FDA Executive Summary

Prepared for the
Spring 2022 review by the
FDA's Pediatric Advisory Committee

H190005
The Tether™ – Vertebral Body Tethering System

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I. INTRODUCTION

In accordance with the Pediatric Medical Device Safety and Improvement Act, this review provides a safety update based on the post-market experience with the use of The Tether™ – Vertebral Body Tethering System ("The Tether™") in pediatric patients since approval in 2019. The purpose of this review is to provide the Pediatric Advisory Committee (PAC) with post-market safety data so the committee can advise the Food and Drug Administration (FDA) on whether they have any new safety concerns and whether they believe that the Humanitarian Device Exemption (HDE) remains appropriate for pediatric use. This document summarizes the safety data the FDA reviewed since HDE approval in August 2019. It includes data from the sponsor's Annual Reports, post-market medical device reporting (MDR) of adverse events, and peer-reviewed literature.

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 Humanitarian Use Designation (HUD) Designation:
The Indication for Use statement was 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 ≥ 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 above falls within the HUD designation.

III. BRIEF DEVICE DESCRIPTION

The Tether™ – Vertebral Body Tethering System is a non-fusion spinal device intended for treatment of idiopathic scoliosis. 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. 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 subject system includes instrumentation for insertion, manipulation, and removal of the implants.

Device Type	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-7NV (ISO 5832-11) Hydroxyapatite (ISO 13779-2)
Set Screw		Diameter: 7 mm Height: 5.7 mm	Ti-6Al-4V ELI (ASTM F136)
Anchor		Diameter: 12 mm	Ti-6Al-4V ELI (ASTM F136)
Tensioning Cord		Diameter: 4.1 mm Implantable length: 300 mm	Polyethylene terephthalate (PET)

IV. REGULATORY HISTORY AND CURRENT STATUS

The Tether™ – Vertebral Body Tethering System received Humanitarian Use Device designation (HUD DEV-2018-0410) on March 28, 2019. The HDE was approved on August 16, 2019 by the Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (H190005). A summary of the HDE and PAS Annual Reports submitted for The Tether™ are presented in Table 1.

Table 1. H190005 Regulatory History

H190005 Reports
HDE 1-year Annual Report
PAS 6-month Annual Report
PAS 1-year Annual Report
PAS 18-month Annual Report
HDE 2-year Annual Report

V. SUMMARY OF CLINICAL DATA USED TO SUPPORT HDE APPROVAL

A clinical study (conducted under Investigational Device Exemption) was performed to support the safety and probable benefit of Tether™ – Vertebral Body Tethering System for subjects with idiopathic scoliosis and documented in the Summary of Safety and Probable Benefit (SSPB). Zimmer Biomet Spine conducted a single-center, non-randomized, clinical study in 57 subjects. The majority of the subjects were female (49/57, 86.0%), and the mean age at time of surgery was 12.4 years. 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 as an adjunct to

spinal fusion (K133164). The Tether™ - Vertebral Body Tethering System includes similar components (including the identical tensioning cord) 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. Adverse events (AEs) were also reported and assessed by each investigator.

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 at risk for increase in curve magnitude which may approach or exceed the threshold where spinal fusion is considered.

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. The mean major 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 major 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).

The risks of this device are based on data collected in a clinical study conducted to support HDE approval. 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), tensioning 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 not require surgical treatment and were not considered at risk for clinically important future curve progression which would require future additional surgical treatment.

Serious adverse events (SAEs) occurred in 8 out of 57 subjects (14.0%) and represented 6.8% of total adverse events for subjects who were treated with The Tether™ – Vertebral Body Tethering System. Overcorrection was reported as the most common event type for SAEs, accounting for 6 of the 9 total SAEs and required secondary surgery. There was one (definitive) tensioning 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 subsequent 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[1] and 9.9% at 60 months[2]. 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.

The Indications 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 or breakage, and the need for subsequent surgical intervention.

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

1. Patient Perspectives

    - 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-22 (SRS-22) outcomes questionnaire: 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, and satisfaction with treatment. 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

   Leading scoliosis surgeons wrote letters of support that were included in the HDE application expressing the preference of patients and surgeons for a non-fusion option for progressive scoliosis.

