SUMMARY OF SAFETY AND PROBABLE BENEFIT (SSPB)

I. GENERAL INFORMATION

Device Generic Name: Vertebral Body Tethering System

Device Trade Name: The Tether™ – Vertebral Body Tethering System

Device Procode: QHP

Applicant's Name and Address: Zimmer Biomet Spine, Inc.
10225 Westmoor Drive
Westminster, Colorado 80021

Date(s) of Panel Recommendation: None

Humanitarian Device Exemption (HDE) Number: H190005

Humanitarian Use Device (HUD) Designation Number: DEV-2018-0410

Date of HUD Designation: March 28, 2019

Date of Notice of Approval to Applicant: August 16, 2019

II. INDICATIONS FOR USE

The Tether™ - Vertebral Body Tethering System is indicated for skeletally immature patients that require surgical treatment to obtain and maintain correction of progressive idiopathic scoliosis, with a major Cobb angle of 30 to 65 degrees whose osseous structure is dimensionally adequate to accommodate screw fixation, as determined by radiographic imaging. Patients should have failed bracing and/or be intolerant to brace wear.

Modifications from the HUD Designation

The indication for use statement has been modified from that granted for the HUD designation. The HUD designation was for "use in the treatment of juvenile and adolescent idiopathic scoliosis in patients, age 5 to 19 years, who are skeletally immature and have a Risser Score of less than 5, that require surgical treatment or have failed non-surgical treatments to obtain and maintain correction of severe, progressive spinal deformities with a Cobb angle of $\geq 30°$." It was modified for the HDE approval as follows: removed age ranges, as well as "juvenile and adolescent," as chronologic age and skeletal maturity vary among populations; added language to specify the patient should have dimensionally adequate osseous structures representative of the age range and diagnosis; removed reference to a specific skeletal maturity scoring system as there are different existing methods, and the HUD analysis was not closely linked to a specific method; and, identified a Cobb angle range to better reflect the study population. The resulting Indications for Use statement falls within the HUD designation.

III. CONTRAINDICATIONS

The Tether™ - Vertebral Body Tethering System should not be implanted in patients with the following conditions:

1. Presence of any systemic infection, local infection, or skin compromise at the surgical site;
2. Prior spinal surgery at the level(s) to be treated;
3. Known poor bone quality defined as a T-score -1.5 or less;
4. Skeletal maturity;
5. Any other medical or surgical condition which would preclude the potential benefit of spinal surgery, such as coagulation disorders, allergies to the implant materials, and patient unwillingness or inability to cooperate with post-operative care instructions.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in The Tether™ - Vertebral Body Tethering System labeling.

V. DEVICE DESCRIPTION

The Tether™ – Vertebral Body Tethering System is a non-fusion spinal device intended for treatment of idiopathic scoliosis. Newton[1] and Braun[2] demonstrated through non-clinical studies the viability of fusion-less treatment of scoliosis using a flexible tether to modulate spinal growth through the Hueter-Volkmann principle. Crawford and Lenke[3] first reported clinical use of anterior vertebral body tethering (AVBT) for correction of idiopathic scoliosis in a skeletally immature patient. Anchors and vertebral body screws are placed laterally from a thoracoscopic or thoracotomy approach into the vertebral body on the convex side of a spinal deformity. A SULENE® polyethylene terephthalate (PET) tensioning cord is secured to the vertebral body screws with set screws to connect the levels of the construct, as shown in Figure 1. The device provides a lateral tension band across the convex side of the spine that, on insertion and tensioning, partially corrects the curvature, and subsequently can arrest or correct the deformity through modulation of remaining spinal growth. In addition, The Tether™ – Vertebral Body Tethering System includes instrumentation for insertion, manipulation, and removal of the implants.

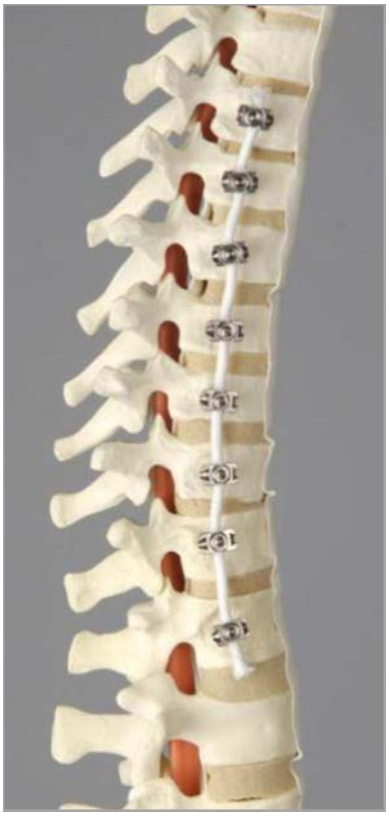
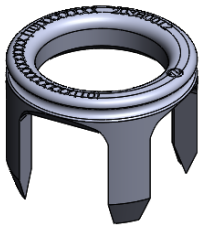
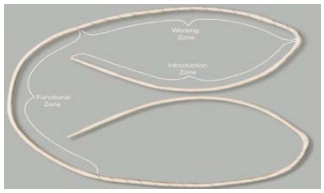


Figure 1: The Tether™ – Vertebral Body Tethering System on Spine Model

The Tether™ – Vertebral Body Tethering is available in a variety of screw diameters and lengths to accommodate a range of patient anatomies and to reflect the intended patient population. All implantable devices are provided sterile with the exception of the anchors. Instruments provided as part of The Tether™ – Vertebral Body Tethering System are provided to the end user non-sterile and must be sterilized prior to use. The available implant sizes as well as device materials are detailed below in Table 1.

Table 1: The Tether™ – Vertebral Body Tethering System Components, Sizes, and Materials

Device Type	Product Image	Sizes	Material
Vertebral Body Screw		Lengths: 20-50 mm (2.5 mm increments) Diameters: 5.5-7.0 mm (0.5 mm increments)	Ti-6Al-7Nb (ISO 5832-11) Hydroxyapatite (ISO 13779-2)
Set Screw		Diameter: 7 mm Height: 5.7 mm	Ti-6Al-4V ELI (ASTM F136)

Device Type	Product Image	Sizes	Material
Anchor		Diameter: 12 mm	Ti-6Al-4V ELI (ASTM F136)
Tensioning Cord		Diameter: 4.1 mm Implantable Length: 300 mm	Polyethylene terephthalate (PET)

Surgery for The Tether™ – Vertebral Body Tethering System begins with visualization of the vertebral body, after which instrumentation is used to prepare the vertebral body for anchor and screw placement. After preparation, the anchor is placed firmly against the outer cortical bone. The screw is then inserted and tightened, securing the components in place. Following placement and inspection of screws and anchors, at all levels, the tensioning cord is passed through the vertebral body screw tulip heads. Tensioning instrumentation is then used to pull the cord taut before tightening the set screws. This secures the cord in place and maintains tension between the screws, and achieves a lateral tension band across the convex side of the scoliotic spine. This tension band provides partial initial curve correction and is intended to arrest growth on the convex side of the spine, while allowing continued growth on the opposite side. This induced asymmetric growth modulation may, over time, provide additional correction depending on the amount of spinal growth remaining. If over-correction is observed, it is possible to surgically sever the tensioning cord, eliminating the lateral tension band effect.

