PINNACLE

A prospective, multicenter, double blind, randomized, clinical study to evaluate the safety and efficacy of the Optilume™ BPH Catheter System in men with symptomatic BPH

PROTOCOL No. PR1087

VERSION J

March 14, 2022

SPONSOR

Urotronic Inc

2495 Xenium Lane N

Minneapolis, MN 55441

USA

This study will be conducted in compliance with the protocol and applicable regulatory requirements.

UROTRONIC

PINNACLE

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I have read this protocol and agree to adhere to the requirements. I will provide copies of this protocol and all pertinent information to the study personnel under my supervision and my hospital's Institutional Review Board (IRB)/Research Ethics Board (REB). I will discuss this material with them and ensure they are fully informed regarding the conduct of the study according to this protocol, ICH Good Clinical Practice (GCP), ISO 14155, Declaration of Helsinki, 21 CFR 50, 56 and 812 and hospital IRB/REB requirements.

I agree to and understand the material presented in this protocol and must not publicly disclose in any manner the design, results or conclusions of this investigation without prior written consent from Urotronic.

_____

Clinical Site Name

_____ _____

Site Investigator Signature Date

_____

Site Investigator, Printed Name

Protocol Summary

Title:	PINNACLE: A prospective, multicenter, double blind, randomized, clinical study to evaluate the safety and efficacy of the Optilume™ BPH Catheter System in men with symptomatic BPH
Investigational Device:	Optilume™ BPH Catheter System
Control Device:	21 Fr sheathed Optilume™ BPH Prostatic Pre-dilation Catheter (modified to prevent inflation)
Objective:	To evaluate the safety and efficacy of Optilume™ BPH Catheter System in the treatment of benign prostatic hyperplasia (BPH)
Study Design:	Prospective, multicenter, double blind, randomized, sham-controlled study with a non-randomized, Pharmacokinetics (PK) study arm
Enrollment:	162 subjects will be randomized and/or treated in the study at up to 30 clinical sites in the United States and Canada (up to 28 sites in the US and up to 2 sites in Canada). 147 subjects will be randomized in the randomized portion of the study, and 15 subjects will be treated in the Pharmacokinetics arm of the study. Individual site treatments in the randomized portion of the study may not exceed 25% of the total randomized study treatments. Up to 625 subjects will be enrolled (i.e. consented) in the study in order to identify 162 eligible subjects to be randomized and/or treated.
Clinical Follow-up:	The following follow-up visits are required post-procedure: • Foley Removal, 14-Day, 30-Day, 3-Month, 6-Month and 12-Month In addition, all subjects treated with the Optilume BPH Catheter System will be followed annually through 5 years
Study Duration	Approximately 8 years
Endpoints	**Primary Efficacy Endpoint**: Change in IPSS In order to meet this endpoint, 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. **Primary Safety Endpoint** : Major Device-Related Serious Complications A major device-related serious complication is defined as 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 • Device-related urethra or prostatic capsule rupture requiring surgical intervention **Secondary Endpoint 1**: Average IPSS improvement in the Test arm at 12 months The average IPSS improvement in the Test arm from baseline to 12 months must be ≥ 30% **Secondary Endpoint 2**: Percentage of responders at 3 months The responder rate at 3 months of subjects randomized to the Test arm will be compared to the responder rate of subjects in the Control arm. A responder for this endpoint is defined as a subject who has an IPSS improvement ≥ 30% post-treatment as compared to baseline. **Secondary Endpoint 3**: Durability – Percentage of responders The responder rate at 12 months of subjects randomized to the Test arm will be compared to the responder rate at 3 months of subjects in the Control arm. A responder for this endpoint is defined as a subject who has an IPSS improvement ≥ 30% post-treatment as compared to baseline. **Secondary Endpoint 4**: Qmax The change or increase in Qmax at 12 months for all treated subjects randomized to the Test arm will be compared to the change or increase in Qmax at 3 months for subjects randomized to the Control arm.

	Ancillary Endpoints: A1: Additional responder analyses with a responder defined as IPSS improvement of 35%, 40% and 50% A2: Change in PVR A3: Change in sexual function A4. Change in BPH-II A5: Change in quality of life A6: Change in pain score A7: Procedure parameters A8: Change in Qmax A9: Proportion of subjects experiencing a return to 'normal' symptom severity
Study Success Criteria	For the study to be declared a success, the Primary Efficacy Endpoint and Secondary Endpoint 1 must be met without any safety concerns.
Randomization Arm 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 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 7. Able to complete the study protocol in the opinion of the investigator
Randomization Arm 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. 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 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 42. In the opinion of the investigator, it is not in the subject's best interest to participate in the study
Pharmacokinetics Arm Inclusion Criteria:	Subjects must meet all the inclusion criteria for the Randomization arm of the study with the exception of Inclusion 3; the subject's

	Qmax must be ≥ 5 ml/sec and ≤ 15 ml/sec (with minimum voided volume of ≥ 150 ml) in order to be eligible to participate in the PK arm of the study
Pharmacokinetics Arm Exclusion Criteria:	In addition to not meeting any of the exclusion criteria for the Randomization arm of the study, subjects must also not meet the following criteria in order to be eligible to participate in the PK arm of the study: • Previous treatment with any device or medical therapy that contains paclitaxel • Unable or unwilling to provide viable semen samples

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List of Abbreviations

AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Amino Transferase
AST	Aspartate Amino Transferase
AUASI	American Urological Association Symptom Index
BPH	Benign Prostatic Hyperplasia; also known as Benign Prostatic Hypertrophy
BPHII	BPH Impact Index (bother Score)
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CMI	Clinically Meaningful Improvement
CMP	Complete Metabolic Panel
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
DCB	Drug Coated Balloon
eCRF	Electronic Case Report Form
EQ-5D	Standardized instrument for use as a measure of health outcome
GCP	Good Clinical Practice
GI	Gastrointestinal
ICF	Informed Consent Form
IFU	Instructions for Use
IIEF	International Index of Erectile Function
IPP	Intravesical Prostatic Protrusion
IPSS	International Prostate Symptom Score
IRB	Institutional Review Board
LHRH	Luteinizing Hormone-Releasing Hormone
LUTS	Lower Urinary Tract Symptoms
LUTS/BPH	LUTS Secondary to BPH
MedDRA	Medical Dictionary for Regulatory Activities
MSHQ-EjD	Male Sexual Health Questionnaire to assess ejaculatory dysfunction
PI	Principal Investigator
PK	Pharmacokinetics
PSA	Prostate Specific Antigen
PTX	Paclitaxel (coating drug on the balloon)
PV	Prostate Volume
PVR	Post Void Residual Urine Volume
Qmax	Peak Flow Rate

QoL	Quality of Life
REB	Research Ethics Board
SAE	Serious Adverse Event
TRUS	Transrectal Ultrasonography
TUAP	Transurethral Anterior Commissurotomy of the Prostate
TUMT	Transurethral Microwave Thermotherapy
TUNA	Transurethral Needle Ablation
TURP	Transurethral Resection of the Prostate
UADE	Unanticipated Adverse Device Effect
USA	United States of America
UTI	Urinary Tract Infection

1 INTRODUCTION

1.1 Disease State Overview and Epidemiology

Benign prostatic hyperplasia (BPH) is a histologic diagnosis that refers to the proliferation of smooth muscle and epithelial cells within the prostatic transition zone.[1,2] BPH with associated lower urinary tract symptoms (LUTS) is a common medical condition in the aging male. The prevalence and the severity of LUTS in the aging male can be progressive, and is an important diagnosis in the healthcare of our patients and the welfare of society. BPH is the second highest reason for patients to seek a urologist.[3] The incidence has been estimated to increase from 40% among males between the ages of 50 and 60 years to 90% among males older than 80 years of age.[4] In 2015, there were 38.1 million men with BPH pathology and 21.3 million with International Prostate Symptom Score (IPSS) >7; 12.2 million of them were managed for LUTS secondary to BPH (LUTS/BPH), primarily with watchful waiting (35%) and drug management (54.8%).[3]

Initially, watchful waiting (observing without treatment) is normally employed. Treatment initiation usually occurs once symptoms of bladder outlet obstruction and bladder irritability interfere with the patient's quality of life. The American Urological Association Symptom Index (AUASI) or its related International Prostate Symptom Score (IPSS) are now considered the gold standard measurement tools for the assessment of LUTS and response to treatment.

Medications are the most common way to control mild to moderate symptoms of BPH and significantly reduce major symptoms for many men who try them. However, medications have systemic side effects, are costly in the long run, and some patients may have difficulty with complying with the medication, particularly in the older population. Further, many patients have moderate to severe symptoms that are not fully alleviated by medical therapy.

Transurethral surgical resection of the enlarged prostate (TURP) is still considered a bench mark for the treatment of moderate-to-severe LUTS/BPH or other BPH-related complications.[5] However, surgical intervention, by definition, is the most invasive option for BPH management.

For this reason, minimally invasive therapies have been gaining favor over medication and over the traditional TURP even though the effectiveness of minimally invasive procedures has been reported to be less than TURP. Development of an effective treatment method but one with shorter treatment time, fewer complications, and faster recovery time, would be an advantage.

1.2 History of Use of Paclitaxel

Paclitaxel has been used extensively and successfully in drug-eluting stents (DES) and drug-coated balloons (DCB) to reduce the rate of stenosis in vascular tissue. Examples of the devices coated with this drug and the dates of approval in the US are shown in Table 1-1. The improvement in restenosis rates led Urotronic to design a similar system to treat obstructive BPH.

