not included due to the limited sample size.

**Table 57: 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% |

Table 58 provides data on 24-month flexion/extension angular range of motion improvement (observed) 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 58: 24 Month Angular Range of Motion Improvement (Observed) – Stratified**

| Evaluation | R activL (N=218) | | | | R Contr (N=106) | | | |
|---|---|---|---|---|---|---|---|---|
| | Device Design | | Treatment Level | | ContrDevice | | 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) |
| ROM, N | 98 | 86 | 47 | 137 | 50 | 35 | 27 | 58 |
| Improved (>0°) | 56.1% | 47.7% | 51.1% | 52.6% | 36.0% | 37.1% | 29.6% | 39.7% |
| Stable (≥-2° but ≤0°) | 13.3% | 22.1% | 17.0% | 17.5% | 22.0% | 8.6% | 22.2% | 13.8% |
| Deteriorated (<-2°) | 30.6% | 30.2% | 31.9% | 29.9% | 42.0% | 54.3% | 48.1% | 46.6% |

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. This histogram uses values obtained by rounding recorded range of motion for each subject 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**

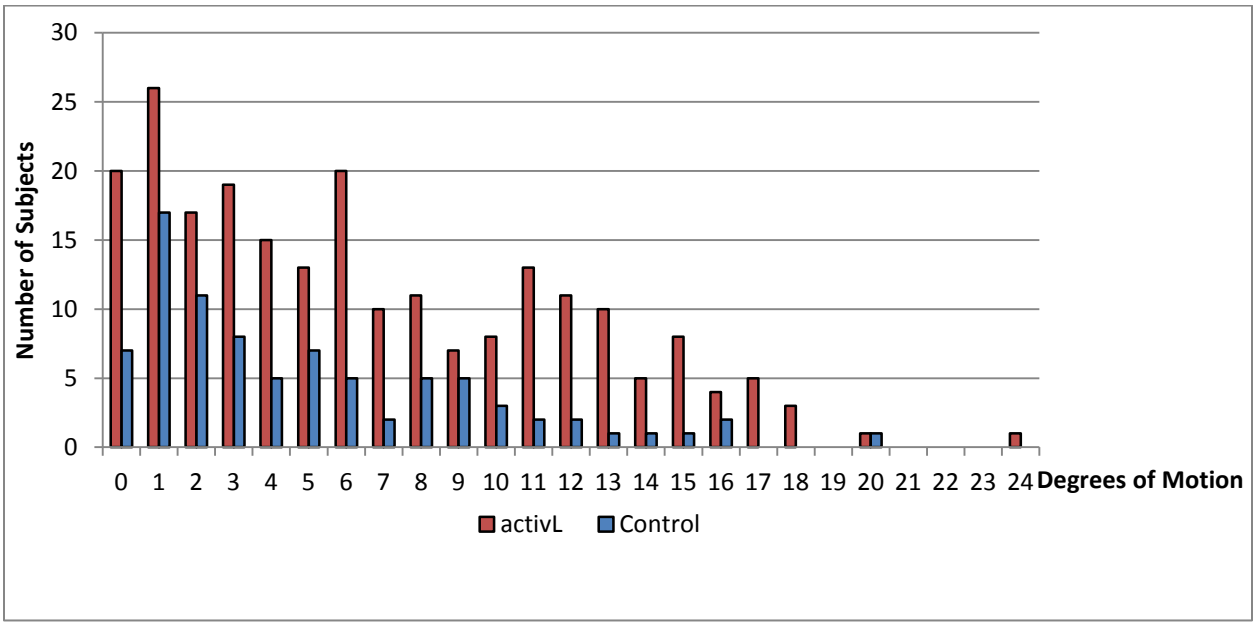



Figure 4**,** Figure 5**,** Figure 6, and Figure 7 present histograms of the flexion/extension angular range of motion at 24 months stratified by activL device design; control device; treatment level for activL subjects; and treatment level for control subjects, respectively.

**Figure 4: Histogram of Flexion/Extension Angular Range of Motion at 24 Months for All activL Subjects (Randomized Plus Non-randomized) Stratified by activL Device Design**

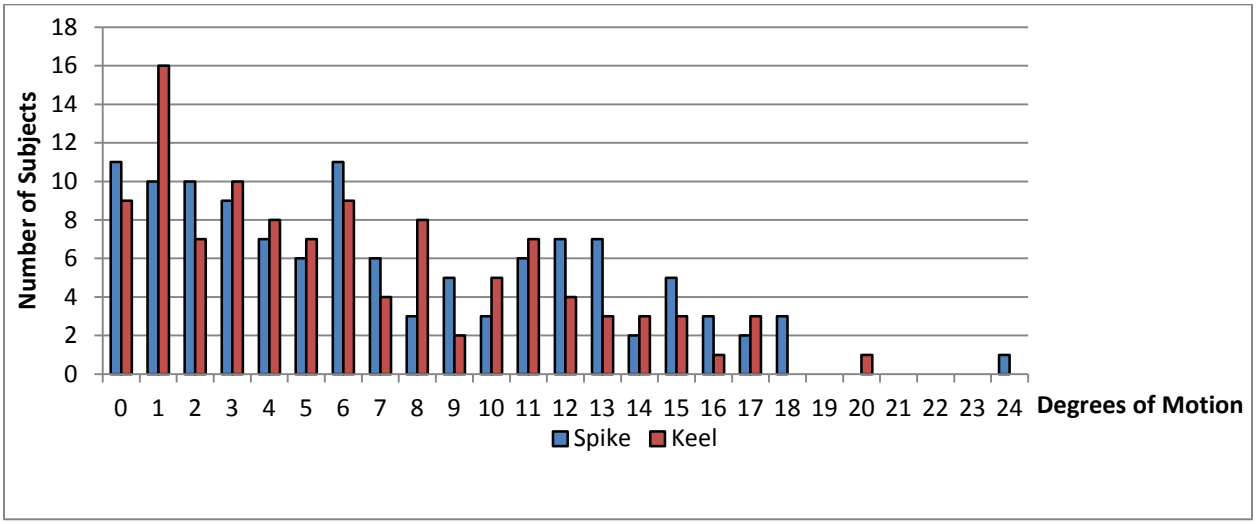



**Figure 5: Histogram of Flexion/Extension Angular Range of Motion at 24 Months for all Control Subjects (Randomized Plus Non-randomized) Stratified by Control Device**

