SUMMARY OF SAFETY AND PROBABLE BENEFIT (SSPB)

I. GENERAL INFORMATION

Device Generic Name: Implant, Fecal Incontinence

Device Trade Name: FENIX® Continence Restoration System

Device Procode: PMH

Applicant's Name and Address: Torax Medical, Inc.
4188 Lexington Avenue North
Shoreview, Minnesota 55126

Date(s) of Panel Recommendation: None

Humanitarian Device Exemption (HDE) Number: H130006

Humanitarian Use Device (HUD) Designation Number: HUD # 13-0308

Date of HUD Designation: September 27, 2013

Date of Notice of Approval to Applicant: December 18, 2015

II. INDICATIONS FOR USE

The FENIX Continence Restoration System is indicated for the treatment of fecal incontinence in patients who are not candidates for or have previously failed conservative treatment and less invasive therapy options (e.g., injectable bulking agents, radiofrequency ablation, sacral nerve stimulation).

The indication for use statement is identical to that which was granted for the HUD designation.

III. CONTRAINDICATIONS

Do not implant the FENIX device in patients with suspected or known allergies to titanium.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the FENIX Continence Restoration System labeling.

V. DEVICE DESCRIPTION

The FENIX Continence Restoration System is comprised of the following components:

- FENIX Implant
- FENIX Anal Sphincter Sizing Tool

- FENIX Introducer Tool

The implantable, single-use, FENIX Implant (see Figure 1) is comprised of an annular series of connected titanium beads. Each bead contains a magnetic core which is magnetically attracted to adjacent beads. Collectively, this attraction augments the native anal sphincter providing needed resistance to involuntary opening of the anal canal (see Figure 2). The FENIX Implant is supplied sterile and is placed through a perineal incision. The FENIX Implant is placed around the external anal sphincter 2-3 cm from the anal verge. The attractive force of the magnetic beads is designed to provide additional strength to restore the function of a weak anal sphincter.

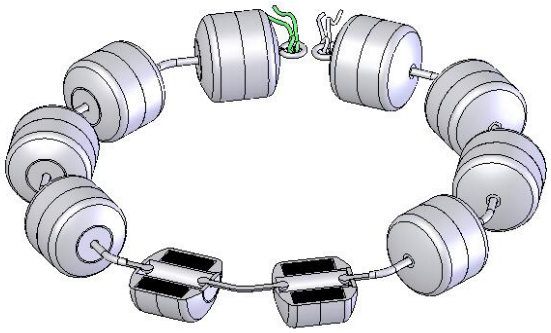


Figure 1. Illustration of FENIX Implant

Principle & Method of Operation

Normal physiologic continence is provided primarily by the barrier function of the anal sphincter muscle. The anal sphincter provides the majority of the resting tone and the squeeze pressure necessary to delay defecation. A weak or damaged anal sphincter may not hold the anus shut against fecal content until a convenient time, thus resulting in incontinence.

Torax Medical, Inc. has designed the FENIX Implant to reinforce the anal sphincter. The implant is introduced in a linear shape, and then closed around the outer muscle layer of the anal sphincter to form an annular shape encircling the anal canal. The attractive magnetic forces of the beads provide additional strength to hold the anus shut against unwanted passage of fecal content (Figure 2).

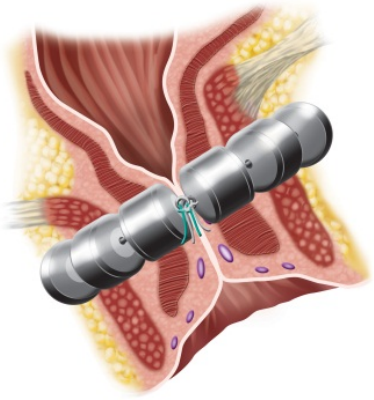


Figure 2. FENIX Implant Around the Anal Canal

During defecation, pressure in the anal canal increases due to peristaltic motion in the rectum and action of the pelvic floor muscles, and the magnetic beads move apart on independent titanium wire links (Figure 3). As the beads move apart, the magnetic forces decrease. This separation of the beads allows normal anal distention for defecation. Upon completion of the defecation, the anal pressure decreases and the magnetic beads return along the independent titanium wire links to the closed position.

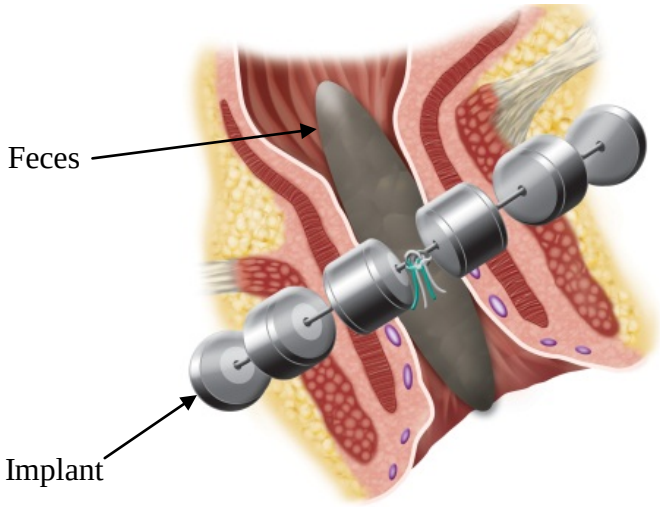


Figure 3. FENIX Implant Actuation During Defecation

Table 1. List of FENIX Implant Sizes

Model Number	Description
FXS14	14-Bead FENIX Implant
FXS15	15-Bead FENIX Implant
FXS16	16-Bead FENIX Implant
FXS17	17-Bead FENIX Implant
FXS18	18-Bead FENIX Implant
FXS19	19-Bead FENIX Implant
FXS20	20-Bead FENIX Implant

