SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Device, Incontinence, Mechanical/Hydraulic

Device Trade Name: ProACT™ Adjustable Continence Therapy for Men

Device Product Code: EZY

Applicant's Name and Address: Uromedica, Inc.
1840 Berkshire Lane North
Plymouth, MN 55441

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P130018

Date of FDA Notice of Approval: November 24, 2015

II. INDICATIONS FOR USE

The ProACT system is indicated for the treatment of adult men who have stress urinary incontinence arising from intrinsic sphincter deficiency of at least twelve months duration following radical prostatectomy or transurethral resection of the prostate (TURP) and who have failed to respond adequately to conservative therapy.

III. CONTRAINDICATIONS

The ProACT system is contraindicated for use in individuals who:

- Have active systemic or urinary tract infections
- Have incontinence due to detrusor instability or over activity
- Have reduced bladder compliance
- Have significant residual volume greater than 100 cc after voiding
- Are presently receiving, or plan to receive within 6 months, radiotherapy and those patients who have received radiotherapy within the last 6 months
- Have primarily urge incontinence
- Are suspected of having bladder cancer

- Have unsuccessfully treated bladder stones

- Have hemophilia or bleeding disorders

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the ProACT™ device labeling.

V. DEVICE DESCRIPTION

Overview

The ProACT™ Adjustable Continence Therapy for Men (ProACT device) is comprised of an implantable device, accessories, and implantation tools, which are described below.

- ProACT Device (Figure 1) is an implantable, volume-adjustable balloon connected to bi-lumen tubing that terminates in a subcutaneous injection port. One lumen provides a fluid pathway to adjust the balloon volume and a second lumen houses the removable push wire during implantation. The ProACT device and pushwire are provided sterile.

- Accessories consist of an inflation syringe, 23-gauge non-coring tip, and extra pushwire, all provided sterile in a package with the ProACT device.

- Implantation Tools (Figure 2) consist of a sharp trocar, blunt trocar, U-channel sheath, and a tissue expanding device (TED II). Each of the implantation tools is constructed of stainless steel and is reusable. The implantation tools are provided non-sterile and require cleaning and terminal (steam) sterilization at the user facility prior to each use.

Figure 1. ProACT Device at varying inflation levels

Figure 2. Implantation Tools

With the use of the implantation tools and accessories, two (2) ProACT devices are implanted in parallel, one on either side of the urethra at the bladder neck. Implantation can be performed using local, spinal, or general anesthesia, and device placement is performed using fluoroscopic guidance. The accessory needle and syringe are used to inject and isotonic mixture of sterile water and contrast media to inflate the balloons. The ports of the two (2) devices are placed subcutaneously on the posterior side of the scrotum and are externally manually palpable for hypodermic needle placement through the skin into the self-sealing port during balloon volume adjustments. A series of volume adjustments can be conducted over time up to a maximum balloon volume of 8 cc.

Component Description

The ProACT device is a fully implantable device that consists of six (6) primary components, plus a non-implantable push wire used to facilitate implantation. A description of the device's primary components is provided in the table below.

Component	Material	Purpose/Function
Septum	Silicone	Provides access to the balloon for adjusting the balloon volume.
Port Liner	Titanium Alloy	Encases septum to form port assembly for access to the balloon for adjusting the balloon volume.

Component	Material	Purpose/Function
Port Subassembly	Silicone	Acts as a transition from the rigid port liner to the Flexible bi-lumen tubing. It provides for gradual change in stiffness, preventing failure due to bending fatigue. A dimensional transition also occurs. Provides a junction between the bi-lumen tubing and the port.
Bi-Lumen Tubing	Silicone	Provides connection between port and balloon. One lumen provides a fluid pathway to fill the balloon and a second lumen houses the push wire during implantation.
Balloon	Silicone	The balloon is used to cause a displacement of the paraurethral tissue resulting in coaptation of the proximal urethra and support of the bladder neck. Inflated by injection of isotonic solution at discretion of the physician.
Radiopaque Marker	90% Pt / 10% Ir	Used to facilitate location of the device using fluoroscopy.
Push Wire	302/304 Stainless Steel	The implantable device is pre-mounted on a push wire. The push wire aids in guiding and pushing the device through the U-channel sheath. The push wire is passivated prior to use.

Device Design Specifications:
Key product dimensional specifications are provided below:

Device	Dimension	Specification	Tolerance
ProACT Implant	Balloon Diameter	24 mm at 8 cc fill	± 2.0 mm
ProACT Implant	Balloon Length	22 mm at 8 cc fill	± 2.0 mm
ProACT Implant	Overall Length	12 or 14 cm	± 0.25 cm

Key performance specifications are summarized below:

Device	Performance Feature	Specification
ProACT Implant	Balloon Burst Volume	16.0 cc minimum
ProACT Implant	Balloon Nominal Volume	8.0 cc

Device	Performance Feature	Specification
ProACT Implant	Lumen Tube Burst Strength	15 PSIG minimum
ProACT Implant	Bond Strength: Balloon to lumen tube	2.0 lbf minimum
ProACT Implant	Bond Strength: Lumen tube to port	2.0 lbf minimum
ProACT Implant	Septum Life	45 needle punctures minimum
ProACT Implant	Shelf Life	5 years

The available configurations and tool model numbers are provided below:

Model Number	Device Length	Configuration Description
800018-01	12 cm	ProACT Patient Pack: Two (2) implantable devices with needle and syringe
800018-02	14 cm	ProACT Patient Pack: Two (2) implantable devices with needle and syringe
800022-01	12 cm	ProACT Patient Pack: One implantable device with needle and syringe
800022-02	14 cm	ProACT Patient Pack: One implantable device with needle and syringe

Tool Number	Description
750009	Implantation Instrument Set (Sharp Trocar with U-channel sheath)
750022	Blunt Trocar
750033	Tissue Expanding Device II Replacement Actuator
750034	Tissue Expanding Device II (with removable actuator arm)

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several alternatives for the treatment of male post-surgical stress urinary incontinence (SUI). These alternative treatments include non-invasive treatments such as pelvic floor muscle exercise and drug therapy, and surgical treatments such as the

Artificial Urinary Sphincter and transobturator suburethral sling. Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with his physician to select the method that best meets his expectations and lifestyle.

VII. MARKETING HISTORY

The ProACT device has been in commercial distribution in the European Union since 2002. Other current markets are Australia, Canada, New Zealand, Norway, and Switzerland.

The ProACT device has not been marketed in the United States.

The ProACT device has not been withdrawn from any market.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

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

- Allergic response (material, contrast media, antibiotic, other)
- Anesthesia risks (general, spinal)
- Bladder spasm
- Cellulitis
- Device calcification
- Device malfunction/leakage/occlusion
- Device wear
- Erosion of tissue (bladder wall, bowel, perineum, rectum, scrotal, urethral, other)
- Erythema, swelling
- False channel creation
- Hematuria
- Hematoma at the site of entry
- Induration at site of the port (perineum, scrotum)
- Infection (urinary tract, wound)
- Pain or discomfort from the balloon or port
- Perforation (bladder wall, urethra, rectum)

- Prosthetic infection
- Prosthetic migration
- Sepsis
- Ulcerations (skin incision)
- Urethral stricture
- Urinary difficulty, retention
- Urinary urgency, frequency
- Worsened incontinence

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

IX. SUMMARY OF PRECLINICAL STUDIES

A. Laboratory Studies

The applicant performed laboratory testing on the ProACT system and implantation tools to verify that the performance attributes are sufficient for the device to perform as intended and minimize the risk of adverse events under anticipated clinical conditions. Testing included units with real-time five-year aging. The specific testing and results are summarized in Tables 1, 2 and 3, below.

Table 1. ProACT Device Verification/Validation Testing Summary

Test	Test Description	Acceptance Criteria	Results
Balloon Size	Balloon is filled with maximum fluid volume and measured.	Length/Diameter ratio between 0.70 and 1.10	The device met established acceptance criteria.
Port Dimensions	The maximum port length and diameter is measured.	Length = 0.400” - 1.000” Diameter = 0.185” - 0.400”	The device met established acceptance criteria.
Strain Relief Bond	Tensile testing evaluated the force at break for the bond.	Force > 2 lbs	The device met established acceptance criteria.
Septum Bond and Penetration Life Testing	Repeated puncturing and pressurizing assessed leak formation and septum bond strength.	The septum must not leak when exposed to a minimum of 45 needle punctures.	The device met established acceptance criteria.
Balloon Bond	Tensile testing evaluated the	Force > 2 lbs	The device met

Test	Test Description	Acceptance Criteria	Results
	force at break for the bond.		established acceptance criteria.
Balloon Burst	Water is infused into the balloon until the balloon bursts.	Burst volume > 16.0 cc	The device met established acceptance criteria.
Device Deflation Time	Time required to remove the filling solution is measured.	Deflation ≤ 2 minutes (120 sec)	The device met established acceptance criteria.
Force to Deliver Device	The maximum delivery force is assessed by conducting an implant in a simulated tissue model.	Force < 1.33 lbs The push wire and device are required to remain functional with a minimum balloon burst volume of 16.0 cc following 5 insertion/ removal cycles of the device along the sheath	The device met established acceptance criteria.
Force to Insert/ Remove Device	A tensile tester is used to push the device through a lubricated simulation hole to assess the force transmitted during insertion through the U-channel sheath. Direction is reversed to assess removal force.	Force < 2 lbs	The device met established acceptance criteria.
Device Insertion Column Strength/ Device Stiffness	A section of conduit with pushwire incorporated is lowered in a tensile tester until it buckles to assess peak force. Stiffness is then assessed without the push wire.	Column strength ≥ 0.11 lbs (with pushwire in place) Device stiffness < 0.18 lbs (with pushwire removed)	The device met established acceptance criteria.
Pushwire Insertion and Lumen Burst	The device is inspected after multiple pushwire insertions to assess pushwire and conduit durability. Conduits are then pressurized under water to confirm absence of damage.	The pushwire must be insertable into the device four (4) times. The conduit must be able to withstand a minimum applied pressure of 20 psig without burst or leakage.	The device met established acceptance criteria.

