SUMMARY OF SAFETY AND PROBABLE BENEFIT (SSPB)

I. GENERAL INFORMATION

Device Generic Name: Posterior Ratcheting Rod System

Device Trade Name: Minimally Invasive Deformity Correction (MID-C) System

Device Procode: QGP

Applicant's Name and Address: ApiFix, Ltd.
17 Tehelet Street
Misgav Business Park, 20174
Israel

Date(s) of Panel Recommendation: None

Humanitarian Device Exemption (HDE) Number: H170001

Humanitarian Use Device (HUD) Designation Number: DEV-2015-0345

Date of HUD Designation: December 21, 2015

Date of Notice of Approval to Applicant: August 23, 2019

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 45 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.

Modifications from the HUD Designation
The indications for use statement has been 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.

III. CONTRAINDICATIONS

The MID-C System should not be implanted in patients meeting any of the following conditions:

- Any type of non-idiopathic scoliosis,
- Thoracic kyphosis in excess of 55 degrees measured between T5 to T12,
- Any main thoracic deformity that includes vertebral levels including cranial to T2,
- Known history of existing malignancy, or any systemic infection, local infection, or skin compromise at the surgical site,
- Spinal cord abnormalities that require treatment,

- Presence of neurological deficit (defined as a motor grade of less than 5 out of 5), or
- Known poor bone quality defined as a T-score -1.5 or less.

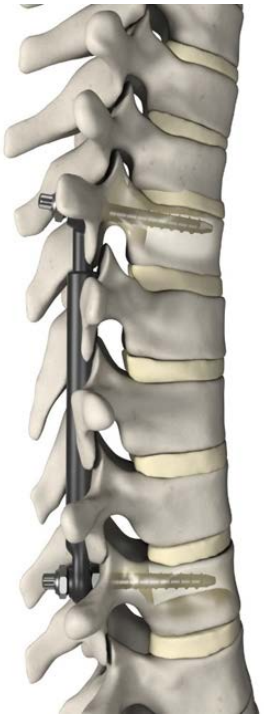
IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the MID-C System labeling.

V. DEVICE DESCRIPTION

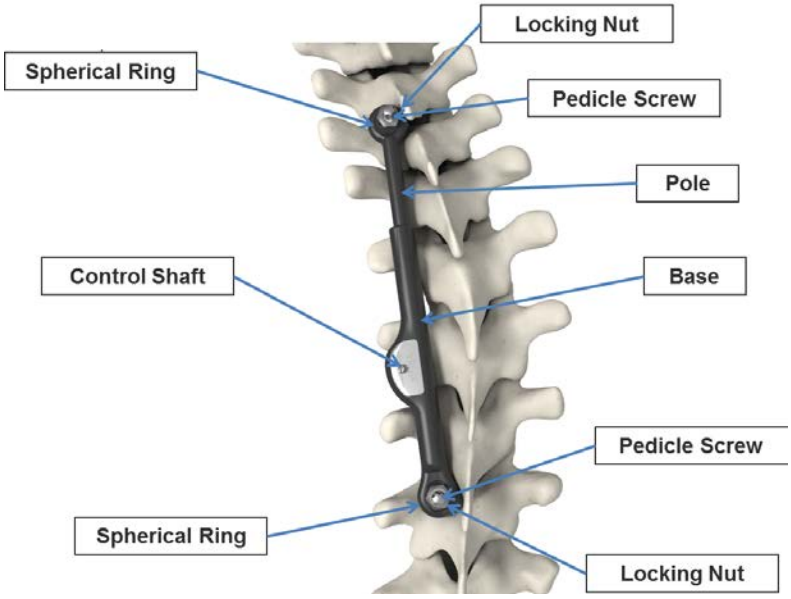
The MID-C System is a ratchet-based, expandable rod that attaches to the spine using two (2) pedicle screws. As shown in Figure 1, the device is implanted at the concave side, around the apex of a flexible single major curve in adolescent idiopathic scoliosis (AIS) patients. The MID-C System acts as an internal brace to achieve correction and stabilization of scoliotic deformity without the need for a spinal fusion. The length of the device expands in 1.3 mm increments. As the device expands via activities such as physical therapy, the curve is corrected incrementally until full device extension. The ratchet mechanism is designed to prevent the device from shortening after expansion and allows for expansion without requiring additional surgery.

Figure 1: Placement of the MID-C System on spine model using two pedicle screws



The device is manufactured from titanium alloy (Ti-6Al-4V ELI) components. The parts that interact for polyaxial mobility (spherical rings, device base and pole) are also coated with an Amorphous Diamond-Like Coating (ADLC). The MID-C System components are specified in Figure 2 below.

Figure 2: MID-C System Components



The device ranges in length from 85 to 125 mm with up to 30 to 40 mm of possible extension, depending on device length (Table 1). Pedicle screws are offered in diameters between 4.5 to 6.5 mm and lengths between 35 to 50 mm. The pedicle screws are inserted into the spherical rings of the construct base and pole which are then compressed together by the tightening of a M6 nut (Figure 3). Polyaxial mobility is achieved via spherical rings interacting between the pedicle screws and its housing in the device base and/or pole with up to 40° of total rotation (Figure 4).

Table 1: MID-C System Rod Lengths and Extension Lengths

Device Length (mm)	Extension Length (mm)
85	30
95	30
105	40
115	40
125	40

Figure 3: Pedicle screw in spherical ring polyaxial joint

Figure 4: Polyaxial angulation of pedicle screws

The ratchet mechanism resides in the control shaft. The control shaft can set the internal ratcheting mechanism to one (1) of the three (3) following positions:

- One-way ratchet position: the standard position set at the time of implantation for correcting the deformity (i.e., one-way expansion of the device in 1.3 mm increments).
- Locked position: where the implant becomes a rigid rod (i.e., no expansion or compression).
- Free position that enables the surgeon to rectify an over correction (i.e., both expansion and compression of the device).