In addition to the FENIX Implant, there are two (2) accessory tools available for the procedure: the FENIX Introducer Tool and the FENIX Anal Sphincter Sizing Tool.

The re-usable FENIX Introducer Tool (see Figure 4) is made from surgical grade stainless steel. The tool has a pre-formed shape and a hole through the distal end which is used to engage the suture from the sizing device as well as the suture of the FENIX Implant and thereby assist in their passage around the anal canal following tunnel creation by the

surgeon's fingers. The introducer tool is supplied non-sterile and is cleaned and (steam) sterilized at the hospital prior to use.

Figure 4. FENIX Introducer Tool

The single-use device, FENIX Anal Sphincter Sizing Tool (see Figure 5), is made from ePTFE with a printed scale utilized to encircle the anal sphincter and thereby associate the anal sphnicter size to an appropriate FENIX Implant. The Sizing Tool is labeled with the respective number of beads for each implant size available and features a tension indicator for added repeatability. The sizing tool is supplied sterile to the customer.

Figure 5. FENIX Anal Sphincter Sizing Tool

VI. ALTERNATIVE PRACTICES AND PROCEDURES

Conventional procedures used in the treatment of fecal incontinence are explained in Table 2 below.

Table 2. Fecal Incontinence Therapy Options

Therapy	Description
Diet	Addition of fiber to daily diet
Anti-diarrheal medication	Addition of daily medication to facilitate a more solid stool
Biofeedback	Pelvic floor muscle exercises
Injectable bulking agents	Injection of hyaluronic acid based bulking agent
Radiofrequency energy	Delivery of radiofrequency energy to the anal canal
Sacral nerve stimulation (SNS)	Sacral nerve stimulation to the nerve that innervates the pelvic floor
Sphincteroplasty	Stitching the separated ends of the sphincter muscles back together
Artificial bowel sphincter (ABS)	A fluid filled, solid silicone elastomer device consisting of a cuff,

Therapy	Description
	pressure regulating balloon and a patient activated control pump
Colostomy	Creation of a stoma for fecal diversion

VII. MARKETING HISTORY

The FENIX Continence Restoration System obtained CE mark designation in November 2011 and is currently being marketed in France, United Kingdom, Ireland, and Germany. The FENIX Implant has not been withdrawn from marketing for any reason related to safety or lack of benefit.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

The following is a list of potential adverse effects (i.e., complications) associated with the implantation of the FENIX Device. These may include, but may not be limited to the following: bleeding, death, device erosion, device explant/re-operation, device failure, device migration (device does not appear to be at implant site), impaction or defecatory disorder, impaired colonic motility, inability to pass gas, infection, injury to the anus, rectum, or vagina, pain, pruritus ani, recto-vaginal fistula, and worsening of pre-operative symptoms.

Potential adverse events associated with the surgical procedure and anesthesia include adverse reaction to anesthesia (headache, muscle pain, nausea), anaphylaxis, cardiac arrest, death, fever, hypotension, hypoxemia, infection, myocardial infarction, pneumonia, pulmonary embolism, respiratory distress, thrombophlebitis, and vomiting.

For the specific adverse events that occurred in the clinical study, please see Section X below.

IX. SUMMARY OF PRECLINICAL STUDIES

A. Laboratory Studies

Testing Summary

Thorough *in vitro* testing has been performed to ensure safe and reliable performance of the FENIX Implant. Mechanical and performance characteristics of the device were tested, including corrosion resistance and the static magnetic field present around the device. The shelf life of the device was deemed to be 6 months, with an acceptable protocol. Table 3 provides a testing summary.

Table 3. FENIX Implant Test Summary

Test Performed	Test Article	Description	Test Results
Hermetic Seal	Individual Magnetic Beads	100% testing of production magnetic encased titanium beads by means of gross & fine leak test methods	NA
Functional Separation Force Testing	Complete Assembly	100% testing of production devices to confirm all bead-to-bead separation forces are within specification	NA
Mechanical Strength	Complete Assembly	Tensile testing of individual welded components as well as full unit tensile for connector wire strength	Pass
Corrosion Test ASTM F 2129	Complete Assembly	Cyclic Potentiodynamic Polarization testing to determine Breakdown Potential and risk of Pitting Corrosion when tested in a protein based (Serum) solution	Pass
Life Cycle Testing	Complete Assembly	Test for cyclic wear on expanding and contracting device over a 10 simulated years	Pass
Magnetic Field Strength Testing	Complete Assembly	Magnetic field strength vs distance evaluation as compared to other consumer products tested in the same manner	Pass

Biocompatibility Testing Summary

The FENIX Implant is a tissue/bone contacting permanent implant for which FDA's Blue Book Memorandum G95-1 and ISO-10993 "Biological Evaluation of Medical Devices Part-1" suggest consideration of the following testing: cytotoxicity, sensitization, irritation, acute systemic toxicity, sub-chronic toxicity, genotoxicity, implantation, chronic toxicity, and carcinogenicity (Table 4).