Test	Test Description	Acceptance Criteria	Results
Life Cycle Testing	Devices are cycled in a simulated implant environment to confirm balloon durability.	The device must maintain the system volume (± 0.5 cc) when compressed 2mm +0.3/-0.2 mm for 100,000 cycles.	The device met established acceptance criteria.
MRI Testing	Magnetic resonance imaging (MRI) testing was conducted on the device to determine the presence of magnetic field interactions (displacement force and torque), heating, and artifacts associated with the use of an MR system.	Deflection angle < 45° No rapid, forceful alignment to the magnetic field. Heating testing per ASTM 2182-02a. Artifact testing per ASTM F2119-07.	The device met established acceptance criteria. The device is considered "MR-conditional" under the specified conditions of use (ASTM F2503-05).

Table 2. Accessory Verification/Validation Testing Summary

Test	Test Description	Acceptance Criteria	Results
Needle Cannula Length	The needle cannula length is measured.	Length ≥ 1"	The device met established acceptance criteria.
Syringe Function	The syringe is repeatedly filled with a specified amount of deionized water then emptied into a container to verify expected volume is released.	Fluid volume delivery = 5.0 cc ± 0.3 cc Syringe and needle must withstand 6 fluid insertion/withdrawal cycles of 3.0 cc ± 0.3 cc	The device met established acceptance criteria.
Needle Insertion Force/Column Strength	A tensile tester is used to lower the needle into the septum of a port to assess force required for puncture. The needle is then lowered to the buckling point to assess column strength.	Insertion force ≤ 2.9 lbs Column strength > 5.5 lbs	The device met established acceptance criteria.

Table 3. Implantation Tools Verification/Validation Testing Summary

Test	Test Description	Acceptance Criteria	Results
U-channel Sheath Length and OD	The length and outer diameter are measured.	Shaft length ≥ 30 mm Outer diameter ≤ 0.190" (tissue contacting	The device met established

Test	Test Description	Acceptance Criteria	Results
		portion)	acceptance criteria.
U-channel Sheath Function after Compression/ Deflection	The sheath is compressed between two (2) surfaces using a tensile tester. With a load applied a gauge pin is slid through the sheath to determine if the minimum inner diameter is maintained. Sheath ends are positioned on a fixture, which allows the middle portion to be unsupported under a tensile load. The trocar is placed in the sheath to confirm the sheath remains functional (i.e., trocar fits through sheath, locks within sheath, unlocks from sheath, and can be removed from sheath).	Inner diameter ≥ 0.150” Remain functional after exposure to a 2.0 lbf deflection force	The device met established acceptance criteria.
U-channel Sheath/Trocar Column Strength	The U-channel sheath and blunt trocar are assembled. The blunt trocar tip is placed into the lower mount of a tensile tester. After compression, the tool set is assessed to verify the blunt trocar can be unlocked and removed from sheath.	Column strength ≥ 11 lbs	The device met established acceptance criteria.
TED II Tool Function	Tool is placed in a U-channel sheath and engagement, removal, and reinsertion is verified to ensure the tool jaw opens and closes when the handle is actuated. To assess actuator interchangeability, each actuator is removed from the initial tool and then placed in all the other test tools. Proper actuator fit is verified. Visual inspection is conducted to verify: no visible cracks, no observable bending of tool components, and no evidence of corrosion (rust, flaking, pitting). Tool is placed in sheath then oriented on a tensile tester under load. Each tool is inspected to verify: jaws open and close, tool engages and disengages with sheath, no visible damage (cracking, bending), and tool can be disassembled and reassembled. Tool is placed in sheath; the tip is opened and closed 5 times. The tool is	All actuators and tools must be interchangeable and function when each of the actuators from the others are placed in the tool. Tools must function after exposure to specified load (18 lb), must not be damaged, and must be able to be disassembled and reassembled. The tool must engage, lock and unlock, actuate, and be removed from the sheath.	The device met established acceptance criteria.

Test	Test Description	Acceptance Criteria	Results
	unlocked and removed. Process is repeated for a total of 120 cycles. Tool is inspected to verify the jaws open and close, tool engages and disengages from sheath, no visible damage (cracking, bending), and tool can be disassembled and reassembled.		
Tool Interaction and Function	Each sharp/blunt trocar and each TED II tool is used with each U-channel sheath verifying fitting through sheath, locking within sheath, unlocking from sheath, and removal from sheath. With the TED II tool locked within the sheath, it is also verified that each jaw can fully open and close when the handle is actuated. After the insertion cycles, each trocar and TED II tool is visually inspected to verify: no visible cracks, no observable bending of tool component, and no evidence of corrosion (rust, flaking, pitting). Upon completion of the interaction evaluations with the sharp trocar, blunt trocar and TED II tool, each sheath is visually inspected without magnification to verify: no visible cracks, no observable bending of tool component, and no evidence of corrosion (rust, flaking, pitting).	All components of the surgical tool family must be able to engage, lock and unlock, actuate (TED II only) and be removed from the sheath prior to use, following surgical delivery of the device and after cleaning and sterilization.	The device met established acceptance criteria.

Sterility and Packaging Testing

The ProACT system is sterilized with a validated gamma radiation sterilization process to achieve a minimal sterility assurance level (SAL) of 10^{-6}. Dose audits are conducted for each production batch to detect any bioburden changes over time. The aged packaging evaluation indicated that the packaging would remain acceptable for the 5-year shelf life of the ProACT system.

Biocompatibility and Toxicology Testing

The applicant conducted a toxicology assessment to characterize the risk profile of the implantable materials. Levels of extractable chemicals were analytically quantitated and determined to be within their safe level of exposure. Based on the current risk assessment, no adverse biological sequelae are expected. The ProACT system was also

assessed by tests considered appropriate under ISO 10993-1 for a permanent (> 30 days) implantable, tissue-contacting device. The results of all biocompatibility tests, summarized below in Tables 4, 5, and 6, provide evidence that the ProACT system (including the implanted devices, tools, and accessories) is biocompatible and non-pyrogenic for the indicated conditions of use.

Table 4. ProACT Device Biocompatibility Test Summary

Toxicity Endpoint	Evaluation Method	Results
Cytotoxicity	L929 MEM Elution 10993-5	Non-Cytotoxic
Sensitization	Kligman Maximization 10993-10	Non-Sensitizing
Irritation	Intracutaneous Injection 10993-10	Non-Irritant
Systemic Toxicity (acute toxicity)	Systemic Injection Test 10993-11	Non-Toxic
Materials Mediated Pyrogenicity	Rabbit Pyrogen Test 10993-11	Non-Pyrogenic
Subacute and subchronic toxicity	28 Day Repeat IV Dose Intravenous Toxicity Test	No Adverse Biological Effects
	28 Day Toxicity Study in Rats	No Adverse Biological Effects
Genotoxicity	Gene Mutations: Ames Reverse Mutation Assay, 10993-3	Non-Mutagenic
	CHO Chromosomal Aberration, 10993-3	Non-Clastogenic
		Non-Mutagenic
	Micronucleus Assay in Mice, 10993-3	Non-Clastogenic
Implantation	Rabbit Muscle Implant (1 Week)	Similar to Control
	Rabbit Muscle Implant (4 Weeks)	Similar to Control
	Rabbit Muscle Implant (13 Weeks)	Similar to Control
Chronic Toxicity	Toxicological risk assessment	No Significant Risk
Carcinogenicity	Toxicological risk assessment	No Significant Risk

Table 5. Tool Biocompatibility Test Summary

Toxicity Endpoint	Evaluation Method	Results
Cytotoxicity	L929 MEM Elution 10993-5	Non-Cytotoxic
Sensitization	Kligman Maximization 10993-10	Non-Sensitizing
Irritation	Intracutaneous Injection 10993-10	Non-Irritant
Systemic Toxicity (acute toxicity)	Systemic Injection Test 10993-11	Non-Toxic
Materials Mediated Pyrogenicity	Rabbit Pyrogen Test 10993-11	Non-Pyrogenic

Table 6. Accessory Biocompatibility Test Summary

Toxicity Endpoint	Evaluation Method	Results
Cytotoxicity	L929 MEM Elution 10993-5	Non-Cytotoxic
Irritation	Intracutaneous Injection 10993-10	Non-Irritant

B. Animal Studies

The applicant performed a 12-month Good Laboratory Practice (GLP) study in canines to assess organ and tissue reaction following chronic implant with the ProACT device. A total of 13 female, 5.5-6.5 month old, mixed breed hound dogs started the study. One dog died in a non-study related accident and was replaced. Therefore, a total of 14 canines were used in the study.