The Tether™ - Vertebral Body Tethering System includes instruments to insert and manipulate the implants. Instruments specific to the implantation of The Tether™ – Vertebral Body Tethering System include anchor inserters and tensioners which are outlined in Table 2.

Table 2: The Tether™ – Vertebral Body Tethering System Device-Specific Instruments

Instrument	Image	Intended Use	Material
Anchor Inserter	 Anchor inserter with awl feature  Anchor inserter with tap feature	- Placement and implantation of anchor - Bone screw preparation	Stainless Steel per ASTM F899 and ASTM F564
Tensioner	 Example of the tensioner and counter-tensioner during use	Used with a counter-tensioner to accomodate a thoracoscopic approach. Tension is maintained until trigger is pulled to release tension. An indicator is provided to provide feedback on the tension applied (no tension-maximum tension).	Stainless Steel per ASTM F899 and ASTM F564

General surgical instruments to be used with The Tether™ – Vertebral Body Tethering

System include: Awls, Anchor Inserter Handles, Tap, Sounder, K-wire, Screw Drivers, Cord Alignment Rod, Torque Limiting handles, and an Extension Spring Tube.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

Idiopathic scoliosis is characterized by a lateral spinal curvature in excess of 10 degrees with vertebral rotation due to an unknown cause[4]. Management options for idiopathic scoliosis include observation with or without physical therapy, treatment with an external orthosis (brace), and surgical treatment, most commonly consisting of growing rods for younger children and posterior spinal instrumentation and fusion for adolescents.

VII. MARKETING HISTORY

The Tether™ - Vertebral Body Tethering System has not been marketed in the United States or any foreign country. However, it has been used in limited quantities through international special access pathways for the treatment of individual patients.

VIII. PROBABLE ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (i.e., complications) associated with the use of the device.

Potential device or procedure-related adverse events (AEs)

- Overcorrection of the coronal deformity, potentially requiring revision or removal of implants
- Inadequate curve correction
- Loss of curve correction
- Development of new curves above and/or below the instrumented levels
- Trunk imbalance
- Worsening of existing deformities in non-tethered spine segments
- Unintended spontaneous fusion at the instrumented levels
- Pulmonary complications including atelactasis, pneumonia or adverse events related to temporary single lung ventilation
- Anesthesia complications
- Wound infection, superficial or deep
- Wound dehiscence
- Damage to surrounding organs and structures including blood vessels, spinal cord, nerves, lungs, or vertebral bodies
- Vascular complications including bleeding, hemorrhage, or vascular damage leading to anemia or requiring blood transfusion
- Neurologic complications including damage to neurological structures, cerebrospinal fluid leakage, or meningocele
- Problems during device placement including anatomic/technical difficulty and device-sizing issues
- Loosening or migration of the implants
- Bending, fracturing, fraying, kinking, loosening, bending, or breaking of any or all implant components
- Fretting and crevice corrosion at interfaces between components

- Pain, discomfort, or abnormal sensations due to device presence
- Material sensitivity reactions and/or particulate wear debris

Systemic AEs

- Deep vein thrombosis
- Pulmonary embolism
- Atelectasis, pneumonia
- Cardiac AEs
- Dysphagia
- Dysphonia
- Gastrointestinal (ileus, ulceration, bleeding, malnutrition)
- Foreign body reaction
- Pressure sores
- Genitourinary (infection, urinary retention)
- Infection (systemic)
- Hematologic
- Endocrine/metabolic
- Hepatobiliary
- Immunologic
- Gynecologic
- Ophthalmologic
- Psychological
- Surgical procedure: non-spinal
- Wound infection: non-spinal
- Death

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

IX. SUMMARY OF NON-CLINICAL STUDIES

A. Laboratory Studies

Mechanical and Biomechanical Testing

The following mechanical and biomechanical tests were conducted on The Tether™ – Vertebral Body Tethering System as outlined in Table 3 below. The objectives of the laboratory studies were to characterize and evaluate the performance of The Tether™ – Vertebral Body Tethering System in a worst-case construct. All tension bending testing was conducted at a worst-case test block angle of 20 degrees based on Cobb angle data obtained during the clinical study.

Table 3: Summary of The Tether™ – Vertebral Body Tethering System Laboratory Tests

Test Name	Purpose	Method	Acceptance Criteria	Results
Static Tension Bending	To characterize the performance of The Tether™ – Vertebral Body Tethering System under static axial tension bending with the vertebral body screw offset from the bone	Six (6) device constructs were tested under static tension in 37° phosphate buffered saline (PBS) at a rate of 25 mm/min until failure	Demonstrate that the device can withstand loads of a safety factor of ≥ 2 compared to expected physiologic loads (900N)	Pass – acceptance criterion met
Dynamic Tension Bending	To characterize the performance of The Tether™ – Vertebral Body Tethering System under dynamic axial tension bending with the vertebral body screw offset from the bone interface to create a worst-case construct	Six (6) device constructs were tested under dynamic tension in 37° PBS at 6 Hz to 10 million cycles runout to establish run-out loads and fatigue curves. Additional confirmatory testing was conducted on two (2) samples at 2 Hz to confirm original run-out loads and identify any frequency-related differences	Demonstrate that the device can withstand loads of a safety factor of ≥ 2 compared to expected physiologic loads (900N)	Pass – acceptance criterion met
Dynamic Tension Bending (Surgical Technique)	To characterize the performance of The Tether™ – Vertebral Body Tethering System under dynamic tension bending in a worst-case configuration where the cord is tightened and then repositioned intraoperatively	Four (4) device constructs were tested under dynamic tension in 37° PBS to run-out at 6 Hz and 2 Hz (two (2) samples each) to confirm run-out loads following intraoperative repositioning of the cord	Demonstrate that the device was able to meet an equal run-out load compared to the standard Dynamic Tension Bending testing	Pass – acceptance criterion met

Test Name	Purpose	Method	Acceptance Criteria	Results
Static Axial Grip	To characterize the strength of the interconnection between the cord and the vertebral body screw of The Tether™ – Vertebral Body Tethering System	Six (6) device constructs were tested in a modified ASTM F1798-13 construct in 37° PBS at a rate of 25mm/min to failure	Demonstrate that the device can withstand loads of a safety factor of ≥ 2 compared to expected physiologic loads (900N)	Pass – Acceptance criterion met
Creep Testing	Samples were evaluated for creep behavior	Six (6) cords were loaded at 300N for 20 hours. The resulting deformation was measured	No acceptance criteria - for characterization only	n/a
Stress Relaxation	Samples were evaluated for stress relaxation behavior	Six (6) cords were loaded to 380N and held in displacement control for 168 hours. The resulting force as a percentage of the initial load was measured	No acceptance criteria - for characterization only	n/a
Wear Testing	To determine the wear and durability characteristics of The Tether™ – Vertebral Body Tethering System under tension bending loads with the bone screw flush to the bone as a worst-case, and to characterize resulting particulate	Two (2) device constructs were tested under dynamic tension bending in 37° PBS at the previously established run-out load to 10 million cycles, using a sinusoidal wave form with R=10 at 6 Hz	No gross failure observed. Wear rate < 4 mg / 4.2 kg patient weight[5]	Pass – acceptance criterion met

In addition, a coating characterization and validation study was conducted on the titanium alloy screws coated with a hydroxyapatite (HA) plasma sprayed coating. Per the FDA guidance document: *510(k) Information needed for Hydroxyapatite Coated Orthopedic Implants - 10 March 1995*, and the following *ISO standards: ISO 13779-2: Implants for surgery - Hydroxyapatite - Part 2: Coatings of hydroxyapatite - 2008, ISO13779-3: Implants for surgery - Hydroxyapatite - Part 3: Chemical analysis and characterization of crystallinity and phase purity - 2008, ISO 13779-6 Implants for*

surgery - Hydroxyapatite - Part 6: Powders - 2015, and ASTM F1185-03 Standard Specification for Composition of Hydroxyapatite for Surgical Implants - 2014., the applicant has demonstrated that the HA coating used on the The Tether™ - Vertebral Body Tethering System chemically and mechanically meets acceptance criteria.

