DE NOVO CLASSIFICATION REQUEST FOR iTIND SYSTEM

REGULATORY INFORMATION

FDA identifies this generic type of device as:

> **Temporarily-placed urethral opening system for symptoms of benign prostatic hyperplasia.** A temporarily-placed urethral opening system for symptoms of benign prostatic hyperplasia (BPH) is a prescription use device that is inserted transurethrally and deployed at the prostate. The implant is designed to increase prostatic urethral patency by increasing prostatic opening. It is intended for the treatment of symptoms due to urinary outflow obstruction secondary to BPH in men.
>
> **NEW REGULATION NUMBER:** 21 CFR 876.5510
>
> **CLASSIFICATION:** Class II
>
> **PRODUCT CODE:** QKA

BACKGROUND

> **DEVICE NAME:** iTind System
>
> **SUBMISSION NUMBER:** DEN190020
>
> **DATE OF DE NOVO:** April 20, 2019
>
> **CONTACT:** Medi-Tate Ltd.
> 14 Hailan St.
> Or Akiva, ISRAEL
> 3060000

INDICATIONS FOR USE

The iTind System is intended for the treatment of symptoms due to urinary outflow obstruction secondary to benign prostatic hyperplasia (BPH) in men age 50 and above.

LIMITATIONS

- The iTind System is restricted to use by prescription only.
- The iTind System should only be used by clinicians trained in endo-urological procedures and the management of their complications.
- The iTind system is for single use. Do not re-sterilize or reuse any part of the system.
- The iTind System is contraindicated in patients with:

- active urinary tract infection or prostatitis;
- artificial urinary sphincter or any implant (metallic or nonmetallic) within the urethra;
- any patient condition which, to the implanting physician's opinion, may cause complications during the deployment of the device;

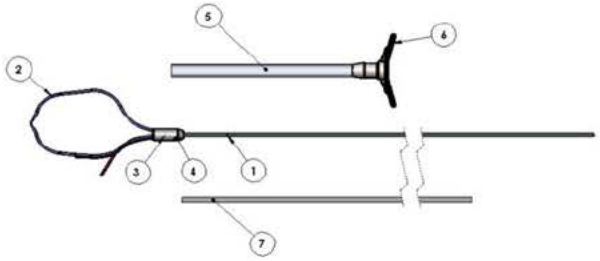
- A thorough clinical evaluation should be performed on all patients presenting for treatment for BPH such as recommended by the American Urological Association (AUA) Guidelines for Surgical Management of BPH.
- The risks of implanting the iTind System in patients with blood coagulation disorders, compromised immune systems, or any other conditions that would compromise healing should be carefully considered against the possible benefits.
- Do not use the iTIND System if the patient has a known allergy to nickel.
- Potential complications from the cystoscopy procedure, and/or the presence of the iTind device in the prostatic urethra or the deployment/retrieval procedure, include:
  - Fever
  - Blood in urine (hematuria)
  - Pain
  - Urinary tract infection (UTI)

PLEASE REFER TO THE LABELING FOR A COMPLETE LIST OF WARNINGS, PRECAUTIONS AND CONTRAINDICATIONS.

DEVICE DESCRIPTION

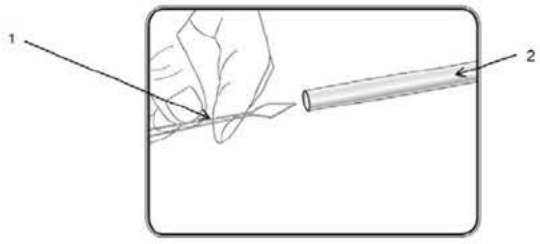
The iTind System consists of the iTind implant, delivery system, and retrieval kit. The components are described below.

Figure 1. iTind implant and delivery system.



Component
iTind implant (Item 1, 2, 3, 4)
Introducer Sheath (Item 5 and 6)
Guide Wire (Item 7)

Figure 2. iTind retrieval kit (snare).



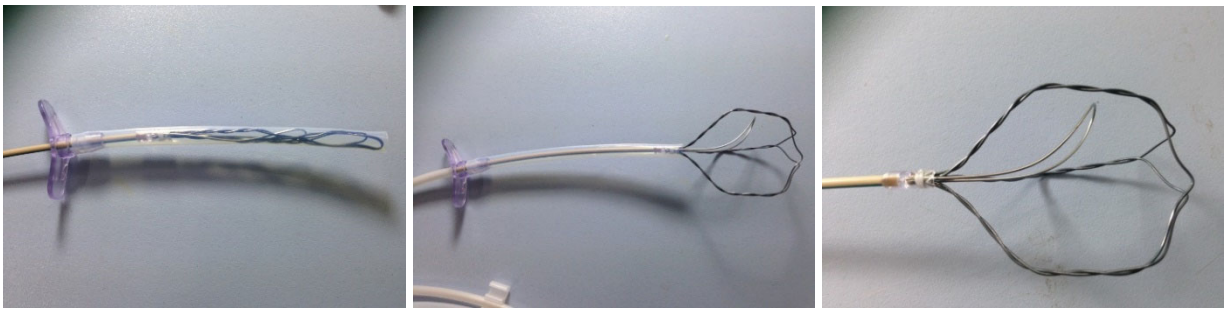
Component
Snare (Item 1)
Sheath (Item 2)

iTind implant

The iTind implant is made of nitinol and pre-mounted on a dedicated guide wire. In its folded configuration (Figure 3, left figure), the implant is inserted through a cystoscope sheath and deployed within the bladder neck and prostatic urethra where it assumes its expanded

configuration (Figure 3, center & right figures) (maximum diameter 33mm; length 50mm). When expanded, the struts of the implant exert radial force on the bladder neck and prostatic urethra, pushing obstructive tissue away from the urinary path. The implant is designed to cover the entire length of the prostatic urethra, from the bladder neck to a point proximal to the external urinary sphincter. It is left in position for 5–7 days and subsequently removed using a Foley catheter. The deployment and removal of the implant are described in the Instructions for Use supplied by Medi-Tate. The device is compatible with commercial cystoscopes at least 20Fr in diameter.

