SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Drug Coated Prostatic Dilation Catheter for Benign Prostatic Hyperplasia

Device Trade Name: Optilume® BPH Catheter System

Device Procode: QXB

Applicant's Name and Address: Urotronic, Inc.
2495 Xenium Lane N
Minneapolis, MN 55441

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P220029

Date of FDA Notice of Approval: June 30, 2023

II. INDICATIONS FOR USE

The Optilume BPH Catheter System is indicated for the treatment of obstructive urinary symptoms associated with Benign Prostatic Hyperplasia (BPH) in men ≥ 50 years of age.

III. CONTRAINDICATIONS

The Optilume BPH Catheter is contraindicated for use in:

- Patients with known hypersensitivity to paclitaxel or structurally related compounds
- Patients with an active urinary tract infection
- Patients with an artificial urinary sphincter
- Patients with a penile prosthesis

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Optilume BPH Catheter System labeling.

V. DEVICE DESCRIPTION

The Optilume BPH Catheter System is device/drug combination product that consists of two catheters:

- Optilume BPH Prostatic Pre-dilation Catheter (a non-drug coated catheter for pre-dilation)
- Optilume BPH Prostatic Dilation DCB Catheter (a drug (paclitaxel) coated catheter)

The Pre-dilation Catheter is used to start a commissurotomy between the lateral lobes of the prostate. The DCB Catheter further dilates and completes the commissurotomy and transfers drug to the pre-dilated prostatic urethra and anterior commissure. The Pre-dilation Catheter is constructed identically to the DCB Catheter, but without the paclitaxel drug coating. The Pre-dilation Catheter and DCB Catheter are packaged separately.

Optilume BPH Catheters

Both Optilume BPH Catheters are single inflation lumen balloon catheters that terminate in an atraumatic tip. The folded balloon has a 14.5F profile. The catheters are inserted through the outer sheath of a rigid cystoscope and can be visualized in a side-by-side fashion with a rigid cystoscope. The distal lobe of the balloon inflates in the bladder and aids in anchoring the device, while the proximal lobe of the balloon is positioned in the prostatic urethra to dilate the prostate and create the anterior commissurotomy. The proximal end of the catheter is tapered to allow the attachment of a 9F Tuohy-Borst valve and stopcock for inflation.

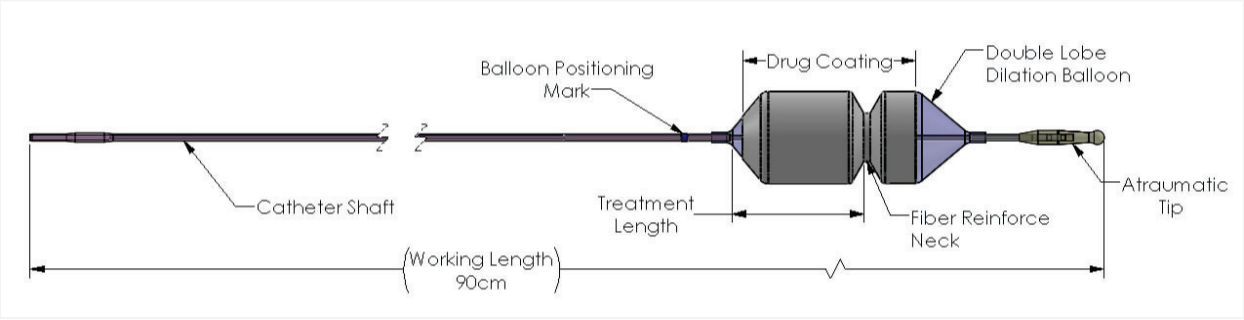


Figure 1. Inflated DCB Catheter

The Optilume BPH catheters are available in a range of balloon sizes to accommodate different prostate sizes. There are two Pre-Dilation Catheter sizes and four DCB Catheter sizes as listed in Table 1. The nominal paclitaxel dose also varies by DCB Catheter size as described in Table 1.

Table 1: Catheter Sizes and Nominal Paclitaxel Dose

Balloon Diameter	Balloon Treatment Length	Nominal Paclitaxel Dose (µg)
Optilume BPH Prostatic Pre-dilation Catheter		
30 mm (90F)	30 mm	N/A
30 mm (90F)	35 mm	N/A
Optilume BPH Prostatic Dilation DCB Catheter		
30 mm (90F)	30 mm	10,262
30 mm (90F)	35 mm	11,433
30 mm (90F)	40 mm	12,567
30 mm (90F)	45 mm	13,661

The Optilume BPH Pre-dilation and DCB catheters will be provided in convenience kits including all accessories required to perform the Optilume BPH procedure. Each kit will include an Optilume BPH Pre-dilation Catheter, an Optilume DCB Catheter, an inflation device, a stopcock, and two Tuohy-Borst adapters.

Drug Coating

The proprietary drug coating consists of the active pharmaceutical ingredient (API) paclitaxel and excipients. Paclitaxel is a lipophilic, antimitotic agent that stabilizes microtubules and inhibits cell mitosis. Several studies in animal models have also shown that paclitaxel applied locally inhibits smooth muscle cell and fibroblast proliferation and migration.

The Chemical Abstracts Service (CAS) registry number of paclitaxel is 33069-62-4. The chemical name is (2aR-(2aα,4β,4aβ,6β,9α(α R*,βS*),11α,12α,12bα))-β-(Benzoylamino) α-hydroxybenzenepropanoic acid 6,12b-bis(acetyloxy)-12-(benzoyloxy)-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-4,11-dihydroxy-4a,8,13,13-tetramethyl-5-oxo-7,11-methano-1H-cyclodeca(3,4)benz(1,2-b)oxet-9-yl ester and the chemical formula is $C_{47}H_{51}NO_{14}$. The chemical structure of paclitaxel is illustrated in Figure 2.

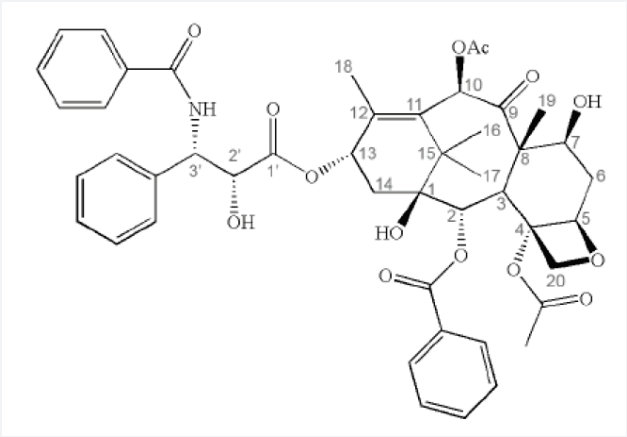


Figure 2. Chemical Structure of Paclitaxel

The drug coating is evenly applied on the DCB with a dose density of 2.4 µg/mm^2. The nominal paclitaxel dose per balloon is shown in Table 1. The excipients used in the drug coating are pentaerythritol ethoxylate 15/4 (PEE 15/4) and pentaerythritol ethoxylate 3/4 (PEE 3/4). The excipients function to assist in the release of the drug coating from the balloon catheter during deployment (balloon inflation).

Mode of Action

The primary mode of action is mechanical dilation to achieve commissurotomy of the lateral prostate lobes and open the prostatic urethral lumen. The increase in cross-sectional area of the prostatic urethra from the anterior commissurotomy allows for increased urine flow. The secondary mode of action is the transfer of paclitaxel drug from the surface of the balloon to the dilated area to inhibit cell proliferation and maintain urethral patency.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for the treatment of lower urinary tract symptoms (LUTS) secondary to BPH including pharmacological therapies, minimally invasive treatments, or surgical procedures. Pharmacological therapies are typically used initially to control mild to moderate symptoms of BPH. Minimally invasive treatments include different methods to resect or ablate the prostate (e.g., laser, vapor) or permanent implants to lift and hold the prostate. Surgical procedures may include prostatectomy or transurethral resection of the prostate (TURP). 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 expectations and lifestyle.

VII. MARKETING HISTORY

The Optilume BPH Catheter System is commercially available in Canada. The device has not been withdrawn from marketing for any reason related to its safety or effectiveness.

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.

Potential adverse effects after treatment with the Optilume BPH Catheter System are similar to standard cystoscopic procedures and mechanical dilation and include, but are not limited to the following:

- Fever,
- Bleeding
- Pain
- Urinary tract infection
- False route of the urethra
- Dysuria
- Difficult urination
- Frequency/urgency/irritative urinary symptoms
- Urinary retention and related symptoms
- Blood in urine (hematuria)
- Urinary incontinence
- Urethrorrhagia
- Blood in semen (hematospermia)
- Ejaculatory dysfunction
- Bladder perforation
- Urethral and/or bladder neck strictures
- Injury or perforation to the urethra
- Sphincter or prostatic capsule
- Inflammation of genitourinary system (prostatitis, orchitis, balanitis).

Although systemic effects from the paclitaxel coating are not anticipated, adverse effects observed during intravenous administration of paclitaxel for chemotherapy include, but are not limited to the following:

- Allergic reaction
- Alopecia
- Anemia
- Gastrointestinal symptoms
- Hematological dyscrasia (including leucopenia, neutropenia, thrombocytopenia)

- Hepatic enzyme changes
- Myalgia/arthralgia
- Myelosuppression
- Peripheral neuropathy

Maximum systemic paclitaxel levels after treatment with the Optilume BPH DCB are more than 100 times lower than with intravenous administration of paclitaxel for chemotherapy.

The Optilume BPH DCB contains paclitaxel, a known genotoxic aneugen that is capable of injuring chromosomes in sperm. Paclitaxel is present in semen for an extended duration after treatment with the Optilume BPH procedure. The total duration of time that paclitaxel remains in the semen post-procedure is unknown. The risks associated with paclitaxel in the semen are unknown. The current data are inadequate to conclude a timeframe of when paclitaxel is cleared from the semen. For this reason, the post-procedure period for patients to use highly effective contraception (to avoid fathering children) is currently unknown. Urologists should engage in a discussion with prospective patients regarding this risk and their individual family planning situation (e.g., consideration of sperm banking) or limit treatment with Optilume BPH DCB to patients who completed fathering children.

Paclitaxel was detectable (i.e., equal to or greater than lower limit of quantitation of 0.1 ng/mL) in semen in 4/5 (80.0%) subjects, 5/7 (71.4%) subjects, and 1/1 (100%) of evaluable subjects at 1 month, and 3 months, and 6 months post-treatment, respectively.

Maximum paclitaxel concentrations in semen were 8.9, 7.5, and 1.8 ng/mL at 1 month, and 3 months, and 6 months, respectively, while group mean (SD) paclitaxel concentrations in semen at those same timepoints were 2.34 (3.69), 1.30 (2.76), and 1.75 (NA) ng/mL. In one subject that had evaluable data at 6 months post-treatment, paclitaxel concentration in semen was 1.75 ng/mL.

The risks associated with these paclitaxel concentrations in semen are unknown. The effect of treatment with the Optilume BPH DCB on sperm and spermatogenesis is also unknown.

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

IX. SUMMARY OF NONCLINICAL STUDIES

The non-clinical studies performed included mechanical testing, analytical testing, biocompatibility testing, sterilization validation, shelf-life and stability testing and animal testing. A summary of each of these evaluations is provided below.

A. Laboratory Studies

1. Mechanical Testing
   The Optilume BPH catheters underwent functional engineering testing as summarized in Table 2 to ensure the design met the requirements for its intended use.

