FDA Executive Summary

Prepared for the
Spring 2025 Review by the
FDA's Pediatric Advisory Committee

The Tether™ – Vertebral Body Tethering System (H190005)

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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

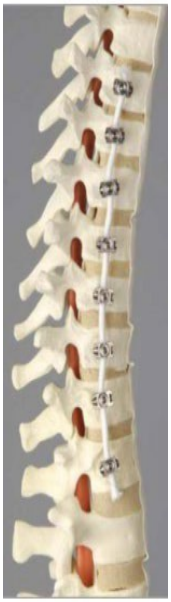
The Tether™ – Vertebral Body Tethering System is indicated for skeletally immature patients that require surgical treatment to obtain and maintain correction of progressive idiopathic scoliosis, with a major Cobb angle of 30 to 65 degrees whose osseous structure is dimensionally adequate to accommodate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

Modifications from the Humanitarian Use Device (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 $\geq 30°$." 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 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	Status
HDE 1-year Annual Report	Report OK
PAS 6-month Annual Report	Report OK
PAS 1-year Annual Report	Report OK
PAS 18-month Annual Report	Report OK
HDE 2-year Annual Report	Report OK
PAS 24-month Annual Report	Report OK
HDE 3-year Annual Report	Report OK
PAS 36-month Annual Report	Report OK
HDE 4-year Annual Report	Report OK
PAS 48-month Annual Report	Report OK

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. POST-MARKET 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 fifth HDE Annual Report was submitted on November 20, 2024 which included the Reporting Period from August 16, 2023 through August 15, 2024. Table 2 provides the number of device components distributed in the fifth year (August 2020-August 2024) in the United States. To date, there have been 1,962 cases of HDE approved The Tether™ in the U.S. market, with the first case performed on September 11, 2019.

Table 2. Annual Distribution Number (ADN)

	Vertebral Body Assemblies	Anchors	Tensioning Cord	Total Cases
AND Limit	54,320	54,320	8,000	8,000
2020 Total	3,564	2,175	539	405
2021 Total	3,835	2,396	553	436
2022 Total	3,525	1,933	517	411
2023 Total	3,150	1,851	466	368
2024 Total (as of 8/15/24)	1,855	1,112	277	217

VII. POST-MARKET 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 48-month report was received on March 25, 2024. As of this date, ten clinical sites have been selected for patient enrollment and have received Institutional Review Board (IRB) approval. Nine sites have commenced with patient enrollment with 83 total patients enrolled. Per the HDE Approval Letter, this PAS study is estimated to be completed by January 2027, 84-months from date of original PAS approval.

In this PAS report, 82 patients had surgery, 79 patients have first erect radiographic data available, 70 patients have 6-month data available, 60 patients have 1-year data available, and 32 patients have 2-year data available. Outcomes data from the Setting Scoliosis Straight Foundation (SSSF) registry are available for the 80 patients with pre-op, surgical, and first erect visit information. Patient demographics and follow-up are summarized below in Table 3 and Table 4.

Table 3. PAS Patient Demographics

Patient Demographics	
N	79
Age at Surgery (years)	12 ± 2
Sex	76% (61/80) Females 24% (19/80) Males
Lenke Class	51% (29/56*) Lenke 1 10% (8/56*) Lenke 2 13% (6/59*) Lenke 3 3% (2/72*) Lenke 4 17% (8/56*) Lenke 5 7% (5/56*) Lenke 6
Risser Sign (at pre-op)	36% (28/78*) Risser 0 40% (31/78*) Risser 1 18% (14/78*) Risser 2 5% (4/78*) Risser 3 1% (1/78*) Risser 4 17% (12/78*) Risser 5 7% (5/78*) Risser 6

Source: Constructed based on data from H190005 annual reports

* Indicates missing data from PAS report with a reduced sample size from 79 patients

Table 4. PAS Patient Follow-up Status

Patient Follow-up per Study Visit	
Study Visit	Completed
First erect	79
6-months	70
12-months	60
24-months	32
60-months	N/A

Source: Constructed based on data from H190005 annual reports

Interim Results:

Probable Benefit:

At the first erect visit, 63 patients (80%, 63/79) for whom data were available had achieved a major Cobb angle less than 40° with a mean of 23° ± 9° The secondary Cobb angle for all patients was improved from the pre-operative angle and therefore no curve progression occurred. Table 5 contains a summary of the probable benefit data, including the percent Cobb angle correction between the pre-op and first erect radiographs.

