# FDA Executive Summary

Prepared for the **Spring 2021**, Meeting of 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 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 toT12.

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.

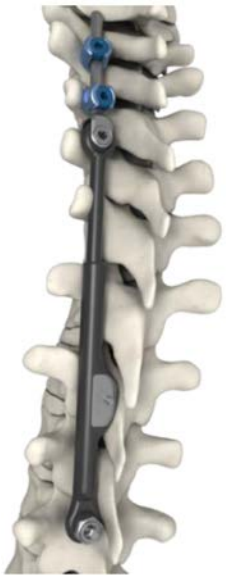
Modifications from the Humanitarian Use Device (HUD) Designation:
The Indication for Use statement was modified from that granted for the HUD designation to have a more stringent (30 versus 35 degrees) major curve side-bending reduction criterion to ensure a flexible curve and Cobb angle criteria were 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)<br><br>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)<br><br>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**

| File | Content | Status |
|---|---|---|
| H170001/R001 | PAS 6-Month Report | Report OK |
| H170001/R002 | HDE Annual Report | Report OK |
| H170001/R003 | PAS 12-Month 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 adverse event (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.

This device offers patients 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 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.

## VI. POSTMARKET DATA: ANNUAL DISTRIBUTION NUMBER

Section 520(m)(6)(A)(ii) of The Food, Drug, and Cosmetic Act (FD&C) 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 first HDE Annual Report (H170001/R001) was submitted on August 24, 2020 which included the Reporting Period from August 23, 2019 through August 23, 2020. The 12-Month Post-Approval Study (PAS) Report was submitted on September 23, 2020 and included the Reporting Period from August 23, 2020 through September 17, 2020. Table 2 provides the number of devices distributed in the first year (August 2019-August 2020) as well as the number of devices distributed in the following month in the United States. To date, there have been 6 cases of the HDE approved MID-C System on the U.S. market, with the first case performed on June 30, 2020.

**Table 2. Annual Distribution Number – Reporting Period: August 2019-September 2020**

| Device | Annual Distribution Limit | HDE Reporting Period (as of 8/23/20) | 12-month PAS Reporting Period Total | Reporting Period Total (8/2019-9/2020) |
|---|---|---|---|---|
| MID-C System | 8,000 | 3 | 6 | 6 |

Of note: the first procedure conducted with the MID-C System was conducted OUS in April 2012. From that date until December 2020 a total of 446 devices have been distributed worldwide with the same number of procedures performed. Thus, 440 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 is 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**

ApiFix is in the process of initiating the post-approval study. Twenty hospitals have been identified as potential sites and contacted regarding their potential participation in the PAS.

The PAS was approved on October 23, 2019. The twelve-month report was approved on October 8, 2020. As of this date, five (5) of the 20 potential clinical sites have been selected for patient enrollment with a total of 6 patients enrolled. This study is estimated to last a total of 84 months from the date of PAS approval.

## VIII. ADVERSE EVENTS

### Known Adverse Events

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. Two hundred and fifty-two (252) patients were implanted with the device and 45 patients (17.9%) required reoperation; however, with the expanded US indications cleared in the HDE expansion of patient population in November of 2019 the patients total drops to forty-nine (49) with 6 (12.2%) requiring reoperation. Table 3 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 3. Known Adverse Event Types**

| AEs Related to Device or Procedure | Potential Systemic AEs |
|---|---|
| 1. Screw/nut loosening<br>2. Device loosening, migration, breakage, malposition<br>3. Sizing issues<br>4. Anatomic/technical difficulty<br>5. Inability to implant the device<br>6. Intraoperative device revision<br>7. Loss or inadequate curve correction<br>8. Curve development above and/or below the instrumented levels<br>9. Requirement for subsequent surgical intervention<br>10. Neurologic<br>11. Heterotopic ossification<br>12. Trunk imbalance<br>13. Interference with imaging<br>14. Unintended spontaneous fusion<br>15. Bone fracture<br>16. Dural tear/leakage<br>17. Surgical site seroma, bursitis, crepitus<br>18. Skin penetration by device<br>19. Wound dehiscence<br>20. Hematoma<br>21. Wound infection, superficial, deep<br>22. Intraoperative neurologic injury<br>23. Intraoperative vascular injury, excessive blood loss, hypotension<br>24. Anesthesia, airway, ventilation<br>25. Visceral injury<br>26. Blood transfusion<br>27. Allergic reaction | 1. Deep vein thrombosis<br>2. Pulmonary embolism<br>3. Atelectasis, pneumonia<br>4. Cardiac<br>5. Dysphagia<br>6. Dysphonia<br>7. Gastrointestinal (ileus, ulceration, bleeding, malnutrition)<br>8. Foreign body reaction<br>9. Pressure sores<br>10. Genitourinary (infection, urine retention)<br>11. CSF leak/meningocele<br>12. Chest tube insertion<br>13. Infection (systemic)<br>14. Hematologic<br>15. Endocrine/metabolic<br>16. Hepatobiliary<br>17. Immunologic<br>18. Gynecologic<br>19. Ophthalmologic<br>20. Psychological<br>21. Surgical procedure: non-spinal<br>22. Wound infection: non-spinal<br>23. Death |