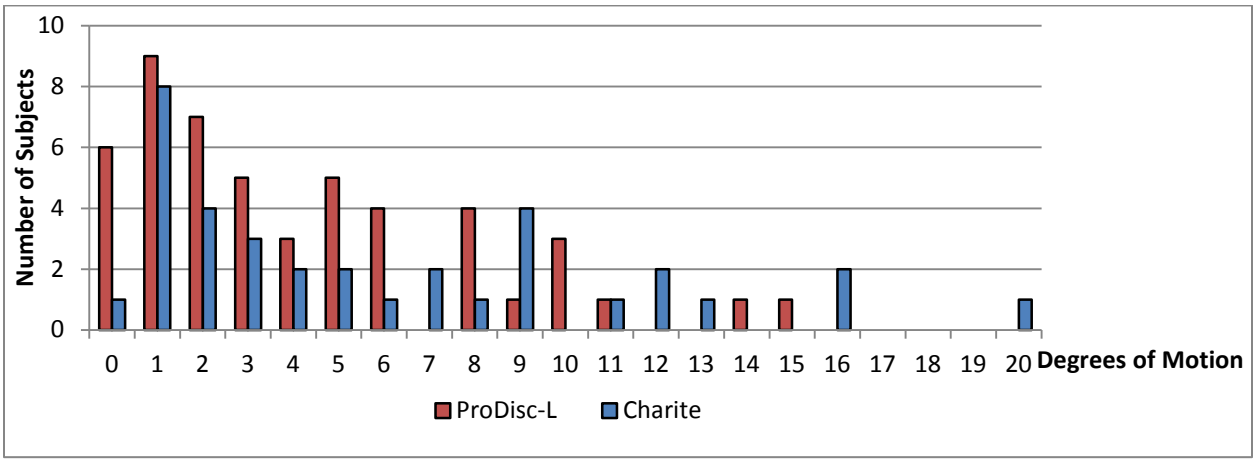


**Figure 6: Histogram of Flexion/Extension Angular Range of Motion at 24 Months for All activL Subjects (Randomized Plus Non-randomized) Stratified by Treatment Level**

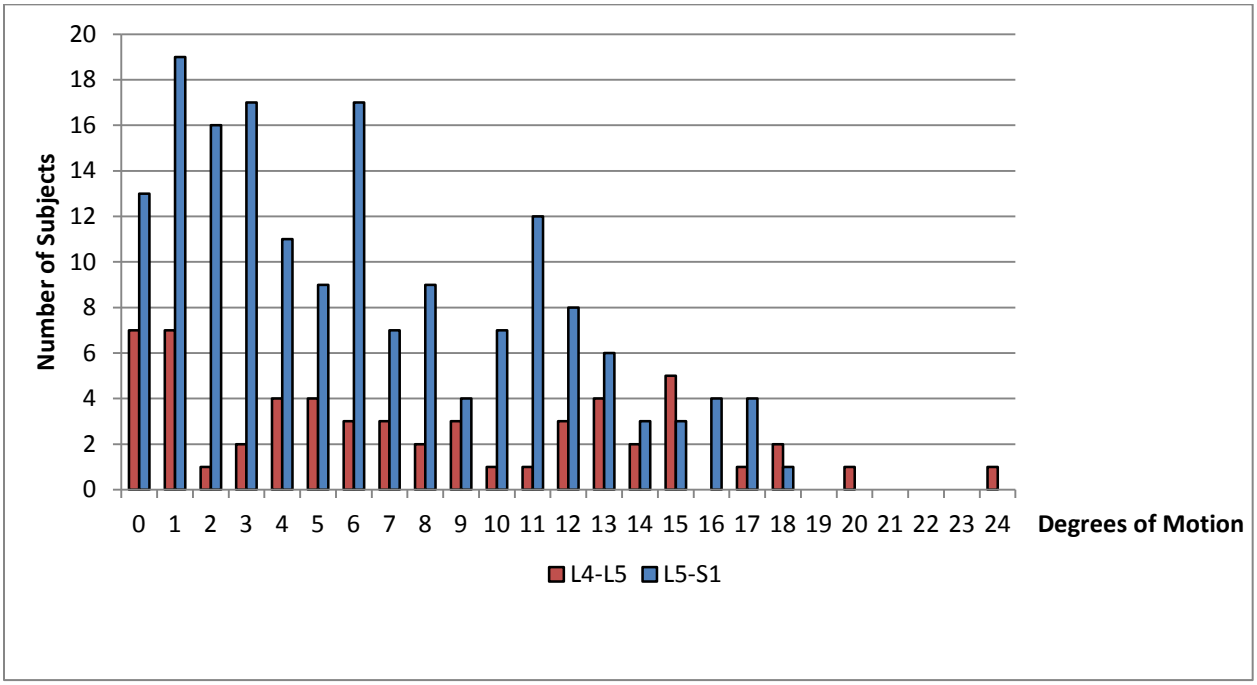



**Figure 7: Histogram of Flexion/Extension Angular Range of Motion at 24 Months for All Control Subjects (Randomized Plus Non-randomized) Stratified by Treatment Level**

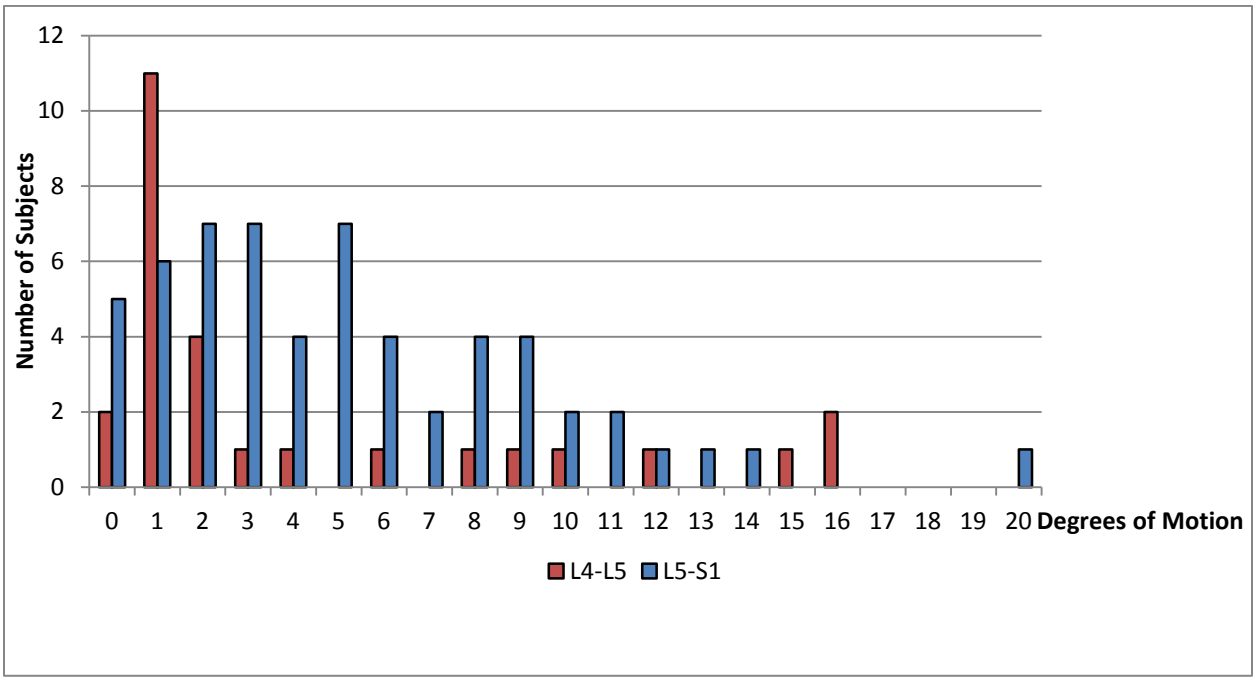


Table 59 compares the observed angular range of motion data to "normal" angular range of motion at the operative level at preoperative baseline as well as at 6, 12, and 24 months postoperative.