Table 1-1: US Approved Paclitaxel-Coated Devices

Paclitaxel-Coated Device	US Approval Date
Boston Scientific TASUX DES	2004
Cook Medical Zilver PTX DES	2012
BD Lutonix DCB	2014
Medtronic In.Pact Admiral DCB	2015
Covidien/Spectranetics/Philips Stellarex DCB	2017

1.3 Previous Clinical Experiences of DCB use for BPH

The Optilume™ BPH Catheter System is currently under investigation. The EVEREST-I pilot study has completed enrollment and the treatment of 80 subjects with BPH at six Latin American investigational sites, two in Panama and four in the Dominican Republic. Subject follow-up is currently ongoing. As of July 3, 2019, 79 subjects had completed the 3-Month follow-up visit, 53 subjects had completed the 6-Month follow-up visit and 45 subjects had completed the 1-Year follow-up visit.

1.3.1 EVEREST-I Efficacy Results

The EVEREST-I clinical efficacy data show that the percentage of study therapeutic responders, defined as ≥ 40% improvement in IPSS at the 3-Month follow-up from baseline, was 81.3% (65/80). It means that the study Primary Efficacy Endpoint was met.

The average IPSS improved from severely symptomatic at baseline (IPSS=22.3) to mildly moderate symptomatic at 3-Month follow-up (IPSS = 8.1), which is durable at 6-Month (IPSS = 8.0) and at 1-Year (IPSS = 8.2) follow-ups. The average improvements in IPSS at 3-Month, 6-Month and 1-Year were 14.2, 14.7 and 14.0 points. The minimal clinically important difference (MCID) of IPSS for patients with mild-to-moderate LUTS is 2 points, whereas for patients with severe LUTS is 6 points. It means that the IPSS improvement after Optilume BPH Catheter /procedure is considered clinically meaningful improvement (CMI).

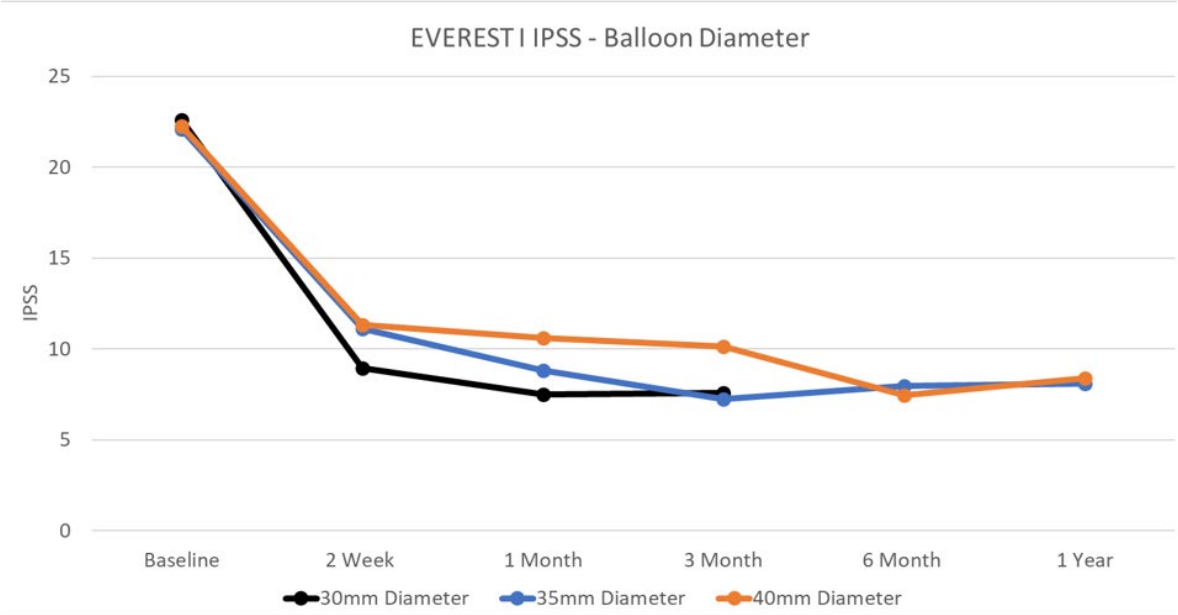

Figure 1-1: Effect of Optilume BPH Prostatic DCB on IPSS

The improvement observed in IPSS is also seen in the improvement in Qmax. Mean Qmax increased from 10.9 ml/sec at baseline to 20.5 ml/sec at 3-Month, 21.7 ml/sec at 6-Month and 19.3 ml/sec at 1-Year follow-ups. The average improvements in Qmax were 9.6, 11.0 and 8.2 ml/sec from baseline to 3-Month, 6-Month and 1-Year follow ups. The minimal clinically important difference (MCID) for Qmax is 2 ml/sec. It means that Qmax improvement after Optilume BPH Catheter /procedure is considered clinically meaningful improvement (CMI).

Furthermore, the averages of PVR were reduced from 63.1 ml at baseline, to 34.3 ml at 3-Month, 27.5 ml at 6-Month and 32.4 ml at 1-Year follow-ups. The average improvements in PVR from baseline were 30.0 ml, 42.5 ml and 41.1 ml at 3-Month, 6-Month and 1-Year respectively. These improvements indicate that the subjects were able to void more completely, thus alleviating the lower urinary tract symptoms (LUTS) secondary to BPH.

1.3.2 EVEREST-I Safety Results

The Primary Safety Endpoint was defined as any of the following device- or procedure-related serious adverse events at 3 months:

- Device- or procedural-related new onset severe urinary retention lasting > 14 consecutive days post-healing
- Device- or procedural-related unresolved new onset stress urinary incontinence by 90 days
- Device- or procedure-related bleeding requiring transfusion

One major device- or procedure-related complication (1.3%, 1/80) was identified, which was stress urinary incontinence.

As of July 3, 2019, a total of 103 AEs was reported, regardless of relationship to the study device or procedure. 58 of the AEs were reported from the 58 subjects treated with either a 30 mm or 35 mm diameter DCB, and 45 of the AEs were reported from the 22 subjects treated with a 40 mm diameter DCB.

The most frequently reported adverse events in the EVEREST-I study are listed in Table 1-2.

Table 1-2: EVEREST-I Most Frequent Adverse Events

AE Name	Events in All Subjects (N=80)	Events in Subjects Treated with 30 or 35 mm DCB (N=58)	Events in Subjects Treated with 40 mm DCB (N=22)
Urinary symptoms: Urethrorrhagia or Hematuria	12/80 (15.0%)	5/58 (8.6%)	7/22 (31.8%)
Urinary Tract Infection	9/80 (11.3%)	5/58 (8.6%)	4/22 (18.2%)
Urinary clot retention	9/80 (11.3%)	6/58 (10.3%)	3/22 (13.6%)
Ejaculatory dysfunction	7/80 (8.8%)	6/58 (10.3%)	1/22 (4.5%)
Urinary symptoms: Dysuria	7/80 (8.8%)	3/58 (5.2%)	4/22 (18.2%)
Urinary symptoms: Incontinence - Stress	6/80 (7.5%)	1/58 (1.7%)	5/22 (22.7%)
Stricture	5/80 (6.3%)	4/58 (6.9%)	1/22 (4.5%)
Urinary symptoms: Incontinence - Urge	4/80 (5.0%)	1/58 (1.7%)	3/22 (13.6%)

No unanticipated adverse device effects (UADE) have been reported.

1.3.3 EVEREST-I Pharmacokinetics Results

Pharmacokinetic (PK) testing was studied for paclitaxel in a subset of EVEREST-I subjects on the plasma, urine and semen samples collected. Test results confirmed that the amount of drug found in the plasma and semen following treatment is very small and does not present a health hazard. The pharmacokinetics of the drug in the plasma, semen and urine is shown in Figure 1-2. The majority of the drug delivered was limited to the surface of the urethra/prostate. Very low amounts of drug were found in plasma. The amount of drug in the semen correlate with the amount of drug in the urine since semen is expelled through the urethra.

Drug concentration in the urine dropped significantly between the procedure and the 4-Day follow-up.

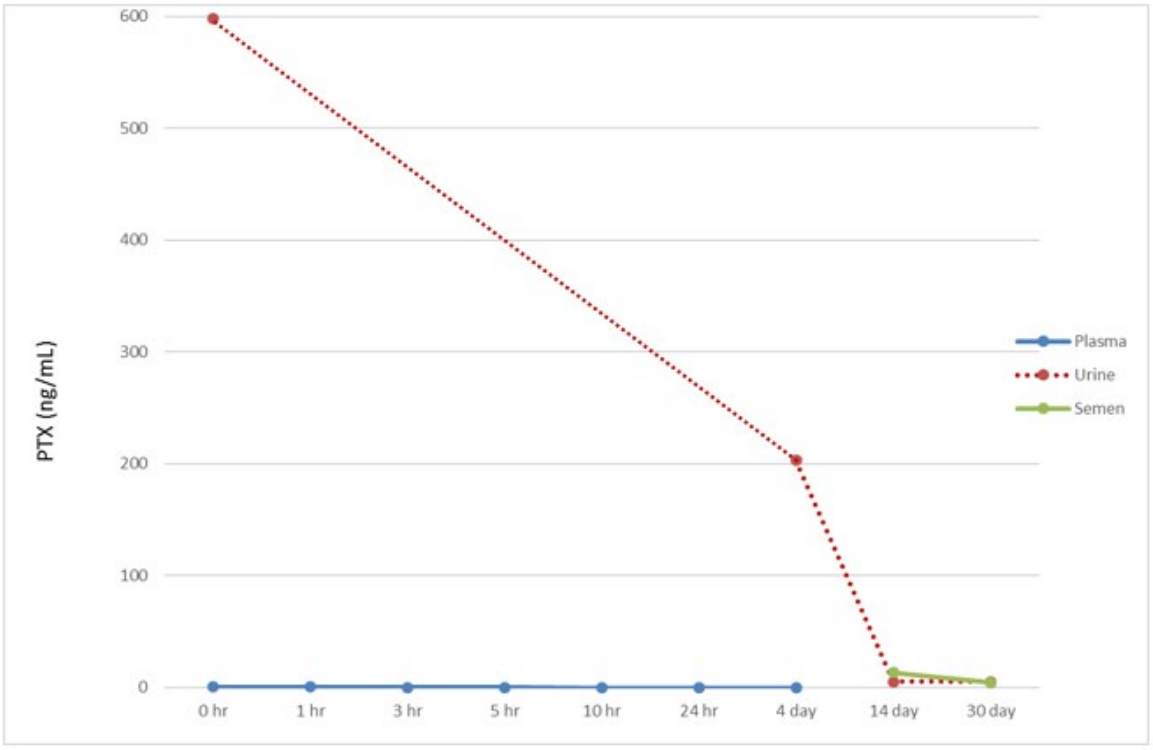

Figure 1-2: Summary of EVEREST-I PK Data

1.4 Rationale for Study

Balloon dilation is one of the least invasive interventional therapies to treat BPH. Extensive clinical research on balloon dilation of the prostate was completed in the 1990s using balloon sizes ranging from 20-35mm. These studies showed that balloon dilation was safe and well tolerated by patients. However, mixed efficacy at 3-6 months in certain patient populations and 12-month LUTS reoccurrence for many patients caused the technology to be abandoned.