Table 4. Biocompatibility Testing for the FENIX Implant

Test Performed	Test Article	Extract(s)	Extract conditions (time, temperature)	Test Results
Cytotoxicity ISO 10993-5	Entire Packaged, Sterilized Implant (Magnetic Beads, Wire Links, Eyelets, Suture)	L929-MEM	24hrs, 37°C	Pass
Sensitization ISO 10993-10 Murine Local Lymph Node Assay (LLNA)	Entire Packaged, Sterilized Implant (Magnetic Beads, Wire Links, Eyelets, Suture)	0.9% NS (Normal Saline) PEG (Polyethylene Glycol)	72hrs, 50°C 72hrs, 50°C	Pass Pass
Sensitization ISO 10993-10	Entire Packaged, Sterilized Implant	0.9% NS	72hrs, 50°C	Pass

Test Performed	Test Article	Extract(s)	Extract conditions (time, temperature)	Test Results
Guinea Pig Maximization Sensitization	(Magnetic Beads, Wire Links, Eyelets, Suture)	Sesame Oil (SO)	72hrs, 50°C	Pass
Irritation/ Intracutaneous Reactivity ISO 10993-10	Entire Packaged, Sterilized Implant (Magnetic Beads, Wire Links, Eyelets, Suture)	0.9% NS CSO (Cotton seed oil)	72hrs, 50°C 72hrs, 50°C	Pass Pass
Systemic Toxicity Systemic injection ISO 10993-11	Entire Packaged, Sterilized Implant (Magnetic Beads, Wire Links, Eyelets, Suture)	0.9% NS CSO	72hrs, 50°C 72hrs, 50°C	Pass Pass
Subchronic Toxicity - Subchronic 14-day (repeat dose) toxicity ISO 10993-11	Entire Packaged, Sterilized Implant (Magnetic Beads, Wire Links, Eyelets, Suture)	0.9% NS	72hrs, 50°C	Pass
Genotoxicity: Gene mutation (Ames Assay) ISO 10993-3	Entire Packaged, Sterilized Implant (Magnetic Beads, Wire Links, Eyelets, Suture)	0.9% NS PEG	72hrs, 50°C 72hrs, 50°C	Pass Pass
Pyrogenicity (USP Pyrogen Test Procedure, Section 151 and Limulus Amoebocyte Lysate Test)	Entire Packaged, Sterilized Implant (Magnetic Beads, Wire Links, Eyelets, Suture)	0.9% NS Water, Lysate	24hrs, 70°C <15 minutes, 37°C	Pass Pass
Implantation	All materials used have been used in commercially available medical devices with no reports of toxicity. This device does not have any new chemistry or formulations. In addition, for each of the animals included in the GLP animal study, the area of implant was prepared for histopathology evaluation for each of the 6-week, 3-month, and 6-month GLP animals with no adverse findings. Additionally, the major organs were visually observed at 6-week, 3-month, and 6-month necropsy with no adverse findings. In addition to the localized gross and microscopic histological analysis, blood and body weights were collected for each of the GLP animals at baseline, mid-study, and sacrifice to assess systemic effects.			
Hemocompatibility	Not required for tissue contact devices.			
Chronic Toxicity	All materials used have been used in commercially available medical devices with no reports of toxicity. This device does not have any new chemistry or formulations. In addition, major organs were visually evaluated at 6-week, 3-month, and 6-month necropsy with no adverse findings. The 14-day subchronic toxicity testing also provides indication for lack of toxic effect from the implant material.			

Test Performed	Test Article	Extract(s)	Extract conditions (time, temperature)	Test Results
Carcinogenicity	All materials used have been used in commercially available medical devices with no reports of genotoxicity and carcinogenicity.			

B. Animal Studies

Chronic Animal Studies Summary

Twenty-five (25) adult canines were each implanted with the FENIX™ Device in compliance with Good Laboratory Practice (GLP) per 21 CFR 58. Table 5 describes the animal study. The main objectives of the chronic animal studies were to evaluate device stability and functionality, and histological response over time. At sacrifice, all animals had devices encapsulated in fibrous tissue and, when evaluated histologically, appeared stable.

