SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Prosthesis, posterior spinal elements

Device Trade Name: TOPS™ System

Device Procode: QWK

Applicant's Name and Address:

Premia Spine, Ltd.
7 Giborey Israel Street
Ramat Poleg, Netanya HaMerkaz,
Israel 4250407

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P220002

Date of FDA Notice of Approval: June 15, 2023

Breakthrough Device: Granted breakthrough device status on October 26, 2020, because the device and proposed indication for use met the criteria.

II. INDICATIONS FOR USE

The TOPS™ System is a motion-preserving spinal implant that is inserted into the lumbar spine via pedicle screws. The TOPS™ System is intended to stabilize the spine following a lumbar decompression without rigid fixation.

The TOPS™ System is indicated for patients between 35 and 80 years of age with symptomatic degenerative spondylolisthesis up to Grade I, with moderate to severe lumbar spinal stenosis and either the thickening of the ligamentum flavum and/or scarring of the facet joint capsule at one level from L3 to L5.

III. CONTRAINDICATIONS

The TOPS™ System is contraindicated in patients with:

- Presence of extruded or free fragment disc herniation at the index level
- Spondylolisthesis greater than Grade I
- Traumatic, dysplastic or lytic spondylolisthesis
- Back or non-radicular leg pain of unknown etiology
- Stenosis where the etiology is considered to be congenital, iatrogenic, post-traumatic, or metabolic

- Known allergy or sensitivity to PEEK, titanium, and/or polyurethane
- Scoliosis greater than 10 degrees by major Cobb angle (both angular and rotational)
- Morbid obesity defined as a body mass index greater than 40
- Lumbar spine T-score less than -2.0
- Active infection - systemic or local
- Cauda equina syndrome or neurogenic bowel/bladder dysfunction

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the TOPS™ System labeling.

V. DEVICE DESCRIPTION

The TOPS™ System presented in **Figure 1** below is a motion-preserving spinal implant that is inserted into the lumbar spine via pedicle screws. The device is implanted via a posterior surgical approach to replace the degenerated skeletal elements such as the lamina and the facet joints that are removed during the decompression.

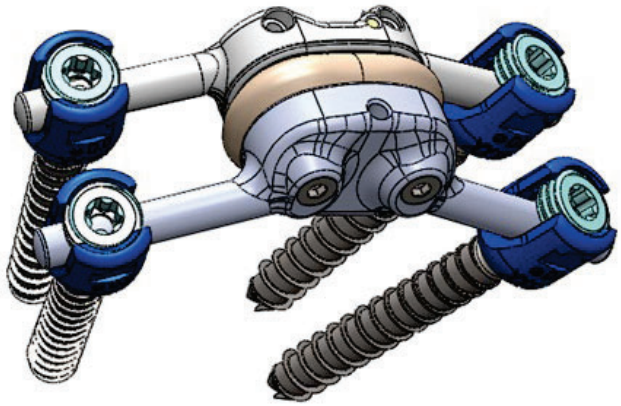


Figure 1: The TOPS™ System (TOPS™ Motion Implant and Pedicle Screws)

The TOPS™ System is comprised of a motion device ("TOPS™ Motion Implant") and four pedicle screws. The TOPS™ Motion Implant is comprised of two Titanium Endplates connected by a polycarbonate urethane (PcU) Boot. Housed between the Titanium Endplates is an internal motion mechanism comprised of titanium and PcU articulating parts and an interlocking woven Polyether Ether Ketone (PEEK) ribbon (see **Figure 2**). The Top Articulating and Bottom Articulating parts are attached to their respective upper and lower Titanium Endplates. The flexible Boot and the internal articulating parts allow relative movement between the endplates. The device is designed to maintain motion in axial rotation, lateral bending, extension, and flexion, and to block translation when implanted into the human spine.

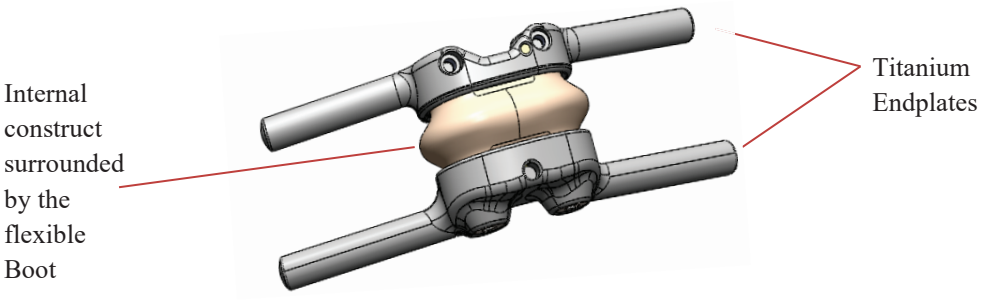
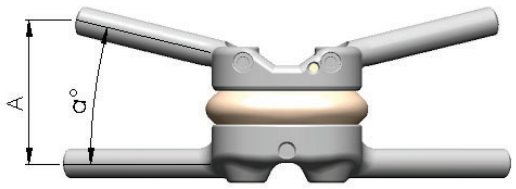


Figure 2: Illustration of the TOPS™ Motion Implant

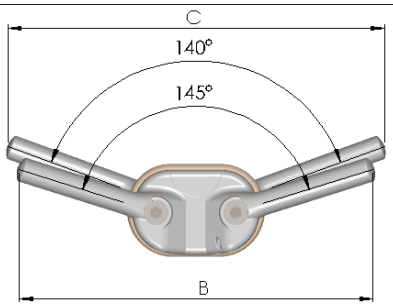
The TOPS™ Motion Implant is available in various sizes to meet a range of human anatomy, as depicted in **Table 1**.

Table 1: TOPS™ Motion Implant Configurations

	Version	α (deg	A (mm)	B (mm)	C (mm)
1	TOPS™ - 21 L	0	21	87	93
2	TOPS™ - 30 L	14	30		
3	TOPS™ - 38 L	26	38		
4	TOPS™ - 21 M	0	21	77	83
5	TOPS™ - 30 M	14	30		
6	TOPS™ - 38 M	26	38		
7	TOPS™ - 21 S	0	21	67	73
8	TOPS™ - 30 S	14	30		
9	TOPS™ - 38 S	26	38		



α= The angle between the arms (Top plate and Bottom plate); A= Inter-Pedicular Distance (IPD), defined by the configuration of the Top Plate.



B= Top Plate length
C= Bottom plate length

Note:
**All dimensions indicated in the table are rounded and for reference only.*
***The IPD (21,30,38) is defined by the configuration of the Top Plate, which is available in 9 configurations: 21(L,M,S), 30(L,M,S) and 38(L,M,S), while the Bottom and Top Plates are available in 3 length configurations - L,M,S*

The TOPS™ System utilizes four polyaxial pedicle screws for fixation to the vertebrae. The Pedicle Screws are made of titanium alloy (Ti-6AI-4V in compliance with ASTM F136). Each polyaxial pedicle screw consists of a screw body, an insert, a screw Tulip, and a locking Set Screw. The Set Screw is threaded into the pedicle screw Tulip to secure the interconnection of the TOPS™ Motion Implant's arm and lock the polyaxial orientation in place. The Pedicle Screws are available in diameters of 5.5 mm, 6.5 mm and 7.5 mm. Their lengths vary in 5 mm increments from 25 to 60 mm. The heads of the pedicle screws are color anodized to allow for easy identification of screw diameter (5.5 mm - green, 6.5 mm - magenta, and 7.5 mm - blue).

The assembled TOPS™ Motion Implant, and each pedicle screw are packaged in a Polyethylene Terephthalate Glycol (PETG) double blister, sealed with a Tyvek® lid, and sterilized by gamma radiation. All implants have a shelf life of five years.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for the correction of lumbar spinal stenosis (LSS), degenerative spondylolisthesis (DS) and facet joint osteoarthritis (FJ OA). Non-operative treatments include, but are not limited to, physical therapy, chiropractic care, medications, and spinal injections are the first treatment approaches. When non-operative treatments cease to be effective, there are several surgical alternatives, which include but are not limited to, surgical decompression alone and surgical decompression with spinal instrumentation and fusion. Each option has advantages and disadvantages. Patients should discuss risks, benefits and alternatives to all treatment options with their physicians.

VII. MARKETING HISTORY

The TOPS™ System has been marketed outside of the United States since 2012. The TOPS™ System is commercially available in several European Union countries, in Australia, and in several Asian countries. The TOPS™ System has not been withdrawn from any distribution/marketing in any country for safety or effectiveness reasons.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (e.g., complications) associated with the use of the device. The adverse effects are sub-divided into three categories: (1) those commonly associated with any surgical procedure; (2) those associated with lumbar spinal surgery procedures using a posterior approach; and (3) those associated with posterior spinal implants, including those pertaining to the TOPS™ System. In addition to the risks listed below, there is also the risk that the procedure may not be effective and may not relieve or may cause worsening of pre-operative symptoms. Additional surgery may be required to correct some of the potential adverse effects.

Possible risks associated with any surgical procedure include:

- Anesthesia complications including allergic reaction, anaphylaxis, or other reactions to anesthesia

- Reactions to transfused blood
- Anemia
- Blood loss/ hemorrhage
- Heart or vascular complications including:
    - excessive bleeding or injury to blood vessels
    - edema
    - hematoma or seroma
    - hypotension or hypertension
    - ischemia
    - cardiac event
    - myocardial infarction,
    - embolism including pulmonary embolism
    - thrombosis
    - thromboembolism
    - thrombophlebitis
    - phlebitis
    - stroke
    - hemorrhage or vascular damage resulting in catastrophic or potentially fatal bleeding
- Septicemia
- Cerebral Vascular Accident (Stroke)
- Pulmonary complications including atelectasis, pneumothorax or pneumonia, pulmonary edema and respiratory distress
- Blindness secondary to pressure on the eye during surgery
- False aneurysm
- Headache
- Infection (wound, local, and/or systemic) abscess, or cellulitis
- Soft tissue damage or fluid collections, including edema, hematoma or seroma, which may require drainage, aspiration, or debridement or other intervention
- Surgical wound dehiscence, necrosis, or scarring of tissue around the wound
- Post-surgical pain, bruising, tenderness or discomfort at the surgical site or incision and/or skin or muscle sensitivity over the incision which may result in skin breakdown, pain, and/or irritation
- Impairment of the gastrointestinal system including ileus or bowel obstruction, nausea or vomiting
- Impairment of the genitourinary system including incontinence, bladder dysfunction, urinary tract infection, or reproductive system complications
- Neurological complications including nerve damage, paralysis, seizures or convulsions, changes to mental status, or reflex sympathetic dystrophy
- Psychological illness
- Injury to muscles, or organs
- Insomnia
- Narcotic addiction
- Numbness
- Complications of pregnancy including miscarriage or congenital defects
- Inability to resume activities of daily living

- Death

Possible risks associated with the posterior lumbar spinal surgery procedure include:

- Risks to neurological structures:
  - dural tear dural leak and/or dural injury with or without CSF leakage
  - arachnoiditis
  - compressive neuropathy
  - neurologic deterioration - injury to nerves or nerve roots associated with the spinal cord (resulting in pain, weakness, paralysis (partial or complete), paresthesia, altered reflexes, numbness, tingling, or other changes in sensation)
  - coordination abnormalities
  - dysphasia
  - gait disturbance
  - headache
  - otitis media
  - tremors
  - cerebrospinal fluid leakage
  - cerebrospinal fistula
  - Reflex Sympathetic Dystrophy (RSD)
- Cauda equina syndrome
- Damage to nerves, blood vessels, and nearby tissues
- Impaired muscle or nerve function
- Epidural bleeding, hematoma, or fibrosis
- Bone necrosis
- Degenerative changes in adjacent segment
- Surgery at incorrect level
- Osteolysis
- Loss of bowel or bladder function
- Incontinence (loss of bowel or bladder control)
- Fracture of the vertebrae, spinous process, or other damage to bony structures during or after surgery
- Postoperative muscle and tissue pain
- Development of disc degeneration at adjacent levels
- Inflammatory conditions
- Loss of disc height
- Disc herniation
- Undesirable change in lordosis
- Scarring or soft tissue damage
- Spinal instability
- Spondylolisthesis acquisita (vertebral slippage)
- Retrolisthesis
- Spinal stenosis (narrowing of the spinal canal)
- Spondylosis
- Facet joint deterioration
- Infection of the bone, or surrounding soft tissue
- Musculoskeletal spasms (back or leg)

- Perineural fibrosis
- Surgery may not reduce the preoperative pain experienced
- Pain and discomfort associated with the presence of implants
- Pain and discomfort associated with the surgical procedure (e.g., cutting of muscles, ligaments, and tissue) and healing
- The spine may undergo adverse changes or deterioration including loss of proper spinal curvature, correction, height, and/or reduction, or malalignment, and another surgery may be required
- Adverse bone/implant interface reaction

Possible risks associated with posterior lumbar spinal implants including the TOPS™ System:

- Adverse reaction or allergy to the device materials [Titanium, Polycarbonate Urethane (PCU), and Polyether Ether Ketone (PEEK)], 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, adverse tissue reaction, osteolysis, tumor formation, autoimmune disease, metallosis, scarring, or other symptoms
- Interference with radiographic imaging because of the presence of the device
- Adverse reaction or allergy to contrast media
- Herniated nucleus pulposus
- Heterotopic ossification
- Risks directly related to the device position and condition, including
    - implants malposition
    - implant breakage
    - implant degradation
    - implant disassembly
    - implant displacement
    - implant migration, subsidence, loosening or dislocation
    - implant separation
    - improper sizing
    - anatomical difficulties during the surgery
- Misplaced screws in pedicle
- Nerve root or spinal cord impingement or injury
- Neurologic deterioration
    - cauda equina
    - clumsiness
    - foot drop
    - limp
    - numbness
    - paralysis
    - short step
    - slow moving gait
    - weakness
- Osteophyte resorption
- Osteolysis or vertebral inflammation

- Reoperation including revision, removal, or supplemental fixation
- Vertebral overload resulting in device failure and the need for additional surgery
- 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
- Implantation at the wrong spinal level
- Issues with the device instruments (e.g., bending/damage or breakage) including the possibility that a fragment of a broken instrument may remain in the patient after implantation, and improperly cleaned/disinfected instruments
- Device/joint noise
- 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
- Development of a new or recurrent spinal problem at the surgery level, or at levels above or below the treated spinal level
- Fracture of the vertebrae, spinous process, or other damage to bony structures during or after surgery
- 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
- Device failure which may require a subsequent surgical intervention at the treated spinal level or at levels above or below the treated spinal level (including removal of the TOPS™ System, revision, re-operation or supplemental fixation
- Additional radiography and contrast media may be used during the subsequent surgical intervention

For the specific adverse events (AEs) that occurred in the clinical study, please see Section X below.

IX. SUMMARY OF NON-CLINICAL STUDIES

A variety of non-clinical tests were conducted to characterize the properties and performance of the TOPS™ System. These non-clinical evaluations included mechanical testing and animal studies to evaluate safety and performance, as well as biocompatibility testing, sterilization, shelf life and packaging validation, and magnetic resonance (MR) compatibility testing. The testing is summarized in the following table and described further below.

Table 2: Summary of Non-clinical Studies

Test	Purpose	Acceptance Criteria	Results
Mechanical Testing of the TOPS™ Motion Implant	To evaluate the TOPS™ Motion Implant for the following endpoints: flexion loading, extension loading,	See **Table 3** for acceptance criteria for each test	Pass

Test	Purpose	Acceptance Criteria	Results
	lateral bending rotation, axial rotation loading, sagittal translation, flexion / extension fatigue, lateral bending fatigue, axial rotation fatigue, coupled motion fatigue, axial compression fatigue, shear fatigue, and wear particulate of PcU		
Mechanical Testing of the TOPS™ System Pedicle Screws	To evaluate the pedicle screws for the following endpoints: ultimate compression bending load, compression bending fatigue, ultimate flexion bending load, axial gripping load, and axial pull-out strength	See **Table 3** for acceptance criteria for each test	Pass
Animal Testing	To evaluate possible histopathologic effects (acute neural, local and systemic inflammatory responses) to particulate wear debris of the TOPS™ System materials when implanted within the epidural space	No histopathologic or other evidence of acute neural, local or systemic inflammatory response during 3-month and 6-month follow-up periods	Pass
Biocompatibility	To assess the following endpoints: Cytotoxicity, Sensitization, Irritation, Acute Systemic Toxicity, Material-Mediated Pyrogenicity, Subacute/Subchronic Toxicity, Genotoxicity (Bacterial Gene Mutation Assay, Mammalian Chromosomal Aberration, and Mouse Bone Marrow Micronucleus), and Implantation	In combination with toxicological risk evaluation, the testing demonstrates biocompatibility in line with the requirements of ISO 10993-1 for a permanent implant in contact with bone. Test-specific acceptance criteria were defined per the applicable part of ISO 10993.	Pass
Sterilization Validation	To establish 25 kGy as the sterilization dose	Acceptance criteria defined per ISO 11137 to ensure a Sterility Assurance Level of at least 10^{-6}	Pass
Shelf-Life and Packaging Validation	To determine the effect of transportation simulation and aging (accelerated real-time)	Seal strength testing was conducted per ASTM F88/F88M-15 and bubble	Pass

Test	Purpose	Acceptance Criteria	Results
	on packaging integrity, sterile seal, and device functionality	leak testing was conducted per ASTM F2096-11.	
MR Compatibility	To evaluate the safety and compatibility of the TOPS™ System in the MR environment Non-clinical testing and MRI simulations, that included in vivo, clinically relevant modelling, were performed.	Demonstrate TOPS™ System is MR Conditional and define the conditions for safe MR scanning in patients implanted with the device.	Pass; see **Section IX.C.4** below for MR scanning conditions

A. Laboratory Studies

A summary of the conducted mechanical testing on the TOPS™ System is provided below. The tests were conducted on the TOPS™ System (TOPS™ Motion Implant and 4 Pedicle Screws). In addition, the Pedicle Screws were tested according to ASTM-F1717 and ASTM F1798 with Premia Spine's ProMIS Fixation Systems (K150388 and K170061) and VersaLink Fixation Systems (K182598) that use the same pedicle screws.

Table 3: Summary of Laboratory Studies

Test	Method	Acceptance Criteria	Results
Static Flexion to Failure	Each TOPS™ Motion Implant was held by 4 pedicle screws in a flexion test jig connected to tensile machine. Constant displacement rate of 10 mm/min is applied until failure or testing fixture's limit is reached.	20 Nm moment static load testing for flexion.	All samples exceeded 20 Nm flexion moment with no failure.
Static Extension to Failure	Each TOPS™ Motion Implant was held by 4 pedicle screws in an extension test jig connected to tensile machine. Constant displacement rate of 10 mm/min is applied until failure or testing fixture's limit is reached.	25 Nm moment static load testing for extension.	All samples exceeded 80 Nm extension moment with no failure, thus exceeding the acceptance criteria of 25 Nm moment static load testing for extension. Test was stopped after a displacement of 16º.
Static Lateral Bending to Failure	Each TOPS™ Motion Implant was held by 4 pedicle screws in a lateral	8° lateral bending rotation per side shall be exceeded.	All samples exceeded 8° lateral

Test	Method	Acceptance Criteria	Results
	bending test jig connected to tensile machine. Constant displacement rate of 10 mm/min is applied until failure or testing fixture's limit is reached.		bending rotation per side with no failure.
Static Axial Rotation to Failure	Each TOPS™ Motion Implant was held by 4 pedicle screws in an axial rotation test jig connected to tensile machine. Constant displacement rate of 10 mm/min was applied until failure or testing fixture's limit is reached.	25 Nm moment load testing for axial rotation.	All samples exceeded criteria of 25 Nm axial rotation moment.
Static Sagittal Translation to Failure	TOPS™ Motion Implant in a sagittal translation test jig connected to tensile machine. Constant displacement rate of 10 mm/min is applied until failure.	Exceeds shear force of 500 N.	All samples exceeded 500N shear force static load acceptance criteria.
Monoaxial Flexion Extension Test	Based on ASTM WK7479, a dedicated fatigue motion control tester and test fixture were used to apply cyclic 7.5° Flexion and 2° Extension, accompanied with constant 150 N shear force, at frequency of 2Hz for 10 million cycles.	All samples should remain functional, no visible failures (breaks or cracks) in the metal parts. No side-to-side tear in PcU boot larger than 2.1 cm, PEEK ribbon shall not be broken or torn over 50% of its cross section, stiffness of samples should not change by more than 50%, overall PcU wear shall be less than 75 mg (over 10 MC).	All the samples tested remained functional in the end of the test. No visible failures were found: no tear in PcU Boot was observed and no damage to PEEK ribbon was observed. The stiffness of the samples did not change by more than 50%. The overall wear was 6 mg per 10 MC.