**Table 59: Time Course of Observed Angular Range of Motion Compared to "Normal" Angular Range of Motion**

| | Baseline | | | 6 mo | | | 12 mo | | | 24 mo | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | NR activL | R activL | R Contr | NR activL | R activL | R Contr | 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%) | 7/10 (70.0%) | 36/58 (62.1%) | 19/32 (59.4%) | 6/10 (60.0%) | 36/58 (62.1%) | 16/31 (51.6%) | 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%) | 20/32 (62.5%) | 102/143 (71.3%) | 42/63 (66.7%) | 19/31 (61.3%) | 103/142 (72.5%) | 43/65 (66.2%) | 20/31 (64.5%) | 102/139 (73.4%) | 40/58 (69.0%) |

"Normal" ROM definitions [7]:
L4-L5: ROM ≥ 6 degrees and ≤ 20 degrees, ± 2 degrees
L5-S1: ROM ≥ 5 degrees and ≤ 20 degrees, ± 2 degrees

The applicant evaluated the correlation between 24-month range of motion in rotation as well as translation and 24-month pain and function outcomes as shown in Table 60 for the randomized subjects treated in the trial as well as the non-randomized activL subjects. The non-randomized control data is not included due to the limited sample size. In the randomized activL group, there was a statistically significant inverse correlation between angular range of motion and back pain (r = -0.1569, p-value = 0.0339) and angular range of motion and function (r = -0.2013, p-value = 0.0060). Although an inverse correlation was found between these measures in the control group, it was not found to be statistically significant (motion/back pain: r = -0.0582, p-value = 0.5970), motion/function: r = -0.0683, p-value = 0.5346). The clinical significance of these results is not clear.

**Table 60: Correlation Between 24-Month Motion/Stability and Pain/Function Outcomes**

| Pain / Function Variable | 24 Month Motion (Flexion/Extension (Rotation) | | | 24 Month Stability (Flexion/Extension (Translation) | | |
|---|---|---|---|---|---|---|
| | NR activL r (p-value) | R activL r (p-value) | R Contr r (p-value) | NR activL r (p-value) | R activL r (p-value) | R Contr r (p-value) |
| Pain (Back Pain VAS) | -0.0086 (0.9578) | -0.1569 (0.0339) | -0.0582 (0.5970) | -0.1818 (0.2615) | -0.0713 (0.3390) | -0.1212 (0.2693) |
| Pain (Leg Pain VAS) | 0.0158 (0.9230) | -0.1148 (0.1239) | -0.1228 (0.2628) | -0.1568 (0.3338) | -0.0364 (0.6275) | -0.1511 (0.1674) |
| Function (ODI) | 0.1659 (0.3064) | -0.2013 (0.0060) | -0.0683 (0.5346) | -0.0079 (0.9613) | -0.1128 (0.1274) | -0.1834 (0.0929) |

*Disc Height*

Radiographic evaluation of mean disc height for the treated level at the preoperative, 6-month, 12-month and 24-month time points are shown in Table 61 by treatment group for the randomized subjects treated in the study as well as the non-randomized activL subjects. The non-randomized control data is

not included due to the limited sample size. Data on the number of subjects with > 3mm change in disc height compared to preoperative baseline at 6, 12, and 24 months by treatment group is also provided.

**Table 61: Time Course of Radiographic Disc Height (Observed)**

| | Baseline | | | 6 mo | | |
|---|---|---|---|---|---|---|
| | NR activL | R activL | R Contr | NR activL | R activL | R Contr |
| Mean Disc Height (mm); Mean ± Std Dev (Range) | 8.3 ± 2.2 (3.8 to 12.5) N=46 | 7.9 ± 1.9 (3.4 to 12.9) N=214 | 8.0 ± 1.8 (3.8 to 12.7) N=104 | 14.1 ± 1.6 9.6 to 17.8 N=43 | 14.1 ± 1.9 (9.5 to 20.1) N=200 | 14.2 ± 1.9 (9.9 to 21.6) N=96 |
| >3mm change in disc height vs. baseline | N/A | N/A | N/A | 38/43 (88.4%) | 185/198 (93.4%) | 84/95 (88.4%) |

| | 12 mo | | | 24 mo | | |
|---|---|---|---|---|---|---|
| | NR activL | R activL | R Contr | NR activL | R activL | R Contr |
| Mean Disc Height (mm); Mean + Std Dev (Range) | 14.1 ± 1.6 (9.3 to 18.0) N=41 | 14.0 ± 1.8 (9.3, 19.8) N=199 | 14.1 ± 1.9 (9.7, 21.3) N=95 | 14.0 ± 1.5 (9.2 to 17.5) N=41 | 14.0 ± 1.58 (9.1, 19.4) N=186 | 14.0 ± 1.9 (9.5, 21.2) N=87 |
| >3mm change in disc height vs. baseline | 37/41 (90.2%) | 182/197 (92.4%) | 81/94 (86.2%) | 37/41 (90.2%) | 173/184 (94.0%) | 76/87 (87.4%) |

Note: Data presented as mean ±standard deviation (min to max)

Table 62 provides data on 24-month disc height (observed) 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 62: 24 Month Disc Height (Observed) – Stratified**

| Evaluation | R activL (N=218) | | | | R Contr (N=106) | | | |
|---|---|---|---|---|---|---|---|---|
| | Device Design | | Treatment Level | | Contr 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) |
| Mean Disc Height (mm) Mean ± St Dev (Range) | 13.9 ± 1.8 (9.1 to 18.6) N=99 | 14.1 ± 1.9 (10.6 to 19.4) N=87 | 13.4 ± 2.0 (9.1 to 19.4) N=48 | 14.2 ± 1.7 (10.0 to 18.6) N=138 | 13.1 ± 1.4 (9.5 to 16.4) N=51 | 15.4 ± 1.7 (12.9 to 21.2) N=36 | 13.6 ± 1.5 (11.4 to 17.0) N=27 | 14.3 ± 2.1 (9.5 to 21.2) N=60 |
| >3mm change in disc height vs. baseline | 92/98 (93.9%) | 81/86 (94.2%) | 41/47 (87.2%) | 132/137 (96.4%) | 41/51 (80.4%) | 35/36 (97.2%) | 22/27 (81.5%) | 54/60 (90.0%) |

Table 63 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 63: 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%) |

*Heterotopic Ossification*

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 64 presents time course data on HO by treatment group for the randomized subjects as well as the non-randomized activL subjects. The non-randomized control data is not included due to the limited sample size. 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.