Table 5. Animal Study

Animal Group	Follow-up	Tests Performed
42 Day Survival 5 Animals	None until sacrifice	Acute manometry, acute bolus retention force, chronic device actuation, chronic defecation pattern, chronic device stability, short-term histology, adverse events.
91 Day Survival 5 Animals	42-Day and sacrifice	Acute manometry, acute bolus retention force, chronic device actuation, chronic defecation pattern, chronic device stability, intermediate-term histology, adverse events.
182 Day Survival 5 Animals	42-Day, 91-Day, and at sacrifice	Acute manometry, acute bolus retention force, chronic device actuation, chronic defecation pattern, chronic device stability, long-term histology, adverse events.
365 Day Survival 5 Animals	42-Day, 91-Day, 182-Day, 273-Day, and at sacrifice	Acute manometry, acute bolus retention force, chronic device actuation, chronic defecation pattern, chronic device stability, long-term histology, adverse events.
365 Day Survival 5 Animals*	42-Day, 91-Day, 182-Day, 273-Day, and at sacrifice	Acute manometry, acute bolus retention force, chronic device actuation, chronic defecation pattern, chronic device stability, long-term histology, adverse events.

*The additional 5 animals at 1 year were implanted under a separate protocol with 150g force devices to evaluate safety of a higher force implant; all other implants are 100g.

All animals were sacrificed at the scheduled 42-day, 91-day, 182 –day and 365-day endpoint to evaluate histological response.

All but one of the study animals tolerated surgical placement of the FENIX device well as evidenced by no early deaths or surgical complications. The one animal presenting with infection at the incision site was treated unsuccessfully initially with antibiotics. The device was removed 120 days post-implant and the incision site debrided. The animal recovered well and was healthy at scheduled sacrifice. Additionally, all animals survived to their predefined survival periods as defined previously. At sacrifice, all animals, excluding the device removal animal, had devices encapsulated in fibrous tissue and, when evaluated histologically, appeared stable.

X. SUMMARY OF CLINICAL INFORMATION

The FENIX Implant has been evaluated in a clinical study under IDE G080145. Subjects were implanted with the FENIX device between December 9, 2008 and March 22, 2011. The clinical data from 35 subjects provided in the HDE submission reflected a database lock of November 26, 2014, and follow-up is ongoing. A total of 15 subjects were enrolled in the U.S and 20 subjects were enrolled outside the U.S., in France and Denmark. The safety and probable benefit data in this summary are complete for 6, 12, 24 and 36-month visits after the implant procedure.

A. Study Design

A multicenter, prospective, non-randomized clinical study was conducted to demonstrate the safety and probable benefit of the FENIX implant. A total of 35 subjects were enrolled. Fifteen (15) subjects were enrolled at two (2) institutions in the U.S and 20 subjects were enrolled at two (2) institutions outside the U.S. Subjects enrolled in the study had severe fecal incontinence (FI) and had previously failed conservative and/or less invasive therapies.

The primary safety parameter was the rate of all adverse events (AEs) monitored through the entire course of the clinical study from implant through subject withdrawal. AE reporting was based on the investigator's reporting of onset, relatedness to device and/or procedure, severity and status. Device and/or procedure-related events were summarized separately.

Probable benefit of the FENIX implant was characterized as the reduction of FI symptoms evaluated by a subject-completed bowel diary and improved quality of life using a self-administered questionnaire, the Fecal Incontinence Quality of Life (FIQOL).

Enrollment was limited to subjects that met the following inclusion criteria:

- Age $\geq$ 19 years, < 85 years, life expectancy >3 years
- Documented history of severe fecal incontinence for at least 6 months
- Subject diary documents $\geq$ 2 episodes per week on average over diary period, leakage greater than seepage
- Subject had failed standard conservative and medical therapy
- Subject was a surgical candidate
- Subject was willing and able to cooperate with follow-up examinations
- Subject has been informed of the study procedures and the treatment and has signed an informed consent form and provided authorization to use and disclose information for research purposes.

Subjects were not permitted to enroll in the FENIX study if they met any of the following exclusion criteria:

- Patient had a history of significant obstructed defecation or other significant chronic defecatory motility disorders
- Patient had current, external full thickness rectal or vaginal prolapse
- Patient had an electric or metallic implant within 10 cm of the area of device placement
- Patient had Inflammatory Bowel Disease
- Patient had Irritable Bowel Syndrome
- Patient has systemic disease as source of FI (scleroderma, neurologic disorders, Crohn's)
- Patient had active pelvic infection
- Patient had chronic diarrhea
- Patient diagnosed with anal, rectal, or colon cancer within 2 years
- Patient had prior anterior resection of the rectum
- Patient had undergone pelvic radiation therapy
- Patient had significant scarring of the recto-vaginal septum, or a history of recto-vaginal fistula
- Patient had previous anorectal posterior compartment surgery
- The procedure was an emergency procedure
- Patient was being treated with another investigational drug or device
- Patient couldn't understand trial requirements or was unable to comply with follow-up schedule
- Patient was pregnant, nursing, or planned to become pregnant
- Patient had a history of complex anal fistula.

B. <u>Accountability of HDE Cohort</u>

Forty-three (43) subjects provided written informed consent to participate in the study. Eight (8) of these subjects were withdrawn due to not meeting one or more of the inclusion or exclusion criteria and were considered screening failures. Thirty-five (35) subjects were implanted with the FENIX™ device. Table 6 displays subject disposition through the database lock date.

