FDA Executive Summary

Prepared for the
Spring 2024 review by the
FDA's Pediatric Advisory Committee

H170001
Minimally Invasive Deformity Correction (MID-C) 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 Minimally Invasive Deformity Correction System ("MID-C") from ApiFix, Ltd. 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 October 2019. It includes data from the sponsor's Annual Report, post-market medical device reporting (MDR) of adverse events (AEs), and peer-reviewed literature.

II. INDICATIONS FOR USE

The MID-C System is indicated for use in patients with adolescent idiopathic scoliosis (AIS) for treatment of single curves classified as Lenke 1 (thoracic major curve) or Lenke 5 (thoracolumbar/lumbar major curve), having a Cobb angle of 40 to 60 degrees which reduces to less than or equal to 30 degrees on lateral side-bending radiographs, and thoracic kyphosis less than 55 degrees as measured from T5 to T12.

Use of the MID-C System in patients with curves of lower magnitudes (i.e., less than 40 degrees) is based on the risk for curve progression.

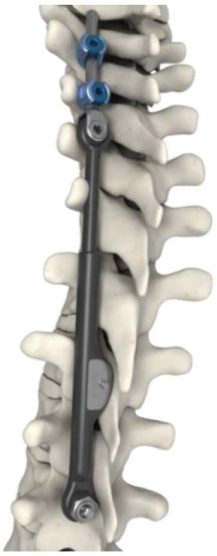
Modifications from the Humanitarian Use Device (HUD) Designation:
The Indication for Use statement was modified from that granted for the HUD designation to have a more stringent (30 versus 35 degrees) major curve side-bending reduction criterion to ensure a flexible curve and Cobb angle criteria were updated from 45-60 degrees to 40-60 degrees. An additional statement was added to the Indications for Use ("Use of the MID-C System in patients with curves of lower magnitudes (i.e., less than 40 degrees) based on the risk for curve progression") in a regulatory submission after the original HDE approval.

III. BRIEF DEVICE DESCRIPTION

The MID-C System is a non-fusion spinal device intended for treatment of adolescent idiopathic scoliosis and acts as an internal brace to achieve correction and stabilization of scoliotic deformity without the need for a spinal fusion. The device is a ratchet-based, expandable rod that attaches to the spine using two pedicle screws, one placed superior and one inferior to the apex of the curve. An optional extender is available composed of a 5.5mm rod and two pedicle screws to anchor the superior end of the implant with two screws rather than one. The MID-C System is made of titanium alloy (Ti-6Al-4V ELI) components, with some components coated in an amorphous diamond-like coating (ADLC). The device is implanted on the concave side of the spinal deformity, around the apex of a flexible single major curve, and acts as an internal brace to correct and stabilize scoliotic deformity via incremental ratchet lengthening. The system passively elongates when tensile load is applied via the pedicle screws and the length of the device expands in 1.3 mm increments. The ratchet and pawl mechanism permit one-way

elongation while maintaining the length of the device under compressive loads. In addition, the subject system includes instrumentation for insertion, manipulation, and removal of the implants.

Device Type	Image	Sizes	Material
Pedicle Screws		Lengths: 30-50mm (5mm increments) Diameters: 5.0-7.0mm (0.5mm increments)	Ti-6Al-4V ELI (ASTM F136) Coated with ADLC
MID-C System		Device Lengths: / Extension Lengths: 85mm / 30 95mm / 30 105 / 40 115 / 40 125 / 50	Ti-6Al-4V ELI (ASTM F136) Coated with ADLC
Optional Extender		Configurations: 0° or 15° (left and right) Diameter: 5.5mm	Ti-6Al-4V ELI (ASTM F136)



IV. REGULATORY HISTORY AND CURRENT STATUS

The MID-C System received Humanitarian Use Device designation (HUD DEV-2015-0345) on December 21, 2015; however, an expansion of patient population was granted on November 14, 2019. The HDE was approved on August 20, 2019 (and the expanded patient population approved by supplement on December 16, 2019) by the Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration. A summary of the HDE and Post-Approval Study (PAS) annual reports submitted for the MID-C System are presented in Table 1.

Table 1. H170001 Regulatory History

H170001 Reports	Status
PAS 6-Month Report	Report OK
HDE 1-year Annual Report	Report OK
PAS 12-Month Report	Report OK
PAS 18-Month Report	Report OK
PAS 24-Month Report	Report OK
HDE 2-year Annual Report	Report OK
PAS 36-Month Report	Report OK
HDE 3-year Annual Report	Report OK
PAS 48-Month Report	Report OK
HDE 4-year Annual Report	Report OK

V. SUMMARY OF CLINICAL DATA USED TO SUPPORT HDE APPROVAL

A clinical study was performed to support the safety and probable benefit of the Minimally Invasive Deformity Correction System for subjects with adolescent idiopathic scoliosis and documented in the Summary of Safety and Probable Benefit (SSPB). As of September 15, 2018, the MID-C System was implanted in 252 patients outside the US (OUS) and included clinical data from the following sources: (1) OUS prospective, multi-center, non-randomized, open label

investigation in 20 subjects, (2) OUS commercial use on 197 patients, (3) OUS commercial use post-market prospective study on 26 subjects, and (4) OUS special access on 9 patients.