Table 5. PAS Probable Benefit Summary

Major Cobb Angle					
	Pre-op mean ± std (min - max)	**First Erect** mean ± std (min - max)	**6-months** mean ± std (min - max)	**1 year** mean ± std (min - max)	**2 years** mean ± std (min - max)
Major Cobb Angle (°)	47 ± 9 (22-67)	23 ± 9 (8-50)	21 ± 9 (8-50)	19 ± 9 (1-52)	19 ± 10 (4-38)
Primary Cobb Correction (%)		50 ± 18	56 ± 18	61 ± 19	61 ± 17
Secondary Cobb Angle (°)	33 ± 10 (10-64)	22 ± 8 (8-44)	19 ± 8 (5-44)	17 ± 7 (1-40)	19 ± 5 (5-31)
Secondary Cobb Correction (%)		31 ± 23	43 ± 21	50 ± 17	47 ± 22

Source: Constructed based on data from H190005 annual reports

Safety:

Eight additional SAEs were reported since the 2024 PAC Executive Summary for a total of 14 SAEs (Table 6).

The following SAEs were reported in previous PAC Executive Summaries:

- One patient had post-operative constipation, a gastrointestinal complication. Five days

after surgery, the patient was readmitted, treated, and all symptoms were resolved. As this AE required readmittance, it was categorized as a SAE. It was determined that this

AE was related to the surgery and is not unanticipated.

- One patient had an instrumentation complication that resulted in an explant surgery and re-tensioning due to post-operative loss of correction. Eighty-four days after the initial surgery, the patient had a secondary surgical intervention to replace the set screws and

tether and re-tension the construct. Upon investigation, it was determined that despite the surgeon reporting to have applied maximum tension to five of the nine instrumented levels using the provided tensioner instrument and was satisfied with the intra-operative level of correction, the patient experienced post-operative loss of correction. The sponsor investigated this event and found no similar incidents of loss of correction as a result of the tensioner and determined this to be a unique event. As this AE required a secondary surgical intervention, it was categorized as an SAE. As the surgeon noted they were satisfied with the curve correction intra-operatively, this suggests that the loss of correction is likely a result of other surgical or patient specific factors. It was determined that this AE was related to the initial surgery and is not unanticipated.

- One patient had an overcorrection of greater than 10° that resulted in explant surgery. The overcorrection was first observed during her 6-month post-operative assessment in her main thoracic curve leading to progression of the untreated thoracolumbar deformity. The patient was still skeletally immature with a significant amount of growth remaining (Sanders 3A) which was believed would lead to continued overcorrection and deformity progression, if not addressed. The revision surgery occurred 1 month later. During this surgery, the set screws were removed from T11-T12, and the cord was removed from T10-T12. The patient was discharged the same day with no perioperative complications. As this AE required a secondary surgical intervention, it was categorized as an SAE. It was determined that this AE was related to the surgery and is not unanticipated.
- One patient required a revision surgery to re-tension the cord. Three days after the initial surgery, the cord was replaced at L4 and the tether was revised at L2/L3. As this AE required a secondary surgical intervention, it was categorized as an SAE. It was determined that this AE was related to the surgery and is not unanticipated.
- One patient required a revision surgery to evacuate a hematoma at the surgical site two days after the initial surgery. Two days after the initial surgery, the patient's chest tube output increased and hemoglobin dropped resulting in a revision surgery to drain the hematoma. During this surgery, no active bleeding was found. Observation of the lower chest and upper retroperitoneum was done for 5-7 minutes and did not identify any significant areas of concern. A couple areas were cauterized but those were not actively bleeding. Tissue around the T10, T11 and T12 screws were retracted and irrigated vigorously to try to induce bleeding but no obvious bleeding was observed. Following irrigation of the chest, the diaphragm was closed and a hemostatic agent was placed around the screws. Following surgery, the patient's chest tube output was appropriate and the patient was discharged with no other complications. As this AE required a secondary surgical intervention, it was categorized as an SAE. It was determined that this AE was related to the surgery and is not unanticipated.
- One patient required a thoracentesis procedure. At 10 weeks after the initial surgery, the patient presented to the Emergency Department with right upper quadrant pain that worsened with movement causing shortness of breath. The patient was readmitted and underwent an ultrasound-guided thoracentesis procedure with interventional radiology and remained in the hospital for 2 nights. No infection or chyle was observed and no shortness of breath was noted. At 12 weeks after the initial surgery, the patient was