Table 6. Subject Accountability Through Study Completion

Subject Status	Month 12	Month 24	Month 36	Month 48	Month 60
Follow-up Visit Completed	28	26	24	16	6
Follow-up Visit Pending	0	0	0	8	18
Explanted	6	6	7	7	7
Deceased[×]	0	0	1	1	1
Missed Visit^/LTF[†]/Exited*	1	3	3	3	3
Total Subjects	35	35	35	35	35

* One subject completed the study requirements at month 12.
^ One 24 month visit was missed
[†] One subject was Lost to Follow-up (LTF)
[×]Patient death reported as caused by cirrhosis of the liver; unrelated to device or procedure.

C. Study Population Demographics and Baseline Parameters

The baseline demographics for study subjects are summarized below:

- There were 34 females (97.1%) and 1 male (2.9%)
- Mean age at the time of enrollment was 64.1 years (range 41.5 to 77.7 years)
- 100% were Caucasian
- Mean body mass index was 26.8 (range 18.1 to 48.5)
- Etiology of FI by percentage of subjects was 53.1% obstetric trauma, 25.0% neuropathic and 18.8% idiopathic
- FI type by percentage of subjects was 12.1% passive incontinence (no awareness of stool loss), 24.2% urge incontinence (inability to deter defecation), and 63.6% both.

The FENIX Feasibility study enrolled consecutive patients who met the study criteria at four centers. The selection ratio of men versus women was reflective of the frequency of patients who seek treatment for the disease. According to Munoz-Yauge[1], men present at approximately 15% of the fecal incontinence population as they are not subject to obstetric causes and are generally reticent to seek treatment.

Baseline values for the bowel diary and FIQOL are summarized in Table 7.

Table 7. Severity of Fecal Incontinence at Baseline*

	Baseline N=35
Bowel Diary Parameters	
FI Episodes per Week	13.9±6.7
FI Days per Week	6.0±1.3
Urgency Episodes per Week	6.7±5.5
FIQOL	
Lifestyle Score	2.5±0.8
Coping/Behavior Score	1.5±0.6
Depression/Self Perception Score	2.4±0.7
Embarrassment Score	1.8±0.7

*Plus–minus values are means ±SD

The subjects implanted with the FENIX™ device had previously failed conservative and/or less invasive therapies, such as bowel management, biofeedback, and sacral nerve stimulation (Table 8).

Table 8. Distribution of Subjects by Prior Less Invasive Treatments

Type of Previous Treatment	Total Subjects*	Percent %†
Bowel Management	27	77.1
Biofeedback	25	71.4
Sacral Nerve Stimulation (SNS)	14	40.0

* Subjects with multiple types of treatments were counted more than once. Therefore, the total number of subjects reported for all treatments is greater than the number of subjects enrolled.

† Percentages are based on the proportion of subjects reporting the treatment by actual subjects enrolled.

D. Safety and Probable Benefit Results

1. Safety Results

The safety analysis was based on a cohort of 35 evaluable subjects through the database lock. The key safety outcomes for this study are presented in Tables 9 through 13.

Adverse events (AEs) were assessed and documented from the time of implant throughout study participation. Determination of AE severity and causality was made by each investigator at the time of reporting using the definition provided in the protocol. All data available at the time of the applicable reporting is presented. The types of adverse events reported were comparable to those reported for other surgically implanted devices for the treatment of FI. No deaths (due to the implant), life-threating conditions or unanticipated adverse device effects were reported in the clinical study.

A total of 25 adverse events in 19 subjects were reported as related to the device and/or procedure or had unknown causality (Table 9). The most frequently reported adverse events related to the device and/or procedure included pain, impaction/defecatory disorder, device erosion, infection, and bleeding.

Table 9. Adverse Events Related to Device and/or Procedure or Relationship Unknown (includes complete 36 month follow-up data set and partial data sets at 48 and 60 months)

Adverse Event	Related or Unknown		Mild[3]		Moderate[3]		Severe[3]	
	AE (n)	Subj. % (n)[1]	AE (n)	Subj. % (n)	AE (n)	Subj. % (n)	AE (n)	Subj. % (n)
Pain	6	17.1% (6)	4	11.4% (4)	2	5.7% (2)	0	0%
Impaction or defecatory disorder	5	11.4% (4)	1	2.9% (1)	3	5.7% (2)	1	2.9% (1)
Device Erosion	4	11.4% (4)	1	2.9% (1)	2	5.7% (2)	1	2.9% (1)
Infection	4	11.4% (4)	0	0%	0	0%	4	11.4% (4)
Bleeding	3	8.6% (3)	2	5.7% (2)	1	2.9% (1)	0	0%
Other[2]	3	8.6% (3)	2	5.7% (2)	1	2.9% (1)	0	0%
Total	25	54.3% (19)	10	25.7% (9)	9	22.9% (8)	6	17.1% (6)

[1]Subjects may have had more than one type of event. Subjects may have had more than one event of the same type.

[2]Events reported as 'Other' include: Perineal bleeding (mild), Sleeplessness (mild), and Allergy inflammation reaction (moderate).

[3]The rating of severity (mild, moderate or severe) describes the extent for which the adverse event impacts the subject's ability to perform usual activities. An AE is considered to be severe if found to be incapacitating with inability to do work or usual activities.