The Optilume™ BPH Catheter System is used to perform a TransUrethral Anterior commissurotomy of the Prostate (TUAP). The system combines the procedural advantage of simplicity with improved efficacy over other balloon dilation through its unique balloon geometry with a localized application of paclitaxel to prevent future cellular proliferation and excessive scar tissue generation during the healing process. The goal of this technology is to provide immediate relief via balloon dilation and create lasting durable results to alleviate LUTS associated with BPH.

This study is designed to assess the safety and efficacy of the Optilume BPH Catheter System to alleviate moderate-to-severe LUTS/BPH.

2 DEVICE DESCRIPTION

The Optilume™ BPH Catheter System consists of two investigational catheters:

- Optilume™ BPH Prostatic Pre-dilation Catheter
- Optilume™ BPH Prostatic Dilation DCB Catheter

The pre-dilation catheter is constructed identically to the drug coated balloon catheter, but without the paclitaxel drug coating. The pre-dilation and drug coated balloon catheters are packaged separately.

The Optilume™ BPH, Prostatic Pre-dilation Catheter is a dilation catheter used to exert radial force to dilate the prostatic urethra resulting in a commissurotomy. The distal end of the catheter has a semi-compliant inflatable double lobe balloon with a neck separating the two sections. The balloon neck is reinforced which makes the neck section non-compliant thereby minimizing diameter growth in the neck during the inflation process.

The Optilume™ BPH, Prostatic Dilation DCB has a double lobe balloon that is coated with a proprietary coating containing the active pharmaceutical paclitaxel. (See Figure 2-1).

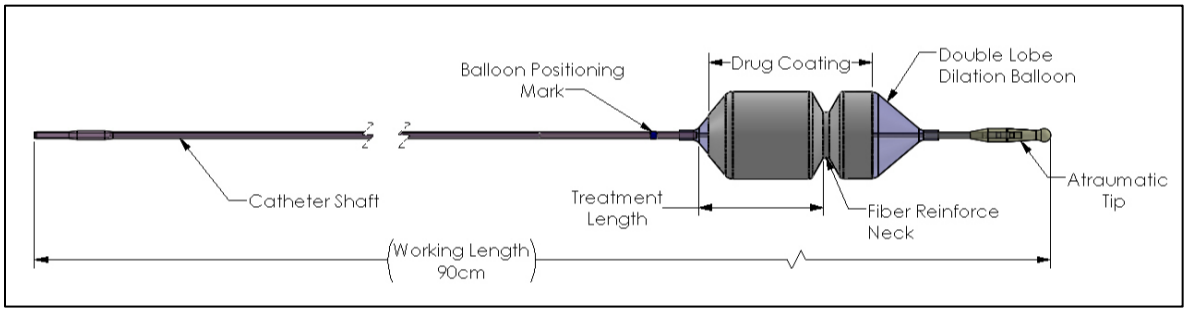

Figure 2-1: Inflated Drug Coated Balloon

The double lobe design allows the balloon neck to naturally seek and seat in the bladder neck during inflation and inhibits migration of the balloon into the bladder. 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 and dilates the prostate separating the anterior prostatic commissure. The balloon body and a portion of the proximal cone are coated with the active pharmaceutical ingredient (API), paclitaxel, as shown in Figure 2-1. The pre-dilation balloon has the same design but provided uncoated.

All materials used in the construction of the Optilume™ BPH Catheter System are known biocompatible materials and are commonly used in the medical device industry.

The device is supplied STERILE for single use only (ethylene oxide sterilization).

The full device description and balloon sizes available for the study are described in the Instructions for Use.

3 RISK-BENEFIT ANALYSIS

3.1 Risk Analysis

Balloon dilation to treat BPH is an established treatment and the risk associated with the procedure is well understood. The investigational device contains a drug coated balloon that is intended to suppress cellular proliferation and hence potentially mitigate the risk of recurrence of LUTS/BPH at the treatment site.

Refer to Instructions for Use as well as the Section 11 Definition of Adverse Event(s) of this protocol for the associated risks.

3.1.1 Risk Assessment

In conducting the risk analysis, the concepts of risk estimation, risk acceptability, risk control and overall risk evaluation were applied in accordance with ISO 14971. The intended use and treatment procedure was taken into consideration along with the materials and mechanical features of the Optilume BPH Catheter System. Based on an evaluation of residual risk acceptability, it was determined that no individual residual risks values are considered unacceptable and that all individual risks are balanced against the benefit of the device.

3.1.2 Risk Mitigation

The potential AEs and device issues associated with the Test device are not fully understood in the treatment of BPH, so there is the potential for device issues and adverse events not previously identified to occur. To minimize potential risks, the device shall only be used by physicians who are specialized in urology and have been trained on the use of the device. The patients will be carefully screened against the inclusion and exclusion criteria before randomization/treatment in the study. All device deficiencies and adverse events from the study will be closely monitored.

A potential health risk of study participation is due to the paclitaxel drug coating. Paclitaxel is a lipophilic, anti-mitotic agent that has been reported to prevent proliferation of smooth muscle cells, inflammatory cells and fibroblast. The purpose of using paclitaxel in the coating of the device is to prevent or reduce recurrence of LUTS by inhibiting smooth muscle cell proliferation and urothelial hyperplasia. The potential risks of paclitaxel in the coating include:

- Chromosomal abnormalities and the risk of cancer
- Fetal harm when a pregnant woman is exposed
- Anaphylaxis and hypersensitivity with paclitaxel intravenous infusion have been reported
- It may inhibit the healing of the urethra post procedure
- Potential effect on the liver and kidneys is unknown and have not been studied

The amount of the paclitaxel delivered is much lower than a single dose of chemotherapy provided to cancer patients and the drug appears essentially localized to the urethra.

Therefore, the risk of drug toxicity is anticipated to be very low as the concentration of the drug in the body fluid is very low. The complete list of potential anticipated adverse events is provided in Section 11.6 of this protocol.

3.2 Potential Benefit

The subjects participating in this study potentially could benefit from the reduction in LUTS or BPH symptoms. Data from EVEREST-I showed that majority of the subjects treated received a benefit from the treatment. The data obtained from this study will be used to establish the safety and efficacy of the device and this data may benefit others in the future.

3.3 Study Participation Associated Risks

In addition to the risk to health, there is a risk of violation of subject's privacy during the data collection and monitoring of the subject's health data. All precaution will be taken to prevent the accidental disclosure of subject's medical records. All subjects will be listed by the study ID and no personal data will be collected.

The risks associated with study participation (Table 3-1) are those associated with standard clinical diagnostic and evaluative practice procedures. All subjects will provide informed consent prior to participating in the study.

The procedures required per study protocol are consistent with standard of care procedures given the indication for the associated treatment.

Table 3-1: Study Participation Associated Risks

Study Procedure	Risk(s)
Medical History, Physical Exam, Quality of Life Questionnaires	None, minimal
Urinalysis	None, minimal
Uroflowmetry and Post-Void Residual	Written informed consent consistent with clinic policy
Cystoscopy	Written informed consent consistent with clinic policy
TRUS	Written informed consent consistent with clinic policy
Laboratory Testing	Usual risks associated with phlebotomy

4 STUDY OBJECTIVES AND DESIGN

4.1 Objective

The objectives of the study are:

- To assess the efficacy of Optilume BPH Catheter System to alleviate LUTS believed to be secondary to BPH (LUTS/BPH)
- To evaluate the safety of Optilume BPH Catheter System in the treatment of LUTS/BPH

4.2 **Study Design**

This is a prospective, multi-center, double blind, randomized controlled clinical trial in a 2:1 allocation of Test versus sham Control. In addition, a single arm of 15 non-randomized subjects will be added to study the Pharmacokinetics of the drug.

A total of 162 subjects will be randomized and/or treated in the study at up to 30 clinical sites in the United States and Canada (up to 28 sites in the US and up to 2 sites in Canada). One hundred and forty seven (147) subjects will be randomized (2:1) and treated with either the Optilume BPH Catheter System or a sham procedure at up to 30 clinical sites. Some of the 30 clinical sites will also be participating in the PK arm of the study. Fifteen (15) non-randomized subjects will be treated in the PK arm. Up to 625 subjects will be enrolled (i.e. consented) in the study in order to screen and identify 162 eligible subjects to be treated.

All subjects will be followed up post-treatment at Foley removal, 14 days, 30 days, 3 months, 6 months and 12 months. In addition, all subjects treated with the Optilume BPH Catheter System will be followed annually through 5 years.

The number of subjects randomized at an individual site may not exceed 25% (n=37) of the total randomized study sample size. There is no site enrollment/treatment limitation for the PK arm.

The study duration is anticipated to be approximately 8 years.