Observations for mortality, morbidity, injury, and the availability of food and water were conducted twice daily for all animals. Additional examination data were collected and included external examination, abdominal palpation, and body weight. Data collection for analyses included blood samples and urine samples. After sacrifice, necropsy examinations were performed, organ weights recorded, and selected tissues were microscopically examined. Sections of the urethral tissue were selected, processed, and examined adjacent to the balloon.

Implantation of the test device was not associated with any unexpected mortality, body weight changes, hematology or urinalysis changes, macroscopic observations, or organ weight changes. Mild increases in clinical chemistry parameters were found in the implanted dogs. This pattern may be related to animal maturation, but a mild device-related effect of minimal to no clinical significance cannot be definitively ruled out. These findings are not considered adverse as the elevation was at or just greater than the interval normal ranges for canine as demonstrated by the control values and were consistent with changes expected for the canine as it matures. Individual clinical chemistry values for implanted dogs remained within expected historical ranges.

Examination of explanted devices revealed a fibrous capsule of variable thickness, with well-organized layers of mature collagen around the device components. At the interface of the fibrotic response and the device artifacts, a lamina of macrophages and

fibroblasts was noted. Minimal to mild chronic inflammation, characterized by an infiltration within and around the fibrous capsule of lymphocytes, macrophages, and plasma cells, was observed in a few sections, and occasional hemorrhage was noted in one dog around both implants. The fibrous capsule is an expected finding for an implant of this type. The microscopic observations of minimal to mild chronic inflammation associated with the implantation site were considered to be typical of a stable foreign body response. These findings were not considered to be adverse as the observations were minimal to mild. The microscopic findings in the kidneys, limited to lymphocytic infiltration and mineralization, are not unusual in canine.

Based upon the results detailed above, the ProACT device demonstrated acceptable tissue response during chronic implantation.

X. SUMMARY OF PRIMARY CLINICAL STUDY

The applicant performed a clinical study to collect data for the purpose of establishing a reasonable assurance of safety and effectiveness of treatment with the ProACT device in adult men who have stress urinary incontinence arising from intrinsic sphincter deficiency of at least twelve (12) months duration following radical prostatectomy or transurethral resection of the prostate (TURP) and who have failed to respond adequately to conservative therapy. The study was performed in the U.S. under IDE # G040196, and in Canada and New Zealand under the same protocol. Data from this clinical study were the basis for the PMA approval decision. A summary of the clinical study is presented below.

A. Study Design

Patients were enrolled between July 2005 and June 2007, and the date of the last 18 month follow-up visit was February 2009. The database for this PMA reflected data collected through October 2012 and included 124 patients in the intent-to-treat cohort. There were 11 investigational sites (8 in the U.S., 2 in Canada, and 1 in New Zealand). One U.S. site did not implant any subjects.

The study was a prospective, multi-center, single-arm, open-label clinical study. Multiple measurements using 24-hour pad weight and pad count, validated questionnaires, and voiding diaries were used to evaluate the achievement of study objectives. Subjects were followed for a minimum of 18 months following implantation. The study was based on the primary and secondary endpoints at 18 months, with a plan for patients to continue follow-up until PMA approval.

The primary effectiveness endpoint was based on the average of two (2) 24-hour pad weight measurements conducted at baseline and compared to the average of two (2) 24-hour pad weight measurements conducted at 18 months. Individual patient success was defined as $\geq$ 50% reduction in 24-hour pad weight at 18 months compared to baseline. Overall study success criteria was defined as an exact 95% binomial confidence interval lower boundary of $\geq$ 50% patient success at 18 months.

The ProACT study included an 18 month follow-up period to demonstrate stability of the treatment effect for a clinically meaningful period of time. For the ProACT device, the gradual adjustment protocol needed to avoid initial excessive inflation, but it also raised concerns in how to quantify the stability of the therapy. An 18 month follow-up period was chosen to allow observation of a 12 month period after adjustment completion, with the expectation that optimal adjustment would be completed within six (6) months of implantation. Thus, any device balloon volume adjustment occurring more than 6 months after the implant was considered to be a durability failure.

The analysis plan used frequentist methodology. All comparisons were made against baseline, pre-implant data, thus using each patient as his own control. The statistics used varied by endpoint and are summarized below.

- Safety - primary/secondary endpoints, adverse events: Statistics consisted of a simple percent and a Kaplan-Meier product limit analysis for complications, and for all adverse events.

- Safety - secondary endpoint, bladder function: Descriptive statistics for baseline, 18 months, and change. Significance determined using Wilcoxon's matched pairs signed ranks test.

- Effectiveness - primary endpoint: Baseline 24-hour pad weight was compared with 18 month 24-hour pad weight for each patient. Patients with $\geq 50\%$ reduction were categorized as a success. The exact 95% binomial confidence interval was calculated.

- Effectiveness - secondary endpoints, see Section X.A.3(a)-(d): For these endpoints the hypothesis was improvement, as measured by mean change at 18 months compared with baseline. Significance was determined using Wilcoxon's matched pairs signed ranks test. A set-up procedure developed by Hochberg was used to control the family-wise error rate.

- Effectiveness - secondary endpoints, see Section X.A.3(e): This endpoint was measured by mean change at 18 months compared with pre-implant. Significance was determined using Wilcoxon's matched pairs signed ranks test.

- Trial sample size: Sample size calculation, based on the primary endpoint, yielded a minimum sample size of 92 patients. This calculation assumed an exact 95% binomial confidence interval of $\pm$ 0.10 with a success rate of 0.50.

1. Inclusion and Exclusion Criteria
   Enrollment in the ProACT study was limited to patients who met the following inclusion criteria:

- Underwent either a radical prostatectomy, transurethral resection of the prostate or other prostate surgery at least twelve (12) months prior without radiation therapy.
- Demonstrates primary stress urinary incontinence.
- Male subject at least 45 years of age.
- Has positive 24-hour pad weight tests (> 8 gram pad weight increase demonstrated in two 24-hour pad weight tests).
- Experiences at least three (3) incontinence episodes per day during two (2) baseline voiding diaries.
- Has a negative urine culture.
- Has no known urogenital malignancy other than previously treated prostate cancer.
- Physician determines subject to be a suitable surgical candidate.

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

- Has primary urge incontinence.
- Has detrusor instability or over-activity.
- Has a residual volume greater than 100 ml or > 25% of the total bladder capacity after voiding.
- Had/has or is suspected of having bladder cancer.
- Has a history of recurrent bladder stones.
- Neurogenic bladder that is atonic or has detrusor sphincter dyssynergia.
- Has known hemophilia or a bleeding disorder.
- Has an abnormal PSA, according to sites laboratory standards, unless further investigation confirms no underlying prostate malignancy.
- Has a known severe contrast solution allergy (e.g., anaphylaxis, cardiac or respiratory arrest).
- Has insulin-dependent diabetes.
- Has a known auto-immune disease (e.g., Crohn's disease, lupus, AIDS) or is on immuno-suppressive therapy.
- Has a genitourinary mechanical prosthesis other than previous sling procedure (e.g., Artificial Urinary Sphincter, implantable penile prosthesis).
- Has a urethral stricture that prevents passage of an 18 Fr cystoscope or has had more than one urethrotomy.

- Underwent bulking procedure within 6 months of baseline assessment.
- Is currently enrolled or plans to enroll in another drug or device clinical trial.
- Is currently utilizing an indwelling or condom catheter for treatment of incontinence and is not willing to discontinue use at least 4 weeks prior to the baseline assessment.

2. Follow-up Schedule

Data was collected preoperatively for screening and baseline assessments, and patients were scheduled to return for follow-up examinations postoperatively at 6 weeks, 6 months, 12 months, 18 months, and annually thereafter. Adverse events and complications were recorded at all visits. The data collection schedule is summarized in Table 7, below. Data from the key time points are provided below in the section summarizing safety and effectiveness results.