The MID-C System also includes several surgical instruments that are manufactured from stainless steel with their purposes described below.

- Pedicle Screw Holder: Holds the pedicle screw and drives it into the pedicle.
- Screw Extender: Connected to the first pedicle screw. Guides the surgeon to insert the second screw in a generally parallel path, within anatomical limitations.
- Size Selection Gauge: Measures the distance between the heads of the two (2) pedicle screws after insertion, to select the appropriate length of the MID-C implant.
- Control Pin Driver: Switches the Control Pin between Ratchet, Idle, and Locked Positions.
- Nut Holder: Holds the nut of the pedicle screw when placed on the screw's upper thread, prior to final tightening.
- Torque Wrench: Tightens the nut on the pedicle screw to the right torque. Comprises of torque wrench handle, counter torque handle, and torque rod.
- Distractor: Used by surgeon to initially distract the MID-C System.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

Adolescent idiopathic scoliosis (AIS) is characterized by a lateral spinal curvature in excess of 10 degrees with vertebral rotation due to an unknown cause.[1] Management options for AIS include observation with or without physical therapy, treatment with an external orthosis (brace), and surgical treatment, most commonly consisting of growing rods for younger children and posterior spinal instrumentation and fusion for adolescents.

VII. MARKETING HISTORY

The MID-C System has been marketed outside of the United States since 2013 in France, Germany, Greece, Holland, Israel, Italy, Poland, Romania, and Singapore. The MID-C System has also been used in Canada since 2017 under a Special Access Program.

The MID-C System has not been withdrawn from marketing for any reason relating to the safety and effectiveness of the device.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (i.e., complications) associated with the use of the device:

Potential device or procedure-related adverse events (AEs)

- Screw/nut loosening
- Device loosening, migration, breakage, malposition
- Sizing issues
- Anatomic/technical difficulty
- Inability to implant the device
- Intraoperative device revision
- Inadequate curve correction
- Loss of curve correction
- Curve development above and/or below the instrumented levels
- Requirement for subsequent surgical intervention
- Neurologic
- Heterotopic ossification
- Trunk imbalance
- Interference with imaging
- Unintended spontaneous fusion
- Bone fracture
- Dural tear/leakage
- Surgical site seroma, bursitis, crepitus
- Skin penetration by device
- Wound dehiscence
- Hematoma
- Wound infection, superficial, deep
- Intraoperative neurologic injury
- Intraoperative vascular injury, excessive blood loss, hypotension
- Anesthesia, airway, ventilation
- Visceral injury
- Blood transfusion
- Allergic reaction
- Ophthalmic injury, including blindness
- Pain (back, surgical site, extremity, other)

Potential systemic AEs

- Deep vein thrombosis
- Pulmonary embolism
- Atelectasis, pneumonia
- Cardiac
- Dysphagia
- Dysphonia
- Gastrointestinal (ileus, ulceration, bleeding, malnutrition)
- Foreign body reaction
- Pressure sores
- Genitourinary (infection, urine retention)
- CSF leak/meningocele
- Chest tube insertion
- Infection (systemic)
- Hematologic

- Endocrine/metabolic
- Hepatobiliary
- Immunologic
- Gynecologic
- Ophthalmologic
- Psychological
- Surgical procedure: non-spinal
- Wound infection: non-spinal
- Death

For the specific AEs that were reported in the clinical study, please see Section X below.

IX. SUMMARY OF NON-CLINICAL STUDIES

A. Laboratory Studies

Mechanical and Biomechanical Testing
The following mechanical and biomechanical tests were conducted on the MID-C System as outlined in Table 2 below:

Table 2: Summary of MID-C System Laboratory Tests

Test Name	Purpose	Method	Acceptance Criteria	Results
Static Compression Testing	To characterize the performance of the MID-C System under static axial compressive loading.	Three (3) MID-C System constructs (fully extended) were tested under static compression in ambient air at a rate of 10 mm/min until failure	Static axial compression testing must demonstrate that the device can withstand loads equivalent to thoracolumbar pedicle screw system (217 N yield load)[2]	Pass – acceptance criterion met
Static Tension Testing	To characterize the performance of the MID-C System under static axial tensile loading.	Three (3) MID-C System constructs were tested under static tension in ambient air at a rate of 10 mm/min until failure	100 N for margin of safety as no significant tensile forces are anticipated in the spine	Pass – acceptance criterion met
Static Torsion Testing	To characterize the performance of the MID-C System under static torsional loading.	Three (3) long MID-C System constructs (fully extended) were tested under static torsion in ambient air at a rate of 10 deg/min until failure	10 Nm for margin of safety as polyaxial joint prevents significant torsional moments	Pass – acceptance criterion met
Dynamic Compression Testing	To characterize the performance of the MID-C System under static dynamic	Six (6) MID-C System constructs (fully extended) using 5.5 mm diameter screws were tested under dynamic compression in phosphate	Dynamic axial compression testing must demonstrate that the device can withstand loads	Pass – acceptance criterion met