Table 2. Summary of Mechanical Testing

Test	Acceptance Criteria	Result
Catheter Profile	≤ 0.208 in	Pass
Trackability	Track through 19.5F Sheath	Pass
Catheter Working Length	≥ 80 cm	Pass
Balloon Treatment Length	45 +2/-4 mm 40 +2/-4 mm 35 +2/-4 mm 30 +2/-4 mm	Pass
Balloon Diameters	Treatment Diameter: 30 ± 2 mm Neck Diameter: 12 ± 2 mm	Pass
Rated Burst Pressure	≥ 4.0 ATM	Pass
Balloon Fatigue	5 cycles unconstrained to rated burst pressure (RBP) without damage	Pass
Balloon Compliance	≤ 15 %	Pass
Balloon Neck Compliance	≤ 5 %	Pass
Inflate/Deflate Time	Inflate: ≤ 60 sec Deflate: ≤ 60 sec	Pass
Tensile & Compressive Strength	Proximal Balloon Bond ≥ 54.0 N Distal Balloon Bond ≥ 30.0 N Tip to Catheter Shaft ≥ 54.0 N Catheter Shaft ≥ 54.0 N Hypotube to Mandrel ≥ 15.0 N Fixed Wire to Dist Bond ≥ 30.0 N Fixed Wire to Prox Bond ≥ 30.0 N	Pass
Kink Resistance	No kink around 2.0” radius	Pass
Balloon Recovery	Force required to remove balloon ≤ 45 N	Pass

Test	Acceptance Criteria	Result
Fiber Reinforcement Integrity	Fiber reinforcement remains attached after inflation/deflation and balloon removal	Pass
Catheter Shaft OD	Shaft OD ≤ 0.105 in	Pass
Tuohy Borst Compatibility	Proximal Shaft OD ≤ 0.120 in	Pass

2. Analytical Testing
Analytical testing was performed on all balloon sizes to determine the identity, safety, purity, and quality of the drug substance used in the Optilume BPH DCB as summarized in Table 3.

Table 3. Summary of Analytical Testing

Test	Test Purpose	Acceptance Criteria	Result
Appearance	Visual inspection to verify the drug coating meets appearance specification	Must meet visual standard	Pass
Identification	Test the drug substance for identity to ensure conformity to incoming specifications	Identity confirmed via two different tests	Pass
Assay	Total paclitaxel content is quantified to ensure individual devices contain the labeled dosage	Average within 90.0-110.0% of label claim	Pass
Impurities and Degradants	The type and amount of degradants and impurities are quantified to ensure they remain within acceptable levels	ICH Q3B(R2)	Pass
Content Uniformity	Paclitaxel content uniformity from balloon to balloon is verified to ensure content uniformity meets specification	USP <905>	Pass
Coating Uniformity	Paclitaxel content on circumferential segments of an individual balloon is measured	Average of each segment must be within specified range	Pass
	The paclitaxel content on longitudinal segments of an individual balloon is measured	Average of each segment must be within specified range	Pass
Dissolution	The in vitro release profile of paclitaxel from the finished device is verified to meet pre-specified criteria	USP <711>	Pass

3. Biocompatibility

Biocompatibility testing was performed in accordance with ISO 10993-1:2018 to demonstrate that the catheters are biocompatible for their intended use. Testing was conducted separately on the drug coated balloon and the uncoated balloon catheters. The catheters were categorized as a surface device in contact with breached or compromised mucosal tissue with limited contact duration.

Table 4. Summary of Biocompatibility Testing

Test	Test Description	Test Sample Configuration			Result
		Balloon Coated with Drug and Excipient	Balloon Coated with Excipient	Full Uncoated Catheter	
Cytotoxicity (ISO 10993-5:2009)	ISO MEM Elution Assay with L-929 Mouse Fibroblast Cells	X[1]	X	X	Pass (non-cytotoxic)
Sensitization (ISO-10993-10:2010)	ISO Guinea Pig Maximization	X	X	X	Pass (non-sensitizer)
Intracutaneous Reactivity (ISO-10993-10:2010)	ISO Intracutaneous Reactivity	X	X	X	Pass (non-irritant)
Acute Systemic Toxicity (ISO-10993-11:2017)	ISO Acute Systemic Toxicity	X	X	X	Pass (non-toxic)
Material-mediated Pyrogenicity (ISO-10993-11:2017)	USP Materials Mediated Pyrogenicity	X		X	Pass (non-pyrogenic)

[1]Serial dilution was completed for the drug coated catheter.

An excipient qualification Good Laboratory Practices (GLP) study was performed to evaluate the excipient toxicity in buccal cavities of male Syrian hamsters (elevated dose versus saline control). Results showed that the excipients were safe and non-toxic when exposed to mucosal membrane

4. Sterilization

The Optilume BPH catheters are sterilized in their primary packaging using 100% ethylene oxide (EO) gas sterilant. Sterilization validation was performed using the overkill approach and met the requirements of ISO 11135:2014 to provide a minimum sterility assurance level (SAL) of 10^{-6}. EO residual levels were within acceptable limits per ISO 10993-7:2008,

5. Shelf Life and Stability Testing
   Shelf life and stability studies were conducted to establish the shelf life of the Optilume BPH DCB and Pre-Dilation Catheters with real time and accelerated samples. The catheters were subject to 1X EO sterilization, environmental conditioning per ISTA 3A, and distribution simulation per ASTM D4169-16 prior to shelf life and stablity testing.

   The shelf-life of the Optilume BPH DCB Catheter is based on the following tests:

   - Mechanical testing of two year aged samples. Please refer to section IX.A.1 for mechanical tests conducted.
   - Packaging testing of two year aged samples. Packaging testing included Tyvek packaging seal strength (ASTM F88:2015), bubble leak Tyvek (ASTM F2096:2019), packaging seal appearance (ASTM F1886:2016), bubble leak foil (ASTM F2096:2019), and seal strength foil (ASTM F88:2015), label adherence and legibility (ASTM D4169 and ISTA 3A).
   - Drug stability testing of one year real time and accelerated aged samples per USP and ICH guidelines.

   The data generated from the mechanical, package integrity, and drug stability studies support a 12-month shelf life for the Optilume BPH DCB Catheter. The Optilume BPH DCB Catheter will be labeled with a 12-month shelf life.

   The shelf-life of the Pre-dilation Catheter is based on results of mechanical and packaging testing, as there is no drug coating on this device. The two-year accelerated aging mechanical and packaging testing results demonstrate that the Pre-dilation Catheter meets specifications through two years. The Pre-dilation Catheter will be labeled with a two-year shelf life.

B. Animal Studies

A GLP animal study was conducted to evaluate the treatment safety, pharmacokinetics, and local tissue response to standard and maximum dosing DCB treatments in a canine prostatic urethral model. A total of 32 male mongrel canines were allocated to 3 treatment arms, including a maximum dose arm (1.4x the local exposure of the maximum paclitaxel dose of the device), standard dose arm (0.5x the local exposure of the maximum paclitaxel dose of the device), and a control arm (uncoated balloon) as shown in Table 5. Study endpoints included overall animal health, quantitative urethra analysis, tissue paclitaxel content, plasma paclitaxel content, and cellular response to treatment.

Table 5. Number of Animals by Treatment Arm

Treatment Arm	Treatment Description	Number of Animals	Termination Time Points
Maximum Dose	Two overlapping DCBs for total paclitaxel dose of 19.6 mg	10	Day 28, Day 70

Treatment Arm	Treatment Description	Number of Animals	Termination Time Points
Standard Dose	One DCB with paclitaxel dose of 6.8 mg	18	Day 0 [1 hr], Day 7, Day 28, Day 70
Control	One uncoated balloon	4	Day 7, Day 28

The results demonstrated that all balloon inflations in the prostatic urethra were successful without major procedural device-related complications and no device malfunctions. The animal study results do not raise concerns for safety of the subject device.

X. SUMMARY OF PRIMARY CLINICAL STUDY(IES)

The applicant performed a clinical study (PINNACLE) to establish a reasonable assurance of safety and effectiveness the Optilume BPH Catheter System for the treatment of LUTS secondary to BPH under IDE G190217. Data from this clinical study were the basis for the PMA approval decision. A summary of the clinical data is presented below.

A. Study Design

Patients were treated between January 2020 and September 2021. The database for this PMA reflected data collected through October 4, 2022 and included 148 patients. There were 18 investigational sites.

The PINNACLE study was a prospective, multicenter, double blind, 2:1 randomized, sham-controlled, crossover clinical study, with a non-randomized, pharmacokinetics (PK) study arm (15 subjects). Subjects randomized to the Sham arm were allowed to cross over to receive the Optilume BPH Catheter System prior to the close of their 12-month visit window.

Treatment with the Optilume BPH Catheter System included use of the Pre-dilation Catheter to initiate an anterior commissurotomy followed by dilation with the DCB Catheter to further dilate and deliver drug to the prostatic urethra.

A Data Monitoring Committee oversaw the safety of the study. Adverse events were adjudicated by an independent Clinical Events Committee.

The control group (sham) utilized a sheathed Optilume Pre-dilation Catheter that was modified to prevent inflation.

1. Clinical Inclusion and Exclusion Criteria

Enrollment in the PINNACLE study was limited to patients who met the following inclusion criteria:

1. Male subject 50-80 years of age who has symptomatic BPH;
2. International Prostate Symptom Score (IPSS) ≥ 13;
3. Peak urinary flow rate (Qmax) ≥ 5 ml/sec and ≤ 12 ml/sec (with minimum voided volume of ≥ 150 ml);
4. Prostate volume 20 to 80 gm as determined by transrectal ultrasound (TRUS);
5. Prostatic urethral length ≥ 32 mm and ≤ 55 mm as determined by TRUS;
6. History of inadequate response, contraindication, or refusal of BPH medical therapy; and
7. Able to complete the study protocol in the opinion of the investigator.

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

1. Unable or unwilling to sign the Informed Consent Form (ICF) and/or comply with all the follow-up requirements;
2. Unwilling to abstain or use protected sex for the first 30 days post treatment;
3. Unwilling to abstain from sexual intercourse or use a highly effective contraceptive for at least 6 months post-procedure;
4. Presence of an artificial urinary sphincter or stent(s) in the urethra or prostate;
5. Any prior minimally invasive intervention (e.g., transurethral needle ablation (TUNA), Balloon, Microwave, Rezūm, UroLift) or surgical intervention of the prostate ;
6. PSA ≥ 10 ng/ml unless prostate cancer is ruled out by biopsy;
7. Confirmed or suspected malignancy of prostate or bladder;
8. Active or history of epididymitis within the past 3 months;
9. Previous pelvic irradiation or pelvic trauma surgery;
10. Active urinary tract infection (UTI) confirmed by culture ;
11. Bacterial prostatitis within the last 12 months;
12. Non-bacterial prostatitis within the last 5 years;
13. Visible or invisible hematuria (> 4 red blood cells (RBCs) per high power field) on 2 separate urine specimens within the last 3 months without a known contributing factor;
14. Neurogenic bladder or sphincter abnormalities or neurological disorders that might affect bladder or sphincter function;
15. History of urinary incontinence;
16. Previous or current diagnosis of urethral strictures, bladder neck contracture or detrusor muscle spasms;
17. Previous rectal surgery, other than hemorrhoidectomy;
18. Use of antihistamines, anticonvulsants, or antispasmodics within 1 week prior to baseline assessment unless there is documented evidence of stable dosing for at least 6 months;