In conclusion, given the available information above, the data on The Tether™ – Vertebral Body Tethering System collected under the study support that the probable benefits outweigh the probable risks for use of this device for treatment of select skeletally immature patients with progressive pediatric idiopathic scoliosis.

VI. POSTMARKET DATA: ANNUAL DISTRIBUTION NUMBER

Section 520(m)(6)(A)(ii) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) allows HDEs indicated for pediatric use to be sold for profit as long as the number of devices distributed in any calendar year does not exceed the annual distribution number (ADN). On December 13, 2016, the 21st Century Cures Act (Pub. L. No. 114-255) updated the definition of ADN to be the number of devices "reasonably needed to treat, diagnose, or cure a population of 8,000 individuals in the United States." Based on this definition, FDA calculates the ADN to be 8,000 multiplied by the number of devices reasonably necessary to treat an individual. Since The Tether™ system includes one tensioning cord and an average of 6.79 instrumented vertebral levels, the total ADN for the tensioning cords is 8,000 and the total ADN for the vertebral body assemblies (one vertebral body screw and one set screw) and the anchors is 54,320.

The second HDE Annual Report was submitted on August 31, 2021 which included the Reporting Period from August 16, 2020 through August 15, 2021. Table 2 provides the number of device components distributed in the second year (August 2020-August 2021) in the United States. To date, there have been 733 cases of HDE approved The Tether™ on the U.S. market, with the first case performed on September 11, 2019.

Table 2. Annual Distribution Number - Reporting Period: August 2020-August 2021

Device Type	Annual Distribution Limit	2020 Total	2021 Total (as of 8/15/21)	Reporting Period Total
Vertebral Body Assemblies	54,320	3,564	2,550	3,861
Anchors	54,320	2,175	1,592	2,407
Tensioning Cords	8,000	539	361	561

VII. POSTMARKET DATA: POST-APPROVAL STUDY (PAS)

PAS Conditions of Approval:

The Tether™ HDE (H190005) was approved on August 16, 2019.

The objective of the PAS study is to assess the ongoing safety and probable benefit of The Tether™ – Vertebral Body Tethering System in a registry population.

The PAS is a prospective, multi-center, single-arm, 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 time point 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 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 probable benefit endpoint is maintenance of major Cobb angle less than or equal to 40 degrees at 60-months post-surgery.

Secondary probable benefit 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.

All 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-operative time points. 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 study population is comprised of skeletally immature patients that require surgical treatment to obtain and maintain correction of progressive idiopathic scoliosis who receive the device in the post market environment. There is no comparator group.

PAS Study Status:

Subject enrollment and data collection will be managed by the Harms Study Group (HSG) and Setting Scoliosis Straight Foundation (SSSF) Registry. Institutions that are HSG members or affiliates, with Investigators/surgeons that are trained and approved to perform surgeries with The Tether, will participate in the registry. Ten sites from this group will be identified as study sites specific to this Tether Post-Approval Study (PAS).

The latest PAS protocol was approved on June 4, 2021. The 18-month report was received on August 31, 2021. As of this date, ten (10) clinical sites have been selected for patient enrollment and have initiated the Institutional Review Board (IRB) submission process. Eight (8) sites have received local site-specific IRB approval and five (5) sites have commenced with patient enrollment with a total of 19 patients enrolled.

Per the HDE Approval Letter, this PAS study is estimated to be completed by January 2027, 84-months from the date of original PAS approval.

Ten (10) patients have surgery dates scheduled, seven patients have first erect radiographic data available, and one patient has 6-month data available. Outcomes data from the Setting Scoliosis Straight Foundation (SSSF) registry are available for the first five (5) patients. Patient demographics and follow-up are summarized below in Table 3 and Table 4.

Table 3. PAS Patient Demographics

Patient Demographics	
N	5
Age at Surgery (years)	13.6 ± 2.2
Sex	80% (4/5) Females 20% (1/5) Males
BMI	20.48 ± 3.4
Lenke Class	60% (3/5) Lenke 1 40% (2/5) Lenke 5
Levels Instrumented	40% (2/5) Thoracolumbar 60% (3/5) Thoracic

Source: Constructed based on data from H190005 annual reports

Table 4. PAS Patient Follow-up Status

Patient Follow-up per Study Visit	
Study Visit	Completed
First erect	7
6-months	1
12-months	N/A
24-months	N/A
60-months	N/A

Source: Constructed based on data from H190005 annual reports

Interim Results:

Probable Benefit:

At the first erect visit, all five patients (100%) for whom data were available had achieved a major Cobb angle less than 40° (Table 5). The secondary Cobb angle for all patients was improved from the pre-operative angle and therefore no curve progression occurred (Table 6). No device integrity failures, including tensioning cord breakage and screw migration, occurred.