The schematics of the study treatment arms and cross-over are shown in Figure 4-1 and Figure 4-2.

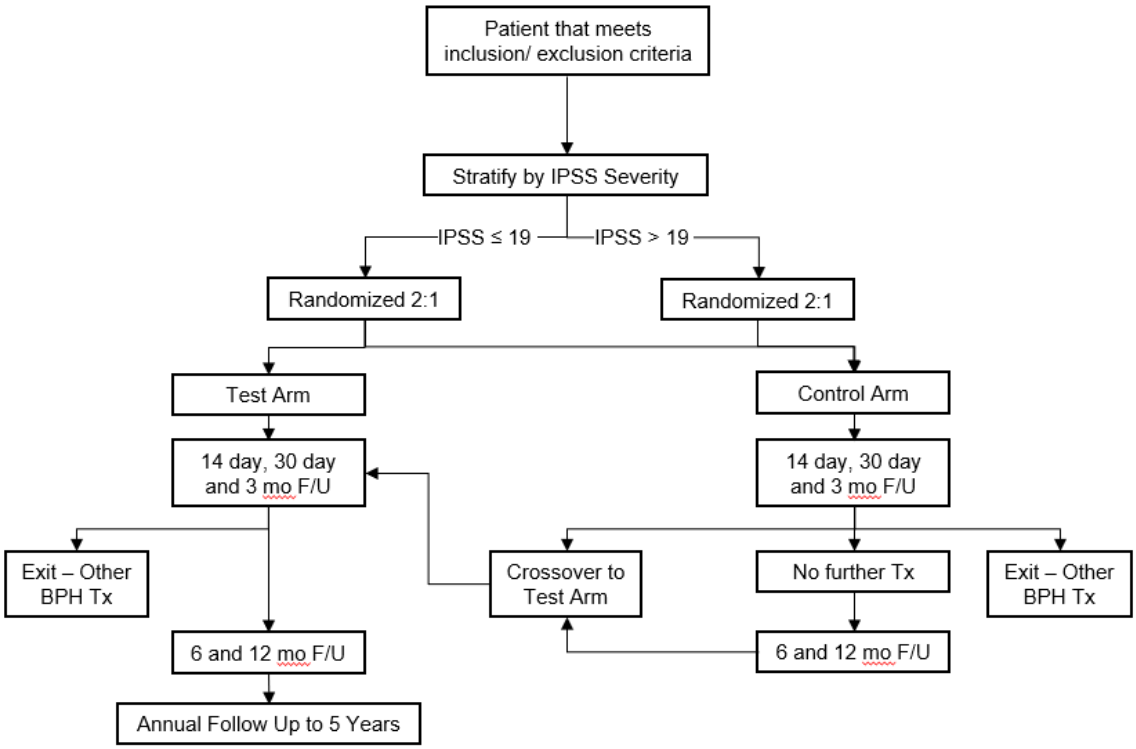

Figure 4-1: Schematic of Study Randomization and Cross-over

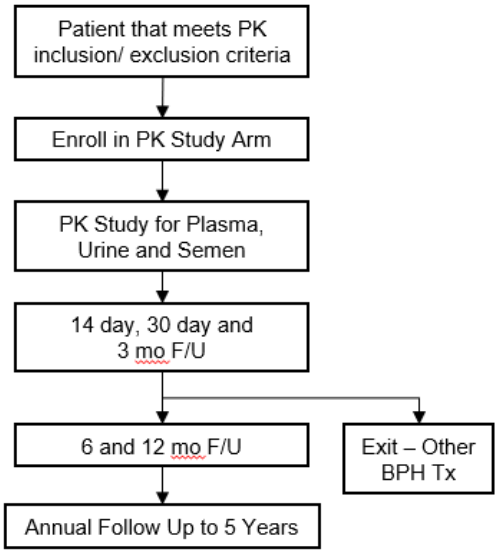

Figure 4-2: Schematic of PK Arm

4.2.1 Test Arm Description

Subjects randomized to the Test arm will be treated with the Urotronic Optilume BPH Catheter System. For the Primary Endpoint, the analysis population will be intent to treat (ITT). Data from subjects randomized to this arm will be used in the analyses.

4.2.2 Control Arm Description

Subjects randomized to the Control arm will receive a sham procedure. A cystoscopy will be performed followed by insertion of the 21 Fr Optilume BPH, Prostatic Pre-dilation Catheter within the sheath. The catheter hub of the sham device will be modified to prevent inflation of the balloon.

4.2.3 Cross-over/Alternative Therapy

If a subject's condition did not improve after the assigned index treatment (either Test or Control) the blinded site personnel will counsel the subject on available treatment options, including 'watchful waiting' while continuing to perform study required follow up visits. During this ongoing subject counseling, the blinded personnel will describe the ability for the patient to cross over to the Treatment arm after the 3-Month follow-up visit has been completed. Although every effort should be made to maintain blinding for 12 months in each study arm, subjects may opt to be unblinded and seek alternative BPH therapy at any time.

This counseling will be consistent regardless of which study arm the subject was randomized to in order to maintain study blinding. The subject may choose at any time to receive an alternative BPH therapy (e.g. TURP, medication) and forego the opportunity to cross over. If the subject chooses to receive an alternative BPH therapy, they will be discontinued from the standard study follow up once the alternative therapy is received and be followed for general health only. See Figure 4-1.

After the 3-Month follow-up visit, if a subject continues to be symptomatic and determines that they wish to receive an alternative BPH therapy, the Investigator will unblind the subject and counsel the subject on available treatment options, including cross-over treatment with the Optilume BPH Catheter System for subjects that were randomized to the Control arm. A cross-over treatment must be complete before the end of the subject's 12-Month follow-up visit window.

Subjects must meet all the study inclusion criteria and no exclusion criteria in order to qualify to cross-over. The safety and efficacy data collected post-cross-over will be summarized separately. Cross-over subjects will be followed out to 5 years, starting from the cross-over procedure, under the same subject ID.

4.3 Pharmacokinetics Arm Description

In the subset of 15 non-randomized subjects at selected sites, small amounts of blood, urine and semen will be collected for pharmacokinetic testing and sperm quality testing.

Efforts should be made to include only those subjects who will be available to provide all required samples. A PK Manual with detailed instructions and materials will be provided to select sites.

In order to qualify for participation in the PK arm of the study, subjects must meet all the study eligibility criteria with the exception of Inclusion 3; the Qmax, which must be ≥ 5 ml/sec and ≤ 15 ml/sec (with minimum voided volume of ≥ 150 ml) for subjects to qualify for the PK sub-study. Any subjects who have been treated with any device or medical therapy that contains paclitaxel or are unable or unwilling to provide viable semen samples are excluded from participation in the PK testing.

All qualified subjects who are enrolled in the Pharmacokinetics arm of the study will be treated with the Optilume BPH Catheter System. A minimum of five PK subjects must be treated with the 30 x 45 mm Optilume BPH DCB.

A central core laboratory in the United States, Inotiv, will be utilized for analysis of the PK samples. Supplies for collection, storage and shipment of samples will be provided by the Sponsor.

4.3.1 Blood PK Collection

A total of 9 blood samples for PK analysis will be collected per subject. (See Table 4-1) The first blood sample is collected at baseline, and the following 4 (#2-5) blood samples will be drawn post-procedure and prior to discharge. The 6th blood sample will be drawn post-discharge at the Foley Removal Visit. The remaining 3 blood samples will be drawn at the 30-Day, 3-Month and 6-Month Visits. If paclitaxel is still present in a subject's 6-Month blood sample, that subject will be asked to provide additional blood samples at least every six months until paclitaxel is no longer detected.

Table 4-1: Blood PK Sample Collection Times

Sample No.	Time Point	Compliance Window
1	Baseline	Within 30 days prior to procedure
2	0 Hour*	0 - 30 min post-procedure
3	1 Hour	60 - 90 min post-procedure
4	3 Hours	2 - 4 hrs post-procedure
5	5 Hours	4 - 6 hrs post-procedure
6	Foley Removal	≥ 48 hrs post-procedure
7	30-Day Visit	23 - 37 days post-procedure
8	3-Month Visit	76 - 104 days post-procedure
9	6-Month Visit	150 - 210 days post-procedure

*0 hours post-procedure is defined as after collecting the 2nd void urine sample

4.3.2 Urine PK Collection

A total of 6 urine samples for PK analysis will be collected per subject. Table 4-2 lists the samples and their associated timepoints. If paclitaxel is still present in a subject's 6-Month urine sample, that subject will be asked to provide additional urine samples at least every six months until paclitaxel is no longer detected.

Table 4-2: Urine PK Sample Collection Times

Sample No.	Time Point	Compliance Window
1	Pre-Procedure	Within 30 days prior to procedure
2	Post-Procedure 2nd Void	Before subject exits procedure room
3	Foley Removal	≥ 48 hrs post-procedure
4	30-Day Visit	23 - 37 days post-procedure
5	3-Month Visit	76 - 104 days post-procedure
6	6-Month Visit	150 - 210 days post-procedure

4.3.3 Semen PK Collection

A total of 4 semen samples will be collected per subject. (See Table 4-3)

A baseline semen sample will be collected within 30 days prior to the procedure. Semen samples will also be collected at the 30-Day, 3-Month and 6-Month Visits. If paclitaxel is still present in a subject's 6-Month semen sample, that subject will be asked to provide additional semen samples at least every six months until paclitaxel is no longer detected. The semen samples will be split when the sample size is sufficient; half for sperm quality assessment by the site's lab and the other half divided into 2 aliquots to be sent to Inotiv for PK analysis. A minimum sample volume of 0.3 mL is required for PK analysis. If a semen sample does not contain enough volume to split while maintaining this minimum volume, the PK analysis aliquot 1 sample will be prioritized followed by the sample for sperm quality. The PK analysis aliquot 2 sample will only be prepared when the total semen sample is at least 1 mL.

