FDA Executive Summary

Prepared for the
Spring 2022 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.

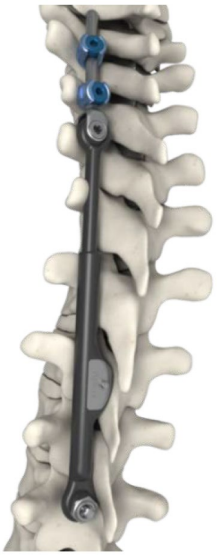
Modifications from the Humanitarian Use Device (HUD) Designation:
The Indication for Use statement was modified from that granted for the HUD designation to have a more stringent (30 versus 35 degrees) major curve side-bending reduction criterion to ensure a flexible curve and Cobb angle criteria were 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) is 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:	Ti-6Al-4V ELI (ASTM F136) Coated with ADLC
		85mm	30	
		95mm	30	
		105	40	
		115	40	
		125	50	
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 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

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 to be 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. POSTMARKET DATA: ANNUAL DISTRIBUTION NUMBER

Section 520(m)(6)(A)(ii) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) allows HDEs indicated for pediatric use to be sold for profit as long as the number of devices distributed in any calendar year does not exceed the annual distribution number (ADN). On December 13, 2016, the 21st Century Cures Act (Pub. L. No. 114-255) updated the definition of ADN to be the number of devices "reasonably needed to treat, diagnose, or cure a population of 8,000 individuals in the United States." Based on this definition, FDA calculates the ADN to be 8,000 multiplied by the number of devices reasonably necessary to treat an individual. 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 second HDE Annual Report was submitted on August 24, 2021 which included the Reporting Period from August 24, 2020 through August 23, 2021. The 24-Month PAS Report was submitted on August 19, 2021 and included the Reporting Period from August 23, 2019 through August 15, 2021. Table 2 provides the number of devices distributed in the second year (August 2020-August 2021). To date, there have been 79 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 2020-August 2021

Device	Annual Distribution Limit	Previous Reporting Period Total (as of 8/23/20)	Reporting Period Total (8/2020-8/2021)
MID-C System	8,000	3	76

Of note: the first procedure conducted with the MID-C System was conducted OUS in April 2012. From that date until December 1, 2021 a total of 95 devices have been distributed in the US while a total of 598 devices have been distributed worldwide with the same number of procedures performed. Thus, 503 devices have been distributed OUS since April 2012.

VII. POSTMARKET 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 twenty-four-month PAS report was approved on September 13, 2021. As of this date, fifteen (15) sites have study IRB approval with a total of seventy-one (71) patients enrolled and five (5) more sites are under active IRB review. This study is estimated to last a total of 84 months from the date of PAS approval.

Seventy-one (71) patients have surgery dates scheduled, sixty-nine (69) patients have undergone implantation, sixty-two (62) patients have six-week follow-up, twenty-six (26) patients have six-month follow-up, and three (3) patients have twelve-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	69
Age (years) at Surgery	14.7 ± 2.2
Sex	75% (53/71) Females 25% (18/71) Males
Risser Sign	0 – 24.3% (17/70) 1 – 4.3% (3/70) 2 – 7.1% (5/70) 3 – 17.1% (12/70) 4 – 31.4% (22/70) 5 – 15.7% (11/70)
Lenke Class	67.1% (47/70) Lenke 1 32.9% (23/70) Lenke 5

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	71
6-week	62
6-month	26
12-month	3
24-month	N/A
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 18.2° ± 6.8° and at the 6-month visit, all 15 patients (100%) had maintained a major Cobb angle less than 40° (Table 5). At the 6-week and 6-month visits, the secondary Cobb angle was improved from the pre-operative angle to 16.6° ± 10.1° and 18.8° ± 11.0°, respectively, and therefore no curve progression had occurred (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	51	45	15	3	0	0
Cobb Angle	46.4 ± 7.5°	18.2 ± 6.8°	19.3 ± 9.6°	*	-	-

Source: Constructed based on data from H170001 annual reports, * Cobb angle measurements pending

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	50	45	15	3	0	0
Cobb Angle	29.2 ± 7.4°	16.6 ± 10.1°	18.8 ± 11°	*	-	-

Source: Constructed based on data from H170001 annual reports, * Cobb angle measurements pending

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 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	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) 14. Hematologic 15. Endocrine/metabolic 16. Hepatobiliary 17. Immunologic 18. Gynecologic 19. Ophthalmologic

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	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 December 9, 2021 utilizing the following search criteria:

1. Product code QGP (Posterior Ratcheting Rod System)
    - 46 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. Brand Name contains: "MINIMALLY” and “INVASIVE” and “DEFORMITY"
    - No events not already contained in search criterion 1

The search resulted in forty-six (46) MDRs for the MID-C System. Five (5) MDRs took place within the US, while 41 MDRs took place OUS.