Test	Method	Acceptance Criteria	Results
Monoaxial Lateral Bending Test	Based on ASTM-WK7479, a dedicated fatigue motion control tester and test fixture were used to apply cyclic lateral bending of 6° bending (right and left), accompanied with constant 150 N shear force, at frequency of 2Hz for 10 million cycles.	All samples should remain functional, no visible failures (breaks or cracks) in the metal parts. No side-to-side tear in PcU boot larger than 2.1 cm, PEEK ribbon shall not be broken or torn over 50% of its cross section, stiffness of samples should not change by more than 50%, overall PcU wear shall be less than 75 mg (over 10 MC).	All the samples tested remained functional in the end of the test. No visible failures were found: no tear in PcU Boot and no damage to PEEK ribbon. The stiffness of the samples did not change by more than 50%. The overall wear was 10.9 mg per 10 MC.
Monoaxial Axial Rotation Test	Based on ASTM F2624-12, a dedicated fatigue load control tester and test fixture were used to apply cyclic Axial- Rotation of 10 Nm (right and left), accompanied with constant 300 N shear force, at frequency of 1Hz for 10 million cycles.	All samples should remain functional. No visible failures (breaks or cracks) in the metal parts. No side-to-side tear in PcU boot larger than 2.1 cm. PEEK ribbon shall not be broken or torn over 50% of its cross section. Stiffness of samples should not change by more than 50%. Overall PcU wear shall be less than 75 mg (over 10 MC).	All the samples tested remained functional in the end of the test. No visible failures were found: no tear in PcU Boot and no damage to PEEK ribbon. The stiffness of the samples did not change by more than 50%. The overall wear was 48.5 mg per 10 MC.
Coupled Motion Simulator Test	A dedicated fatigue motion control tester and test fixture were used to apply cyclic motion of 4° Flexion, 2° Extension, 3° right and left lateral bending, and 1° right and left axial rotation, accompanied with constant 150 N shear force, at frequency of 1.2Hz. for 5 million cycles.	Wear results should be similar to the monoaxial tests wear results.	Overall wear was 7.3 mg per 5 MC; or 14.6 mg for 10 MC (extrapolated), which is comparable to the monoaxial wear test results.

Test	Method	Acceptance Criteria	Results
Axial Compression Fatigue Test	Per ASTM F1717, with a dedicated fixture and jig to accommodate the TOPS™ System. 600 N applied force divided to 2 implants that bear 300 N each. Load control test: Metal core was assembled instead of polycarbonate urethane internal core to test the outer plates. Test conducted at a frequency of 5 Hz, for 10 MC.	No visible breaks or cracks in metal parts. No loosening of the pedicle screws connection with the TOPS™ arms.	All specimens reached a run-out of 10 MC without failure and passed the acceptance criteria successfully.
Shear Fatigue Test	Based on ASTM F1717, with a dedicated fixture, cyclic shear load of 15 N-150 N, frequency of 5 Hz, for 10 MC.	Reaching a run-out of 10 MC without failure. No visual breaks, or cracks in metal parts	All specimens reached a run-out of 10 MC without failure and passed the acceptance criteria successfully.
Pedicle Screws Static Compression Bending Test	Per ASTM F1717-15	Ultimate bending load per all systems shall exceed 400 N	All samples exceeded ultimate bending load of 600 N, thus exceeded acceptance criteria.
Pedicle Screws Compression Bending Fatigue Test	Per ASTM F1717-15, frequency 3 Hz, 5 million cycles. In maximum load of 190 N, 210 N, 230 N and 250 N for runout.	At least 2 specimens should pass the test with at least 185 N load without breaks or cracks in the rods and the pedicle screws, and no loosening in the connection between the pedicle screws and the rods.	All 4 specimens completed the test successfully with 190 N, 210 N, 230 N and 250 N, respectively, for runout, thus exceeded the acceptance criteria.
Pedicle Screw Static Flexion Bending Test	Per ASTM F1798-13	Ultimate Bending load shall exceed 560 N.	All 5 specimens exceeded ultimate bending load of 1,134 N, yield bending moment of 25.8 Nm.
Pedicle Screws Static Axial Gripping Test	Per ASTM F1798-13. Axial load was carried on this interconnection of screw-rod until failure or until exceeds 50% of acceptance criteria.	Gripping load shall exceed 1180 N.	All specimens exceeded the acceptance criteria.

Test	Method	Acceptance Criteria	Results
Pedicle Screws Static Axial Pull-Out Test	Per ASTM F543	Pull-out strength of 307 ± 61 N	All screws exceeded the acceptance criteria.
Polycarbonate Urethane (PcU) Gravimetric Wear	Per ASTM F1877, particles of different loading directions and loading cycles were analyzed in respect to particle size and shape.	Particle size and shape and particle size distribution are comparable to the results of the in-vivo rabbit study.	Wear particulate characterization was consistent with prior in vivo evaluation, supporting safety.

B. Animal Studies

An *in vivo* study was performed to evaluate local and systemic inflammatory responses to particulate wear debris, using New Zealand White Rabbits as the experimental model. The study was undertaken to investigate the possible histopathologic effects of particulate wear debris of the TOPS™ System materials implanted within the epidural space. The study provides an experimental model and technique to assess the local/systemic histologic response to two materials – Titanium Alloy (Ti Alloy) and Polycarbonate Urethane (PcU) – used in dynamic spinal stabilization.

30 skeletally mature New Zealand White Rabbits were divided into the following 3 groups:

- Control Group Surgical Control (Sham);
- Group - Particulate #1 (Ti Alloy);
- Group - Particulate #2 (PcU).

The particle size, concentration and methods of sterilization were based on studies published in the literature that examined the effects of particulate wear debris in the lumbar spine. A dosage was selected for the test that, when normalized from a 5kg rabbit to a 70kg human, the implanted materials are the equivalent of a 112mg dosage in humans. Moreover, this application is a one-time acute dose applied directly to the spinal cord while wear is generated gradually during clinical use.

The animals were evaluated for inflammatory reaction at 12 and 24 weeks. All cases were also monitored for signs of severe pain, neurologic complications and other adverse events throughout the course of the study. Overall, based on the 3 and 6-month post-operative time periods, there was no evidence of an acute neural, local or systemic histopathologic response to the materials of the TOPS™ System.

C. Additional Studies

1. Biocompatibility

Biocompatibility of the device was evaluated according to International Organization for Standardization (ISO) 10993-1:2018 and FDA Guidance Document "Use of International Standard ISO 10993-1, Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process." The TOPS™ System (TOPS™ Motion Implant and Pedicle Screws) is manufactured from Titanium alloy (Ti-6Al-4V), Polycarbonate Urethane (PcU), and Polyether Ether Ketone (PEEK). All implant materials are well characterized, have a long history of successful orthopedic clinical use and well-established biocompatibility. There are no color additives in the TOPS™ System.

The following tests were performed per their respective ISO 10993 standards on representative sterile subassemblies that were manufactured according to final manufacturing methods:

- Cytotoxicity
- Sensitization
- Irritation
- Acute Systemic Toxicity
- Material-Mediated Pyrogenicity
- Subacute/subchronic Toxicity
- Genotoxicity (bacterial reverse mutation, mammalian chromosomal aberration, and mouse bone marrow micronucleus)
- Implantation

Results of testing in combination with toxicological risk evaluation demonstrated biocompatibility in line with the requirements of ISO 10993-1 for a permanent implant in contact with bone. Biocompatibility assessments were also performed on the surgical instruments.

2. Sterilization Validation

Sterilization validation was conducted for the TOPS™ System per ISO 11137 to establish 25kGy as the sterilization dose to achieve a Sterility Assurance Level (SAL) of at least 10^{-6}. Separate validations were performed for the TOPS™ Motion Implant and for the Pedicle Screws. Sterilization validation was conducted for the TOPS™ System instruments per ANSI/AAMI ST79, AAMI TIR12, and ISO 17665-1.

3. Shelf Life and Packaging Validation

Shelf life and packaging studies, including accelerated and real-time aging and simulated distribution (shipping and handling), were conducted to determine the effect of transportation simulation on the packaging integrity and demonstrate that the device packaging can maintain a sterile barrier over a 5-year shelf life. Seal strength

testing was conducted per ASTM F88/F88M-15 and bubble leak testing was conducted per ASTM F2096-11. Continued functionality testing was also performed.

4. MR Compatibility

Non-clinical testing and MRI simulations, that included *in vivo*, clinically relevant modelling, were performed to evaluate the safety and compatibility of the TOPS™ System in the MR environment. The non-clinical testing demonstrated that the TOPS™ System is MR Conditional. A person with the TOPS™ System may be safely scanned under the following conditions:

Table 4: MR Compatibility Conditions

Static Magnetic Strength (B0)	1.5 or 3.0 T
Maximum Spatial Field Gradient	20 T/m
RF Excitation	Circularly Polarized
RF Transmit Coil Type	There are no Transmit Coil Restrictions
Operating Mode	Normal Operating Mode
Maximum Whole-Body SAR	2 W/kg (Normal Operating Mode)
Scan Duration	2 W/kg whole-body average SAR for 60 minutes of continuous RF (a sequence or back-to-back series/scan without breaks)
MR Image Artifact	The presence of this implant may produce an image artifact. Some manipulation of scan parameters may be needed to compensate for the artifact. In non-clinical testing, the image artifact caused by the TOPS™ (Total Posterior Spine) System extends approximately 10 mm from this device when imaged with a gradient echo pulse sequence and a 3T MRI system.

X. SUMMARY OF PRIMARY CLINICAL STUDY

The applicant performed a clinical study to establish a reasonable assurance of safety and effectiveness of the TOPS™ System for treatment of degenerative spondylolisthesis up to Grade I, with moderate to severe lumbar spinal stenosis and either the thickening of the ligamentum flavum and/or scarring of the facet joint capsule at one level from L2 to L5 in the US under IDE # G160168. Data from this clinical study were the basis for the PMA approval decision. A summary of the clinical study is presented below.

A. Study Design

Subjects in the TOPS™ System pivotal study were treated between 2017 and 2022. Enrollment included 321 patients at 37 investigational sites in the US. The database for this PMA reflected data collected through July 2022 and included 306 patients who had been randomized and had undergone surgery. The regulatory decision for

this PMA relied primarily on a subset of 168 patients who had theoretically reached 24-month follow-up after the operative intervention (Month 24).

The study was a prospective, multi-center randomized, concurrently controlled pivotal study of the TOPS™ System. Subjects were randomized in a 2:1 ratio to the TOPS™ System or the control treatment, a lumbar spinal fusion. The study pre-specified an initial interim analysis after 240 subjects were enrolled and a second interim analysis after 300 subjects were enrolled, in order to assess sample size as well as safety and effectiveness. The first interim analysis evaluated the primary endpoint for non-inferiority, and the second interim analysis evaluated the primary endpoint for superiority.

The objective of the study was to evaluate the safety and effectiveness of the TOPS™ System compared to lumbar spinal fusion in subjects undergoing decompression surgery and instrumentation at a single lumbar level between L2 and L5 to alleviate leg pain, with or without back pain, stemming from all of the following conditions: (1) degenerative spondylolisthesis or retrolisthesis up to Grade I; (2) moderate to severe spinal stenosis (LSS); and (3) thickening of the ligamentum flavum and/or scaring of the facet joint capsule. The primary endpoint for this study was the composite clinical success (CCS) at Month 24.

The following hypotheses pertaining to clinical non-inferiority were planned to be tested:

Ho: $\pi_I - \pi_C \leqslant -0.10$ (the CCS rate of investigational device was clinically inferior to control)

Ha: $\pi_I - \pi_C > -0.10$ (the CCS rate of investigational device was not clinically inferior to control),

where π_I, π_C are CCS rate at Month 24 for the investigational device and control respectively. In all circumstances, non-inferiority hypotheses were based on the *a priori* selected non-inferiority margin, $\delta = -0.10$. Hypotheses pertaining to clinical superiority were tested after the null hypothesis of non-inferiority was successfully rejected:

Ho: $\pi_I - \pi_C = 0$ (the CCS rate investigational device was the same with that of control)

Ha: $\pi_I - \pi_C > 0$ (the CCS rate of investigational device was superior to that of control).

Bayesian posterior distribution with a non-informative prior (Beta(1,1)) were used to test the study hypotheses. The adaptive trial design allowed a minimum of 300 subjects and up to a maximum number of 500 subjects to be randomized, with interim analyses. The interim analyses allowed for sample size adjustment (including early stopping of the trial for futility) and for claiming early study success on non-inferiority and superiority. Driven by the superiority test, the minimum sample size was based on at least 80% power for testing superiority assuming the true CCS rates are 0.80 and 0.65 for the

investigational and control arm respectively. This sample size also allowed higher than 80% power for non-inferiority test.

1. Clinical Inclusion and Exclusion Criteria

To be eligible for the TOPS™ System IDE study, subjects had to meet all of the following inclusion criteria:

- Be between 35 to 80 years of age;
- Must demonstrate at the level to be treated (L2/3, L3/4 or L4/5) all three of the following;
    - Degenerative spondylolisthesis or retrolisthesis up to Grade I, as determined by the investigator based on flexion/extension X-rays, and
    - At least moderate lumbar spinal stenosis, defined as greater than a 33% reduction in either the central canal, the lateral recess space, and/or the foramen when compared to an adjacent level, as determined by the investigator based on MRI, and
    - Thickening of the ligamentum flavum and/or scarring of the facet joint capsule as identified by the investigator based on MRI.
- At least six (6) months of failed conservative treatment prior to surgery (e.g., physical therapy, use of anti-inflammatory medications at maximum recommended dosage; administration of epidural/facet injections and/or nerve block);
- Oswestry Disability Index (ODI) score of at least 40/100 at baseline;
- Leg pain with a Visual Analog Scale (VAS) score of at least 40/100 for at least one leg at baseline[1];
- Neurogenic claudication (as defined by worsening leg/buttock symptoms when walking or standing, which is reduced when sitting or bending forward);
- Demonstrate worse symptoms (e.g., pain, numbness, burning sensation, pin prick sensation, etc.) in the legs/buttock than in the lower back;
- Be psychosocially, mentally, and physically able to fully comply with the clinical protocol;
- Be willing to adhere to the follow-up schedule and protocol requirements;
- Be willing and able to understand and sign study-specific, IRB-approved consent form.

Subjects were not permitted to enroll in the IDE study if they met any of the following exclusion criteria:

- More than one motion segment involved in the degenerative pathology that requires a surgical procedure;
- Presence of free fragment disc herniation or prior discectomy at the index level or either adjacent level;
- Less than 4mm of disc height at the index level;
- Spondylolisthesis greater than Grade I;
- Traumatic or dysplastic spondylolisthesis;
- Lytic spondylolisthesis;

[1] The leg with the higher pain score was considered "Worst Leg."

- Back or non-radicular leg pain of unknown etiology;
- Stenosis caused by an extruded spinal disc fragment (e.g., herniation) or where the etiology is considered congenital, iatrogenic, post-traumatic, or metabolic;
- Known allergy or sensitivity to Polyether Ether Ketone (PEEK), titanium, cobalt chrome, and/or polyurethane;
- Prior surgery at any lumbar vertebral level with instrumentation;
- Prior surgery at the index vertebral level or either adjacent lumbar vertebral level without instrumentation [exception – prior intervention of posterior elements at index level (e.g. rhizotomy, laminectomy, foraminotomy and/or facetectomy)][2]; Clinically compromised vertebral bodies at the affected level due to any traumatic, neoplastic, metabolic or infectious pathology;
- Scoliosis greater than 10 degrees by major Cobb angle (both angular and rotational);
- Morbid obesity defined as a body mass index greater than 40;
- Lumbar spine T-score less than -2.0[3];
- Paget's disease, gout, osteomalacia, osteogenesis imperfecta, thyroid and/or parathyroid gland disorder and/or any other metabolic bone disease not stabilized with ongoing medication for at least 1 year;
- Active infection - systemic or local;
- Active hepatitis;
- AIDS, HIV, Rheumatoid arthritis or other autoimmune disease;
- Tuberculosis - active or in the past 3 years;
- Active malignancy - history of any invasive malignancy (except non-melanoma skin cancer) unless prior treatment with curative intent and no clinical signs or symptoms of the malignancy for at least 5 years;
- Any medical condition requiring treatment with any drug known to potentially interfere with bone/soft tissue healing or receiving radiation therapy that is expected to continue for the duration of the study;
- Cauda equina syndrome or neurogenic bowel/bladder dysfunction;
- Vascular claudication due to severe arterial insufficiency of the legs (Prospective subjects screened by physical examination for diminution or absence of dorsalis pedis or posterior tibialis pulses. If diminished or absent by palpation, then arterial ultrasound is required with vascular plethysmography. If the absolute arterial pressure is below 50 mm Hg at the calf or ankle level, then patient has severe arterial insufficiency and must be excluded.);
- Sustained pathologic lumbar fractures of the vertebra or multiple lumbar fractures of the vertebra or hip;

[2] Prior intervention of posterior elements that involve the lamina, foramen, or and/or facets, the extent of which must not be greater than the decompression that would be necessary to implant TOPS.

[3] All subjects were screened for osteoporosis using an osteoporosis risk score (SCORE). Subjects with a SCORE value greater than 6 were to be referred for dual x-ray absorptiometry (DEXA) Scan. DEXA was required to be performed within the 6 months prior to surgery.

- Significant peripheral neuropathy causing decreased sensation in a stocking-like or non-radicular and non-dermatomal distribution in the lower extremities;
- Insulin-dependent diabetes mellitus (unless well-controlled defined as HbA1c less than 7%)[4];
- Immunologically suppressed, receiving steroids for greater than 1 month out of the past year;
- Currently taking anticoagulants other than aspirin unless subject can be taken off of anticoagulant prior to and during surgery;
- Life expectancy of less than 3 years;
- Currently experiencing an episode of major mental illness (psychosis, major affective disorder, or schizophrenia), or manifesting physical symptoms without a diagnosable medical condition to account for the symptoms, which may indicate symptoms of psychological rather than physical origin;
- History of or current chemical/alcohol dependency[5];
- Smoking habit of more than 1 pack of cigarettes per week and/or frequent users (greater than 1/week) of chewing tobacco;
- Pregnant or interested in becoming pregnant in the next 3 years (due to need for X-rays)[6];
- Currently involved in active spinal litigation;
- Currently having a workman's compensation claim;
- Currently incarcerated;
- Participation in any other investigational drug, biologic or medical device study within the 30 days prior to the study surgery.

2. Follow-up Schedule

All subjects were scheduled to return for follow-up examinations at 6 weeks (±2 weeks), 3 months (±2 weeks), 6 months (±1 month), 12 months (±2 months), and 24 months (±3 months) post-operatively. Follow-up evaluations at scheduled visits included obtaining x-rays, neurological assessments, ODI, VAS (back and both legs), Zurich Claudication Questionnaire (ZCQ), study-related medications since the prior visit, and adverse events. At 24 months, subjects also underwent an MRI and completed the 12-Item Short Form, version 2 (SF-12v2) Health Survey. The key

[4] HbA1c value must be within 3 months of screening.

[5] A maladaptive pattern of substance use leading to clinically significant impairment or distress, as manifested by one (or more) of the following, occurring within a 12-month period:

1. Recurrent substance use resulting in a failure to fulfill major role obligations at work, school, home (e.g. repeated absences or poor work performance related to substance use; substance-related absences, suspensions, or expulsions from school; neglect of children or household)
2. Recurrent substance use in situations in which it is physically hazardous (e.g. driving as automobile or operating a machine when impaired by substance use)
3. Recurrent substance-related legal problems (e.g. arrests for substance-related disorderly conduct)
4. Continued substance use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the substance (e.g. arguments with spouse about consequences of intoxication, physical fights)

[6] However, pregnancies occurring during the study will not be considered protocol deviations. Additionally, if a subject does become pregnant, no X-ray or MRI should be taken during the pregnancy.

follow-up timepoints are shown in **Table 5** below. Conventional naming of visits was utilized to reflect time elapsed since the operative intervention.