readmitted again with recurrent pleural effusion. The patient underwent another ultrasound-guided thoracentesis procedure with interventional radiology as an outpatient procedure. Following this second procedure, it was noted the pleural effusion was resolved and the patient is doing well. As this AE required readmittance and two thoracentesis procedures, it was categorized as a SAE. It was determined that this AE was related to the surgery and is not unanticipated.

The following SAEs were reported since the 2024 PAC Executive Summary:

- One patient who had previously received a revision surgery due to overcorrection greater than 10° that resulted in explant surgery experienced overcorrection at the six-month follow-up visit from the revision surgery. A second revision surgery was performed to remove the cord from T10-T12. Following the surgery, the patient was discharged with no other complications. As this AE required a secondary surgical intervention, it was categorized as an SAE. It was determined that this AE was related to the surgery and is not unanticipated.
- One patient had an overcorrection greater than 10° that resulted in a revision surgery to release tension in the cord. At the one-year follow-up visit, the overcorrection was observed. One month later, a revision surgery was performed to cut the cord between T9/T10 and T10/T11. As this AE required a secondary surgical intervention, it was categorized as an SAE. It was determined that this AE was related to the surgery and is not unanticipated.
- One patient had an overcorrection of greater than 10° that resulted in a revision surgery to release tension in the cord. Approximately 18 months from the initial surgery, a revision surgery was performed to release the T10-L1 cord on the left side. An additional cord was added from T11-L1, resulting in an overall construct extending from T5 to L1. As this AE required a secondary surgical intervention, it was categorized as an SAE. It was determined that this AE was related to the surgery and is not unanticipated.
- One patient received a second revision surgery due to overcorrection greater than 10° approximately seven months after the first overcorrection surgery. It was also noted that the patient had a prior ureter injury requiring multiple surgeries and hospital stays. In the 2024 PAC Executive Summary for this device, MDRs were reported for a patient with damage to their left ureter during the tether surgery. It is not clear if this SAE is the same as the previously reported MDR. As with the previous MDRs, a definite root cause cannot be determined. This SAE could possibly be attributed to unknown patient factors, operational factors, or surgical factors. Ureteral injury is not an unexpected adverse event following surgery, particularly near the lower thoracic and lumbar regions of the spine.
- One patient had an overcorrection of greater than 10° that resulted in a revision surgery to release tension in the cord. Approximately 16 months from the initial surgery, a revision surgery was performed to cut the cord between T12/L1 and L1/L2. As this AE required a secondary surgical intervention, it was categorized as an SAE. It was determined that this AE was related to the surgery and is not unanticipated.
- One patient had an overcorrection of greater than 10° that resulted in a revision surgery to release tension in the cord. Approximately 15 months from the initial surgery, a revision surgery was performed to remove set screws at T5/T6 and remove the cord from T5-T7.

As this AE required a secondary surgical intervention, it was categorized as an SAE. It was determined that this AE was related to the surgery and is not unanticipated.