Biocompatibility Testing

The Tether™ – Vertebral Body Tethering System components are manufactured from the materials identified in Table 4 below:

Table 4: Summary of The Tether™ – Vertebral Body Tethering System Component Materials and Patient Contact Type

Device	Material	Patient Contact Potential
Implants- Cord	SULENE® polyethylene terephthalate (PET)	Direct, Permanent Implant – bone/tissue contacting
Implants-Screws	Titanium Alloy Ti-6Al-7Nb ELI per ISO 5832-11; hydroxyapatite coating per ISO 13779-2	Direct, Permanent Implant – bone/tissue contacting
Instruments	Various stainless steel materials, coated with chrome (SS) or TiN	Direct, Limited External communicating – tissue/bone/dentin

These materials have a long history of use in medical implants with no significant biocompatibility safety issues.

Biocompatibility assessments have been conducted on The Tether™ – Vertebral Body Tethering System in compliance with applicable requirements in the Good Laboratory Practice (GLP) regulations in 21 CFR 58, applicable ISO 10993 standard, *Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process*, and the FDA guidance, *Use of International Standard ISO 10993-1, "Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process*," published June 16, 2016.

For The Tether™ – Vertebral Body Tethering System, as an implanted device with permanent duration contact (> 30 days) with tissue/bone, the biocompatibility evaluation addressed the following: cytotoxicity, sensitization, irritation, acute systemic toxicity, materials mediated pyrogenicity, implantation, subacute/subchronic toxicity, chronic toxicity, genotoxicity, and carcinogenicity endpoints. The biocompatibility evaluation included cytotoxicity testing, extractables and leachables testing, along with material characterization through chemical analysis testing and a toxicological risk assessment. In addition, the materials and manufacturing processes were compared to those of previously cleared components for use in the spine and other orthopedic applications. The results of these evaluations support the conclusion that The Tether™ – Vertebral Body Tethering System is biocompatible for its intended use.

In addition, a similar analysis was conducted for device-specific instruments. The results of these evaluations support the conclusion that The Tether™ – Vertebral Body Tethering System instruments are biocompatible for their intended use.

Usability Testing

The investigators involved in the Investigational Device Exemption (IDE) study G150001 independently conducted a usability study in cadaveric specimens at a minimum of three (3) spinal levels, and used both tensioning techniques outlined in the Surgical Technique Manual. This study identified a need for modification of the guide wires used to place the vertebral body screws. No other improvements or changes were necessary to show that The Tether™ – Vertebral Body Tethering System could be implanted for its intended use.

Sterilization, Reprocessing, Packaging, and Shelf-Life Testing

The Tether™ – Vertebral Body Tethering System cord, bone screws, and set screws are provided sterile using gamma radiation. The sterilization process was validated to achieve a sterility assurance level (SAL) of 10^{-6} using a 20-25 kGy gamma irradiation dose in accordance with ISO 11137-1:2006, *Sterilization of health care products - Radiation - Part 1: Requirements for development, validation and routine control of a sterilization process for medical devices,* and ISO 11137-2:2006, *Sterilization of health care products - Radiation - Part 2: Establishing the sterilization dose*. The Tether™ - Vertebral Body Tethering System bone screws, set screws, and cord are provided sterile in a double barrier system and has been validated to have a shelf life of 5 years via accelerated aging per ASTM F1980, bubble leak test per ASTM F2096, and seal strength test per ASTM F88. The anchor component is provided non-sterile for steam sterilization by the end user. Implantation of The Tether™ - Vertebral Body Tethering System requires a set of instruments for access to the anterior spine and implantation of the device-specific components. These instruments are made of stainless steel materials that have a long history of safe use in contact with human tissue and fluids. Steam sterilization of the instruments and the anchor component was validated according to ISO 17665-1:2006. Validation of sterilization and reprocessing instructions for the instruments was conducted per the instructions listed in the Instructions for Use and Surgical Technique Manual and included comparison to previously validated families of device components.

Magnetic Resonance Imaging (MRI) Conditional Evaluation

Per FDA Guidance *Establishing Safety and Compatibility of Passive Implants in the Magnetic Resonance (MR) Environment - December 2014*, The Tether™ – Vertebral Body Tethering System was evaluated for the following:

- Radiofrequency Induced Temperature Rise
- Force Displacement
- Induced Torque
- Image Artifact

No new worst-case device was found compared to devices previously found to be MR Conditional. Thus, The Tether™ – Vertebral Body Tethering System was found to be MR Conditional using the instructions outlined in the labeling.

X. SUMMARY OF CLINICAL INFORMATION

Clinical Data Overview

Zimmer Biomet Spine conducted a single-center, non-randomized, clinical study under IDE application G150001 in 57 subjects. The purpose of this study was to assess the safety and probable benefit of the device in subjects with idiopathic scoliosis. Spinal tethering subjects were retrospectively evaluated for clinical and radiographic outcomes and were then prospectively followed until 30 out of 57 (47.4%) reached skeletal maturity by the time of database lock. All subjects were surgically treated utilizing components of the Dynesys® Top-Loading Spinal System which is cleared for spinal fusion (K133164). The Tether™ - Vertebral Body Tethering System includes similar components, but differs from the Dynesys® System in that screws have a lower profile head. A common primary assessment collected for all subjects was curve magnitude as determined by Cobb angle. Radiographic images were analyzed using a single core laboratory for assessment of coronal Cobb angle, device loosening, and device breakage. AEs were also reported and assessed by each investigator.

Enrollment Criteria

The following enrollment criteria were utilized to select subjects for this IDE study.

Inclusion Criteria

Enrollment was limited to subjects who met the following inclusion criteria:

- Pediatric subjects at least 10 years of age on the day of surgery who met the following criteria:
  - Diagnosis of idiopathic scoliosis
  - Failure of brace treatment (as defined by greater than 5 degrees of progression and/or intolerance to brace wear)
  - Treatment with an anterior vertebral body tethering procedure for idiopathic scoliosis via thoracoscopic access or mini-thoracotomy
  - Lenke type 1 curve with a lumbar modifier of A or B
  - Pre-operative major curve Cobb angle $\geq$ 30 degrees and $\leq$ 65 degrees
  - Pre-operative thoracic scoliometer reading $\leq$ 20 degrees
  - Structural, thoracic curve corrected to $\leq$ 30 degrees pre-operatively on supine or standing side bending radiographs
  - Sanders stage $\leq$ 5 or Risser sign of $\leq$ 3 at the time of surgery
  - No additional procedures for treatment of idiopathic scoliosis other than tether re-tensioning
- Consent/assent to participation in a prospective surveillance study and demonstration of English proficiency