Table 5. PAS Probable Benefit Summary: Major Cobb Angle

Major Cobb Angle						
Patient ID	Pre-op	First Erect	6-month	12-month	24-month	60-month
1	40°	14°	N/A	N/A	N/A	N/A
2	47°	23°	N/A	N/A	N/A	N/A
3	58°	27°	N/A	N/A	N/A	N/A
4	52°	22°	N/A	N/A	N/A	N/A
5	51°	10°	N/A	N/A	N/A	N/A
Average	50°	19°	N/A	N/A	N/A	N/A

Source: Constructed based on data from H190005 annual reports

Table 6. PAS Probable Benefit Summary: Secondary Cobb Angle

Secondary Cobb Angle						
Patient ID	Pre-op	First Erect	6-month	12-month	24-month	60-month
1	23°	17°	N/A	N/A	N/A	N/A
2	36°	21°	N/A	N/A	N/A	N/A
3	24°	16°	N/A	N/A	N/A	N/A
4	31°	17°	N/A	N/A	N/A	N/A
5	33°	15°	N/A	N/A	N/A	N/A
Average	29°	17°	N/A	N/A	N/A	N/A

Source: Constructed based on data from H190005 annual reports

Safety:

One serious adverse event was reported (Table 7). This patient had post-operative constipation, a gastrointestinal complication. Five days after surgery, the patient was readmitted, treated, and all

symptoms were resolved. As this adverse event required readmittance, it was categorized as a serious adverse event. It was determined that this adverse event was related to the surgery and is not unanticipated.

Table 7. PAS Safety Summary: Adverse Events

Adverse Events									
Patient ID	Death	Gastro	Instrumentation	Neurological	Pain	Pseudoarthrosis	Pulmonary	Surgical Site	Transfusion
1	0	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0	0
3	0	1	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0	0
5	0	0	0	0	0	0	0	0	0
Total	0	1	0	0	0	0	0	0	0

Source: Constructed based on data from H190005 annual reports

VIII. ADVERSE EVENTS

Known Adverse Events

AEs collected during the clinical study that were used to support the safety and probable benefit of The Tether™ in subjects with pediatric idiopathic scoliosis were presented in the SSPB at the time of HDE approval. One hundred and thirty-two (132) AEs were identified in 49 of the 57 subjects in the study population. Table 8 lists all AE types reported in the clinical study that were classified as related to the device or procedure. 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 tensioning cord breakage (8/57, 14.0%).

Table 8. Known AE Types Related to The Tether™ Device or Procedure

AEs Related to Device or Procedure
1. Acidosis 2. Anemia 3. Bone screw migration 4. Bradycardia 5. Tensioning cord break, definite 6. Tensioning cord break, suspected 7. Development of new curve 8. Hyperchloremia & hypocalcemia 9. Intraoperative hemorrhage 10. Nausea/vomiting 11. Overcorrection of instrumented curve, requiring revision 12. Overcorrection, no revision required 13. Perioperative peripheral nerve injury 14. Pleural effusion 15. Pneumothorax 16. Sympathetic dysfunction 17. Transfusion requirement

18. Worsening of pre-existing secondary curve

From the AEs reported in Table 8, Table 9 summarizes the five (5) AE types classified as device- or procedure-related SAEs. Nine (9) total SAEs were reported for this study. Overcorrection of the major curve following anterior vertebral body tethering (AVBT) which required additional spinal surgery was the most common SAE type, and accounted for 6 of the 9 total SAEs. Overcorrection was defined as any major curve that corrected to any degree in the opposite direction of the original curve convexity. 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. Overcorrection less than 10 degrees may be referred to as spinal asymmetry given that scoliosis is defined as curvature of the spine greater than 10 degrees and represents a radiographic finding which is not associated with any known adverse clinical effect. These subjects have been monitored with radiographs at subsequent follow-up visits. Only one (definite) tensioning cord breakage resulted in a reoperation SAE and none of the screw migration events required reoperation.