A target population (n=25) of all patients implanted with the HDE Device Version of the MID-C System as of September 15, 2018 was initially identified with the following criteria:

Target Population Indications

- Lenke type 1 or 5 curves
- Pre-operative Cobb angle between 45 to 60 degrees (inclusive)
- Flexible major curve (defined as lateral bending correction of 30 degrees or less)
- Thoracic kyphosis less than 55 degrees

To capture a larger sample size, an expanded population (n=49) was included that met an expanded US Indications for Use, as approved by supplement on December 16, 2019, defined by the following criteria:

Expanded Target Population Indications

- Lenke type 1 or 5 curves
- Pre-operative Cobb angle between 40 to 60 degrees (inclusive)
- Flexible major curve (defined as lateral bending correction of 30 degrees or less)
- Thoracic kyphosis less than 55 degrees

The majority of the subjects were female (42/47, 89.4%), and the mean age at time of surgery was 15.0 years. Common primary assessments collected for all subjects were: skeletal maturity as determined by Risser grade and curve magnitude as determined by Cobb angle.

The prespecified primary probable benefit endpoint of the study was:

- Cobb angle at 24 months post-implantation, with success defined as a major Cobb angle of less than or equal to 35 degrees and no curve progression greater than 10 degrees compared to baseline

To more fully understand the probable benefits of the MID-C System, ApiFix also conducted additional subgroup analyses that varied the Cobb angle threshold as described above:

- Main Cobb angle $\leq 40°$ and no curve progression greater than 10° compared to baseline
- Main Cobb angle $\leq 45°$ and no curve progression greater than 10° compared to baseline
- Main Cobb angle $\leq 50°$ and no curve progression greater than 10° compared to baseline

These additional endpoints were assessed based on published literature establishing 40-50° as thresholds at which risk of subsequent curve progression is low.[1]

Individual subject success was defined as achievement of a Cobb angle less than or equal to 35 degrees at 24 months post-surgery. Six (6) out of the 8 subjects in the target population (75%) and 18 out of the 20 subjects in the expanded population (90%) with 24-month data met the success criteria in this study and were considered probable benefit successes. At the last follow-

up visit greater than 24 months, all 20 patients in the expanded population had improvement of the primary Cobb angle (greater than 5 degrees compared to baseline), including the 2 patients who did not meet the primary probable benefit endpoint. The average improvement of the primary Cobb angle for these 20 patients is calculated as approximately 21 degrees compared to the average baseline Cobb angle of 45 degrees, resulting in approximately 40-50% curve correction. Furthermore, assessment of skeletal maturity concludes 86% of these patients were skeletally mature at the 24-month timepoint.

The primary safety endpoint evaluated was reoperation performed for any reason at any timepoint and included all serious adverse events (SAEs) that resulted in reoperation. In this clinical study AE data were classified as either device related AE or SAE. AE data were available for 63 patients and included 21 patients (33.3%) who reported an AE. The most common AE event types reported were pain (11/63, 17.5%), nausea and vomiting (3/63, 4.8%), and limited movement range of the spine (3/63, 4.8%). The non-serious AE data did not raise any notable safety concerns.

Reoperations occurred in 45 out of 252 subjects (17.9%). Many of these reoperations occurred early in the use of the device and were attributed to an initial technology learning curve. This learning curve is present with similar devices used for spinal fusion in AIS with re-operation rates as high as 17.1% reported in a five-year cohort[2]. However, when limiting the reoperation rate to the expanded population, the reoperation rate falls to 6 out of 49 subjects (12.2%) which is comparable to historical literature and database reported rate of 8.5% at 2-years for target AIS population. No deaths or neurologic AEs were reported.

As the MID-C System is a non-fusion treatment, it offers patients the potential to avoid the long-term adverse consequences associated with fusion which include decreased spinal motion, pseudarthrosis, adjacent spinal segment degeneration, neurological complications, pain, implant failure or breakage, and subsequent surgical intervention.

Patient perspectives were considered as an additional factor in the determination of probable benefits and risks for the device through the administration of patient questionnaires.

1. A patient satisfaction questionnaire was administered following the clinical study. Patients were asked to score their responses to three questions on a scale of 1 to 5, with 1 being the most negative response and 5 being the most positive. 36 out of 45 patients (80%) reported they agree or strongly agree that they would have the procedure again (scores of 4 or 5). Similarly, 38 of 45 patients (84%) agreed or strongly agreed that they would recommend the procedure to another person (scores of 4 or 5). Lastly, 38 of 45 patients (84%) rated their general satisfaction with the procedure/treatment as a 4 or 5.