Exclusion Criteria

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

- Prior spine surgery or additional spine surgery defined as:
  - Vertebral body stapling
  - Surgery to correct a Lenke 1 curve following an initial AVBT procedure
  - Instrumentation of vertebral bodies in conjunction with the initial AVBT procedure using surgical approaches other than thoracoscopic access or mini-thoracotomy
- Pregnancy

- Inability or unwillingness to return for prospective follow-up visit(s)
- Major psychiatric disorders (as defined in DSM-5)
- History of substance abuse (as defined in DSM-5)
- Wards of the court
- Enrollment in an active drug or device trial that is more than minimal risk and where participation in the trial would confound the measurements for the present study
- Enrollment in a device trial for efficacy of a musculoskeletal device and where participation in the trial would confound the measurements for the present study
- Less than 30 days from completion of another clinical trial of more than minimal risk or for assessment safety and efficacy
- Investigator deems the subject as unwilling/incapable of participating

Safety and Probable Benefit Assessments

Safety was evaluated through an analysis of all AEs reported and assessed by each investigator. All AEs were also assessed and adjudicated by an independent AE Adjudication Committee (AEAC). The IDE study did not include hypothesis-driven safety endpoints. Investigators ranked each AE by type: Unanticipated Adverse Device Effect (UADE), seriousness (e.g., Serious Adverse Event (SAE)), and relationship (e.g., device- and/or procedure-related). AEs were collected based on a complete review of each subject's medical record at the study site.

Probable benefit was assessed by measurement of coronal curve correction on post-operative radiographs. A subject was considered a success if the Cobb angle of their major curve was less than or equal to 40 degrees at 24 months following treatment with The Tether™ – Vertebral Body Tethering System.

All subjects treated with The Tether™ – Vertebral Body Tethering System (N=57) were included in the safety analysis population. One subject treated with the device was later found to be outside of the eligibility criteria (Lenke type 3 curve), and consequently, was excluded from the probable benefit analysis population (N=56).

Study Population Demographics and Baseline Parameters

At the time of database lock, 57 subjects were enrolled and had evaluable data. Study population demographics are presented in Table 5. The majority of subjects were female (49/57, 86.0%), and the mean age at time of surgery was 12.4 years.

Table 5 Demographic Information for Study Subjects

Demographic/Patient Details		N (%)
Subjects		57
SEX	Female	49 (86.0%)
	Male	8 (14.0%)
AGE AT SURGERY	Mean (SD)	12.4 (1.3)
	Min, Max	10.1, 15.0

Table 6 presents baseline information for the study population. Subjects were skeletally immature as assessed by either Risser Score[6] or Sanders Stage[7]. A total of 43 subjects (43/57, 75.4%) had baseline major curves with a measured Cobb angle between 30 to 44 degrees, of which 31.6% (18/57) were between 40 to 44 degrees. Fourteen (14) subjects

(14/57, 24.6%) had baseline major curves with a measured Cobb angle between 45 to 65 degrees.

Table 6 Baseline Information for Study Subjects

Preoperative Patient Characteristic		Value/N
Total Number of Subjects		**57**
Height (cm) – Mean (SD)		155.4 (10.6)
Weight (kg) – Mean (SD)		44.2 (9.7)
BMI – Mean (SD)		18.1 (2.6)
FEV1 – Mean (SD)		2.27 (0.46)
FVC – Mean (SD)		2.67 (0.55)
Risser Score*	0	39 (68.4%)
	1	9 (15.8%)
	2	5 (8.8%)
	3	1 (1.8%)
	4	1 (1.8%)
	NR	2 (3.5%)
Sanders Stage*	0	0
	1	0
	2	8 (14.0%)
	3	20 (35.1%)
	4	7 (12.3%)
	5	2 (3.5%)
	NR	20 (35.1%)
Cobb Angle	30° - 44°	43 (75.4%)
	45° - 65°	14 (24.6%)

*Values from Imaging Core Lab. NR=Not reported.

Safety Results

Total AEs

One hundred and thirty-two (132) AEs were identified in 49 of the 57 subjects in the study population. These events are summarized in Table 7 and are classified as SAEs or non-serious adverse events (Non-SAEs). In total, nine (9) SAEs (6.8% of 132 total events) were reported in eight (8) out of 57 subjects (14.0%) treated with The Tether™ – Vertebral Body Tethering System.

Table 7: Clinical Study AE Summary

Events	All AEs	Non-SAEs	SAEs
Number of Events N (% of events)	132	123/132 (93.2%)	9/132 (6.8%)
Number of subjects with an event N (% of subjects)	49*	49/57 (86.0%)	8/57 (14.0%)

*Eight subjects did not experience any adverse events.

AEs Categorized by Relationship

A listing of all AEs by preferred term reported in this IDE study is presented in Table 8. The most common AEs reported by number of subjects experiencing an event include back pain (14/57, 24.6%), overcorrection of the instrumented curve (12/57, 21.1%), nausea/vomiting (12/57, 21.1%) and extremity pain (12/57, 21.1%).

Table 8: All IDE Study AEs

AE Preferred Term	Number of Events (N)	Number of Subjects with Event [N (%)]	Days to Event [Mean (range)]
Abrasion	1	1 (1.8)	5 (5, 5)
Acidosis	1	1 (1.8)	0 (0, 0)
Anemia	2	2 (3.5)	1 (1, 1)
Asthma	1	1 (1.8)	311 (311, 311)
Atelectasis	8	8 (14.0)	1 (0, 4)
Back Pain	15	14 (24.6)	789 (35, 1844)
Bone Screw Migration	3	3 (5.3)	934 (692, 1128)
Bradycardia	1	1 (1.8)	0 (0, 0)
Breast Pain	1	1 (1.8)	1309 (1309, 1309)
Buttock Pain	1	1 (1.8)	365 (365, 365)
Chest wall pain	3	3 (5.3)	979 (204, 1681)
Constipation	1	1 (1.8)	2 (2, 2)
Cord break	8	8 (14.0)	1212 (769, 1954)
Definite cord break	1	1 (1.8)	960 (960, 960)
Suspected cord break	7	7 (12.3)	1248 (769, 1954)
Development of new curve	2	2 (3.5)	597 (576, 617)
Dysesthesia	1	1 (1.8)	311 (311, 311)
Dyspnea	2	2 (3.5)	1188 (1051, 1324)
Endocrine disorders	1	1 (1.8)	491 (491, 491)
Extremity Pain	12	12 (21.1)	817 (39, 1840)
Flank Pain	1	1 (1.8)	343 (343, 343)
Fracture	1	1 (1.8)	1051 (1051, 1051)
Gastrointestinal disorders: Crohn’s disease	1	1 (1.8)	1930 (1930, 1930)
Hair loss	1	1 (1.8)	26 (26, 26)
Hip deformity	1	1 (1.8)	489 (489, 489)
Hyperchloremia & hypocalcemia	1	1 (1.8)	1 (1, 1)
Ileus	1	1 (1.8)	579 (579, 579)
Intraoperative hemorrhage	1	1 (1.8)	576 (576, 576)
Low Back Pain	1	1 (1.8)	84 (84, 84)
Myalgia	1	1 (1.8)	89 (89, 89)
Nausea / Vomiting	12	12 (21.1)	2 (1, 3)
Neck Pain	2	2 (3.5)	432 (423, 440)
Overcorrection of Instrumented Curve	13	12 (21.1)	648 (290, 1691)
Overcorrection resulting in revision	6	5 (8.8)	613 (290, 1691)
Overcorrection w/ no revision	7	7 (12.3)	678 (364, 1128)
Paresthesia	8	6 (10.5)	409 (7, 1137)
Perioperative peripheral nerve injury	2	2 (3.5)	46 (0, 91)
Pleural Effusion	3	3 (5.3)	146 (1, 433)
Pneumonitis	1	1 (1.8)	63 (63, 63)
Pneumothorax	5	5 (8.8)	0 (0, 1)