- One patient had an overcorrection of greater than 10° that resulted in a revision surgery to release tension in the cord. At the one-year follow-up visit, the overcorrection was observed in the lumbar region resulting in a Cobb Angle of 30°. Approximately four months later, a revision surgery was performed release tension in the left cord from T11-L2 and the right cord was extended from T12-L3 and re-tensioned. As this AE required a secondary surgical intervention, it was categorized as an SAE. It was determined that this AE was related to the surgery and is not unanticipated.
- One patient had a post-operative complication with their chest tube. Following the initial surgery, cloudy drainage was observed from the chest tube indicating a possible chyle leak. This patient continued to be monitored and after approximately two weeks, the incision was noted to be well approximated without drainage, redness, or swelling. At the six-month follow-up, the incision was fully healed, and the patient was no longer experiencing complications. As this AE required readmittance and a prolonged hospital stay, it was categorized as a SAE. It was determined that this AE was related to the surgery and is not unanticipated.

Table 6. PAS Safety Summary: Adverse Events

Adverse Events								
Death	Gastro	Instrumentation	Neurological	Pain	Pseudoarthrosis	Pulmonary	Surgical Site	Transfusion
	1	10				2	1	

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 7 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 7. 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 7, Table 8 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 8. 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 June 2023 through August 2024. Scoliosis, tether, tethering, spine, anterior vertebral body tethering, 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 subject device, equivalent device, and/or benchmark device(s), or

- It provides relevant information regarding performance and/or safety of the subject device, equivalent device, and/or benchmark device(s), or
- It provides information relevant to risk/benefit assessment of the subject device, equivalent device, and/or benchmark device(s), and
- It contains sufficient information for a rational and objective assessment, and
- It is based on an appropriate study design

Exclusion Criteria:

- Duplicate articles
- Non-clinical studies (e.g., non-human, biomechanical, cadaver, finite-element, etc.)
- Case studies
- Study not relevant (does not address the subject device pathology, anatomy, indications, target population)
- Studies that do not reflect the intended performance/ use of the subject device
- Studies that do not report either/any safety or clinical/functional outcomes
- Article not in English
- Full text not available
- No ethical principles for medical research involving human subjects (e.g., Declaration of Helsinki, equivalent to Helsinki, local ethics committee and written) consent, etc.
- Participation (subject number) too small for statistical significance
- Study lacks sufficient information to make a rationale or objective assessment (e.g., review articles that do not include literature review methods, technical notes, and conference and meeting abstracts)
- Subject device studies lacking variant identification or stratified results
- Studies with duplicate data sets (data sets published in another article)

After removing duplicates, and reading the titles, abstracts, and full-texts, 34 articles were determined to be relevant based on the sponsor's inclusion and exclusion criteria.

An additional clinical literature search in PubMed was performed by FDA for articles published from December 2023 to December 2024. 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, five (5) additional articles were found. For the purposes of this executive summary, only articles that contain adverse event information are included. A total of 24 articles are discussed below.[2-26]

Out of the 24 total articles, 16 were from US sites, four were from outside the United States (OUS) sites, and four included data from both US and 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 1,745 patients were reported on across these 24 articles with 761 adverse events:

- Spinal curvature overcorrection
    - 3.3% (n = 58) compared to 22% from the SSPB clinical data results

- Loss of spinal curvature correction
    - 1.7% (n = 29) compared to 1.8% from the SSPB clinical data results
- Broken tethers
    - 20% (n = 349) compared to 14% from the SSPB clinical data results
- Other mechanical complications (screw loosening/pullout/migration/misplacement, tether loosening)
    - 0.8% (n = 14) compared to 5.3% from the SSPB clinical data results
- Pulmonary/thoracic complications (pneumothorax, pleural effusion, chylothorax, pulmonary edema, pneumonia, pulmonary embolism)
    - 0.9% (n = 16) compared to 14.0% from the SSPB clinical data results
- Revision surgeries
    - 8.9% (n = 155) compared to 14% from the SSPB clinical data results
- Radiculopathy
    - 0.2% (n = 3) compared to 1.8% from the clinical data results
- Convert to spinal fusion
    - 2.1% (n = 36) compared to 1.8% from the SSPB clinical data results
- CSF leak
    - 0.2% (n = 3) compared to 0 from the SSPB clinical data results
- Infection
    - 0.2% (n = 3) compared to 0 from the SSPB clinical data results
- Ureteral Injury
    - 0.1% (n = 1) compared to 0 from the SSPB clinical data results

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 132 AEs 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, infection, and ureteral injury.