19. Use of antidepressants with adrenergic effects (i.e., duloxetine, imipramine, and amitriptyline), long-acting anticholinergics (LAAC) for chronic obstructive pulmonary disease (COPD), or androgens within 2 weeks prior to baseline assessment unless there is documented evidence of stable dosing for at least 3 months prior to baseline assessment;
20. Use of Luteinizing Hormone-Releasing Hormone (LHRH) analogs within 12 months prior to baseline assessment;
21. Use of Type II 5-alpha reductase inhibitor (e.g., finasteride (Proscar, Propecia)) within 3 months of baseline assessment;
22. Use of 5-alpha reductase inhibitor [e.g., dutasteride (Avodart)] within 6 months of baseline assessment;
23. Use of estrogen or drugs producing androgen suppression unless there is documented evidence of stable dosing for 3 months prior to baseline assessment;
24. Use of alpha blockers or daily dose PDE5 inhibitor (e.g., Cialis) within 2 weeks of baseline assessment;
25. Use of warfarin or novel oral anti-coagulants (e.g., apixaban (Eliquis), fondaparinux (Arixtra), rivaroxaban (Xarelto) or edoxaban (Savaysa)), unless the medication is safely discontinued prior to the procedure and is not planned to be restarted for at least 5 days post-procedure;
26. Use of anti-platelet medications (e.g., clopidogrel, aspirin) within 10 days prior to the procedure or planned use within 5 days post-procedure;
27. History of hypersensitivity reactions to paclitaxel, on medication that may have negative interaction with paclitaxel, presence of solid tumor with a baseline neutrophil count of <1500 cells/mm^3 or AIDS-related Kaposi's sarcoma with baseline neutrophil count of <1000 cells/mm^3;
28. Incidence of spontaneous urinary retention within 6 months prior to baseline assessment;
29. Current post-void residual volume > 300 ml or catheter dependent bladder drainage;
30. Known poor detrusor muscle function (e.g., Qmax < 5 ml/sec);
31. Current bladder or prostatic urethral stones;
32. Biopsy of prostate within 40 days prior to procedure;
33. History of cancer in non-genitourinary system which is not considered in complete remission (except basal cell or squamous cell carcinoma of the skin). A potential participant is considered in complete remission if there has been no evidence of cancer within five years;
34. Current uncontrolled diabetes (i.e., hemoglobin A1c ≥ 8%);
35. History of clinically significant comorbidities or presence of unstable conditions [e.g., cardiovascular, lung, renal (serum creatinine > 2.0 mg/dl), hepatic, bleeding disorders or metabolic impairment] that may confound the results of the study or have a risk to subject per investigator's opinion;
36. Any cognitive disorder that interferes with or precludes direct and accurate communication with the study investigator regarding the study or affects the ability to complete the study quality of life questionnaires;
37. Life expectancy < 10 years;

38. Anatomy (e.g., presence of false passage or size of meatus) is not suitable for treatment in this study;
39. Significant median lobe component (e.g., intravesical prostatic protrusion (IPP) > 1 cm);
40. Device that corresponds with the subject's prostate size is not available;
41. Currently enrolled in or plan to enroll in another investigational clinical study for any disease except for observational only study; and

In the opinion of the investigator, it is not in the subject's best interest to participate in the study.

2. Follow-up Schedule

All patients were scheduled to return for follow up examinations at the time of Foley removal (typically 2-5 days), 14 days, 30 days, 3 months, 6 months, and 12 months postoperatively. Subjects in both arms were blinded to treatment received through 12 months. Long-term follow-up is planned through 5 years for subjects treated with the Optilume BPH Catheter System, including sham arm subjects who crossed over to received treatment with the study device.

Baseline and follow-up clinical assessments included:

- International Prostate Symptom Score (IPSS) questionnaire;
- Uroflowmetry, including peak flow rate (Qmax) and post-void residual (PVR);
- Visual Analog Scale (VAS) for pain (procedure through 30 days);
- BPH Impact Index (BPH-II) questionnaire;
- International Index of Erectile Function (IIEF) questionnaire;
- Male Sexual Health Questionnaire – Ejaculatory Dysfunction (MSHQ-EjD) questionnaire;
- Physical exam; and
- Laboratory testing.

Adverse events were recorded at all follow-up visits.

The key timepoints are shown below in the tables summarizing safety and effectiveness.

3. Clinical Endpoints

With regards to safety, the primary safety endpoint is a composite endpoint of major device-related serious complications, defined as the proportion of subjects experiencing any of the following events through 12 months:

- Device-related rectal fistula or gastrointestinal (GI) fistula;
- Device-related formation of fistula between the rectum and urethra;
- Device-related new onset severe urinary retention lasting > 14 consecutive days post-healing;
- Device-related unresolved new onset stress urinary incontinence by 90 days;

- Device-related bleeding requiring transfusion; and
- Device-related urethra or prostatic capsule rupture requiring surgical intervention.

With regards to effectiveness, the primary efficacy endpoint is improvement in IPSS, evaluating the change from baseline to 3 months in the Sham arm against the change from baseline to 12 months in the Optilume BPH arm. For this endpoint to be a success, the observed improvement in IPSS at 12 months post-treatment in the Test arm must be at least 25% greater than that of the Control arm at 3 months based on the following statistical hypotheses:

$$H_o: \pi_{Test,12mo} - 1.25\pi_{Control,3mo} \leq 0$$
$$H_A: \pi_{Test,12mo} - 1.25\pi_{Control,3mo} > 0$$

where $\pi_{Test,12m}$ is the mean reduction in IPSS from baseline for the Optilume BPH arm at 12 months and $\pi_{Control,3mo}$ is the mean reduction in IPSS from baseline for the Control arm at 3 months. The statistical hypothesis test for the primary efficacy endpoint is based on a two-sample t-test at the one-sided 0.025 alpha level.

The hypothesis tested secondary endpoints included:
- Average IPSS improvement in the Optilume BPH arm at 12 months;
- Responder rate at 3 months (responder is a subject with IPSS improvement ≥30% from baseline);
- Responder rate at 12 months in the Optilume BPH arm compared to the responder rate at 3 months in the Control arm; and
- Change in Qmax at 12 months in the Optilume BPH arm compared to the change in Qmax at 3 months in the Control arm.

Ancillary endpoints included:

- A1: Additional responder analyses with a responder defined as IPSS improvement of 35%, 40% and 50%
- A2: Change in post-void residual (PVR) urine volume
- A3: Change in sexual function (International Index of Erectile Function (IIEF), Male Sexual Health Questionnaire - Ejaculatory Dysfunction (MSHQ-EjD))
- A4. Change in BPH impact index (BPH-II)
- A5: Change in quality of life (EQ-5D)
- A6: Change in pain score
- A7: Procedure parameters
- A8: Change inpeak urinary flow (Qmax)
- A9: Proportion of subjects experiencing a return to ‘normal’ symptom severity (IPSS<8)

B. Accountability of PMA Cohort

At the time of database lock, of 477 patients enrolled in the PMA study, 24.1% (115) are available for analysis at the completion of the study, the 12 month post-operative visit. Thirty-one (31)% (148) are randomized, and 2.9% (14) included in the PK sub-study. Subject disposition and visit compliance for the randomized cohort through 12 months is summarized in Table 6 and Figure 3.

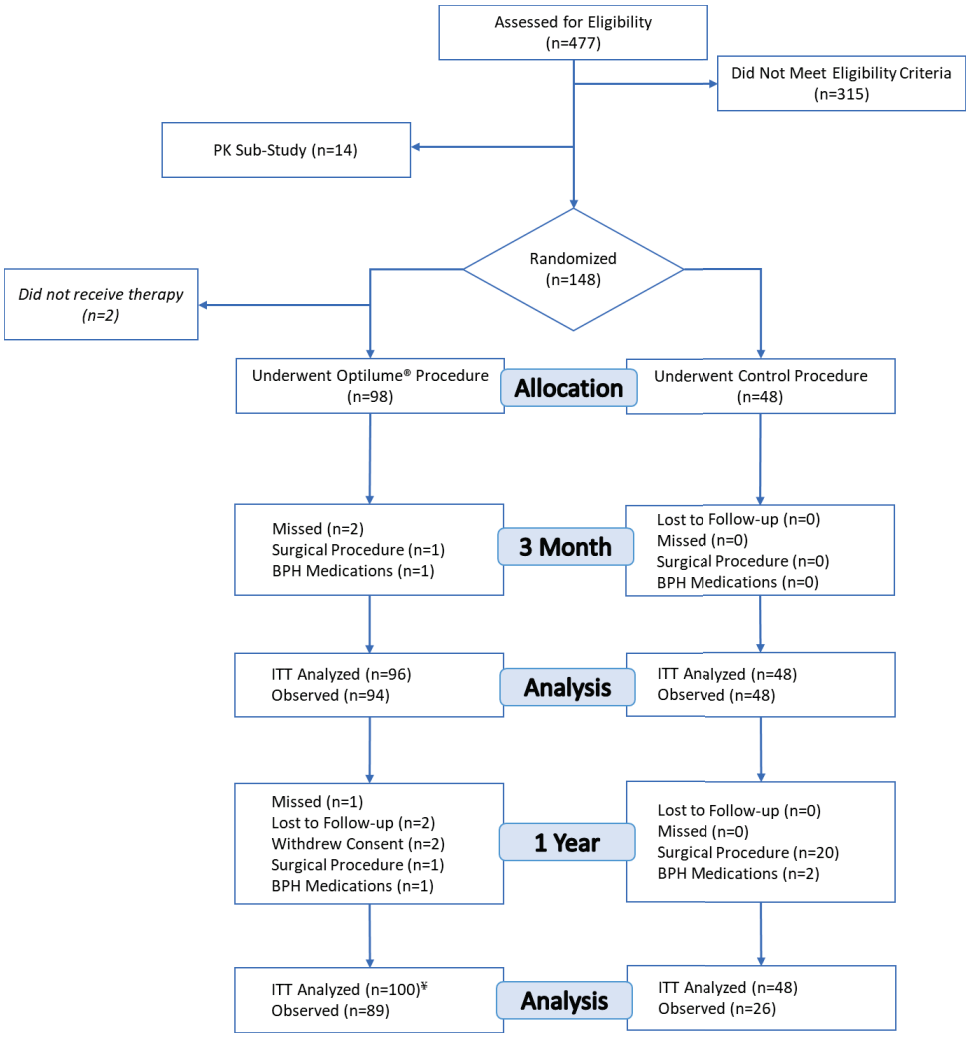
Withdrawals prior to the 12-month visit included 10 subjects randomized to the Optilume BPH arm (2 withdrew prior to receiving the study treatment, 2 lost to follow-up, 2 withdrew consent, 2 underwent a BPH surgical procedure, 2 initiated BPH medications) and 2 subjects randomized to the Sham arm (2 initiated BPH medications). Twenty subjects in the Sham arm crossed over to receive Optilume BPH prior to the 12-month visit.

Primary efficacy and secondary endpoint analyses were performed using the intent-to-treat (ITT) data set which included all randomized subjects. Safety analyses were performed using the as-treated (AT) data set based on the treatment received. The AT data set excludes two subjects who were randomized to the Optilume BPH arm but did not receive the study treatment.

Table 6. Visit Compliance for Randomized Cohort

Study Visit	Visit Compliance[1]	
	Optilume BPH (n=100)	Sham (n=48)
Participants who received study treatment	98.0% (98/100)	100.0% (48/48)
Participants who completed Foley Removal	100.0% (98/98)	100.0% (48/48)
Participants who completed 14 Day visit	98.0% (96/98)	97.9% (47/48)
Participants who completed 30 Day visit	99.0% (97/98)	100.0% (48/48)
Participants who completed 3 Month visit	97.9% (94/96)	100.0% (48/48)
Participants who completed 6 Month visit	97.9% (91/94)	97.2% (35/36)
Participants who completed 12 Month visit	98.9% (89/90)	100.0% (26/26)

[1] Denominator represents the number of subjects eligible for a visit, while the numerator represents the number of visits completed. Subjects that are withdrawn from the study prior to the visit window opening are excluded from the denominator.