Figure 3. The iTind implant: retracted (left), expanded (middle), and expanded-closeup (right).



Placement

The iTind implant is advanced into the bladder using a delivery system through a standard cystoscope. The iTind implant, with its suture attached to it, is preloaded on the delivery system. The cystoscope is inserted through the urethra until reaching the bladder as in routine cystoscopy procedures. At this stage, the optic fiber is withdrawn and the loaded delivery system is inserted through the cystoscope sheath. The delivery system is completely withdrawn, leaving the iTind implant connected to the guide wire only by means of the suture. At this stage, regular cystoscope optics are used over the guide wire for final positioning of the iTind implant at the prostatic urethra under visualization. As soon as the iTind implant is positioned, the knot at the end of the thread protruding from the guide wire is cut, and the guide wire is withdrawn as well.

Retrieval

To remove the iTind implant, the retrieval kit (snare) is used. The snare is inserted through a Foley catheter and the retrieval suture is tied to the loop of the snare. The snare (with the attached suture) is then pulled completely out of the Foley catheter. With the retrieval suture held taut, the Foley catheter is inserted into the meatus and guided through the urethra until it meets the iTind implant. The retrieval suture is then pulled firmly to retract the implant into the Foley catheter. The Foley catheter, along with the enclosed implant, are then removed from the urethra.

SUMMARY OF NONCLINICAL/BENCH STUDIES

BIOCOMPATIBILITY/MATERIALS

The iTind System is a surface contacting device in contact with the mucosal membrane for a prolonged duration. Therefore, cytotoxicity, sensitization, intracutaneous reactivity, implantation, and material-mediated pyrogenicity were performed on the iTind implant, delivery system and retrieval kit in accordance with the FDA Guidance "Use of International Standard ISO 10993-1, Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process" (June 16, 2016). In addition, sub-acute systemic toxicity testing (4-week study in rats) and genotoxicity testing (mouse lymphoma assay only) were conducted, and genotoxicity/sub-acute systemic toxicity was also assessed via analytical chemical characterization followed by toxicological risk assessment. Biocompatibility testing was conducted under GLP conditions on the final, finished iTind System device, as shown in Table 1. All tests were passed, indicating that the device materials are biocompatible and appropriate for the indication for use. The results support the biocompatibility of the iTind System.

Table 1. Biocompatibility testing performed on the iTind System

Biological Effect	**Test**	**Standard**	**Result**
Cytotoxicity	MEM elution	ISO 10993-5	Passed
Sensitization	Guinea pig maximization sensitization	ISO 10993-10	Passed
Intracutaneous Reactivity	Intracutaneous toxicity study in rabbits	ISO 10993-10	Passed
Implantation	Muscle implantation study in rabbits	ISO 10993-6	Passed
Material-mediated Pyrogenicity	Rabbit pyrogen test	USP 34<151>	Passed
Sub-acute systemic toxicity	4-week repeat dose IV and IP study in rats	ISO 10993-11	Passed
Genotoxicity	Mouse lymphoma assay	ISO 10993-3	Passed
Genotoxicity/Sub-acute systemic toxicity	Analytical chemical characterization followed by toxicological risk assessment	ISO 10993-18 ISO 10993-17	Passed

STERILITY

The iTind implant/delivery system and retrieval kit are supplied as a single-use, disposable, sterile procedure kit. The iTind implant and delivery system are packaged together, and the retrieval kit is packaged separately. The system components are sterilized using Ethylene Oxide (EO) gas sterilization. EO sterilization validation was

conducted in conformance with ISO 11135:2014 and demonstrated a Sterility Assurance Level (SAL) of 10^{-6}. Further, the device was tested for EO residuals in conformance with ISO 10993-7 to ensure that the maximum residual levels of EO and ethylene chlorohydrin (ECH) remaining on the product after sterilization do not exceed the recommended limits for medical devices in prolonged exposure with the patient.

SHIPPING DISTRIBUTION, SHELF LIFE AND PACKAGING INTEGRITY

The iTind implant/delivery system and retrieval kit packaging configurations consist of a single barrier Tyvek® pouch. The iTind implant/delivery system is pouched and placed into a cardboard box. Ten (10) labeled retrieval kits pouches (i.e., snares) are packaged in a cardboard box. Each box includes an Instructions for Use ("IFU") pamphlet. Packaging validation testing was completed on lot controlled, finished, aged, finished product that met all dimensional and visual requirements.

Simulated shipping distribution was conducted on iTind System components after EO sterilization and environmental conditioning in conformance with ASTM D4332 and ASTM D4169, respectively. Post-simulated shipping distribution and environmental conditioning, packaging integrity was tested via visual inspection and packaging integrity tests. Specifically, samples were tested via dye penetration test per ASTM F1929 and seal strength test per ASTM 88/F88M. All tests met the predetermined acceptance criteria.

A shelf life of two (2) years was established for the iTind System through accelerated and real-time aging studies of EO-sterilized test articles. Accelerated aging was conducted in conformance with ASTM F1980. Post-aging, packaging integrity was tested via visual inspection and packaging integrity tests. Specifically, samples were tested via dye penetration test per ASTM F1929, seal strength test per ASTM 88/F88M, and burst test per ASTM F1140/F1140. All tests met the predetermined acceptance criteria.

In addition, visual and functional testing also assessed the tensile force at break, device dimensions, crimpability, radial force, force required to insert the device through a cystoscope, and deployment tests. All tests met their predetermined acceptance criteria. The results support the sterility of the iTind System and demonstrate that the packaging materials can withstand the rigors of shipping and distribution maintaining the integrity of the sterile barrier and the device will perform as intended through the indicated shelf life.