**Table 64: Time Course of Heterotopic Ossification**

| Time Period / HO Class | NR activL | R activL | R Contr |
|---|---|---|---|
| **6-Month Follow-Up** | | | |
| None | 41/44 (93.2%) | 192/202 (95.0%) | 87/97 (89.7%) |
| Class I | 2/44 (4.5%) | 6/202 (3.0%) | 6/97 (6.2%) |
| Class II | 1/44 (2.3%) | 4/202 (2.0%) | 3/97 (3.1%) |
| Class III | 0/44 (0.0%) | 0/202 (0.0%) | 0/97 (0.0%) |
| Class IV | 0/44 (0.0%) | 0/202 (0.0%) | 0/97 (0.0%) |
| Indeterminate | 0/44 (0.0%) | 0/202 (0.0%) | 1/97 (1.0%) |
| Not Assessed | 0/44 (0.0%) | 0/202 (0.0%) | 0/97 (0.0%) |
| *Stable vs. Baseline* | *44/44 (100.0%)* | *189/202 (93.6%)* | *86/97 (88.7%)* |
| *Progressive vs. Baseline* | *0/44 (0.0%)* | *13/202 (6.4%)* | *11/97 (11.3%)* |
| **12-Month Follow-Up** | | | |
| None | 36/41 (87.8%) | 179/201 (89.1%) | 78/96 (81.3%) |
| Class I | 4/41 (9.8%) | 10/201 (5.0%) | 10/96 (10.4%) |
| Class II | 0/41 (0.0%) | 10/201 (5.0%) | 4/96 (4.2%) |
| Class III | 1/41 (2.4%) | 2/201 (1.0%) | 2/96 (2.1%) |
| Class IV | 0/41 (0.0%) | 0/201 (0.0%) | 0/96 (0.0%) |
| Indeterminate | 0/41 (0.0%) | 0/201 (0.0%) | 2/96 (2.1%) |
| Not Assessed | 0/41 (0.0%) | 0/201 (0.0%) | 0/96 (0.0%) |
| *Stable vs. Baseline* | *37/41 (90.2%)* | *179/201 (89.1%)* | *84/96 (87.5%)* |
| *Progressive vs. Baseline* | *4/41 (9.8%)* | *22/201 (10.9%)* | *12/96 (12.5%)* |
| **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%)* |
| **3-Year Follow-Up** | | | |
| None | 22/37 (59.5%) | 90/138 (65.2%) | 38/71 (53.5%) |
| Class I | 11/37 (29.7%) | 32/138 (23.2%) | 24/71 (33.8%) |
| Class II | 2/37 (5.4%) | 12/138 (8.7%) | 4/71 (5.6%) |
| Class III | 2/37 (5.4%) | 3/138 (2.2%) | 2/71 (2.8%) |
| Class IV | 0/37 (0.0%) | 0/138 (0.0%) | 0/71 (0.0%) |
| Indeterminate | 0/37 (0.0%) | 1/138 (0.7%) | 3/71 (4.2%) |
| Not Assessed | 0/37 (0.0%) | 0/138 (0.0%) | 0/71 (0.0%) |
| *Stable vs. Baseline* | *29/37 (78.4%)* | *107/138 (77.5%)* | *54/71 (76.1%)* |
| *Progressive vs. Baseline* | *8/37 (21.6%)* | *31/138 (22.5%)* | *17/71 (23.9%)* |
| **4-Year Follow-Up** | | | |
| None | 11/18 (61.1%) | 28/40 (70.0%) | 10/25 (40.0%) |
| Class I | 5/18 (27.8%) | 5/40 (12.5%) | 10/25 (40.0%) |
| Class II | 1/18 (5.6%) | 5/40 (12.5%) | 2/25 (8.0%) |
| Class III | 1/18 (5.6%) | 2/40 (5.0%) | 1/25 (4.0%) |
| Class IV | 0/18 (0.0%) | 0/40 (0.0%) | 0/25 (0.0%) |

| Time Period / HO Class | NR activL | R activL | R Contr |
|---|---|---|---|
| Indeterminate | 0/18 (0.0%) | 0/40 (0.0%) | 2/25 (8.0%) |
| Not Assessed | 0/18 (0.0%) | 0/40 (0.0%) | 0/25 (0.0%) |
| *Stable vs. Baseline* | *16/18 (88.9%)* | *36/40 (90.0%)* | *19/25 (76.0%)* |
| *Progressive vs. Baseline* | *2/18 (11.1%)* | *4/40 (10.0%)* | *6/25 (24.0%)* |

Table 65 provides data on 24-month HO (observed) for the randomized activL group stratified by device design and treatment level and for the randomized control group stratified by control device type and treatment.

**Table 65: 24 Month Heterotopic Ossification (Observed) – Stratified**

| | R activL (N=218) | | | | R Contr (N=106) | | | |
|---|---|---|---|---|---|---|---|---|
| | Device Design | | Treatment Level | | Contr 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) |
| **24-Month Follow-Up** | | | | | | | | |
| None | 80/99 (80.8%) | 76/88 (86.4%) | 37/48 (77.1%) | 119/139 (85.6%) | 39/51 (76.5%) | 22/36 (61.1%) | 16/27 (59.3%) | 45/60 (75.0%) |
| Class I | 12/99 (12.1%) | 2/88 (2.3%) | 5/48 (10.4%) | 9/139 (6.5%) | 8/51 (15.7%) | 9/36 (25.0%) | 6/27 (22.2%) | 11/60 (18.3%) |
| Class II | 5/99 (5.1%) | 7/88 (8.0%) | 3/48 (6.3%) | 9/139 (6.5%) | 1/51 (2.0%) | 5/36 (13.9%) | 4/27 (14.8%) | 2/60 (3.3%) |
| Class III | 0/99 (0%) | 3/88 (3.4%) | 3/48 (6.3%) | 0/139 (0%) | 1/51 (2.0%) | 0/36 (0%) | 1/27 (3.7%) | 0/60 (0.0%) |
| Class IV | 0/99 (0%) | 0/88 (0%) | 0/48 (0%) | 0/139 (0%) | 0/51 (0.0%) | 0/36 (0%) | 0/27 (0%) | 0/60 (0.0%) |
| Indeterm. | 2/99 (2.0%) | 0/88 (0%) | 0/48 (0%) | 21/139 (1.4%) | 2/51 (3.9%) | 0/36 (0%) | 0/27 (0%) | 2/60 (3.3%) |
| Not Assessed | 0/99 (0.0%) | 0/88 (0.0%) | 0/48 (0.0%) | 0/139 (0.0%) | 0/51 (0.0%) | 0/36 (0.0%) | 0/27 (0.0%) | 0/60 (0.0%) |
| *Stable vs. Baseline* | *87/99 (87.9%)* | *80/88 (90.9%)* | *45/48 (93.8%)* | *122/139 (87.8%)* | *47/51 (92.2%)* | *27/36 (75.0%)* | *25/27 (92.6%)* | *49/60 (81.7%)* |
| *Progressive vs. Baseline* | *12/99 (12.1%)* | *8/88 (9.1%)* | *3/48 (6.3%)* | *17/139 (12.2%)* | *4/51 (7.8%)* | *9/36 (25.0%)* | *2/27 7.4%)* | *11/60 (18.3%)* |

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, defined as class 3 and class 4 HO. All subjects with severe HO were primary endpoint failures, regardless of treatment group. There were no clear trends for any other success components.