Table 4-3: Semen Sample Collection Times

Sample No.	Time Point	Compliance Window
1	Pre-Procedure	Within 30 days prior to procedure
2	30-Day Visit	23 - 37 days post-procedure
3	3-Month Visit	76 - 104 days post-procedure
4	6-Month Visit	150 - 210 days post-procedure

4.4 Study Endpoints

4.4.1 Primary Efficacy Endpoint : Change in IPSS

In order to meet this endpoint, 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.

IPSS is a non-invasive measure of subjects' symptoms and is universally accepted to assess severity of LUTS/BPH.

4.4.2 Primary Safety Endpoint : Major Device-Related Serious Complications

A major device-related serious complication is defined as any of the following events through 12 months:

- Device-related rectal fistula or 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
- Device-related urethra or prostatic capsule rupture requiring surgical intervention

A composite endpoint is being used due to the low incidence rate of each of the device-related serious complications.

The Primary Safety Endpoint will be analyzed with descriptive statistics and nominal 95% confidence interval. There will be no formal statistical hypothesis test.

4.4.3 Secondary Endpoint 1: Average IPSS improvement in the Test arm at 12 months

The average IPSS improvement in the Test arm from baseline to 12 months must be ≥ 30%

4.4.4 Secondary Endpoint 2: Percentage of responders at 3 months

The responder analysis will provide the actual rate of subjects who benefited from the study treatment. The responder rate at 3 months of subjects randomized to the Test arm will be compared to the responder rate of subjects in the Control arm.

A responder is defined as a subject who has an IPSS improvement of ≥ 30% post-treatment as compared to baseline.

4.4.5 Secondary Endpoint 3: Durability - Percentage of responders

The responder rate at 12 months of subjects randomized to the Test arm will be compared to the responder rate at 3 months of subjects in the Control arm.

A responder is defined as a subject who has an IPSS improvement ≥ 30% post-treatment as compared to baseline.

4.4.6 Secondary Endpoint 4: Qmax

The maximum urinary flow rate (Qmax) provides an objective, non-invasive measurement of the subject's BPH symptoms.

The change or increase in Qmax at 12 months for all treated subjects randomized to the Test arm will be compared to the change or increase in Qmax at 3 months for subjects randomized to the Control arm.

4.4.7 Ancillary Endpoints

The following Ancillary Endpoints are to provide additional characterization of the safety and efficacy of the Optilume BPH Catheter System in the treatment of LUTS/BPH.

- A1: Additional responder analyses with a responder defined as IPSS improvement of 35%, 40% and 50%
- A2: Change in PVR
- A3: Change in sexual function
- A4: Change in BPH-II
- A5: Change in quality of life
- A6: Change in pain score
- A7: Procedure parameters
- A8: Change in Qmax
- A9: Proportion of subjects experiencing a return to 'normal' symptom severity

5 SUBJECT SELECTION

Only subjects who meet all inclusion criteria and no exclusion criteria, agree to comply with the follow-up visit schedule and provide informed consent will be eligible to be randomized/treated and participate in the study. If a subject moves away during the study, every effort should be made to maintain the follow-up schedule including having an appropriate physician follow the subject.

5.1 Entrance Criteria for Randomization Arm

5.1.1 Inclusion Criteria for Randomization Arm

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 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
7. Able to complete the study protocol in the opinion of the investigator

5.1.2 Exclusion Criteria for Randomization Arm

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

5.2 Entrance Criteria for Pharmacokinetics Arm

5.2.1 Inclusion Criteria for PK Arm

Subjects must meet all the eligibility criteria for the Randomization arm of the study with the exception of Inclusion 3; the subject's Qmax, which must be ≥ 5 ml/sec and ≤ 15 ml/sec (with minimum voided volume of ≥ 150 ml) in order to be eligible to participate in the PK arm of the study.

5.2.2 Exclusion Criteria for PK Arm

- In addition to not meeting any of the exclusion criteria for the Randomization arm of the study, subjects must also not meet either of the following exclusion criteria in order to be eligible to participate in the PK arm of the study:
- Treated with any device or medical therapy that contains paclitaxel
- Unable or unwilling to provide viable semen samples

6 SITE SELECTION

Sites will be selected based on the availability of the subject pool to be included in the study and the sites' ability to perform the research with sufficient resources and in compliance with GCP and other applicable guidelines and regulations.

In addition, the sites must be able to comply with any country-specific requirements as well as other requirements specified by their respective Institutional Review Board (IRB)/Research Ethics Board (REB).

7 PHYSICIAN SELECTION

Physicians selected must have experience in performing cystoscopy and endoscopic treatment of BPH. Selected physicians will be trained in the use of Urotronic's Optilume BPH Catheter System prior to enrolling subjects. The primary investigator at each site will ensure that only trained sub-investigators who satisfy the physician selection criteria can perform the study interventional procedure.

Healthcare professionals or site staff that assist or perform the follow-up evaluations do not need to be trained on the use of the device but must be delegated and trained to perform the follow-up visit procedures.

7.1 **Training**

The Sponsor, or designee, will be responsible for training of appropriate clinical site personnel. Prior to the start of study enrollment at a study site, the Sponsor or designee will perform formal device and study training for study site personnel to ensure proper procedural technique, uniform data collection and protocol compliance. At this training session material will include, but may not be limited to:

- Investigational Plan
- Techniques for the identification of eligible subjects
- Device Training
- Instructions on data collection including adverse events
- Schedules for subject follow-up
- Regulatory requirements

A site initiation visit will be conducted as a final check of the site readiness. If a site is not able to enroll its first subject 3 months after "Ready to Enroll" status, the Sponsor may elect to terminate the investigational site and allocate the slot to another candidate site.

8 STUDY PROCEDURES

8.1 **Pre-screening, Screening, and Baseline**

The site may pre-screen potential subjects by reviewing medical records to identify potential study subjects. Once identified, these subjects are approached to discuss the study, asked to participate and sign the IRB/REB approved informed consent form. The site may not initiate any study-specific (non-standard of care) procedures without first obtaining informed consent.

All baseline testing and evaluations must be done as close to the time of scheduled treatment as possible and repeated if needed. Any required procedures performed before obtaining informed consent as part of the standard of care may be used in lieu of the study tests.

The evaluations listed in Table 8-1 are to be conducted and recorded for all subjects prior to randomization/treatment in the study. Subjects who require a washout period should have these evaluations, with the exception of informed consent, conducted following completion of the washout period. Cystoscopy and TRUS that were performed as standard of care within 90 days of the procedure, even if they were performed prior to a required drug washout, are acceptable. Subjects who cannot tolerate a drug washout or are considered high risk from the drug washout should be excluded from the study. See Table 8-2 for the list of drug washout periods.

Table 8-1: Baseline Evaluations

Evaluations	Accepted interval prior to procedure (unless specified otherwise)	Condition
Informed consent	Prior to any study-specific procedures or drug wash-out	
Medical and Genitourinary history	Within 30 days	Evaluation is complete and adequately documented in source documents
Physical exam evaluation (with genital exam, digital rectal exam, demographics, height, weight and vital signs of body temperature, sitting blood pressure, sitting heart rate and respiratory rate)	Within 30 days	Evaluation is complete and adequately documented in source documents
Current or prior (up to 6 months) medication use	Prior to procedure	A list of current and prior medication from the past 6 months is required to be documented to determine if the dose is stable. Vitamins and supplements do not need to be documented unless the indication is related to urinary symptoms. The medical record must be reviewed for up to 12 months prior to confirm no LHRH analogues have been administered.
Blood analysis • Complete blood cell count (CBC) • Comprehensive Metabolic Panel (CMP)	Within 30 days	CBC includes: hemoglobin, hematocrit, platelets, RBC and WBC. CMP includes: glucose, hemoglobin A1c (as appropriate), calcium, protein (albumin, total protein), electrolytes (bicarbonate, chloride, sodium, potassium), kidney (creatinine, blood urea nitrogen [BUN]), liver (alkaline phosphatase [ALP], alanine amino transferase [ALT], aspartate amino transferase [AST], bilirubin)

Evaluations	Accepted interval prior to procedure (unless specified otherwise)	Condition
Serum prostate-specific antigen level (PSA)	Within 30 days	Must be <10 ng/ml or prostate cancer must be ruled out by biopsy

Semen analysis
• Lab assessment for sperm quality
  ○ Density or concentration
  ○ Total number (Sperm count)
  ○ Motility
  ○ Progressive motility
  ○ Morphology
	Within 30 days	Analysis is complete and includes sperm concentration. These tests are only applicable for the 15 subjects treated in the PK arm of the study

Dipstick urine analysis • Glucose • Protein • Leukocytes • Blood • Nitrite	Within 14 days	Must be negative for indications of infection before index procedure. More comprehensive urinalysis (e.g. microscopy) may be utilized in lieu of a dipstick test. Urine samples for this test must be taken 7 days or more after discontinuation of all antibiotics
Urine culture for infection	Within 14 days	Must be negative for infection before index procedure Urine samples for this test must be taken 7 days or more after discontinuation of all antibiotics
Uroflowmetry • Voided volume (must be ≥ 150 mL or test must be repeated for all the uroflow tests) • Voiding time • Peak flow rate (Qmax) • Post-void residual urine volume (PVR; may be measured by either ultrasound or catheterization but the same method must be used pre- and post-treatment)	Within 30 days	Must be performed before cystoscopy or ≥14 days after cystoscopy There must be no evidence of UTI prior to conducting test. If the baseline urine culture is performed after the baseline uroflowmetry and comes back positive for UTI, the uroflowmetry must be repeated after confirmation that the UTI has resolved. The PVR method used during screening must be the same as that used in the follow-up tests
Cystoscopy	Within 90 days prior to treatment up to the day of the procedure	Prior cystoscopy before index procedure is acceptable only if images were collected in the last 3 months and images are available for source documentation
Transrectal ultrasound (TRUS)	Within 90 days	Determine prostate volume (PV), length, width and height, and to measure any intravesical prostatic protrusion (IPP)
Subject questionnaires • International Prostate Symptoms Score (IPSS) - Standard	Within 30 days	There must be no evidence of UTI prior to administering the IPSS at baseline. If the baseline urine culture is performed after the baseline IPSS and comes back positive for UTI,