MAGNETIC RESONANCE (MR) COMPATIBILITY

Non-clinical testing and MRI simulations were performed to evaluate the iTind implant. Testing was performed on the device in two configurations: 1) fully expanded for displacement, torque, and artifact testing, and 2) compressed (17 mm diameter) for RF heating testing. RF simulations showed that at both 1.5 and 3.0 Tesla, the maximum heating occurred in the compressed configuration. The heating extents predicted by the simulations were then confirmed by bench testing showing similar levels of heating in 1.5 and 3.0 Tesla MR systems. The testing demonstrated that the iTind implant is MR

Conditional. A patient with an implant can be scanned safely in an MR system under the following conditions:

- Static magnetic field of 1.5 Tesla or 3 Tesla, only;
- Maximum spatial gradient magnetic field of 4,000 gauss/cm (40 T/m);
- Maximum MR system reported, whole body averaged specific absorption rate (SAR) of 2 W/kg for 15 minutes of scanning (i.e., per pulse sequence) in the Normal Operating Mode.

Under the scan conditions defined, an implant from the iTind Device is expected to produce a maximum temperature rise of 3.7°C after 15 minutes of continuous scanning (i.e., per pulse sequence). In non-clinical testing, the image artifact caused by the iTind implant extends only approximately 5 mm from the device when imaged with a gradient echo pulse sequence and a 3 Tesla MR system. The results support that the iTind System can be labeled as MR Conditional.

PERFORMANCE TESTING – BENCH

The preclinical testing demonstrates that the device performs as intended per the device specifications. Further, the preclinical tests described below are consistent with the principles of the FDA guidance, "Guidance for the Non-Clinical and Clinical Investigation of Devices Used for the Treatment of Benign Prostatic Hyperplasia (BPH)," August 17, 2010 ("FDA's Guidance").

Functional Performance (Bench) Testing of iTind System

Functional performance testing demonstrated that the iTind implant (and delivery system) and retrieval kit consistently met its acceptance criteria according to FDA recognized standards and pre-defined acceptance criteria. All tests were conducted on samples that were EO sterilized and exposed to shipping and distribution conditions, at baseline followed by 2 years of accelerated aging before testing the device. Each of the functional bench tests is summarized below.

Crimping

The iTind implant is crimped into a delivery system prior to implantation. This test is meant to ensure that the crimping and releasing of the iTind implant does not cause any damage to the device components and that the device resumes its design and expanded dimensions following crimping and release. The testing was completed to do the following:

- To demonstrate that the iTind implant can withstand crimping, loading into the delivery system and expansion, and that the iTind implant will change less than 2mm in its dimensions following multiple crimping cycles.
- To demonstrate the symmetry and uniformity of the device after expansion.
- To demonstrate that the device does not experience any defects during crimping, loading, and expansion.

The crimping testing was done on 30 systems, in order to meet 90% reliability and 95% confidences in accordance with ISO 2859-1 Second Edition 1999-11-15,

Sampling Procedures For Inspection By Attributes - Part 1, which are designed to test functionality of final assembled implants. The testing was performed using a tensile test (b) (4) and a (b) (4) Radial Expansion Force Gauge. Crimping the iTind implant through the PTFE Delivery Tube: Not more than (b) (4) after 10% over the acceptance limit defined, the test could be stopped. The acceptance criterion is (b) (4) as this is the greatest force exerted on the device during insertion. All test samples met the acceptance criterion.

Radial Force

The purpose of this test is to challenge the iTind implant by crimping and measuring the radial force at different diameters. The results are used to evaluate the pressure of the device on the tissue. The radial force test was conducted on 30 systems, in order to meet 90% reliability and 95% confidences, according to ISO 2859-1 Second Edition 1999-11-15, Sampling Procedures For Inspection By Attributes - Part 1, which is designed to test functionality of final assembled implant. The testing was performed using a (b) (4) Radial Expansion Force Gauge. The acceptance criterion was "≥ 1.0 N in crimping diameter of 5 mm to 11 mm, after (b) (4) cycles of crimping and expanding." The acceptance criterion is based on the amount of force required to imprint itself into the tissue. This was derived from systolic blood pressure, peripheral pressure and device area. Based on this calculation, the iTind implant should apply more than 0.5 N in order to imprint itself into the tissue. Therefore, the acceptance criterion was set to 1.0 N. All test samples met the acceptance criterion.

Tensile Force at Break

The iTind implant and delivery system is a collection of machined and extruded parts that are connected by various means; the system must perform the mechanical action needed for the implantation procedure, without any failure of either the bonds between the various parts of the system, or of the moving parts within the system in accordance to specifications. The tensile FAB test was conducted on 30 systems, in order to meet 90% reliability and 95% confidences according to ISO 2859-1 Second Edition 1999-11-15, Sampling Procedures For Inspection By Attributes - Part 1, which are designed to test every bond or connection within the iTind implant. The test was performed using a tensile test (b) (4) The devices were arranged in accordance with the test figures. Each device is connected to the machine to conduct tensile testing. After (b) (4) over the acceptance limit defined (b) (4) the test should be stopped. The acceptance criterion was selected to be (b) (4) because it is 2.5 times the forces encountered during device insertion and retrieval. All test samples met the acceptance criterion.

Deployment

iTind implant was deployed through a silicone anatomical model of the bladder neck, which mimics the resistance in the urethra. The tested iTind implants were visually checked for correct deployment, removal and correct positioning. The Deployment test was conducted on 30 systems, in order to meet 90% reliability and 95% confidence, according to ISO 2859-1 Second Edition 1999-11-15, Sampling Procedures For Inspection By Attributes - Part 1, which are designed to test functionality of final assembled implant. iTind implant was deployed through a silicone anatomical model of the bladder neck, which mimics the resistance in the urethra. The criterion is based on visual inspection. Sample must be compared to the gold standard picture of full setup with close views of important parts. All test samples met the acceptance criterion.

iTind Implant Dimensions

The purpose of this test is to ensure the device dimensions comply with the pre-defined acceptance criterion. The dimension testing was completed on 30 systems, in order to meet 90% reliability and 95% confidence, according to ISO 2859-1 Second Edition 1999-11-15, Sampling Procedures For Inspection By Attributes - Part 1, which are designed to test functionality of final assembled implant. All dimensions of the device were measured using a caliper and confirmed to be consistent with the technical drawings. All devices were tested prior to crimping and after (b) (4) cycles of crimping and expanding. The difference in dimensions before and after crimping should be less than 2mm. The acceptance criteria of 2mm was deemed appropriate to allow for proper deployment given the size of the bladder neck. All test samples met the acceptance criterion. For all 30 units, the difference between each set of the before and after measurements was less than 0.3mm.