**Pain Management**

Table 66 presents data on pain medication use at baseline preoperative and at 24 months postoperative by treatment group for the randomized subjects as well as the non-randomized activL subjects. The non-randomized control data is not included due to the limited sample size. Use of pain medication was similar in all treatment groups.

**Table 66: Pain Medication Usage at Baseline and 24 Months Postoperative (Observed)**

| Visit Interval | NR activL n/N (%) | R activL n/N (%) | R Contr n/N (%) |
|---|---|---|---|
| **Baseline** | | | |
| No Pain Medication | 4/46 (8.7%) | 22/218 (10.1%) | 8/106 (7.5%) |
| Any Pain Medication | 42/46 (91.3%) | 196/218 (89.9%) | 98/106 (92.5%) |
| Narcotic/Narcotic Combination Analgesics | 34/42 (81.0%) | 141/196 (71.9%) | 65/98 (66.3%) |
| Other Controlled Analgesic Medication | 10/42 (23.8%) | 30/196 (15.3%) | 17/98 (17.3%) |
| NSAID/Combination NSAID | 21/42 (50.0%) | 96/196 (49.0%) | 40/98 (40.8%) |
| Salicylate/Combination Salicylate | 1/42 (2.4%) | 4/196 (2.0%) | 2/98 (2.0%) |
| Acetaminophen/Combination Acetaminophen | 6/42 (14.3%) | 22/196 (11.2%) | 4/98 (4.1%) |
| Steroid | 1/42 (2.4%) | 0/196 (0.0%) | 1/98 (1.0%) |
| Muscle Relaxant | 15/42 (35.7%) | 61/196 (31.1%) | 34/98 (34.7%) |
| Agonist/Antagonist | 0/42 (0.0%) | 0/196 (0.0%) | 0/98 (0.0%) |
| **24-Month Follow-Up** | | | |
| No Pain Medication | 19/41 (46.3%) | 82/189 (43.4%) | 39/87 (44.8%) |
| Any Pain Medication | 22/41 (53.7%) | 107/189 (56.6%) | 48/87 (55.2%) |
| Narcotic/Narcotic Combination Analgesics | 13/22 (59.1%) | 58/107 (54.2%) | 29/48 (60.4%) |
| Other Controlled Analgesic Medication | 2/22 (9.1%) | 7/107 (6.5%) | 4/48 (8.3%) |
| NSAID/Combination NSAID | 7/22 (31.8%) | 56/107 (52.3%) | 24/48 (50.0%) |
| Salicylate/Combination Salicylate | 2/22 (9.1%) | 9/107 (8.4%) | 1/48 (2.1%) |
| Acetaminophen/Combination Acetaminophen | 5/22 (22.7%) | 16/107 (15.0%) | 4/48 (8.3%) |
| Steroid | 1/22 (4.5%) | 2/107 (1.9%) | 1/48 (2.1%) |
| Muscle Relaxant | 5/22 (22.7%) | 31/107 (29.0%) | 15/48 (31.3%) |
| Agonist/Antagonist | 0/22 (0.0%) | 1/107 (0.9%) | 0/48 (0.0%) |

Table 67 summarizes all subjects who received any postoperative pain management procedures at either the index or adjacent level by procedure type. The most common types of procedures were Facet Injections and Epidural Steroid Injections. These were more common in the control group (10.4% and 17.0%, respectively) than in both activL groups (randomized activL: 8.7% and 6.0%, non-randomized activL: 6.5% and 10.9%, respectively).

**Table 67: Subjects Receiving Any Postoperative Pain Management Procedures at Either the Index or Adjacent Level Classified by Procedure Type (Observed)**

| Procedure | NR activL n/N (%) | R activL n/N (%) | R Contr n/N (%) |
|---|---|---|---|
| **Injections** | **13/46 (28.2%)** | **54/218 (24.8%)** | **50/106 (47.2%)** |
| Coccyx Injection | 0/46 (0.0%) | 1/218 (0.5%) | 2/106 (1.9%) |
| Epidural Steroid Injection | 5/46 (10.9%) | 13/218 (6.0%) | 18/106 (17.0%) |
| Facet Injection | 3/46 (6.5%) | 19/218 (8.7%) | 11/106 (10.4%) |
| Interspinous Ligament Injection | 0/46 (0.0%) | 0/218 (0.0%) | 2/106 (1.9%) |
| Nerve Root Block | 1/46 (2.2%) | 4/218 (1.8%) | 4/106 (3.8%) |
| Paravertebral Nerve Block | 0/46 (0.0%) | 0/218 (0.0%) | 1/106 (0.9%) |
| Pars Injection | 0/46 (0.0%) | 0/218 (0.0%) | 1/106 (0.9%) |
| Sacroiliac Injection | 2/46 (4.3%) | 7/218 (3.2%) | 6/106 (5.7%) |
| Selective Nerve Root Block | 0/46 (0.0%) | 0/218 (0.0%) | 1/106 (0.9%) |

| Procedure | NR activL n/N (%) | R activL n/N (%) | R Contr n/N (%) |
|---|---|---|---|
| Sympathetic Injection | 0/46 (0.0%) | 1/218 (0.5%) | 0/106 (0.0%) |
| Sympathetic Nerve Block | 0/46 (0.0%) | 1/218 (0.5%) | 0/106 (0.0%) |
| Transforaminal Epidural Steroid Injection | 2/46 (4.3%) | 6/218 (2.8%) | 3/106 (2.8%) |
| Trigger Point Injection | 0/46 (0.0%) | 1/218 (0.5%) | 0/106 (0.0%) |
| Trochanteric Steroid Injection | 0/46 (0.0%) | 1/218 (0.5%) | 1/106 (0.9%) |
| **Implants** | **2/46 (4.3%)** | **2/218 (1.0%)** | **2/106 (1.9%)** |
| Morphine pump implant | 0/46 (0.0%) | 1/218 (0.5%) | 0/106 (0.0%) |
| Peripheral Nerve Root Stimulator | 0/46 (0.0%) | 1/218 (0.5%) | 0/106 (0.0%) |
| Spinal Cord Stimulator Implant | 2/46 (4.3%) | 0/218 (0.0%) | 2/106 (1.9%) |
| **Surgical Procedures** | **1/46 (2.2%)** | **9/218 (4.1%)** | **4/106 (3.8%)** |
| Ablation | 0/46 (0.0%) | 1/218 (0.5%) | 1/106 (0.9%) |
| Medial Branch Block | 1/46 (2.2%) | 6/218 (2.8%) | 3/106 (2.8%) |
| Radiofrequency Ablation | 0/46 (0.0%) | 2/218 (0.9%) | 0/106 (0.0%) |
| Rhizotomy | 2/46 (4.3%) | 9/218 (4.1%) | 5/106 (4.7%) |
| Removed Stimulator | 0/46 (0.0%) | 1/218 (0.5%) | 0/106 (0.0%) |

### Adjacent Level Treatment

Some subjects went on to receive postoperative treatment at an adjacent level, as shown in Table 68, with specific procedures reported in Table 69. The proportion of subjects with adjacent level fusion was lower in the activL group (2.2% in NR activL subjects and 0.9% in R activL subjects) than in the control group (2.8%). However, adjacent level rhizotomy was performed more often in activL subjects (0.0% in NR activL subjects and 4.1% in R activL subjects) than in control subjects (1.9%).