Table 9. Known SAE Types Related to The Tether™ Device or Procedure

SAEs Related to Device or Procedure
1. Overcorrection of instrumented curve
2. Tensioning cord break, definite
3. Tensioning cord break, suspected
4. Development of new curve
5. Bone screw migration

Literature Review

The sponsor performed a clinical literature search in their HDE Annual Report of articles published from September 2020 through August 2021. Scoliosis, tether, spine, anterior vertebral body tethering, and investigators' last names who previously published on AVBT including Samdani, Larson, Miyanji, Diab, Hoernschemeyer, Betz, Cuddihy, and Antonacci, were used as search terms and the following inclusion/exclusion criteria were used to further refine the articles to criteria relevant for this HDE.

Inclusion Criteria:

- It provides relevant information regarding technical and clinical features of the device subject to the search, or
- It provides relevant information regarding performance and/or safety of the device subject to the search, or
- It provides information relevant to determining the probable benefit of the subject device, and
- It contains sufficient information for a rational and objective assessment, and
- It is based on an appropriate study design

Exclusion Criteria:

- Those involving implants other than those of interest
- Isolated case reports

- Random experience
- Reports lacking sufficient detail to permit scientific evaluation
- Unsubstantiated opinions
- Non-clinical studies
- Foreign language (non-English) literature

After removing duplicates, and reading the titles, abstracts, and full-texts, twelve (12) articles were determined to be relevant based on the inclusion and exclusion criteria.[3-14]

An additional clinical literature search in PubMed was performed by FDA for articles published from December 2020 to November 2021. The following search terms were used: scoliosis, tether. After reading the titles, abstracts, and full-texts, and excluding non-clinical studies, review papers, tethered spinal cord studies, non-AVBT studies, and studies that did not report any adverse events, one (1) additional article was found.[15]

Out of the thirteen (13) total articles, seven (7) were from US sites and six (6) were from outside the United States (OUS) sites. It is important to note that the literature articles do not indicate the specific device type used. However, all literature articles did study AVBT devices and therefore were included in this analysis. A total of 714 patients were reported on across these 14 articles with 287 adverse events:

- Spinal curvature overcorrection
    - 4.6% (n = 33) compared to 22% from clinical data results in the SSPB
- Loss of spinal curvature correction
    - 2.5% (n = 18) compared to 0 from clinical data results in the SSPB
- Broken tethers
    - 10.2% (n = 73) compared to 14.0% from clinical data results in the SSPB
- Broken tethers that required revision
    - 1.1% (n = 8) compared to 1.8% from clinical data results in the SSPB
- Other mechanical complications (screw loosening/pullout/migration/misplacement, tether loosening)
    - 1.0% (n = 7) compared to 5.3% from clinical data results in the SSPB
- Pulmonary/thoracic complications (pneumothorax, pleural effusion, chylothorax, pulmonary edema, pneumonia, pulmonary embolism)
    - 3.6% (n = 26) compared to 14.0% from clinical data results in the SSPB
- Radiculopathy
    - 0.6% (n = 4) compared to 1.8% from clinical data results in the SSPB
- Infection
    - 0.4% (n = 3) compared to 0 from clinical data results in the SSPB
- Cerebrospinal Fluid (CSF) Leak
    - 0.6% (n = 4) compared to 0 from clinical data results in the SSPB

Summary of Literature

The studies found in this literature review suggest probable benefits of AVBT systems such as The Tether™ with respect to the treatment of skeletally immature patients with idiopathic

scoliosis. From the clinical data documented in the SSPB used to support safety and probable benefit for The Tether™, a total of 91 adverse events were observed for 49 of the 57 total subjects. All event types from the literature search were identified at time of HDE approval as potential adverse effects (e.g., adverse events) as documented in the SSPB except for CSF leak. A CSF leak may occur if a misaligned screw breaches the vertebral body and penetrates the dural sac. The two articles that reported CSF leaks were both OUS and represented early use of The Tether™ during the learning curve; it was also noted that all CSF leaks were resolved for all patients. Additionally, the CSF leaks were not associated with any additional post-operative infections. The authors noted that this complication is expected to diminish with additional surgeon experience.[3, 11] Increased training, clinical presentations, and published literature on implantation techniques may also lead to decreases in AEs related to misaligned implants. Other potential etiologies of CSF leaks are being investigated and CSF leaks as an AE type are being monitored.