Table 7. Clinical Study Data Collection Schedule

	Enrollment	Baseline	Implant	6 wk	6 mo	12 mo	18 mo	Annual
Informed Consent	X							
Physical Evaluation (Pre-op exam)	X							
Urologic assessment	X			X	X	X	X	X
Urinalysis		X	X[1]					
Prostate Specific Antigen (PSA)	X							
Urodynamic Testing		X[2]					X	
24-hour pad weight		X[3]			X	X	X[3]	X
4-day Voiding Diary		X[3]			X	X	X[3]	X
Urinary Stress Test	X							
Free Uroflow	X			X	X	X	X	X
Post void residual (by ultrasound)	X	X		X	X	X	X	X
Quality of Life (IQOL)		X			X	X	X	X
Sexual Function (IIEF)		X			X	X	X	X
Urinary Function (UCLA-PCI Urinary Function)		X			X	X	X	X

	Enrollment	Baseline	Implant	6 wk	6 mo	12 mo	18 mo	Annual
Satisfaction Questionnaire							X	
Plain Film X-ray			X					
Cystourethroscopy		X[2]						
Adverse Events			X	X	X	X	X	X
Follow-up Scheduling Window				+2 wks -2 days	± 2 wks	± 4 wks	±4 wks	±4 wks

[1] Repeat urinalysis if not done 2 weeks prior to surgery or if baseline urinalysis was positive.
[2] Results from testing conducted within 6 months of the baseline assessment may be used, if all study required tests were recorded.
[3] Two (2) evaluations completed at each time point and averaged to obtain result.

3. Clinical Endpoints

Safety

The primary safety endpoint was complication frequency measured through 18 months of follow-up.

The first secondary safety endpoint was characterization of the frequency and severity of all trial-related adverse events through 18 months.

The second secondary safety endpoint, bladder function, included characterization of changes from baseline in detrusor stability, voiding pressure at peak flow, and bladder pressure at full volume, all measured at 18 months.

Effectiveness

The primary effectiveness endpoint was based on the average of two (2) 24-hour pad weight measurements conducted at baseline and compared to the average of two (2) 24-hour pad weight measurements conducted at 18 months. Individual patient success was defined as ≥ 50% reduction in 24-hour pad weight at 18 months compared to baseline. Overall study success criteria was defined as an exact 95% binomial confidence interval lower boundary of ≥ 50% patient success at 18 months.

Additional analyses involving 24-hour pad weight include classification as dry, improved, unchanged or worse at 18 months, and treatment effect durability through 18 months.

Key secondary effectiveness endpoints were selected to support findings of the primary endpoint to evaluate consistency of the trial results. The secondary endpoints, listed below, were all measured at 18 months.

a. Change in number of incontinence episodes;
b. Change in pad count;
c. Change in urinary function as measured by the UCLA Prostate Cancer Index (PCI) Urinary Function questionnaire;
d. Change in quality of life as measured by Incontinence Quality of Life (I-QOL) instrument; and
e. Change in sexual function as measured by the International Index of Erectile Function (IIEF).

B. Accountability of PMA Cohort

Patient accountability information is summarized below in Figure 3. At the time of database lock, of 160 subjects enrolled in the PMA study, there were 124 subjects who qualified for implantation (intent-to-treat cohort). However, only 123 subjects were implanted because one subject had an anatomical anomaly that did not permit implantation. At the 18 month post-operative visit, a total of 98 subjects had the 24-hour pad weight determination (primary outcome measure). Prior to the 18 month evaluation, eight (8) subjects were permanently explanted, one (1) was lost to follow-up, one (1) was terminated due to an adverse event, and two (2) died. Pad weight data at the 18 month visit was not available for 13 additional subjects and their data were imputed using data from a prior or subsequent visit. At 18 months, the follow-up rate for the primary outcome assessment was 79% (98/124).

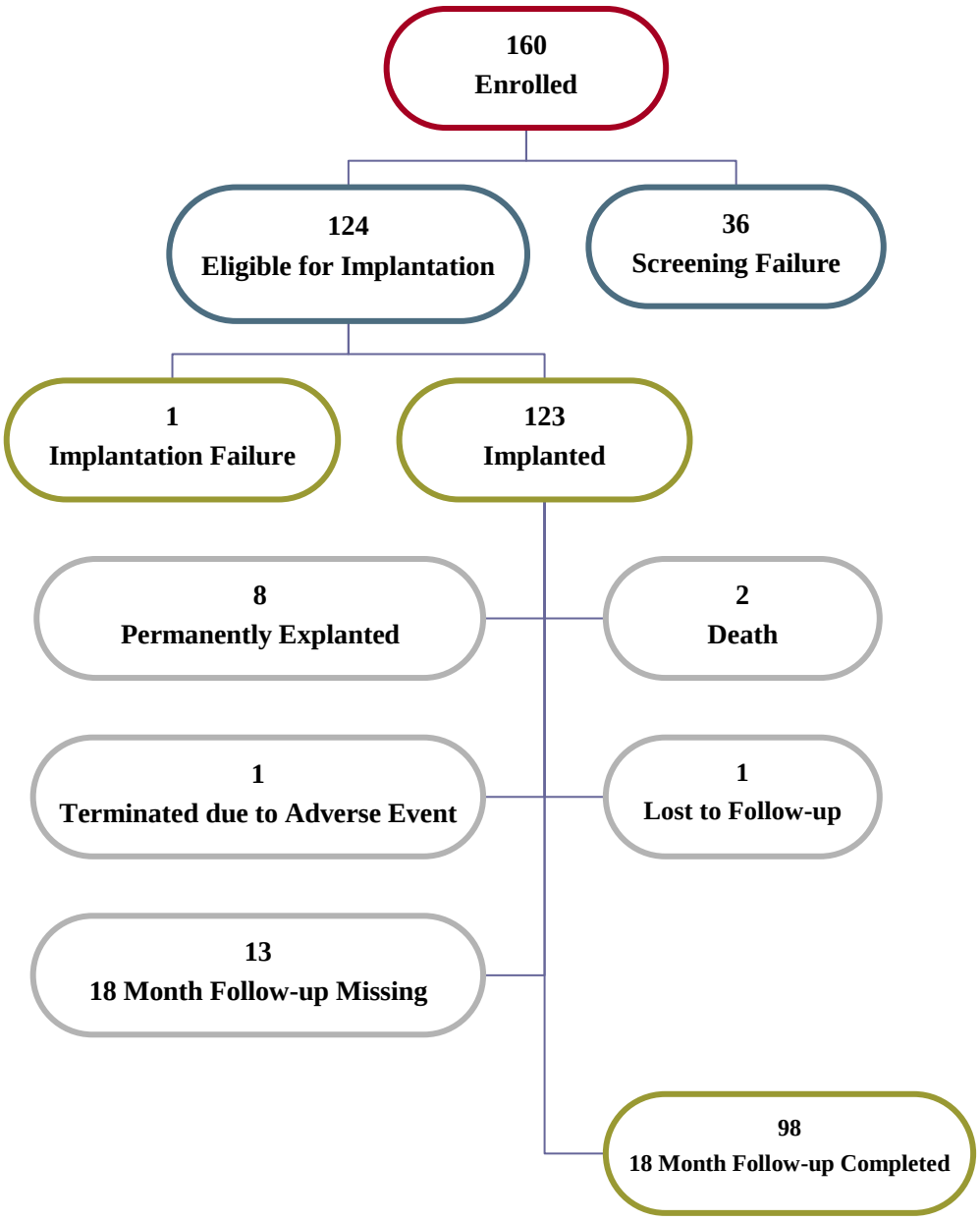


Figure 3. Subject Accountability for PMA Study of ProACT

C. Study Population Demographics and Baseline Parameters

Table 8 lists the study population demographics and baseline characteristics of the ProACT study population. The demographics of the U.S. study population are typical for a male stress urinary incontinence study performed in the U.S.

The study included 124 eligible subjects at 11 investigational sites (8 in the U.S., 2 in Canada, and 1 in New Zealand). One U.S. site did not implant any subjects. Of the 124 subjects in the intent-to-treat cohort, 68 (55%) were enrolled at the seven (7) participating U.S. sites and 56 (45%) at the 3 sites outside the U.S. The median

number of subjects enrolled per site was 7.5 with a range of 3 to 40. Six (6) of the sites enrolled fewer than 10 subjects.

The patient population consisted of adult males: 112 (90%) were Caucasian, 8 (6%) were African-American, and 4 (3%) were Asian, with an average age of 70 (50-93) years**.** Baseline stress urinary incontinence severity was none (11%), mild (26%) moderate (44%), and severe (19%), based on stress testing. Mean baseline 24-hour pad weight was 399 ml (SD 435, range 9 – 2483 ml). Ninety-four percent (94%) of the patients underwent prior radical prostatectomy and 10% underwent prior transurethral resection of the prostate (TURP). Prior incontinence treatments received by the patients included anticholinergic medications (34%), pelvic floor muscle exercises (69%), injectable bulking agents (13%), and other (10%). Two (2) patients had a prior artificial urinary sphincter that was removed prior to enrollment and 11 had a prior transobturator suburethral sling placed. None of the patients had been treated with radiation therapy.