In this study, a related serious adverse event (SAE) was defined as any medical occurrence, whether related to the study device or procedure, which met one or more of the following criteria:

- Results in death
- Is life-threatening
- Requires subject hospitalization >24 hours
- Requires prolongation of an existing hospitalization
- Results in persistent or significant disability/incapacity
- Results in fetal distress, fetal death or a congenital anomaly or birth defect
- Requires intervention to prevent impairment or damage.

Serious Adverse Events (SAEs) related to the device and/or procedure or having unknown causality were reported in six (6) subjects as seen in Table 10. All severe adverse events were also classified as serious adverse events. All SAEs resolved with no residual effects.

Table 10. Serious Adverse Events (Related or Unknown) (includes complete 36 month follow-up data set and partial data sets at 48 and 60 months)

Serious Adverse Event	Events (n)	Subjects %(n)[1]	Device Explant (n)	Days from Onset to Implant
Infection	4	11.4% (4)	3	7, 9, 15, and 251
Device erosion	1	2.9% (1)	1	28
Allergy, inflammation reaction	1	2.9% (1)	0	2
Impaction or defecatory disorder	1	2.9% (1)	0	23
Total	7	17.1 % (6)	4	Not Applicable

[1]Subjects may have had more than one type of event.

A summary of device explants and surgical interventions are summarized in Tables 11 and 12. During the study, there were eight (8) subjects who had the device explanted and/or underwent other surgical intervention. Seven (7) subjects had the device explanted, two (2) of these subjects underwent stoma placement and one subject underwent a reoperation for sacral nerve stimulation placement. One subject underwent reoperation for a stoma creation, but continues to have the FENIX device implanted.

Table 11. Device Explant by Reason and Number of Events (includes complete 36 month follow-up data set and partial data sets at 48 and 60 months)

Reason for Device Explant	Number of Events
Infection	3
Device erosion	3
Lack of effect	1
Total	7

Table 12. Device Explants and Other Surgical Intervention (includes complete 36 month follow-up data set and partial data sets at 48 and 60 months)

Subject	Device Explant	Reason for Device Explant	Other Surgical Intervention	Number of Surgical Interventions
01	Yes	Device Erosion	No	None*
02	Yes	Device Erosion	No	1
03	Yes	Infection	No	1
04	Yes	Infection	No	1
05	Yes	Continuing FI	Stoma, lack of effect	1†
06	Yes	Infection	Stoma, lack of effect	2
07	Yes	Device Erosion	Sacral nerve stimulation, lack of effect	2
08	No	NA	Stoma, impaction/defecatory	1

Subject	Device Explant	Reason for Device Explant	Other Surgical Intervention	Number of Surgical Interventions
			disorder	

*Subject 01: Device eroded through mucosa and is suspected to have passed through the anus; no intervention required.
†Subject 05: Device explant and stoma performed during the same surgical procedure.

Details of the device explants and other surgical interventions are provided below:

- One subject upon pelvic x-ray was found to have the device separated at the suture. No intervention was performed. It was presumed that the device passed through the anal mucosa during toileting at 47 days post-implant. The event resolved without sequelae.
- One subject was noted to have device erosion during a rectal exam 27 days post-implant. The device was explanted 28 days post-implant.
- One subject developed an infection that was not responsive to antibiotics. The device was explanted 47 days post-implant due to the infection.
- One subject continued to have fecal incontinence symptoms and at 69 days post-implant elected to have the device removed and underwent reoperation for a stoma creation.
- One subject experienced an infection, which resulted in device explant 41 days post-implant. After removal, the subject underwent reoperation for the creation of a stoma.
- One subject elected to have the device explanted and sacral nerve stimulation implanted 906 days post-implant due to reoccurring vaginal discharge secondary to device erosion.
- One subject experienced an infection that resulted in device explant 261 days post-implant.
- One subject underwent stoma creation for defecatory disorder (constipation) 154 days post-implant. The FENIX Device was not explanted

2. Probable Benefit Summary

The study had no formal hypothesis or probable benefit endpoints. Improvement was evaluated by bowel diary parameters compared to baseline and improvement in FIQOL scores compared to baseline.

Success criteria applied to the bowel diary data were as follows:

- Proportion of subjects achieving at least a 50% reduction in FI episodes per week when compared to baseline
- Proportion of subjects achieving at least a 50% reduction in FI days per week when compared to baseline
- Proportion of subjects achieving at least 50% reduction in urgent episodes per week when compared to baseline

For evaluable subjects (subjects completing a bowel diary at follow-up), a reduction of at least 50% was achieved in a clinically significant number of evaluated subjects for FI

episodes, FI days, and urgent episodes (Table 13). The treatment group (all subjects implanted) showed the majority of subjects had a reduction of at least 50% in FI episodes per week at all follow-up intervals through 36 months (Table 14).