2. Scoliosis Research Society (SRS-22) survey: The SRS-22 survey was collected for the 20 patients in the pilot study. This survey consists of 22 questions, which are grouped into the following sub-score categories: function, pain, self-image, mental health and satisfaction with back management. For each sub-score, higher scores indicate more positive responses. Overall, there was consistent improvement across sub-scores to two years in both cohorts.

In conclusion, given the available information above, the data on the Minimally Invasive Deformity Correction System collected under the study support that the probable benefits outweigh the probable risks for use of this device for treatment of select patients with adolescent 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. Given that only one of the MID-C systems should be necessary to treat an individual the total ADN for MID-C System is 8,000.

The fourth HDE Annual Report was submitted on August 21, 2023, which included the Reporting Period from August 24, 2022 through July 1, 2023. The 48-Month PAS Report was submitted on August 9, 2023 and included the Reporting Period from August 23, 2019 through June 18, 2023. Table 2 provides the number of devices distributed in the fourth year (August 2022-July 2023). To date, there have been 226 HDE approved MID-C System devices distributed on the U.S. market, with the first patient treated with the device on June 30, 2020.

Table 2. Annual Distribution Number – Reporting Period: August 2022-July 2023

Device	Annual Distribution Limit	Total since HDE Approval (as of 7/1/23)	Reporting Period Total (8/2022-7/2023)
MID-C System	8,000	226	90

Of note: the first procedure conducted with the MID-C System was conducted OUS in April 2012. From that date until October 1, 2023 a total of 254 devices have been distributed in the US while a total of 861 devices have been distributed worldwide with the same number of procedures performed. Thus, 607 devices have been distributed OUS from April 2012 to October 1, 2023.

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

PAS Conditions of Approval

The MID-C System HDE (H170001) was approved on August 20, 2019.

The objective of the PAS is to assess the ongoing safety and probable benefit of the MID-C System in a registry population.

The MID-C System Registry is a multi-center, single-arm, prospective post-approval registry study to provide ongoing safety and probable benefit assessment of the MID-C System in treatment of patients with adolescent idiopathic scoliosis. Skeletal maturity will be assessed using the Risser grade, Sanders score, or a combination of the two. All patients treated in the first 24-months should be enrolled and followed through 60-months from the time of each patient's index surgery, with interim visits at the immediate post-operative time point up to 6-weeks, 6-months, 12-months and annually thereafter post-procedure. A minimum number of 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 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, AE severity and rate of reoperation, including by type of reoperation.

The current primary probable benefit endpoint identified as a Condition of Approval in the HDE Approval Order is maintenance of major Cobb angle less than or equal to 40 degrees at 60-months post-surgery.

Secondary endpoints will be analyzed annually up to 60-months post-surgery, and will include the following:

1. Maintenance of major Cobb angle less than or equal to 40 degrees.
2. Curve progression no greater than 10 degrees of the secondary curve above or below the implant.
3. Composite endpoint analysis (maintenance of major Cobb angle less than or equal to 40 degrees AND freedom from SAEs during MID-C 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 curve progression at defined follow-up compared to baseline OR death OR permanent disability.

All safety and probable benefit data will be collected at the following time points: pre-operative, immediate post-operative up to 6-weeks, 6-months, 12-months, and annually thereafter until 60-month post-operative data from each patient are collected. 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 pediatric patients (defined as persons younger than 22 years of age) that require surgical treatment or have failed non-surgical treatments to obtain and maintain correction of progressive spinal deformities with a Cobb angle of 30-60 degrees, with a flexible curve, and thoracic kyphosis less than 55 degrees, as measured from T5 to T12.

PAS Study Status

The original PAS protocol was accepted on October 23, 2019 and the forty-eight-month PAS report was approved on September 7, 2023. As of this date, eighteen (18) sites have study IRB approval with a total of one hundred and fifty-five (155) patients enrolled. This study is estimated to last a total of 84 months from the date of PAS approval.

One hundred and fifty-five (155) patients have surgery dates scheduled, one hundred and fifty-five (155) patients have undergone implantation, one hundred and forty-five (145) patients have six-week follow-up, one hundred and twenty-one (121) patients have six-month follow-up, eighty-nine (89) patients have twelve-month follow-up, and twenty-eight (28) patients have twenty-four-month follow-up. Patient demographics and follow-up are summarized below in Table 3 and Table 4.