Table 5: Study Schedule

Time Point	Pre-op[1d]	Rx	Post-op	6 wks	3, 6 & 12 mo[3]	24 mo	36 & 48 mo	60 mo	D/C or Termination
Informed Consent	X								
Bone Quality Assessment[1a]	X								
Medical History & Physical Examination	X								
Pregnancy Screening (within 30 days of surgery)[1b]	X								
MRI[1c]	X					X		X	X
Standing AP & Lateral X-rays[4]	X		X[5]	X	X	X	X	X	X
Standing Flexion & Extension X-rays[4]	X				X	X	X	X	X
Standing Lateral Bending[4]	X				X	X	X	X	X
Radiographic Core Lab Assessments	X		X[5]	X	X	X	X	X	X
Neurologic Exam	X			X	X	X	X	X	X
ODI	X			X	X	X	X	X	X
VAS	X			X	X	X	X	X	X
ZCQ	X			X	X	X	X	X	X
Treatment Satisfaction				X	X	X	X	X	X
Medications Taken[2]	X		X[5]	X	X	X	X	X	X
SF-12v2 Health Survey	X					X		X	
Adverse Event Assessment	N/A	As needed							
Study Completion / Termination	N/A	As needed							

1. Pre-treatment evaluations;
   a. All subjects will be screened for osteoporosis using an osteoporosis risk score (SCORE). Subjects with a SCORE value greater than 6 will be referred for DEXA Scan. DEXA must be performed within the 6 months prior to surgery.
   b. All female prospective subjects that are of child-bearing potential must undergo a pregnancy test. Results must be within 30 days prior to surgery.
   c. MRI may be taken up to 6 months prior to surgery.
   d. All other pre-treatment measurements must be done within 90 days of surgery.
2. Record only study-related medications.
3. Follow up visit evaluations will be taken at 6 weeks (± 2 weeks), 3 months (± 2 weeks), 12 months (± 2 months), and 24, 36, 48, and 60 months thereafter (± 3 months).
4. Radiographic films should be taken with the subject standing to the extent clinically possible. If subject is not able to stand, the films should be taken as clinically possible.
5. Postoperative evaluations are taken between 12 hours and 4 weeks postoperatively. Post-operative standing AP and lateral films must be taken prior to discharge.

If a subject does become pregnant, no X-ray or MRI should be taken during the pregnancy.

3. Clinical Endpoints

The safety and effectiveness of the TOPS™ System were assessed using a composite endpoint, as described below. Outcomes of the TOPS™ System investigative group were compared to the outcomes of the control group undergoing fusion operative treatment. Study success was based on the hypothesis that the TOPS™ System is

superior to the lumbar spinal fusion control in achieving Month 24 composite clinical success (CCS).

Primary Endpoint

The primary endpoint was evaluated using a CCS endpoint at Month 24. Each subject was determined to have achieved CCS only if they met all of the following criteria:

- A reduction of 15 points or more in ODI;
- No new neurologic deficit, nor worsening and persistent neurologic deficit (see description of neurological failure below);
- No epidural steroid injection, facet joint injections, nerve block procedures or implantable spinal cord stimulator to treat back or leg pain symptoms at any lumbar level;
- Any TOPS™ subject was considered a failure if fusion occurred. Any control subject was considered a failure if fusion did not occur (see definitions of fusion and non-fusion below);
- No revision or removal of implants; [7]
- No supplemental fixation at the index level or at the immediately adjacent levels; [7]
- No occurrence of a major device related adverse event (see definition of major device-related adverse event below).

A subject was considered a neurological failure if they were categorized as a failure for any of the following:

- *Sensory (SN)*: A subject was considered an SN failure if he/she had an increase in sensory deficit in his/her Worst Leg pain at any dermatomal level at 24 months compared to baseline.
- *Muscle Strength (MS)*: A subject was considered an MS failure if his/her 24-month minimum value is a two-grade or more decrease in motor strength at any muscle group evaluated, compared to baseline. A one-grade decrease is not considered a significant change with the exception of a decrease from 1 to zero.
- *Straight leg raising (SLR)*: The summary endpoint for SLR was defined as positive (bad) if Worst Leg pain is positive. A subject was considered an SLR failure if he/she had a positive 24-month summary endpoint but negative SLR summary endpoint prior to index surgery.
- *Side Lying Femoral Stretch (FS)*: The summary endpoint for FS was defined as positive (bad) if Worst Leg pain is positive. A subject was considered an FS failure if he/she had a positive 24-month summary endpoint but negative FS summary endpoint prior to index surgery.

<u>Fusion vs. Non-Fusion</u>

Fusion was defined as:

[7] In this document the term "reoperations" is used to collectively refer to revisions, removals, and supplemental fixations.

- Presence of bridging trabecular bone across the involved motion segment, and
- Angular motion < 3° from flexion to extension, and
- Translational motion < 2 mm from flexion to extension.

Non-fusion was defined as:

- Absence of bridging trabecular bone across the involved motion segment, or
- Angular motion ≥ 3° from flexion to extension, or
- Translational motion ≥ 2 mm from flexion to extension.

Major Device-Related Adverse Events

A major device-related AE was defined as any of the following, which were related to the device system or to a device component:

- Device component degradation or breakage;
- Device component separation or disassembly;
- Device component loosening including screw loosening;
- An increase in spondylolisthesis by one grade or more at the operative level.

Highlighted Secondary Endpoints With Control of Type I Error

Five secondary endpoints were selected *a priori* to be tested in the following sequence following demonstration of superiority based on the primary CCS endpoint.

1. Range-of-Motion: Greater range-of-motion through flexion-extension at the index level at Month 24;
2. Fusion success: Any TOPS™ investigational subject was considered a failure if fusion occurs as defined in the radiographic protocol. Any control subject was considered a failure if fusion (as defined in the radiographic protocol) did not occur. This assessment was made by a core lab;
3. No Month 24 narcotics use and no epidural steroid injection, facet joint injections, nerve block procedures, or spinal cord stimulators to treat back or leg pain symptoms at any lumbar level up to Month 24;
4. No new neurologic deficit nor worsening and persistent neurological deficit at Month 24;
5. Time to revision or removal or supplemental fixation at either the index level or adjacent level (based on log-rank statistic).

Additional Secondary Endpoints (No Type I Error Control)

In addition, the following additional secondary endpoints were pre-specified to evaluate general device performance for purposes of evaluating the two treatment groups and superiority of the investigational device relative to control:

- Individual components of Month 24 CCS;
- 20 mm improvement in VAS scores for back pain and Worst Leg pain as compared to baseline (the higher of the two leg scores at baseline was designated the Worst Leg for analysis purposes);
- ZCQ findings;

    - Improvement of ≥0.5 in ZCQ physical function score and symptom severity, and subject satisfaction score of ≤2.5 at Month 24 where 1 is very satisfied and 4 is very dissatisfied,
    - Two component ZCQ success defined as meeting ≥2 individual ZCQ success criteria.
    - Three component ZCQ success defined as meeting all three individual ZCQ success criteria.
- Reduction in physical component score on SF-12;
- Length of hospital stay, surgery time (skin-to-skin), blood loss and narcotic use for lower back pain and leg pain.
- Range of motion in flexion/extension were evaluated at the index and immediately adjacent levels at Month 24 to evaluate the effect of the treatment. This result was monitored as an additional outcome and was separately compared with the subject's physical functioning (ODI, ZCQ and VAS) scores.

B. Accountability of PMA Cohort

Pursuant to the design of this IDE study, interim analysis for early study success was conducted before all randomized subjects had reached the Month 24 visit (the final visit evaluated for safety and effectiveness as the basis for the PMA submission). At the time of database lock, 321 subjects were enrolled in the IDE study and 52.3% (168/321) had theoretically reached the Month 24 visit (at least 730 days post-surgery). Of the subjects who theoretically reached Month 24, 91.7% (154/168) were available for the primary endpoint analysis of CCS.

Subject enrollment and accounting are illustrated in the figure and table below, followed by descriptions of the analysis populations.

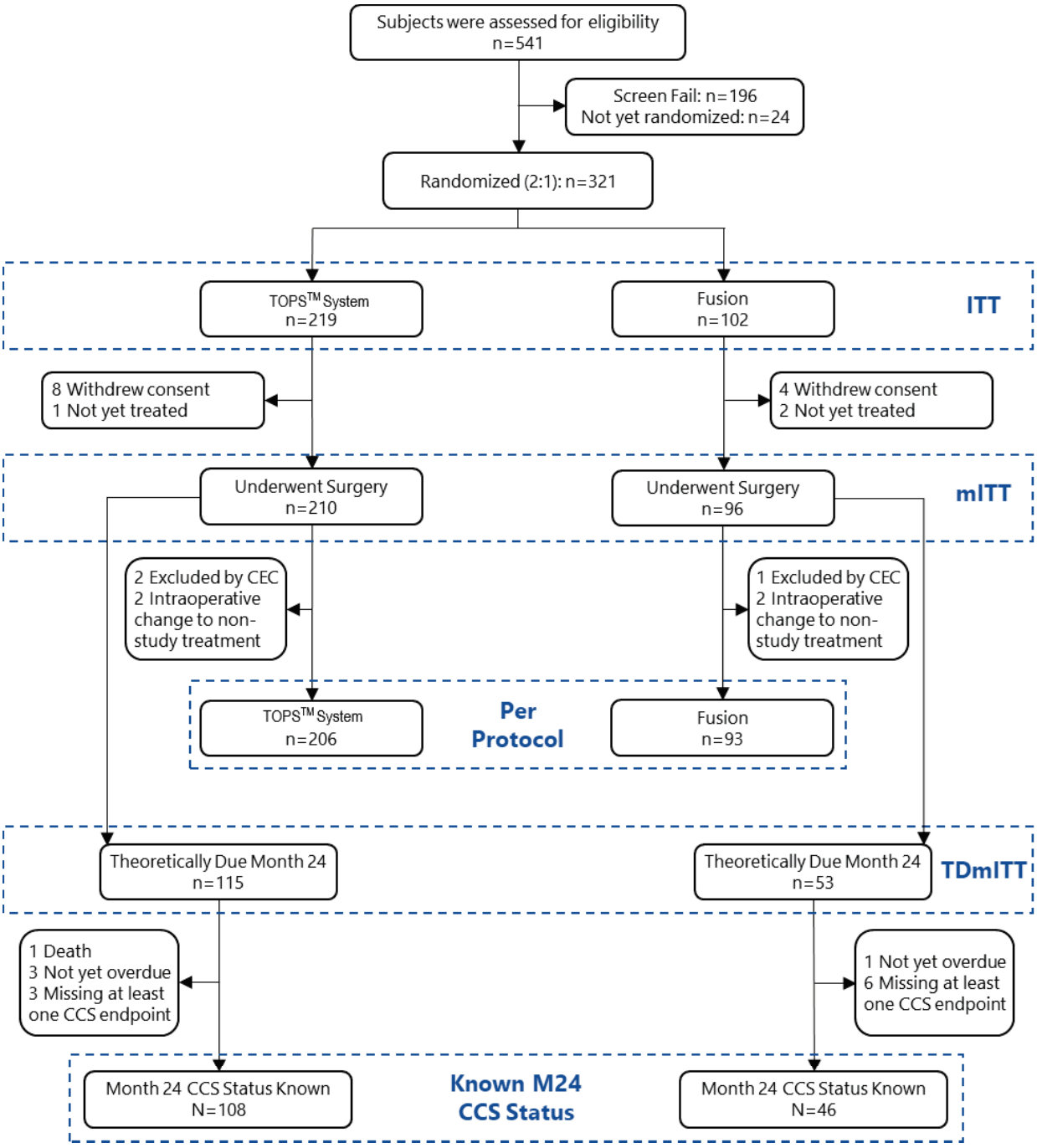


Figure 3: Subject Accountability Tree

Table 6: Subject Accounting at the Time of Database Lock

	TOPS™	Fusion	Total
[1] All randomized subjects (ITT)	219	102	321
[1a] Randomized and underwent surgery (mITT/AT) [1]	**210**	**96**	**306**
[1b] Withdrawn prior to surgery	8	4	12
[1c] Not yet treated	1	2	3
A. Randomized in mITT Analysis Set and Theoretically Due for Month 24 Visit (TDmITT) [2]	**115**	**53**	**168**
A1. Excluded from Per Protocol Analysis Set	2	2	4
A1a. Eligibility violation identified by CEC	2	1	3
A1b. Intraoperative change to non-study treatment	0	1	1
A2. Included in Per Protocol Analysis Set [3]	**113**	**51**	**164**
A2a. Death by Month 24 and not terminal CCS failures	1	0	1
A2b. Not yet overdue for Month 24 and not terminal CCS failures	3	1	4
A2c. Known Month 24 CCS Status	106	44	150
A2d. Missing ≥1 CCS component or LTF and not a known failure	3	6	9
B. Randomized in mITT Analysis Set and Not Theoretically Due for Month 24 Visit	**95**	**43**	**138**
B1. Excluded from Per Protocol Analysis Set	2	1	3
B1a. Eligibility Violation Identified by CEC	0	0	0
B1b. Intraoperative Change to Non-Study Treatment	2	1	3
B2. Included in Per Protocol Analysis Set [3]	**93**	**42**	**135**
B2a. Early failures (have not reached Month 24 visit but known CCS terminal failure)	3	0	3
B2b. Death by Month 24 and not terminal CCS failures	0	0	0
B2c. Have not reached Month 24 visit and not failure (CCS pending)	86	38	124
B2d. Observed Month 24 visit prior to day 730 and non-missing CCS	4	3	7
B2e. Observed Month 24 visit prior to day 730 missing ≥1 CCS component and not a known failure	0	1	1
C. Month 24 CCS Status in TDmITT Analysis Set	**115**	**53**	**168**
C1. Known Month 24 CCS Status	108	46	154
C2. Missing Month 24 CCS Status	7	7	14

Notes:
[1] Full safety analysis set (AT) includes all patients in [1a], also equal to A + B
[2] Primary endpoint analysis set (TDmITT) includes all patients in A. As shown in C, within TDmITT, 108 TOPS™ and 46 Fusion have a known Month 24 CCS status.
[3] Per Protocol analysis set includes all patients in A2 + B2

Intent-to-Treat (ITT) Analysis Set – 321 subjects: Subjects in this group were randomized and are classified according to their assigned treatment. This analysis set includes all randomized subjects, including subjects who withdrew prior to surgery and subjects who were waiting to undergo their study procedure at the time of database lock.

Modified Intent-to-Treat (mITT) Analysis Set – 306 subjects: Subjects in this group underwent surgery and were classified according to their assigned treatment, regardless of whether the subject was intraoperatively changed to another a non-study treatment or failure to complete any required follow-up examinations; it did not include subjects who were not yet treated or who withdrew prior to surgery. In **Table 6** above, the mITT population includes all patients in row [1a].

As-Treated (AT) Analysis Set – 306 subjects: The AT analysis set included patients in the mITT analysis set, classified according to the treatment received by the patient. Since surgery for the assigned study treatment was initiated in all subjects, the AT analysis set is identical to the mITT analysis set. For clarity, four subjects began surgery for their assigned study treatment but were intra-operatively changed to a non-study treatment; since the surgery for the study treatment was initiated, these subjects are classified according to their attempted study treatment. The AT analysis set was the pre-specified primary safety analysis population.

Per Protocol (PP) Analysis Set – 299 subjects: The PP analysis set included patients in the AT analysis set who were a part of the intended target population. The PP analysis set excluded patients who were randomized in error or were subsequently found to not meet clinically important inclusion or exclusion criteria that are objectively determined. In total, 7 subjects were excluded: 2 TOPS™ and 2 Fusion subjects who were changed intra-operatively to a non-study treatment, and 2 TOPS™ and 1 Fusion subject who were subsequently found to not meet clinically important inclusion or exclusion criteria that were objectively determined. The PP analysis set was the pre-specified primary efficacy analysis population. In **Table 6** above, the PP analysis set includes all patients in rows A2 + B2.

Modified Intent-to-Treat Analysis Set Theoretically Due Month 24 Visit (TDmITT) – 168 subjects: The TDmITT analysis set included patients in the mITT population who were theoretically due for the Month 24 visit (at least 730 days post-surgery) at the time of the interim analysis. In coordination with FDA, the TDmITT analysis set was designated the primary endpoint analysis population for basis of PMA approval. In **Table 6** above, the TDmITT analysis set includes all patients in row A.

C. Study Population Demographics and Baseline Parameters

Demographics and baseline parameters are provided for the full mITT analysis set (210 TOPS™; 96 Fusion) (all randomized subjects in whom a study treatment was attempted) and the TDmITT analysis set (115 TOPS™; 53 Fusion) (randomized subjects in whom a study treatment was attempted and who were theoretically due for

their Month 24 visit at the time of interim analysis). All available demographics and baseline data are presented. The tables below summarize the following information:

- Baseline and Demographic Continuous Variables (**Tables 7-8**)
- Baseline and Demographic Categorical Variables (**Tables 9-10**)
- Summary of Operative Continuous Variables (**Tables 11-12**)
- Summary of Operative Categorical Variables (**Tables 13-14**)

As shown in **Tables 7-10** below, overall in both analysis sets, the treatment groups had similar gender distribution, mean age, BMI, smoking history, race, and ethnicity. In addition, the treatment groups had a comparable proportion of patients in both groups who underwent prior lumbar surgery. In addition to the similarities in demographics, the TOPS™ and Fusion groups in both analysis sets had similar baseline scores, including mean VAS Worst Leg score, VAS low back pain, VAS right leg pain, VAS left leg pain, VAS Other Leg pain, ZCQ, ODI scores, and SF-12 physical scores. In summary, randomization was effective in providing a well-balanced study population, with similar demographic, baseline, and clinical characteristics between the TOPS™ and control groups.

Table 7: Baseline and Demographic Continuous Variables - mITT Analysis Set

	TOPS™						Fusion						TOPS™ - Fusion[1]		
Demographics - All	**N**	**Mean**	**SD**	**Med**	**Min**	**Max**	**N**	**Mean**	**SD**	**Med**	**Min**	**Max**	**Diff**	**LB**	**UB**
Age (yrs)	210	63.4	8.2	64.0	38.0	80.0	96	64.0	8.5	66.0	43.0	80.0	-0.5	-2.6	1.5
Height (in)	210	66.9	4.0	66.7	58.0	80.5	96	66.9	4.3	66.3	53.8	74.0	0.1	-0.9	1.0
Weight (lbs)	210	188.6	38.0	187.0	105.0	280.0	96	190.0	39.4	187.5	118.0	295.0	-1.4	-10.7	7.9
BMI (kg/m^2)	210	29.5	4.9	28.9	17.4	40.3	96	29.8	5.3	29.3	19.6	39.7	-0.3	-1.6	0.9
Demographics - Male	**N**	**Mean**	**SD**	**Med**	**Min**	**Max**	**N**	**Mean**	**SD**	**Med**	**Min**	**Max**	**Diff**	**LB**	**UB**
Age (yrs)	93	64.7	8.0	66.0	43.0	79.0	46	64.4	8.3	66.0	43.0	78.0	0.3	-2.5	3.2
Height (in)	93	70.4	2.7	70.0	65.0	80.5	46	70.2	2.7	70.8	64.0	74.0	0.2	-0.7	1.2
Weight (lbs)	93	210.5	32.9	209.0	132.0	280.0	46	205.6	38.2	206.5	128.0	295.0	4.8	-7.5	17.2
BMI (kg/m^2)	93	29.9	4.5	30.0	19.1	40.0	46	29.3	4.7	29.1	21.7	39.3	0.6	-1.0	2.2
Demographics - Female	**N**	**Mean**	**SD**	**Med**	**Min**	**Max**	**N**	**Mean**	**SD**	**Med**	**Min**	**Max**	**Diff**	**LB**	**UB**
Age (yrs)	117	62.4	8.4	63.0	38.0	80.0	50	63.6	8.8	64.5	46.0	80.0	-1.2	-4.0	1.7
Height (in)	117	64.2	2.4	64.0	58.0	69.0	50	63.8	3.0	64.3	53.8	70.0	0.4	-0.5	1.2
Weight (lbs)	117	171.2	32.5	166.0	105.0	250.0	50	175.6	35.0	176.5	118.0	242.3	-4.4	-15.5	6.7
BMI (kg/m^2)	117	29.2	5.2	28.0	17.4	40.3	50	30.3	5.8	30.8	19.6	39.7	-1.1	-2.9	0.7
Baseline Functional Status	**N**	**Mean**	**SD**	**Med**	**Min**	**Max**	**N**	**Mean**	**SD**	**Med**	**Min**	**Max**	**Diff**	**LB**	**UB**
VAS Low Back Pain Score	210	68.5	23.1	72.5	0.0	100.0	96	69.7	21.9	75.0	0.0	100.0	-1.2	-6.7	4.3
VAS Right Leg Pain Score	210	64.8	29.9	74.0	0.0	100.0	96	67.4	30.6	78.0	0.0	100.0	-2.7	-10.0	4.6

	TOPS™						Fusion						TOPS™ - Fusion[1]		
VAS Left Leg Pain Score	210	66.2	29.5	77.0	0.0	100.0	96	66.0	32.0	76.5	0.0	100.0	0.2	-7.2	7.6
VAS Worst Leg Pain Score	210	82.5	13.5	86.0	40.0	100.0	96	85.1	10.8	87.0	50.0	100.0	-2.6	-5.6	0.5
VAS Other Leg Pain Score	210	48.5	31.7	51.5	0.0	100.0	96	48.4	34.1	56.5	0.0	99.0	0.1	-7.8	8.0
ZCQ Symptom Severity Scale[2]	210	3.72	0.58	3.71	2.43	5.00	96	3.71	0.56	3.71	2.57	5.00	0.0	-0.1	0.2
ZCQ Physical Function Scale[2]	210	2.93	0.42	3.00	1.40	3.80	96	2.91	0.43	3.00	1.60	4.00	0.0	-0.1	0.1
ODI Score	210	56.4	12.0	56.0	34.0	98.0	96	55.9	12.9	54.0	38.0	100.0	0.4	-2.6	3.4
SF-12 Physical Health T-score	208	25.5	7.0	25.0	8.6	45.1	95	27.1	7.0	26.7	12.1	46.7	-1.6	-3.3	0.1

Notes:
[1]Estimated mean difference and 95% confidence interval between TOPS™ and Fusion (95% CI not adjusted for multiplicity).
[2]The third component of the ZCQ (patient satisfaction with treatment) is only assessed post-treatment and is therefore not included in this table.