Corrosion Testing

The corrosion resistance test was intended to establish that the iTind System shows no sign of corrosion. The sample size consisted of (b) (4) final device configurations (i.e., the iTind System). Test Methods: Real-time immersion testing with open circuit potential monitoring; Immersion in urine or a urine substitute at (b) (4) under aerated conditions; (b) (4) day duration, as this is a worst-case assessme s compared to a 7 day implantation time; Monitoring the open circuit voltage, visual assessment, comparing the appearance of the surface before and after the test, and SEM assessment to examine for presence of pitting or other corrosion. Study success was defined as no visual evidence of corrosion and no sudden changes in open circuit voltages. There shall be no signs of corrosion on the blade of the test specimen. All samples met the predetermined acceptance criterion.

SUMMARY OF CLINICAL INFORMATION

The De Novo request presents the outcomes of three prospective studies (as shown in Table 2, below), including one controlled, pivotal study, which have a total of (b) (4) enrolled subjects, with > (b) (4) iTind-treated subjects who have undergone follow-up evaluation out to at least 12 months.

Table 2. Studies with Prospective Data

Study	**Subjects Enrolled (completed 12-month FU)**
MT-01 (OUS) - One-arm, multi-center, two-steps international feasibility and prospective study to assess the safety and efficacy of Medi-Tate Temporary Implantable Nitinol Device (TIND) in subjects presenting Bladder Outlet Obstruction secondary to BPH.	32 iTind (31)
MT-02 (OUS) - One-arm, multi-center, international prospective study to assess the efficacy of Medi-Tate Temporary Implantable Nitinol Device (TINDTM) in subjects with Benign Prostatic Hypertrophy (BPH).	81 iTind (67)
MT-03 (US/OUS) - A pivotal study, randomized, controlled, efficacy-assessor-blinded, multi-center, international prospective study to assess the safety and effectiveness of Medi-Tate i-Temporary Implantable Nitinol Device (iTind) in subjects with symptomatic Benign Prostatic Hyperplasia (BPH).	118 iTind (81) 57 Sham (NA)

MT-01 Study

MT-01 was a one-arm, multi-center, two-step, international feasibility and prospective study to assess the safety and efficacy of Medi-Tate Temporary Implantable Nitinol Device (TIND) in subjects presenting Bladder Outlet Obstruction secondary to BPH**.** The studyincluded 31 subjects completing follow-up to 36 months. This study was conducted outside the United States and was designed as a single-arm, feasibility study. The objective of the study was to assess the safety and efficacy of the TIND System in male subjects age 50 and older with bladder outlet obstruction (BOO) secondary to BPH. The primary efficacy endpoint was to increase maximal urinary peak flow by at least 5 ml/s in at least 75% of patients at 3, 6 and 12 months. The primary safety objective was the incidence of unexpected serious adverse events related to the TIND implant and the implantation/retrieval procedures. Increases in maximal urinary peak flow of 4.1, 4.1 and 4.9 ml/s were attained at the 3, 6 and 12-month time-points. There was a statistically significant increase in peak urinary flow rate (Qmax) from baseline, and reduction in International Prostate Symptom Score (IPSS*) and Quality of Life (QoL**) scores over 36 months. At 12 months, 25/32 subjects reported an IPSS improvement of at least 5 points. Four (4) expected early-onset complications were reported, including urinary retention, transient incontinence, prostatic abscess and urinary tract infection. These were managed via catheter placement, early removal of device, readmission/antibiotics, and oral antibiotics, respectively. All resolved within 30 days without sequelae. No further complications were recorded during the follow-up period.

* Total IPSS score is based on the sum of patient responses to items 1 to 8 of the IPSS questionnaire (for lower urinary symptoms; scored 0-5 for each item, for a total score ranging from 0 to 40).

** IPSS QoL Score, which corresponds to item 8 of the IPSS questionnaire, separately.

MT-02 Study

MT-02 was an international, prospective, single-arm, multi-center, safety and efficacy study on the iTind device used to treat Benign Prostatic Hyperplasia (BPH). A total of 81 subjects were enrolled in this study. The primary efficacy and safety endpoints were a ≥ 3-point IPSS score reduction in at least 75% of the subjects at 6 months follow-up and the incidence of unexpected serious adverse events related to the device and/or implantation/retrieval procedures, respectively. At the 6-month follow-up visit, 85.3% of treated patients (N=70) reported a ≥ 3-point improvement in IPSS. At the 12-month follow-up visit, 88.9% of treated patients (n=67) reported a ≥ 3-point improvement in IPSS. Further, patients reported enhanced quality of life, and an increase in mean Qmax, from 7.6 ml/s at baseline to 12 ml/s at 12 months.

Three (3.7%) patients experienced serious adverse events that were subsequently resolved within 10 days. The vast majority of complications were low-grade, self-limiting, and consisted mostly of hematuria and expected lower urinary tract symptoms, with 43.2% of all patients experiencing some AE (18.5% related; 22.2% device- and/or procedure-related; 14.8% procedure related). None of the sexually active patients reported any erectile or ejaculatory dysfunction.

MT-03 Study

The MT-03 pivotal study was an FDA-approved Investigational Device Exemption (IDE) Study. The study is a randomized, controlled, efficacy-assessor-blinded, multi-center, international prospective study to assess the safety and effectiveness of Medi-Tate i-Temporary Implantable Nitinol Device (iTind) in subjects with symptomatic Benign Prostatic Hyperplasia (BPH).

A total of 185 subjects were randomized (128 in the iTind group and 57 in Sham) and included in the Intent-to-Treat (ITT) population. A total of 175 patients underwent iTind implantation/Sham treatment, including 118 in the iTind group and 57 in the Sham group. The sham procedure consisted of insertion and removal of a Foley catheter. Of the ten patients that were assigned to the iTind arm but did not undergo implantation, nine were screen failures that were randomized by mistake and one was excluded intraoperatively due to a stricture.