AE Preferred Term	Number of Events (N)	Number of Subjects with Event [N (%)]	Days to Event [Mean (range)]
Respiratory disorders: bronchitis	1	1 (1.8)	248 (248, 248)
Spondylolisthesis	1	1 (1.8)	174 (174, 174)
Sympathetic Dysfunction	1	1 (1.8)	1 (1, 1)
Vertebral Disc Degeneration	1	1 (1.8)	311 (311, 311)
Worsening of pre-existing secondary curve	1	1 (1.8)	310 (310, 310)
Wound complication	1	1 (1.8)	7 (7, 7)
Wrist Fracture	1	1 (1.8)	195 (195, 195)

AEs Categorized by Relatedness

All AEs reported in the clinical study that were categorized as related to the device or procedure are listed in Table 9. Twenty-four (24) device-related AEs were identified in 23 out of 57 subjects (40.4%). The most common device or procedure-related AEs by subject occurrence include overcorrection of the instrumented curve (12/57, 21.1%), nausea/vomiting (12/57, 21.1%), and definite/suspected cord breakage (8/57, 14.0%).

Table 9: Clinical Study AEs Related to Device or Procedure

Adverse Event	Number of Events (N)	Number of subjects with Event [N (%)]	Days to Event [Mean (range, if applicable)]
Acidosis	1	1 (1.8)	0
Anemia	2	2 (3.5)	1
Bone screw migration	3	3 (5.3	934 (692, 1128)
Bradycardia	1	1 (1.8)	0
Cord break definite	1	1 (1.8)	960
Cord break suspected	7	7 (12.3)	1248 (769, 1954)
Development of new curve	2	2 (3.5)	597 (576, 617)
Hyperchloremia & hypocalcemia	1	1 (1.8)	1
Intraoperative hemorrhage	1	1 (1.8)	579 (revision)
Nausea/vomiting	12	12 (21.1)	2 (1, 3)
Overcorrection of instrumented curve	13	12 (21.1)	648 (290, 1691)
Overcorrection requiring revision	6	5 (8.8)	613 (290, 1691)
Overcorrection/no revision	7	7 (12.3)	678 (364, 1128)
Perioperative peripheral nerve injury	1	1 (1.8)	0
Pleural effusion	3	3 (5.3)	146 (1, 433)
Pneumothorax*	5	5 (8.8)	0 (0, 1)
Sympathetic dysfunction	1	1 (1.8)	1
Transfusion Requirement	8	8 (14.0)	0 (0, 1)
Worsening of pre-existing secondary curve	1	1 (1.8)	310

*No interventions required

AEs Categorized by Seriousness

Nine (9) SAEs were reported as described in Table 10 below. Overcorrection of the major curve following AVBT which required additional spinal surgery was the most common SAE type, and accounted for 6 of the 9 total SAEs. Only one (definite) cord breakage resulted in a reoperation SAE and none of the screw migration events required

reoperation.

The applicant considered any major curve that corrected to any degree in the opposite direction of the original convexity to be overcorrected. Seven (7) overcorrection AEs did not require secondary surgery based on curve magnitude (<10 degrees, N=3; 11-20 degrees, N=3; 24 degrees, N=1), and the subject's skeletal maturity status. These subjects have been monitored with radiographs at subsequent follow-up visits.

Table 10: Summary of All Adverse Events (AEs) Classified as Serious Adverse Events (SAEs)

Adverse Event	Total Events (N)	SAEs* (N)	SAEs requiring Secondary Surgeries	Subjects with SAE [N (% of 57)]	Days to SAE [Mean (range, if applicable)]
Overcorrection of Instrumented Curve	13	6	6	5 (8.8%)	612.8 (290, 1691)
Definite cord break	1	1	1	1 (1.8%)	960
Development of new curve	1	1	1	1 (1.8%)	576
Spondylolisthesis**	1	1	1	1 (1.8%)	174.0
Bone screw migration	3	0	0	0	934 (692, 1128)
Suspected cord break	7	0	0	0	1248 (769, 1954)
Total	26	9	9	8	

*SAEs captured include both device-related events and non-device-related AEs which 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
- Resulted in subject hospitalization or prolongation of existing hospitalization
- Resulted in medical or surgical intervention to prevent permanent impairment to body structure or a body function
- Results in fetal distress, fetal death or a congenital or abnormality/birth defect

**Late-occurring SAE observed at non-index levels and not related to AVBT procedure

Secondary Surgeries

Overall, there have been nine (9) secondary surgeries affecting eight (8) subjects. The most common reason for secondary surgery was overcorrection (6/9, 66.7%). Table 11 below lists the secondary surgeries performed in the study.

The applicant classified secondary surgeries into two (2) groups – Revision and Reoperation. Revisions are defined as secondary surgeries involving modification of The Tether™ – Vertebral Body Tethering System (e.g., expanding the tether to additional vertebral levels, replacing a tether cord, surgically severing a cord). Reoperations are defined as secondary surgeries which involve implantation of a different spinal device or fusion surgery. Seven (7) of the secondary surgeries were classified as revisions and two (2) were identified as reoperations. There was, therefore, an overall 14.0% subsequent

surgery rate comprised of a revision rate of 12.3% (7/57) and a reoperation rate of 3.5% (2/57). Note that one subject underwent both a revision and reoperation procedure.

Overcorrection of instrumented curves occurred on average 665.6 days post-operatively (about 22 months) with a range between 290 and 1691 days (9.5-55.6 months). The revision procedures for overcorrection included:

- Cutting the tether cord (N=2)
- Cutting the tether cord and screw removal and/or replacement (N=2)
- Cutting the tether cord and screw loosening and re-tightening (N=2)

Revisions to either replace, remove, or add tether device components provide these subjects the potential benefit of arrest of curve progression and avoidance of fusion later in life. One study subject required a fusion reoperation for treatment of progressive overcorrection after one revision procedure, and one tether extension reoperation, failed to limit curve progression.

Table 11: Secondary Surgery Listing*

Revision Subject	Secondary Surgery Type	Months to Secondary Surgery	Cause (Preferred Term) & Event Description
1	Revision	25	Overcorrection of instrumented curve, Tether was cut at the T5-T6, T9-T10, T10-T11, T11-T12 interspaces. A T5 screw was removed.
2	Revision	21	Overcorrection of instrumented curve, Tether was cut between T9-T10, T10-T11, and T11-T12.
3	Revision	14	Overcorrection of instrumented curve. Surgery to fix over-correction. Tether was cut between L1 and L2. Screws were loosened then tightened at L1, T12, T11.
4	Revision	26	Overcorrection of instrumented curve, Tether was cut between T11-T12 and T12-L1. Screws and tether were removed and replaced from T7-T11.
4	Reoperation	60	Overcorrection of instrumented curve. Posterior spinal fusion T8-L2 was performed.
5	Revision	51	Definite Cord Breakage. Treatment initiated with bracing, but progression of curve led to replacement of the AVBT (T5-T12) and placement of an additional screw at L1.
6	Reoperation	41	Spondylolisthesis (unrelated). Treatment with L5 laminectomy, posterior spinal instrumentation and transforaminal L5-S1 interbody fusion.
7	Revision	27	Development of new curve. AVBT added from T12 to L3.
8	Revision	17	Overcorrection of instrumented curve. When curve overcorrection reached -20 degrees a tether cutting procedure was recommended and took place at 9 months post-operatively.