Table 3. PAS Patient Demographics

Patient Demographics	
N	155
Age (years) at Surgery	14.8 ± 2.1
Sex	75% (117/155) Females 25% (38/155) Males
Risser Sign	0 – 18.7% (29/155) 1 – 5.8% (9/155) 2 – 7.1% (11/155) 3 – 17.4% (27/155) 4 – 31.6% (49/155) 5 – 18.7% (29/155) Missing – 0.6% (1/155)
Lenke Class	66.5% (103/155) Lenke 1 32.9% (51/155) Lenke 5 0.6% (1/15) Missing

Source: Constructed based on data from H170001 annual reports

Table 4. PAS Patient Follow-up Status

Patient Follow-up per Study Visit	
Study Visit	Completed
Pre-Op	155
6-week	145
6-month	121
12-month	89
24-month	28
60-month	N/A

Source: Constructed based on data from H170001 annual reports

Interim Results:

Probable Benefit:

At the 6-week visit, the average major Cobb angle was 18.6° ± 6.9°, at the 6-month visit, all 117 patients (100%) had maintained a major Cobb angle less than 40°, 82 patients (99%) maintained a major Cobb angle less than 40° at the 12-month visit and 28 patients (100%) maintained a major Cobb angle less than 40° at the 24-month visit (Table 5). In 98% (81/83) of patients at the 6-month visit and 100% (31/31) of patients at the 12-month visit showed the secondary Cobb angle was improved from the pre-operative angle to 17.6° ± 9.3° and 17.4° ± 11.5°, respectively, and therefore showed reduction in curve size and no increase above 10° in the secondary curve (Table 6).

Table 5. PAS Probable Benefit Summary: Major Cobb Angle

Major Cobb Angle						
	Pre-Op	6-week	6-month	12-month	24-month	60-month
N	151	146	117	83	31	0
Cobb Angle	45.8 ± 7.0°	18.6 ± 6.9°	17.3 ± 8.5°	16.5 ± 9.6°	20.1 ± 9.2	-

Source: Constructed based on data from H170001 annual reports

Table 6. PAS Probable Benefit Summary: Secondary Cobb Angle

Secondary Cobb Angle						
	Pre-Op	6-week	6-month	12-month	24-month	60-month
N	151	146	115	83	31	0
Cobb Angle	30.1 ± 7.8°	18.0 ± 9.7°	17.6 ± 9.3°	17.4 ± 11.5	18.2 ± 11.0	-

Source: Constructed based on data from H170001 annual reports

Safety:

No serious adverse events have been reported to date.

VIII. ADVERSE EVENTS

Known Adverse Events

AEs collected during the clinical study that were used to support the safety and probable benefit of MID-C System in patients with adolescent idiopathic scoliosis were presented in the SSPB at the time of approval. For the initial target study population (n=252), 45 patients (17.9%) required reoperation. For the expanded target study population (n=49), 6 patients (12.2%) required reoperation. Table 7 lists all AE types reported in the clinical study, or identified by clinical experts, that were classified as related to the device or procedure.

Table 7. Known Adverse Event Types

AEs Related to Device or Procedure	Systemic AEs
1. Screw/nut loosening 2. Device loosening, migration, breakage, malposition 3. Sizing issues 4. Anatomic/technical difficulty 5. Inability to implant the device 6. Intraoperative device revision 7. Loss or inadequate curve correction 8. Curve development above and/or below the instrumented levels 9. Requirement for subsequent surgical intervention 10. Neurologic 11. Heterotopic ossification 12. Trunk imbalance	1. Deep vein thrombosis 2. Pulmonary embolism 3. Atelectasis, pneumonia 4. Cardiac 5. Dysphagia 6. Dysphonia 7. Gastrointestinal (ileus, ulceration, bleeding, malnutrition) 8. Foreign body reaction 9. Pressure sores 10. Genitourinary (infection, urine retention) 11. CSF leak/meningocele 12. Chest tube insertion 13. Infection (systemic)

13. Interference with imaging 14. Unintended spontaneous fusion 15. Bone fracture 16. Dural tear/leakage 17. Surgical site seroma, bursitis, crepitus 18. Skin penetration by device 19. Wound dehiscence 20. Hematoma 21. Wound infection, superficial, deep 22. Intraoperative neurologic injury 23. Intraoperative vascular injury, excessive blood loss, hypotension 24. Anesthesia, airway, ventilation 25. Visceral injury 26. Blood transfusion 27. Allergic reaction 28. Ophthalmic injury, including blindness 29. Pain (back, surgical site, extremity, other) 30. Infection 31. Device malfunction 32. Screw pull-out	14. Hematologic 15. Endocrine/metabolic 16. Hepatobiliary 17. Immunologic 18. Gynecologic 19. Ophthalmologic 20. Psychological 21. Surgical procedure: non-spinal 22. Wound infection: non-spinal 23. Death

From the AEs reported in Table 7, Table 8 summarizes the six (6) AE types that were classified as device or procedure-related SAEs. All SAEs required reoperation with device loosening, migration, breakage, and malposition being the most common (9/252, 3.6%) followed by loss or inadequate curve correction (8/252, 3.2%), infection (8/252, 3.2%), device malfunctions (6/252, 2.4%), screw pull-out (5/252, 2%), and screw/nut loosening (5/252, 2%). When restricting the analysis to patients who met the expanded US indications, the most common SAE requiring reoperation was procedure related (5/49, 10.2%) followed by device related (1/49, 2%).