¥ For the primary endpoint intent-to-treat (ITT) analysis, subjects receiving alternative BPH therapy were imputed as having no improvement, while endpoint status for subjects with missing data were imputed via multiple imputation.

Figure 3. Subject Accountability Diagram for Randomized Cohort

C. Study Population Demographics and Baseline Parameters

The demographics of the study population are typical for a BPH study performed in the US.

Demographics, baseline genitourinary medical history, and baseline prostate characteristics were well matched between groups.

Table 7. Demographics and Genitourinary Medical History

Characteristic	Optilume BPH (N=100)	Sham (N=48)	P-Value[1]
Demographics			
Age	64.5 ± 6.4 (98)	65.5 ± 5.6 (47)	0.3769
Race			
American Indian or Alaska Native	0.0% (0/100)	0.0% (0/48)	0.1877
Asian	2.0% (2/100)	0.0% (0/48)	
Black or African American	3.0% (3/100)	10.4% (5/48)	
Hawaiian or Pacific Islander	0.0% (0/100)	0.0% (0/48)	
White	94.0% (94/100)	89.6% (43/48)	
Multi-Racial	1.0% (1/100)	0.0% (0/48)	
Ethnicity			
Hispanic or Latino	13.0% (13/100)	6.3% (3/48)	0.2157
Not Hispanic or Latino	87.0% (87/100)	93.8% (45/48)	
BMI	29.32 ± 4.45 (100)	29.06 ± 4.72 (48)	0.7420
Medical History			
Urinary Incontinence			
No	100.0% (100/100)	100.0% (48/48)	N/A
Yes	0.0% (0/100)	0.0% (0/48)	
LUTS			
Dysuria	16.0% (16/100)	16.7% (8/48)	0.9180
Frequency	91.0% (91/100)	100.0% (48/48)	0.0586
Hesitancy	73.0% (73/100)	79.2% (38/48)	0.4173
Incomplete Voiding	85.0% (85/100)	91.7% (44/48)	0.2564
Nocturia	91.0% (91/100)	95.8% (46/48)	0.3445
Poor Stream	89.0% (89/100)	91.7% (44/48)	0.7745
Terminal Dribbling	49.0% (49/100)	52.1% (25/48)	0.7254
Urgency	80.0% (80/100)	91.7% (44/48)	0.0715
Hematuria	6.0% (6/100)	2.1% (1/48)	0.4284
Retention	13.0% (13/100)	18.8% (9/48)	0.3573

Characteristic	Optilume BPH (N=100)	Sham (N=48)	P-Value[1]
Other Genitourinary History			
Kidney Stone	13.0% (13/100)	20.8% (10/48)	0.2182
Erectile Dysfunction	56.0% (56/100)	54.2% (26/48)	0.8336
Bladder Stone	3.0% (3/100)	0.0% (0/48)	0.5512
Urinary Tract Infection	6.0% (6/100)	4.2% (2/48)	0.7235
Bacterial Prostatitis	5.0% (5/100)	4.2% (2/48)	1.0000
Cystitis	2.0% (2/100)	0.0% (0/48)	0.5587
Other	34.0% (34/100)	29.2% (14/48)	0.5565
Prostate Specific Antigen (ng/mL)	2.42 ± 1.98 (100)	2.20 ± 1.82 (48)	0.5135
IPSS Score	23.4 ± 5.5 (100)	24.3 ± 5.8 (48)	0.3916
Qmax (mL/sec)	8.85 ± 2.17 (100)	8.95 ± 1.80 (48)	0.7888
Post-Void Residual Volume (mL)	84.1 ± 70.2 (99)	89.4 ± 73.9 (48)	0.6750

[1]Continuous variables tested with two-sample t-test and categorical variables tested with chi square test. When expected cell counts were < 5, then an Exact Chi-Square test was used

Table 8. Baseline Prostate Characteristics

Prostate Characteristics	Optilume BPH (N=100)	Sham (N=48)	P-Value[1]
Prostate Width (mm)	48.90 ± 6.72 (100)	49.99 ± 5.05 (48)	0.2754
Prostate Height (mm)	37.07 ± 7.52 (100)	36.18 ± 7.14 (48)	0.4976
Prostate Length (mm)	46.62 ± 6.33 (100)	46.46 ± 5.39 (48)	0.8791
Prostate Volume (mL)	44.88 ± 14.53 (100)	45.00 ± 13.16 (48)	0.9633
Intravesical Prostatic Protrusion	28.0% (28/100)	33.3% (16/48)	0.5064
IPP Size (mm)	5.07 ± 2.19 (28)	5.31 ± 1.54 (15)	0.7059

[1] Continuous variables tested with two-sample t-test and categorical variables tested with chi-square test.

D. Safety and Effectiveness Results

1. Safety Results

   The analysis of safety was based on the ITT cohort of 148 patients (48 sham subjects and 100 Optilume BPH subjects) available for the 12 month evaluation.

The key safety outcomes for this study are presented below in Table 9. Adverse effects are reported in Tables 10 to 12.

Primary Safety Endpoint

The primary safety endpoint was defined as the proportion of subjects experiencing a composite of major device-related serious complications through 12 months post-procedure. No subjects experienced an event qualifying for the pre-defined composite of serious device-related complications through 12 months post-procedure as adjudicated by the CEC.

Table 9. Primary Safety Endpoint

Endpoint	Sham Arm (N=48)	Optilume BPH (N=100)	Difference (95% CI)
Major device-related complications at 12 months post-treatment	0.0% (0/48)	0.0% (0/100)	0.0% (0.0%, 0.0%)

Adverse effects that occurred in the PMA clinical study:

A total of 299 adverse events (AEs) were reported in 111 subjects (75.0%), including 18 serious adverse events (SAEs).

Table 10. Summary of Adverse Events

	Optilume BPH (N=98)		Sham (N=48)	
Event Types	Events	Participant % (n/N)	Events	Participant % (n/N)
Adverse Events	241	82.7% (81/98)	58	62.5% (30/48)
Serious Adverse Events	15	13.3% (3/98)	3	6.3% (3/48)
Treatment Related AEs	143	71.4% (70/98)	15	25.0% (12/48)
Device Related AE	121	67.3% (66/98)	11	16.7% (8/48)
Procedure Related AE	22	18.4% (18/98)	4	8.3% (4/48)
Treatment Related SAE	6	6.1% (6/98)	0	0% (0/0)
Device Related SAE	5	5.1% (5/98)	0	0% (0/0)
Procedure Related SAE	1	1.0% (1/98)	0	0% (0/0)

Serious Adverse Events

Serious adverse event rates by MedDRA system organ class (SOC) and Common Terminology Criteria for Adverse Events (CTCAE) term are shown in Table 11. A total of 18 SAEs were reported in the study, including 15 in the Optilume BPH arm and 3 in the Control arm. Five SAEs were classified as related to the study device: 4 post-procedure hematuria events which resolved without sequelae and

one urethral false passage requiring extended catheterization. One event of bladder perforation was adjudicated as related to the study procedure but not related to the study device. No unanticipated adverse device effects (UADEs) occurred.

Table 11. Serious Adverse Events

System Organ Class/ CTC Term	Optilume BPH (N=98)				Sham (N=48)			
	Grade 1-2		Grade 3+		Grade 1-2		Grade 3+	
	Events	Participant % (n/N)	Events	Participant % (n/N)	Events	Participant % (n/N)	Events	Participant % (n/N)
Cardiac Disorders	**1**	**1.0% (1/98)**	**2**	**2.0% (2/98)**	**2**	**4.2% (2/48)**	**0**	**0.0% (0/48)**
Atrial fibrillation	1	1.0% (1/98)	0	0.0% (0/98)	0	0.0% (0/48)	0	0.0% (0/48)
Atrial flutter	0	0.0% (0/98)	0	0.0% (0/98)	1	2.1% (1/48)	0	0.0% (0/48)
Cardiogenic shock	0	0.0% (0/98)	1	1.0% (1/98)	0	0.0% (0/48)	0	0.0% (0/48)
Chest pain - cardiac	0	0.0% (0/98)	0	0.0% (0/98)	1	2.1% (1/48)	0	0.0% (0/48)
Myocardial infarction	0	0.0% (0/98)	1	1.0% (1/98)	0	0.0% (0/48)	0	0.0% (0/48)
Gastric And Gastroenteric Infections	**1**	**1.0% (1/98)**	**0**	**0.0% (0/98)**	**0**	**0.0% (0/48)**	**0**	**0.0% (0/48)**
Gastroenteritis	1	1.0% (1/98)	0	0.0% (0/98)	0	0.0% (0/48)	0	0.0% (0/48)
General Disorders And Administration Site Conditions	**1**	**1.0% (1/98)**	**0**	**0.0% (0/98)**	**0**	**0.0% (0/48)**	**0**	**0.0% (0/48)**
Chest pain (non-cardiac)	1	1.0% (1/98)	0	0.0% (0/98)	0	0.0% (0/48)	0	0.0% (0/48)
Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)	**0**	**0.0% (0/98)**	**1**	**1.0% (1/98)**	**0**	**0.0% (0/48)**	**0**	**0.0% (0/48)**

System Organ Class/ CTC Term	Optilume BPH (N=98)				Sham (N=48)			
	Grade 1-2		Grade 3+		Grade 1-2		Grade 3+	
	Events	Participant % (n/N)	Events	Participant % (n/N)	Events	Participant % (n/N)	Events	Participant % (n/N)
Multiple myeloma	0	0.0% (0/98)	1	1.0% (1/98)	0	0.0% (0/48)	0	0.0% (0/48)
Nervous System Disorders	**0**	**0.0% (0/98)**	**1**	**1.0% (1/98)**	**0**	**0.0% (0/48)**	**0**	**0.0% (0/48)**
Cervical radiculopathy	0	0.0% (0/98)	1	1.0% (1/98)	0	0.0% (0/48)	0	0.0% (0/48)
Psychiatric Disorders	**1**	**1.0% (1/98)**	**0**	**0.0% (0/98)**	**0**	**0.0% (0/48)**	**0**	**0.0% (0/48)**
Suicidal depression	1	1.0% (1/98)	0	0.0% (0/98)	0	0.0% (0/48)	0	0.0% (0/48)
Renal And Urinary Disorders	**1**	**1.0% (1/98)**	**5**	**5.1% (5/98)**	**0**	**0.0% (0/48)**	**0**	**0.0% (0/48)**
Bladder perforation	0	0.0% (0/98)	1	1.0% (1/98)	0	0.0% (0/48)	0	0.0% (0/48)
Post procedural hematuria	0	0.0% (0/98)	4	4.1% (4/98)	0	0.0% (0/48)	0	0.0% (0/48)
Urethral false passage	1	1.0% (1/98)	0	0.0% (0/98)	0	0.0% (0/48)	0	0.0% (0/48)
Vascular Disorders	**0**	**0.0% (0/98)**	**1**	**1.0% (1/98)**	**0**	**0.0% (0/48)**	**1**	**2.1% (1/48)**
Atherosclerosis	0	0.0% (0/98)	0	0.0% (0/98)	0	0.0% (0/48)	1	2.1% (1/48)
Pulmonary embolism	0	0.0% (0/98)	1	1.0% (1/98)	0	0.0% (0/48)	0	0.0% (0/48)

Device/Procedure Related Adverse Events

A summary of events adjudicated by the CEC as related to the study device or procedure occurring in more than 5% of subjects is shown in Table 12 by CTCAE Grade. The most common treatment related adverse event experienced by subjects treated with the Optilume BPH Catheter System was hematuria and/or post-procedural hematuria with a total of 41 events occurring in 39 subjects (39.8%) with most events being mild or moderate in severity (37/41, 90.2%) and a median time to

resolution of 34 days. There were no life threatening (Grade 4) or fatal (Grade 5) events related to either the study device or procedure.