*T: Thoracic Spine. L: Lumbar Spine. S: Sacral Spine

Probable Benefit Results

The primary probable benefit endpoint of this single-arm study was defined based on the Cobb angle measurement of the subject's major coronal curve at 24 months post-procedure. Individual subject success was defined as a major curve less than or equal to 40 degrees at 24 months post-surgery.

Mean Cobb Angle Correction

Table 12 describes the change in Cobb angle from baseline, at the 24-month timepoint, and for the last follow-up visit at or beyond 24 months. The mean main Cobb angle improved 65% from 40.4 degrees to 14.3 degrees at 24 months. At the last available follow-up visit after surgery (at or beyond 24 months), the mean main Cobb angle correction was maintained or improved compared to pre-operative baseline curve magnitude with correction from 40.4 degrees to 17.6 degrees (56.4% curve improvement).

Table 12: Change in Cobb Angle from Baseline at 24-months and Last Visit

Cohort	N	Cobb angle*				
		Preop (N=56)	24 months (N=44)		Last visit ≥ 24 months† (N=56)	
		Mean (sd)* [min, max]	Mean (sd)* [min, max]	Δ (%Δ)	Mean (sd)* [min, max]	Δ (%Δ)
All subjects	56	40.4 (6.7) [29,56]	14.3 (8.8) [1,30]	26.1 (64.6%)	17.6 (14.7) [-29,41]	22.8 (56.2%)

* Measurement of the major thoracic (MT) Cobb angle where the superior end vertebra and the inferior end vertebra are defined at pre-op and held constant across all timepoints.

† Mean follow-up of 49.8 months at last radiograph.

Individual Subject Probable Benefit Success

Individual subject success was defined as achievement of a Cobb angle less than or equal to 40 degrees at 24 months post-surgery. Forty-three (43) out of 44 subjects with 24-month data (97.7%) met the success criteria in this study. At the last follow-up visit greater than 24 months, 52 out of 56 subjects (92.8%) had a coronal Cobb angle of less than 40 degrees (Table 13).

Table 13: Overall Study Success (Cobb Angle Less Than or Equal To 40 degrees) at 24 Months Post-Op and Most Recent Visit by Pre-operative Cobb Angle

Cohort	N	Success % (n/N)		Last Visit Cobb Angle (n, %)
		Visit at 24 months	Last Visit ≥ 24 months	
All subjects	56	97.7% (43/44)	92.8% (52/56)	< 30° (43, 76.7%) < 35° (48, 85.7%) < 40° (52, 92.8%)
Pre-Op Cobb < 45°	43	97.3% (36/37)	90.6% (39/43)	< 30° (35, 81.4%) < 35° (38, 88.3%) < 40° (39, 90.6%)
Pre-Op Cobb ≥ 45°	13	100% (7/7)	100% (13/13)	< 30° (8, 61.5%) < 35° (10, 76.9%) < 40° (13, 100%)

Sensitivity analyses were also conducted to determine how the results were affected by changing the threshold for Cobb angle reduction for the probable benefit success endpoint. For all treated subjects, the success rates are 85.7% (48/56) and 76.7% (43/56) when the probable benefit success is defined as a major Cobb angle of less than 35 degrees and 30 degrees, respectively, at a subject's last follow-up visit.

The probable benefit results were further stratified for those subjects with pre-op Cobb angles less than 45 degrees (N=43) and pre-op Cobb angles of greater than or equal to 45 degrees (N=13), respectively. For subjects with pre-op Cobb angles less than 45 degrees, probable benefit success rates were 90.6%, 88.3%, and 81.4% based on probable benefit success defined as a major Cobb angle of less than 40 degrees, 35 degrees, and 30 degrees, respectively, at a subject's last follow-up visit. For subjects with pre-op Cobb angles greater than 45 degrees probable benefit success rates were 100.0%, 76.9%, and 61.5% based on probable benefit success as defined as a major Cobb angle of less than 40 degrees, 35 degrees, and 30 degrees, respectively, at a subject's last follow-up visit.

Three (3) subjects with a last visit beyond 24 months had curves greater than 40 degrees and did not meet the individual subject success endpoint. In addition, one subject, while meeting the 24-month Cobb angle success criterion, required a revision procedure and subsequent fusion for overcorrection, and therefore was a treatment failure.

Improvement in Axial Trunk Rotation

Pre-operatively, the mean measurement in the thoracic region was 13.6 ± 3.9 degrees and 6.9 ± 3.0 degrees in the thoracolumbar region. At the last visit timepoint, the mean thoracic measurement was 8.7 ± 4.8 degrees and the mean thoracolumbar measurement was 3.8 ± 3.5 degrees. Although there is a scoliometer measurement error range of 5 degrees[8], there appeared to be overall improvement in the mean thoracic and thoracolumbar axial trunk rotation of 4.9 degrees and 3.1 degrees, respectively, equating to 36% and 45% rotational reductions, respectively.

Maintenance of Growth Through Instrumented Levels

Total vertical thoracic spine length increased between baseline and the last visit by 24.8 mm on average, showing continued spinal growth following vertebral tethering.

Improvement in Patient Reported Outcomes and Quality of Life (QoL)

Patient-reported outcomes and QoL assessments performed in the clinical study include the Adolescent Pediatric Pain Tool (APPT), Pediatric Quality of Life Inventory (PedsQL™), and the Scoliosis Research Society outcomes questionnaire (SRS-22). Overall, the results of these assessments are positive and indicate overall patient satisfaction and improvement in function with AVBT.

However, some uncertainty in these assessments arises from the retrospective study design. The applicant presented the patient-reported and QoL outcomes from the 24-month post-operative timepoint through the last available visit/skeletal maturity. However, there are no baseline data for APPT, PedsQL, and SRS-22 as these assessments were not part of the applicant's standard-of-care assessments.

Spinal Alignment

Spinal alignment was evaluated at each post-operative timepoint and consisted of measurements of thoracic kyphosis, lumbar lordosis, sagittal balance, coronal balance, and total vertical spine length. On standing full-spine/pelvis EOS images, sagittal balance was measured by the distance between a C7 plumb line and the postero-superior aspect of the S1 vertebral body. Displacement of the C7 plumb line anterior to the sacral reference reflects positive sagittal balance and displacement posterior to the sacral reference reflects negative sagittal balance. Coronal balance was measured by the distance between a C7 plumb line and the central sacral vertical line (CSVL). Table 14 below summarizes radiographic parameters examined in the clinical study:

Table 14: Summary of Radiographic Measures in Subjects at ≥ 24 Months Post-Tether (Measures reported as mean (SD))

Follow-up	N	Thoracic kyphosis (*)	Lumbar lordosis (*)	Sagittal balance (mm)*	Cornoal balance (mm)**	Total vertical thoracic spine length (mm)
Pre-op	54	15.8 (10.1)	52.2 (11.5)	1.5 (26.6)	2.1 (15)	246.4 (19.3)
LV≥2 years[+]	**56**	**19.4 (12.9)**	**54.9 (11.9)**	**-10.1 (33.1)**	**-2.1 (15.8)**	**271.2 (19.7)**

*Sagittal balance: positive value indicates anterior shift; negative indicates posterior shift.