Test Name	Purpose	Method	Acceptance Criteria	Results
	axial compressive loading.	buffered saline ("PBS") at 37 ± 3° C to 10 million cycles, using a sinusoidal wave form with R=10 at 5Hz	equivalent to thoracolumbar pedicle screw system (100 N runout load)[2]	
		Six (6) MID-C System constructs (fully extended) using 4.5 mm diameter screws were tested under dynamic compression in ambient air to 10 million cycles, using a sinusoidal wave form with R=10 at 10 Hz.		
Wear Testing	To determine the wear and durability characteristics of the MID-C System under physiologic conditions.	<u>Ratchet Mechanism</u> Six (6) MID-C System constructs (fully extended) were tested under a dynamic 100 N compressive load in ringer solution to 10 million cycles, using a sinusoidal wave form with R=10 at 10 Hz. <u>Polyaxial Joint</u> Six (6) constructs of the polyaxial joint were assembled and tested under a constant 100 N axial load with ± 4° of flexion-extension and ± 2° of axial rotation in diluted bovine calf serum at 37 ± 3° C for 10 million cycles at 1 Hz. <u>Polyaxial Joint-High Loads</u> Six (6) constructs of the polyaxial joint were assembled and tested under a constant 150 N axial load with ± 4° of flexion-extension and ± 2° of axial rotation in diluted bovine calf serum at 37 ± 3° C for 2 million cycles at 1 Hz. After 2 million cycles, the axial load was increased to 200 N for another 2.5 million cycles. <u>Device Impingement</u> Three (3) constructs of the screw and pole were assembled and tested under a dynamic 100 N compressive load at a 25 mm	Wear rate less than 5mg/Mc (based upon particle load used in pre-clinical rabbit study)	Pass – acceptance criterion met

Test Name	Purpose	Method	Acceptance Criteria	Results
		distance from polyaxial joint in diluted bovine calf serum at 37 ± 3° C for 2 million cycles with R=10 at 5 Hz <u>Extreme Range of Motion</u> Three (3) constructs of the screw and pole were assembled to maximum range of motion and tested under a dynamic 100 N compressive load at a 25 mm distance from polyaxial joint in diluted bovine calf serum at 37 ± 3° C for 2 million cycles with R=10 at 5 Hz		
Cadaveric Assessment of Range of Motion	To characterize spinal range of motion after implantation with MID-C System	Testing was performed with no instrumentation, with MID-C System, and with rigid fixation. Six cadaveric human spines were loaded at 4 Nm to induce flexion-extension (FE), lateral bending (LB), and axial rotation (AR) Testing was performed with no instrumentation, with MID-C System, and with rigid fixation. Six cadaveric porcine spines were loaded at 2 Nm to induce flexion-extension (FE), lateral bending (LB), and axial rotation (AR)	Greater range of motion (ROM) for MID-C System than thoracolumbar pedicle screw system	Pass – acceptance criterion met

<u>Biocompatibility Testing</u>
The MID-C System components are manufactured from titanium alloy (Ti-6Al-4V ELI) conforming to ASTM F136. An Amorphous Diamond-Like Coating is also applied to some MID-C System components, and deposited upon a chromium nitride (CrN) intermediate coating. The titanium alloy and chromium nitride materials have a long history of use in medical implants with no significant biocompatibility safety issues.

Biocompatibility assessments have been conducted on the MID-C System in compliance with applicable requirements in the Good Laboratory Practice (GLP) regulations in 21 CFR 58, applicable ISO 10993 standard, *Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process*, and the FDA guidance, *Use of International Standard ISO 10993-1, "Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process*," published June 16, 2016.

For the MID-C System, as an implanted device with permanent duration contact (> 30 days) with tissue/bone, the biocompatibility evaluation addressed the following: cytotoxicity, sensitization, irritation, acute systemic toxicity, materials mediated pyrogenicity, implantation, subacute/subchronic toxicity, chronic toxicity, genotoxicity, and carcinogenicity endpoints. The biocompatibility evaluation included cytotoxicity testing, extractables and leachables testing, along with material characterization through chemical analysis testing and a toxicological risk assessment. The results of these evaluations support the conclusion that the MID-C System is biocompatible for its intended use.

Additionally, in-vitro animal study was conducted to evaluate potential local tissue and systemic response to MID-C System wear debris particulate. In compliance with applicable requirements in the Good Laboratory Practice (GLP) regulations in 21 CFR 58, MID-C System wear debris particulate was injected in the epidural space at the lumbar region in New Zealand White rabbits. The study collected clinical observations, blood specimens, neurological observations, and body weight measurements. Six (6) animals from the test and control group were terminated at 3 and 6 months after injection for evaluation of tissues. No adverse reactions or responses were noted in the test animal group, with similar results for both test and control group.

Sterilization, Reprocessing, Packaging, and Shelf-Life Testing

The MID-C System is provided sterile using gamma radiation. The sterilization process was validated to achieve a sterility assurance level (SAL) of 10^{-6} using a 25 kGy gamma irradiation dose in accordance with ISO 11137-1:2006, *Sterilization of health care products - Radiation - Part 1: Requirements for development, validation and routine control of a sterilization process for medical devices*, and ISO 11137-2:2006, *Sterilization of health care products - Radiation - Part 2: Establishing the sterilization dose*. The MID-C System is provided sterile in a double barrier system and has been validated to have a shelf life of 5 years. Implantation of the MID-C System requires a set of instruments suitable for posterior spinal surgery. These instruments are made of stainless steel and silicone materials that have a long history of safe use in contact with human tissue and fluids. Validation testing of reprocessing instructions was conducted with the instruments, including cleaning, and steam sterilization (according to ISO 17665-1:2006).

Magnetic Resonance Imaging (MRI) Safety Information

The MID-C System has not been evaluated for safety and compatibility in the MR environment. It has not been tested for heating, migration, or image artifact in the MR environment is unknown. The safety of the MID-C System in the MR environment is unknown. Scanning a patient who has this device may result in patient injury.

X. SUMMARY OF CLINICAL INFORMATION

Clinical Data Overview

ApiFix conducted a prospective, multi-center, non-randomized, open label clinical study in Hungary, Romania, and Israel in twenty (N=20) subjects. The purpose of the study was to assess the safety and probable benefit of the device in AIS patients. In addition, the company has collected data outside the United States (OUS) from post-market clinical

studies (N=26), through commercial use (N=197) in the European Union, Singapore, and Israel, and from special access cases in Canada (N=9). A total of 252 OUS patients have been implanted with the MID-C System.