Table 12. Device/Procedure Related Adverse Events (As Treated)

System Organ Class/ CTC Term	Optilume BPH (N=98)				Sham (N=48)			
	Grade 1-2		Grade 3		Grade 1-2		Grade 3	
	Events	Participant % (n/N)	Events	Participant % (n/N)	Events	Participant % (n/N)	Events	Participant % (n/N)
Gastrointestinal Disorders	**0**	**0.0% (0/98)**	**0**	**0.0% (0/98)**	**1**	**2.1% (1/48)**	**0**	**0.0% (0/48)**
Abdominal pain	0	0.0% (0/98)	0	0.0% (0/98)	1	2.1% (1/48)	0	0.0% (0/48)
General Disorders And Administration Site Conditions	**0**	**0.0% (0/98)**	**0**	**0.0% (0/98)**	**1**	**2.1% (1/48)**	**0**	**0.0% (0/48)**
Fever	0	0.0% (0/98)	0	0.0% (0/98)	1	2.1% (1/48)	0	0.0% (0/48)
Infections And Infestations	**12**	**11.2% (11/98)**	**0**	**0.0% (0/98)**	**4**	**6.3% (3/48)**	**0**	**0.0% (0/48)**
Bladder infection	0	0.0% (0/98)	0	0.0% (0/98)	1	2.1% (1/48)	0	0.0% (0/48)
Urinary tract infection	12	11.2% (11/98)	0	0.0% (0/98)	3	4.2% (2/48)	0	0.0% (0/48)
Injury, Poisoning And Procedural Complications	**0**	**0.0% (0/98)**	**0**	**0.0% (0/98)**	**0**	**0.0% (0/48)**	**0**	**0.0% (0/48)**
Investigations	**2**	**2.0% (2/98)**	**0**	**0.0% (0/98)**	**0**	**0.0% (0/48)**	**0**	**0.0% (0/48)**
Elevated prostate specific antigen [PSA]	2	2.0% (2/98)	0	0.0% (0/98)	0	0.0% (0/48)	0	0.0% (0/48)
Musculoskeletal And Connective Tissue Disorders	**2**	**1.0% (1/98)**	**0**	**0.0% (0/98)**	**0**	**0.0% (0/48)**	**0**	**0.0% (0/48)**
Groin pain	1	1.0% (1/98)	0	0.0% (0/98)	0	0.0% (0/48)	0	0.0% (0/48)

System Organ Class/ CTC Term	Optilume BPH (N=98)				Sham (N=48)			
	Grade 1-2		Grade 3		Grade 1-2		Grade 3	
	Events	Participant % (n/N)	Events	Participant % (n/N)	Events	Participant % (n/N)	Events	Participant % (n/N)
Low back pain	1	1.0% (1/98)	0	0.0% (0/98)	0	0.0% (0/48)	0	0.0% (0/48)
Product Issues	**1**	**1.0% (1/98)**	**0**	**0.0% (0/98)**	**0**	**0.0% (0/48)**	**0**	**0.0% (0/48)**
Catheter blockage	1	1.0% (1/98)	0	0.0% (0/98)	0	0.0% (0/48)	0	0.0% (0/48)
Renal And Urinary Disorders	**99**	**65.3% (64/98)**	**5**	**5.1% (5/98)**	**7**	**12.5% (6/48)**	**0**	**0.0% (0/48)**
Bladder cancer	0	0.0% (0/98)	0	0.0% (0/98)	1	2.1% (1/48)	0	0.0% (0/48)
Bladder perforation	0	0.0% (0/98)	1	1.0% (1/98)	0	0.0% (0/48)	0	0.0% (0/48)
Bladder spasm	6	6.1% (6/98)	0	0.0% (0/98)	0	0.0% (0/48)	0	0.0% (0/48)
Dysuria	8	8.2% (8/98)	0	0.0% (0/98)	1	2.1% (1/48)	0	0.0% (0/48)
Frequency of micturition	3	3.1% (3/98)	0	0.0% (0/98)	1	2.1% (1/48)	0	0.0% (0/48)
Hematuria	11	10.2% (10/98)	0	0.0% (0/98)	1	2.1% (1/48)	0	0.0% (0/48)
Leukocyturia	1	1.0% (1/98)	0	0.0% (0/98)	0	0.0% (0/48)	0	0.0% (0/48)
Lower urinary tract symptoms	5	4.1% (4/98)	0	0.0% (0/98)	0	0.0% (0/48)	0	0.0% (0/48)
Meatal stenosis	1	1.0% (1/98)	0	0.0% (0/98)	1	2.1% (1/48)	0	0.0% (0/48)
Nocturia	3	3.1% (3/98)	0	0.0% (0/98)	0	0.0% (0/48)	0	0.0% (0/48)
Overactive bladder	2	2.0% (2/98)	0	0.0% (0/98)	0	0.0% (0/48)	0	0.0% (0/48)

System Organ Class/ CTC Term	Optilume BPH (N=98)				Sham (N=48)			
	Grade 1-2		Grade 3		Grade 1-2		Grade 3	
	Events	Participant % (n/N)	Events	Participant % (n/N)	Events	Participant % (n/N)	Events	Participant % (n/N)
Post micturition dribble	1	1.0% (1/98)	0	0.0% (0/98)	0	0.0% (0/48)	0	0.0% (0/48)
Post procedural hematuria	26	25.5% (25/98)	4	4.1% (4/98)	0	0.0% (0/48)	0	0.0% (0/48)
Stress urinary incontinence	7	7.1% (7/98)	0	0.0% (0/98)	0	0.0% (0/48)	0	0.0% (0/48)
Urethral false passage	1	1.0% (1/98)	0	0.0% (0/98)	0	0.0% (0/48)	0	0.0% (0/48)
Urethral pain	2	2.0% (2/98)	0	0.0% (0/98)	0	0.0% (0/48)	0	0.0% (0/48)
Urethral stricture	4	4.1% (4/98)	0	0.0% (0/98)	1	2.1% (1/48)	0	0.0% (0/48)
Urethritis	1	1.0% (1/98)	0	0.0% (0/98)	0	0.0% (0/48)	0	0.0% (0/48)
Urinary incontinence (U*rge/Mixed)*	5	5.1% (5/98)	0	0.0% (0/98)	1	2.1% (1/48)	0	0.0% (0/48)
Urinary retention	3	3.1% (3/98)	0	0.0% (0/98)	0	0.0% (0/48)	0	0.0% (0/48)
Urinary urgency	6	6.1% (6/98)	0	0.0% (0/98)	0	0.0% (0/48)	0	0.0% (0/48)
Voiding difficulty	3	2.0% (2/98)	0	0.0% (0/98)	0	0.0% (0/48)	0	0.0% (0/48)
Reproductive System And Breast Disorders	**21**	**15.3% (15/98)**	**0**	**0.0% (0/98)**	**2**	**4.2% (2/48)**	**0**	**0.0% (0/48)**
Anejaculation	1	1.0% (1/98)	0	0.0% (0/98)	0	0.0% (0/48)	0	0.0% (0/48)
Ejaculation decreased	1	1.0% (1/98)	0	0.0% (0/98)	1	2.1% (1/48)	0	0.0% (0/48)
Epididymitis	0	0.0% (0/98)	0	0.0% (0/98)	1	2.1% (1/48)	0	0.0% (0/48)

System Organ Class/ CTC Term	Optilume BPH (N=98)				Sham (N=48)			
	Grade 1-2		Grade 3		Grade 1-2		Grade 3	
	Events	Participant % (n/N)	Events	Participant % (n/N)	Events	Participant % (n/N)	Events	Participant % (n/N)
Hematospermia	4	4.1% (4/98)	0	0.0% (0/98)	0	0.0% (0/48)	0	0.0% (0/48)
Painful ejaculation	1	1.0% (1/98)	0	0.0% (0/98)	0	0.0% (0/48)	0	0.0% (0/48)
Painful orgasm	1	1.0% (1/98)	0	0.0% (0/98)	0	0.0% (0/48)	0	0.0% (0/48)
Pelvic pain	6	5.1% (5/98)	0	0.0% (0/98)	0	0.0% (0/48)	0	0.0% (0/48)
Penile pain	1	1.0% (1/98)	0	0.0% (0/98)	0	0.0% (0/48)	0	0.0% (0/48)
Perineal pain	3	3.1% (3/98)	0	0.0% (0/98)	0	0.0% (0/48)	0	0.0% (0/48)
Prostatitis	1	1.0% (1/98)	0	0.0% (0/98)	0	0.0% (0/48)	0	0.0% (0/48)
Retrograde ejaculation	2	2.0% (2/98)	0	0.0% (0/98)	0	0.0% (0/48)	0	0.0% (0/48)
Respiratory, Thoracic And Mediastinal Disorders	**1**	**1.0% (1/98)**	**0**	**0.0% (0/98)**	**0**	**0.0% (0/48)**	**0**	**0.0% (0/48)**
Aspiration pneumonia	1	1.0% (1/98)	0	0.0% (0/98)	0	0.0% (0/48)	0	0.0% (0/48)

2. Effectiveness Results

The analysis of effectiveness was based on the 148 evaluable patients (48 sham subjects at 3 months and 100 Optilume BPH subjects at 12 months). Key effectiveness outcomes are presented in Tables 13 to 28.

Primary Efficacy Endpoint

The primary efficacy endpoint was a comparison of the improvement in IPSS at 3 months for the Control group to the improvement in IPSS at 12 months for the Optilume BPH group. The endpoint incorporated a super-superiority margin of 25% for the sham effect at 3 months.

Subjects undergoing alternative therapy for ongoing/recurrent LUTS prior to the scheduled timepoint were imputed as having no change from baseline. Missing data were accounted for using multiple imputation.

Incorporating the 25% super superiority margin, the imputed difference between arms was +1.4 (p=0.178). The improvement in IPSS for the Optilume BPH arm at 12 months did not reach statistical significance with a 25% super-superiority margin when compared to the improvement in the Sham arm at 3 months (Table 13).

Table 12. Primary Efficacy Endpoint – Improvement in IPSS (ITT, Multiple Imputation)

Variable	Sham Arm (3 Months)	Optilume BPH (12 Months)	Difference [95%CI]
Improvement in IPSS Mean [95%CI]	8.0 [5.8, 10.3]	11.5 [9.7, 13.2]	3.4 [0.6, 6.2]
Improvement in IPSS *(w/25% Margin)* Mean [95%CI]	10.0 [7.5, 12.5]		1.4 [-1.6, 4.5]

A post-hoc analysis was performed comparing the improvement in IPSS at 12 months for the Optilume BPH group to the improvement of a historical sham control at 3 months based on a systematic review of the literature of sham endoscopic procedures in randomized trials for BPH. A total of 8 studies were included in the analysis and used to generate the pooled sham effect (weighted average) across studies.[1-8] Four studies reported a paired change in IPSS from baseline to 3 months. [3,4,6,7] Comparing the improvement in IPSS against the pooled sham effect from the literature as a performance goal shows a benefit for Optilume BPH both with and without a 25% super-superiority margin (Table 14). A similar outcome is seen when utilizing only those publications reporting paired change scores.