**Coronal blalnce: positive values indicates right cornoal shift; negative value indicates left coronal shift.

[+]Mean Follow-up of 49.8 months. "LV" refers to last visit.

XI. FINANCIAL DISCLOSURE

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included one investigator who had disclosable financial interests/arrangements (significant payment of other sorts) as defined in 21 CFR 54.2(a), (b), (c) and (f). The applicant has adequately disclosed the financial interest/arrangements with its clinical investigator. Furthermore, the applicant conducted the clinical study under IDE, and adjudicated AEs as well as radiographic data using independent third-parties. The information provided does not raise any questions about the reliability of the data.

XII. SAFETY AND PROBABLE BENEFIT ANALYSIS

The Tether™ - Vertebral Body Tethering System was implanted in 57 subjects with idiopathic scoliosis in a single-center, non-randomized, clinical study under IDE G150001. Safety was evaluated based upon the AEs reported and assessed by the study investigator, as well as adjudicated through the AEAC. Secondary surgeries, classified as either Revisions or Reoperations, were also assessed. The applicant compared AEs and secondary surgery data to literature describing posterior instrumented spinal fusion for treatment of idiopathic scoliosis.

Probable benefit was based upon the level of correction of the Cobb angle of the major curve provided by The Tether™ - Vertebral Body Tethering System. The data provide a sufficient basis upon which to draw conclusions regarding the safety and probable benefit of The Tether™ - Vertebral Body Tethering System.

A. Probable Benefit Conclusions

The primary probable benefit endpoint of the study evaluated the Cobb angle at 24 months post-implantation, with success defined as a major Cobb angle of less than 40 degrees following treatment with The Tether™ - Vertebral Body Tethering System. This probable benefit endpoint was chosen as curves of this magnitude at skeletal maturity are not expected to progress to the point where surgical intervention with spinal fusion would be required later in life. Spinal curves in skeletally immature subjects with progressive idiopathic scoliosis who have failed bracing and/or are intolerant to brace wear are likely to increase in magnitude and approach or exceed the threshold where spinal fusion is considered.

The indication for use of The Tether™ - Vertebral Body Tethering System is to correct and stabilize a spinal deformity without fusion by harnessing the patient's remaining growth. This device offers the patient a non-fusion treatment with the potential to avoid the adverse consequences associated with fusion which include decreased spinal motion, pseudarthrosis, adjacent spinal segment degeneration, neurological complications, pain, implant failure/breakage, and subsequent surgical intervention.

Forty-three (43) out of 44 subjects with evaluable data at 24 months were considered a probable benefit success. The applicant also conducted an analysis for all treated subjects based upon their last follow-up visit greater than 24 months, and the probable benefit success in this case was 92.8% (52/56). Sensitivity analyses were also conducted to determine how the results were affected by changing the threshold for Cobb angle reduction in the probable benefit success endpoint. For all treated subjects, the success rates are 85.7% (48/56) and 76.7% (43/56) when the probable benefit success is defined as a major Cobb angle of less than 35 degrees and 30 degrees, respectively, at a subject's last follow-up visit. The probable benefit results were further stratified by pre-op Cobb angle for those subjects with pre-op Cobb angles less than 45 degrees (N=43) and pre-Op Cobb angles of greater than or equal to 45 degrees, respectively. For subjects with pre-op Cobb angles less than 45 degrees, probable benefit success rates were 90.6%, 88.3% and 81.4% based on probable benefit success defined as a major Cobb angle of less than 40 degrees, 35 degrees, and 30 degrees, respectively, at a subject's last follow-up visit. For subjects with pre-op Cobb angles

greater than 45 degrees probable benefit success rates were 100.0%, 76.9%, and 61.5% based on probable benefit success as defined as a major Cobb angle of less than 40 degrees, 35 degrees, and 30 degrees, respectively, at a subject's last follow-up visit.

With respect to major curve correction provided by The Tether™ - Vertebral Body Tethering System, the mean major Cobb angle correction was 65% at 24 months, and was maintained at 56.4% correction despite the absence of fusion at the latest follow-up visit, at or beyond 24 months. For comparison regarding the ability to achieve curve correction, posterior pedicle screw-and-rod-based spinal instrumentation systems intended for spinal fusion predictably achieve correction of the instrumented major curves in treated subjects and provide approximately 63% correction of the major coronal Cobb angle[9].

These analyses of the probable benefit endpoint suggest that patients are likely to experience the benefit of avoiding spinal fusion during the study time period. Based upon the level of correction observed in the study, The Tether™ - Vertebral Body Tethering System achieves a level of correction in a comparable range versus posterior spinal instrumentation and fusion.

B. **Safety Conclusions**

The risks of the device are based on data collected in a clinical study conducted to support HDE approval as described above. The Tether™ - Vertebral Body Tethering System is an implantable device which requires anterior exposure of the spine and general anesthesia, both of which are associated with inherent risks.

In this clinical study there were 132 AEs reported in 49 out of 57 subjects (86%). Twenty-six (26) AEs were classified as either serious or device-related, with the most common event types reported as overcorrection of the instrumented curve (N=13 in 12 subjects), cord breakage (N=8), and bone screw migration (N=3). Six (6) subjects with overcorrection events required subsequent surgical procedures and six (6) subjects were diagnosed with radiographic overcorrections which did require surgical treatment, and were not considered at risk for clinically important future curve progression which would require future additional surgical treatment.

SAEs (6.8% of total events) occurred in 8 out of 57 subjects (14.0%) who were treated with The Tether™ – Vertebral Body Tethering System, with overcorrection also reported as the most common event type for SAEs, accounting for 6 of the 9 total SAEs due to the necessity for secondary surgery. There was one (definitive) cord breakage which resulted in a reoperation SAE. None of the screw migrations required reoperation.

The revision rate reported for subjects in the study was 12.3% (7 events in 57 subjects), and the reoperation rate was 3.5% (2 events in 57 subjects), resulting in an overall 14.0% rate of subsequent surgery. One subject underwent both a revision and reoperation procedure. There were no deaths or neurologic AEs, and only one subject so far has required conversion to fusion.

To compare secondary surgery rates for The Tether™ – Vertebral Body Tethering System with spinal fusion, a literature review was conducted to identify the subsequent surgery rates at 24 months for patients undergoing spinal instrumentation and fusion for treatment of idiopathic scoliosis in the US. For US patients who undergo treatment with spinal instrumentation and fusion for idiopathic scoliosis, the rates of subsequent surgery have been reported as 4.1% at 24 months[10] and 9.9% at 60 months[11]. Compared to spinal fusion treatment, the subsequent surgery rate of 14% associated with treatment with The Tether™ – Vertebral Body Tethering System in this IDE study at 24 months is numerically higher. In assessing the AEs reported for The Tether™ – Vertebral Body Tethering System in this IDE study, the categories of AEs such as implant loosening, implant failure and nausea/vomiting are similar to those AEs reported for spinal fusion. Based on the available data, The Tether™ – Vertebral Body Tethering System can be considered safe for its indication for use, based upon the similar types of AEs observed, types of revisions and reoperations reported in this IDE study, and the fact that only one subject required a subsequent surgical procedure which resulted in spinal fusion.