CSF leaks were reported in the 2022 PAC Executive Summary for this device. A CSF leak may occur if a misaligned screw breaches the vertebral body and penetrates the dural sac. However, it was noted that all CSF leaks were resolved for all patients and were not associated with any post-operative infections. 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. Infection is not an unexpected adverse event following any surgical procedure, including spinal tether surgery. Ureteral injury is not an unexpected adverse event following surgery particularly near the lower thoracic and lumbar regions of the spine. Additionally, the ureteral injury noted in the literature may be the same event previously documented as an MDR in the 2024 PAC Executive Summary.

One limitation to the adverse events published in the literature is there may be redundancy in the adverse event reporting. As researchers increase their publications on spinal tether patients, they appear to be reusing the same patient data, or a subset of patient data, in different articles to present different findings. Therefore, it is not possible to know if an adverse event has already been reported in the literature without patient level data. Given this potential for redundancy, we believe that the 761 adverse events for the 1,745 patients published in these 24 articles may be an overrepresentation of the adverse events. These 761 adverse events are likely a conservative overestimation for these 1,745 patients. If any redundancies were able to be removed, it would only help to improve the safety profile of this device type.

While the list of adverse events is much more comprehensive in the SSPB 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 in November 2024 utilizing the following search criteria:

1. Product code QHP (Vertebral Body Tethering System); Manufacturer Name ("Zimmer", "ZimVie", or "Highridge Medical"); Brand Name/Generic Name/Concomitant Product ("Tether")
    - 35 MDRs found
2. Brand Name/Generic Name/Concomitant Product ("Tether"); Narrative Text ("Zimmer", "ZimVie", or "Highridge")
    - No new events that were not already captured from other search criteria were found.
3. Document number (H190005)
    - No new events that were not already captured from other search criteria were found.

In several cases, MDRs were submitted for every component that was implanted into the patient. After removing redundant events, a total of 24 unique patient events were reported. Of these 24 events, 22 occurred within the U.S. and two occurred outside the U.S. Descriptive summaries of the 24 unique MDRs are provided below.

<u>MDR# 1: 3012447612-2023-00363</u>
A revision surgery was reported for a patient (age unknown) due to overcorrection. During the revision surgery, the cord was cut in two locations and no implant components were removed. Overcorrection is a well-documented risk with tether surgery, as noted in the literature and the SSPB.

<u>MDR #2-4: 3012447612-2024-00013 through 3012447612-2024-00015</u>
A revision surgery was reported for an 11-year-old female due to overcorrection greater than 10°. During the revision surgery, the set screws at T5 and T6 were removed, and the cord was released between T6 and T7 to prevent overcorrection. Overcorrection is a well-documented risk with tether surgery, as noted in the literature and the SSPB.

MDR #5-7: 3012447612-2024-00016, 3012447612-2024-00177, and MW5149327
A revision surgery was reported for a 14-year-old female due to overcorrection greater than 10°. During the revision surgery, the cord on the left side was removed from T11 to L1. On the right side, screws were added from T12 to L2, and the entire cord was replaced from T5 to L2. Overcorrection is a well-documented risk with tether surgery, as noted in the literature and the SSPB.

MDR #8-11: 3012447612-2023-00319 through 3012447612-2023-00322
A revision surgery was reported for a 12-year-old female due to overcorrection greater than 10°. During the revision surgery, the set screws at T5 and T6 were removed, and the cord was removed between T5 and T7. Overcorrection is a well-documented risk with tether surgery, as noted in the literature and the SSPB.