Table 8. Study Population Demographics and Baseline Characteristics

Characteristic	**Value**
Age (years)	Mean: 70 (range: 50-93)
Race	90% Caucasian 6% African-American 3% Asian
Prior prostate surgery	94% Radical Prostatectomy 10% TURP
Time since prior prostate surgery (months)	Mean: 52 (range: 4 – 290)
Prior incontinence treatments	69% Pelvic floor muscle exercises 34% Anticholinergic medications 13% Injectable bulking agents 10% Other[1]
Incontinence severity	11% None 26% Mild 44% Moderate 19% Severe
24-hour Pad Weight (ml)	Mean: 399 (range: 9-2483)
Number of incontinence episodes per day	Mean: 9.9 (range: 0 to 24)
Valsalva leak point pressure	Mean: 75 cm-H_2O (range: 0 to 196)

Characteristic	Value
Incontinence Quality of Life	Mean: 50 (range: 6 to 98)

[1] Treatments included biofeedback (3 patients), collagen implant (2), Kegel and bladder training (1), Neotonus therapy (1), Botox (1), self-catheterization (1), use of clamp (1), behavior modification (1), and exercise (1).

D. Safety and Effectiveness Results

1. Safety Results

The analysis of safety was based on adverse event information collected through the 18 month evaluation on the cohort of 123 implanted subjects. Additional safety data were reported through 24 months of follow-up.

The following three (3) serious adverse events related to the device or procedure were observed through 18 months of follow-up (Table 9):

Table 9. Serious Adverse Events through the 18 Month Visit

Event Type	Device or Procedure Relatedness	Events	Patients with an Event	
		N	N	%
Retention	Device or Procedure Related	1	1	0.8
Low Heart Rate	Not device related; procedure related unknown	1	1	0.8
Ulcerative colitis	Not procedure related; device related unknown	1	1	0.8

Through 24 months of follow-up, there were 574 total adverse events reported in 114 of 123 implanted subjects. Ninety-eight (98) patients experienced adverse events that were non-serious and that were related, or possibly related, to the device or procedure (Table 10). Patients may have experienced more than one adverse event.

Table 10. Device- or Procedure-Related Adverse Events Reported through 24 Months

	Patients with an Event		Events	Device-Related			Procedure-Related		
Adverse Event	N	%	N	Yes	Ukn	No	Yes	Ukn	No
Total	98	79.7%	310	155	78	77	105	64	141
Pain or discomfort	33	26.8%	44	13	18	13	16	10	18
Worsening Incontinence	35	28.5%	38	19	15	4	9	9	20
Device Migration	23	18.7%	35	34	0	1	3	10	22
Urinary retention	19	15.4%	24	13	5	6	8	7	9
Perforation of bladder or	19	15.4%	23	0	0	23	23	0	0

	Patients with an Event		Events	Device-Related			Procedure-Related		
Adverse Event	**N**	**%**	**N**	**Yes**	**Ukn**	**No**	**Yes**	**Ukn**	**No**
urethra									
Device Failure	18	14.6%	21	19	1	1	5	1	15
Device Leakage	15	12.2%	17	17	0	0	1	1	15
Difficulty urinating	10	8.1%	12	8	4	0	1	4	7
Device Erosion	11	8.9%	12	11	1	0	2	3	7
Urinary urgency	11	8.9%	11	2	9	0	4	4	3
Urinary frequency	10	8.1%	10	1	4	5	6	3	1
Urinary Tract Infection	8	6.5%	8	2	5	1	1	2	5
Erythema of perineum, penis, or scrotum	6	4.9%	7	1	3	3	6	0	1
Device Occlusion	3	2.4%	3	3	0	0	0	0	3
Hematuria	3	2.4%	3	1	2	0	0	1	2
Induration in perineum or scrotum	3	2.4%	3	1	1	1	2	0	1
Abdominal pain	2	1.6%	2	0	1	1	1	1	0
Allergic Reaction to Antibiotic	2	1.6%	2	0	0	2	2	0	0
Bladder spasm	2	1.6%	2	0	2	0	0	1	1
Cellulitis	2	1.6%	2	0	0	2	1	1	0
Procedural failure	2	1.6%	2	1	0	1	1	0	1
Anesthetic-related bradycardia	1	0.8%	1	0	0	1	0	1	0
Asymptomatic heart murmur	1	0.8%	1	0	0	1	0	1	0
Bruising of the scrotum	1	0.8%	1	0	0	1	1	0	0
Decreased urine stream	1	0.8%	1	0	1	0	0	0	1
Device Kinking	1	0.8%	1	1	0	0	1	0	0
Doesn't feel empty after urinating	1	0.8%	1	1	0	0	0	0	1
Drainage from incision site	1	0.8%	1	0	1	0	0	0	1
Ecchymosis	1	0.8%	1	1	0	0	1	0	0
Enuresis	1	0.8%	1	0	1	0	0	0	1
Fever 100 degrees	1	0.8%	1	0	1	0	0	1	0

	Patients with an Event		Events	Device-Related			Procedure-Related		
Adverse Event	**N**	**%**	**N**	**Yes**	**Ukn**	**No**	**Yes**	**Ukn**	**No**
Foley greater than 24 hours	1	0.8%	1	1	0	0	1	0	0
Increased incontinence due to urge	1	0.8%	1	0	1	0	0	0	1
Infection: Proximal portion of surgical site for the ProACT	1	0.8%	1	0	0	1	1	0	0
Infection: Superficial infection at site of induration R scrotum	1	0.8%	1	0	0	1	1	0	0
Infection: Superficial scrotal infection	1	0.8%	1	1	0	0	0	0	1
Inguinal hernia	1	0.8%	1	0	0	1	1	0	0
Minor bleeding at incision site	1	0.8%	1	0	0	1	1	0	0
Not passing urine through catheter	1	0.8%	1	0	0	1	1	0	0
Numbness at incision site	1	0.8%	1	0	0	1	1	0	0
Numbness at the end of penis	1	0.8%	1	1	0	0	0	1	0
Other (no improvement of incontinence symptoms)	1	0.8%	1	1	0	0	0	0	1
Pulmonary edema	1	0.8%	1	0	0	1	1	0	0
Purulent discharge from Foley catheter	1	0.8%	1	0	0	1	1	0	0
Residual volume	1	0.8%	1	0	1	0	0	0	1
Scrotal incision opened	1	0.8%	1	0	0	1	1	0	0
Small hemorrhagic cerebrovascular accident	1	0.8%	1	0	0	1	0	1	0
Swelling of right side of perineum	1	0.8%	1	1	0	0	0	1	0
Ulcerative colitis	1	0.8%	1	0	1	0	0	0	1
Urine dribbling	1	0.8%	1	1	0	0	0	0	1

There were two (2) device-related unanticipated adverse events during the clinical study. In two (2) patients, the balloon separated from the tubing of the device during explantation. All other device-related adverse events were anticipated.

There were no device- or procedure-related deaths in the ProACT clinical study.

There were no reports of urethral strictures as a result of device implantation, perforation, or erosion; however, the lack of follow-up for patients who were dropped from the study may have caused any delayed complications, such as stricture, to go undetected.

2. Effectiveness Results

Pre-Specified Analysis:
The analysis of effectiveness was based on the intent-to-treat cohort of 124 subjects at the 18 month time point.

The success (responder) rate for the primary implant for the 124 patients in the intent-to-treat population using the primary endpoint of ≥ 50% reduction in 24-hour pad weight was 46% (57/124) (95% confidence interval 37% to 55%), which did not meet the performance goal because the lower bound of the 95% confidence interval was 37%, which is below the target responder rate of 50%.

Per the study protocol, patients who underwent ProACT device explantation or explantation and reimplantation within 18 months of the original implantation were considered treatment failures.

Hypothesis testing of the primary efficacy endpoint conducted using exact binomial methods under one-sided tests resulted in an associated p-value of 0.82 for the specified performance goal of 50% reduction in 24-hour pad weight.

The success rate based on the primary endpoint varied significantly across study sites (Table 12).

Table 12. Success rate for the primary endpoint by study site.

Study Site	Number of subjects	Primary Endpoint Success
CHUS Fleurimont	40	45% (18/40)
Kansas City Urology	24	71% (17/24)
Kaiser Permanente	19	21% (4/19)
Promed Urology	12	75% (9/12)
Other (6 sites)	29	31% (9/29)
All Patients	124	46% (57/124)

Significant differences were observed across study sites with regard to several demographic and baseline (pre-implant) variables, and outcomes relating to the primary and secondary endpoints. None of the baseline demographic and disease

characteristics was predictive of outcome; the only predictor of outcome was investigational site.

Due to concerns with the validity of pooling data across investigational sites and the presence of a site effect after accounting for differences in patient baseline characteristics, an analysis using a random-effects model was conducted to provide a more conservative estimate of the treatment effect. It resulted in a 95% confidence interval lower bound of 31%, which is below the target responder rate of 50%.

Based on the analyses above, it was concluded that the study's primary effectiveness endpoint was not met.