C. Probable Benefit-Risk Conclusions

The probable benefits of the device are also based on data collected in a clinical study conducted to support HDE approval as described above.

The primary probable benefit of The Tether™ – Vertebral Body Tethering System is correction and maintenance of the magnitude of the patient's major spinal curve below the threshold where spinal fusion is indicated, thereby potentially avoiding associated adverse consequences of spinal fusion. Based on the data provided, the probable benefit success rate of curve correction and maintenance below 40 degrees is greater than or equal to 92.8% at or beyond the 24-month follow-up timepoint. Additionally, the data reports a 1.8% (1 out of 57 subjects) rate of conversion to spinal fusion at 24-month follow-up, which suggests a likely probability of a patient experiencing the benefit of avoiding spinal fusion.

The probabl risks of the device are also based on data collected in a clinical study conducted to support HDE approval as described above. Device risks reported as SAEs include (from most frequent to least frequent): overcorrection, cord breakage, and screw migration. Only 6 out of 9 SAEs required a revision procedure, and only one subject required a reoperation due to cord breakage.

Additional factors considered in determining probable risks and benefits for the device included patient and surgeon perspectives.

1. Patient Perspectives

   This submission did not include specific information on patient or caregiver perspectives for this device. However, patient and caregiver preference for a non-fusion option for progressive idiopathic scoliosis may be inferred by their informed consent to the procedure. In addition, patient-reported outcomes and QoL assessments were favorable, although not captured pre-operatively.

- Adolescent Pediatric Pain Tool (APPT): The APPT results include a word graphic rating scale (WGRS), which is a 10-point graphic to measure pain intensity from 'no hurt' to 'hurts worst' and a list of pain quality descriptors. The APPT results for the study subjects reported low pain levels (mean score 20% of the maximum pain level) at the last visit greater than or equal to 24 months.

- Pediatric Quality of Life Inventory (PedsQL): The PedsQL is a brief, standardized, generic assessment instrument that assesses patients and parents perceptions of health-related quality of life in pediatric and adolescent patients with chronic health conditions. The highest possible total PedsQL score is 2300; the mean score reported for study subjects was 2117 (90.8%), indicating a positive quality of life.

- The Scoliosis Research Society outcomes questionnaire (SRS-22): The SRS-22, designed to evaluate domains of physical and mental function in patients with adolescent idiopathic scoliosis, is a self-administered instrument that contains 22 questions organized in five (5) domains covering the following aspects of patients' quality of life: function/activity, pain, self-image, mental health (5 items each), and satisfaction with treatment (2 items). The mean total SRS-22 score reported for study subjects was 4.5/5 (89.9%), indicating overall good patient satisfaction and function.

2. Surgeon Perspectives:

The preference of patients and surgeons for a non-fusion option for progressive scoliosis was communicated to the applicant in writing by leading scoliosis surgeons. Their letters of support were included in this HDE application.

In conclusion, given the available information above, the data on The Tether™ – Vertebral Body Tethering System collected under the study support treatment of progressive idiopathic scoliosis, and the probable benefits outweigh the probable risks.

C. **Overall Conclusions**

The data in this HDE application support the reasonable assurance of safety and probable benefit of The Tether™ – Vertebral Body Tethering System when used in accordance with the indications for use. This device can be considered safe for its intended use, based upon consideration of the types of SAEs, device- and procedure-related AEs, and subsequent surgical procedures reported. The probable benefit success rate, defined as maintenance of a Cobb angle of 40 degrees or less, is equal to or greater than 92.8% at or beyond 24 months. This probable benefit endpoint is considered representative of the likelihood of avoidance of the need for spinal fusion during this time period. The benefit of a device which avoids spinal fusion during the study time period but does not preclude treatment with spinal fusion if needed in the future, is considered to outweigh the higher rate of subsequent surgical intervention when compared to posterior spinal instrumentation and fusion.

Therefore, it is reasonable to conclude that the probable benefit to health from using the device for the target population outweighs the risk of illness or injury, taking into account the probable benefits and risks of currently available devices or alternative forms of treatment when used as indicated in accordance with the directions for use.

XIII. PANEL RECOMMENDATION

This HDE was not taken to a meeting of the Orthopaedic and Rehabilitation Devices Panel of the Medical Devices Advisory Committee because the information in this HDE did not raise any unanticipated safety concerns.

XIV. CDRH DECISION

CDRH has determined that, based on the data submitted in the HDE, The Tether™ – Vertebral Body Tethering System will not expose patients to an unreasonable or significant risk of illness or injury and the probable benefit to health from using the device outweighs the risks of illness or injury. CDRH issued an approval order on August 16, 2019. The final conditions of approval cited in the approval order are described below.

Based on the protocol summary received on June 04, 2019, The Tether™ – Vertebral Body Tethering System Registry Post-Approval Study (PAS): The Tether™ – Vertebral Body Tethering System Registry is a multi-center, single-arm, prospective post-approval US registry study to provide ongoing safety and probable benefit assessment of The Tether™ – Vertebral Body Tethering System in treatment of skeletally immature patients with idiopathic scoliosis. Skeletal maturity will be assessed using both the Risser grade and Sanders score. It is planned that all patients treated in the first 18-months (up to a maximum of 200 patients) should be enrolled and followed through 60-months from the time of each patient's index surgery, with interim visits at immediate post-operative up to 6-weeks, 6-months, 12-months, 24-months and 60-months post-procedure. Two-hundred (200) patients will be enrolled in this study, with at least 50 patients enrolled by 24-months, 100 patients enrolled by 36-months (should enrollment still be ongoing), and 200 patients enrolled by 48-months (should enrollment still be ongoing). This study will include a minimum of 10 US centers with sequential enrollment from each site that agrees to participate.

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

The primary probable benefit endpoint is maintenance of major Cobb angle less than or equal to 40 degrees at 60-months post-surgery. Secondary endpoints will be analyzed up to 60-months post-surgery, and will include the following:

1. Curve progression no greater than 10 degrees of any secondary curve above or below the implant, or development of a new curve equal to or greater than 40 degrees.

2. Device integrity failures including cord breakage and screw migration.

3. Composite endpoint analysis (maintenance of major Cobb angle less than or equal to 40

degrees AND freedom from SAEs during The Tether™ – Vertebral Body Tethering System procedure and procedure/device related SAEs following surgery).

4. Analysis of the failure attributable to conversion to another spinal implant OR major Cobb angle that exceeded 40 degrees at defined follow-up visit OR any progression of the major curve at defined follow-up compared to baseline OR death OR permanent disability.

These safety and probable benefit data will be collected from each patient at pre-operative, immediate post-operative up to 6-weeks, 6-months, 12-months, 24-months, and 60-months post-operatively. This study is estimated to last a total of 84-months.

Descriptive statistics and 95% confidence intervals will be presented for all analyses. For continuous variables, means and standard deviations will be shown. For categorical variables, frequencies and percentages will be presented.

The applicant's manufacturing facilities have been found to be in compliance with the device Quality System (QS) regulation (21 CFR 820), via the supporting documentation provided in H190005, and through a risk-based assessment.

XV. APPROVAL SPECIFICATIONS

Directions for use: See the device labeling.

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

Post-approval Requirements and Restrictions: See approval order.

XVI. REFERENCES

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