Results – Effectiveness

The first co-primary endpoint, which was the difference in IPSS score between iTind and Sham groups at 3 months (Table 3, below), showed an improvement of approximately 10 points from baseline for the iTind group, which did not achieve statistical significance when compared with the Sham group under the pre-specified statistical model. In addition, 79% of iTind patients were responders (those who showed a ≥ 3-point reduction), compared to 60% in the sham group.

Table 3. Changes in IPSS Score at 3 Months*

Treatment Group	N (baseline)	N (3 months)	IPSS (Baseline)	IPSS (3 months)	IPSS (Change from Baseline)	95% Lower Limit	95% Upper Limit	P-Value
iTind	127	84	26.7	15.7	-10.6	-11.8	-8.1	NA
Sham	57	40	27.7	19.2	-8.3	-10.1	-4.8	
Sham - iTind	NA	NA	1.0	3.5	2.5	-0.5	5.6	0.104

*SAP Mixed Model; Intend-to-Treat (ITT) Population

The second co-primary endpoint of the study, which was the change in IPSS Score at 12 months compared to the baseline for the iTind group (Table 4, below), showed a significant improvement of IPSS scores. The sham group could not be compared at 12 months because their follow up was limited to 3 months to enable them to resume active treatment.

Table 4. Changes in IPSS Score at 12 Months*

Treatment Group	N (12 months)	Visit	Change from Baseline (at 12 months)	95% Lower Limit	95% Upper Limit	P-Value
iTind	81	12 Months	-8.7	-10.6	-6.9	< 0.001

*SAP Mixed Model; Intend-to-Treat (ITT) Population

The secondary endpoints (comparisons to baseline at 3 months for peak flow rate, post-void residual urine volume, total SHIM (Sexual Health Inventory for Men), and Total IIEF (International Index of Erectile Function)), were to be tested for significance if both co-primary endpoints were met. Although only one of the two co-primary endpoints was met, the secondary endpoints were analyzed to provide descriptive statistics (Table 5, below).

- The peak flow rate (PFR) increased over time for both groups. The average increase in PFR at 3 months was greater in the iTIND group than in the Sham group (4.4 ml/sec vs. 2.9 ml/sec), yielding the difference of 1.5 ml/sec between the groups.
- The change in post-void residual (PVR) urine volume obtained in the iTIND group was more effective than that obtained in the sham group. The sham group at 3 months displayed some worsening compared to baseline, while the iTIND group still showed improvement from baseline.

Table 5 Changes in Clinical Outcome Measures*

		iTind			Change (from Baseline)			Sham	Change (from Baseline)
Clinical Outcome	Visit	n	X	SD	*n*	$\bar{X}$	*SD*	(b) (4)	
Peak Flow Rate (ml/sec)	Baseline	125	8.7	3.3	–	–	–		
	3 Months	82	13.1	7.0	*81*	*4.4*	*7.0*		
Post-Void Residual Urine Volume (ml)	Baseline	125	61.6	55.5	–	–	–		
	3 Months	80	55.9	53.2	*79*	*-5.0*	*55.3*		
International Index of Erectile Function (IIEF) Score	Baseline	125	38.3	20.7	–	–	–		
	3 Months	84	43.7	22.2	*83*	*4.0*	*19.1*		
Sexual Health Inventory for Men (SHIM) Score	Baseline	127	13.2	7.3	–	–	–		
	3 Months	84	13.6	7.8	*84*	*0.4*	*7.0*		

*Descriptive Statistics; ITT Population

Results – Safety

The safety results demonstrate a favorable safety profile for the iTind device. Mean time to return to preoperative activity was 6.2 days. None of the 118 subjects experienced *de novo* sustained sexual dysfunction (erectile or ejaculatory dysfunction). A total of 5 procedure and/or device related serious adverse events (SAEs) were observed in 3 patients from the iTind group. Adverse events associated with iTind were comparable to other minimally invasive surgical therapies as well as standard cystoscopy. The most frequent AEs observed in the study included dysuria (22.9% of subjects), hematuria (13.6%), pollakiuria (6.8%), urinary retention (5.9%), and micturition urgency (5.1%). The majority of the adverse events in the iTind group occurred within 7 days of treatment, while the device was in the body. Most were mild, anticipated and resolved within 1-4 weeks. Of the 109 total AEs, 54 (49.5%) required no intervention, (33.0 %) were managed pharmacologically, 12 (11.0%) were managed non-surgically, and 4 (3.6%) were managed surgically. Of the AEs that were managed surgically, one subject had dental caries, one subject had an upper limb fracture, one subject had worsening of urinary symptoms that led to a transurethral prostatectomy, and one subject had worsening hematuria, clots and an inability to void (successfully treated by catheterization, subsequent clot removal, and bladder fulguration). Relevant noted potential adverse events are listed in the table below.

Table 6. Most Frequent Adverse Events*

Preferred Term	Treatment Group					
	iTind (N=118)			Sham (N=57)		
	No. Events	No. Subj.	% Subj.	No. Events	No. Subj.	% Subj.
Total AEs	109	45	38.1	19	10	17.5
Dysuria	27	27	22.9	5	5	8.8
Hematuria	17	16	13.6			
Pollakiuria	8	8	6.8	1	1	1.8
Urinary retention	8	7	5.9			
Micturition urgency	6	6	5.1	1	1	1.8

*Most frequent defined as experienced by more than 5% of subjects in at least one study arm.