| | |
|---|---|
| 28. Ophthalmic injury, including blindness<br>29. Pain (back, surgical site, extremity, other)<br>30. Infection<br>31. Device malfunction<br>32. Screw pull-out | |

From the AEs reported in Table 3, Table 4 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 patients to those 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 4. 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<br>2. Loss or inadequate curve correction<br>3. Infection<br>4. Device malfunctions<br>5. Screw pull-out<br>6. Screw/nut loosening |

## Literature Review

A clinical literature search in PubMed was performed by the FDA for articles published from January 2019 to November 2020. 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 study
- 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.[3] This study was conducted OUS with a total of 45 patients and reported 4 adverse events, all of which led to revision surgeries:

- Screw misplacement/nut loosening/ratchet malfunction:
    - 6.6% (n=3) compared to 0 from clinical data results in the SSPB
- Screw pull-out
    - 2.2% (n=1) compared to 1.6% from clinical data results in the SSPB
- Total revisions
    - 8.9% (n=4) compared to 17.9% in the total population and 12.2% in the expanded population from the clinical data results in the SSPB

*Summary of Literature*

While the studies found in this literature review were limited, they suggest probable benefits of non-fusion spinal devices with respect to skeletally immature patients with idiopathic scoliosis. From the clinical data documented in the SSPB used to support safety and probable benefit for the MID-C System, a total of 66 adverse events were observed for 66 of the 252 total patients. All event types from the literature search were identified at time of HDE approval as potential adverse effects (i.e. complications) as documented in the SSPB. 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 MID-C 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.

*MDR's Associated with the MID-C System*

The FDA's internal MDR Database was searched on December 1, 2020 utilizing the following search criteria:

1. Product code QGP (Posterior Ratcheting Rod System)
    - 16 unique MDRs found
2. Manufacturer or Company Name "ApiFix"
    - 16 unique MDRs found; all relevant MDRs identical to results from search criterion 1
3. Brand Name or Generic Name or Concomitant Product contains: "MID-C"
    - 18 unique MDRs found; 3 were not relevant and the remaining 15 were identical to results from search criterion 1
4. Brand Name contains: "MINIMALLY" and "INVASIVE" and "DEFORMITY"
    - 0 unique MDRs found
5. Catalog Number begins with: "AF1", "AF8", or "AF9"
    - 48 unique MDRs found; 34 were not relevant and the remaining 14 were identical to results from search criterion 1
6. UDI Number contains: "729001499"
    - 14 unique MDRs found; all identical to results from search criterion 1
7. Voluntary Reports with Narrative Text containing: "APIFIX" or "MID-C"
    - 79 unique MDRs found; 0 relevant results

The search resulted in sixteen (16) MDRs, all of which occurred OUS between July 1, 2020 to November 16, 2020.

MDR #1: 3013461531-2020-00001
The surgeon reported to the sponsor that the one-year follow-up x-ray of a 16-year old patient (gender unknown) indicated an increase in the lumbar curve (11° to 27°). The thoracic curve correction is maintained and did not progress. ApiFix investigated this event and stated that this result is an outcome of placing the system in the wrong location; specifically, the implant was placed two levels above the recommended location.

MDR #2: 3013461531-2020-00002
The surgeon reported to the sponsor that a 14-year old patient (gender unknown) presented with insufficient curve correction in addition to trunk imbalance. ApiFix reviewed pre-op x-rays and determined the patient had a double curve (Lenke 2) with lateral bending of 50°. Since the MID-C System is indicated for patients with AIS classified as Lenke 1 or Lenke 5 having a Cobb angle up to 60° with only a single curve, the sponsor stated this result is an outcome of incorrect patient selection due to surgeon error.