United States (US) MDRs

MDR #1: 3013461531-2020-00018
The distributor reported to the sponsor that the patient (age and gender unknown) complained about lumbar pain and requested that the implant be removed. ApiFix investigated this event and stated pain is an identified AE. Additionally, post-removal the patient looks balanced with good correction maintained.

MDR #2: 3013461531-2021-00016
The surgeon reported to the sponsor that the patient (age and gender unknown) felt local discomfort and had a bursa over the distal implant. ApiFix investigated this event and stated the patient was implanted with an old version of the pedicle screw which, when implanted in smaller and thinner patients, runs the risk of being prominent. In response to this type of complaint, ApiFix has introduced low-profile pedicle screws which have decreased the rate of implant prominence from 1.5% to 0.53%.

MDR #3: 3013461531-2021-00033
The surgeon reported to the sponsor that the MID-C rod implanted in a patient (age and gender unknown) broke. X-ray evaluation implied that the failure was caused due to progression of the kyphosis. ApiFix investigated this event and stated that implant breakage can result from development of hyperkyphosis. At the time of this event, device breakage rate due to any reason was 4.28%.

MDR #4: 3013461531-2021-00034
The surgeon reported to the Sponsor that the distal screw implanted in a patient (age and gender unknown) had begun to pull out. ApiFix investigated this event and stated that the surgical technique was not followed correctly during implantation. The surgeon was contacted and retrained on the surgical technique. At the time of this event, the current device screw pull-out rate due to any reason was 1.39%.

MDR #5: 3013461531-2021-00035
X-rays of the patient (age and gender unknown) demonstrated implant breakage. ApiFix investigated this event and stated that patient exercise might have contributed to the implant breakage. At the time of this event, the current device breakage rate due to any reason is 4.46%.
A summary of all 5 unique US MDRs to date (including MDRs from previous years) is shown in Table 9.

Table 9. US MDRs

Adverse Event Type	Number of Events*	Source
Implant Breakage/Issues	3	FDA's internal MDR search
Curve Correction Issues	1	FDA's internal MDR search
Pain	2	FDA's internal MDR search
Secondary Surgery	0	FDA's internal MDR search
Infection	0	FDA's internal MDR search
Bursitis	0	FDA's internal MDR search
Dorsal Fusion	0	FDA's internal MDR search

*Events are from a total of 5 MDRs with each MDR often containing multiple event types.

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 41 unique OUS MDRs to date (including MDRs from previous years) is shown in Table 10.

Table 10. OUS MDRs

Adverse Event Type	Number of Events*	Source
Implant Breakage/Issues	51	FDA's internal MDR search
Curve Correction Issues	10	FDA's internal MDR search
Pain	16	FDA's internal MDR search
Secondary Surgery	23	FDA's internal MDR search
Infection	2	FDA's internal MDR search
Bursitis	2	FDA's internal MDR search
Dorsal Fusion	1	FDA's internal MDR search

*Events are from a total of 41 MDRs with each MDR often containing multiple event types.

Most OUS MDRs contained expected AEs and clinical findings; however, two contained novel references to a "black residue" or a "black discoloration." These MDRs are discussed below.

MDR #3013461531-2021-00025
The distributor reported to the sponsor that the patient (age and gender unknown) had a removal surgery for an unknown reason. Furthermore, the distributor stated that during the procedure the "MID-C construct was contaminated with strange black residue inside the ratchet component. The material was (sic) been sent to histopathology for examination." In addition, the surgeon wrote to the company that signs of inflammation were present near the "junction connector-apifix." ApiFix investigated this event and requested additional information as well as the histological report findings four times, however, the surgeon did not reply.

MDR #3013461531-2021-00037
The surgeon decided to perform elective surgery to replace the existing MID-C rod implant with a longer size implant since the patient (age and gender unknown) had grown and the implant reached its maximal elongation. "During the reoperation, the surgeon detected a black discoloration of the tissue in the area of the implant." ApiFix investigated this event and stated that the surgeon took a tissue sample for laboratory investigation, however the tissue specimens were lost by the hospital and never delivered to the company. Neither the patient nor the surgeon mentions any related complaints or symptoms, including no systemic symptoms reported.

Discussion on Black Residue/Black Discoloration

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. The reported "black residue" / "black discoloration" may be the result of ADLC wear which was a known occurrence at HDE approval. 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	

Summary of MDR's

As of December 2021, a total of sixty-two (62) worldwide MDRs have been identified related to the ApiFix MID-C System since HDE approval, and all patients with reported gender/sex information were female. Though discoloration of tissue reported in two OUS MDRs 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 95 subjects currently implanted and only 3 subjects reporting data out to 12 months (as of August 15, 2021). Table 12 summarizes all MDR rates associated with the MID-C System. As of December 2021, the MDRs reported represent a 5.26% AE rate in the US and a 10.37% AE rate worldwide all resulting in reoperation. 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%.[4] Based on the comparable AE rate leading to reoperation for the MID-C System to both fusion and other non-fusion spinal devices, the MID-C System does not appear to present a new safety signal at this time.