Most of the AEs in both groups occurred within 90 days from implantation (99 AEs in 44 (37.3%) patients in iTind group and 15 AEs in 10 (17.5%) patients in sham). Most of the AEs were anticipated. The unanticipated AEs occurred in 12.7% of patients in iTind group and 10.5% of patients in the sham group. During the course of study, 16 SAEs were observed in 10 patients from the iTind group and 2 SAEs in the sham group. For the iTind group, 2 SAEs occurred during the Device-in-Body phase and 14 SAEs occurred during the Post-Retrieval phase. None of the SAEs were categorized as definitely related to the device. Only 3 SAEs from 2 iTind patients during the Post Retrieval Phase were found to be possibly related to the device. One AE (mild postoperative urinary retention) was found to be related to the procedure. One patient in the iTind group died from pancreatic cancer complications, which was not related to the device. Three AEs (lung neoplasm, retention, and UTI) were not resolved/recovered by study completion in one patient in iTind group, and one AE (chest pain) was not resolved/recovered in a patient in the sham group. All these AEs were not related to the device. In the Safety Population, there were 29/118 (24.6%) patients in the iTind group and 15/57 (26.3%) patients in the sham group who terminated the study early. Among them, 10/29 (34.5%) in iTind group, and 3/15 (20.0%) in Sham group experienced AEs.

For all patients, the procedure was conducted in the same day. The iTind implantation procedure was shown to be simple and not to cause more than moderate discomfort, with a mean implantation duration of 4.2 minutes and mean VAS pain score of 4.2. On average it took 12.2±17.1 days and 6.2±17.0 days for iTind patients to return to preoperative activities after implantation procedures and retrieval procedures, respectively, times which are similar to the sham patients as well as to other minimally invasive endourological therapies, such as UroLift. (UroLift is another non-ablative, cystoscopically-delivered, minimally-invasive device treatment option for lower urinary tract symptoms secondary to BPH. It consists of a short section of monofilament with a metallic tab on each end (one rests on the outer prostatic-capsule, the other on the urethral prostatic surface, with the monofilament stretched taut in-between) that facilitates retraction of sections of the prostatic lobes. Typically, 4-5 implants are needed for relief from lower urinary tract symptoms. The procedure is sometimes referred to as a prostatic lift.)

Adverse events associated with iTind, although of greater incidence than in the Control group, were comparable to other minimally invasive endourological therapies as well as standard

cystoscopy. None of the 118 subjects experienced *de novo* sustained sexual dysfunction (erectile or ejaculatory dysfunction).

Summary

The pivotal study met one of the two co-primary endpoints, showing a significant improvement of IPSS scores at 12 months compared to the baseline. For the other co-primary endpoint, IPSS score at 3 months was not statistically significantly better for the iTind treatment group when compared to the sham. Analyses of the secondary endpoints demonstrated improvements in the iTind group for all the tested clinical outcome measures, including urinary flow rate, bladder emptying, and male sexual health at 3 months. Safety results demonstrated a favorable safety profile for the iTind device, with a low rate of serious adverse events (none were deemed to be definitely related to the device, though four were deemed to be possibly related). After device removal, the rate of additional AEs decreased significantly. Most of the AEs observed in the study were anticipated and were mild, with 49.2% resolving without intervention and 34.3% resolving with pharmaceutical intervention.

Comparison to Alternative Therapies

The primary analysis used the Total IPSS Score (see above) and was used in studies for other BPH treatment modalities, including the pivotal study to support the marketing of NeoTract UroLift (DEN130023). As such, it allows for a comparison between iTind and treatment methods investigated in other studies. UroLift stands as a balanced comparator to iTind for several reasons. In addition to having very similar indications for use in treating lower urinary tract symptoms (LUTS) secondary to BPH, are placed cystoscopically, offer preservation of sexual function, offer rapid relief, require minimal down-time, are non-ablative device-based treatments, typically require no post-operative catheterization, and both devices/procedures are minimally invasive.

Patient Populations

The patient populations in the iTind and UroLift studies, though not compared head-to-head, were similar in terms of baseline values, as shown in the table, below.

Table 7. Comparison of iTind and UroLift patient populations (baseline)

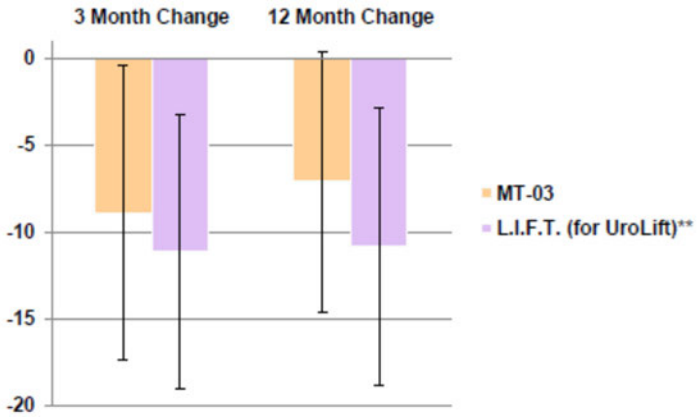
	iTIND [Mean (SD)]		**UroLift** [Mean (SD)]	
	Experimental	**Control**	**Experimental**	**Control**
n	126	56	123	66
Age	61.5 (6.5)	60.1 (6.3)	67 (8.6)	65 (8.0)
Ht (in)	68.8 (4.2)	69.7 (3.9)	70.1 (2.5)	69.4 (3.6)
Wt (lbs)	193.6 (41.1)	198.4 (42.7)	197.3 (2.5)	187.8 (30.2)
BMI (kg/m2)	28.8 (5.7)	28.8 (5.7)	28.3 (4.2)	27.4 (3.6)
Prostate Vol (cc)	43.4 (15.5)	43.8 (13.3)	44.5 (12.4)	40.9 (10.8)
IPSS	26.7 (7.7)	27.7 (6.8)	22.2 (5.4)	24.4 (5.8)
Qmax (ml/s)	8.7 (3.3)	8.5 (2.4)	8.9 (2.2)	8.8 (2.2)
PVR (ml)	61.6 (55.5)	61.9 (54.2)	85.5 (69.2)	87.7 (72.4)
QoL	4.6 (1.3)	4.9 (1.0)	4.6 (1.1)	4.7 (1.1)