Table 8: Summary of Baseline and Demographic Continuous Variables (TDmITT)

	TOPS™						Fusion						TOPS™ - Fusion[1]		
Demographics - All	**N**	**Mean**	**SD**	**Med**	**Min**	**Max**	**N**	**Mean**	**SD**	**Med**	**Min**	**Max**	**Diff**	**LB**	**UB**
Age (yrs)	115	63.1	8.0	64.0	38.0	79.0	53	64.3	8.3	66.0	43.0	80.0	-1.2	-3.9	1.5
Height (in)	115	67.1	4.1	67.0	58.0	80.5	53	66.8	4.3	66.0	53.8	74.0	0.3	-1.1	1.6
Weight (lbs)	115	194.2	38.5	196.2	106.1	280.0	53	194.4	41.9	190.0	123.0	295.0	-0.2	-13.2	12.8
BMI (kg/m^2)	115	30.2	5.0	30.0	17.4	40.3	53	30.5	5.4	29.7	20.8	39.7	-0.3	-2.0	1.4
Demographics - Male	**N**	**Mean**	**SD**	**Med**	**Min**	**Max**	**N**	**Mean**	**SD**	**Med**	**Min**	**Max**	**Diff**	**LB**	**UB**
Age (yrs)	53	64.1	8.1	66.0	43.0	79.0	27	64.5	7.7	66.0	43.0	78.0	-0.4	-4.1	3.4
Height (in)	53	70.6	2.7	71.0	65.0	80.5	27	69.8	2.9	71.0	64.0	74.0	0.8	-0.5	2.1
Weight (lbs)	53	217.4	29.6	218.0	149.0	280.0	27	209.2	43.3	209.0	128.0	295.0	8.2	-8.2	24.6
BMI (kg/m^2)	53	30.6	4.1	30.3	22.0	39.4	27	30.0	5.1	29.3	21.7	39.3	0.6	-1.5	2.7
Demographics - Female	**N**	**Mean**	**SD**	**Med**	**Min**	**Max**	**N**	**Mean**	**SD**	**Med**	**Min**	**Max**	**Diff**	**LB**	**UB**
Age (yrs)	62	62.2	8.0	62.0	38.0	76.0	26	64.0	9.0	65.5	46.0	80.0	-1.9	-5.7	2.0
Height (in)	62	64.1	2.4	64.0	58.0	68.5	26	63.7	3.2	64.3	53.8	70.0	0.4	-0.9	1.6
Weight (lbs)	62	174.3	34.0	166.5	106.1	250.0	26	179.0	35.0	180.5	123.0	242.3	-4.7	-20.7	11.2
BMI (kg/m^2)	62	29.9	5.7	29.1	17.4	40.3	26	31.0	5.8	32.4	20.8	39.7	-1.2	-3.8	1.5
Baseline Functional Status	**N**	**Mean**	**SD**	**Med**	**Min**	**Max**	**N**	**Mean**	**SD**	**Med**	**Min**	**Max**	**Diff**	**LB**	**UB**
VAS Low Back Pain Score	115	65.8	25.3	70.0	6.0	100.0	53	66.0	23.8	75.0	0.0	98.0	-0.1	-8.3	8.0
VAS Right Leg Pain Score	115	63.9	31.2	74.0	0.0	100.0	53	64.6	30.5	75.0	0.0	100.0	-0.7	-10.9	9.4
VAS Left Leg Pain Score	115	66.3	30.2	76.0	0.0	100.0	53	62.7	34.0	75.0	0.0	100.0	3.5	-6.8	13.8

	TOPS™						Fusion						TOPS™ - Fusion[1]		
VAS Worst Leg Pain Score	115	83.1	13.6	87.0	40.0	100.0	53	83.7	10.9	85.0	50.0	100.0	-0.5	-4.7	3.6
VAS Other Leg Pain Score	115	47.0	32.4	50.0	0.0	100.0	53	43.6	34.0	53.0	0.0	99.0	3.4	-7.4	14.1
ZCQ Symptom Severity Scale[2]	115	3.8	0.6	3.9	2.4	5.0	53	3.7	0.6	3.7	2.6	4.9	0.1	-0.1	0.3
ZCQ Physical Function Scale[2]	115	2.9	0.4	3.0	2.0	3.8	53	2.9	0.4	3.0	1.8	3.6	0.0	-0.1	0.2
ODI Score	115	56.4	12.3	56.0	34.0	98.0	53	56.1	11.9	54.0	38.0	82.0	0.3	-3.7	4.3
SF-12 Physical Health T-score	114	25.4	7.0	24.3	8.6	45.1	52	27.9	6.9	28.5	16.2	46.7	-2.5	-4.8	-0.2

Notes:
[1]Estimated mean difference and 95% confidence interval between TOPS™ and Fusion (95% CI not adjusted for multiplicity).
[2]The third component of the ZCQ (patient satisfaction with treatment) is only assessed post-treatment and is therefore not included in this table.

Table 9: Baseline and Demographic Categorical Variables - mITT Analysis Set

	TOPS™		Fusion		TOPS™ - Fusion[1]		
	N	**%**	**n**	**%**	**Diff (%)**	**LB**	**UB**
Number of subjects	210		96				
Males	93	44.3	46	47.9	-3.6	-15.7	8.4
Females	117	55.7	50	52.1	.	.	.
Race	**N**	**%**	**n**	**%**	**.**	**.**	
White	195	92.9	89	92.7	.	.	
Black	3	1.4	3	3.1	.	.	
Asian	3	1.4	2	2.1	.	.	
Pacific Islander	0	0.0	0	0.0	.	.	
American Indian or Alaskan Native	1	0.5	1	1.0	.	.	
Other	5	2.4	1	1.0	.	.	
Unknown	3	1.4	0	0.0	.	.	
Hispanic or Latino	**N**	**%**	**n**	**%**	**Diff (%)**	**LB**	**UB**
Yes	6	2.9	2	2.1	-0.8	-4.4	2.9
No	204	97.1	94	97.9	.	.	.
Use of nicotine products	**N**	**%**	**n**	**%**	**.**	**.**	
No, never smoked	128	61.0	62	64.6	.	.	
No, but prior history	76	36.2	32	33.3	.	.	
Current smoker	6	2.9	2	2.1	.	.	
Prior Lumbar Surgery	**N**	**%**	**n**	**%**	**Diff (%)**	**LB**	**UB**
Yes	12	5.7	6	6.3	-0.5	-6.3	5.2
No	198	94.3	90	93.8	.	.	.
Index Leg (Worst VAS at Baseline)	**N**	**%**	**n**	**%**	**.**	**.**	
Right Leg	90	42.9	45	46.9	.	.	
Left Leg	98	46.7	44	45.8	.	.	
Both Legs	22	10.5	7	7.3	.	.	

	TOPS™		Fusion		TOPS™ - Fusion[1]		
Index Leg (Right Assigned if Equal)	**N**	**%**	**n**	**%**	**Diff (%)**	**LB**	**UB**
Right Leg	112	53.3	52	54.2	-0.8	-12.9	11.2
Left Leg	98	46.7	44	45.8	.	.	.

Notes:
[1] Device group differences in proportions and 95% confidence intervals (CI) for group differences (95% CI not adjusted for multiplicity)

Table 10: Summary of Baseline and Demographic Categorical Variables (TDmITT)

	TOPS™		Fusion		TOPS™ - Fusion[1]		
	n	**%**	**n**	**%**	**Diff (%)**	**LB**	**UB**
Number of subjects	115		53				
Males	53	46.1	27	50.9	-4.9	-21.1	11.4
Females	62	53.9	26	49.1	.	.	.
Race	**n**	**%**	**n**	**%**	**.**	**.**	
White	110	95.7	51	96.2	.	.	
Black	1	0.9	1	1.9	.	.	
Asian	1	0.9	0	0.0	.	.	
Pacific Islander	0	0.0	0	0.0	.	.	
American Indian or Alaskan Native	0	0.0	1	1.9	.	.	
Other	2	1.7	0	0.0	.	.	
Unknown	1	0.9	0	0.0	.	.	
Hispanic or Latino	**n**	**%**	**n**	**%**	**Diff (%)**	**LB**	**UB**
Yes	5	4.3	1	1.9	-2.5	-7.7	2.8
No	110	95.7	52	98.1	.	.	.
Use of nicotine products	**n**	**%**	**n**	**%**	**.**	**.**	
No, never smoked	72	62.6	35	66.0	.	.	
No, but prior history	42	36.5	17	32.1	.	.	
Current smoker	1	0.9	1	1.9	.	.	
Prior Lumbar Surgery	**n**	**%**	**n**	**%**	**Diff (%)**	**LB**	**UB**
Yes	7	6.1	5	9.4	-3.3	-12.3	5.7
No	108	93.9	48	90.6	.	.	.
Index Leg (Worst VAS at Baseline)	**n**	**%**	**n**	**%**	**.**	**.**	
Right Leg	47	40.9	23	43.4	.	.	
Left Leg	56	48.7	26	49.1	.	.	
Both Legs	12	10.4	4	7.5	.	.	
Index Leg (Right Assigned if Equal)	**n**	**%**	**n**	**%**	**Diff (%)**	**LB**	**UB**
Right Leg	59	51.3	27	50.9	0.4	-15.9	16.6
Left Leg	56	48.7	26	49.1	.	.	.

Notes:
[1] Device group differences in proportions and 95% confidence intervals (CI) for group differences (95% CI not adjusted for multiplicity)

As shown in **Tables 11-14** below, there were no apparent differences in operative characteristics between the TOPS™ and Fusion control groups in the mITT analysis set (210 TOPS™; 96 Fusion) or TDmITT analysis set (115 TOPS™; 53 Fusion). Note that **Table 13** indicates a single Fusion group subject within the mITT was treated at L5/S1 (this subject was not due for Month 24 and thus is not included in the TDmITT analysis set); however, the subject is among the Intraoperative Change to Non-Study Treatment group because the fusion procedure was extended to a second level.

Table 11: Summary of Operative Continuous Variables - mITT Analysis Set

	TOPS™						Fusion						TOPS™ - Fusion[1]		
Demographics - All	**N**	**Mean**	**SD**	**Med**	**Min**	**Max**	**N**	**Mean**	**SD**	**Med**	**Min**	**Max**	**Diff**	**LB**	**UB**
Time in Surgery (min)	210	183.7	58.1	173.0	74.0	359.0	96	176.9	56.9	167.5	77.0	357.0	6.8	-7.2	20.8
Length of Hospital Stay (days)	208	2.9	3.60	2.0	0.0	51.0	94	2.9	1.7	2.0	0.00	14.0	0.00	-0.7	0.8
Estimated Blood Loss (cc)	210	202.0	146.5	162.5	0.0	900.0	96	212.7	133.2	200.0	0.0	550.0	-10.7	-45.3	23.8
Demographics - Male	**N**	**Mean**	**SD**	**Med**	**Min**	**Max**	**N**	**Mean**	**SD**	**Med**	**Min**	**Max**	**Diff**	**LB**	**UB**
Time in Surgery (min)	93	194.5	54.1	193.0	89.0	332.0	46	174.7	61.6	160.0	84.0	357.0	19.9	-0.3	40.0
Length of Hospital Stay (days)	91	2.7	1.4	2.0	0.0	9.0	44	2.7	2.0	2.0	0.0	14.0	0.0	-0.6	0.6
Estimated Blood Loss (cc)	93	223.4	146.7	200.0	35.0	800.0	46	215.4	130.5	200.0	0.0	520.0	8.0	-42.4	58.5
Demographics - Female	**N**	**Mean**	**SD**	**Med**	**Min**	**Max**	**N**	**Mean**	**SD**	**Med**	**Min**	**Max**	**Diff**	**LB**	**UB**
Time in Surgery (min)	117	175.0	60.0	159.0	74.0	359.0	50	178.9	52.7	184.5	77.0	304.0	-3.9	-23.2	15.5
Length of Hospital Stay (days)	117	3.0	4.6	2.0	0.0	51.0	50	3.0	1.5	3.0	0.0	7.0	0.0	-1.3	1.4
Estimated Blood Loss (cc)	117	184.9	144.7	150.0	0.0	900.0	50	210.3	136.9	175.0	0.0	550.0	-25.4	-72.9	22.2

Notes:
[1]Estimated mean difference and 95% confidence interval between TOPS™ and Fusion (95% CI not adjusted for multiplicity).

Table 12: Summary of Operative Continuous Variables (TDmITT)

	TOPS™						Fusion						TOPS™ - Fusion[1]		
Demographics - All	**N**	**Mean**	**SD**	**Med**	**Min**	**Max**	**N**	**Mean**	**SD**	**Med**	**Min**	**Max**	**Diff**	**LB**	**UB**
Time in Surgery (min)	115	193.3	61.4	182.0	74.0	332.0	53	177.2	61.5	174.0	77.0	357.0	16.2	-4.0	36.3

	TOPS™						Fusion						TOPS™ - Fusion[1]		
Length of Hospital Stay (days)	115	3.06	4.67	2.00	0.00	51.00	52	3.21	2.15	3.00	0.00	14.00	-0.15	-1.49	1.19
Estimated Blood Loss (cc)	115	223.6	166.2	200.0	0.0	900.0	53	231.2	139.0	200.0	0.0	550.0	-7.6	-59.4	44.3
Demographics - Male	**N**	**Mean**	**SD**	**Med**	**Min**	**Max**	**N**	**Mean**	**SD**	**Med**	**Min**	**Max**	**Diff**	**LB**	**UB**
Time in Surgery (min)	53	205.0	54.2	204.0	102.0	332.0	27	174.6	65.6	163.0	84.0	357.0	30.4	3.0	57.8
Length of Hospital Stay (days)	53	2.62	1.18	2.00	0.00	6.00	26	2.96	2.51	3.00	0.00	14.00	-0.34	-1.16	0.48
Estimated Blood Loss (cc)	53	238.2	154.2	200.0	50.0	800.0	27	230.9	125.7	200.0	0.0	520.0	7.4	-61.0	75.8
Demographics - Female	**N**	**Mean**	**SD**	**Med**	**Min**	**Max**	**N**	**Mean**	**SD**	**Med**	**Min**	**Max**	**Diff**	**LB**	**UB**
Time in Surgery (min)	62	183.3	65.8	165.5	74.0	329.0	26	179.8	58.1	186.5	77.0	304.0	3.5	-26.1	33.1
Length of Hospital Stay (days)	62	3.4	6.3	3.0	1.0	51.0	26	3.5	1.7	3.0	0.0	7.0	0.0	-2.5	2.5
Estimated Blood Loss (cc)	62	211.1	176.2	150.0	0.0	900.0	26	231.5	154.2	200.0	50.0	550.0	-20.4	-99.4	58.6

Notes:
[1]Estimated mean difference and 95% confidence interval between TOPS™ and Fusion (95% CI not adjusted for multiplicity)

Table 13: Summary of Operative Categorical Variables - mITT Analysis Set

	TOPS™		Fusion	
	n	**%**	**n**	**%**
Number of subjects	210		96	
Level Implanted	**n**	**%**	**n**	**%**
L1/L2	0	0.0	0	0.0
L2/L3	0	0.0	0	0.0
L3/L4	10	4.8	6	6.3
L4/L5	200	95.2	89	92.7
L5/S1	0	0.0	1	1.0
Operative Blood Loss	**n**	**%**	**n**	**%**
<100 cc	34	16.2	12	12.5
100 - <250 cc	106	50.5	49	51.0
250 - <400 cc	46	21.9	20	20.8
≥400 cc	24	11.4	15	15.6

Table 14: Summary of Operative Categorical Variables (TDmITT)

	TOPS™		Fusion	
	n	**%**	**n**	**%**
Number of subjects	115		53	
Level Implanted	**n**	**%**	**n**	**%**
L1/L2	0	0.0	0	0.0
L2/L3	0	0.0	0	0.0
L3/L4	5	4.3	3	5.7
L4/L5	110	95.7	50	94.3
L5/S1	0	0.0	0	0.0
Operative Blood Loss	**n**	**%**	**n**	**%**
<100 cc	19	16.5	4	7.5
100 - <250 cc	53	46.1	28	52.8
250 - <400 cc	25	21.7	11	20.8
≥400 cc	18	15.7	10	18.9

D. Safety and Effectiveness Results

The safety results below are presented for the AT analysis set (N=210 TOPS™ and 96 Fusion) and TDmITT analysis set (N=115 TOPS™ and 53 Fusion); the effectiveness results below are presented for the TDmITT analysis set (N=115 TOPS™ and 53 Fusion).

The safety endpoint evaluated the rate of AEs, categorized by severity (mild, moderate or severe), relationship to the implant or procedure, and serious adverse events (SAEs). All adverse events were reviewed by a convened Clinical Events Committee (CEC) and adjudicated for severity and relationship to the implant or procedure based on the following definitions:

Severity

- Mild - An experience that is noticeable to the patient but does not impede routine activity.
- Moderate - An experience that impedes the patient's routine activity but responds to symptomatic therapy or rest.
- Severe - An experience that significantly limits the patient's ability to perform routine activities despite symptomatic therapy.

Causality (relation to device and to procedure)

- Not Related - A temporal relationship to device implantation or with ongoing use of the device, which makes a causal relationship clearly due to extraneous causes, such as other drugs, other devices, chemicals, underlying diseases, environment, etc. The event is clearly not-related to the device implanted or to a function/malfunction.
- Possibly Related - Occurring within a reasonable period of time relative to device implantation or with ongoing use of the device, which makes a causal relationship possible, but plausible explanations can likely be

attributed to other causes, such as other drugs, products, chemicals, underlying disease, environment, etc.

- Probably Related - Occurring within a reasonable period of time relative to device implantation or with ongoing use of the device, which makes a causal relationship probable where the plausible explanations cannot likely be attributed to other causes, such as other drugs, products, chemicals, underlying disease, environment, etc.
- Definitely Related - Occurring within a reasonable period of time relative to device implantation or with ongoing use of the device, and which definitely cannot be attributed to other causes, such as other drugs, products, chemicals, underlying disease, environment, etc.

An event was considered an SAE if it resulted in death or led to a serious deterioration in the health of the subject that resulted in a life-threatening illness or injury; resulted in a permanent impairment of a body structure or a body function; required in-patient hospitalization or prolongation of an existing hospitalization; or resulted in medical or surgical intervention to prevent permanent impairment to a body structure or a body function. Note that a device-related SAE is different than a "major device related adverse event," which is a term specific to the primary composite clinical success endpoint that encompasses only device component breakage, degradation, separation, disassembly, and loosening, and increase in spondylolisthesis by at least 1 grade at the operative level.

1. Safety Results

The pre-specified analysis of safety was based on the AT analysis cohort of 306 subjects treated (210 randomized and treated TOPS™ subjects and 96 Fusion control subjects). As requested by FDA, *post-hoc* safety analyses were performed for the TDmITT population (115 TOPS™; 53 Fusion). Safety results are reported below for both populations. The TDmITT results provide the primary safety comparisons on which FDA based the regulatory decision for this PMA; the AT results show all safety events observed up to the point of database lock. AEs for both populations are reported in **Tables 15** to **26**, organized by high level term.[8] AE counts and per-patient incidence rates, along with differences and 95% normal-based confidence intervals, are provided. All available AE data are reported.

Overall, in the TDmITT population (115 TOPS™; 53 Fusion), TOPS™ exhibited comparable adverse event rates as compared to the Fusion control. A summary of AE rates is provided in **Table 17** below. The rate of occurrence of any AE was

[8] "High level term" is part of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Medical Dictionary for Regulatory Activities (MedDRA) hierarchy for grouping of adverse events. High level terms are umbrella terms that group together related medical concepts (e.g., signs, symptoms, procedures) based on anatomy, pathology, physiology, etiology or function (e.g., the symptom "nausea" is covered by the high level term "Nausea and Vomiting Symptoms").