Given that the clinical data provided to support this HDE comes from OUS sources, including post-marketing experience, practitioners have, in some cases, elected to use the MID-C System outside of the recommended indications for use. Also, in the first three (3) years of use in Europe (2012 to 2015) a portion of these patients were operated using older versions of the device, not the described MID-C System that is subject to this application.

A common primary assessment collected for all patients was curve magnitude as determined by Cobb angle, though radiographic data were collected without a uniform radiographic protocol. Radiographic images were analyzed using a single core laboratory for assessment of Risser grade (skeletal maturity status), Lenke classification, magnitude of major and minor curves, lumbar lordosis, thoracic kyphosis, bridging bone, and safety data related to pedicle screw migration, pedicle screw pullout, device loosening, and device failure/breakage.

The purpose of the clinical evaluation was to demonstrate the safety and probable benefit of the MID-C System when used in the indicated population.

Safety Endpoint and Analysis Populations

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. Other AEs related to the device or procedure that did not result in reoperation were only captured within the first 3-months post-operatively in a subset of patients at four (4) centers (63 out of 252 patients). Safety data was analyzed for three populations:

1. **All** (N=252): This population includes all OUS patients implanted with the MID-C System as of September 15, 2018.

2. **Target Population** (N=25): This includes all patients implanted with the HDE Device Version of the MID-C System, as of September 15, 2018, that meet the US Indications for Use defined by the following criteria:
   - Lenke type 1 or 5 curves;
   - Risser grade 2 or above;
   - Pre-operative Cobb angle between 45 to 60 degrees;
   - Flexible major curve (defined as lateral bending correction to 30 degrees or less);
   - Thoracic kyphosis less than 55 degrees.

3. **Expanded Target Population** (N=49): This includes all patients implanted with the HDE Device Version of the MID-C System, as of September 15, 2018, that meet an Expanded US Indications for Use which includes patients (N=24) with 40 to 44 degree curves as defined by the following criteria:
   - Lenke type 1 or 5 curves;
   - Risser grade 2 or above;
   - Pre-operative Cobb angle between 40 to 60 degrees;

- Flexible major curve (defined as lateral bending correction to 30 degrees or less);
- Thoracic kyphosis less than 55 degrees.

Note that a 5-degree difference in the 2-dimensional Cobb angle measurement is within the range of intra- and inter-observer reliability.[3] The Expanded Target Population safety analysis population was a combination of the Target Population (N=25) and patients (N=24) with 40 to 44 degree curves.

Probable Benefit Endpoint and Analysis Populations

The probable benefit endpoint for evaluation is defined as primary Cobb angle less than or equal to 35 degrees and no curve progression at 24-months compared to baseline following treatment with the MID-C System. There are two (2) patient populations for evaluation of probable benefit: Target Population and Expanded Target Population. These analysis populations are defined using the same criterion for the safety analysis above, with the additional requirement of reaching the post-operative timepoint of 12- and 24-months. A summary of the probable benefit patient populations is outlined below.

1. **Target Population**
   - Reached post-operative timepoint of 12-months (N=17)
   - Reached post-operative timepoint of 24-months (N=10)

2. **Expanded Target Population**
   - Reached post-operative timepoint of 12-months (N=32)
   - Reached post-operative timepoint of 24-months (N=22)

Patient Demographics

A summary of the patient demographics for the Target Population and Expanded Target Population can be found in Table 3 below, with the number of patients with evaluable data for each demographic parameter identified.

Table 3: Key Patient Demographics

	Target Population	**Expanded Target Population**
Gender		
N	24	47
Female	21 (87.5%)	42 (89.4%)
Male	3 (12.5%)	5 (10. 6%)
Age (Years)		
N	20	36
Mean ± SD	14.7 ± 1.7	15.0 ± 1.7
Median	14.2	15.0
Min, Max	13.0, 18.7	13.0, 19.0
Risser Grade		
N	25	49
2	2 (8%)	6 (12.2%)
3	2 (8%)	7 (14.3%)
4	16 (64%)	22 (44.9%)

	Target Population	Expanded Target Population
5	5 (20%)	14 (28.6%)
Pre-op Major Cobb Angle		
N	25	49
Mean ± SD	49.5 ± 4.4	45.9 ± 4.9
Median	48.0	45.0
Min, Max	45.0, 59.0	40.0, 59.0
Pre-op Secondary Cobb Angle		
N	24	48
Mean ± SD	29.7 ± 8.3	27.7 ± 8.0
Median	29.0	25.5
Min, Max	16.0, 46.0	16.0, 46.0
Pre-op Lumbar Lordosis (superior endplate of L1 to the superior endplate of S1)		
N	8	17
Mean ± SD	55.5 ± 14.8	53.8 ± 12.3
Median	54.5	52.0
Min, Max	26.0, 78.0	26.0, 78.0
Pre-op Thoracic Kyphosis (superior endplate of T5 to the superior endplate of T12)		
N	9	19
Mean ± SD	23.2 ± 12.8	20.2 ± 12.3
Median	23.0	19.0
Min, Max	4.0, 45.0	3.0, 45.0
Pre-op Major Cobb Angle on Lateral Bending		
N	25	49
Mean ± SD	19.3 ± 6.6	16.6 ± 7.8
Median	20.0	18.0
Min, Max	1.0, 30	0.0, 30
Lenke Curve Pattern*		
N	25	49
1a	9	17
1b	2	6
1c	2	5
5a	3	4
5b	0	2
5c	9	15

* The Lenke Classification System[4] relies on measurements taken from standard x-rays. The surgeon evaluates x-rays of the patient from the front, side, and in bending positions. Each scoliosis curve is then classified in three (3) ways:

- By the curve type based on which of the three (3) regions of the spine; the proximal thoracic, main thoracic, and thoracolumbar/lumbar is structural or non-structural.
- A lumbar spine modifier based on the distance of the center of the lumbar spine to the midline; and
- A sagittal thoracic modifier based on the amount of side (lateral) curvature to the thoracic region.