PSA (ng/ml)	2.2 (2.3)	1.8 (1.8)	2.4 (2.0)	2.1 (1.6)
IIEF-5	13.2 (7.3)	14.2 (6.6)	13.0 (8.4)	13.5 (8.5)
Comparison of Subject Selection Criteria				
Age (yr)	50-80		>50	
IPSS	≥ 10		≥ 13	
Prostate (cc)	25-75		≤ 80	
Comparison of Other Miscellaneous Study Parameters				
Sham (Insertion)	NA	Foley (In & Out)	NA	Cystoscopy +audio
Sham (Retrieval)	NA	Foley (In & Out)	NA	NA
Sites	14 US (2 OUS)	-	14 US (5 OUS)	-
In-study meds*	13	7		

* During the iTIND study, the investigator had the discretion to treat patients with alternative BPH treatment methods (medications, surgeries, or other devices) when necessary. The alternative treatments included alpha blockers (Rapaflo, Uroxatrol, Tamsulosin, Flomax, Labetalol, Carvedilol), surgery (TURP, UroLift), Antimuscarinics (Ditropan, Aclidinium Bromure, Solifenacine). All efficacy measurements from the day of alternative treatment onwards were considered "missing" and imputed as baseline values (resulting in treatment failures with no change from baseline).

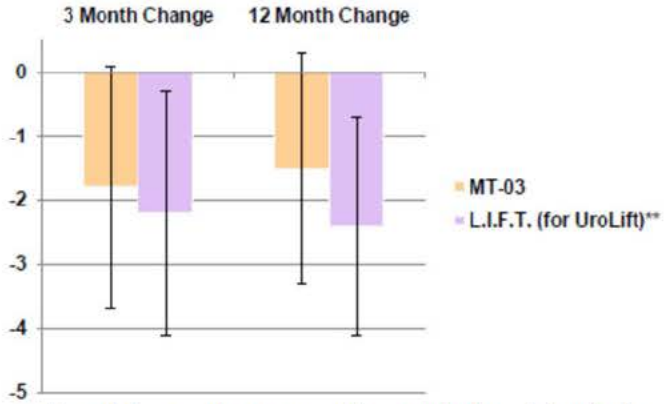
Results - Effectiveness

Figure 4. Comparing IPSS scores between iTind (MT-03) and UroLift (L.I.F.T.) studies



** Roehrborn *et al*. 2013; Error bar: Standard Deviation (SD)

Figure 5. Comparing QoL scores between iTind (MT-03) and UroLift (L.I.F.T) studies



** Roehrborn *et al*. 2013; Error bar: Standard Deviation (SD)

While the iTind results in the MT-03 pivotal study were not significantly different compared to the sham (Table 5), the observed IPSS and QoL improvements were similar to the UroLift study at 3 months, as summarized in Figures 4 and 5. Thus, the data further support the clinical benefit of the iTind system.

Secondary outcomes in the iTind group were also comparable to those for the UroLift. As shown in Table 8, below, the improvement of PFR (Qmax) in the iTind group at 3 months was comparable to that observed in the LIFT study for UroLift. Patients in the iTind group also had smaller improvement in PVR but greater improvement in SHIM than the UroLift group at 3 months. The differences compared to UroLift were not statistically significant.

Table 8. Comparing Outcome Measures between iTind and UroLift

Outcome Measurement	**iTind**			**UroLift***			
	n	**Mean**	**SD**	**n**	**Mean**	**SD**	
PFR/Qmax	81	4.4	7.0	126	4.3	5.2	
PVR	79	-5.0	55.3	140	-9.7	85.5	
SHIM/IIEF-5	84	0.4	7.0	132	0.1	5.8	

* Roehrborn et al. 2013.

iTind MT-03 study results showed fewer adverse events compared to those reported in the pivotal study for UroLift. Table 9, below, compares the overall AEs and SAEs between iTind and UroLift.

Results - Safety

Table 9. Comparing AEs between iTind and UroLift

	iTind (N=118)		UroLift* (N=140)	
	No. Events	**No. Subjects (%)**	**No. Events**	**No. Subjects (%)**
All AEs	109	45 (38.1%)	412	122 (87.1%)
Related AEs	82	38 (32.2%)**	247	113 (80.7)
Serious AEs	16	10 (8.5%)	25	16 (11.4)
Related SAEs	5	3 (2.5%)**	2	2 (1.4%)

* Roehrborn et al. 2013. ** The numbers for related AEs and SAEs for iTind included events that were determined to be related or possibly related to the device or the procedure. Therefore, the numbers represent the worst-case estimates. For UroLift, it is unclear from the published article whether the related AEs and SAEs include possibly related events.

As shown in the table, above, iTind treated patients had fewer AEs compared to patients treated with UroLift. The SAE rate is also lower for iTind than that for UroLift. Furthermore, when comparing the incidence rate for individual AE types, iTind also demonstrates a lower rate for almost all urinary disorders, as shown in Table 10, below.

Table 10. Comparison of Urinary Adverse Events

	iTind (N=118)	UroLift* (N=140)
	% Subject	**% Subject**
Dysuria	22.9	35
Hematuria	13.6	26.4
Micturition urgency	5.1	9.3
Incontinence	3.4	7.9
Urinary retention	5.9	5.7

* K130651 Decision Summary.

Conclusions

Clinical improvement was seen in patients for up to 12 months following 5-7-day iTind implantation. The study met one of the two co-primary endpoints and showed a statistically and clinically significant improvement of IPSS scores at 12 months compared to the baseline. For the other co-primary endpoint at 3 months, the iTind treatment group showed a trend toward significance when compared to the sham. Analyses of the secondary endpoints demonstrated positive treatment effects in the iTind group for all the tested clinical outcome measures, including urinary flow rate, bladder emptying, and male sexual health. The iTind treatment also showed an improvement in the patient's quality of life. Safety results demonstrated a favorable safety profile for the iTind device, with a low rate of serious adverse events. After the device removal, the AE rate decreased significantly. Most of the AEs observed in the study were anticipated and were mild. In addition, when compared to NeoTract UroLift, which is intended for permanent implantation, the iTind system showed fewer AEs and SAEs, and a lower rate for almost all urinary disorders.