**Table 68: Subjects with Adjacent Level Treatment by Visit Interval (Observed)**

| Time Period | NR activL n/N (%) | R activL n/N (%) | R Contr n/N (%) |
|---|---|---|---|
| Surgery/Discharge | 0/46 (0.0%) | 0/218 (0.0%) | 0/106 (0.0%) |
| 6-Week Follow-up | 0/46 (0.0%) | 0/214 (0.0%) | 0/105 (0.0) |
| 3-Month Follow-up | 0/46 (0.0%) | 0/209 (0.0%) | 0/101 (0.0%) |
| 6-Month Follow-up | 0/45 (0.0%) | 1/203 (0.5%) | 1/97 (1.0%) |
| 12-Month Follow-up | 0/41 (0.0%) | 6/202 (3.0%) | 1/96 (1.0%) |
| 24-Month Follow-up | 0/41 (0.0%) | 4/189 (2.1%) | 5/87 (5.7%) |
| 3-Year Follow-up | 1/37 (2.7%) | 2/140 (1.4%) | 1/72 (1.4%) |
| 4-Year Follow-up | 0/19 (0.0%) | 1/41 (2.4%) | 0/26 (0.0%) |
| 5-Year Follow-up | 1/2 (50.0%) | 0/17 (0.0%) | 0/8 (0.0%) |
| Total Subjects | 2/46 (4.3%) | 13/218 (6.0%) | 10/106 (9.4%) |
| Total Treatments | 2 | 18 | 10 |

Note: Subjects with treatment prior to a visit are assigned to that visit. If the treatment date is missing, then the AE onset date is used for comparison.

**Table 69: Types of Adjacent Level Treatments**

| Adjacent Level Treatment | NR activL n/N (%) | R activL n/N (%) | R Contr n/N (%) |
|---|---|---|---|
| Ablation | 0/46 (0.0%) | 0/218 (0.0%) | 1/106 (0.9%) |
| Foraminotomy/decompression | 0/46 (0.0%) | 0/218 (0.0%) | 1/106 (0.9%) |
| Fusion | 2/46 (4.3%) | 2/218 (0.9%) | 5/106 (4.7%) |
| Microdiscectomy | 2/46 (4.3%) | 0/218 (0.0%) | 0/106 (0.0%) |
| Other | 0/46 (0.0%) | 1/218 (0.5%) | 2/106 (1.9%) |
| Rhizotomy | 0/46 (0.0%) | 9/218 (4.1%) | 2/106 (1.9%) |

**Return to Work**

Table 70 provides return to work data by treatment group for the randomized subjects as well as the non-randomized activL subjects. The non-randomized control data is not included due to the limited sample size. The median return to work time was slightly shorter in the activL groups as compared to the control group.

**Table 70: Summary of Kaplan-Meier Analysis for Return to Work**

| | NR activL n/N (%) | R activL n/N (%) | R Contr n/N (%) | Log-Rank P-value (Randomized Groups) |
|---|---|---|---|---|
| Median Time (Days) Return to Work<br>(95% CI) | 68.5<br>(42 , 114) | 68<br>(52 , 90) | 97<br>(69 , 143) | 0.084 |

# XI PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

In accordance with the provisions of section 515(c)(2) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Orthopaedic and Rehabilitation Devices Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

# XII CONCLUSIONS DRAWN FROM NONCLINICAL AND CLINICAL STUDIES

## A. Effectiveness Conclusions

In the clinical trial of the activL® Artificial Disc conducted to support PMA approval, 379 subjects were treated (R activL = 218, NR activL = 48, R Contr = 106, NR Contr = 7), all had reached the 24-month post-operative visit, and 230 of the 272 expected randomized subjects (85.0%) had 24-month data available for analysis. Statistical analysis demonstrated that the results from all sites were poolable to determine safety and effectiveness. Analysis of subject demographic and baseline covariates showed that the two randomized treatment groups were comparable at baseline.

Overall success at 24 months postoperative was defined in the protocol as improvement in pain and disability using the Oswestry Disability Index, maintenance or improvement in neurological status motor and sensory evaluations, maintenance or improvement in range of motion (ROM) at the index level, no subsequent surgery at the index level, and no serious device-related adverse events as determined 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 when comparing the two randomized treatment groups, FDA requested an additional analysis of overall success without the ROM success component.

The randomized trial results, using both sets of overall success criteria, indicate that the activL is non-inferior (10% delta) to the control group in the overall composite success rate at 24 months (R activL = 42.2% missing imputed as failures (49.7% observed); R Contr = 28.3% missing imputed as failures (33.3% observed) including the ROM success component). After removal of the ROM component, non-inferiority was still met (R activL = 61.9% missing imputed as failures (71.4% observed); R Contr = 52.8% missing imputed as failures (62.5% observed)). Note that the control group success rates achieved in this trial were lower than the respective success rates achieved in the prior IDE trials of the control devices; however, the differences were felt to be largely due to differences in the definitions of success in this trial as compared to the prior IDE trials.

To assess the impact of subjects with unknown outcomes at 24 months postoperative or other potential biases, various pre-defined sensitivity analyses were conducted to confirm the robustness of the trial conclusions. The results of nearly all sensitivity analyses indicate that the activL is non-inferior to the control group in the composite overall success rate at 24 months. In addition, post hoc comparisons of activL versus each of the two control devices alone show that the non-inferiority hypothesis test is met at the 10% delta level.

This PMA includes clinical data for two different versions of the activL device (spike version and keel version). Both versions have an identical articulation; the only difference is the method of initial fixation of the device endplate to the vertebral body. The 24-month overall success rate in the randomized activL Spike group was 41.7% missing imputed as failures (50.0% observed) compared to 43.1% missing imputed as failures (49.4% observed) in the randomized activL Keel group for overall success including the ROM success component. Similarly, for overall success without the ROM success component, the 24 month overall success rate in the randomized activL Spike group was 60.0% missing imputed as failures (70.4% observed) compared to 64.7% missing imputed as failures (72.5% observed) in the randomized activL Keel group.

The PMA also includes clinical data for treatment of two different lumbar spine levels (L4-L5 and L5-S1). The 24-month overall success rate for randomized activL subjects treated at L4-L5 was 35.5% missing imputed as failures (47.8% observed) compared to 44.9% missing imputed as failures (50.4% observed) for randomized activL subjects treated at L5-S1 for overall success including the ROM success component. Similarly, for overall success without the ROM success component, the 24-month overall success rate for randomized activL subjects treated at L4-L5 was 58.1% missing imputed as failures (73.5% observed) compared to 63.5% missing imputed as failures (70.7% observed) for randomized activL subjects treated at L5-S1. For the index levels L4-L5 and L5-S1, higher success rates were observed for activL versus control at both levels (12% higher at L4-L5; 14.3% higher at L5-S1; missing imputed as failures analysis), both favoring activL.