Every aspect of the curve is also evaluated for its relative stiffness or flexibility on side bending x-rays. The triad system, therefore, combines the curve type (1-6) with the lumbar modifier (A, B, C) and the sagittal thoracic modifier (-, N, +) to form the complete classification. For example, the most common type is a 1AN curve classification.

Safety Results

Reoperations

Overall, 45 reoperations were reported for the 252 (17.9%) patients treated with the MID-C System. Reoperation rates according to analysis population are reported in Table 4. For the All population the reoperation rate was 17.9% (45 out of 252 patients). The rates for any reoperations in the Target Population and Expanded Target Population are 12% (3 out of 25 patients) and 12.2% (6 out of 49 patients), respectively.

Table 4: Reoperation Rates

Safety Population	Total (N)	Reoperations (N)	Reoperation Rate (%)
All	252	45	**17.9%**
Expanded Target Population	49	6	**12.2%**
Target Population	25	3	**12.0%**

Reoperations According to Post-Procedure Timepoint

For the 45 reported reoperations, the mean post-operative timepoint of the reoperation was 13 months. Furthermore, 26 of the 45 (57.8%) reoperations occurred within the first 12-months post-procedure as shown in Table 5. Reoperations within the first 12-months were performed for the following reasons: device malfunctions, nut loosening, misplaced screws, screw pullout, infection, screw fracture, and rod fracture.

Table 5: Number of Reoperations at Post-Procedure Timepoints

Timepoint of reoperation (months post-procedure)	Number of reoperations
≤ 6 months	15
7 to 12 months	11
13 to 24 months	13
> 24 months	6

Relationship of Reoperation to Device or Procedure

The number of patients determined to have a reoperation that was definitely, probably, or possibly related to the device was six (6) out of 252 (2.4%). The number of patients determined to have a reoperation that was definitely, probably, or possibly related to the procedure was 27 out of 252 (10.7%) patients. It was noted that 12 of the 252 (4.8%) reoperations could not be attributed to either the device or the procedure.

Reoperations Reported as Serious Adverse Events (SAEs)

Table 6 below lists the number of patients for all the reoperations reported as SAEs (N=45) within the clinical dataset (N=252). The most common reason for reoperation was pedicle screw misplacement/migration, which resulted in nine (9) reoperations (3.6%). There were eight (8) reoperations reported (3.2%) due to insufficient curve correction, and six (6) of these patients are known to have undergone conversion to spinal fusion. Infection was reported as the reason for eight (8) reoperations (3.2%), with one case of infection potentially causing screw migration. Additionally, screw pull-out was observed in five (5) patients (2.0%) and nut loosening was observed in five (5) patients (2.0%) and resulted in reoperations. One (1) patient experienced screw fracture that resulted in reoperation. There were six (6) reoperations reported for device malfunctions: unspecified device failure (N=1), ratchet failure (N=1), screw dislocation from the rod (N=2), and rod breakage (N=2). Other reported reoperations were for pain (N=1), unintended additional distraction of the device (N=1), and misalignment of the extender component (N=1), which is not a current component of the MID-C System.

As shown in Table 6 below, 13 patients (5.2%) underwent reoperation with conversion to spinal fusion and instrumentation or treatment with another non-fusion spinal device. It is known that 11 out of 252 patients (4.4%) have undergone conversion to spinal fusion and instrumentation, and two (2) patients were treated with non-fusion devices. Reasons for reoperation with conversion to spinal fusion were insufficient curve correction, screw misplacement, screw breakage, and infection. The MID-C System was removed in 12 patients (4.8%) and it is unknown if any of these patients required further surgical intervention for the treatment of their scoliotic curve. One patient was converted to the Shilla Growth Guidance System (a marketed device) during a reoperation procedure after observation of screw pull-out. Also, one patient was converted to a vertebral body tethering device during a reoperation procedure after observation of rod breakage. A total of 15 patients (6.0%) underwent a reoperation procedure to modify the MID-C System due to pedicle screw placement, nut tightening, or device alignment issues. An additional five (5) patients (2.0%) required MID-C System replacement.

Table 6: Listing of Reoperations Reported as SAEs by Procedure Type

Reoperation Type	Total Number of Reoperations	Number of Conversions to Fusion or Other or Non-fusion Device	Number of Device Removals	Number of Device Corrections	Number of Device Replacements
Screw misplacement/migration	9	3	3	3	-
Insufficient curve correction	8	6	1	-	1
Infection	8	1	4	2	1
Screw pullout	5	1	1	1	2
Locking nut loosening	5	-	-	5	-
Rod fracture	2	1	1	-	-
Screw dislocation from rod	2	-	-	1	1

Reoperation Type	Total Number of Reoperations	Number of Conversions to Fusion or Other or Non-fusion Device	Number of Device Removals	Number of Device Corrections	Number of Device Replacements
Unexpected rod movement	1	-	-	1	-
Additional device distraction	1	-	-	1	-
Screw fracture	1	1	-	-	-
Pain	1	-	1	-	-
Extender misalignment	1	-	-	1	-
Unspecified device failure	1	-	1	-	-
Total	**45**	**13**	**12**	**15**	**5**

Non-Serious Adverse Events

Non-serious AE data was collected within the first 3 months post-operatively for 63 patients from four (4) centers. This additional safety data (Table 7) reported that 21 out of 63 patients experienced a non-serious AE. These AEs were: seroma (N=2), local hematoma (N=1), headaches (N=1), pain (N=13), limited range of motion of the spine (N=3), screw pull-out (N=1), vasovagal syncope (N=2), superficial wound infection (N=1), skin hypersensitivity (N=1), nausea (N=3), and knee hypoesthesia (N=1). Of note, screw pull-out occurred in one patient at 6 weeks follow-up and was reported as a non-serious AE. This patient was observed and at the 24-month follow-up visit, the screw position was reported as stable and unchanged.