71.3% (82/115) for TOPS™ subjects, compared to 73.6% (39/53) among Fusion control subjects. Device-related AEs occurred in 23.5% (27/115) of TOPS™ subjects, compared to 37.7% (20/53) of Fusion control subjects. Procedure-related AEs occurred in 49.6% (57/115) of TOPS™ subjects, compared to 60.4% (32/53) of Fusion control subjects. The rate of occurrence of any SAE was 34.8% (40/115) for TOPS™ subjects, compared to 28.3% (15/53) for Fusion control subjects. Device-related SAEs occurred in 6.1% (7/115) of TOPS™ subjects, compared to 9.4% (5/53) of Fusion control subjects. The proportion of subjects with major device-related AEs (which may not include all SAEs) is shown below in **Table 27**. AEs observed in the AT analysis population (210 TOPS™; 96 Fusion) are shown in **Table 18**. It is noted that in **Table 18**, not all subjects had Month 24 AE reporting.

Table 15: Comparison of All AEs by Severity for TOPS™ and Fusion Control Subjects Among TDmITT Analysis Set (N=168)

	Mild		Moderate		Severe		Total
	Events	%*	Events	%*	Events	%*	Events
TOPS™ (N=115)	151	47.8%	107	33.9%	58	18.4%	316
Fusion Control (N=53)	67	44.7%	59	39.3%	24	16.0%	150
*Percentage of total events.							

Table 16: Comparison of All AEs by Severity for TOPS™ and Fusion Control Subjects Among AT Analysis Set (N=306)

	Mild		Moderate		Severe		Total
	Events	%*	Events	%*	Events	%*	Events
TOPS™ (N=210)	223	50.5%	150	33.9%	69	15.6%	442
Fusion Control (N=96)	117	52.0%	83	36.9%	25	11.1%	225
*Percentage of total events.							

Table 17: Summary of AE and SAE Incidence Among TDmITT Analysis Set (N=168)

	TOPS™ (N=115)			Fusion (N=53)			TOPS™ - Fusion[1]		
	Events	Subjs	%[3]	Events	Subjs	%[3]	Diff (%)	LB	UB
Any Adverse Event (AE)	316	82	71.3	150	39	73.6	-2.3	-16.7	12.2
Any Device Related[2] AE	39	27	23.5	29	20	37.7	-14.3	-29.4	0.9
Any Procedure Related[2] AE	102	57	49.6	73	32	60.4	-10.8	-26.8	5.2
Any Device and/or Procedure Related[2] AE	104	58	50.4	73	32	60.4	-9.9	-26.0	6.1
Any Serious Adverse Event (SAE)	64	40	34.8	28	15	28.3	6.5	-8.4	21.4
Any Device Related[2] SAE	9	7	6.1	7	5	9.4	-3.3	-12.3	5.7

	TOPS™ (N=115)			Fusion (N=53)			TOPS™ - Fusion[1]		
	Events	Subjs	%[3]	Events	Subjs	%[3]	Diff (%)	LB	UB
Any Procedure Related[2] SAE	25	20	17.4	16	11	20.8	-3.4	-16.3	9.6
Any Death from AE/SAE	3	3	2.6	0	0	0.0	2.6	-0.3	5.5

Notes:
[1] Device group differences in proportions and 95% confidence intervals (CI) for group differences (not adjusted for multiplicity)
[2] Includes events denoted as "Possibly", "Probably" or "Definitely" related to device or procedure (as noted)
[3] Percentage of subjects experiencing specific event.

Table 18: Summary of AE and SAE Incidence Among AT Analysis Set (N=306)

	TOPS™ (N=210)			Fusion (N=96)			TOPS™ - Fusion[1]		
	Events	Subjs	%[3]	Events	Subjs	%[3]	Diff (%)	LB	UB
Any Adverse Event (AE)	442	137	65.2	225	59	61.5	3.8	-7.9	15.5
Any Device Related[2] AE	60	45	21.4	43	27	28.1	-6.7	-17.3	3.9
Any Procedure Related[2] AE	185	104	49.5	110	49	51.0	-1.5	-13.6	10.6
Any Device and/or Procedure Related[2] AE	187	105	50.0	110	49	51.0	-1.0	-13.1	11.0
Any Serious Adverse Event (SAE)	79	53	25.2	29	16	16.7	8.6	-0.9	18.1
Any Device Related[2] SAE	11	9	4.3	7	5	5.2	-0.9	-6.1	4.3
Any Procedure Related[2] SAE	32	27	12.9	16	11	11.5	1.4	-6.4	9.2
Any Death from AE/SAE	3	3	1.4	0	0	0.0	1.4	-0.2	3.0

Notes:
[1] Device group differences in proportions and 95% confidence intervals (CI) for group differences (not adjusted for multiplicity)
[2] Includes events denoted as "Possibly", "Probably" or "Definitely" related to device or procedure (as noted)
[3] Percentage of subjects experiencing specific event.

Table 19 below shows rates of AEs in the TDmITT population by high-level term. The most common types of AEs in both the TOPS™ and Fusion control groups were (1) musculoskeletal and connective tissue disorders, and (2) injury, poisoning and procedural complications. Specifically, 44.3% (51/115) of TOPS™ subjects compared to 52.8% (28/53) of Fusion control subjects experienced musculoskeletal and connective tissue disorder AEs; and, 27.0% (31/115) of TOPS™ subjects and 32.1% (17/53) of Fusion control subjects experienced injury, poisoning, or procedural complication AEs. Similarly, these were the most common types of AEs in both the TOPS™ and Fusion control groups for the AT analysis population, as shown in **Table 20** below.

Table 19: All AEs by High Level Term Among TDmITT Analysis Set (N=168)

	TOPS™ (N=115)			Fusion (N=53)			Diff
	Events	Subjs	%*	Events	Subjs	%*	%
ALL	316	82	71.3%	150	39	73.6%	-2.3%
Blood and Lymphatic System Disorders	1	1	0.9%	3	2	3.8%	-2.9%
Cardiac Disorders	5	5	4.3%	4	2	3.8%	0.6%
Ear and Labyrinth Disorders	2	2	1.7%	0	0	0.0%	1.7%
Eye Disorders	7	7	6.1%	1	1	1.9%	4.2%
Gastrointestinal Disorders	17	13	11.3%	5	5	9.4%	1.9%
General Disorders and Administration Site Conditions	10	9	7.8%	5	5	9.4%	-1.6%
Hepatobiliary Disorders	0	0	0.0%	1	1	1.9%	-1.9%
Immune System Disorders	3	2	1.7%	0	0	0.0%	1.7%
Infections and Infestations	28	18	15.7%	10	9	17.0%	-1.3%
Injury, Poisoning and Procedural Complications	41	31	27.0%	22	17	32.1%	-5.1%
Investigations	5	4	3.5%	4	3	5.7%	-2.2%
Metabolism and Nutrition Disorders	4	4	3.5%	3	2	3.8%	-0.3%
Musculoskeletal and Connective Tissue Disorders	112	51	44.3%	50	28	52.8%	-8.5%
Neoplasms Benign, Malignant and Unspecified (Incl Cysts And Polyps)	8	7	6.1%	1	1	1.9%	4.2%
Nervous System Disorders	30	19	16.5%	15	12	22.6%	-6.1%
Product Issues	1	1	0.9%	3	2	3.8%	-2.9%
Psychiatric Disorders	3	3	2.6%	5	4	7.5%	-4.9%
Renal and Urinary Disorders	8	7	6.1%	1	1	1.9%	4.2%
Reproductive System and Breast Disorders	2	2	1.7%	2	1	1.9%	-0.1%
Respiratory, Thoracic and Mediastinal Disorders	9	9	7.8%	5	3	5.7%	2.2%
Skin and Subcutaneous Tissue Disorders	5	4	3.5%	3	2	3.8%	-0.3%
Surgical and Medical Procedures	10	9	7.8%	4	4	7.5%	0.3%
Vascular Disorders	5	3	2.6%	3	1	1.9%	0.7%
*Percentage of subjects experiencing specific event.							

Table 20: All AEs by High Level Term Among AT Analysis Set (N=306)

	TOPS™ (N=210)			Fusion (N=96)			Diff
	Events	Subjs	%*	Events	Subjs	%*	%
ALL	442	137	65.2%	225	59	61.5%	3.8%
Blood and Lymphatic System Disorders	4	3	1.4%	3	2	2.1%	-0.7%

	TOPS™ (N=210)			Fusion (N=96)			Diff
	Events	Subjs	%*	Events	Subjs	%*	%
Cardiac Disorders	6	6	2.9%	4	2	2.1%	0.8%
Ear and Labyrinth Disorders	3	3	1.4%	1	1	1.0%	0.4%
Eye Disorders	7	7	3.3%	1	1	1.0%	2.3%
Gastrointestinal Disorders	25	21	10.0%	9	9	9.4%	0.6%
General Disorders and Administration Site Conditions	17	15	7.1%	8	8	8.3%	-1.2%
Hepatobiliary Disorders	0	0	0.0%	1	1	1.0%	-1.0%
Immune System Disorders	3	2	1.0%	0	0	0.0%	1.0%
Infections and Infestations	37	27	12.9%	20	14	14.6%	-1.7%
Injury, Poisoning and Procedural Complications	56	44	21.0%	30	23	24.0%	-3.0%
Investigations	6	5	2.4%	4	3	3.1%	-0.7%
Metabolism and Nutrition Disorders	6	6	2.9%	3	2	2.1%	0.8%
Musculoskeletal and Connective Tissue Disorders	152	77	36.7%	80	41	42.7%	-6.0%
Neoplasms Benign, Malignant and Unspecified (Incl Cysts And Polyps)	8	7	3.3%	2	2	2.1%	1.3%
Nervous System Disorders	49	32	15.2%	23	18	18.8%	-3.5%
Product Issues	4	4	1.9%	3	2	2.1%	-0.2%
Psychiatric Disorders	6	6	2.9%	6	5	5.2%	-2.4%
Renal and Urinary Disorders	11	10	4.8%	4	4	4.2%	0.6%
Reproductive System and Breast Disorders	2	2	1.0%	2	1	1.0%	-0.1%
Respiratory, Thoracic and Mediastinal Disorders	13	13	6.2%	8	5	5.2%	1.0%
Skin and Subcutaneous Tissue Disorders	7	6	2.9%	4	3	3.1%	-0.3%
Surgical and Medical Procedures	11	10	4.8%	5	5	5.2%	-0.4%
Vascular Disorders	9	7	3.3%	4	2	2.1%	1.3%
*Percentage of subjects experiencing specific event.							

As shown in **Table 21**, the most common types of SAEs in the TDmITT population were (1) musculoskeletal and connective tissue disorders, and (2) injury, poisoning, and procedural complications; both types of SAEs occurred in 10.4% (12/115) of TOPS™ and 9.4% (5/53) of Fusion control subjects. SAEs observed in the AT analysis population (210 TOPS™TOPS™; 96 Fusion) are shown in **Table 22**. It is noted that in **Table 22**, not all subjects had Month 24 AE reporting.

Table 21: All SAEs by High Level Term Among TDmITT Analysis Set (N=168)

	TOPS™ (N=115)			Fusion (N=53)			Diff
	Events	Subjs	%*	Events	Subjs	%*	%
ALL	64	40	34.8%	28	15	28.3%	6.5%
Blood and Lymphatic System Disorders	0	0	0.0%	1	1	1.9%	-1.9%
Cardiac Disorders	2	2	1.7%	1	1	1.9%	-0.1%
Gastrointestinal Disorders	4	4	3.5%	0	0	0.0%	3.5%
General Disorders and Administration Site Conditions	1	1	0.9%	1	1	1.9%	-1.0%
Infections and Infestations	8	7	6.1%	1	1	1.9%	4.2%
Injury, Poisoning and Procedural Complications	14	12	10.4%	6	5	9.4%	1.0%
Metabolism and Nutrition Disorders	0	0	0.0%	1	1	1.9%	-1.9%
Musculoskeletal and Connective Tissue Disorders	15	12	10.4%	6	5	9.4%	1.0%
Neoplasms Benign, Malignant and Unspecified (Incl Cysts And Polyps)	3	3	2.6%	1	1	1.9%	0.7%
Nervous System Disorders	3	3	2.6%	1	1	1.9%	0.7%
Product Issues	1	1	0.9%	1	1	1.9%	-1.0%
Psychiatric Disorders	1	1	0.9%	2	2	3.8%	-2.9%
Respiratory, Thoracic and Mediastinal Disorders	2	2	1.7%	3	2	3.8%	-2.0%
Skin And Subcutaneous Tissue Disorders	1	1	0.9%	0	0	0.0%	0.9%
Surgical and Medical Procedures	7	6	5.2%	2	2	3.8%	1.4%
Vascular Disorders	2	2	1.7%	1	1	1.9%	-0.1%
*Percentage of subjects experiencing specific event.							

Table 22: All SAEs by High Level Term Among AT Analysis Set (N=306)

	TOPS™ (N=210)			Fusion (N=96)			Diff
	Events	Subjs	%*	Events	Subjs	%*	%
ALL	79	53	25.2%	29	16	16.7%	8.6%
Blood and Lymphatic System Disorders	0	0	0.0%	1	1	1.0%	-1.0%
Cardiac Disorders	3	3	1.4%	1	1	1.0%	0.4%
Gastrointestinal Disorders	6	6	2.9%	0	0	0.0%	2.9%
General Disorders and Administration Site Conditions	3	3	1.4%	1	1	1.0%	0.4%
Infections and Infestations	11	10	4.8%	1	1	1.0%	3.7%
Injury, Poisoning and Procedural Complications	15	13	6.2%	6	5	5.2%	1.0%

	TOPS™ (N=210)			Fusion (N=96)			Diff
	Events	Subjs	%*	Events	Subjs	%*	%
Metabolism and Nutrition Disorders	0	0	0.0%	1	1	1.0%	-1.0%
Musculoskeletal and Connective Tissue Disorders	16	13	6.2%	7	6	6.3%	-0.1%
Neoplasms Benign, Malignant and Unspecified (Incl Cysts And Polyps)	3	3	1.4%	1	1	1.0%	0.4%
Nervous System Disorders	4	4	1.9%	1	1	1.0%	0.9%
Product Issues	2	2	1.0%	1	1	1.0%	-0.1%
Psychiatric Disorders	2	2	1.0%	2	2	2.1%	-1.1%
Respiratory, Thoracic and Mediastinal Disorders	3	3	1.4%	3	2	2.1%	-0.7%
Skin And Subcutaneous Tissue Disorders	1	1	0.5%	0	0	0.0%	0.5%
Surgical and Medical Procedures	7	6	2.9%	2	2	2.1%	0.8%
Vascular Disorders	3	3	1.4%	1	1	1.0%	0.4%
*Percentage of subjects experiencing specific event.							

Device-related AEs and procedure-related AEs for the TDmITT population (115 TOPS™TOPS™; 53 Fusion) are shown by high-level term in **Table 23** and **Table 25**, respectively. Device-related and procedure-related AEs for the AT population (210 TOPS™; 96 Fusion) are shown by high-level term in **Table 24** and **Table 26**, respectively. It is noted that in **Tables 24** and **Table 26**, not all subjects had Month 24 AE reporting. Similar to the common AEs results, the most common types of device-related and procedure-related AEs in both treatments groups and analysis populations were in the categories of (1) musculoskeletal and connective tissue disorders, and (2) injury, poisoning, and procedural complications.

Table 23: All Device-Related AEs by High-Level Term Among TDmITT Analysis Set (N=168)

	TOPS™ (N=115)			Fusion (N=53)			Diff
	Events	Subjs	%*	Events	Subjs	%*	%
ALL	39	27	23.5%	29	20	37.7%	-14.3%
Infections and Infestations	1	1	0.9%	0	0	0.0%	0.9%
Injury, Poisoning and Procedural Complications	6	5	4.3%	6	6	11.3%	-7.0%
Investigations	1	1	0.9%	1	1	1.9%	-1.0%
Musculoskeletal and Connective Tissue Disorders	25	18	15.7%	17	13	24.5%	-8.9%
Nervous System Disorders	5	5	4.3%	2	2	3.8%	0.6%
Product Issues	1	1	0.9%	3	2	3.8%	-2.9%
*Percentage of subjects experiencing specific event.							

Table 24: All Device-Related AEs by High-Level Term Among AT Analysis Set (N=306)

	TOPS™ (N=210)			Fusion (N=96)			Diff
	Events	Subjs	%*	Events	Subjs	%*	%
ALL	60	45	21.4%	43	27	28.1%	-6.7%
General Disorders and Administration Site Conditions	0	0	0.0%	1	1	1.0%	-1.0%
Infections and Infestations	1	1	0.5%	0	0	0.0%	0.5%
Injury, Poisoning and Procedural Complications	8	7	3.3%	6	6	6.3%	-2.9%
Investigations	1	1	0.5%	1	1	1.0%	-0.6%
Musculoskeletal and Connective Tissue Disorders	34	26	12.4%	24	18	18.8%	-6.4%
Nervous System Disorders	12	11	5.2%	7	5	5.2%	0.0%
Product Issues	4	4	1.9%	3	2	2.1%	-0.2%
Vascular Disorders	0	0	0.0%	1	1	1.0%	-1.0%
*Percentage of subjects experiencing specific event.							

Table 25: All Procedure Related AEs by High-level Term Among TDmITT Analysis Set (N=168)

	TOPS™ (N=115)			Fusion (N=53)			Diff
	Events	Subjs	%*	Events	Subjs	%*	%
ALL	102	57	49.6%	73	32	60.4%	-10.8%
Blood and Lymphatic System Disorders	0	0	0.0%	3	2	3.8%	-3.8%
Cardiac Disorders	0	0	0.0%	2	1	1.9%	-1.9%
Eye Disorders	1	1	0.9%	0	0	0.0%	0.9%
Gastrointestinal Disorders	2	2	1.7%	2	2	3.8%	-2.0%
General Disorders and Administration Site Conditions	3	3	2.6%	2	2	3.8%	-1.2%
Infections and Infestations	4	4	3.5%	2	2	3.8%	-0.3%
Injury, Poisoning and Procedural Complications	23	20	17.4%	13	12	22.6%	-5.3%
Investigations	1	1	0.9%	3	2	3.8%	-2.9%
Musculoskeletal and Connective Tissue Disorders	47	31	27.0%	30	19	35.8%	-8.9%
Nervous System Disorders	13	10	8.7%	6	5	9.4%	-0.7%
Product Issues	1	1	0.9%	3	2	3.8%	-2.9%
Psychiatric Disorders	0	0	0.0%	1	1	1.9%	-1.9%
Renal and Urinary Disorders	4	4	3.5%	1	1	1.9%	1.6%
Respiratory, Thoracic and Mediastinal Disorders	2	2	1.7%	3	1	1.9%	-0.1%
Vascular Disorders	1	1	0.9%	2	1	1.9%	-1.0%
*Percentage of subjects experiencing specific event.							

Table 26: All Procedure Related AEs by High-level Term Among AT Analysis Set (N=306)

	TOPS™ (N=210)			Fusion (N=96)			Diff
	Events	Subjs	%*	Events	Subjs	%*	%
ALL	185	104	49.5%	110	49	51.0%	-1.5%
Blood and Lymphatic System Disorders	3	2	1.0%	3	2	2.1%	-1.1%
Cardiac Disorders	1	1	0.5%	2	1	1.0%	-0.6%
Eye Disorders	1	1	0.5%	0	0	0.0%	0.5%
Gastrointestinal Disorders	8	8	3.8%	3	3	3.1%	0.7%
General Disorders and Administration Site Conditions	5	5	2.4%	5	5	5.2%	-2.8%
Infections and Infestations	8	8	3.8%	3	3	3.1%	0.7%
Injury, Poisoning and Procedural Complications	34	30	14.3%	16	15	15.6%	-1.3%
Investigations	2	2	1.0%	3	2	2.1%	-1.1%
Metabolism and Nutrition Disorders	1	1	0.5%	0	0	0.0%	0.5%
Musculoskeletal and Connective Tissue Disorders	72	51	24.3%	48	29	30.2%	-5.9%
Nervous System Disorders	25	19	9.0%	13	10	10.4%	-1.4%
Product Issues	4	4	1.9%	3	2	2.1%	-0.2%
Psychiatric Disorders	2	2	1.0%	1	1	1.0%	-0.1%
Renal and Urinary Disorders	7	7	3.3%	3	3	3.1%	0.2%
Respiratory, Thoracic and Mediastinal Disorders	5	5	2.4%	4	2	2.1%	0.3%
Skin and Subcutaneous Tissue Disorders	1	1	0.5%	0	0	0.0%	0.5%
Surgical and Medical Procedures	1	1	0.5%	0	0	0.0%	0.5%
Vascular Disorders	5	5	2.4%	3	2	2.1%	0.3%
*Percentage of subjects experiencing specific event.							