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. Based on this definition, 128/184 (69.6%) randomized activL subjects were considered range of motion successes at 24 months as compared to 44/84 (52.4%) randomized control group subjects.

In conclusion, the trial data indicate that, at 24 months postoperatively, both versions of the activL® Artificial Disc (Spike version and Keel version) used at both L4-L5 and L5-S1 are at least as effective as the alternative lumber total disc replacement control group (in which subjects were treated with either the ProDisc-L or Charité based on surgeon preference) in terms overall success (both with and without the range of motion success criterion) and the individual components of overall success.

## B. Safety Conclusions

The risks of the activL® Artificial Disc are based on nonclinical laboratory and animal studies as well as data collected in the clinical trial conducted to support PMA approval as described above.

Nonclinical testing performed on the device demonstrated that the activL® Artificial Disc should withstand the expected physiologic loads in the lumbar spine.

In the clinical trial of the activL conducted to support PMA approval, the investigational activL was found to have a reasonable assurance of safety and to be at least as safe as the alternative lumbar total disc replacement control group (in which subjects were treated with either the ProDisc-L or Charité based on surgeon preference). Specifically, the rates of activL subjects who experienced at least one adverse event, an event classified by the CEC as device-related (including those also classified as serious), an event classified by the CEC as procedure-related, or an event classified by the CEC as serious were generally comparable to the corresponding rates in the control group. In addition, the rates of subsequent surgery at the index level were also similar when comparing the two treatment groups (5.5% of subjects in the randomized activL group as compared to 5.7% of subjects in the control group). Qualitatively similar adverse event profiles were demonstrated for the two different versions of the activL device (spike version and keel version) as well as for treatment at L4-L5 as compared to L5-S1.

In addition, at 24 months, the proportion of subjects with no decline in either motor or sensory neurological evaluations was comparable between the two treatment groups (motor evaluations: activL = 97.3%, control = 98.9%; sensory evaluations: activL = 94.1%, control = 93.1%), and comparisons of 24-month neurologic status demonstrated similar outcomes in the activL group as compared to the control group.

In conclusion, the clinical trial data indicate that, at 24 months postoperatively, the activL® Artificial Disc has a reasonable assurance of safety and is at least as safe as the alternative lumbar total disc replacement control group (in which subjects were treated with either the ProDisc-L or Charité based on surgeon preference) in regards to adverse event rates, neurologic status, and the need for subsequent surgery at the index level.

## C. Benefit-Risk Conclusions

The probable benefits of the activL® Artificial Disc are based on data collected in the clinical trial conducted to support PMA approval as described above.

The clinical trial demonstrated several benefits of the activL device used at a single lumbar level (L4-L5 or L5-S1) over the 24-month time period studied.

- The benefit of the activL in terms of clinically meaningful improvement in function (as measured by a 15 point improvement in the Oswestry Disability Index) at 24 months postoperatively was comparable to the alternative lumbar total disc replacement control group (in which subjects were treated with either the ProDisc-L or Charité based on surgeon preference), in that the majority of subjects in both treatment groups in the clinical trial experienced this benefit when considering the observed results (87.7% of randomized activL subjects and 80.2% of randomized control group subjects). The benefit of the activL in terms of neurologic success (maintenance or improvement in motor and sensory status as measured during the neurologic examination done by the investigator) at 24 months postoperatively was also comparable to the alternative lumbar total disc replacement control group in that the majority of subjects in both treatment groups in the clinical trial experienced this benefit when considering the observed results (93.1% of randomized activL subjects and 93.0% of randomized control group subjects).
- In terms of improvement in back and leg pain (as measured by ≥ 20mm improvement in pain on a Visual Analog Scale as compared to baseline), at 24 months postoperatively, the benefit of the activL was at least comparable to the alternative lumbar total disc replacement control. The majority of subjects in both treatment groups experienced clinically meaningful improvement in back pain at 24 months when considering the observed results (90.0% of randomized activL subjects and 82.8% of randomized control group subjects). Fewer subjects in both treatment groups experienced clinically meaningful improvement in leg pain at 24 months when considering observed results; however, preoperative leg pain was not a requirement for inclusion in the trial.
- Radiographic range of motion success was defined as maintenance or improvement from baseline in angular ROM at the index level as measured on flexion/extension radiographs (i.e., flexion/extension angular ROM at follow-up minus flexion/extension angular ROM at baseline ≥ 0 with 2° measurement error applied) and no fusion as defined in the radiographic protocol (i.e., evidence of continuous bridging bone and < 3° of angular motion from flexion to extension). At 24 months postoperatively, the benefit of activL in terms of ROM success was qualitatively greater than the control group when considering the observed results (activL = 69.6%, control = 52.4%).

The clinical trial demonstrated that the risks associated with use of the activL device were comparable to those associated with the control group devices through 24 months follow-up. In addition, there was a relatively low rate of subsequent surgical intervention at the index level in both treatment groups (5.5% of subjects in the randomized activL group as compared to 5.7% of subjects in the control group). In addition, at 24 months postoperatively, the activL group was comparable to the control group in terms of adverse event rates and maintenance or improvement in neurologic status.

Although data on subject tolerance for risk and perception of benefit was not formally collected, subject satisfaction was measured at annual follow-up visits. At 24 months, the majority of subjects in both treatment groups responded that they were very or somewhat satisfied with their treatment when considering the observed results (94.2% of randomized activL subjects and 93.1% of randomized control group subjects).

Several additional factors were considered in determination of the probable benefits and risks for the activL device. Limitations of the clinical study design included imperfect subject masking with regard to treatment assignment, reliance on subjective endpoints, and subjectivity in adverse event classification. In addition, the impact of missing data and the robustness of the sensitivity analyses provided to address the missing data, as well as the generalizability of the study results were also considered. Finally, alternative available treatments and risk mitigation strategies were considered as was the fact that the only available indicator of subject tolerance for risk and perspective on benefit was subject satisfaction data.

Note that other theoretical benefits of lumbar total disc replacement devices, such as the activL, include preservation of range of motion and potential for decreased risk of adjacent segment degeneration. However, the clinical trial conducted to support PMA approval of the activL was not specifically designed or powered to study these potential benefits as primary endpoints. In addition, any potential benefit in terms of clinically significant reduction in adjacent level degeneration would not necessarily be expected in the two year time period of the clinical trial.

In conclusion, given the available information above, the data support that for reconstruction of the disc at one level (L4-L5 or L5-S1) following single-level discectomy for symptomatic degenerative disc disease (DDD) with no more than Grade I spondylolisthesis at the involved level and specific clinical and radiographic findings as outlined above in the Indications for Use, the probable benefits of the activL® Artificial Disc outweigh the probable risks through 24-months follow-up.

### D. Overall Conclusions

The nonclinical and clinical data presented in this application 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.

## XIII CDRH DECISION DRAFT

CDRH issued an approval order on June 11, 2015. The final conditions of approval cited in the approval order are described below.