Table 12. AE Rate

	Total (OUS and US)		US	
	MDRs	Rate	MDRs	Rate
Up to December 1, 2020	16	3.59% (16/446)	0	0% (0/6)
2021	46	30.26% (46/152)	5	5.62% (5/89)
Cumulative	62	10.37% (62/598)	5	5.26% (5/95)

Literature Review

A clinical literature search in PubMed was performed by the FDA for articles published from December 2020 through November 2021. The following terms were used: "ApiFix", "MID-C". 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 only one article was found.[5] This study was conducted OUS with a total of 20 patients where 4 serious adverse events were reported in 10 patients, all of which led to revision surgeries:

- Osteolysis:
  - 30% (n=6) compared to 0% (0/252) from clinical data results in the SSPB
- Screw and/or rod breakage:
  - 10% (n=2) compared to 1.2% (3/252) from clinical data results in the SSPB
- Failure of the ratchet mechanism:
  - 5% (n=1) compared to 0% (0/252) from the clinical data results in the SSPB
- Pain without explainable cause:
  - 5% (n=1) compared to 0.4% (1/252) from the clinical data results in the SSPB
- Total revisions
  - 50% (n=10) compared to 17.9% (45/252) in the total population and 12% (3/25) in the expanded population from the clinical data results in the SSPB

Summary of Literature

The 20-subject study found in this literature review shows a high percentage of subjects undergoing revision surgery (n=10, 50%) with a large proportion of revisions due to osteolysis (n=6, 30%). In comparison to this 20 subject study, five hundred and ninety-eight (598) devices have been implanted worldwide with sixty-two (62) reported MDR events of which 3 mention osteolysis. FDA requested further information from the manufacturer regarding these events. It was noted that the surgical technique for the ApiFix MID-C System has been updated since the initiation of the study, which could be contributing to the disproportionately high reoperation rate seen at the study center when compared to all other centers as seen in Table 13.

Table 13. Reoperations in Stadhouder et al.[5] Compared to All Other Sites

UMCA Study Center		All Other Centers
	% at UMCA Study Center (n=20)	Current Rate Controlled for Mitigation (n=250+)
Implant Breakage	5%	2.5%
Late Infection	15%	Not Reported
Pain	10%	Not Reported
Ratchet Backup	5%	1.1%
Screw Breakage	5%	1%
Screw Loosening	5%	0.5%

The study was also conducted using a second-generation MID-C System and a different Indications for Use than approved under the US HDE. The MID-C System approved for use in the US is the fourth-generation device with updated Indications for Use. To compare OUS data to that of the US, Table 14 was created by restricting OUS data to only patients implanted with devices and using Indications for Use identical to those cleared for use in the US. This comparison shows that when OUS data is restricted to the Indications for Use and MID-C device version of those approved for use in the US, the AE rate seen worldwide (7.68%) is comparable to the AE rate seen in the US (5.26%).

Table 14. OUS Data Restricted to US Approval

US Relevant Population Treated with Extender		
Re-operation Root Cause	N	Re-operation Rate Following Mitigations
Curve Progression	244	0.41%
Device Breakage	244*	2.28%
Late Infection	244	0.41%
Noise	244	0%
Pain	244	0.41%
Pedicle Breakage	244	0%
Prominent Hardware	244	0%
Ratchet Malfunction	244**	0.47%
Screw Breakage	173	0%
Nut Loosening	244**	0%
Screw Loosening	244	0.41%
Screw Pull-out	244	0.82%
Screw Misplacement/Migration	244	0.82%
Screw Protrusion	244	0%
Extender Misalignment	244	1.23%
Extender Selection	244	0.41%
Total		7.68%

*244 for most causes of device breakage, 214 for implants breakage due to end of way
**for ratchet malfunction not associated with trauma or sports N=215

While the list of adverse events is 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 MID-C System. Therefore, based on the lower AE rate seen in the HDE PAS to date (5.26%), the lower AE rate seen in the OUS data restricted to the approved US device generations and indications (7.68%), the lower AE rate seen worldwide (10.37%), the different surgical technique used at the center referenced in Stadhouder et al., and a newer generation of MID-C System with updated Indications for Use approved for use in the US under HDE, it does not appear that any safety signals nor significant concerns have arisen since HDE approval. However, FDA will continue to closely monitor the performance of the MID-C System and ensure a safe and probable benefit device profile is maintained for its intended patient population.

IX. SUMMARY

Evaluation of data available to CDRH, including the HDE 2-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 re-designed 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 2023:

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

X. REFERENCES

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