Table 13. Comparison of Literature Sham Improvement in IPSS at 3 Months to Optilume BPH at 12 Months

Variable	Literature Sham (3 Months)	Optilume BPH (12 Months)
Composite Literature Outcomes	5.9 (n=401)	11.5 ± 7.8 (n=94)
Composite Literature Outcomes (w/ 25% Super Superiority Margin)	7.4 (n=401)	
Composite Literature Outcomes (paired)	5.6 ± 8.0 (n=215)	

Variable	Literature Sham (3 Months)	Optilume BPH (12 Months)
Composite Literature Outcomes (paired, w/ 25% Super Superiority Margin)	7.0 ± 10.0 (n=215)	
Optilume BPH mean improvement utilizing 'Retreatments Imputed' methodology, where those receiving alternative treatment are imputed as having no improvement.		

Secondary Endpoints

Hypotheses for the secondary endpoints were not formally tested because the study failed to meet its primary effectiveness endpoint.

Average IPSS Improvement in Optilume BPH Arm at 12 Months

The average percent improvement in IPSS from baseline to 12 months was compared against a performance goal of 30%. Subjects undergoing alternative therapy for ongoing/recurrent LUTS prior to the scheduled timepoint were considered as having no improvement. The average improvement from baseline to 12 months for the Optilume BPH arm was 49%, which is greater than the target 30% threshold.

Table 15. Secondary Endpoint 1 – Average IPSS Improvement at 12 Months

Endpoint	Optilume BPH
% Change in IPSS Mean ± SE [95% CI]	 49.1% ± 3.2% [42.7%, 55.4%]

Responder Rate at 3 Months (Optilume BPH) vs 3 Months (Sham)

The rate of responders at 3 months in the Optilume BPH arm was compared to the rate of responders at 3 months in the Sham arm. A responder is defined as a subject who has an IPSS improvement of ≥ 30% at the listed timepoint compared to baseline. Subjects undergoing alternative therapy for ongoing/recurrent LUTS prior to the scheduled timepoint were considered as having no improvement in the analysis. The responder rate at 3 months was higher in the Optilume BPH arm than in the Sham arm (68.8% vs 52.1%).

Table 16. Secondary Endpoint 2 – Responder Rate at 3 Months

Endpoint	Sham	Optilume BPH
Responder Rate (≥30%) [95% CI]	52.1% (25/48) [37.2%, 66.7%]	68.8% (66/96) [58.5%, 77.8%]

Endpoint	Sham	Optilume BPH
N=4 patients excluded from analysis due to missing values.		

Responder Rate at 12 Months (Optilume BPH) vs 3 Months (Sham)

The rate of responders at 12 months in the Optilume BPH arm was compared to the rate of responders at 3 months in the Sham arm. A responder is defined as a subject who has an IPSS improvement of ≥ 30% at the listed timepoint compared to baseline. Subjects undergoing alternative therapy for ongoing/recurrent LUTS prior to the scheduled timepoint were considered as having no improvement in the analysis. The responder rate at 12 months in the Optilume BPH arm was higher than the responder rate at 3 months in the Sham arm (76.6% vs 52.1%).

Table 17. Secondary Endpoint 3 – Responder Rate at 12 Months

Endpoint	Sham (3 months)	Optilume BPH (12 months)
Responder Rate (≥30%) [95% CI]	52.1% (25/48) [37.2%, 66.7%]	76.6% (72/94) [66.7%, 84.7%]
N=6 patients excluded from analysis due to missing values.		

Change in Qmax

The change in Qmax at 12 months in the Optilume BPH arm was compared to the change in Qmax at 3 months in the Sham arm. Subjects opting to receive alternative therapy or withdrawing due to perceived lack of effectiveness were considered as having no improvement. The Optilume BPH arm showed a higher increase in Qmax at 12 months when compared to the increase in Qmax in the Sham arm at 3 months.

Table 18. Secondary Endpoint 4 – Change in Qmax

Variable	Optilume BPH – 12 Months (n=87)	Sham – 3 Months (n=43)	Point Estimate of Difference [95%CI]
Change in Qmax (Mean ± SD, [95% CI])	9.7 ± 10.14 [7.5, 11.8]	5.5 ± 7.44 [3.2, 7.8]	-4.2 [-7.6, -0.8]
Uroflows with a voided volume <150mL were excluded from this analysis.			

Ancillary Endpoints

A1: Additional responder analyses with a responder defined as IPSS improvement of 35%, 40% and 50%

The change in IPSS for both arms is presented using a Retreatments Imputed analysis which carries forward baseline values for subjects considered treatment failures (Table 19). The proportion of subjects with at least 35%, 40% and 50% improvement in IPSS is higher in the Optilume BPH arm compared to the Sham arm at all timepoints evaluated (Table 20).

Table 19. Change in IPSS Over Time (Retreatments Imputed)

Group	Baseline	14 Day	30 Day	3 Month	6 Month	12 Month
Optilume BPH (N=100)						
n	100	87	97	96	94	94
Mean ± SD	23.4 ± 5.5	15.7 ± 8.9	13.4 ± 7.0	13.0 ± 7.6	12.8 ± 7.8	11.8 ± 7.6
Median	23.0	14.0	13.0	12.0	12.5	10.0
Min, Max	13, 34	1, 35	1, 35	0, 32	1, 33	0, 32
Sham (N=48)						
n	48	47	48	48	47	48
Mean ± SD	24.3 ± 5.8	15.1 ± 7.6	15.0 ± 8.0	16.2 ± 8.9	18.1 ± 7.8	19.5 ± 9.2
Median	25.5	13.0	13.0	15.0	18.0	21.0
Min, Max	12, 34	3, 33	2, 33	4, 34	5, 32	4, 34

Table 14. Responder Rate Based on IPSS Improvement of 35%, 40% and 50%

Visit	Improvement of percentage in IPSS (%)					
	≥35%		≥40%		≥50%	
	Optilume BPH	Sham	Optilume BPH	Sham	Optilume BPH	Sham
30 Day						
% (n/N)	63.9% (62/97)	54.2% (26/48)	59.8% (58/97)	52.1% (25/48)	43.3% (42/97)	37.5% (18/48)
95% CI[1]	53.5%, 73.4%	39.2%, 68.6%	49.3%, 69.6%	37.2%, 66.7%	33.3%, 53.7%	24.0%, 52.6%
3 Month						
% (n/N)	66.7% (64/96)	50.0% (24/48)	61.5% (59/96)	45.8% (22/48)	47.9% (46/96)	39.6% (19/48)
95% CI[1]	56.3%, 76.0%	35.2%, 64.8%	51.0%, 71.2%	31.4%, 60.8%	37.6%, 58.4%	25.8%, 54.7%

Visit	Improvement of percentage in IPSS (%)					
	≥35%		≥40%		≥50%	
	Optilume BPH	Sham	Optilume BPH	Sham	Optilume BPH	Sham
6 Month % (n/N) 95% CI[1]	68.1% (64/94) 57.7%, 77.3%	36.2% (17/47) 22.7%, 51.5%	60.6% (57/94) 50.0%, 70.6%	31.9% (15/47) 19.1%, 47.1%	45.7% (43/94) 35.4%, 56.3%	25.5% (12/47) 13.9%, 40.3%
12 Month % (n/N) 95% CI[1]	71.3% (67/94) 61.0%, 80.1%	31.3% (15/48) 18.7%, 46.3%	69.1% (65/94) 58.8%, 78.3%	27.1% (13/48) 15.3%, 41.8%	59.6% (56/94) 49.0%, 69.6%	22.9% (11/48) 12.0%, 37.3%
Note: Timepoints after study exit due to treatment failure or crossover to treatment are imputed a s failures [1]Confidence intervals (CI) are estimated using the Clopper-Pearson (exact) approach.						

A2 and A8: Change in PVR Urine Volume and Qmax

Table 15. Change in Qmax and PVR Over Time (Retreatments Imputed)

Measure	Group	Baseline	30 Day	3 Month	6 Month	12 Month
QMax (mL/sec)	Optilume BPH (N=100)					
	n	98	79	81	86	87
	Mean ± SD	8.9 ± 2.2	17.6 ± 9.0	18.6 ± 9.7	16.9 ± 8.9	18.5 ± 10.2
	Median	8.9	16.8	17.2	14.7	17.0
	Min, Max	5, 12	4, 49	4, 66	5, 59	5, 60
	Sham (N=48)					
	n	48	43	43	43	48
	Mean ± SD	8.9 ± 1.8	13.2 ± 6.3	14.5 ± 7.8	13.2 ± 6.8	12.1 ± 6.5
	Median	9.0	11.5	13.0	10.9	10.0
	Min, Max	6, 12	5, 32	5, 42	6, 38	6, 38

Measure	Group	Baseline	30 Day	3 Month	6 Month	12 Month
PVR (mL)	Optilume BPH (N=100)	99	92	91	90	90
	n	84.1 ± 70.2	60.5 ± 54.4	69.5 ± 68.6	61.4 ± 58.8	59.5 ± 52.6
	Mean ± SD	69.0	47.5	55.0	45.0	42.5
	Median	0, 298	0, 248	0, 435	0, 313	0, 202
	Min, Max					
	Sham (N=48)					
	n	48	46	48	47	47
	Mean ± SD	89.4 ± 73.9	91.8 ± 81.6	98.4 ± 102.4	96.9 ± 103.8	93.4 ± 98.0
	Median	66.0	76.5	57.0	56.0	69.0
	Min, Max	0, 284	0, 348	0, 385	10, 534	0, 500
Voided volumes < 150 mL are excluded from the Qmax analysis.						

A3: Change in sexual function (IIEF, MSHQ-EjD)

Table 16. IIEF Over Time (As Observed)

Measure	Group	Baseline	3 Month	6 Month	12 Month
Erectile Function	Optilume BPH (N=98)	97	92	91	87
	n	15.6 ± 10.3	16.5 ± 10.8	17.3 ± 11.0	17.1 ± 11.1
	Mean ± SD	15.0	16.5	19.0	16.0
	Median	1, 30	1, 30	1, 30	1, 30
	Min, Max				
	Sham (N=48)				
	n	48	47	35	26
	Mean ± SD	16.8 ± 9.3	17.6 ± 9.8	19.8 ± 8.7	20.1 ± 8.4
	Median	19.0	18.0	22.0	22.5
	Min, Max	1, 30	1, 30	1, 30	4, 30

Measure	Group	Baseline	3 Month	6 Month	12 Month
Intercourse Satisfaction	Optilume BPH (N=98)				
	n	98	92	91	88
	Mean ± SD	5.7 ± 5.0	5.8 ± 5.2	6.5 ± 5.4	6.4 ± 5.4
	Median	7.0	7.0	8.0	8.0
	Min, Max	0, 15	0, 14	0, 15	0, 15
	Sham (N=48)				
	n	48	47	35	26
	Mean ± SD	6.3 ± 4.9	6.9 ± 5.0	7.5 ± 4.5	8.3 ± 4.4
	Median	8.0	7.0	9.0	9.5
	Min, Max	0, 15	0, 15	0, 13	0, 14
Orgasmic Function	Optilume BPH (N=98)				
	n	98	92	91	88
	Mean ± SD	5.8 ± 3.8	5.6 ± 3.9	6.7 ± 3.9	6.3 ± 3.8
	Median	6.5	6.0	8.0	8.0
	Min, Max	0, 10	0, 10	0, 10	0, 10
	Sham (N=48)				
	n	48	47	35	26
	Mean ± SD	6.1 ± 3.5	6.3 ± 3.5	6.6 ± 2.9	7.3 ± 2.9
	Median	6.5	7.0	6.0	8.0
	Min, Max	0, 10	0, 10	0, 10	0, 10
Sexual Desire	Optilume BPH (N=98)				
	n	97	92	91	89
	Mean ± SD	6.3 ± 2.2	6.5 ± 2.1	6.6 ± 2.2	6.5 ± 2.2
	Median	6.0	7.0	7.0	7.0
	Min, Max	2, 10	2, 10	2, 10	2, 10
	Sham (N=48)				
	n	48	47	35	26
	Mean ± SD	6.4 ± 1.9	6.1 ± 1.8	6.3 ± 1.7	6.4 ± 2.0
	Median	7.0	6.0	6.0	6.5
	Min, Max	2, 10	2, 9	3, 10	2, 10

Measure	Group	Baseline	3 Month	6 Month	12 Month
Overall Satisfaction	Optilume BPH (N=98)				
	n	96	92	91	86
	Mean ± SD	5.6 ± 2.7	6.2 ± 2.8	6.3 ± 2.9	6.3 ± 2.9
	Median	6.0	6.0	6.0	6.0
	Min, Max	2, 10	2, 10	2, 10	2, 10
	Sham (N=48)				
	n	47	45	35	26
	Mean ± SD	5.4 ± 2.7	5.9 ± 2.8	6.4 ± 2.8	6.5 ± 2.8
	Median	5.0	6.0	6.0	6.5
	Min, Max	2, 10	2, 10	2, 10	2, 10
Note: A higher score indicates higher sexual function.					