2. Effectiveness Results

Primary Endpoint – Clinical Composite Success

The primary endpoint was evaluated using a CCS endpoint at Month 24. Each subject was determined to achieve CCS if they met all of the following criteria:

- A reduction of 15 points or more in ODI;
- No new neurologic deficit, nor worsening and persistent neurologic deficit;
- No epidural steroid injection, facet joint injections, nerve block procedures or implantable spinal cord stimulator to treat back or leg pain symptoms at any lumbar level;

- Any TOPS™ subject was considered a failure if fusion occurs as defined in the radiographic protocol. Any control subject was considered a failure if fusion (as defined in the radiographic protocol) did not occur;
- No revision or removal of implants; [7]
- No supplemental fixation at the index level or at the immediately adjacent levels; [7]
- No occurrence of a major device related adverse event.

For endpoint evaluations of the TDmITT analysis set, subjects that began surgery but were intra-operatively changed to a non-study treatment were counted as overall Month 24 CCS failures but were not evaluated for the above components of the CCS.

The primary endpoint analysis was testing the study hypotheses using Bayesian posterior distribution with non-informative prior (Beta(1,1). The planned interim analysis used Bayesian posterior probability based on enrolled subjects at various stages of follow-up. The predefined criteria for triggering the interim analysis was met and the data was subsequently submitted to FDA. For subjects who had not yet reached the Month 24 visit and had unknown Month 24 CCS, a probability model was used to predict these subjects' CCS status at Month 24. However, due to lack of validation of the prediction model which generated a high percentage (about 50%) of the endpoint data (CCS at Month 24), FDA did not utilize the analysis results that were based on the model with predicted Month 24 CCS to support the PMA approval.

The applicant and FDA agreed on an interim analysis cohort to evaluate the TOPS™ System's safety and effectiveness. The interim analysis cohort, TDmITT, consists of subjects who were randomized, underwent surgery, and theoretically reached the Month 24 visit, which was the final study visit for safety and effectiveness analysis for this PMA application. The data comprising this interim analysis consists of 115 patients implanted with a TOPS™ device and 53 Fusion control patients. The TDmITT analysis set data are presented below and provide the data reviewed for PMA approval. Bayesian analysis performed on the 168 TDmITT subjects (with imputation for 14 missing Month 24 CCS data) yields a posterior probability of superiority > 0.9999 and 95% Bayesian Credible Interval for the difference [35.7%, 63.2%], demonstrating superiority of the TOPS™ compared to the Fusion control with respect to the primary endpoint CCS rates at Month 24. The observed CCS rates at Month 24 were 75.9% (82/108) for the TOPS™ group and 23.9% (11/46) for the Fusion group (difference 52.0%, $p<0.00000001$). Multiple imputation analysis in the same data set (115 TOPS™, 53 Fusion) showed a very similar between-group difference of 52.5% (95% CI 37.9% to 67.0%), with worst-case and best-case scenarios yielding a range of between-group differences from 37.3% to 56.6%, supporting the robustness of the superiority result with regard to missing endpoints.

[7] In this document the term "reoperations" is used to collectively refer to revisions, removals, and supplemental fixations.

As shown in **Table 27**, within the individual CCS components, the greatest between-group differences were found in:

- *ODI reduction of ≥15 points*: 94.7% (90/95) of TOPS™ and 78.8% (26/33) of Fusion subjects showed success in this CCS component, after excluding subjects with missing data (9 TOPS™ and 11 Fusion control subjects) and subjects who underwent a reoperation or lumbar injection before outcome measurement (11 TOPS™ and 9 Fusion control subjects).
- *No new or worse neurological deficit*: 97.2% (103/106) of TOPS™ and 87.8% (36/41) of Fusions subjects showed successes in this CCS component, after excluding subjects with missing data (9 TOPS™ and 12 Fusion control subjects).
- *Fusion status*: 98.1% (101/103) of TOPS™ and 56.4% (22/39) of Fusion subjects showed success in this CCS component, after excluding subjects with missing data (8 TOPS™ and 10 Fusion control subjects) and subjects who underwent a reoperation before outcome measurement (4 TOPS™ and 4 Fusion control subjects).

Table 27: Month 24 Composite Clinical Success Endpoint Summary (TDmITT)

	Number and Percentage Meeting Criteria						TOPS™ - Fusion [1]			
	TOPS™ (N=115)			Fusion (N=53)						
Endpoint	**N** [2]	**n**	**%**	**N** [2]	**n**	**%**	**Diff (%)**	**LB**	**UB**	**p** [3]
CCS: Multiple Imputation †	**115**	**--**	**76.7**	**53**	**--**	**24.3**	**52.5**	**37.9**	**67.0**	**<0.0001**
CCS: Observed Data Only	108	82	75.9	46	11	23.9	52.0	37.3	66.7	<0.00000001
Missing Month 24 CCS [4]	115	7	6.1	53	7	13.2	.	.	.	.
CCS: Worst Case ‡	115	82	71.3	53	18	34.0	37.3	22.2	52.5	<0.0001
CCS: Best Case ‡	115	89	77.4	53	11	20.8	56.6	43.3	70.0	<0.0001
No Intraoperative Failure [5]	115	115	100.0	53	52	98.1	1.9	-1.8	5.5	.
No Reoperation or Lumbar Injection	115	102	88.7	52	40	76.9	11.8	-1.1	24.6	.
No Reoperations [6]	115	110	95.7	52	46	88.5	7.2	-2.3	16.6	.
No Lumbar Injections (LI) [6]	115	104	90.4	52	46	88.5	2.0	-8.2	12.2	.
No Major Device Adverse Event [7]	103	97	94.2	39	37	94.9	-0.7	-9.0	7.6	.
No Device Breakage, Disassembly, Screw Loosening [6,8]	103	97	94.2	40	38	95.0	-0.8	-9.0	7.3	.
No Increase in Spondylolisthesis Grade [9]	103	103	100.0	37	37	100.0	.	.	.	.
ODI Reduction of ≥15 Points [10]	95	90	94.7	33	26	78.8	15.9	1.3	30.6	.
No New or Worsening Neurological Deficit [11]	106	103	97.2	41	36	87.8	9.4	-1.1	19.9	.
No Sensory Deficit	105	102	97.1	41	37	90.2	6.9	-2.7	16.5	.
No Muscle Strength Deficit	105	105	100.0	41	41	100.0	.	.	.	.
No Straight Leg Raise Deficit	104	104	100.0	38	38	100.0	.	.	.	.
No Side Lying Femoral Stretch Deficit	97	97	100.0	36	35	97.2	2.8	-2.6	8.1	.
No Fusion Status Failure [7,12]	103	101	98.1	39	22	56.4	41.6	25.9	57.4	.

Notes:

† Multiple imputation (MI) model included simplified CCS at Week 6 and at Months 3, 6, 12, as well as age, sex, BMI, and baseline ODI, VAS back pain, VAS worse leg pain, ZCQ symptom severity score and ZCQ physical function score. Simplified CCS included

	Number and Percentage Meeting Criteria						TOPS™ - Fusion [1]			
	TOPS™ (N=115)			Fusion (N=53)						
Endpoint	**N [2]**	**n**	**%**	**N [2]**	**n**	**%**	**Diff (%)**	**LB**	**UB**	**p [3]**
ODI reduction ≥15 and terminal failures (reoperation, LI, major device adverse event). "n" is not reported since the results are averages over 20 MI data sets. The 95% CI and p-value account for between and within imputation variance.										
‡ Worst case assumes missing TOPS™ subjects as failures and missing Fusion subjects as successes. Best case is the reversed scenario.										
[1] Device group differences in proportions and 95% confidence intervals (CI) for group differences (95% CI of component endpoint not adjusted for multiplicity)										
[2] Number of subjects for each category. For individual CCS components, "N" includes all available data (i.e., all subjects with data for the component, even if subject has missing data for any other component). For some components, subjects who underwent reoperation or lumbar injection prior to the component measurement were excluded.										
[3] P-value from Fisher's exact test comparing TOPS™ to Fusion control										
[4] Month 24 CCS endpoint considered missing if overall CCS status cannot be determined; since success in the CCS endpoint requires success in every CCS component, overall CCS status cannot be determined when a subject is missing data for 1 or more components and is not otherwise considered a study failure due to failure on a component where data is available (e.g., reoperation).										
[5] Subjects intraoperatively changed to non-study treatment (i.e., intraoperative failures) are included in the Overall CCS endpoint as failures, but are excluded from individual CCS components.										
[6] Terminal Failure										
[7] Subject excluded if experienced a reoperation prior to outcome measurement										
[8] If device condition recorded as indeterminate, unable to assess, not applicable or not recorded, endpoint considered missing										
[9] Increase in Spondylolisthesis Grade defined as |change at Month 24| ≥ 25%, unless final result is Grade 1 (-25%, 25%), based on change from pre-op to Month 24 in TOPS™ patients and change from post-op to Month 24 in Fusion controls										
[10] Subject excluded if Reoperation or Lumbar Injection occurred prior to outcome measurement										
[11] Neurological deficit endpoint considered missing only if all four components equal to missing										
[12] Fusion defined as presence of bridging trabecular bone across the involved motion segment and angular motion <3° and translational motion <2 mm. If bony bridging is indeterminate/unable to assess, fusion assumed to not have occurred.										

As shown in **Figure 3: Subject Accountability Tree**, in the TDmITT analysis set, the 7 TOPS™ and 7 Fusion subjects without Month 24 CCS data were missing due to: death before Month 24 (n=1 TOPS™); no Month 24 visit but not yet overdue (thus not lost to follow-up; n=3 TOPS™, n=1 Fusion); and loss to follow-up or otherwise missing data for a CCS component (n=3 TOPS™, n=6 Fusion). To understand the robustness of the observed associations to the missing data, a worst-case scenario was evaluated in which all missing TOPS™ subjects (n=7) were considered CCS endpoint failures and all missing Fusion subjects (n=7) were considered CCS endpoint successes. In this worst-case scenario, TOPS™ maintains superiority to the Fusion control, with a worst-case composite clinical success rate of 71.3% (82/115) in TOPS™ and 34.0% (18/53) in Fusion and a between-group difference (95% CI) of 37.3% (22.2%, 52.5%). Therefore, results in the observed data are robust to missing information.

Highlighted Secondary Endpoints with Type I Error Control

The study pre-specified five "highlighted" secondary endpoints with Type I error control that were evaluated in a pre-specified order following demonstration of superiority on the primary CCS endpoint. By the closed testing principle, there was no need to adjust for multiple comparisons since the order of testing is pre-specified. A demonstration of superiority was achieved on the first two highlighted secondary endpoints (change in range of motion at 24 months and fusion status success at 24 months).

- Range-of-Motion: Greater range of motion through flexion-extension at the index level at Month 24;
- Fusion success: Any TOPS™ subject was considered a failure if fusion occurred as defined in the radiographic protocol. Any Control subject was considered a failure if fusion (as defined in the radiographic protocol) does not occur. This assessment was made by a core lab;
- Narcotics use: No narcotics use, epidural steroid injection, facet joint injections, nerve block procedures, or spinal cord stimulators to treat back or leg pain symptoms at any lumbar level up to Month 24;
- Neurologic deficit: No new neurologic deficit nor worsening and persistent neurological deficit at Month 24;
- Revision, Removal, Supplemental Fixation: Time to revision or removal or supplemental fixation at either the index level or adjacent level (based on logrank statistic).

Results for the highlighted secondary endpoints are presented in the TDmITT analysis set (N=115 TOPS™ and 53 Fusion).

Table 28: Summary of Results for Highlighted Secondary Endpoints (TDmITT)

Test Order	Highlighted Secondary Endpoint	Assessment	TOPS™ (N=115)		Fusion (N=53)		p [2]
			n [1]	Result	n [1]	Result	
1	Range of motion (ROM)	Change in ROM through flexion-extension from Pre-Op to Month 24 (mean; SD)	105	-0.01° (3.29)	39	-3.04° (2.94)	<0.00001
2	Fusion success [3]	% subjects with no fusion status failure at Month 24	103	98.1% (101/103)	39	56.4% (22/39)	<0.00000001
3	Pain management	% subjects with no use of opioids or lumbar injection at Month 24	107	83.2% (89/107)	45	75.6% (34/45)	0.366
4	Neurological deficit [3]	% subjects with no new neurologic deficit, nor worsening and persistent neurological deficit at Month 24	106	97.2% (103/106)	41	87.8% (36/41)	0.0386
5	Time to revision, removal, or supplemental fixation at index or adjacent level	Cumulative survival rate at Month 24, based on logrank statistic (%; SE)	115	95.6% (2.25)	53	86.8% (5.96)	0.0743 [4]
Notes:							

Test Order	Highlighted Secondary Endpoint	Assessment	TOPS™ (N=115)		Fusion (N=53)		p [2]
			n [1]	Result	n [1]	Result	
[1] For each endpoint, "n" represents the subjects among those in the TDmITT analysis set (115 TOPS™; 53 Fusion) with available data; note that Fusion Success presents all available data after exclusion of subjects who had a reoperation prior to endpoint measurement. [2] Unless otherwise noted, p-value is from Fisher's Exact test comparing TOPS™ to Fusion control. [3] This is also a CCS component; evaluation of success in this highlighted secondary endpoint used the same approach as evaluation of success for the corresponding CCS component. [4] Logrank p							

Highlighted Secondary Endpoint: Range of Motion through Flexion-Extension

In the TDmITT analysis set (115 TOPS™; 53 Fusion), data were available in 105/115 TOPS™ and 39/53 Fusion control subjects regarding change from baseline to 24 months in flexion extension range of motion at the index level. The difference (95% CI) between the TOPS™ group and Fusion control was 3.03 degrees (1.85, 4.22). This difference was statistically significant (Fisher's exact p<0.00001). The range of motion for the Fusion control group substantially decreased from baseline, as expected, over the first 12 months and this change was maintained through 24 months (-3.02 at 12 months and -3.04 at 24 months). The TOPS™ group demonstrated a similar range of motion at 24 months compared to baseline as the range of motion decreased at smaller rate (-0.13 at 12 months and -0.01 at 24 months). Therefore, these results demonstrate that patients treated with the TOPS™ System maintained a higher range of motion in flexion/extension compared to the Fusion control at Month 24, with TOPS™ patients retaining nearly all of their baseline motion (approximately 4 degrees), and the control group retaining little motion, consistent with the objectives of fusion.

Table 29: Summary of Radiographic Flexion Extension (F to E) (deg) at Baseline and Follow-up (TDmITT)

	TOPS™						Fusion						TOPS™ - Fusion[1]		
Index Level	N[2]	Mean	SD	Med	Min	Max	N[2]	Mean	SD	Med	Min	Max	Diff	LB	UB
Pre-Operative	115	3.89	2.82	3.3	0.3	11.9	51	4.43	3.17	4.4	0.1	14.4	-0.54	-1.52	0.43
Month 12	111	3.76	2.94	3.3	0.0	18.4	46	1.32	0.85	1.3	0.0	3.9	2.44	1.57	3.32
Month 24	105	3.88	2.95	3.2	0.1	20.9	40	1.17	0.76	1.2	0.0	2.8	2.71	1.77	3.65
Change from Pre-Op to Month 12	111	-0.13	3.36	-0.1	-10.5	8.3	45	-3.02	2.93	-2.9	-12.7	0.9	2.89	1.76	4.03
Change from Pre-Op to Month 24	105	-0.01	3.29	0.2	-9.8	9.5	39	-3.04	2.94	-2.5	-13.2	0.8	3.03	1.85	4.22
Notes: [1]Estimated mean difference and 95% confidence interval between TOPS™ and Fusion (95% CI not adjusted for multiplicity). [2]"N" represents the number of subjects among those in the TDmITT analysis set (N=115 TOPS™ and 53 Fusion) with available data															

Highlighted Secondary Endpoint: Fusion Success

Success in this highlighted secondary endpoint was defined as the absence of fusion for the TOPS™ group and as the presence of fusion for the Fusion control group. If bony bridging was indeterminate/unable to assess, fusion was assumed to not have occurred. If a subject experienced a reoperation prior to fusion status measurement at Month 24, this subject was excluded from the fusion status analysis at Month 24. This is also how fusion success was evaluated for the primary CCS endpoint.

Accounting for reoperations, the total number of subjects evaluable for fusion status success decreased by 8 total subjects (n=4 TOPS™ and n=4 Fusion control). Reoperations occurred in n=5 TOPS™ subjects (as shown in **Table 27** above), but fusion status was missing in 1 of these subjects. The other 4 TOPS™ subjects with reoperations had fusion absent (n=3) or fusion unable to assess (n=1) at Month 24. For Fusion control subjects, reoperations occurred in n=6 subjects, but fusion status was missing in 1 of these subjects, and Month 24 fusion status was measured before the reoperation in another of these subjects (thus this subject was included in the fusion status analysis, although the subject was considered a CCS failure because the reoperation occurred before reaching the full 24 months). The other 4 Fusion control subjects with reoperations had fusion absent (n=1), fusion present (n=2), or fusion unable to assess (n=1) at Month 24. In the analysis for this highlighted secondary endpoint, these n=4 TOPS™ and n=4 Fusion control subjects were excluded, therefore reducing the total number of subjects in the fusion success analysis from 107 to 103 TOPS™ subjects, and from 43 to 39 Fusion control subjects.

Fusion success was evaluated in the TDmITT analysis set (115 TOPS™; 53 Fusion) in 103 TOPS™ and 39 Fusion control subjects who had an observed fusion status and had not undergone a reoperation prior to outcome measurement at Month 24. For the 103 TOPS™ subjects, n=100 showed fusion absent, n=2 showed fusion present, and n=1 was unable to assess. For the 39 Fusion control subjects, n=13 showed fusion absent, n=22 showed fusion present, n=4 were unable to assess. In both treatment groups, “unable to assess” status occurred due to bony bridging being indeterminate or unable to assess, so fusion was assumed to not have occurred in these subjects. In sum, fusion success occurred in 98.1% (101/103) of TOPS™ subjects and 56.4% (22/39) of Fusion control subjects. The difference (95% CI) in fusion success rate was 41.6% (25.9%, 57.4%) in favor of TOPS™, and the result was statistically significant (Fisher’s exact $p<0.00000001$). Therefore, TOPS™ demonstrated superior performance compared to the Fusion control treatment in achieving the intended fusion status (for TOPS™: fusion absent; for Fusion control: fusion present).

For completeness and transparency of subject accounting, all available fusion status data were provided regardless of reoperation or not. In the TDmITT analysis set (115 TOPS™; 53 Fusion), 107/115 TOPS™ and 43/53 Fusion control

subjects had an observed fusion status at Month 24. In the TOPS™ group, fusion was absent in 103/107 subjects, present in 2/107, and unable to be assessed in 2/107. In the Fusion control group, fusion was absent in 14/43 subjects, present in 24/43, and unable to be assessed in 5/43. If fusion success had been analyzed without the exclusion, the results would be similar to the results with the exclusion: fusion status success in 105/107 (98.1%) TOPS™ subjects and 24/43 (55.8%) Fusion control subjects.

Highlighted Secondary Endpoint: Pain Management

The third highlighted secondary endpoint pertained to pain management, and in particular evaluated the percentage of subjects who did not use opioids or lumbar injection (LI) at Month 24. In the TDmITT analysis set (115 TOPS™; 53 Fusion), data regarding use of opioids or LI at Month 24 was available for 107 TOPS™ and 45 Fusion control subjects. Among these subjects, 83.2% (89/107) of TOPS™ and 75.6% (34/45) of Fusion control subjects did not use opioids or undergo lumbar injections. The difference between the TOPS™ and Fusion control groups was not statistically significant (Fisher's exact p=0.366). Therefore, TOPS™ did not show superiority compared to the Fusion control with respect to use of opioids or LI for pain management.

Highlighted Secondary Endpoint: Neurologic Deficit

In the TDmITT analysis set (N=115 TOPS™ and 53 Fusion), 24-month neurological deficit data were available for 106 TOPS™ and 41 Fusion subjects. Among these subjects, 97.2% of TOPS™ subjects (103/106) and 87.8% of Fusion control subjects (36/41) demonstrated no new worsening or neurological deficit at 24 months. The difference in favor of the TOPS™ group was statistically significant (p=0.0386). Superiority was not claimed because the hierarchical assessment had already ended.

Highlighted Secondary Endpoint: Time to Revision, Removal or Supplemental Fixation at Index or Adjacent Level

In the TDmITT analysis set (N=115 TOPS™ and 53 Fusion), data were available for all subjects for the fifth highlighted secondary endpoint, i.e., time to revision, removal or supplemental fixation at either the index level or adjacent level (based on a log-rank statistic). Among the 115 TOPS™ and 53 Fusion control subjects included in this analysis, there were 5 failures in the TOPS™ group: 3 failures at 1 month, 1 failure at 7 months, and 1 failure at 17 months. In the Fusion group, there were 6 failures, 1 failure at the following post-operative time points: 1 month, 2 months, 5 months, 10 months, 21 months, and 24 months. The between-group difference were not statistically significant, and superiority was not achieved.