Evaluations	Accepted interval prior to procedure (unless specified otherwise)	Condition
• International Index of Erectile Function (IIEF) • BPH Impact Index (BPHII) • EQ-5D • MSHQ-EjD • VAS Pain Scale		the IPSS must be repeated after confirmation that the UTI has resolved. If multiple same questionnaires were filled out, the last questionnaire will be used to qualify for the study
PK samples: • Plasma • Urine • Semen	Within 30 days	These tests are only applicable for the 15 subjects treated in the PK arm of the study

Table 8-2: Drug Washout Periods Prior to Baseline Assessment

Drug	Washout Period
Luteinizing Hormone-Releasing Hormone (LHRH) analogs	12 months
5-alpha reductase inhibitor [e.g. dutasteride (Avodart)]	6 months
Type II 5-alpha reductase inhibitor [e.g. finasteride (Proscar or Propecia)]	3 months
Estrogen	Drug is excluded (unless there is documented evidence of stable dosing for the last 3 months)
Drug-producing androgen suppression	Drug is excluded (unless there is documented evidence of stable dosing for the last 3 months)
Daily dose of PDE5 inhibitor (e.g. Cialis)	2 weeks
Alpha blockers	2 weeks
Antidepressants with adrenergic effects (i.e. duloxetine, imipramine and amitriptyline)	2 weeks (unless there is documented evidence of stable dosing for the last 3 months)
Long-acting anticholinergics (LAAC) for chronic obstructive pulmonary disease (COPD)	2 weeks

	(unless there is documented evidence of stable dosing for the last 3 months)
Androgens	2 weeks (unless there is documented evidence of stable dosing for the last 3 months)
Anti-platelets (e.g. clopidogrel, aspirin)	10 days prior to procedure
Antihistamines	1 week (unless there is documented evidence of stable dosing for the last 6 months)
Anticonvulsants	1 week (unless there is documented evidence of stable dosing for the last 6 months)
Antispasmodics	1 week (unless there is documented evidence of stable dosing for the last 6 months)
Warfarin and novel oral anti-coagulants [e.g., apixaban (Eliquis), fondaparinux (Arixtra), rivaroxaban (Xarelto) or edoxaban (Savaysa)]	Prior to procedure

8.2 **Subject Enrollment**

Only subjects who meet the entrance criteria, agree to comply with the follow-up visit schedule and provide informed consent will be eligible to participate in the study.

If the subject is on BPH medication or any excluded medication, they will then go through a washout period. Subjects who cannot tolerate a drug washout or are considered high risk from the drug washout should be excluded from the study. Subjects must provide informed consent before beginning a washout that is specifically for the study. If the subject successfully goes through the washout period and still meets the entrance criteria, the subject will be eligible to participate in the study After the subject provides informed consent, the subject will be considered enrolled and will be entered into the study database and assigned a unique subject identification code (ID). Consented subjects meeting all inclusion criteria and no exclusion criteria may be randomized to a study treatment or treated in the non-randomized PK arm.

A subject is considered enrolled in the study when informed consent is provided.

A subject is eligible for randomization when:

- It is confirmed that ALL the inclusion criteria are met
- It is confirmed that NO exclusion criteria are met

A subject is considered evaluable in the PK arm of the study upon treatment with the Optilume BPH System (i.e. insertion of the pre-dilation catheter into the urethra).

8.3 **Concomitant Therapy**

Therapy (medication and non-medication therapies) not restricted by protocol may be used during the study for the treatment or prevention of disease or to maintain good health. However, the subjects should not take concomitant medications that affect the urinary symptoms which might confound the study results, per physician's discretion. Pyridium may be given prophylactically for 3 days post-procedure if it is given to all subjects in both the Test and Control arms at the study site. Antispasmodics (e.g. hyoscyamine) may also be given prophylactically the day prior to and the day of the procedure and for up to 3 days post-procedure if standard-of-care at the site.

8.4 **Randomization**

Subjects in the Randomization arm of the study will be randomized in a 2:1 allocation of Test (Optilume BPH Catheter System) to Control (sham). Randomization will be stratified by IPSS severity using permuted blocks within each site using an Electronic Data Capture (EDC) system. Each subject will be randomized after it is confirmed that he meets all the inclusion criteria and none of the exclusion criteria and prior to initiation of the Test / Control procedure. Only randomized subjects will be considered evaluable in the Randomization arm. Those subjects who do not meet all entrance criteria after baseline evaluation will be counted as screening failures and will not be randomized.

8.5 **Blinding**

In order to execute this study design, since the treating physicians in the Randomization arm of the study will be unblinded, they will not be allowed to conduct the study follow-up visits on any subject they treated themselves until the subject is unblinded. A blinded person at the study site will be conducting all study follow-up visits through the 12-Month follow-up visit (or until the subject is unblinded) to maintain blinding.

Subjects in the Randomization arm of the study will be blinded to the treatment received through their 12-Month follow-up visit, at which point the subjects will be unblinded. All Test and Control procedures will take place in the same setting at each investigational site (in-office, hospital or ambulatory surgical center). The treatment procedure location must be identified upfront and used for all study treatments, Test or Control. Switching between study treatment locations at a site will not be allowed unless the switch is made for all study treatments.

In order to maintain subject blinding during the treatment procedure, a sheet should be placed to block the subject's view of the treatment area for all randomized subjects. For all subjects, the

Optilume and sham devices will be visible in the treatment room when subject is being prepped for the procedure irrespective of treatment assignment. Noise cancelling headphones with music playing will be used by all subjects who are conscious during a randomized procedure. If noise cancelling headphones are not available, a script will be used during the Control procedures to replicate the discussion associated with the Test arm.

Subjects will be unblinded after the 12-Month follow-up examination, or to protect the subject's health prior to the 12-Month follow-up. If any subject returns to the urologist with no improvement or worsening LUTS and receives further treatment for BPH, they will be considered a failure for the purposes of endpoint analyses.

Every effort should be made to maintain the study blind in all subjects for 12 months after the Test or Control arm treatment. To allow for proper care of the subject who receives further treatment for BPH however, the subject's assignment to Test versus Control arms may be made known prior to 12 months at the time the subject has opted to receive additional BPH treatment and wishes to further discuss treatment options. To aid in maintaining the blind, a blinded member of the site will counsel the subject on available treatment options as described in Section 4.2.3. If a non-urgent clinical need requires the subject to be unblinded prior to the 12-Month follow-up and if time allows, the physician will notify the Sponsor prior to unblinding the subject.

The study blind may be broken at any time during the study due to medical necessity. All subjects will complete the Subject Satisfaction questionnaire at the 3-Month and 12-Month follow-up visits; the subjects will be asked which treatment they think they received and their degree of certainty.

Blinding procedures will be reviewed at the time of each Site Initiation Visit (SIV) by a Sponsor representative. Blinding procedures and instructions are summarized in Table 8-3**.**

Table 8-3: Blinding Procedures

Time Point	**Blinding Procedure**
Informed Consent	During the informed consent process, the study procedures, treatments and blinding procedure should be discussed with the subject and family/caretakers as appropriate.
Randomization	The randomization assignment should be communicated to the Investigator in a way to prevent the subject from overhearing which group they have been assigned to if applicable. Each site should develop a process that works best with their treatment location and processes.

Time Point	Blinding Procedure
Treatment	All treatment procedures will take place in the same setting at each investigational site (in-office, hospital or ambulatory surgical center). The treatment procedure location must be the same for all study treatment arms. Switching treatment locations based on treatment arms will not be allowed. During the treatment procedure, a sheet should be placed to block the subject's view of the treatment area for all subjects. For all subjects, the Optilume and sham devices will be visible in the treatment room when subject is being prepped for the procedure irrespective of treatment assignment. Noise cancelling headphones with music will be used by all subjects who are conscious during a randomized procedure. If noise cancelling headphones are not available, a script will be used during the Control procedures to replicate the discussion associated with the Test arm. The number of medical personnel exposed to the randomization assignment should be limited as far as possible on a need to know basis.

Time Point	Blinding Procedure
Post-Procedure	All subjects will be provided the same instructions on post-procedure recovery precautions including: 1. ABSTAIN from ALL sexual activities including masturbation for a minimum of fourteen (14) days post-procedure 2. Abstain from sexual activities or use a condom for a minimum of thirty (30) days post-procedure. The time of protected sex may be extended by the physician 3. Abstain from sexual intercourse or use a highly effective contraceptive for at least 6 months post-procedure to prevent harm to an embryo or fetus 4. No strenuous activity (e.g. heavy lifting, running) for 30 days post-treatment Blinded personnel at the study site will be conducting all study follow-up visits through the 12-Month follow-up visit or subject unblinding (whichever comes first). Any recovery and hospital/clinic staff should be educated to the protocol blinding procedures and instructed to not inadvertently unblind the subject and/or family/caretakers during the recovery period. In addition, the subject's medical record should clearly identify the subject as a study participant and not list the treatment assignment.
Follow-up	The site study staff should maintain blinding procedures through the 12-Month follow-up. Clinic staff will be educated to the protocol blinding procedures and instructed not to inadvertently unblind the subject and/or family/caretakers during the follow-up period.
Unblinding	A subject should not be unblinded to the treatment assignment prior to the 12-Month follow-up unless it is determined to be medically necessary by the Investigator. This includes seeking alternative BPH therapy due to continued or recurrent LUTS/BPH symptoms.