MDR #12-16: 3012447612-2024-00058 through 3012447612-2024-00062
A revision surgery was reported for a 19-year-old female due to curve progression and suspected cord breakage. During the revision surgery, a posterior screw [fusion] construct was added without removing the tether construct. Cord breakage and conversion to spinal fusion are both well-documented risks with tether surgery, as noted in the literature and the SSPB.

MDR #17: 3012447612-2024-00157
A revision surgery was reported for a patient (age unknown) due to curve progression and cord breakage. During the revision surgery, a posterior spinal fixation construct was added. Cord breakage and conversion to spinal fusion are both well-documented risks with tether surgery, as noted in the literature and the SSPB.

MDR #18: 3012447612-2024-00158
A revision surgery was reported for a patient (age unknown) due overcorrection. Overcorrection is a well-documented risk with tether surgery, as noted in the literature and the SSPB.

MDR #19: 3012447612-2024-00159
A revision surgery was reported for a patient (age unknown) due curve progression and cord breakage. Cord breakage and curve progression are well-documented risks with tether surgery, as noted in the literature and the SSPB.

MDR #20: 3012447612-2024-00160
A revision surgery was reported for a patient (age unknown) due overcorrection. Overcorrection is a well-documented risk with tether surgery, as noted in the literature and the SSPB.

MDR #21: 3012447612-2024-00161
A revision surgery was reported for a patient (age unknown) due to curve progression and cord breakage. During the revision surgery, a posterior spinal fixation construct was added. Cord breakage and conversion to spinal fusion are both well-documented risks with tether surgery, as noted in the literature and the SSPB.

MDR #22: 3012447612-2024-00162
A revision surgery was reported for a patient (age unknown) due to curve progression and cosmetic appearance. During the revision surgery, a posterior spinal fixation construct was added. Curve progression and conversion to spinal fusion are both well-documented risks with tether surgery, as noted in the literature and the SSPB.

MDR #23: 3012447612-2024-00163
A revision surgery was reported for a patient (age unknown) due to overcorrection. Overcorrection is a well-documented risk with tether surgery, as noted in the literature and the SSPB.

MDR #24: 3012447612-2024-00164
A revision surgery was reported for a patient (age unknown) due to overcorrection. Overcorrection is a well-documented risk with tether surgery, as noted in the literature and the SSPB.

MDR #25: 3012447612-2024-00165
A revision surgery was reported for a patient (age unknown) due to cord breakage. During the revision surgery, a posterior spinal fixation construct was added. Cord breakage and conversion to spinal fusion are both well-documented risks with tether surgery, as noted in the literature and the SSPB.

MDR #26: 3012447612-2024-00166
A revision surgery was reported for a patient (age unknown). During the revision surgery, kyphosis was recreated via a disc release. Disc excisions have previously been documented with tether surgery in previous PAC Executive summaries for this device. Additionally, kyphosis and curve changes are well-documented risks with tether surgery, as noted in the literature and the SSPB.

MDR #27: 3012447612-2024-00167
A revision surgery was reported for a patient (age unknown) due to thoracic outlet syndrome and sacral pain. During the surgery, a sacral laminoplasty and imbrication of a sacral cyst was performed. More information is needed to understand the basis of this event and a definite root cause could not be determined. This event could possibly be attributed to unknown patient factors, operational factors, or surgical factors.

MDR #28: 3012447612-2024-00168
A revision surgery was reported for a patient (age unknown) due to curve progression and cosmetic appearance of a hypertrophic scar. During the revision surgery, a posterior spinal fixation construct was added. Scar revision is not uncommon after surgical procedures and curve progression is a well-documented risk with tether surgery, as noted in the literature and the SSPB.

MDR #29: 3012447612-2024-00169
A revision surgery was reported for a patient (age unknown) due to curve progression and cord breakage. During the revision surgery, a posterior spinal fixation construct was added. Cord breakage and conversion to spinal fusion are both well-documented risks with tether surgery, as

noted in the literature and the SSPB.