Additional Secondary Endpoints

In addition, the following secondary endpoints were pre-specified and assessed:

- Individual components of Month 24 CCS, including: ODI reduction of ≥15 points, no new neurological deficit nor worsening and persistent neurological deficit, fusion status success, no reoperations (revision or removal of implants and supplemental fixation), and no major device-related adverse events;
- 20 mm improvement in VAS values for back pain and Worst Leg pain as compared to baseline;
- ZCQ findings;
    - Improvement of ≥0.5 in ZCQ physical function score and symptom severity score, and subject satisfaction[9] score of ≤2.5 at Month 24 where 1 is very satisfied and 4 is very dissatisfied,
    - Two component ZCQ success defined as meeting ≥2 individual ZCQ success criteria.
    - Three component ZCQ success defined as meeting all three individual ZCQ success criteria.
- Reduction in physical component score on SF-12;
- Mean length of hospital stay, mean surgery time (skin-to-skin), blood loss and narcotic use for lower back pain and leg pain;
- Range of motion in flexion/extension will be evaluated at the index and immediately adjacent levels at Month 24 to evaluate the effect of the treatment. This result will be monitored as an additional outcome and will be separately compared with the subject's physical functioning (Oswestry, Zurich and VAS) scores.

All secondary endpoint outcomes are reported below in the TDmITT analysis set (N=115 TOPS™ and 53 Fusion).

Table 30: Summary of Results for Additional Secondary Endpoints (TDmITT)

Additional Secondary Endpoint	TOPS™ (N=115)	Fusion (N=53)
ODI Reduction of ≥15 points [1]	94.7% (90/95)	78.8% (26/33)
No New Neurological Deficit Nor Worsening and Persistent Neurological Deficit [2]	97.2% (103/106)	87.8% (36/41)
Fusion Status Success [3]	98.1% (101/103)	56.4% (22/39)
No Reoperations (Revision or Removal of Implants and Supplemental Fixation) [4]	95.7% (110/115)	88.5% (46/52)
No Major Device Related Adverse Events [5]	94.2% (97/103)	94.9% (37/39)
VAS [6]		
20 mm improvement in Worst Leg Pain	90.5% (86/95)	87.5% (28/32)
20 mm improvement in Low Back Pain	85.3% (81/95)	62.5% (20/32)
ZCQ [7]		

[9] Note, a baseline score for the ZCQ satisfaction was not collected at baseline since this component cannot be assessed until after treatment.

Additional Secondary Endpoint	TOPS™ (N=115)	Fusion (N=53)
Improvement of ≥ 0.5 in physical function score	92.6% (88/95)	84.8% (28/33)
Improvement of ≥ 0.5 in symptom severity score	94.7% (90/95)	84.8% (28/33)
Score of ≤ 2.5 in subject satisfaction at Month 24	92.6% (88/95)	87.9% (29/33)
Two component ZCQ Success (achieving success on 2 of 3 ZCQ components)	91.6% (87/95)	84.8% (28/33)
Three component ZCQ Success (achieving success on all three ZCQ components)	89.5% (85/95)	78.8% (26/33)
Reduction in Physical Component Score on SF-12 (mean improvement at Month 24 compared to baseline) [8]	23.2 ± 12.8 points (n=93)	16.8 ± 14.3 points (n=32)
Mean Length of Hospital Stay (days) [9]	3.06 days (n=115)	3.21 days (n=52)
Mean Surgery Time (minutes) [10]	193.3 min. (n=115)	177.2 min. (n=53)
Mean Blood Loss (cc) [11]	223.6 cc (n=115)	231.2 cc (n=53)
Correlation between range of motion in flexion/extension compared to subject's physical functioning (ODI, ZCQ, and VAS) score	No significant correlation between physical function score and flexion / extension ROM	No significant correlation between physical function score and flexion / extension ROM

Notes

[1] Data for ODI score change from baseline to M24 were analyzed in 95/115 TOPS™ and 33/53 Fusion subjects, accounting for 9 TOPS™ and 11 Fusion subjects with missing data and after excluding data for 11 TOPS™ and 9 Fusion subjects who underwent a reoperation or lumbar injection prior to outcome measurement.

[2] Data for 24-month neurological deficit were analyzed in 106/115 TOPS™ and 41/53 Fusion subjects, accounting for 9 TOPS™ and 12 Fusion subjects with missing data.

[3] 24-month fusion success data were analyzed in 103/115 TOPS™ and 39/53 Fusion subjects, accounting for 8 TOPS™ and 10 Fusion subjects with missing data and after exclusion of data for 4 TOPS™ and 4 Fusion subjects who underwent a reoperation prior to outcome measurement.

[4] 24-month data for revision or removal of implants and supplemental fixation ("reoperations") were analyzed in 115/115 TOPS™ subjects and 52/53 Fusion subjects; 1 Fusion subject was intraoperatively changed to a non-study treatment and by definition could not have experienced a reoperation.

[5] Data for major device related adverse events by Month 24 were analyzed in 103/115 TOPS™ and 39/53 Fusion subjects, after accounting for 11 TOPS™ and 10 Fusion subjects with missing data and after excluding data for 1 TOPS™ and 4 Fusion subjects who underwent a reoperation prior to outcome measurement.

[6] 24-month VAS data for worst leg pain and low back pain were available for 95 TOPS™ and 32 Fusion subjects

[7] 24-month ZCQ data were available for 95 TOPS™ and 33 Fusion subjects

[8] 24-month SF-12 physical component data were available for 93 TOPS™ and 32 Fusion subjects

[9] Data for length of hospital stay were available for 115/115 TOPS™ and 52/53 Fusion subjects; 1 Fusion subject was intraoperatively changed to a non-study treatment and had no follow-up after the conversion

[10] Data for surgery time were available for 115/115 TOPS™ and 53/53 Fusion subjects

[11] Data for blood loss were available for 115/115 TOPS™ and 53/53 Fusion subjects

Additional Secondary Endpoint: ODI Reduction of ≥ 15 points

In the TDmITT analysis set (N=115 TOPS™ and 53 Fusion), Month 24 ODI score data were available for 95 TOPS™ and 33 Fusion subjects, after exclusion of any subjects who underwent a reoperation or lumbar injection prior to outcome measurement.

ODI improvement greater than 15 points at Month 24 for the TOPS™ and Fusion control groups was assessed. Overall, 94.7% (90/95) of the TOPS™ group and 78.8% (26/33) of the Fusion control group experienced an improvement of more than 15 points at Month 24. This responder analysis is consistent with how the metric is reported in the primary CCS table (**Table 27**).

Additional Secondary Endpoint: No New Neurological Deficit Nor Worsening and Persistent Neurological Deficit

In the TDmITT analysis set (N=115 TOPS™ and 53 Fusion), 24-month neurological deficit data were available for 106 TOPS™ and 41 Fusion subjects. Among these subjects, 97.2% (103/106) of TOPS™ subjects and 87.8% (36/41) of Fusion control subjects demonstrated no new or worsening neurological deficit at Month 24. Overall, the primary sources of advantage for TOPS™ were related to sensory deficit and, to a small degree, the femoral stretch test. No subjects in either group demonstrated deterioration in muscle strength or straight leg raise results. This responder analysis is consistent with how the metric is reported in the primary CCS table (**Table 27**), the highlighted secondary endpoints (**Table 28**) and **Table 30**, above.

Additional Secondary Endpoint: Fusion Status Success

In the TDmITT analysis set (N=115 TOPS™ and 53 Fusion), 103 TOPS™ subjects and 39 Fusion subjects had available data for fusion status, after exclusion of subjects who experienced a reoperation prior to outcome measurement. Among these subjects, 98.1% (101/103) of TOPS™ subjects and 56.4% (22/39) of control subjects were determined to be fusion status successes. This responder analysis is consistent with how the metric is reported in the primary CCS table (**Table 27**), the highlighted secondary endpoints (**Table 28**) and **Table 30**, above.

Additional Secondary Endpoint: No Reoperations (Revision or Removal of Implants and Supplemental Fixation)

Overall in the TDmITT analysis set (N=115 TOPS™ and 53 Fusion), 95.7% (110/115) of TOPS™ subjects and 88.5% (46/52[10]) of Fusion subjects did not experience revision, removal, or supplemental fixation within 24 months. The reasons for these interventions are presented in the following tables.

[10] Excludes the n=1 Fusion subject who was intraoperatively changed to non-study treatment and by definition could not have experienced a reoperation event

Table 31: Reoperations by Month 24 (TDmITT)

Category	Reason for Reoperation	TOPS™ Events**	Fusion* Events**
Revision	Unresolved Pain	1	1
	Adjacent Segment Disease	0	1
	Screw Loosening/Implant Migration	0	1
	Durotomy	1	0
	Pedicle Screw Misplacement	1	0
Removal	Durotomy	2	0
	Screw Loosening/Implant Migration	1	0
Supplemental Fixation***	Adjacent Segment Disease	0	2
	Unresolved Pain	0	2

* One subject in the Fusion group underwent 2 supplemental fixation procedures, both for unresolved pain.
** Two subjects (1 TOPS™ / 1 Fusion) underwent more than 1 reoperation.
*** One reoperation in the TOPS™ group is not included in this summary as it was a planned procedure (continuation of anterior/posterior fusion).

Table 32: Summary of Reoperations by Month 24 (TDmITT)

	TOPS™ (N=115) [1]				Fusion (N=52) [2]			
	Events	**Subjs**	**% [3]**	**Avg Days**	**Events**	**Subjs**	**% [3]**	**Avg Days**
Durotomy	3	2	1.7%	15	0	0	0.0%	0
Adjacent Segment Disease	0	0	0.0%	0	3	3	5.8%	380
Pedicle Screw Misplacement	1	1	0.9%	5	0	0	0.0%	0
Screw Loosening / Implant Migration	1	1	0.9%	469	1	1	1.9%	32
Unresolved Pain	1	1	0.9%	197	3	2	3.8%	323
ALL	**6**	**5 [2]**	**4.3%**	**172**	**7**	**6**	**11.5%**	**245**

Notes:
[1] One reoperation in the TOPS™ group is not included in this summary as it was a planned procedure (continuation of anterior/posterior fusion).
[2] Excludes the n=1 Fusion subject who was intraoperatively changed to non-study treatment and by definition could not have experienced a reoperation event
[3] Percentage of subjects experiencing specific event

Additional Secondary Endpoint: No Major Device Related Adverse Event

At Month 24, in the TDmITT analysis set (N=115 TOPS™ and 53 Fusion), major device-related adverse event data were available for 103/115 TOPS™ and 39/53 Fusion subjects, after accounting for 11 TOPS™ and 10 Fusion subjects with missing endpoint data and after exclusion of device condition data for 1 TOPS™ and 4 Fusion subjects who underwent a reoperation prior to outcome measurement. Among these subjects, 94.2% (97/103) TOPS™ and 94.9% (37/39) Fusion subjects experienced no major device-related adverse event.

Additional Secondary Endpoint: 20 mm Improvement in VAS for Worst Leg Pain and Low Back Pain

In the TDmITT analysis set (N=115 TOPS™ and 53 Fusion), VAS data for Worst Leg were available for all subjects at baseline, and for 95 TOPS™ and 32 Fusion subjects at Month 24.

VAS score improvement of at least 20 points at follow-up for the TOPS™ and Fusion control groups was evaluated. Results are reported for all patients in the TDmITT analysis set (115 TOPS™; 53 Fusion) with available VAS data at baseline and the 24-month follow-up, 95 TOPS™ and 32 Fusion subjects. Overall, 90.5% (86/95) of the TOPS™ group and 87.5% (28/32) of the Fusion control group experienced an improvement of at least 20 points at Month 24; this difference was not significant. Favorable trends were also observed in an exploratory analysis of mean VAS Worst Leg Pain by visit. Among the 95 TOPS™ and 32 Fusion subjects with data available at baseline and Month 24, both treatment groups achieved a substantial decrease in Worst Leg pain at 6 weeks compared to baseline (TOPS™: -70.4 ± 25.0; Fusion: -63.1 ± 25.4). In the timepoints after 6 weeks, there was minimal change in VAS scores for both the TOPS™ and Fusion control subjects.

In the TDmITT analysis set (N=115 TOPS™ and 53 Fusion), VAS data for Low Back Pain were available for all subjects at baseline, for 109 TOPS™ and 48 Fusion subjects at 6 weeks, and for 95 TOPS™ and 32 Fusion subjects at Month 24. At the 6-week follow-up time point, 78.9% (86/109) of TOPS™ subjects demonstrated an improvement greater than 20 points in VAS lower back pain scores compared to only 60.4% (29/48) of Fusion control subjects. This treatment benefit was maintained throughout Month 24 where 85.3% (81/95) of TOPS™ subjects demonstrated an improvement greater than 20 points in VAS lower back pain scores compared to only 62.5% (20/32) of Fusion control subjects.

Additional Secondary Endpoint: ZCQ Findings

The following ZCQ findings were evaluated at Month 24:

- Improvement of ≥0.5 in ZCQ physical function score and symptom severity score, and a subject satisfaction score of ≤2.5 at Month 24, where 1 is very satisfied and 4 is very dissatisfied,
- Two component ZCQ success defined as meeting ≥2 individual ZCQ success criteria.
- Three component ZCQ success defined as meeting all three individual ZCQ success criteria.

In the TDmITT analysis set (N=115 TOPS™ and 53 Fusion), ZCQ symptom severity score data were available at baseline for all subjects, for 109 TOPS™ and 48 Fusion subjects at 6 weeks, and for 95 TOPS™ and 33 Fusion subjects at Month 24. Specifically, at the 6-week follow-up time point, 96.3% (105/109) of TOPS™ subjects demonstrated at least 0.5-point improvement in ZCQ symptom

score compared to 91.7% (44/48) of Fusion control subjects. At Month 24, 94.7% (90/95) of TOPS™ subjects demonstrated at least 0.5-point improvement in ZCQ symptom scores compared to 84.8% (28/33) of Fusion control subjects.

In the TDmITT analysis set (N=115 TOPS™ and 53 Fusion), ZCQ physical function score data were available at baseline for all subjects, for 110 TOPS™ and 48 Fusion subjects at 6 weeks, and for 95 TOPS™ and 33 Fusion subjects at Month 24. Results for ZCQ physical function score demonstrated that a higher proportion of TOPS™ subjects exhibited at least 0.5-point improvement in ZCQ physical score compared to Fusion control subjects, although the difference was not significant. Specifically, at the 6-week follow-up time point, 87.3% (96/110) of TOPS™ subjects demonstrated at least 0.5-point improvement in ZCQ physical function score compared to 75.0% (36/48) of Fusion control subjects. This trend was maintained throughout Month 24 where 92.6% (88/95) of TOPS™ subjects demonstrated at least 0.5-point improvement in ZCQ physical scores compared to 84.8% (28/33) of Fusion control subjects.

In the TDmITT analysis set (N=115 TOPS™ and 53 Fusion), ZCQ satisfaction data were available for 110 TOPS™ and 48 Fusion subjects at 6 weeks, and for 95 TOPS™ and 33 Fusion subjects at Month 24. ZCQ satisfaction score for the TOPS™ and Fusion control groups was assessed to determine whether patients were satisfied (at or below a raw score of 2.5 points) or dissatisfied (above a raw score of 2.5 points). At the 6-week follow-up time point, 97.3% (107/110) of TOPS™ subjects demonstrated a ZCQ satisfaction score less than or equal to 2.5-points compared to 95.8% (46/48) of Fusion control subjects. At Month 24, 92.6% (88/95) of TOPS™ subjects demonstrated a ZCQ satisfaction score less than or equal to 2.5-points compared to 87.9% (29/33) of Fusion control subjects.

At 6 weeks the rates of two component ZCQ success (defined as meeting 2 or more individual criteria as described above) for the TOPS™ group and the Fusion control group were similar (TOPS™: 96.4% (106/110); Fusion: 91.7% (44/48)). There were no substantial changes in two component ZCQ success for either the Fusion or control groups through Month 24 (TOPS™: 91.6% (87/95); Fusion: 84.8% (28/33)).

For three component ZCQ success (defined as meeting all 3 individual criteria as described above), in the TDmITT analysis set (N=115 TOPS™ and 53 Fusion), data were available for 109 TOPS™ and 48 Fusion subjects at 6 weeks, and 95 TOPS™ and 33 Fusion subjects at Month 24. At 6 weeks the rates of three component ZCQ success were 85.3% (93/109) for the TOPS™ group and 72.9% (35/48) for the Fusion control group. At Month 24, the three component ZCQ success rates were 89.5% (85/95) for the TOPS™ group and 78.8% (26/33) for the Fusion control group.

Although there was no eligibility criterion for baseline ZCQ score, all but 1 subject (167/168) in the TDmITT analysis set had a baseline ZCQ physical

function score of ≥ 2.0, indicating moderately impaired physical function, while 1 subject (randomized to the Fusion group) had baseline ZCQ physical function score <2.0, indicating mildly impaired physical function.

Additional Secondary Endpoint: Reduction in Physical Component Score on SF-12

SF-12 physical component scores were available in the TDmITT analysis set (N=115 TOPS™ and 53 Fusion) for 114 TOPS™ and 52 Fusion subjects at baseline, and for 93 TOPS™ and 32 Fusion subjects at Month 24. Among these subjects, baseline SF-12 physical component scores for the TOPS™ group and the Fusion control group were similar, with only a mean (95% CI) difference of -2.5 (-4.8, -0.2). The average SF-12 physical component score for the TOPS™ group increased from 24.5 ± 7.0 at baseline to 48.1 ± 11.4 at Month 24 with an overall increase of 23.2 ± 12.8 points. The average SF-12 physical component score for the Fusion control group increased from 27.9 ± 6.9 at baseline to 44.3 ± 13.5 at Month 24 with an overall increase of 16.8 ± 14.3 points.

Additional Secondary Endpoint: Length of Hospital Stay, Surgery Time and Blood Loss

In the TDmITT analysis set (N=115 TOPS™ and 53 Fusion), data for length of hospital stay, surgery time, and blood loss were available for all subjects (except that length of hospital stay was not available for the n=1 Fusion subject who was intraoperatively changed to a non-study treatment, as this subject did not have follow-up after the conversion). As shown in **Table 30** above, the mean time in surgery was similar between the TOPS™ group (193.3 minutes) and the Fusion group (177.2 minutes) with a difference of 16.2 minutes. In addition, subjects in both groups lost a similar amount of blood on average (223.6 cc in the TOPS™ group and 231.2 cc in the Fusion group). Subjects in both groups also had a similar mean hospital stay length, approximately 3 days.

Additional Secondary Endpoint: Range of Motion in Flexion/Extension Compared to Subject's Physical Functioning (Oswestry, Zurich, and VAS) Score

The correlation between baseline radiographic flexion extension total range of motion and the subject's physical function scores at baseline, 12 months post-operatively (Month 12), and Month 24, as well as the change from baseline to Month 12 months and Month 24 were assessed in the TDmITT analysis set (N=115 TOPS™ and 53 Fusion) for all subjects with available endpoint data at each follow-up. The results demonstrated that there was no significant correlation between the subject's physical function scores and the flexion extension total range of motion as all rho values were less than ± 0.5.

Additional Analyses of Observed Data Collected

The following clinical parameters were evaluated on the subset cohorts available for analysis:

- Change in disc height
- Association between preoperative narcotics use and functional and pain outcomes
- Change in use of narcotics between device groups
- Translation on radiographs
- Lateral bending on radiographs
- Use of any pain medications
- Use of narcotics
- Mean ODI score
- Major device-related adverse events without exclusions

Additional Analysis: Change in Disc Height

The radiographic average disc height at baseline and Month 24 for the TOPS™ and Fusion control groups, the anterior disc height at baseline and Month 24, as well as the posterior disc height at baseline and Month 24 were assessed in the TDmITT analysis set (N=115 TOPS™ and 53 Fusion) for all subjects with available endpoint data at each follow-up. At the index level at post-op, the mean (95% CI) difference in average disc height between the TOPS™ and Fusion control group was -0.31 (-0.95, 0.33) mm. The TOPS™ group decreased in average disc height by only 0.73 mm from post-op to Month 24, compared to 1.42 mm for the control.

Additional Analysis: Association Between Preoperative Narcotics Use and Functional and Pain Outcomes

An assessment of the patient reported outcomes for pain stratified by preoperative narcotic use was completed as summarized below in the TDmITT analysis set (N=115 TOPS™ and 53 Fusion) for all subjects with available endpoint data at each follow-up. Specifically, ODI, VAS score for Worst Leg pain, ZCQ findings, as well as the physical SF-12 scores were evaluated. No significant differences in outcomes were discovered between the subset populations of the TOPS™ and Fusion control groups with available data at Month 24.