Time Point	Blinding Procedure
Cross-over	In the event a subject in the Control arm requires BPH treatment due to recurrent LUTS/BPH prior to the 12-Month follow-up, the subject may be unblinded to discuss treatment options, including a cross-over into the Test (Optilume DCB) arm and to consent for treatment with the Optilume DCB if appropriate. The subject may only cross-over into the Test arm after the 3-Month visit has been completed. Subject may choose to opt for non-study treatments, at which point the subject will exit the study upon initiation of the therapy.

8.6 Study Procedure – Randomization Arm

The treatments for the study may be performed in a hospital, ambulatory surgical center or in-office setting. Data collected from each Test or Control procedure will include, but may not be limited to: operating physician, procedure times, device use and disposition, medications used, adverse events and any device malfunctions. A summary of a typical procedure is described in the sections below. See the Instructions for Use (IFU) for additional details. If the summary is different from the IFU, follow the instruction in the IFU.

Use baseline TRUS to determine the prostate volume and dimensions. Select the corresponding pre-dilation balloon catheter and drug coated balloon catheter based on the sizing guides in the IFU and confirm device availability.

The inflation pressure must be recorded for each inflated balloon.

In order to maintain subject blinding during the treatment procedure, a sheet should be placed to block the subject's view of the treatment area for all randomized subjects. For all subjects, the Optilume and sham devices will be visible in the treatment room when subject is being prepped for the procedure irrespective of treatment assignment. Noise cancelling headphones or a script will be used during the Control procedures to replicate the discussion associated with the Test arm.

8.6.1 Peri-procedural Medication

Local block or systemic anesthetics are required; in addition it is recommended that a bolus of lidocaine gel is injected into the urethra 10 minutes prior to the study procedure. In general, the study procedure approach for all arms of the study is similar to cystoscopy, including the administration of a pre-procedure antibiotic as appropriate. The use of any medication (e.g. antibiotic, anesthetic and/or sedative) will be recorded in the Procedure case report form. Any antibiotics should be recorded on the Concomitant Medication Log. The peri-procedural anesthetic and sedative medications do not have to be listed in the Medications CRF.

Peri-procedural short acting anti-spasmodic medication (e.g. hyoscyamine sulfate [Levsin], oxybutynin) is recommended and post-procedural prophylactic medications such as phenazopyridine (Pyridium) may be used at physician's discretion for both the Test and Control arms. These medications should be listed on the Concomitant Medication Log.

8.6.2 Test Arm Procedure Description

8.6.2.1 Pre-dilation

Pre-dilation with the Optilume BPH Pre-dilation Catheter is required for all subjects. Select the correct size pre-dilation catheter (30 x 30 mm or 30 x 35 mm) based on the sizing guide in the IFU. Prepare and use the pre-dilation catheter per the IFU. Document the location of the commissurotomy.

8.6.2.2 DCB Treatment

Select the correct size drug coated balloon catheter based on the sizing guide in the IFU. Prepare the drug coated balloon catheter and complete the procedure per the IFU.

8.6.3 Control Arm Procedure Description

1. Insert cystoscope and survey urethra, prostate and bladder.
2. Remove cystoscope.
3. Prepare the Optilume BPH Prostatic Pre-dilation Catheter modified to prevent inflation, insert it transurethrally and advance to the prostatic urethra.
4. Do NOT pull back the insertion sheath to expose the balloon and do NOT inflate the balloon.
5. Place noise cancelling headphones on the subject or read the prepared script out loud to replicate the discussion associated with the Test arm.
6. Leave the Optilume BPH Prostatic Pre-dilation Catheter modified to prevent inflation in place for a minimum of 5 minutes.
7. Withdraw catheter and sheath from the subject's body and dispose of properly.

8.7 Study Procedure - PK Arm

Some of the study sites will participate in the PK arm of the study. The treatments for the study may be performed in a hospital, ambulatory surgical center or in-office setting. Data collected from each procedure will include, but may not be limited to: operating physician, procedure times, device use and disposition, medications used, adverse events and any device malfunctions. A summary of a typical procedure is described in the sections below. See the Instructions for Use (IFU) for additional details. If the summary is different from the IFU, follow the instruction in the IFU.

Use baseline TRUS to determine the prostate volume and dimensions. Select the corresponding pre-dilation balloon catheter and DCB catheter based on the sizing guide in the IFU and confirm device availability.

The inflation pressure must be recorded for each inflated balloon.

8.7.1 Peri-procedural Medication

Local block or systemic anesthetics are required; in addition it is recommended that a bolus of lidocaine gel is injected into the urethra 10 minutes prior to the study procedure. In general, the study procedure approach for all arms of the study is similar to cystoscopy, including the administration of a pre-procedure antibiotic as appropriate. The use of any antibiotic, anesthetic and/or sedative will be recorded in the case report form.

8.7.2 PK Arm Procedure Description

It is recommended to fill the bladder prior to dilation in order to facilitate urine collection at the end of the procedure.

8.7.2.1 Pre-dilation

Pre-dilation with the Optilume BPH Pre-dilation Catheter is required for all subjects. Prepare and use the pre-dilation catheter per the IFU. Document the location of the commissurotomy.

8.7.2.2 DCB Treatment

Prepare the selected drug coated balloon catheter and complete the procedure per the IFU.

8.7.2.3 Post-Procedure Urine Collection for PK Arm

Collect a post-procedure urine sample from the subject for drug content measurement from the 2nd void sample (prior to catheterization).

1. Palpate the subject's bladder to allow about 1 cup (100 – 150 ml) of fluid to flow out of the urethra to flush any residual coating particles. This is recognized as the 1st void. (If palpation does not produce urine, collection may be done through the Foley catheter.)
2. Then palpate the bladder again, collect the urine sample for about 100 ml or any remaining residual fluid for analysis. This is recognized as the 2nd void.

Refer to Table 4-2 for all urine PK collection times.

8.7.2.4 Post-Procedure Blood Collection for PK Arm

Collect a post-procedure blood sample from the subject for drug content measurement after collecting the 2nd void urine sample.

Refer to Table 4-1 for all blood PK collection times.

8.8 Catheterization

Insert a Foley catheter for a minimum of 48 hours. Record the Foley catheter size. The Foley catheter may be removed or replaced prior to 48 hours if it becomes blocked.

Record the date and time of Foley catheter removal. If the subject requires re-catheterization within 24 hours of the initial removal, document the date and time of the final removal. If re-catheterization

occurs within 24 hours, it is counted as the same catheterization event as the previous catheterization. In this case, this will be considered a continuation of the procedure "healing" phase.

8.9 **In-Hospital to Discharge**

Prophylactic antibiotics are recommended post procedure according to treatment guidelines.

All subjects should be counseled to not take any anti-platelet medications (e.g. aspirin [Bayer, Ecotrin], Brilinta, Effient, Plavix) or oral anti-coagulants (e.g. Arixtra, Coumadin, Eliquis, Pradaxa, Savaysa, Xarelto) for at least 5 days after the procedure.

8.10 **Physical Activities**

All subjects must be counseled about physical activities post-treatment:

- No strenuous activity (e.g. heavy lifting, running) for 30 days post-treatment

8.11 **Sexual Activities**

Paclitaxel can cause serious harm to an embryo or fetus and has been detected in the semen for at least 30 days following the Optilume BPH procedure. The time required for complete clearance of paclitaxel from semen following the Optilume BPH procedure is currently unknown.

All subjects must be counseled about sexual activities post-treatment as follows:

- ABSTAIN from all sexual activities including masturbation for 14 days post-treatment
- Abstain from sexual activities or use a condom for a minimum of 30 days post-procedure
- Abstain from sexual intercourse or use a highly effective contraceptive for at least 6 months post-procedure to prevent harm to an embryo or fetus

8.12 **Scheduled Follow-up Evaluations**

During the post-procedure period, investigators are encouraged to follow the current American Urological Association (AUA) guidelines in managing their subjects for the detection of prostate cancer in addition to the required evaluations in this protocol.

The following evaluations will be completed at each visit as indicated in Table 8-4. All subjects will be evaluated at baseline, immediately post-procedure, at Foley removal, 14 days, 30 days, 3 months, 6 months and 12 months. In addition, all subjects treated with the Optilume BPH Catheter System will be followed annually through 5 years post-procedure or until study close, whichever comes first.

Table 8-4: Scheduled Evaluations and Follow Up

Study Visit	**Baseline**	**Intra-Op**	**Pre-Discharge**	**Foley Removal**	**14-Day**	**30-Day**	**3-Month**	**6- Month**	**12-Month**	**Annual[9] (through 5 years)**	**Unscheduled**
Visit Windows	w/in 30 days[3]	N/A	N/A	≥ 48 hrs post-procedure	±3 days	±7 days	±14 days	±30 days	±30 days	±30 days	
Informed Consent	√										
Medical and genitourinary history	√										
Physical exam	√[4]				√	√	√	√	√[4]	√[4]	if indicated
Review Protected Sexual Activities			√	√	√	√	√	√			
Blood Analysis[5]	√					√	√	√	√	√	if indicated
Prostate specific antigen (PSA)	√								√	√	
TRUS	√										
Cystoscopy	√	√						√			if indicated
Randomization		√[11]									
Balloon Dilation		√									
Uroflow (Qmax + PVR)	√					√	√	√	√	√	if indicated
Urine Analysis	√				√	√	√	√	√	√	optional