The applicant has agreed to provide the following data as part of the PMA annual report:

1. Results from an Explant Analysis Retrieval Study that will be conducted for the 10 years following PMA approval and will include an analysis of all explanted activL® Artificial Discs (including, but not limited to, those retrieved from subjects in the Office of Device Evaluation (ODE) Lead PMA Post-Approval Study (Post-Approval Clinical Study) as well as patients in the Office of Surveillance and Biometrics (OSB) Lead PMA Post-Approval Study (Enhanced Safety Surveillance Study)) as outlined below. The annual results from the Explant Analysis Retrieval Study will include the following information for each known subject who has undergone device removal since the prior Annual Report: a detailed clinical narrative, a copy of the operative report from the original activL® Artificial Disc implantation surgery, copies of operative reports from all subsequent surgeries including the removal surgery, copies of any pathology reports, and a detailed explant analysis per the Aesculap activL® Retrieval Protocol included in the approved Post-Approval Study and Enhanced Surveillance Study protocols.

In addition to the Annual Report requirements, the applicant must provide the following data in post-approval study (PAS) reports for each PAS listed below.

1. ODE Lead PMA Post-Approval Study – Post-Approval Clinical Study to Evaluate the Safety and Effectiveness of the Aesculap activL® Artificial Disc in the Treatment of Degenerative Disc Disease: The Office of Device Evaluation (ODE) will have the lead for this clinical study, which was initiated prior to device approval. This study will be conducted as per the protocol dated May 26, 2015, Version 9.0.

   The Post-Approval Clinical Study to Evaluate the Safety and Effectiveness of the Aesculap activL® Artificial Disc in the Treatment of Degenerative Disc Disease is a 7-year post-approval study (PAS) to evaluate the longer term safety and effectiveness of the activL® Artificial Disc as compared to the alternative lumbar total disc replacement control group (in which subjects were treated with either the ProDisc-L or Charité based on surgeon preference) by following the 376 subjects from the pivotal investigational device exemption (IDE) study (218 randomized activL subjects, 46 non-randomized activL subjects, 106 randomized control subjects, and 6 non-randomized control subjects) annually through 7 years. At each annual (±60 days) visit, the applicant will collect the following data: Oswestry Disability Index (ODI), back and right/left leg pain Visual Analog Scale (VAS), health status survey (SF-36), subject satisfaction, neurological status, radiographic information, medication usage and postoperative treatment for pain management, work status, and all adverse events regardless of cause including all subsequent surgical interventions (SSIs). Radiographic information collected will include: range of motion (ROM) on flexion/extension films (angulation and translation as well as the correlation of range of motion with clinical outcomes), disc height, local segmental lordosis, radiolucency, device condition, device migration, device subsidence, osteophyte formation, and heterotopic ossification (including grade, stability over time, and correlation with subject characteristics and postoperative clinical outcomes). The applicant will also collect clinical and radiographic data on

adjacent level degeneration/disease including both surgical and non-surgical adjacent level treatments as well as adjacent level diagnoses, adjacent level range of motion, and radiographic changes at adjacent levels. The applicant will also analyze all activL® Artificial Discs that are explanted as part of this Post-Approval Study according to the Aesculap activL® Retrieval Protocol and will present the results in the relevant section of each PMA Annual Report, as outlined above.

The primary objective of the PAS is to evaluate individual subject success, which is defined as:

- Improvement of at least 15 points in the ODI score at 7 years compared to baseline;
- Maintenance or improvement in neurological status at 7 years 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 motion at the index level (7 year ROM minus preoperative ROM ≥ 0 with ±2° measurement error applied) and avoidance of fusion as defined in the protocol;
- No device failures requiring revision, reoperation, removal, or supplemental fixation at the index level; and
- Absence of serious device-related adverse events as adjudicated by the Clinical Events Committee (CEC).

In addition, because the ROM success component of the primary endpoint was such a notable driver of the difference in individual subject success rates when comparing the two treatment groups in the IDE study, the applicant has also agreed to conduct the following additional analysis of individual subject success without the ROM success component:

- Improvement of at least 15 points in the ODI score at 7 years compared to baseline;
- Maintenance or improvement in neurological status at 7 years compared to baseline as measured by motor and sensory evaluations with a decrease of one grade in either evaluation considered a failure;
- No device failures requiring revision, reoperation, removal, or supplemental fixation at the index level; and
- Absence of serious device-related adverse events as adjudicated by the Clinical Events Committee (CEC).

Individual subject success rates in the randomized activL and randomized control groups will be compared and assessed for non-inferiority based on a ten percent non-inferiority margin for both definitions of individual subject success. Subjects who were non-recoverable non-responders prior to 24 months will carry forward as failures for each subsequent annual visit. Numerous sensitivity analyses as specified in the protocol will also be done to assess the robustness of the study conclusions.

FDA will expect at least 85% follow-up at the 7-year time point to provide sufficient data to evaluate safety and effectiveness.

The applicant will submit progress reports to FDA for this study every six months during the first two years of the study and annually thereafter. A final report will be submitted within 6 months of the last subject visit.

2. OSB Lead PMA Post-Approval Study – Enhanced Safety Surveillance Study of the Aesculap activL® Artificial Disc: The Office of Surveillance and Biometrics (OSB) will have the lead for studies initiated after device approval. This study will be conducted as per the protocol dated May 20, 2015, Version 1.0.

   The Enhanced Safety Surveillance Study (ESS) of the Aesculap activL® Artificial Disc is a 10-year study to fully characterize adverse events and complaints when the device is used in the intended patient population under general conditions of use in the United States and in the rest of the world as well as to identify new safety concerns that were not observed in the clinical trial.

   The study is an unmasked, uncontrolled surveillance study of all patients treated with the activL® Artificial Disc for the 10 years following PMA approval. The applicant will collect, analyze, and submit all adverse event data including subsequent surgeries, heterotopic ossification, device malfunction, device removal, and other device issues. Data will be collected through annual surgeon surveys, reporting of adverse events, complaints and Medical Device Reports (MDRs), explant analysis, and literature review.

   As part of the active collection of surgeon feedback, the applicant will utilize annual surgeon surveys to collect data related to heterotopic ossification, device malfunction, subsequent surgery at the index level including device removal, and other serious potentially device-related complications. All of the surgeons who have been trained on the use of the activL® Artificial Disc worldwide will be surveyed annually, and the number of surveys issued and received will be reported. If a survey response includes any information related to an adverse event, the applicant will collect additional data as specifically outlined in the ESS protocol and report that data to FDA. The endpoints of the study include information related to patient outcomes, subsequent surgical interventions (SSIs), pain management procedures, device ease of use and satisfaction, device malfunction, and any other serious device-related adverse events.

   The applicant will also analyze all activL® Artificial Discs that are explanted as part of this Enhanced Safety Surveillance Study according to the Aesculap activL® Retrieval Protocol and will present the results in the relevant section of each PMA Annual Report as outlined above.

The applicant will submit progress reports to FDA for this study every six months during the first two years of the study and annually thereafter. A final report will be submitted within 3 months of study completion.

The applicant's manufacturing facilities were inspected and found to be in compliance with the Quality System (QS) regulation (21 CFR 820).

## XIV APPROVAL SPECIFICATIONS

Directions for Use: See device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order.

## XV REFERENCES

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