Table 17. MSHQ-EjD Over Time (As Observed)

Measure	Group	Baseline	3 Month	6 Month	12 Month
Ejaculatory Function[1]	Optilume BPH (N=98)				
	n	98	86	87	87
	Mean ± SD	7.5 ± 3.9	8.5 ± 4.8	8.3 ± 4.5	8.4 ± 4.6
	Median	7.0	9.0	9.0	9.0
	Min, Max	1, 15	1, 15	1, 15	1, 15
	Sham (N=48)				
	n	47	47	35	26
	Mean ± SD	8.0 ± 3.4	8.8 ± 3.9	9.1 ± 3.4	9.9 ± 3.5
	Median	8.0	9.0	10.0	10.0
	Min, Max	1, 15	1, 15	1, 15	4, 15
Ejaculation Bother[2]	Optilume BPH (N=98)				
	n	98	86	87	87
	Mean ± SD	2.5 ± 1.7	1.9 ± 1.6	2.1 ± 1.7	2.0 ± 1.7
	Median	3.0	2.0	2.0	2.0
	Min, Max	0, 5	0, 5	0, 5	0, 5

Measure	Group	Baseline	3 Month	6 Month	12 Month
	Sham (N=48)				
	n	47	47	35	26
	Mean ± SD	2.2 ± 1.7	2.0 ± 1.5	2.1 ± 1.6	2.0 ± 1.8
	Median	2.0	2.0	2.0	1.5
	Min, Max	0, 5	0, 5	0, 5	0, 5
[1]Higher score = Less ejaculation dysfunction (Possible Range 1 - 15) [2]Higher score = Greater bother with ejaculation difficulties (Possible Range 0 - 5)					

A4. Change in BPH-II

Table 18. BPH Impact Index Over Time (As Observed)

Group	Baseline	30 Day	3 Month	6 Month	12 Month
Optilume BPH (N=98)					
n	98	96	93	91	89
Mean ± SD	7.0 ± 2.9	5.3 ± 3.2	4.5 ± 3.2	2.9 ± 2.8	2.3 ± 2.5
Median	7.0	5.0	4.0	2.0	2.0
Min, Max	1, 12	0, 13	0, 12	0, 12	0, 11
Sham (N=48)					
n	48	48	48	35	26
Mean ± SD	7.0 ± 3.0	3.8 ± 3.1	3.9 ± 3.5	3.6 ± 2.7	3.4 ± 3.1
Median	7.0	3.0	3.0	4.0	3.0
Min, Max	0, 12	0, 13	0, 12	0, 9	0, 12

A5: Change in EQ-5D

Table 19. EQ-5D Composite Over Time (As Observed)

Measure	Baseline	30 Day	3 Month	6 Month	12 Month
Optilume BPH (N=98)					
n	98	96	93	90	88
Mean ± SD	0.865 ± 0.123	0.866 ± 0.116	0.875 ± 0.120	0.888 ± 0.132	0.878 ± 0.132
Median	0.861	0.861	0.861	0.876	0.876
Min, Max	0.49, 1.00	0.39, 1.00	0.38, 1.00	0.46, 1.00	0.46, 1.00

Measure	Baseline	30 Day	3 Month	6 Month	12 Month
Sham (N=48)					
n	48	47	47	35	26
Mean ± SD	0.854 ± 0.108	0.900 ± 0.106	0.893 ± 0.101	0.886 ± 0.096	0.887 ± 0.099
Median	0.854	0.876	0.876	0.861	0.861
Min, Max	0.51, 1.00	0.49, 1.00	0.62, 1.00	0.72, 1.00	0.72, 1.00

Table 20. EQ-5D VAS Over Time (As Observed)

Measure	Baseline	30 Day	3 Month	6 Month	12 Month
Optilume BPH (N=98)					
n	98	96	93	90	88
Mean ± SD	81.6 ± 14.4	82.6 ± 13.9	85.8 ± 11.4	84.6 ± 14.0	86.5 ± 10.0
Median	85.0	87.5	90.0	89.0	89.0
Min, Max	25, 100	40, 100	40, 100	10, 100	45, 100
Sham (N=48)					
n	48	47	47	35	26
Mean ± SD	78.9 ± 13.7	83.5 ± 11.0	83.1 ± 10.4	82.8 ± 7.9	84.3 ± 8.9
Median	80.0	85.0	85.0	85.0	85.0
Min, Max	30, 100	50, 100	50, 100	70, 95	57, 100

A6: Change in pain score

Table 21. Peri-operative VAS Pain Scores (As Observed)

Group	Baseline	Procedure	Foley Removal	14 Day	30 Day	3 Month
Optilume BPH (N=98)						
n	98	97	96	95	97	94
Mean ± SD	1.2 ± 2.0	4.1 ± 2.3	2.4 ± 2.2	1.6 ± 1.9	1.4 ± 1.8	1.1 ± 1.6
Median	0.0	4.0	2.0	1.0	1.0	0.0
Min, Max	0, 8	0, 10	0, 10	0, 9	0, 8	0, 6
Sham (N=48)						
n	48	48	48	47	48	48
Mean ± SD	1.3 ± 2.0	2.6 ± 1.9	2.8 ± 2.5	0.9 ± 1.6	0.6 ± 1.3	0.9 ± 1.6
Median	0.0	3.0	2.0	0.0	0.0	0.0
Min, Max	0, 7	0, 7	0, 8	0, 8	0, 6	0, 8

A7: Procedure parameters

Procedures were performed in an ambulatory surgical center (81.5%) or office-based location (18.5%). The average (SD) time for the Optilume BPH procedure from cystoscope insertion to removal of the treatment device was 26.0 (8.2) minutes (n=98).

A9: Proportion of subjects experiencing a return to 'normal' symptom severity (IPSS<8)

Approximately one-third of subjects (30.9%, 29/94) treated with the Optilume BPH Catheter System returned to 'normal' symptom levels by 12 months post-treatment compared to 14.6% (7/48) in the Control group.

Table 22. Proportion of Subjects with IPSS<8

Visit	Proportion of Subjects with IPSS <8	
	Optilume BPH	Sham
3 Month		
% (n/N)	25.0% (24/96)	20.8% (10/48)
95% CI[1]	16.7%, 34.9%	10.5%, 35.0%

Visit	Proportion of Subjects with IPSS <8	
	Optilume BPH	Sham
6 Month % (n/N) 95% CI[1]	 29.8% (28/94) 20.8%, 40.1%	 8.5% (4/47) 2.4%, 20.4%
12 Month % (n/N) 95% CI[1]	 30.9% (29/94) 21.7%, 41.2%	 14.6% (7/48) 6.1%, 27.8%
Note: Timepoints after study exit due to treatment failure or crossover to treatment are imputed as failures [1]Confidence intervals (CI) are estimated using the Clopper-Pearson (exact) approach.		

3. Subgroup Analyses

Crossover Cohort

Baseline prostate characteristics for the Crossover cohort were generally similar to the randomized cohort, with a slightly higher average prostate size (mean 45.90g vs 44.88g in Optilume BPH arm) and a slightly higher proportion of subjects with an IPP (36.0% vs 28.0%). Results for secondary and ancillary endpoints (IPSS, Qmax and PVR) were consistent with the randomized cohort. There was a 40.7% average improvement in IPSS from baseline to 12 months in the Crossover cohort.

Pharmacokinetic Sub-Study

A sub-study including 15 non-randomized subjects was conducted to determine the pharmacokinetic profile of paclitaxel in blood (plasma), urine, and semen after treatment with the Optilume BPH Catheter System. Plasma paclitaxel concentration was evaluated immediately after the procedure, at 1, 3, and 5 hours, and at Foley removal, 30 days, 3 months, and 6 months post-procedure. Urine paclitaxel concentration was evaluated immediately post-procedure, at Foley removal, and at 30 days, 3 months, and 6 months. Semen paclitaxel concentration was evaluated at 30 days, 3 months, and 6 months post-procedure.

A summary of pharmacokinetic parameters, including maximum concentration (C_{max}) and time to maximum concentration (T_{max}) for plasma is shown in Table 23. On average, paclitaxel concentration in plasma fell below the limit of quantitation of the method (0.10 ng/mL or 0.1 part per billion) by the time of Foley removal, while average paclitaxel concentration in urine approached the limit of quantitation by 6 months. Analysis of paclitaxel concentration in semen showed low but persistent levels of paclitaxel in semen through 6 months post-

treatment. Of the 3 subjects with evaluable semen data at 12 months, one had detectable paclitaxel concentration (0.16 ng/mL).

Table 29. Summary of Plasma Pharmacokinetic Parameters

Parameter	Plasma
C_{max} (ng/mL)	
n	15
Mean	0.40 ± 0.54
Min, Max	<0.10, 2.24
T_{max} (hr)	
n	15
Median	1.0 ± 1.71
Min, Max	0.25, 5

Table 23. Paclitaxel Concentration Over Time in Urine

Measure	Baseline	0hr	Foley Removal	30 Days	3 Months	6 Months
Mean ± SD	<0.1 ± 0.0	1,892.8 ± 4,530.6	134.6 ± 221.9	1.3 ± 1.5	0.4 ± 0.7	0.1 ± 0.2
Median	<0.1	536.5	65.1	0.7	0.2	<0.1
Max, Min	<0.1	17,500, 64.4	841, 3.6	5.5, <0.1	2.8, <0.1	0.6, <0.1
Subjects with Measurable Amt	0/13 (0.0%)	14/14 (100.0%)	13/13 (100.0%)	12/14 (85.7%)	9/14 (64.3%)	3/15 (20.0%)

Table 24. Paclitaxel Concentration Over Time in Semen

Measure	Baseline	30 Days	3 Months	6 Months	12 Months
Mean ± SD	<0.10 ± 0.0	2.34 ± 3.69	1.30 ± 2.76	0.29 ± 0.53	0.09 ± 0.06
Median	<0.10	0.86	0.27	<0.10	<0.10
Max, Min	<0.10	8.99, <0.10	7.54, <0.10	1.75, <0.10	0.16, <0.10
Subjects with Measurable Amt	0/6 (0.0%)	4/5 (80.0%)	5/7 (71.4%)	4/10 (40.0%)	1/3 (33.3%)
[α]Only subjects with confirmed or suspected paclitaxel present in their semen at 6 months were required to provide 12-month semen samples.					