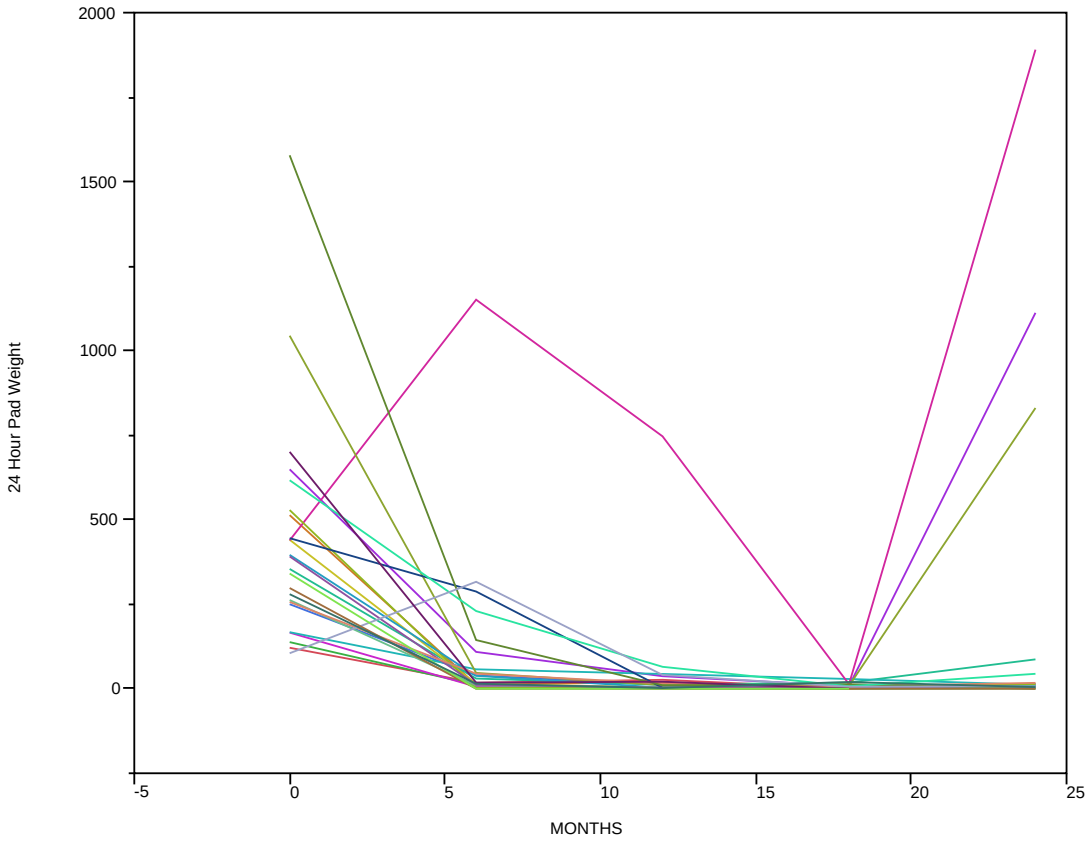
Secondary efficacy endpoints measured in this study included improvement in incontinence episodes per day, improvement in number of pads used per day, improvement in incontinence quality of life measure (I-QOL), improvement in UCLA-PCI urinary function scale, and impact on sexual functioning (International Index of Erectile Function, IIEF). None of these secondary endpoints required further exploration since the study did not meet the primary endpoint.

FDA Post Hoc Analysis:
Analysis of the study results revealed that the number of pads used per day is not a reliable indicator of the degree of incontinence. The published literature assessing the efficacy of treatments of urinary incontinence procedures used pads per day as an efficacy endpoint, with one or fewer pads per day indicating success. In the ProACT study, there were 48 patients who reported using one pad per day at the 18 month time point; no patients used zero pads. The 24-hour pad weight, however, varied greatly in this group, with a range of 0 to 223 grams. Nine (9) of these 48 patients (19%) had 24-hour pad weights greater than 30 grams.

The study protocol's pre-specified approach for defining success (i.e., $\geq$ 50% reduction in 24-hour pad weight) does not necessarily correlate well with the endpoints used in prior studies to assess the efficacy of the artificial urinary sphincter or male suburethral slings. Those studies utilized pad counts and defined success as one or less pad per day. However, that endpoint (one pad per day, called "socially continent") can encompass a wide range of leakage as measured by 24-hour pad weight. Therefore, FDA performed a post hoc responder analysis utilizing a different endpoint based on a clinically meaningful change in 24-hour pad weight. This endpoint assessed how many patients with greater than 100 gm baseline pad weight achieved an 18 month pad weight of less than or equal to 30 gm. There were 86 patients in the intent-to-treat cohort (69%) that had a baseline pad weight of greater than 100 gm. This included the one patient that did not have the implant inserted. The success rate at 18 months for the initial implanted devices using this endpoint was 24 out of 86 patients (28%).

The 24-hour pad weights for those 24 successful patients are depicted in Figure 4. The great majority of those patients had low pad weights both prior to and subsequent to the 18 month time point.

Figure 4. Change in 24-hour pad weight for the 24 patients that had a baseline pad weight of > 100 gm and an 18 month pad weight < 30 gm.



Although the primary endpoint was assessed at 18 months after primary implantation, many of the patients in the intent-to-treat cohort continued follow up. The disposition of the 24 "successful" patients at the time of PMA submission is shown in Table 13. Almost half of those patients were ongoing, but four (4) (17%) underwent subsequent explantation after the 18 month time point and five (5) (21%) died. There was missing data for the 24 month 24-hour pad weight for four (4) of the "successful" patients and five (5) patients had a 24-hour pad weight of significantly greater than 30 gm, so would no longer be considered successful.

Table 13. Disposition of patients: ITT population, and the subset of "successful" patients that met FDA's post hoc analysis definition of success.

Disposition	ITT Population n=124	"Successful" Population n=24
Ongoing	40 (32%)	11 (46%)
Termination due to Adverse Event	1 (1%)	---
Termination due to Completed Study	2 (2%)	---
Termination due to Death	8 (6%)	5 (21%)
Termination due to Explant	44 (35%)	4 (17%)
Termination due to Loss to Follow-Up	20 (16%)	3 (13%)
Termination due to Other	5 (4%)	---
Termination due to Inability to Place Device	1 (1%)	---
Termination due to Withdrawn by Investigator	3 (2%)	1 (4%)

There were 38 patients who had a baseline 24-hour pad weight of less than 100 grams (median 49 grams, range 9 to 99 grams), or mild incontinence. Of those patients, eight (8) had their device removed prior to the 18 month time point and seven (7) had a 24-hour pad weight greater than 30 grams at 18 months. Thus, the "success" rate for the patients with more mild urinary incontinence at baseline was 61% with a single implant.

Urodynamic assessments were performed at baseline in 93 patients and again at 18 months in only 38 of those 93 patients. The results are summarized in Table 14. The median Valsalva leak point pressure at baseline was 78 cm H_2O. For the 38 patients with paired Valsalva leak point measurements (baseline and 18 months), there was no meaningful change in the median value, 80 cm H_2O. Similarly, there was no increased bladder voiding pressure due to outlet obstruction following implantation of the ProACT device. There was no evidence of a correlation between urodynamic findings and success.

Table 14. Urodynamic findings at baseline and at 18 months.

	Baseline n=93	18 Months n=38	Successful n=9
Valsalva leak point pressure (cm H_2O)	78	80	82
Voiding pressure (cm H_2O)	43	44	50

Secondary endpoints were not formally assessed due to failure to meet the primary endpoint. Two (2) patient-reported outcomes instruments were administered during the course of the study: (1) the urinary function scale (5 questions) from the UCLA-Prostate Cancer Index (PCI), and (2) the Incontinence quality of life instrument (I-QOL), both of which have a scale of zero to 100 with a higher score being better. A numeric increase (improvement) for both measures was observed in the intent-to-treat population at the 18 month time point. The scores on both instruments were numerically greater for the subgroups that met either definition of success (i.e., the protocol's pre-specified definition of 50% reduction in 24-hour pad weight, and the post hoc definition of an reduction in pad weight from >100 grams at baseline to < 30 grams at 18 months), but the greatest difference was on the PCI score for the patients that had a 24-hour pad weight of less than 30 grams at 18 months (Table 15).

Table 15. Median scores of the two urinary function instruments for the intent-to-treat population at baseline and at 18 months and for the two successful subgroups at 18 months.