Table 7: Listing of Non-serious AEs through 3 Months from 4 Centers

AE Type	Number of AEs	Number of patients
Seroma	2	2
Local Hematoma	1	1
Headaches due to Epidural Hematoma	1	1
Pain	13	11
Limited movement range of spine	3	3
Screw pull out	1	1
Vasovagal Syncope	2	2
Superficial wound infection	1	1
Hypersensitivity of skin	1	1
Nausea and vomiting	3	3
Hypoesthesia knee	1	1

Probable Benefit Results

Probable benefit was assessed within this HDE as a Cobb angle of less than or equal to 35 degrees and no curve progression at 24-months compared to baseline following treatment with the MID-C System. In addition, probable benefit was also assessed for patients with at least 12-months of follow-up data. Probable benefit results at 12-months and 24-months are reported in Table 8 below. In both analysis populations and at both timepoints, the probable

benefit success using this endpoint was greater than 75% based on data available for analysis.

Analysis of the 24-month radiographic data for the Target Population showed that all eight (8) patients had improvement of the major curve (greater than 5 degrees compared to baseline), including the two (2) patients who did not meet the primary probable benefit endpoint.

Table 8: Probable Benefit Analysis at 12- and 24-Months

Probable Benefit Population	12-month Results			24-month Results		
	Total (N)	Success (N)	Success Rate (%)	Total (N)	Success (N)	Success Rate (%)
Target Population	12	9	**75.0%**	8	6	**75.0%**
Expanded Target Population	26	22	**84.6%**	10	18	**90.0%**

Table 9 shows the average improvement in the major curve for these eight (8) patients was 21 degrees compared to the mean baseline Cobb angle of 49 degrees, which represented a 43% correction of the major curve. Similarly, analysis of the 24-month radiographic data for the Expanded Target Population showed a mean 47% correction of the major curve in 20 patients.

Table 9: Assessment of Major Curve Correction following MID-C System Treatment

Probable Benefit Population	Baseline Major Curve	Major Curve at 24-months	Degree Correction of Major Curve	Percent Correction of Major Curve
Target Population (N=8)	Mean: 49° Range: 45-59°	Mean: 28° Range: 19-37°	Mean: 21° Range: 9-33°	Mean: 43% Range: 20-58%
Expanded Target Population (N=20)	Mean: 45° Range: 40-59°	Mean: 24° Range: 7-37°	Mean: 21° Range: 9-35°	Mean: 47% Range: 20-83%

In assessment of probable benefit, it is relevant to consider skeletal maturity as a factor that affects the risk of curve progression. Probable benefit results are more informative if a patient has reached or is beyond skeletal maturity as the risk of future curve progression is decreased compared to skeletally immature patients. Table 10 shows the percentage of the patient population that was skeletally mature at 24-months for both populations (Target Population – 90.0%; Expanded Target Population – 86.4%).

Table 10: Percent of Skeletally Mature* Patients at 24-Months Follow up

Probable Benefit Population	Skeletally Mature at 24-Months Follow-Up	Not Skeletally Mature at 24-Months Follow-Up
Target Population (N=10)	9 (90.0%)	1 (10.0%)
Expanded Target Population (N=22)	19 (86.4%)	3 (13.6%)

* Skeletal maturity defined in the Radiographic Protocol as Risser Grade 5 by the North American Risser grading system

Secondary probable benefit endpoints of blood loss, operative time, and length of hospital stay were retrospectively evaluated, and the MID-C System was compared to spinal fusion treatment at two (2) centers. The retrospective analysis included 43 patients treated with the MID-C System and 33 patients treated with spinal fusion. Results of these secondary probable benefit endpoints report shorter operative time, less blood loss, and shorter hospital stay for the patients treated with the MID-C System as compared to patients treated with spinal fusion (Table 11).

Table 11: Secondary Probable Benefit Endpoints Analysis

Secondary Probable Benefit Endpoint	MID-C System (N=43)	Spinal Fusion (N=33)
Average number of spinal levels spanned	5.3	9.4
Average number of anchor points	2.1	14.1
Average operative time (hours)	1.2	3.5
Average blood loss (ml)	15.7	728
Average length of hospital stay (days)	2.2 (N=18)	7.4 (N=15)

XI. FINANCIAL DISCLOSURE

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included 13 investigators. None of the clinical investigators had disclosable financial interests/arrangements as defined in sections 54.2(a), (b), (c), and (f). The information provided does not raise any questions about the reliability of the data.

XII. SAFETY AND PROBABLE BENEFIT ANALYSIS

The ApiFix MID-C System has been implanted in 252 patients with AIS. Twenty (20) subjects were evaluated in a prospective, multi-center, non-randomized, open label clinical study. Data for the remaining 232 patients were obtained from post-market and commercial use outside of the US, with enrollment of patients inside and outside of the proposed US indications for use. With commercial use, there was no pre-specified protocol for monitoring the multiple study sites for AEs aside from reoperations, which were pre-specified as SAEs. Nonetheless, the data provide a sufficient basis upon which to draw conclusions regarding the safety and probable benefit of the MID-C System.

In regard to safety, reoperation rates reported for the MID-C System were compared to literature describing the 24-month and 60-month reoperation rate for posterior instrumented

spinal fusion for treatment of adolescent idiopathic scoliosis. The limited AE data collected from four (4) centers (N=63 patients) were also evaluated to determine if there were any unexpected AEs as compared posterior spinal fusion surgery. Based on the level of correction provided by the MID-C System (as measured by a reduction in major Cobb angle), it was determined that the threshold for probable benefit under the HDE paradigm was met. In addition, details related to the hospital stay and surgical procedure were compared between the MID-C System and instrumented spinal fusion and considered in this safety and probable benefit assessment.