While the list of adverse events is much more comprehensive in the SSBP as compared to the literature, this search demonstrates that the types of adverse events documented in the literature are expected given the clinical data published in the SSPB for The Tether™ – Vertebral Body Tethering System. It does not appear that any additional safety signals nor concerns have arisen since HDE approval.

Overview of MDR Database

Strengths and Limitations of MDR Data

Each year, the FDA receives several hundred thousand MDRs of suspected device-associated deaths, serious injuries and malfunctions. The MDR database houses MDRs submitted to the FDA by mandatory reporters (manufacturers, importers and device user facilities) and voluntary reporters such as health care professionals, patients and consumers. The FDA uses MDRs to monitor device performance, detect potential device-related safety issues, and contribute to benefit-risk assessments of these products. MDR reports can be used effectively to:

- Establish a qualitative snapshot of adverse events for a specific device or device type
- Detect actual or potential device problems used in a "real world" setting/environment, including:
    - Rare, serious or unexpected adverse events;
    - Adverse events that occur during long-term device use;
    - Adverse events associated with vulnerable populations;
    - Off-label use; and
    - Use error

Although MDRs are a valuable source of information, this passive surveillance system has limitations, including the potential submission of incomplete, inaccurate, untimely, unverified or biased data. In addition, the incidence or prevalence of an event cannot be determined from this reporting system alone due to potential under-reporting of events and lack of information about frequency of device use. Because of this, MDRs comprise only one of the FDA's several important post-market surveillance data sources. Other limitations of MDRs and FDA's internal MDR database include:

- MDR data alone cannot be used to establish rates of events, evaluate a change in event rates over time, or compare event rates between devices. The number of reports cannot be interpreted or used in isolation to reach conclusions about the existence, severity, or frequency of problems associated with devices.
- Confirming whether a device caused a specific event can be difficult based solely on information provided in each report. Establishing a cause-and-effect relationship is especially difficult if circumstances surrounding the event have not been verified or if the device in question has not been directly evaluated.
- MDR data is subjected to reporting bias, attributable to potential causes such as reporting practice, increased media attention, and/or other agency regulatory actions.
- MDR data does not represent all known safety information for a reported medical device and should be interpreted in the context of other available information when making device-related or treatment decisions.

MDRs Associated with The Tether™

FDA's internal MDR Database was searched on December 7, 2021 utilizing the following search criteria:

1. Product code QHP (Vertebral Body Tethering System)

    - 102 MDRs found
2. Brand name, generic name, or concomitant product "Tether"
    - No new events that were not already captured from other search criteria were found. Two MDRs were captured for a different AVBT system and removed from this analysis

The search resulted in 100 MDRs for The Tether™. In several cases, MDRs were submitted for every component that was implanted into the patient. After removing redundant events, a total of seven (7) unique patient events were reported. All seven events occurred within the U.S. and were received in 2021.

MDRs # 1-19: 3012447612-2021-00038 through 3012447612-2021-00056
A patient (age unknown) had a delayed presentation of inferior vena cava injury resulting in blood loss in the right hemithorax following a tether construct implanted from T6-L2. This required a return to the operating room on post-operation day two and a multi-unit red blood cell transfusion. The patient recovered well following this event with no additional complications. This type of vascular event is most likely due to the implantation of components in the thorax as was noted in the SSPB as a potential risk.

MDRs # 20-50: 3012447612-2021-00057 through 3012447612-2021-00069; 3012447612-2021-00137 through 3012447612-2021-00140; 3012447612-2021-00146 through 3012447612-2021-00157; 3012447612-2021-00161 and 3012447612-2021-00162
A 14-year-old female was reported to need a spinal fusion (T5-L4) four months following a tether procedure. This patient had two tensioning cords implanted, one in the thoracic region and one in the lumbar region. While the patient's thoracic curve corrected from 68° to 50° and their lumbar curve corrected from 51° to 19°, they developed a 30° thoracic trunk rotation and a new Lenke Type 1A curve pattern. It was decided to remove The Tether™ constructs and fuse the associated levels (T5-L4). Per the SSPB, this secondary surgery to convert to a spinal fusion is considered a reoperation. Given that the implantation of two tensioning cords is off label use and the 3D nature of scoliosis curves, the development of a new curve pattern and trunk rotation is not unexpected.