	Intent-to-Treat		**Successful**	
	Baseline N=124	**18 Months n=110**	**50% Reduction n=57**	**< 30 grams n=24**
I-QOL	51	83	90	92
PCI	22	53	65	73

Device Explants:

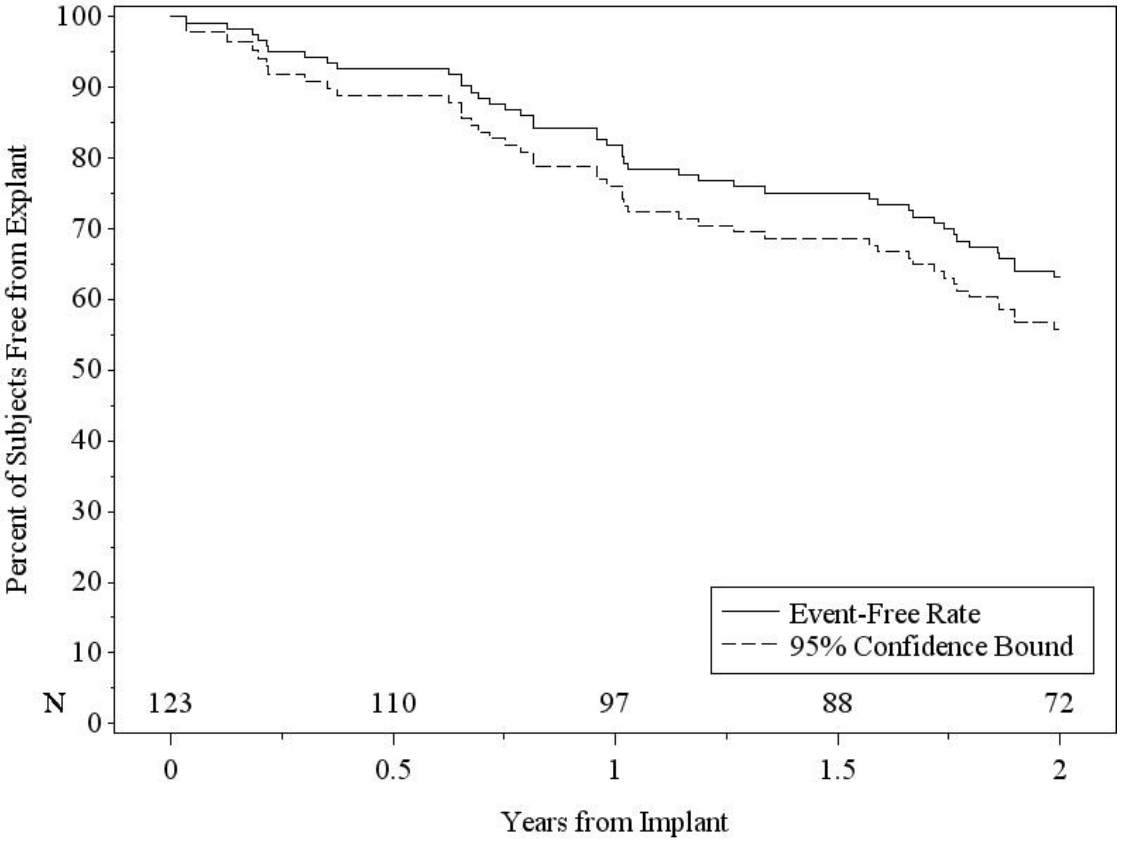
Overall, reimplantation was associated with fewer successful outcomes. During the first 18 months of the study, 30 patients underwent explantation of their ProACT device(s) one or more times. Sixteen (16) patients underwent explantation of both devices and fourteen (14) underwent explantation of one side only. Of the sixteen (16) patients who had both devices explanted within the first 18 months, three (3) had multiple procedures. One patient had both devices removed, subsequent reimplant, followed by removal of one device. Another patient had one device removed, subsequent reimplant, followed by removal of both devices and then reimplantation. An additional patient underwent sequential removal of the right and left devices, subsequent re-implant, removal of both devices again, and re-implant again, all prior to the 18 month time point. Device explant information through 18 and 24 months is summarized in Table 16.

Table 16. Device Explants

Reason for Explant	Through 18 months		Through 24 months	
	Number of Devices	Number (%) of Patients	Number of Devices	Number (%) of Patients
Clinical failure	11	6 (5%)	15	8 (7%)
Erosion	7	7 (6%)	10	10 (8%)
Infection	3	2 (2%)	3	2 (2%)
Mechanical failure	2	2 (2%)	9	9 (7%)
Migration	17	13 (11%)	26	18 (15%)
Other	12	10 (8%)	20	17 (14%)
Total:	**52**	**30 (24%)**	**83**	**44 (36%)**

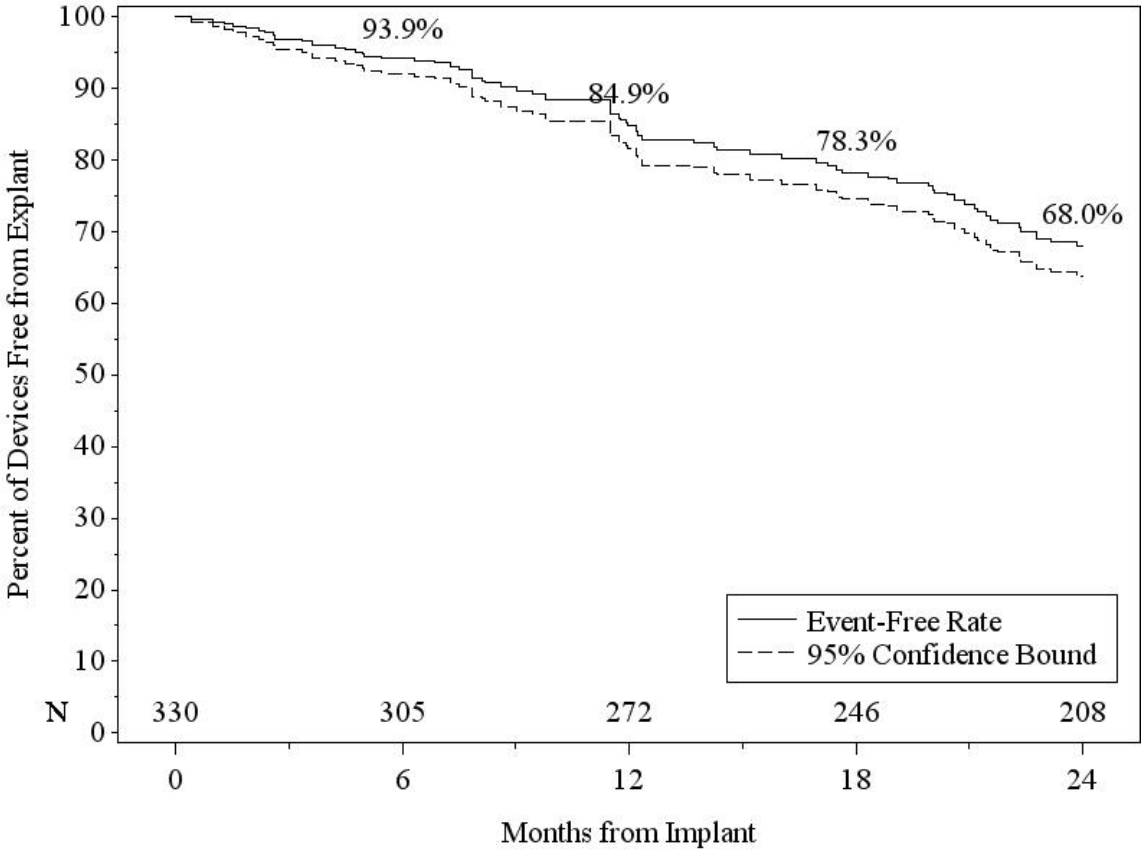
The graph below depicts the survival in vivo of index devices over time. For example, at one year post implant, 82% of the implanted subjects had their index devices still implanted (not explanted), with a lower one-sided 95% confidence interval of 76%.

Figure 5. Kaplan-Meier probability of remaining free of device explant.



A total of 125 explant procedures were performed on 75 of the 124 patients (60%). These were performed from 0.4 to 91 months after the initial procedure with a median of 21 months. Hence, more than half of these patients underwent explant of their device after the 18 month assessment period. There were 67 re-implant procedures in 55 patients. Of these, 24 patients underwent 27 re-implant procedures during the first 18 months after the initial device implant. During the course of the study, there were a total of 330 devices implanted in 123 patients. The median survival of these implants was greater than 24 months. The Kaplan-Meier survival curve is shown in Figure 6.

Figure 6. Kaplan-Meier survival curve for the 330 devices implanted in 123 patients.



Device Adjustments:

Periodic, gradual balloon inflation via fluid level adjustments is a design feature of the ProACT device. Balloon volume adjustments are necessary as part of the process to optimize the device's potential therapeutic effect while avoiding potential risks such as urinary retention. Adjustments involve inserting a 23-gauge hypodermic needle through the skin into the port and adding or removing fluid to potentially cause a therapeutic response.

In the ProACT study, balloon volume adjustments were expected to be complete within 6 months of implant; however, many adjustments were performed beyond 6 months. In total, 119 of 123 implanted patients underwent adjustment of their

device during the first 18 months. Four (4) patients had implantation of their devices without any subsequent adjustments of whom three (3) experienced a reduction in 24-hour pad weight > 50%. Eighty-eight (88) patients underwent a total of 419 adjustments during the first 18 months without having their devices explanted. The median number of adjustments of balloon volume was four (4) per patient with a range of 1 to 11. One hundred and fifty-two (152) of the adjustments (36%) were performed outside the clinical study protocol's designated 6-month adjustment window.