Table 8. Known SAE Types Related to the MID-C System or Procedure

SAEs Related to MID-C System or Procedure
1. Device loosening, migration, breakage, malposition 2. Loss or inadequate curve correction 3. Infection 4. Device malfunctions 5. Screw pull-out 6. Screw/nut loosening

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 regulated devices. 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.

MDR's Associated with the MID-C System

The FDA's internal MDR Database was searched on October 1, 2023 utilizing the following search criteria:

1. Manufacturer Name "ApiFix and Brand Name "MID-C"
    - 74 unique MDRs were found
2. Manufacturer or Company Name "ApiFix"
    - No events not already contained in search criterion 1
3. Brand Name or Generic Name or Concomitant Product contains: "MID-C"
    - No events not already contained in search criterion 1
4. PMA/510K: "H170001" OR "170001"
    - No events pertaining to MID-C not already contained in search criterion 1

The search resulted in seventy-four (74) MDRs for the MID-C System. Thirty-one (31) MDRs took place within the US, while 43 MDRs took place OUS. Descriptive summaries of all 31 unique US MDRs this year are provided below.

United States (US) MDRs

MDR #1: 3013461531-2022-00052
The surgeon reported to the sponsor that at the one-year follow-up the patients (14-year-old female) implant had reached maximum elongation. Two months later, the surgeon successfully implanted a longer version of the implant. ApiFix investigated this event and stated that reoperation due to reaching max elongation is a known risk and the current incident rate was within the rate reported in the clinical trial.

MDR #2: 3013461531-2022-00055
The surgeon reported to the sponsor that during the index procedure the patient (16-year-old female) experienced a cerebral spinal fluid leak. After a blood patch procedure was performed, the patient was discharged. ApiFix investigated this event and stated that a Dural leak was a known risk, and the current incident rate was within the rate reported in the clinical trial.

MDR #3: 3013461531-2022-00057
The surgeon reported to the sponsor that after a motor vehicle accident, the patient (17-year-old male) experienced back pain. Imaging demonstrated implant breakage of the MID-C rod. The broken rod, extender, and two proximal screws were retrieved and replaced. ApiFix investigated this event and stated that, while uncommon, implant breakage can result from, among other causes, trauma or practicing high-demand sports.

MDR #4: 3013461531-2022-00059
The surgeon reported to the sponsor that at the one-month follow-up, the patient (16-year-old female) had wound dehiscence. The patient was hospitalized for one day for spine wound exploration, irrigation, debridement, and wound closure. ApiFix investigated this event and stated that wound complications were a known risk, and the current incident rate was within the rate reported in the clinical trial.

MDR #5: 3013461531-2022-00062
The surgeon reported to the sponsor that the patient (age and gender unknown) wanted the device removed. No reason was given.

MDR #6: 3013461531-2022-00066
The surgeon reported to the sponsor that the patient (19-year-old male) experienced back pain. Imaging showed screw migration. The surgeon removed the migrated screw and implanted a larger screw in its place. ApiFix investigated this event and stated that the current incident rate for screw misplacement/migration was within the reported rate in the clinical trial.

MDR #7: 3013461531-2022-00072
The surgeon reported to the sponsor that the patient's (18-year-old male) implant had broken at end-of-way. The surgeon removed the broken implant and replaced it with a larger MID-C

device. ApiFix investigated this event and stated that reoperation due to implant breakage and the implant reaching max elongation is a known risk and the current incident rate was within the rate reported in the clinical trial.

MDR #8: 3013461531-2022-00101
The surgeon reported to the sponsor that the patient's (17-year-old male) implant had a ratchet malfunction. The surgeon removed the malfunctioning implant and replaced it with a new implant. ApiFix investigated this event and stated that reoperation due to ratchet malfunction was within the rate reported in the clinical trial.

MDR #9: 3013461531-2022-00078
The surgeon reported to the sponsor that the patient (17-year-old female) was experiencing pain and wanted the device removed. ApiFix investigated this event and stated that pain is a known risk and was within the rate reported in the clinical trial.

MDR #10: 3013461531-2022-00076
The surgeon reported to the sponsor that the patient (20-year-old female) was experiencing back pain after throwing a football. Imaging showed a fractured screw. Revision surgery was conducted to replace the screw and implant a smaller MID-C System. ApiFix investigated this event and stated that the current incident rate for screw fracture was within the reported rate in the clinical trial.

MDR #11: 3013461531-2023-00001
The surgeon reported to the sponsor that the patient (17-year-old male) had a reoperation due to ratchet malfunction (MDR #8 above) and a new MID-C System was implanted. The device was removed due to early infection. ApiFix investigated this event and stated that early infection is a known risk and was within the rate reported in the clinical trial.

MDR #12: 3013461531-2023-00002
The surgeon reported to the sponsor that the patient (20-year-old female) had a revision surgery to replace a broken screw and implant a shorter MID-C System. ApiFix investigated this event and stated that screw fracture is a known risk and was within the rate reported in the clinical trial.