MDR #3: 3013461531-2020-00003
The surgeon reported to the sponsor that at the 2-year follow-up a 10-year old female patient presented with light pain located at the thoracic hub for roughly 2-3 months prior and, on x-ray, a breakage of the MID-C System implant was seen. ApiFix investigated this event and stated that from the time of implantation to the 2-year follow-up the patients kyphosis significantly increased (from 49° at pre-op to roughly 70° at the last follow-up) and likely pushed against the center of the implant causing it to break.

MDR #4: 3013461531-2020-00004
A patient (age and gender unknown) will undergo a revision surgery due to secondary curve progression. ApiFix reviewed the patient's x-rays and determined that the secondary curve progressed (below the instrumented curve) likely related to the AIS disease state rather than the implant. Given the general complexity of the AIS disease state this type of event is not unexpected.

MDR #5: 3013461531-2020-00005
The surgeon reported to the sponsor that a patient (age and gender unknown) had a revision surgery due to implant breakage (screw and rod breakage) as indicated by x-ray. ApiFix reviewed the patient's x-rays and determined the implant breakage was likely due to an incorrect placement of the upper screw in the wrong trajectory locking the polyaxiality of the joint. Since the sponsor's training presentation in use during device implantation (November 2015) did not include an explanation of screw trajectory, the sponsor updated their training (November 2017) to include screw trajectory. No adverse events related to screw trajectory have been reported since the updated training.

MDR #6: 3013461531-2020-00006
The surgeon reported to the sponsor that a female patient (age unknown) presented with sudden pain and weakness and an x-ray indicated a breakage of the cranial screw. ApiFix investigated this event and stated that the risk of screw breakage had been quantified at the time of the event and an incident rate of 5.66% was found to be well within the rate reported in literature (0.2%-15.5%). However, the sponsor identified that 4.5mm screws many not be strong enough in some cases and stopped using them in 2018. To date, 356 patients were implanted with a larger screw size or an extender that is being supported by two screws resulting in no upper screw breakages reported since.

MDR #7: 3013461531-2020-00007
The surgeon reported to the sponsor a female patient (age unknown) heard and felt a "snap" in her back while sitting down and implant breakage was confirmed on x-ray. ApiFix reviewed the patient x-ray and stated that the system reached its maximal elongation length, which is the weakest point of the rod. Thus, in this position, the transverse process below the implant may generate a force acting on the system large enough to cause rod breakage. The sponsor states that this surgery was performed using a minimally invasive approach (MIS) which is not recommended by the sponsor as it makes correct sizing of the implant challenging. At the time of this report (August 2020) the incident rate due to implant breakage at maximal elongation is 0.93% and the overall incident rate for this category is 6.21% which is well within the reported literature for this category (0.2%-15.5%).

MDR #8: 3013461531-2020-00008
The surgeon reported to the sponsor a patient (age and gender unknown) had a follow-up x-ray which indicated a ratchet malfunction. ApiFix reviewed the patient x-ray and determined that the patient was outside the indications with a primary curve of 62° and a lateral bending of 40°. The patient was corrected to approximately 40° and the poor correction was attributed to a ratchet malfunction. Since the implant was not available for evaluation, the root cause of this event could not be determined.

MDR #9: 3013461531-2020-00009
The surgeon reported to the sponsor a 16-year old female patient demonstrated an implant breakage on x-ray. ApiFix reviewed the patient x-ray and stated that the system reached its maximal elongation length, which is the weakest point of the rod. Thus, in this position, the transverse process below the implant may generate a force acting on the system large enough to cause rod breakage. The sponsor states that this surgery was performed using a MIS approach which is not recommended by the sponsor as it makes correct sizing of the implant challenging. Given the reported literature rates for this category (0.2%-15.5%) the incident rate due to implant breakage at maximal elongation (0.98%) for the MID-C System and the overall incident rate for this category (6.5%) is not unexpected.

MDR #10: 3013461531-2020-00010
The surgeon reported to the sponsor a female patient (age unknown) complained of back pain located near the left scapula and, with time, the pain migrated above the upper screw. Blood tests did not show any signs of inflammation and her CT scan indicated that the screw slightly migrated into the spinal canal. This resulted in the surgeon removing the implant. ApiFix

investigated this event and stated that hospital lab tests verified late infection around the screw, which the sponsor stated caused the screw migration. Given the literature rates of infection in the AIS population (12.5%) the rate of infection at the time of the event (August 2020) for the MID-C System (4.87%) is not unexpected.

MDR #11: 3013461531-2020-00011
The surgeon reported to the sponsor a female patient (age unknown) demonstrated an implant breakage on x-ray. ApiFix investigated this event and stated that the patient was outside the device indications as she had a rigid curve as indicated by her lateral bending of 36° (the MID-C System is indicated for patients with an upper lateral bending limit of 30°). Furthermore, the sponsor states that this surgery was performed using a MIS approach which is not recommended by the sponsor. Given the reported literature rates for this category (0.2%-15.5%) the MID-C System overall incident rate for this category (6.5%) is not unexpected.