A. **Probable Benefit Conclusions**

The primary probable benefit endpoint of this study evaluated Cobb angle at 24 months, with success defined as a Main Cobb angle of less than or equal to 35 degrees following treatment with the MID-C System, and no curve progression compared to baseline at 24-months post-procedure. This probable benefit endpoint was chosen as curves of this magnitude at skeletal maturity are not expected to progress and require surgical intervention later in life.

Spinal fusion has historically been the standard of care treatment procedure that is recommended for patients that meet the MID-C System indications for use. The intended use of the MID-C System is to correct and stabilize a spinal deformity without fusion. If curve correction is maintained in the long-term, this device offers the potential to avoid spinal fusion and the associated adverse consequences of an instrumented spinal fusion later in life. Among the AEs associated with spinal fusion are: decreased spinal motion, pseudoarthrosis, adjacent spinal segment degeneration, neurological complications, pain, implant failure/breakage, and subsequent surgical intervention.

The probable benefit success rate at 24-months in the Target Population is 75% (6/8). Consistent results are observed in the Expanded Target Population with a probable benefit success of 90% (18/20). Additionally, the results for probable benefit at 12-months are similar to the results concluded at 24-months. Analysis of the probable benefit endpoint suggests that patients are likely to experience the benefit of avoiding spinal fusion during this time period.

An analysis of the curve correction achieved with the MID-C System was conducted. Major curve correction achieved with the MID-C System in the Target Population at 24-months (N=8) ranged from 20% to 58%, with a mean curve correction of 43%, for the mean baseline major Cobb angle of 49 degrees. Similarly, major curve correction achieved with the MID-C System in the Expanded Target Population at 24-months (N=20) ranged from 20% to 83%, with a mean curve correction of 47%, for the mean baseline major Cobb angle of 45 degrees. In comparison, posterior pedicle screw-and-rod-based spinal instrumentation systems intended for spinal fusion achieve approximately 63% correction of the major Cobb angle in coronal plane and also provide maximal transverse plane correction leading to major reduction of thoracic and lumbar prominences.[5]

In addition, the MID-C System thus far has provided the following additional benefits to patients and their parents: shorter hospitalization and less blood loss than the standard-of-care instrumented fusion. In conclusion, the clinical data compiled show the device

to have a probable benefit of achieving its primary purpose of avoiding the need for spinal fusion through 24-months.

B. **Safety Conclusions**

The risks of the device are based on laboratory studies, as well as data collected in a clinical study and from post-market and commercial use data to support HDE approval as described above.

The primary safety endpoint evaluated was reoperation performed for any reason at any timepoint and included all SAEs that resulted in reoperation. Other AEs related to the device or procedure that did not result in reoperation were only captured within the first 3-months post-operatively in a subset of patients (63 out of 252 patients). The overall safety failure rate was 17.9% (45 out of 252 patients). However, the reoperation rate assumes that all reoperations constitute a failure, and many of the reoperations were to correct screw misplacement and nut-loosening related AEs. When the primary safety endpoint is evaluated for the Target Population, the reoperation rate decreases to 12.0%. Similarly, the reoperation rate for the Expanded Target Population was 12.2%.

No deaths or serious neurological injuries were reported. Notable safety-related AEs include subsequent surgical intervention due to device failures (N=28), sub-optimal clinical outcome (insufficient correction of spinal curve; N=8), infection (N=8), or device-related pain (N=1). Reasons for device failure include screw misplacement/migration (N=9), screw pullout (N=5), device loosening (N=5), device fracture/dislocation (N=5), extender misalignment (not currently part of MID-C System, N=1), and other unspecified reasons (N=2).

To compare reoperation rates of the MID-C System with spinal fusion, a literature review was conducted to identify the reoperation rate at 24-months for patients undergoing spinal instrumentation and fusion for treatment of AIS in the US. A patient treated with spinal instrumentation and fusion surgery for AIS in the US can expect a reoperation rate of approximately 4.1% at 24-months[6] and approximately 9.9% at 60-months.[7] Compared to the spinal fusion treatment, the MID-C System reoperation rate is higher. However, it is notable that six (6) of the eight (8) cases of reoperation for insufficient curve correction were observed in the first 21 patients implanted with the device. In addition, other types of SAEs associated with reoperations included screw misplacement, implant, and nut loosening. The remaining categories of AEs, such as infection, are similar to those AEs reported for spinal fusion. Based on the available MID-C System data, despite a higher reoperation rate than reported in the literature for spinal fusion for AIS (12% versus 4.1[6] to 9.9%[7]), the MID-C System can be considered as safe for its indications for use in view of the mitigation measures undertaken such as modifications to the device design and surgical technique, as well as the types of AEs which were observed.

C. **Probable Benefit-Risk Conclusions**

The probable benefits of the device are based on data collected in a clinical study as well as from commercial use data to support HDE approval as described above.

The primary probable benefit of the MID-C System is correction and maintenance of the magnitude of the patient's major spinal curve below the threshold where spinal fusion is indicated, thereby potentially avoiding associated adverse consequences of spinal fusion. Based on the data provided, the probable benefit success rate of curve correction and maintenance below 35 degrees is greater than or equal to 75% over the 24-month duration of follow-up. Additionally, the data reports a 4.4% (11 out of 252 patients) rate of conversion to spinal fusion at 24-month follow-up, which suggests a likely probability of a patient experiencing the benefit of avoiding spinal fusion. Other, more immediate, benefits include shorter hospitalization, and less blood loss compared to posterior spinal fusion.

The probable risks of the device based on data collected in a clinical study and from commercial use data conducted to support HDE approval were considered adequate to support safety of the MID-C System. Device risks reported as SAEs include (from most frequent to least frequent): device misplacement/migration, insufficient correction of spinal curve, infection, device loosening, device failure, and pain. All of these SAEs resulted in a subsequent surgical procedure.

Additional factors to be considered in determining probable risks and benefits for the MID-C System device included patient perspectives.