Table 13. Reduction in FI from Baseline (Evaluable Subjects)

Outcome (per week)	6 Months % (n/N)	12 Months % (n/N)	24 Months % (n/N)	36 Months % (n/N)
≥50% reduction in FI episodes	82.1% (23/28)	78.6% (22/28)	70.4% (19/27)	90.9% (20/22)
≥50% reduction in FI days	71.4%(20/28)	67.9% (19/28)	59.3% (16/27)	77.3% (17/22)
≥50% reduction in urgent episodes	84.6% (22/26)	50.0% (13/26)	48.0% (12/25)	65.0% (13/20)

Table 14. Reduction in FI from Baseline (Treatment Group)

Outcome (per week)	6 Months % (n/N)	12 Months % (n/N)	24 Months % (n/N)	36 Months % (n/N)
≥50% reduction in FI episodes	65.7% (23/35)	62.9% (22/35)	54.3% (19/35)	57.1% (20/35)
≥50% reduction in FI days	57.1% (20/35)	54.3% (19/35)	45.7% (16/35)	48.6% (17/35)
≥50% reduction in urgent episodes	62.9% (22/35)	37.1% (13/35)	34.3% (12/35)	37.1% (13/35)

Improvement in bowel diary parameters reported as number of FI episodes and urgent episodes, or days per week are presented in Table 15. The reduction in number of FI days per week, FI episodes per week, and urgency episodes per week as reported by subjects reduced significantly from 13.9 episodes at baseline to 3.4 episodes per week at 36 months. The mean number of FI days per week decreased from 6.0 days per week at baseline to 2.0 at 36 months, and urgency episodes decreased from 6.7 episodes per week to just 2.0 at 36 months post-implant.

Table 15. Bowel Diary Parameters Reported as Mean FI Episodes or Days per Week[1]

Bowel Diary Parameters	Baseline N=35	6 Months N=28	12Months N=28	24 Months N=27	36 Months N=22
FI Episodes per Week	13.9±6.7	3.0±3.3	3.8±5.1	4.5±5.8	3.4±4.3
FI Days per Week	6.0±1.3	2.0±1.9	2.2±2.5	2.5±2.3	2.0±2.0
Urgency Episodes per Week[2]	6.7±5.5	1.7±2.7	3.5±4.9	3.8±4.5	2.0±3.0

[1] Values are means ± SD

[2] Two (2) subjects had incomplete data for urgent episodes; therefore the number of subjects reporting this parameter is two (2) less than the total for visit interval

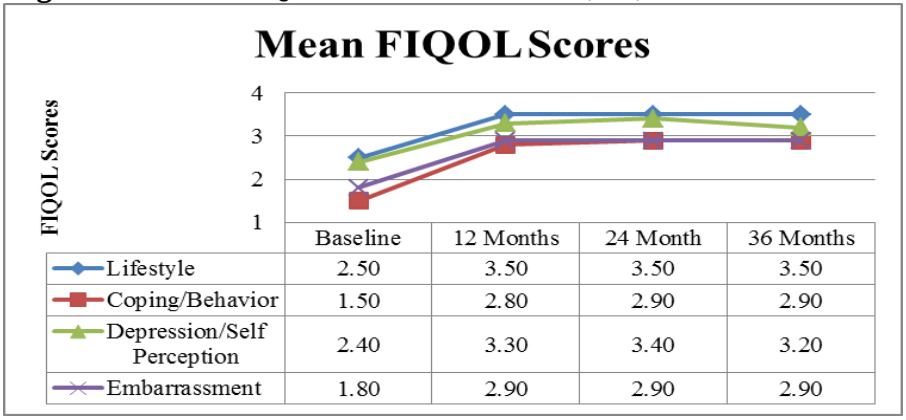
The FIQOL questionnaire is a patient-completed questionnaire designed to assess the impact of FI on various aspects of a patient's life. The FIQOL questionnaire is comprised

of four (4) scales: Lifestyle, Coping/Behavior, Depression/Self-Perception, and Embarrassment. Scores range from 1 to 4, with a score of 1 indicating the lowest functional status of quality-of-life. Figure 6 presents the mean FIQOL data for subjects that fully completed the questionnaire. In some instances, subjects completed only a portion of the questionnaire, not providing sufficient data to calculate a score for that particular scale. This results in a varying number of respondents at each time point for each of the four (4) scales.

The total subjects providing complete responses for each of the four (4) scales at all intervals included in the mean FIQOL Score calculation are provided below. Improvements from baseline are seen in all four (4) scales at all follow-up intervals.

- Lifestyle: Baseline (n=34), 12 months (n=28), 24 months (n= 25), 36 months (n=24)
- Coping/Behavior: Baseline (n=35), 12 months (n=28), 24 months (n=26), 36 months (n=24)
- Depression/Self Perception: Baseline (n=33), 12 months (n=27), 24 months (n=26), 36 months (n= 23)
- Embarrassment: Baseline (n=34), 12 months (n=28), 24 months (n=26), 36 months (n=24)

Figure 6. Mean FIQOL Scores at Baseline, 12, 24 and 36 Months



	Baseline	12 Months	24 Month	36 Months
Lifestyle	2.50	3.50	3.50	3.50
Coping/Behavior	1.50	2.80	2.90	2.90
Depression/Self Perception	2.40	3.30	3.40	3.20
Embarrassment	1.80	2.90	2.90	2.90

In summary:

- The probable benefit of the device is shown as the Responder$_{50}$ Rate of 63% at 12 months. The Responder$_{50}$ Rate was also 54% and 27% for the reduction of FI days and reduction in urgent episodes, respectively.