To mitigate risks associated with paclitaxel presents in semen at/after 12 months, the labeling includes warnings for the potential risk of paclitaxel to spermatogenesis and sperm and that the risks associated with paclitaxel in semen are unknown. The warning also states that men with partners of child-bearing potential should use highly effective contraceptive (to avoid fathering children) for at least 12 months

post-procedure, and urologists should engage in a discussion with prospective patients regarding this risk and their individual family planning situation, with consideration of longer duration contraceptive use or other precautions based on a shared decision making process. In addition, to better understand the length of time paclitaxel remains in the semen, the sub-study of the PEAK post approval study will collect semen samples at 1-, 3-, 6-, and 12-months post-procedure and continue periodically (every 3 months) thereafter until paclitaxel is no longer detectable (i.e., below the limit of quantitation).

4. Pediatric Extrapolation
   In this premarket application, existing clinical data was not leveraged to support approval of a pediatric patient population.

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 23 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. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

EVEREST-I pilot study was a prospective, non-randomized, open label, multicenter study to evaluate the safety and efficacy of the Optilume BPH Catheter system for the treatment of LUTS secondary to BPH. Eligible subjects were men >50 years of age with LUTS secondary to BPH, IPSS ≥13, peak urinary flow rate 5-15 mL/sec, post-void residual ≤250 mL, prostate volume 20-80 grams, and prostatic urethral length 35-55 mm. Key exclusions included prior minimally invasive or surgical intervention of the prostate, intravesical prostatic protrusion >1 cm, and confounding urologic conditions (e.g., neurogenic bladder, stricture). Subjects had to undergo drug washouts prior to treatment including alpha blockers for 3 weeks and 5-alpha reductase inhibitors for 6 months. Subjects were followed at Foley removal, 2 weeks, 30 days, 3 months, 6 months, and 1-year post-treatment, and annually thereafter through 5 years.

A total of 80 subjects were enrolled and treated at 6 clinical sites in Panama (2 sites) and the Dominican Republic (4 sites). Subject follow-up is complete through 3 years. Subjects were 65 years old on average with a prostate volume of 35.9 grams. The primary efficacy endpoint was the responder rate at 3 months based on an improvement in IPSS ≥ 40% from baseline without requiring additional therapy. At 3 months, 81.3% (65/80) were considered responders with a lower 90% confidence limit of 72.6% which met the performance goal of 50%.

Table 32. EVEREST-I Results Summary

Measure	Baseline	3 months	6 months	1 year	2 years	3 years
IPSS n Mean ± SD	80 22.3 ± 4.85	79 8.1 ± 6.05	77 8.0 ± 7.17	75 7.9 ± 7.63	68 8.2 ± 7.28	63 9.8 ± 7.97
IPSS QoL n Mean ± SD	80 4.6 ± 0.86	79 1.5 ± 1.33	77 1.6 ± 1.62	75 1.3 ± 1.38	68 1.6 ± 1.58	63 1.8 ± 1.74
Qmax (mL/sec) n Mean ± SD	80 10.9 ± 2.92	77 20.5 ± 9.54	74 19.6 ± 8.67	74 18.4 ± 8.21	56 17.2 ± 8.98	58 16.7 ± 10.63
PVR (mL) n Mean ± SD	80 63.1 ± 55.01	77 34.3 ± 33.08	74 28.8 ± 29.53	74 34.4 ± 35.25	56 45.0 ± 50.94	58 49.1 ± 79.29

The primary safety endpoint was a composite of device and procedure related serious complications at 3 months including new onset severe urinary retention lasting >14 consecutive days post-healing, unresolved new onset stress urinary incontinence by 90 days, and bleeding requiring transfusion. Two subjects experienced stress urinary incontinence meeting the endpoint criteria for a rate of 2.5%. Both subjects were treated with a larger diameter balloon that will not be marketed.

Forty-six (46) subjects participated in pharmacokinetic (PK) testing of plasma, urine, and semen samples. Average paclitaxel concentration in plasma fell below the limit of quantitation of the method by 10 hours. Low but detectable levels of paclitaxel in plasma were detected in 13% (4/30) of subjects after Foley removal (approximately 4 days post-procedure). Paclitaxel concentration in urine was maximal immediately post procedure and was reduced by >99% by 1-month post-procedure. Paclitaxel was detectable (i.e., equal to or greater than lower limit of quantitation of 0.1 ng/mL) in semen in 4/5 (80.0%), 5/7 (71.4%), 4/10 (40%), and 1/3 (33.3%) of evaluable subjects at 1 month, 3 months, 6 months, and 12 months post-treatment, respectively.

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

In accordance with the provisions of section 515(c)(3) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Gastroenterology-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.

XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

The effectiveness of the Optilume BPH Catheter System was based on a randomized, double blind, sham controlled pivotal study which demonstrated reasonable assurance of effectiveness for the device when used in the indicated patient population. The improvement in IPSS in the Optilume BPH arm at 12 months was higher than the improvement in the Sham arm at 3 months (11.5 vs 8.0); however, the difference did not reach statistical significance when incorporating a 25% super-superiority margin in sham values (p=0.178). Improvement was also observed when comparing the improvement in IPSS in the Optilume BPH arm at 12 months to the improvement at 3 months based on a systematic review of the literature of sham endoscopic procedures in randomized trials of BPH, both with and without a 25% super super-superiority margin. The responder rate based on a 30% improvement in IPSS was higher in the Optilume BPH arm at 12 months compared to the Sham arm at 3 months (76.6% vs 52.1%). Improvement in peak urinary flow was also higher in the Optilume BPH arm at 12 months when compared to Sham at 3 months (9.7 vs 5.5). Subjects in the study will be followed for 5 years to evaluate the durability of the treatment effect.

B. Safety Conclusions

The risks of the device are based on non-clinical bench testing, animal studies, and data collected in a clinical study conducted to support PMA approval as described above. Safety results of the randomized clinical study demonstrated reasonable assurance of safety for the device when used in the indicated patient population in accordance with the instructions for use. No subjects experienced a serious device-related complication meeting the definition of the primary safety endpoint in the PINNACLE study. Treatment-related serious adverse events were reported in 6 (6.1%) subjects, most commonly post-procedure hematuria (4 events) which resolved without sequelae. The most frequently reported treatment-related adverse events included hematuria (39.8%), urinary tract infection (11.2%), dysuria (8.2%), and mild stress urinary incontinence (7.1%). Treatment-related adverse events were mostly mild or moderate in severity (138/143, 97%).

C. Benefit-Risk Determination

The probable benefits are also based on data collected in a clinical study conducted to support PMA approval as described above. The probable benefit is maintained urethral patency after anterior commissurotomy of the prostate following dilation with the Optilume BPH Catheter System. Clinical results show an improvement in IPSS at 12 months when compared to the improvement in sham treated subjects at 3 months. The probability that a patient will experience a benefit is high; approximately 77% of subjects in the Optilume BPH arm experienced a clinically meaningful improvement in IPSS at 12 months. Clinical benefits include an improvement in IPSS, uroflow parameters (Qmax, PVR), and quality of life.

The probable risks are also based on data collected in a clinical study conducted to support PMA approval as described above. The safety profile of the device has been characterized through 12 months post-procedure. Probable risks are mild or moderate adverse events including hematuria, urinary tract infection, dysuria, and mild stress incontinence as well as the risk of persistent paclitaxel present in semen. Hematuria was the most frequent treatment-related serious and non-serious adverse event. Postoperative care guidelines were implemented during the study which reduced the incidence and severity of hematuria events; these instructions are included in the labeling to mitigate the risk of severe hematuria events.

1. Patient Perspective
   This submission either did not include specific information on patient perspectives or the information did not serve as part of the basis of the decision to approve or deny the PMA for this device.

In conclusion, given the available information above, the data support that for the treatment of obstructive urinary symptoms associated with BPH in men ≥ 50 years of age, the probable benefits outweigh the probable risks.

D. Overall Conclusions

The PINNACLE study data demonstrate a benefit of decreasing the bladder neck level obstruction resulting from BPH with an acceptable risk profile (less than the apparent benefit) in the indicated patient population. The overall uncertainty of both benefit and safety are low. Therefore, 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.

XIV. CDRH DECISION

CDRH issued an approval order on June 30, 2023. The final clinical conditions of approval cited in the approval order are described below.

1. The PINNACLE study (PR1087 version J provided in P220029 original submission) is designed to conduct follow-up at Foley removal, 14-, 30-days, 3-, 6-, and 12-months post-procedure, and to continue the follow-up annually thereafter through 5 years. It is intended to verify the continued safety and effectiveness of the Optilume BPH Catheter System after 12-months follow-up for the subjects who received the Optilume BPH Catheter System in the PINNACLE study. Each patient's follow-up will be continued out to 5 years post-treatment. Study reports will continue to be generated and written in accordance with the endpoint definitions specified in the PINNACLE Statistical Analysis Plan for the randomized, crossover, and pharmacokinetics (PK) cohorts. The endpoints are as follows:
    a. responder analyses with a responder defined as International Prostate Symptom Score (IPSS) improvement of 35%, 40%, and 50%,
    b. change in post-void residual (PVR) urine volume,
    c. change in sexual function (International Index of Erectile Function (IIEF), Male Sexual Health Questionnaire – Ejaculatory Dysfunction (MSHQ-EjD),
    d. change in BPH impact index (BPH-II),
    e. change in quality of life (EQ-5D)
    f. change in pain score,
    g. change in peak urinary flow (Qmax),
    h. proportion of subjects experiencing a return to 'normal' symptom severity (IPSS<8)), and
    i. frequency and severity of all adverse events (AEs),

    For any subjects with available data at 12 months, the applicant should provide change in semen quality characteristics and semen paclitaxel PK.

    Progress reports will be submitted to the FDA annually after PMA approval.

2. The PEAK (Safety and Effectiveness of the Optilume BPH Catheter System in a Post-market Study) post approval study (PR1309, received in a June 8, 2023 email) is a prospective, single arm, multi-center, post market clinical trial evaluating the continued safety and effectiveness of the Optilume BPH Catheter System. This PAS includes a semen sub-study evaluating semen quality and paclitaxel pharmacokinetics (PK) in a subset of subjects. The study will enroll up to 92 subjects at up to 15 sites in the United States and at least 34 of the enrolled subjects will be evaluated for semen quality and PK. The study will be open to men 50 years of age or older who meet the selection criteria. Clinical follow-up wil be conducted at 1-, 3-, 6-, and 12-months post-procedure, and annually thereafter through 5 years. For subjects enrolled in the semen sub-study, semen PK samples will be collected at 6 months and 12 months. Samples collection will continue periodically (every 3 months) thereafter until paclitaxel is no longer detectable (i.e., below the limit of quantitation). In addition,

semen quality will be assessed at baseline, 3 months, 6 months, and 12 months. The primary effectiveness endpoint is improvement in the International Prostate Symptom Score (IPSS) at 12 months. The mean percent reduction in IPSS at 12 months will be compared to a performance goal of 30%. Ancillary endpoints include improvement in IPSS, improvement in international continence society (ICS) male short form (SF), improvement in Qmax (fastest flow rate), and improvement in post-void residual volume (PVR) at each follow-up, and freedom from repeat intervention. The primary safety endpoint is freedom from composite treatment related serious adverse events (SAEs) (device-related rectal fistula or gastrointestinal (GI) fistula, device-related formilation of fistula between the rectum and urethra, device-related new onset severe urinary retention lasting >14 consecutive days post-healing, device-related unresolved new onset stress urinary incontinence by 90 days, device-related bleeding requiring transfusion, and device-related urethra or prostatic capsule rupture requiring surgical intervention). The secondary safety endpoint is average change in sperm concentration from baseline to 3 months. The ancillary safety endpoints include frequency and severity of all adverse events (AEs), change in semen quality characteristics from baseline over time (semen sub-study only), and semen paclitaxel PK (semen sub-study only).

The applicant's manufacturing facilities have been inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XV. APPROVAL SPECIFICATIONS

Directions for use: See 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.

XVI. REFERENCES

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