1. Patient Perspectives

   Patient perspectives considered during the review included:

   Patients who participated in the prospective study (N=20) completed the Scoliosis Research Society-22 (SRS-22) questionnaire at all study timepoints. The SRS-22 questionnaire assesses health-related quality of life via scoring of five (5) domains: intensity of pain, self-image, function/activity, mental health, and satisfaction from treatment. Each domain score ranges from 1 to 5, with higher scores indicating better outcomes. The SRS-22 questionnaire is commonly used and has been found to be reliable and valid for both the pediatric and the adult population. Results report consistent improvement across SRS-22 questionnaire scores out to two (2) years, with the data including patients requiring reoperation (Table 12).

Table 12: Average SRS-22 sub scores over time (N=20)

		Time Point				2 Year Δ (%)
		Baseline (N=20)*	**6 Month (N=14)**	**1 Year (N=18)**	**2 Years (N=16)**	
Subscales	**Function**	21.5	22.29	20.67	22.75	+1.25 (5.81%)
	Pain	19.55	20.29	19.78	21.5	+1.95 (9.97%)
	Self-Image	16.15	17.93	18.5	19.94	+3.79 (23.47%)
	Mental Health	18.9	19.86	19.83	20.31	+1.41 (7.46%)
	Satisfaction with Back Management	5.9	8.14	8.22	8.63	+2.73 (46.27%)
Total		82.00	88.51	87	93.13	+11.13 (13.57%)

* One patient at baseline did not answer any satisfaction questions

Additionally, patient perspective data were collected from a three (3)-question survey of responses from a subset of patients in the Expanded Target Population (N=18), and from a subset of patients who have undergone a reoperation procedure for device correction, device replacement, or device removal (N=22). The three (3) questions and results from the survey responses are compiled below in Table 13 and Table 14 for each of these patient populations. Satisfaction scores ranged from 1 to 5 for each question corresponding to strongly disagree to strongly agree, respectively. In summary, the survey responses report overall patient satisfaction with their treatment with the MID-C System; one caveat is that this survey has not been validated.

Table 13: Patient Satisfaction Survey for Expanded Target Population

Survey Question	Survey Score				
	1	2	3	4	5
	N	N	N	N	N
How satisfied are you with the treatment you received?	0	0	2	6	10
If you had to choose treatment again, how likely would you be to choose the same treatment?	0	0	0	3	15
If you had a friend who needed treatment for the same condition, how likely would you recommend this treatment?	0	0	2	2	14

Table 14: Patient Satisfaction Survey for Patients Who Underwent Reoperation

Survey Question	Survey Score				
	1	2	3	4	5
	N	N	N	N	N
How satisfied are you with the treatment you received?	1	0	2	7	12
If you had to choose treatment again, how likely would you be to choose the same treatment?	1	0	1	5	15
If you had a friend who needed treatment for the same condition, how likely would you recommend this treatment?	1	0	0	5	16

2. Surgeon Perspectives:

   The preference of patients and surgeons for a non-fusion option for progressive scoliosis was communicated to the applicant in writing by leading scoliosis surgeons. Their letters of support were included in this HDE application.

In conclusion, given the available information above, the data support that for AIS patients as described in the Indications for Use section above, the probable benefits outweigh the probable risks.

D. **Overall Conclusions**

The data in this HDE application support the reasonable assurance of safety and probable benefit of the MID-C System when used in accordance with the indications for use. As described above, the overall reoperation rate is 17.9% for all 252 patients and 12.0% for the Target Population. Although the available MID-C System data

representative of the target population shows a higher reoperation rate than reported in the literature for spinal instrumentation and fusion for AIS (12% versus 4.1[6] to 9.9%[7]), the MID-C System can be considered to be safe for its indications for use considering the type of AEs presented and mitigation measures taken such as modifications to the device design and surgical technique. The probable benefit success rate, as described above, is 75 to 90% for the analysis populations at 24-months. This probable benefit endpoint can be considered representative of likelihood of avoidance of the need for spinal fusion during this time period.

Therefore, it is reasonable to conclude that the probable benefit to health from using the device for the target population outweighs the risk of illness or injury, taking into account the probable risks and benefits of currently available devices or alternative forms of treatment when used as indicated in accordance with the directions for use.

XIII. PANEL RECOMMENDATION

This HDE was not taken to a meeting of the Orthopaedic and Rehabilitation Devices Panel of the Medical Devices Advisory Committee because the information in this HDE did not raise any unanticipated safety concerns.

XIV. CDRH DECISION

CDRH has determined that, based on the data submitted in the HDE, the MID-C System will not expose patients to an unreasonable or significant risk of illness or injury and the probable benefit to health from using the device outweighs the risks of illness or injury. CDRH issued an approval order on August 23, 2019. The final conditions of approval cited in the approval order are described below.

MID-C System Registry PAS: The MID-C System Registry is a multi-center, single-arm, prospective post-approval US 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 immediate post-operative 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 US centers with sequential enrollment from each site that agrees to participate.

The primary safety endpoints are SAEs, and device- or procedure-related AEs. Additional safety analyses will include the: rate of AEs, including by relatedness to device or procedure and severity; and, rate of reoperation, including by type of reoperation.

The primary probable benefit endpoint 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 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.

These safety and probable benefit data will be collected at 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 applicant's manufacturing facilities have been inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XV. APPROVAL SPECIFICATIONS

Directions for use: See the device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and AEs in the labeling.

Post-approval Requirements and Restrictions: See approval order.

XVI. REFERENCES

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scoliosis: how it organizes curve patterns as a template to perform selective fusions of the spine." Spine. 2003: 28 (20), 199-207.

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7. Mignemi, M. E. et al. "Repeat Surgical Intervention Following Definitive Instrumentation and Fusion for Adolescent Idiopathic Scoliosis: A 25 Year Update." Spine Deformity. 2018: 6 (4), 409-416.