- There was an improvement of FIQoL lifestyle sub-score from 2.5 to 3.5 (1.0 difference), an improvement in coping/behavior sub-score from 1.5 to 2.8 (1.3 difference), and improvement in depression/self-perception sub-score from 2.4 to 3.3 (0.9 difference) and an improvement of embarrassment sub-score from 1.8 to 2.9 (1.1 difference).

- There were also 6 (17%) subjects that experienced a SAE and 13 (37%) subjects that experienced an AE among the study population of 35 subjects. Wound infections, perineal abscess, and device erosions accounted for 5 of the 7 SAEs among 5 of the 6 subjects. These 5 subjects all underwent device removals.

- The potential benefits of the device are somewhat unclear because of the limited long-term information. The risks of wound infections, perineal abscess, and device erosions have to be assessed in the scenario of use of the device in patients who have failed every other therapeutic option. Given this reasoning, despite the limited availability of long-term benefits, there is a reasonable benefit-risk ratio to approve the HDE.

- Based on the overall safety and probable benefit data, the device has demonstrated sufficient evidence to support the conclusion of overall safety and probable benefit.

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 two (2) US investigators and two (2) OUS 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. PANEL RECOMMENDATION

This HDE was not taken to a meeting of the Gastroenterology – Urology Devices Panel because the Gastroenterology – Urology Devices Panel has previously reviewed similar implants. It was determined, therefore, that the clinical issues raised by this HDE are similar to those previously reviewed by this Panel.

XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

FI is a common and underreported abnormality. Although not a medical disease, the condition results in considerable impairment in quality of life. Many patients will have improvement of FI with conservative medical therapy which includes the use of bulking agents in the diet, anti-diarrheal medications such as loperamide, or biofeedback training.

Nevertheless, many patients have little or incomplete relief of their FI and seek more aggressive and invasive interventions. Since FI can be of many origins, such as anal sphincter structural damage (i.e., from childbirth) or sensory/motor functional impairment (i.e., related to diabetes or spinal cord injury), no single intervention will benefit everyone.

Results from the FENIX Study showed that the probable benefits of the FENIX Continence Restoration System outweigh the risks when used in patients with severe fecal incontinence not responsive to conservative medical therapy. The FENIX Implant not only restored or improved continence for the majority of evaluable patients with fecal incontinence, but also improved their quality of life and symptom severity. The risks were as expected for a surgical procedure to address fecal incontinence. If needed, the FENIX device can be explanted without limiting future treatment options. In the intended population, the FENIX Implant has the potential to positively impact the lives of people suffering from fecal

incontinence, giving patients and physicians more options to treat this debilitating condition. The therapeutic success rate of the FENIX Implant, combined with its acceptable safety outcomes, results in a positive risk/probable benefit profile for the FENIX Implant.

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.

XIV. CDRH DECISION

CDRH has determined that, based on the data submitted in the HDE, the FENIX® Continence Restoration 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 December 18, 2015. The final conditions of approval cited in the approval order are described as follows:

ODE Lead HDE Post Approval Study - Continued Follow up Study*:*
This study must be conducted per Protocol 4578, dated January 2015. This study is a multi-center, single arm, prospective continued follow-up of the FENIX Continence Restoration System (also known as Magnetic Anal Sphincter) feasibility study, conducted in the US and France. It will evaluate the long-term safety and probable benefit of the FENIX Continence Restoration System.

All 24 remaining patients (7 patients exited due to device explant, 3 patients exited due to lost to follow-up/missed visit, and 1 patient deceased) of the 35 feasibility study enrolled from 3 investigational sites will be followed annually through 60 months post-procedure.

The study objectives and endpoints are as follows:

Safety Objective:
To evaluate the incidence of all adverse events at various time points including implant, 6 weeks, 3 months, 6 months, 12 months, and then annually through 60 months post-implant.

Probable Benefit Objective:
To monitor the improvement of FI symptoms and anal sphincter function at various time points including 6 weeks, 3 months, 6 months, 12 months, and annually for 60 months post-implant.

Study Endpoints:
1. There are no statistically derived endpoints for this feasibility study. The safety objective will be met by reporting all adverse events at various time points including implant, 6 weeks, 3 months, 6 months, 12 months, and annually for 60 months post-implant. Serious device and procedure-related adverse events will be summarized separately. Safety will be characterized by physical examination and pelvic x-ray evaluations.

2. The probable benefit of the device will be characterized as the reduction of FI symptoms by subjective measurements using the Fecal Incontinence Severity Index, Wexner, and

Fecal Incontinence Quality of Life Scale scores and three week diary documenting episodes of incontinence. Additional information tracked during the course of the study will include subjective measurements of obstructed defecation syndrome (ODS).

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 Adverse Events in the labeling.

Post-approval Requirements and Restrictions: See approval order.

XVI. REFERENCES

1.Munoz-Yague T. et al, Fecal Incontinence in men: Causes and clinical and manometric features. World J Gastroenterol 2014 June 28;20 (24): 7933-7940).