MDR #12: 3013461531-2020-00012
The surgeon reported to the sponsor a patient (age and gender unknown) had osteolysis of the proximal screw which migrated into the spinal canal resulting a removal surgery. ApiFix investigated this event and stated that osteolysis is often related to late-onset infection but is currently collecting information and as such the root cause of this event could not be determined.

MDR #13: 3013461531-2020-00013
The surgeon reported to the sponsor a patient (age and gender unknown) presented with the angle between the extender and rod increasing and the location of lower of the two cranial screws (T11) drifting. ApiFix investigated this event and stated that the surgeon did not use the extender measurement instrument correctly resulting in an incorrect angle between the extender and the MID-C rod. The incident rate due to extender misalignment (1.59%) at the time of this report (October 2020) does not increase the probability risk assessment and is therefore not unexpected.

MDR #14: 3013461531-2020-00014
The surgeon reported to the sponsor a patient (age and gender unknown) demonstrated ratchet malfunction on x-ray. ApiFix examined the x-rays and stated that the ratchet mechanism collapsed likely due tissue growth into the ratchet mechanism. Since the implant was not available for evaluation, the root cause of this event could not be determined. Given that the current incident rate of ratchet malfunction (7.99%) at the time of this event (November 2020) is in line with the rate of device related adverse events (15.5%), this type of event is not unexpected.

MDR #15: 3013461531-2020-00015
The surgeon reported to the sponsor a patient (age and gender unknown) that demonstrated implant breakage on x-ray. ApiFix investigated this event and stated that the patient was outside the device indications as they had a Lenke 3 curve. Furthermore, they stated the method of implant breakage is thought to be side forces acting on the implant due to the lower screw being inserted in an incorrect trajectory causing the lower part of the implant to be located above the spine instead of beside it. At the time of the report (November 2020) the rate of base breakage (0.69%) does not increase the probability risk assessment and is therefore not unexpected.

MDR #16: 3013461531-2020-00016
The surgeon reported to the sponsor a 14-year old female patient demonstrated ratchet malfunction on x-ray. ApiFix examined the x-rays and stated that the ratchet mechanism collapsed likely due tissue growth into the ratchet mechanism. Since the implant was not available for evaluation, the root cause of this event could not be determined. Given that the current incident rate of ratchet malfunction (6.78%) at the time of this event (November 2020) is in line with the rate of device related adverse events (15.5%), this type of event is not unexpected.

*Summary of MDR's*

As of December 2020, a total of sixteen (16) MDRs were identified related to the ApiFix MID-C System, and all patients with reported gender/sex information were female. . The MDRs found are all expected given the nature of the device surgery, immobilization and venous status while the patient is recumbent under anesthesia, and foreign body reaction. Table 5 summarizes all MDRs associated with the MID-C System. As of November 2020, the MDRs reported represent a 6.78% AE incident rate.

**Table 5. MDRs for the MID-C System**

| Adverse Event Type | Number of Events | Patient Age and Sex (if known) | Reason for AE | Source |
|---|---|---|---|---|
| Implant breakage | 7 | 10, female<br>16, female<br>3 Unknown ages, females<br>2 Unknown ages & genders | Maximal implant elongation :2<br>Off label use: 2<br>AIS progression: 1<br>Surgeon error: 1<br>Unknown: 1 | FDA's internal MDR search |
| Ratchet malfunction | 3 | 14, female<br>2 Unknown ages & genders | Tissue ingrowth: 2<br>Off label use: 1 | FDA's internal MDR search |
| Implant migration | 3 | Unknown age, female<br>2 Unknown ages & genders | Infection: 1<br>Surgeon error: 1<br>Unknown: 1 | FDA's internal MDR search |
| Increase in lumbar curve | 1 | 16, Unknown gender | Surgeon error: 1 | FDA's internal MDR search |
| Insufficient curve correction | 1 | 14, Unknown gender | Off-label use: 1 | FDA's internal MDR search |
| Secondary curve progression | 1 | Unknown age & gender | AIS progression: 1 | FDA's internal MDR search |

Note: Off-label use is defined as selection of patient outside indicated disease state.

## IX. SUMMARY

Evaluation of data available to CDRH, including the first 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. 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 2022:

- Annual distribution number
- Literature review
- MDR review

## X. REFERENCES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