MDR #13: 3013461531-2023-00009
The surgeon reported to the sponsor that at the two-year follow-up, imaging showed that the patient's (13-year-old female) implant had reached max elongation and broken. The MID-C System was removed and not replaced. ApiFix investigated this event and stated that reoperation due to implant breakage and the implant reaching max elongation is a known risk and the current incident rate was within the rate reported in the clinical trial.

MDR #14: 3013461531-2023-00010
The surgeon reported to the sponsor that the patient (18-year-old female) underwent a removal of the MID-C System as the implant had reached max elongation. ApiFix investigated this event and stated that reoperation due to the implant reaching max elongation is a known risk and the current incident rate was within the rate reported in the clinical trial.

MDR #15: 3013461531-2023-00013
The surgeon reported to the sponsor that the patient's (19-year-old male) implant was broken. The patient noted they had a fall 6 months earlier which might have contributed. Reoperation replaced the MID-C System. ApiFix investigated this event and stated that, while uncommon, implant breakage can result from, among other causes, trauma or practicing high-demand sports.

MDR #16: 3013461531-2023-00016
The surgeon reported to the sponsor that the patient (age unknown female) fell while doing box jumps and started experiencing pain and hearing noises around the device. Initial imaging did not show signs of breakage, so the surgeon recommended conservative treatment in lieu of reoperation. Two months later, the surgeon saw the patient at the two-year follow-up and imaging showed implant breakage; however, the patient opted for no reoperation as no pain remained. ApiFix investigated this event and stated that, while uncommon, implant breakage can result from, among other causes, trauma or practicing high-demand sports.

MDR #17: 3013461531-2023-00017
The surgeon reported to the sponsor that the patient (16-year-old male) underwent revision surgery due to implant breakage at max elongation. A larger MID-C System was implanted with no issue. ApiFix investigated this event and stated that reoperation due to implant breakage and the implant reaching max elongation is a known risk and the current incident rate was within the rate reported in the clinical trial.

MDR #18: 3013461531-2023-00022
The surgeon reported to the sponsor that the patient (14-year-old male) underwent revision surgery due to screw pull-out and spinal imbalance. One year later, the implant was removed the patient was converted to fusion. ApiFix investigated this event and stated that the patient did not have AIS and was therefore, outside the Indications for Use.

MDR #19: 3013461531-2023-00023
The surgeon reported to the sponsor that the patient (age unknown female) underwent reoperation due to screw fracture of a non-ApiFix pedicle screw. ApiFix investigated this event and stated that screw fracture is a known risk and was within the rate reported in the clinical trial.

MDR #20: 3013461531-2023-00024
The surgeon reported to the sponsor that the patient's (12-year-old female) implant had reached max elongation, so reoperation replaced the MID-C System with a larger device. ApiFix investigated this event and stated that reoperation due to the implant reaching max elongation is a known risk and the current incident rate was within the rate reported in the clinical trial.

MDR #21: 3013461531-2023-00026
The surgeon reported to the sponsor that the patient (17-year-old male) experienced pain off and on with activities and imaging confirmed that the implant broke. The implant was removed, and the patient was converted to fusion. During the reoperation, the surgeon noted grade 1 metallosis, but did not biopsy as there was no concerning tissue nor signs of infection. ApiFix investigated this event and stated that, while uncommon, implant breakage can result from, among other causes, trauma or practicing high-demand sports. Additionally, ApiFix believes the metallosis

noted by the surgeon is wear of the ADLC coating which was known and characterized by the clinical trial/biocompatibility testing to be non-harmful.

MDR #22: 3013461531-2023-00027
The surgeon reported to the sponsor that the patient (14-year-old female) underwent removal surgery due to imaging showing screw migration. The patient was converted to MAGEC Rods as temporizing device until definitive fusion. ApiFix investigated this event and stated that reoperation due to the screw migration is a known risk and the current incident rate was within the rate reported in the clinical trial.

MDR #23: 3013461531-2023-00031
The surgeon reported to the sponsor that the patient (14-year-old female) was experiencing pain and imaging confirmed a broken screw. Reoperation replaced the broken screw. ApiFix investigated this event and stated that screw fracture is a known risk and was within the rate reported in the clinical trial.

MDR #24: 3013461531-2023-00032
The surgeon reported to the sponsor that the patient (15-year-old female) underwent reoperation due to ratchet malfunction. A new MID-C System was implanted. ApiFix investigated this event and stated that reoperation due to ratchet malfunction was within the rate reported in the clinical trial.

MDR #25: 3013461531-2023-00033
The surgeon reported to the sponsor that the patient (13-year-old female) underwent reoperation due to a loose screw and the device had reached max elongation. A larger device was successfully implanted. ApiFix investigated this event and stated that reoperation due to the implant reaching max elongation is a known risk and the current incident rate was within the rate reported in the clinical trial.