3. Subgroup Analyses

The effects of a number of variables on the primary efficacy endpoint (50% reduction in pad weight at 18 months) and the primary safety endpoint (complications between implant and 18 month) were analyzed. The variables included the following:

- age;
- body mass index;
- type of prior prostate surgery;
- time since prior prostate surgery;
- previous incontinence treatments;
- baseline incontinence severity
- urodynamic parameters;
- receiving balloon volume adjustments between 6-18 months; and
- having devices explanted and reimplanted within 18 months.

Receiving balloon volume adjustments between 6-18 months was a factor associated with a higher probability of efficacy. This association was expected since late-occurring adjustments would be anticipated in patients who had poorer outcomes and who were seeking to achieve a therapeutic benefit. Factors associated with higher complication rates included (1) body mass index > 25 kg/m^2, (2) less than one year since prior prostate surgery, (3) more severe incontinence at baseline, (4) receiving balloon volume adjustments between 6-18 months, and (5) having devices explanted and reimplanted within 18 months. In general, patients with severe or moderate incontinence at baseline had more complications than patients with mild incontinence. Furthermore, ProACT reimplants and re-adjustments were associated with lower success relative to the index ProACT devices.

E. 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 11 principal investigators and six (6) sub-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.

XI. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

In accordance with the provisions of section 515(c)(2) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Gastroenterology and Urology Devices Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

The PMA clinical study did not meet its pre-specified primary efficacy endpoint of a ≥ 50% reduction in 24-hour pad weight from baseline. The 95% confidence interval lower bound was 31%, which is below the study's target responder rate of 50%.

However, this endpoint is not necessarily clinically relevant since patients may not find a 50% reduction in urine leakage to be meaningful. Patients are generally more interested in a "cure" or being pad-free. Furthermore, the study's primary endpoint does not necessarily correlate well with the endpoints used in prior studies to assess the efficacy of the artificial urinary sphincter or male suburethral slings. Those studies utilized pad counts and defined success as one or less pad per day. However, that endpoint (one pad per day, called "socially continent") can encompass a wide range of leakage as measured by 24-hour pad weight.

Therefore, FDA performed a post hoc responder analysis utilizing a different endpoint based on a clinically meaningful change in 24-hour pad weight. This endpoint assessed how many patients with greater than 100 gm baseline pad weight achieved an 18 month pad weight of ≤30 gm. There were 86 patients in the intent-to-treat cohort (69%) that had a baseline pad weight of >100 gm. The success rate at 18 months for the initially implanted devices using this endpoint was 24 out of 86 patients (28%).

In general, patients with severe or moderate incontinence at baseline had a poorer therapeutic response and more complications than patients with mild incontinence. Furthermore, ProACT reimplants and re-adjustments were associated with lower success relative to the index ProACT devices.

Urodynamic assessments were performed at baseline and again at 18 months. There was no meaningful change in median Valsalva leak point pressure. Similarly, there was no increased bladder voiding pressure due to outlet obstruction following implantation of the ProACT device. There was no evidence of a correlation between urodynamic findings and success.

B. Safety Conclusions

The probable risks of the device are based on nonclinical laboratory and animal studies as well as data collected in a clinical study conducted to support PMA approval as described above.

The applicant conducted a series of nonclinical tests, including mechanical testing, and evaluations of MRI compatibility, sterility, and biocompatibility, in accordance with accepted test protocols and pass/fail criteria. The applicant also conducted a canine chronic implantation study using ProACT. The results of nonclinical testing support the safety of the device.

The device's risk profile is based largely on the results of the PMA clinical study, which included 123 subjects implanted with the ProACT device. The study did not include a specific safety endpoint. There were three (3) serious adverse events related to the device or procedure, which included urinary retention, low heart rate, and ulcerative colitis. The most frequent types of non-serious device- and procedure-related risks and their probability are summarized below. Note that the great majority of device-related adverse events required surgical intervention, but were not counted as serious adverse events since the explant procedure is performed on an outpatient basis.

	Patients with an Event		Events	Device-Related			Procedure-Related		
Adverse Event	**N**	**%**	**N**	**Yes**	**Ukn**	**No**	**Yes**	**Ukn**	**No**
Total	98	79.7%	310	155	78	77	105	64	141
Pain or discomfort	33	26.8%	44	13	18	13	16	10	18
Worsening Incontinence	35	28.5%	38	19	15	4	9	9	20
Device Migration	23	18.7%	35	34	0	1	3	10	22
Urinary retention	19	15.4%	24	13	5	6	8	7	9
Perforation of bladder or urethra	19	15.4%	23	0	0	23	23	0	0
Device Failure	18	14.6%	21	19	1	1	5	1	15
Device Leakage	15	12.2%	17	17	0	0	1	1	15
Difficulty urinating	10	8.1%	12	8	4	0	1	4	7
Device Erosion	11	8.9%	12	11	1	0	2	3	7

	Patients with an Event		Events	Device-Related			Procedure-Related		
Adverse Event	**N**	**%**	**N**	**Yes**	**Ukn**	**No**	**Yes**	**Ukn**	**No**
Urinary urgency	11	8.9%	11	2	9	0	4	4	3
Urinary frequency	10	8.1%	10	1	4	5	6	3	1
Urinary Tract Infection	8	6.5%	8	2	5	1	1	2	5
Erythema of perineum, penis, or scrotum	6	4.9%	7	1	3	3	6	0	1

The study did not follow subjects for a sufficiently long period to enable an assessment of the probability of possible late-developing adverse events such as urethral stricture and device erosion. The study also was not designed to evaluate whether failed treatment with ProACT might affect the clinical outcomes of subsequent urinary incontinence therapies such as a suburethral sling or artificial urinary sphincter. To address these concerns, the planned post-approval study will collect safety data on a new cohort of subjects followed for five (5) years.

C. Benefit-Risk Conclusions

The probable benefits and risks of the device are based on data collected in a clinical study conducted to support PMA approval as described above.

Additional factors considered in determining the risks and benefits for the ProACT device included FDA's post hoc assessment of the results of the PMA study, based on an absolute measure of urinary incontinence at 18 months, revealed that 28% of patients were successfully treated with a single implant procedure. The indicated patient population had already failed medical and minimally invasive treatment options with the only remaining treatment option being surgery, including male sling or artificial urinary sphincter. Given the relatively minimally invasive nature of the procedure and the low risk profile, many patients may want to have the option of a greater than one in four chance of achieving a successful outcome while avoiding or deferring a more invasive procedure.

The clinical study enrolled men aged 50-93 years (mean 70 years). A covariate analysis showed no correlation between age and safety or effectiveness outcomes. Because there is no reasonable expectation for age to be a significant contributory factor to clinical outcomes, FDA concluded that it would be appropriate for the device to be indicated for use in adult men and to not restrict use of the device to the age range of the study population.

In conclusion, given the available information summarized above, the probable benefits outweigh the probable risks for the intended use of the ProACT Adjustable Continence Therapy for Men in the treatment of adult men who have stress urinary incontinence arising from intrinsic sphincter deficiency of at least 12 months duration following

radical prostatectomy or transurethral resection of the prostate (TURP) and who have failed to respond adequately to conservative therapy.

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use. Despite not achieving the primary efficacy endpoint (50% responder rate), there was a significant portion of the patient population (28%) who achieved a clinically significant reduction in the amount of daily urine leakage. Given the relatively minimally invasive nature of the procedure and the low risk profile, this device provides a therapeutic alternative to more invasive alternative procedures.

XIII. CDRH DECISION

CDRH issued an approval order on November 24, 2015.

The applicant's manufacturing facilities have been inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820). The final condition of approval cited in the approval order is described below.

OSB Lead PMA Post-Approval Study - ProACT Post-Approval Study: This is a 5-year prospective, open-label, multi-center study designed to evaluate the long-term incidence of urethral stricture and device erosion after ProACT implantation. In addition, the study will evaluate whether treatment with ProACT affects clinical outcomes after subsequent SUI therapies.

In this new enrollment study, 145 subjects will be enrolled at 5 to 7 sites in the U.S and, with an estimated 20% screen failure rate, 116 subjects are expected to be successfully implanted with the ProACT device. Subject follow-up will occur at 6 weeks, 6 months, and 1, 2, 3, 4, and 5 years post-treatment. With an estimated 20% attrition rate over 5 years of follow-up, 93 subjects are expected to complete the 5-year visit.

Data will be collected on the following study outcomes: cumulative incidence of urethral strictures over 5 years of follow-up; cumulative incidence of device erosions over 5 years of follow-up; Incontinence Quality of Life (I-QoL) Questionnaire over 5 years of follow-up; and the choice of subsequent SUI therapy(ies) post ProACT treatment.

XIV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

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

Post-approval Requirements and Restrictions: See approval order.