LABELING

The iTind System complies with the labeling requirements under 21 CFR 801.109 for prescription devices in the provided physician labeling. In addition, the labeling includes contraindications, warnings and precautions, clinical data on the device and specific instructions for the safe and effective use of the device. The labeling identifies the validated shelf life of the device. The labeling also indicates that if the sterile barrier has been compromised, the device must not be used.

RISKS TO HEALTH

Table 11 below identifies the risks to health that may be associated with use of a temporarily-placed urethral opening system for symptoms of benign prostatic hyperplasia and the measures necessary to mitigate these risks.

Table 11. Identified Risks to Health and Mitigation Measures

Identified Risks to Health	Mitigation Measures
Adverse tissue reaction	Clinical performance testing Biocompatibility evaluation Labeling
Infection	Clinical performance testing Sterilization validation Shelf life testing Labeling
Untreated symptoms due to device deployment failure	Clinical performance testing Non-clinical performance testing Shelf life testing Labeling
Bleeding, perforation, trauma, obstruction, incontinence, dysuria, urgency due to device failure or difficult removal	Clinical performance testing Non-clinical performance testing Shelf life testing Labeling

SPECIAL CONTROLS

In combination with the general controls of the FD&C Act, the temporarily-placed urethral opening system for symptoms of benign prostatic hyperplasia is subject to the following special controls:

1. Clinical performance testing with the device under anticipated conditions of use must evaluate improvement in urinary outflow symptoms and document the adverse event profile.

2. The patient-contacting components of the device must be demonstrated to be biocompatible.

3. Performance data must demonstrate the sterility of the patient-contacting components of the device.

4. Performance data must support the shelf life of the device by demonstrating continued sterility, package integrity, and device functionality over the labeled shelf life.

5. Non-clinical performance testing must demonstrate that the device performs as intended under anticipated conditions of use. The following performance characteristics must be tested:
   a) Deployment and removal; and
   b) Mechanical strength.

6. Labeling must include:
   a) Instructions for use, including the recommended training for safe use of the device;
   b) A summary of the clinical performance testing conducted with the device, including device- and procedure-related adverse events; and
   c) A shelf life.

BENEFIT/RISK DETERMINATION

The benefits and risks of the iTind System when used to treat symptoms due to urinary outflow obstruction secondary to benign prostatic hyperplasia (BPH) in men age 50 and above are based on non-clinical and clinical data.

The benefits of the iTind System include a clinically meaningful decrease in urinary outflow obstruction symptoms and an increased quality of life sustained to 12 months, as demonstrated by reduced IPSS and QoL scores, respectively. The insertion and retrieval procedures are minimally invasive, each performed via cystoscopy. The iTind implant is temporary, residing at the prostatic urethra for a duration of ≤ 1 week. The entire implant is removed, with no components or materials left behind that might otherwise impact future prostate or regional procedures. Fewer adverse events are experienced with the iTind System than with other more invasive treatment options.

The risks of the iTind System include risks associated with cystoscopy, and also include adverse tissue reaction, infection, failure to deploy, failure of device while implanted, removal complications, and genito-urinary adverse events. Specific adverse events include dysuria (pain on urination), hematuria (blood in urine), micturition urgency (increased urinary urgency), pollakiuria (frequent urination during the day), urinary retention, urinary incontinence, hemospermia, retrograde ejaculation, bladder neck strictures, priapism. The rate of adverse events (AE) in the supporting pivotal study is relatively low, at 38%, with the rate of occurrence

of new events decreasing substantially after device removal. Several serious adverse events (SAE) were reported during the pivotal study, with four categorized as possibly related but none were categorized as definitely related to the device.

Elements of the clinical study design, conduct and analysis did contribute to uncertainty in the evaluation of the benefits and risks of the iTind System. The limited sample size compared to the intended population and the limited duration of the pivotal study both contribute to the uncertainty in evaluating the benefit and risk. Also, the inter-goup difference in the baseline-to-12-month IPSS score changes could not be determined, as Control group subjects were allowed to and did receive alternative therapies after 3 months. Therefore, no controlled comparison at the 12-month time point could be made and this contributes uncertainty in determining the benefit of the device. Similarly, the inability to definitively attribute AEs to either the device or the procedure lends uncertainty to the determination of risk of the device. The 30% loss-to-follow-up reduces the strength of the data, also contributing to uncertainty in the evaluation of the risks and benefits. While these uncertainties exist, their extent is low and they are similar to uncertainties in other studies for BPH treatments, including the UroLift device. The overall benefits continue to outweigh the overall risks.

Based on the available data, the probable benefits of the iTind System, as a treatment for symptoms due to urinary outflow obstruction secondary to benign prostatic hyperplasia (BPH) in men age 50 and above, outweigh the probable risks.

Patient Perspectives

Patient perspectives considered for the iTind System included quality of life (QOL) questionnaires such as the International Prostate Symptom Score (IPSS). The IPSS consists of eight questions (seven regarding symptoms and one specifically regarding quality of life) and is used as a screening, diagnostic and symptom tracking tool for BPH. Improvement is defined as a decrease of at least 3 points. In the supporting pivotal study, the group treated with the iTind System showed > 10-point reductions in IPSS from baseline to follow-up at 3 and 12 months, and an improvement in QoL score by almost two points, though this outcome was similar between groups. In two outside-U.S. (OUS), single-arm, investigational studies, subjects demonstrated a ≥ 10-point improvement in IPSS at 12 months and, in one of the studies, a ≥ 3-point improvement in IPSS at 36 months.

Benefit/Risk Conclusion

In conclusion, given the available information above, the data support that, for use of the iTind System for the treatment of symptoms due to urinary outflow obstruction secondary to benign prostatic hyperplasia (BPH) in men age 50 and above, the probable benefits outweigh the probable risks. The device provides benefits and the risks can be mitigated by the use of general controls and the identified special controls.

CONCLUSION

The De Novo request for the Medi-Tate iTind System is granted and the device is classified under the following:

Product Code: QKA
Device Type: Temporarily-placed urethral opening system for symptoms of benign prostatic hyperplasia
Class: II
Regulation: 21 CFR 876.5510