Additional Analysis: Change in Use of Narcotics Between Device Groups

In general, in the TDmITT analysis set (N=115 TOPS™ and 53 Fusion) for all subjects with available endpoint data at each follow-up, subjects who did not utilize narcotics pre-operatively did not continue using narcotics after 3 months. Among the no pre-operative narcotics use group, at 3 months post-operatively 10.5% (9/86) of TOPS™ subjects and 9.1% (3/33) of Fusion control subjects utilized narcotics. For subjects who did utilize narcotics pre-operatively, more

Fusion control subjects continued to use narcotics at 3, 6, 12, and 24 months post-operatively compared to TOPS™ subjects.

Additional Analysis: Translation and Lateral Bending

Range of motion data were collected for translation and lateral bending, and these data were evaluated as a supplementary exploratory analysis.

Translation. In the TDmITT analysis set (115 TOPS™; 53 Fusion), data were available for 105/115 TOPS™ and 38/53 Fusion control subjects regarding change from baseline to Month 24 in translation at the index level. The difference (95% CI) between the TOPS™ group and the Fusion control was 0.67 mm (0.27, 1.06). Specifically, translation motion for the Fusion control group decreased by 0.79 mm from baseline to Month 24, and the TOPS™ group decreased by 0.13 mm from baseline to Month 24. Therefore, the results indicated that patients treated with the TOPS™ System maintained more translation motion compared to the Fusion control at Month 24.

Lateral bending. In the TDmITT analysis set (115 TOPS™; 53 Fusion), data were available for 79/115 TOPS™ and 29/53 Fusion control subjects regarding change from baseline to Month 24 in lateral bending at the index level. The difference (95% CI) between the TOPS™ group and the Fusion control at the index level was 2.49 degrees (1.15, 3.84). Specifically, the lateral bending range of motion for the Fusion control group decreased by 2.18 degrees from baseline to Month 24, and the TOPS™ group increased by 0.32 degrees from baseline to Month 24. Therefore, these results indicated that patients treated with the TOPS™ System maintained more lateral bending motion compared to the Fusion control at Month 24.

Additional Analysis: Use of Any Pain Medication and Use of Narcotics

Pain management data were collected at baseline and at each post-operative follow-up regarding use of any pain medication and use of opioids alone, and these data were evaluated as a supplementary exploratory analysis.

Any pain medication. In the TDmITT analysis set (115 TOPS™; 53 Fusion), baseline data for any pain medication use were available for all subjects and Month 24 data were available in 107 TOPS™ and 45 Fusion subjects. At Month 24, 46.7% (50/107) of TOPS™ subjects utilized any pain medication compared to 80.9% (93/115) of subjects at pre-op. In comparison, for subjects in the Fusion control group, 60.0% (27/45) used pain medication at Month 24 compared to 86.8% (46/53) of subjects using pain medication at pre-op.

Opioids alone. In the TDmITT analysis set (115 TOPS™; 53 Fusion), baseline data for opioid use were available for all subjects and 24-month data were available in 107 TOPS™ and 45 Fusion subjects. At Month 24, 11.2% (12/107) of

TOPS™ subjects utilized opioid pain medication compared to 23.5% (27/115) of subjects at pre-op. In comparison, for subjects in the Fusion control group, 17.8% (8/45) used opioids at Month 24 compared to 32.1% (17/53) at pre-op.

Additional Analysis: Mean ODI Score

In the TDmITT analysis set (115 TOPS™; 53 Fusion), among subjects with data available at 24 months, TOPS™ subjects (N=95) demonstrated an average (±SD) ODI score of 9.3 ± 14.0 indicating minimal disability where the subject can cope with most living activities. In comparison, at Month 24, Fusion control subjects (N=33) demonstrated an average (±SD) ODI score of 19.1 ± 21.4 indicating that these subjects experienced more pain and difficulty with sitting, lifting, and standing.

Additional Analysis: Major Device-Related Adverse Events Without Exclusions

All available major device-related adverse event data without exclusions were analyzed. In the TDmITT analysis set (115 TOPS™; 53 Fusion), device condition information was available for 107 TOPS™ and 43 Fusion subjects. Among these subjects, 91.6% of TOPS™ devices (98/107) were intact, 5.6% (6/107) were determined to have loose screws as defined as radiographic lucency, and 2.8% (3/107) were unable to be assessed at Month 24. Comparatively, 97.7% (42/43) of the Fusion control devices were determined to be intact at Month 24 with 1/43 (2.3%) Fusion control device unable to be assessed. An additional 2 Fusion control subjects experienced a major device adverse event, with n=1 showing loose screws at 3, 6, and 12 months post-operatively, and n=1 showing fractured hardware at 6 and 12 months post-operatively; although these 2 Fusion control subjects had theoretically reached Month 24, neither had attended their Month 24 visit yet at time of database lock. These Fusion control subjects are considered failures for the primary CCS endpoint, because screw loosening and device fracture are terminal failures.

Post-operative radiographs for all subjects identified as having pedicle screw loosening were reviewed in more granular detail and the following assessments for each were made:

- Radiolucency: Radiolucent line around the pedicle screw > 1mm surrounding the bone screw interface.
- Double Halo: Radiolucent rim surrounding the screw which is framed by a radiopaque dense bone trabeculae.
- Screw Backing Out: Screwhead not flush with vertical plate, as these screws were omnidirectional this would be rare.
- Periosteal Reaction: New bone formation, typically linear, adjacent to the cortex.
- Bone Destruction: Loss of bone around screws which is more extensive longitudinally, shows and in particular extending in distance away from screw than typical "loosening."

- Variable Lucency: Lucency around screw which is not uniform. Typically, wider close to the surface and narrower as the screw extends deeper into bone.

Among the 6 screw loosening subjects with Month 24 data, all of whom are TOPS™ subjects, 4 of the 6 (67%) are asymptomatic and would otherwise be considered as a CCS success. Therefore, screw loosening, when defined as lucency, may not correlate with poorer clinical outcomes. Additionally, while lucencies were confirmed in the TOPS™ and Fusion control arm subjects, mechanical screw loosening, per standard orthopedic definitions, was not seen in any of the subjects.

Additional Subgroup Analyses (No Type I Error Control)

Performance on the primary composite clinical success outcome remained robust across subgroup analyses in the TDmITT analysis set (N=115 TOPS™ and 53 Fusion) for all subjects with available CCS endpoint data (108/115 TOPS™; 46/53 Fusion) for subgroups analyses based on age, BMI and history of prior index level surgery.

For subjects younger than 65 years old randomized to the TOPS™ and Fusion control groups (n=56 TOPS™, n=21 Fusion), the mean (95% CI) difference in CCS success rate between the TOPS™ and Fusion groups was 63.1% (43.5%, 82.7%). For subjects 65 and older (n=52 TOPS™, n=25 Fusion), the difference (95% CI) between the TOPS™ and Fusion groups for these subjects was 41.2% (19.6%, 62.8%). Therefore, these results are consistent with the primary endpoint analysis and suggest that patient age may not alter the likelihood of successful outcome if treated with TOPS™.

For subjects with a BMI below 30 kg/m^2 (n=52 TOPS™, n=24 Fusion), the difference (95% CI) in CCS success rate between the TOPS™ and Fusion groups was 47.8% (26.3%, 69.2%). For subjects with a BMI equal to or greater than 30 kg/m^2 (n=56 TOPS™, n=22 Fusion), the difference (95% CI) in CCS success rate between the TOPS™ and Fusion groups was 56.8% (37.1%, 76.5%). As in the subgroup analysis by age group, these results are consistent with the primary endpoint analysis and suggest that patient BMI may not alter the likelihood of successful outcome if treated with TOPS™.

3. Pediatric Extrapolation

In this premarket application, existing clinical data was not leveraged to support approval of a pediatric patient population.

E. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 C.F.R. Part 54) requires applicants who submit a marketing application to include certain information

concerning the compensation to, and financial interests and arrangements of, any clinical investigator conducting clinical studies covered by the regulation. Two (2) of the 37 study sites in the TOPS™ System pivotal clinical study had an investigator with a potential financial conflict of interest. In the primary analysis population (TDmITT, N=115 TOPS™, 53 Fusion), 13 TOPS™ and 8 Fusion subjects were treated at these 2 sites. There was no evidence of a difference in results for those patients treated by investigators with a financial interest versus those that did not have a financial interest.

XI. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

Clinical studies conducted outside of the US ("OUS") were provided as supplemental clinical evidence of the TOPS™ System's safety and effectiveness. There were six (6) prior, OUS investigations that evaluated the TOPS™ System:

1. Retrospective, Single-Center Study of 17 Patients Treated with TOPS™ (Vienna, Austria)
2. Prospective, Single Center, Non-Randomized Study of 10 Patients Treated with TOPS™ (Southampton, UK)
3. Prospective, Single Center, Non-Randomized Study of 15 Patients Treated with TOPS™ (Shaare Zedek, Israel)
4. Prospective, Single Center, Non-Randomized Study of up to 10 Patients Treated with TOPS™ (Halle, Germany)
5. Prospective, Single Center, Non-Randomized Study of 1 Patient Treated with TOPS™ (Nottingham, UK)
6. Retrospective, Single-Center Study of 4 Patients Treated with TOPS™ (Napan, Australia)

XII. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

In accordance with the provisions of section 515(c)(3) 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.

XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

The scientific evidence presented provides reasonable assurance that the TOPS™ System is safe and effective for patients between 35 and 80 years of age with symptomatic degenerative spondylolisthesis up to Grade I, with moderate to severe lumbar spinal stenosis and either the thickening of the ligamentum flavum and/or scarring of the facet joint capsule at one level from L3 to L5.

A. Effectiveness Conclusions

Success was achieved in the primary CCS endpoint, comprised of safety and effectiveness endpoints, based on a subset population of randomized subjects with 24 months of follow up after operative intervention (TDmITT). The composite clinical outcomes of the TDmITT population served as the basis of the regulatory decision for this PMA.

In subjects who theoretically reached 24 months after surgery (TDmITT analysis set, N=115 TOPS™, 53 Fusion), 108 TOPS™ and 46 Fusion control subjects had observed results for evaluation of CCS. Among these subjects, the TOPS™ group demonstrated a clinically meaningful and substantial advantage over the Fusion control group with 75.9% (82/108) of subjects randomized to the TOPS™ group achieving composite clinical success, compared to 23.9% (11/46) of subjects randomized to the Fusion control. Based on these results, the TOPS™ System was concluded to be superior to the Fusion control with respect to composite clinical success.

In addition, the TOPS™ System demonstrated superiority in the highlighted secondary endpoints for range of motion in flexion/extension and fusion status success which is not an unexpected result given that the control group treatment eliminates motion while the TOPS™ System is designed to be motion-sparing. The preoperative baseline for range of motion in flexion-extension was maintained in the TOPS™ System group through Month 24. Comparatively, flexion-extension range of motion in the Fusion control group decreased at Month 24 compared to preoperative baseline. Thus, these results suggest that the TOPS™ System is superior to the Fusion control in maintaining range of motion through flexion-extension.

Additionally, the TOPS™ System demonstrated superior performance compared to the Fusion control treatment in achieving the intended radiographic fusion status at 24 months (for TOPS™: fusion absent; for Fusion control: fusion present).

In conclusion, the study data indicate that, at Month 24, the TOPS™ System is superior to the control treatment (Fusion), for the subject population and indications studied in this investigation, in terms of overall success according to the protocol-specified primary endpoint.

B. Safety Conclusions

In the TDmITT analysis set (N=115 TOPS™ and 53 Fusion), the TOPS™ group exhibited comparable AE rates as compared to the Fusion control group. Although a numerically higher percentage of TOPS™ subjects experienced at least one SAE as compared to the Fusion control group (34.8% (40/115) of TOPS™ subjects and 28.3% (15/53) of Fusion control subjects), this difference was not statistically significant as the 95% confidence interval (not adjusted for multiplicity) included zero (0). The percentage of subjects experiencing device-related SAEs was numerically lower for the TOPS™ group than for the Fusion control group (6.1%

(7/115) of TOPS™ subjects and 9.4% (5/53) of Fusion control subjects). The lower device-related SAE rate for the TOPS™ group as compared to the Fusion control group suggests that the difference in SAE rates between the cohorts is not attributable to the TOPS™ device. Further, SAEs experienced by the TOPS™ group are consistent with known SAEs for spinal procedures and the relative rate of occurrence is consistent with, or better than, rates published in literature. Similar trends were observed in safety analyses of the As-Treated analysis set (N=210 TOPS™ and 96 Fusion) though not all subjects in this population had achieved 24 months of follow up.

In conclusion, the clinical study results demonstrate that the TOPS™ System is at least as safe as the Fusion control and that the device has a reasonable assurance of safety.

C. Benefit-Risk Determination

The probable benefits of the device are based on data collected in a clinical study conducted to support PMA approval as described above. The results of the study demonstrate these benefits as described below.

Summary of Benefits

The pivotal study for the TOPS™ System investigated the TOPS™ System compared to lumbar spinal fusion in subjects undergoing decompression surgery and instrumentation at a single lumbar level between L2 and L5 to alleviate leg pain, with or without back pain, stemming from the following conditions: (1) degenerative spondylolisthesis or retrolisthesis up to Grade I; (2) moderate to severe spinal stenosis (LSS); and (3) thickening of the ligamentum flavum and/or scarring of the facet joint capsule.

The assessments used for evaluating the safety and effectiveness of the TOPS™ System are standard, validated metrics commonly administered for evaluating spinal decompression surgery. The primary assessment was the CCS at Month 24, which included the following criteria:

- A reduction of 15 points or more in Month 24 ODI;
- No new neurologic deficit, nor worsening and persistent neurologic deficit;
- No epidural steroid injection, facet joint injections, nerve block procedures or implantable spinal cord stimulator to treat back or leg pain symptoms at any lumbar level;
- Any TOPS™ subject was considered a failure if fusion occurred as defined in the radiographic protocol. Any control subject was considered a failure if fusion (as defined in the radiographic protocol) did not occur;
- No revision or removal of implants;
- No supplemental fixation at the index level or at the immediately adjacent levels;
- No occurrence of a major device related adverse event.

The TOPS™ System presents several benefits over the current spinal fusion standard. Overall, among patients who theoretically reached Month 24 (TDmITT analysis set), TOPS™ demonstrated a substantial advantage over the control with respect to CCS. Among TDmITT subjects with observed CCS status (108/115 TOPS™ and 46/53 Fusion), TOPS™ demonstrated a 52.0% advantage, with 75.9% (82/108) of TOPS™ subjects and 23.9% (11/46) of control subjects meeting all elements required for composite clinical success, which exceeded the pre-determined metric for superiority. These results therefore established superiority of TOPS™ compared to the Fusion control for the intended patient population and indications for use.

Summary of Risks

The risks of the TOPS™ System are based on non-clinical laboratory studies as well as data collected in the clinical study conducted to support PMA approval as described above. Non-clinical testing demonstrated acceptable mechanical properties, biological safety, sterility, stability, and MR safety for the device's intended use. The clinical study conducted to support PMA approval demonstrated that the risks presented by the TOPS™ System are similar to those presented by Fusion for the same patient population. Across all randomized and treated subjects who theoretically reached Month 24 (the TDmITT analysis set), comparable percentages of TOPS™ subjects and Fusion control subjects experienced at least one AE, SAE, device-related AE, and device-related SAE. Although a higher rate of serious AEs was observed in the TOPS™ group (34.8% (40/115)) as compared to the Fusion control group (28.3% (15/53)), the rate of device-related SAEs was higher in the Fusion control group (9.4% (5/53)) compared to the TOPS™ group (6.1% (7/115)), indicating that the differences in SAEs in the clinical study were not attributable to the TOPS™ device. Additionally, no between-group difference in any of the AE outcomes showed statistical significance, as demonstrated by 95% confidence intervals that all included zero (0). The differences in the prevalence of AE severity were also comparable between the groups, with around half of all AEs being of mild severity, around one third moderate and one sixth severe for both treatment groups.

Similar trends were observed in the safety analyses of all randomized subjects who underwent surgery (the AT analysis set, N=210 TOPS™ and 96 Fusion) though not all of these subjects had achieved 24 months of follow up.

As an implant, the TOPS™ System presents two types of risks: risks associated with the implant itself and risks associated with the surgical implantation procedure. Possible adverse events in the post-operative phase include:

- Foreign body or allergic reaction, including adverse response to wear debris;
- Herniated nucleus pulposus;
- Heterotopic ossification;
- Implant breakage;
- Implant degradation;
- Implant disassembly;
- Implant displacement;

- Implant migration, subsidence, loosening or dislocation;
- Implant separation;
- Misplaced screws in pedicle
- Nerve root or spinal cord impingement or injury;
- Neurologic deterioration:
    - Clumsiness,
    - Foot drop,
    - Limp,
    - Numbness;
    - Short step,
    - Slow moving gait,
    - Weakness,
- Osteophyte resorption;
- Osteolysis or vertebral inflammation;
- Reoperation including revision, removal, or supplemental fixation;
- Vertebral overload resulting in device failure.

The 3 most common types of adverse events were (1) musculoskeletal and connective tissue disorders, (2) injury, poisoning and procedural complications, and (3) nervous system disorders. Specifically, in the TDmITT analysis set (115 TOPS™; 53 Fusion), 44.3% (51/115) of TOPS™ subjects compared to 52.8% (28/53) of Fusion control subjects experienced musculoskeletal and connective tissue disorders; 27.0% (31/115) of TOPS™ subjects and 32.1% (17/53) of Fusion control subjects experienced injury, poisoning, or procedural complications; and 16.5% (19/115) of TOPS™ subjects and 22.6% (12/53) of Fusion control subjects experienced nervous system disorders. There were 102 procedure-related adverse events in 57/115 subjects for TOPS™ (49.6% of TOPS™ subjects) and 73 events in 32/53 subjects in the Fusion control group (60.4% of Fusion control subjects).

1. Patient Perspectives

Patient perspectives considered for the TOPS™ System included results from the ODI, VAS and ZCQ questionnaires as described above. These patient reported outcomes were considered as part of the benefit-risk assessment for the subject devices, and as noted above, a greater proportion of subjects in the TOPS™ group reported improved pain and function post-treatment as compared to the subjects in the Fusion control group.

D. Overall Conclusions

The non-clinical and clinical data in this application support the reasonable assurance of safety and effectiveness of the TOPS™ System when used in accordance with the indications for use. Based on the clinical study results, it is reasonable to conclude that the clinical benefits of the use of the TOPS™ System in terms of improvement of pain and disability, and the potential for motion preservation, outweigh the risks, both in terms of the risk associated with the TOPS™ System and surgical procedure when

used in the indicated population in accordance with the directions for use, and as compared to the Fusion control subjects

XIV. CDRH DECISION

CDRH issued an approval order on June 15, 2023. The final conditions of approval cited in the approval order are described below.

The TOPS™ System Continued Follow-up Study: Based on the protocol outline dated December 1, 2022, this post-approval study (PAS) is intended to evaluate the long-term safety and effectiveness of the TOPS™ System compared to a lumbar spinal fusion control in up to 306 subjects in the modified Intent-to-Treat (mITT) analysis population (210 TOPS™ System subjects, 96 control subjects) who were enrolled in the pivotal study. The pivotal study is a prospective, randomized, concurrently controlled, multi-center study of the TOPS™ System compared to a lumbar spinal fusion control for treatment of leg pain with or without back pain at one vertebral level between L3 and L5. Subjects will be followed 60 months from the time of each patient's index surgery (Month 60).

The primary safety endpoints are serious adverse events (SAEs), and device- or procedure-related Adverse Events (AEs). Additional safety analyses will include the rate of AEs, including by relatedness to device or procedure and severity (mild, moderate or severe), time-to-event, including mean and ranges if applicable, and rate of reoperation, including by type of reoperation.

The primary effectiveness endpoint is a composite clinical success (CCS) responder endpoint based on clinical status at Month 60. An individual subject will be regarded as achieving Month 60 CCS only if s/he meets all of the following criteria at Month 60 compared to baseline:

1. A reduction of 15 points or more in Oswestry Disability Index (ODI) compared to baseline.

2. No new neurologic deficit, nor worsening and persistent neurologic deficit.

3. No epidural steroid injections, or reoperations.

4. Fusion status.

5. No occurrence of a major device related adverse event.

The data presentation and statistical analyses will be conducted using observed data on a minimum of 85% follow-up of the pivotal study cohort at 36-months, 48-months, and 60-months post-implantation.

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

XV. APPROVAL SPECIFICATION

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.

XVI. REFERENCES

1. Tuli SK, Yerby SA, Katz JN. Methodological Approaches to Developing Criteria for Improvement in Lumbar Spinal Stenosis Surgery. Spine, 31 no.11 (2006):1276-1280.