MDR #26: 3013461531-2023-00034
The surgeon reported to the sponsor that the patient (11-year-old female) underwent reoperation due to the device reaching max elongation. A larger device was successfully implanted. ApiFix investigated this event and stated that reoperation due to the implant reaching max elongation is a known risk and the current incident rate was within the rate reported in the clinical trial.

MDR #27: 3013461531-2023-00038
The surgeon reported to the sponsor that the patient's (15-year-old male) implant had reached max elongation and the secondary curve had progressed. A larger MID-C System was implanted, but after one year, the patient was converted to fusion due to progression of the thoracic scoliosis. ApiFix investigated this event and stated that reoperation due to curve progression is a known risk and the current incident rate was within the rate reported in the clinical trial.

MDR #28: 3013461531-2023-00040
The surgeon reported to the sponsor that the patient (19-year-old male) underwent reoperation due to screw fracture of a non-ApiFix pedicle screw. ApiFix investigated this event and stated that screw fracture is a known risk and was within the rate reported in the clinical trial.

MDR #29: 3013461531-2023-00041
The surgeon reported to the sponsor that the patient (16-year-old female) underwent reoperation due to the device reaching max elongation. The surgeon moved the proximal screws down one level rather than replace the MID-C System for a larger implant. ApiFix investigated this event and stated that reoperation due to the implant reaching max elongation is a known risk and the current incident rate was within the rate reported in the clinical trial.

MDR #30: 3013461531-2023-00042
The surgeon reported to the sponsor that the patient (17-year-old female) experienced pain and imaging confirmed distal screw breakage. The patient was given a corset brace and followed. No revision surgery occurred. ApiFix investigated this event and stated that screw fracture is a known risk and was within the rate reported in the clinical trial.

MDR #31: 3013461531-2023-00045
The surgeon reported to the sponsor that the patient (17-year-old female) felt clicking for several weeks and imaging confirmed screw breakage. A revision surgery was planned but has not occurred as of the date of this report. ApiFix investigated this event and stated that screw fracture is a known risk and was within the rate reported in the clinical trial.

A summary of all 31 unique US MDRs this year is shown in Table 9.

Table 9. US MDRs

Adverse Event Type	Number of Events	Source
Implant Breakage	7	FDA's internal MDR search
Screw Fracture	7	FDA's internal MDR search
Max Elongation Reached	6	FDA's internal MDR search
Screw Pull Out/Migration	2	FDA's internal MDR search
Ratchet Malfunction	2	FDA's internal MDR search
Implant Removal: Reason Unknown	2	FDA's internal MDR search
Infection	1	FDA's internal MDR search
Wound Dehiscence	1	FDA's internal MDR search
Patient Unhappy	1	FDA's internal MDR search
Lack of Correction	1	FDA's internal MDR search
CSF Leak	1	FDA's internal MDR search
Total	31	FDA's internal MDR search

Outside of the United States (OUS) MDRs

It is important to note that a significant number of devices implanted OUS are of an older MID-C device generation with a wider range of Indications for Use. A higher rate of AEs was observed in devices implanted OUS compared to those approved in the US. As such, OUS AEs are not necessarily indicative of current or future US AEs, however, they are useful to examine. A summary of all 43 unique OUS MDRs this year is shown in Table 10.

Table 10. OUS MDRs

Adverse Event Type	Number of Events	Source
Implant Breakage	7	FDA's internal MDR search
Max Elongation Reached	7	FDA's internal MDR search
Screw Pull Out/Migration	6	FDA's internal MDR search
Implant Removal: Skeletal maturity reached with acceptable correction	5	FDA's internal MDR search
Lack of Correction	5	FDA's internal MDR search
Ratchet Malfunction	4	FDA's internal MDR search
Infection	3	FDA's internal MDR search
Implant Removal: Reason Unknown	2	FDA's internal MDR search
Pain	1	FDA's internal MDR search
Screw Fracture	1	FDA's internal MDR search
Extender Misalignment	1	FDA's internal MDR search
Osteolysis	1	FDA's internal MDR search
Total	43	FDA's internal MDR search

Discussion on Black Residue/Black Discoloration

The black residue/black discoloration in the tissue surrounding the MID-C system that was noted in 2022 in two MDRs and was seen in one MDR this year. ApiFix stated that the black residue/black discoloration may be the result of Amorphous Diamond-Like Coating (ADLC) wear which was a known occurrence at HDE approval. All moving titanium components of the MID-C System are coated with an ADLC layer to improve wear resistance. Examples of ADLC coated components are shown in Table 11. All observations were reported in addition to another primary event; the black discoloration events were observed during the course of reoperation surgery and has not been attributed to any serious or symptomatic AEs.

Table 11. ADLC Coated Components of the ApiFix Rod

Device Region	Image
Base	
Pole	
Spherical Ring	

Additionally, ApiFix conducted histologic evaluations on tissue samples containing said black discoloration. These evaluations largely reported little/no necrosis, and minimal fibrosis while one evaluation reported fibrosis, wear debris, macrophages, and edema. ApiFix states that the minimal levels of necrosis, fibrosis, wear debris, macrophages, and edema found are likely due to the trauma of breakage of the implant and not due to implant composition.