MDRs # 51-57: 3012447612-2021-00213 through 3012447612-2021-00219
A patient (age unknown) was reported to need a revision surgery after their inferior curve began to overcorrect at their one-year post-operative follow up visit. A revision surgery took place to remove the screws and tensioning cord at T12, L1, and L2. Follow up for this patient continues per the recommended protocol to observe their curve progression. At this time, there are no further treatments planned. Overcorrection is a well-documented risk with tether surgery, as noted in the literature and the SSPB.

MDRs # 58-60: 3012447612-2021-00243 through 3012447612-2021-00245
A patient (unknown age) was reported to need a revision surgery after their inferior curve in the lumbar region began to increase. A portion of The Tether™ construct spanning one level was removed and a previously implanted pedicle screw construct was extended to fuse the spinal level in the lumbar region where The Tether™ construct was removed. During the surgery, it was noted that the set screws were found to be cross threaded and the tensioning cord in the

lumbar region was loose. Cross threading of set screws can be a result of a technical mistake on the part of the surgeon during implantation or a mechanical issue with the set screw or vertebral body screw. Investigation is ongoing by the sponsor to further identify a root cause of this event.

MDRs # 61-66: 3012447612-2021-00270 through 3012447612-2021-00275
An 18-year-old female was reported to need a revision surgery to address a loss of correction in the inferior half of The Tether™ construct. During the surgery, a new tensioning cord was implanted and tensioned and a second construct was implanted from T12-L3. It was also noted that the set screws had loosened from the vertebral body screws from T11-L3. As described above, cross threading of set screws can be a result of a technical mistake on the part of the surgeon during implantation or a mechanical issue with the set screw or vertebral body screw. Investigation is ongoing by the sponsor to further identify a root cause of this event.

MDRs # 67-80: 3012447612-2021-00287 through 3012447612-2021-00300
A 45-year-old female was reported to need a revision surgery to remove The Tether™ construct as their curve had not improved and some loss of correction was observed. While loss of correction is a documented risk in the SSPB, The Tether™ is indicated for skeletally immature patients and therefore this is off label use.

MDRs # 81-100: 3012447612-2021-00318 through 3012447612-2021-00337
A female patient (age unknown) was reported to have a reoperation to remove The Tether™, which spanned from T5-L1, construct and replace it with a spinal fusion construct from T3-L3. This decision was made due to the patient's lack of flexibility. It is unknown what this patient's initial (pre-operative) spinal flexibility was and if The Tether™ caused this lack of flexibility. It is also unknown if this patient's curve was being appropriately corrected, lost correction, or was overcorrected.

Summary of MDRs

As of the HDE 2-year Annual Report for The Tether™, the sponsor was notified of six (6) MDR reportable events. These six events were the same found during FDA's internal MDR search (MDR #1-80). This MDR along with the additional report found during FDA's internal MDR search are all expected given the nature of tether surgery. Table 10 summarizes all MDRs associated with The Tether™ since its approval in August 2019. There have been a total of 733 tether cases since its approval, 4 MDRs in 2020, and 7 MDRs in 2021.

Table 10. MDRs for The Tether™

Adverse Event Type	Number of Events	Patient Age (years) and Sex (if known)	Relationship to Device
CSF leak	1	Unknown age and gender	Unknown, investigation ongoing
Hemothorax	1	14, male	Unknown
Vascular event	1	Unknown age and gender	Yes
Overcorrection	1	Unknown age and gender	Yes
Curve progression	4	- 12, unknown gender	Investigation ongoing

		- Unknown age, female - Unknown age and gender - 18, female	
Reduced flexibility	1	Unknown age and gender	Yes
Trunk rotation (off label use)	1	14, female	Yes
Curve progression (off label use)	1	45, female	Yes

IX. SUMMARY

Evaluation of data available to CDRH, including the HDE 2-year Annual Report, MDRs and published scientific literature, has identified no new safety signals compared to what was known and anticipated at the time of HDE approval in August 2019. Based on the available data, and considering the probable benefits and risks, FDA believes that the HDE remains appropriately approved for pediatric use. Therefore, FDA recommends continued surveillance and will report the following to the PAC in 2023:

- Annual distribution number
- Literature review
- MDR review
- Update on the PAS

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