MDR #30: 3012447612-2024-00170
During the initial surgery, the patient (age unknown) aspirated and the surgery was aborted. Three weeks later, the surgery was reattempted and completed without issue. A definite root cause could not be determined. However, surgical and anesthesia complications like this event are not uncommon for this procedure type.

MDR #31: 3012447612-2024-00175
A revision surgery was reported for a 12-year-old female due to overcorrection. During the revision surgery, the cord was removed between T10 and L2. Overcorrection is a well-documented risk with tether surgery, as noted in the literature and the SSPB.

MDR #32: 3012447612-2024-00250
A revision surgery was reported for a 14-year-old male due to cord breakage. During the revision surgery, the cord was removed and replaced from T7 to L3. Cord breakage is a well-documented risk with tether surgery, as noted in the literature and the SSPB.

MDR #33: 3012447612-2024-00256
A revision surgery was reported for a 11-year-old female due to cord breakage at T8. Cord breakage is a well-documented risk with tether surgery, as noted in the literature and the SSPB.

MDR #34: MW5149325
A revision surgery was reported for a 11-year-old female due to overcorrection. During the revision surgery, the cord was released from T5 to T6. Overcorrection is a well-documented risk with tether surgery, as noted in the literature and the SSPB.

MDR #35: MW5156927
A revision surgery was reported for a 15-year-old female due to overcorrection greater than 10°. During the revision surgery, the cord was released from T10 to L2. Overcorrection is a well-documented risk with tether surgery, as noted in the literature and the SSPB.

Summary of MDRs

All 24 MDRs are expected given the nature of tether surgery. Table 9 summarizes all MDRs associated with The Tether™ since its approval in August 2019. There have been a total of 1,962 tether cases since its approval, 4 MDRs in 2020, 7 MDRs in 2021, 6 MDRs in 2022, 13 MDRs in 2023, and 24 MDRs in 2024.

Table 9. MDRs for The Tether™

Adverse Event Type	Number of Events	Patient Age (years) and Sex (if known)	Relationship to Device and/or Procedure
CSF leak	1	- Unknown age and sex	Unknown
Hemothorax	1	- Unknown age and sex	Unknown
Vascular event	1	- Unknown age and sex	Yes
Overcorrection	15	- Unknown age and sex [n = 9] - 11, female - 11, female - 12, female - 12, female - 14, female - 15, female	Yes
Curve progression[α]	15	- Unknown age and sex [n = 8] - 12, unknown sex - Unknown age, female [n = 2] - Unknown age and sex - 18, female - Unknown age, male - 19, female	Yes
Reduced flexibility	1	- Unknown age and sex	Yes
Trunk rotation (off label use)	1	- 14, female	Yes
Curve progression (off label use)	1	- 45, female	Yes
Mechanical complications	4	- Unknown age and sex [n = 4]	Yes
Screwdriver tip fracture	5	- Unknown age and sex [n = 5]	Investigation ongoing
Convert to posterior[β] spinal fusion	8	- Unknown age and sex [n = 7] - 19, female	Yes
Broken tether[α]	9	- Unknown age and sex [n = 6] - 11, female - 14, male - 19, female	Yes
Damage to ureter	1	- Unknown age and sex	Investigation ongoing
Fused levels (off label use)	1	- 14, female	Yes
Thoracic Outlet Syndrome	1	- Unknown age and sex	Investigation ongoing
Aspiration during surgery	1	- Unknown age and sex	Yes

[α] Broken tethers are often reported with curve progression in the MDRs as a single event. For completeness, curve progression and broken tethers are counted separately.

[β] Conversion to spinal fusion are often reported with curve progression in the MDRs as a single event. For completeness, curve progression and broken tethers are counted separately.

IX. SUMMARY

Evaluation of data available to CDRH, including the HDE 4-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 2026:

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

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