True Failure Analysis

True failure rate analysis was performed for all patients with X-ray measurements available in the ApiFix registry. Patients with missing data or available X-rays that were not yet measured were not accounted for in the analysis. Per the study protocol, True failure rate analysis is defined as conversion to another spinal implant OR major Cobb angle that exceeded 40° at defined follow-up visit OR any curve progression at defined follow-up compared to baseline OR death, OR permanent disability. Table 12 demonstrates a success rate of 100%, 96% and 85% at 6-months, 12-months, and 24-months, respectively, from the true failure analysis.

Table 12. True Failure Rate Analysis

Population	Visit	Success		Failure		All	
		n	%	n	%	N	%
PAS all population	6 months	123	100%	0	0%	123	100%
	12 months	86	96%	4	4%	90	100%
	24 months	34	85%	6	15%	40	100%
	Total	147	96%	6	4%	153	100%

Summary of MDRs

As of October 1, 2023, a total of one-hundred and ninety-two (192) worldwide MDRs have been identified related to the ApiFix MID-C System since HDE approval. Though the discoloration of tissue reported last year in two OUS MDRs and this year in one MDR can be a sign of metallosis and additional safety concerns, the discoloration presented by the MID-C System is not an unanticipated finding for metallic implants with ADLC coatings and does not appear to be harmful based on available data. However, additional monitoring will be conducted as minimal data has been collected in the US with only 254 subjects currently implanted and only 89 subjects reporting data out to 12 months (as of June 18, 2023). Table 13 summarizes all MDRs associated with the MID-C System. As of October 2023, the MDRs reported represent a 20.08% rate in the US and a 22.30% rate worldwide most resulting in reoperation. While the MDR rate is not a direct view of the AE rate, it is slightly higher than the AE rate in the Summary of Safety

and Probable Benefit (SSPB) for the MID-C HDE which showed a 12.2% AE rate in the US and a 17.9% AE rate worldwide.[4] By comparison, spinal fusion surgery for AIS can expect a reoperation rate of 4.1% at 24-months[3] and 9.9% at 60-months[2], while The Tether™ – Vertebral Body Tethering System, a non-fusion spinal device intended for treatment of AIS, has a secondary surgery rate, composed of both revisions and reoperations, of 14.0%.[5] The increase in the MID-C System MDR rate makes it slightly higher than the AE rate for both fusion and other non-fusion spinal devices, but does not appear to present a new safety signal at this time and will be closely monitored.

Table 13. MDR Rate

	Total (OUS and US)		US	
	MDRs	Rate	MDRs	Rate
Up to December 1, 2021	62	10.37% (62/598)	5	5.26% (5/95)
December 1, 2021 – October 1, 2022	56	43.08% (56/130)	15	20.27% (15/74)
October 2, 2022 – October 1, 2023	74	50.64% (74/133)	31	36.47% (31/85)
Cumulative	192	22.30% (192/861)	51	20.08% (51/254)

Literature Review

A clinical literature search in PubMed was performed by the FDA for articles published from December 2022 through October 2023. The following terms were used: "ApiFix", "MID-C", "QGP", "Posterior Ratcheting Rod System". The following inclusion/exclusion criteria were used to further refine the articles to ones relevant for this HDE:

Inclusion Criteria:

- It provides relevant information regarding technical and clinical features of the device subject of the search, or
- It provides relevant information regarding performance and/or safety of the device subject of 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

- Review papers
- Tethered spinal cord studies
- Foreign language (non-English) literature

After reading the titles, abstracts, and full-texts, and applying the inclusion/exclusion criteria, two articles were found in this reporting period.[6,7] The first retroactively evaluated the surgical site infection rate of 44 patients between 2016 to 2022.[6] It found two patients with early onset infection and one patient with a skin ulcer due to septic screw loosening. They concluded that the risk of surgical site infection is always present, but more trials should be conducted. The second evaluated the 24-month follow-up reports of 36 patients between 2018 and 2020.[7] It found an improvement in the major curve and 11 AEs, four due to continued growth of the patient and seven due to infections or problems with the anchorage of the implant. They concluded patients with the MID-C System showed significant improvement in the major curve with an expected AE rate.

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 MID-C System. It does not appear that any additional safety signals nor concerns have arisen since HDE approval.

IX. SUMMARY

Evaluation of data available to CDRH, including the HDE 3-year Annual Report, MDRs, published scientific literature, and correspondence with the sponsor, has identified no new safety signals compared to what was known and anticipated at the time of HDE approval in August 2019. Additionally, the MID-C System has been continually redesigned with updates since HDE approval. These changes were intended to mitigate early known AEs and improve the safety and probable benefit profile of the device. Based on the available data, and considering the probable benefits and risks, the 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 2024:

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

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