Study Visit	**Baseline**	**Intra-Op**	**Pre-Discharge**	**Foley Removal**	**14-Day**	**30-Day**	**3-Month**	**6- Month**	**12-Month**	**Annual[9] (through 5 years)**	**Unscheduled**
Visit Windows	w/in 30 days[3]	N/A	N/A	≥ 48 hrs post-procedure	±3 days	±7 days	±14 days	±30 days	±30 days	±30 days	
Urine Culture	√			if indicated	if indicated	if indicated	if indicated	if indicated	if indicated	if indicated	if indicated
IPSS[1]	√				√[6]	√	√	√	√	√	if indicated
BPH Impact Index[1]	√					√	√	√	√	√	if indicated
EQ5D[1]	√					√	√	√	√	√	if indicated
MSHQ-EjD[1]	√						√	√	√	√	if indicated
Sexual function (IIEF) [1]	√						√	√	√	√	if indicated
Pain scale[1]	√		√ [2]	√	√	√	√				
Subject Satisfaction Questionnaire							√		√		
Adverse event(s)		√	√	√	√	√	√	√	√	√	√
All Medication(s) used	√ (prior BPH medications and all current)	√ (since the previous visit)	√ (since the previous visit)	√ (since the previous visit)	√ (since the previous visit)	√ (since the previous visit)	√ (since the previous visit)	√ (since the previous visit)	√ (since the previous visit)	√ (since the previous visit)	√ (since the previous visit)
Blood PK Samples[7]	√		√[8]	√		√	√	√			

Study Visit	Baseline	Intra-Op	Pre-Discharge	Foley Removal	14-Day	30-Day	3-Month	6- Month	12-Month	Annual[9] (through 5 years)	Unscheduled
Visit Windows	w/in 30 days[3]	N/A	N/A	≥ 48 hrs post-procedure	±3 days	±7 days	±14 days	±30 days	±30 days	±30 days	
Urine PK Sample[7]	√		√	√		√	√	√			
Semen PK Sample[7]	√[10]					√[10]	√[10]	√[10]			

[1] If multiple responses to the same questionnaires are available for each visit window, the last questionnaire will be used to qualify for the study

[2] Intra-operative pain scale must be done post-procedure while the subject is in recovery

[3] Cystoscopy and TRUS that were done within 90 days prior to the procedure may be used for the study baseline. Urine analysis and urine culture must be conducted within 14 days prior to the procedure

[4] Baseline physical exam also includes digital rectal exam (DRE), demographics, height, weight and vital signs. Annual physical exams to include DRE.

[5] Blood analysis includes Complete Blood Count (hemoglobin, hematocrit, platelets, red blood cell count and white blood cell count), Blood Chemistry [glucose, calcium, protein (albumin, total protein), Electrolytes (bicarbonate, chloride, sodium, potassium), Kidney (blood urea nitrogen, creatinine), Liver (alkaline phosphatase, alanine amino transferase, aspartate amino transferase, bilirubin)] and Hb A1c as appropriate

[6] IPSS (acute) at the 14-Day Visit

[7] PK samples are only collected for the 15 subjects in the PK arm of the study

[8] Pre-discharge blood PK samples are required at 0 hours (after collecting 2nd void urine sample), 1 hour, 3 hours and 5 hours

[9] All subjects who exit the study for any reason prior to 5 years post-procedure (including Control subjects who complete the 12-Month follow-up) will be requested to allow continued follow up for general health information through 5 years post-procedure

[10] Semen quality analysis will be captured for all Semen PK samples

[11] Randomization must take place after all eligibility criteria has been confirmed but prior to initiating the Test/Control procedure. If the baseline cystoscopy is performed in the same setting as the index procedure, the subject may be randomized after verification of eligibility but prior to initiation of the Test/Control treatment

8.13 Unscheduled Follow-up Visits

If subjects are seen for unscheduled/interim visits because of an AE, appropriate Case Report Form(s) (CRF), including the AE CRF, will be completed. At the investigator's discretion, some of the evaluations and tests may be repeated if indicated. The Sponsor requests that if any additional tests or procedures listed within this protocol are performed during an unscheduled visit, the investigator should provide the results on the Unscheduled Visit CRF(s).

8.14 Lost to Follow-up

If a subject fails to comply with follow-up visits, the investigational site must make at least three repeated attempts to contact the subject. Each attempt to contact the subject and the method used (e.g., telephone contact, registered letter) must be documented in the subject's records.

If a subject misses one of the follow-up visits, but is present at the subsequent follow-up, the subject should be queried retrospectively for basic information (e.g., AEs); however, the IPSS and other questionnaires will be collected prospectively only. The missed visit must be documented on a Protocol Deviation CRF.

8.15 Subject Withdrawal from Study

8.15.1 Voluntary Withdrawal

A subject may voluntarily withdraw from the study at any time. If a subject officially withdraws from the study, the investigator must ensure that the reason for the withdrawal is documented. If the subject had an AE, the subject should be followed until the resolution of the AE, if possible. Data from these subjects will be included in the analysis up to the point of each subject's withdrawal.

All subjects who withdraw from the study will be asked to provide general health information for 5 years post-procedure if possible.

8.15.2 Involuntary Withdrawal

A subject also may be withdrawn by the investigator if the subject's participation in the study will have a negative effect on the safety of the subject. Data obtained up to the date of the subject's withdrawal will be included in the study, if applicable.

All subjects who are withdrawn from the study will be followed for 5 years post-procedure for general health information if possible.

8.15.3 Alternative Treatments

If the subject opts to receive an alternative BPH therapy and does not wish to cross-over to the Test arm or was already randomized to receive treatment with the Optilume BPH catheter system, the subject will be withdrawn from the study at the time the alternative therapy is received unless there is an unresolved device or procedure related adverse event, in which case, they may be followed for another 30 days or until the AE is resolved, whichever comes first. The subject will be asked to provide general health information for 5 years post-procedure if possible. Subjects who receive the

Optilume BPH Catheter System but later decide they require alternative treatment will be considered treatment failures.

8.16 **Follow-up for General Health**

All subjects who exit the study for any reason prior to 5 years post-procedure (including Control subjects who complete the 12-Month follow up) will be requested to allow continued follow up for general health information through 5 years. The information collected includes mortality status and significant safety events that have occurred since the last subject contact. Every effort should be made to collect this information at the annual follow-up visit timepoints. General health information may be collected via telephone and does not require an in-office visit. The inability to collect the information will not constitute a protocol deviation. Any significant safety events occurring after the subject has exited the study will be reported on a General Health Information CRF.

8.17 **End of Study**

All subjects treated with the sham device will be followed as described in Table 8-4 until they complete the 12-Month follow-up, and all subjects treated with the Optilume BPH Catheter System will be followed as described in Table 8-4 until they complete the 5-Year follow-up visit or the study is discontinued by the Sponsor, whichever comes first.

An End of Study CRF will be completed for each subject.

9 SUBJECT EVALUATION DESCRIPTION

9.1 **Place of Service**

Follow-up evaluations are expected to be conducted via an in-office visit to allow for collection of all the required follow-up assessments. Remote follow-up visits may be conducted in the event an in-person visit is not feasible (e.g. due to COVID-19), but the inability to conduct assessments that require an in-office visit as described in Table 8-4 must still be documented as a protocol deviation as described in Section 14.3.3. If the subject is unable to visit the study site, blood analysis, PSA, urinalysis, urine culture and uroflow measurements collected at non-study locations as standard of care may be utilized without the need to document a protocol deviation unless the testing does not meet the requirements of the protocol (e.g. voided volume < 150 mL).

If the 3-Month visit or the 12-Month visit (primary endpoint) is unable to be performed in-person, it is encouraged that site complete a remote visit within the visit window to assess subject safety and administer questionnaires at a minimum. The subject should be brought in for an Unscheduled visit as soon as possible to complete remaining assessments. Questionnaires should be re-administered at this Unscheduled visit.

9.2 **Physical Examination**

A physical examination will be conducted at each scheduled follow-up visit beginning with the 14-Day visit and will include a genital examination by an active study investigator. A digital rectal

examination will be performed by an active study investigator at the 12-Month visit and all annual visits. Vital signs (body temperature, blood pressure and heart rate) will also be collected as part of the physical exam.

9.3 Subject Questionnaires

All questionnaires are preferentially self-administered and will be completed at baseline (with the exception of the Subject Satisfaction Questionnaire) and at required follow-up visits. If the assessment is required to be conducted remotely (e.g. due to COVID-19 limitations), the questionnaires may be mailed or emailed to the subject for completion prior to phone/telemedicine follow up, and the subject may be queried for understanding of the questions during the visit. If subject compliance is uncertain, the IPSS, VAS and Subject Satisfaction questionnaires may be interview administered at the time of the phone/telemedicine follow up. If a questionnaire is interview administered, this should be noted in the source documentation. Evidence exists that interview administration produces equivalent results for these questionnaires.[1,2]

Questionnaires completed at baseline will be compared to those completed at follow-ups to assess the effect of treatment. The major instruments and assessments administered are described in this section. If multiple responses to the same questionnaires are available for each visit window, the last set of scores will be used unless there are valid scientific reasons to exclude one of the readings.

9.3.1 IPSS (Standard)

The International Prostate Symptom Score (IPSS) contains the well-validated, highly reliable and responsive American Urological Association symptom score (AUASS) assessment to identify the severity of BPH symptoms.

The first seven questions in the IPSS address frequency, nocturia, weak urinary stream, hesitancy, intermittence, incomplete emptying, and urgency, and scored on a 6-point scale (0 to 5). The IPSS can be interpreted as follows: 0-7 mildly symptomatic, 8-19 moderately symptomatic, and 20-35 severely symptomatic.

The IPSS also includes the following eighth question that is designed to assess the degree of "bother" associated with the subject's urinary symptoms: "If you were to spend the rest of your life with your urinary condition just the way it is now, how would you feel about that?" Answers range from "delighted" to "terrible" (0-6). This question correlates well with the overall BPH symptom score and summarizes the impact of urologic symptoms on quality of life.

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[1] Plante M, Corcos J, Gregoire M, et al. The International Prostate Symptom Score: Physician vs Self-Administration in the Quantification of Symptomology. *Urology*. 1996;47:326-8.

[2] Von Korff M, Jensen MP, Karoly P. Assessing Global Pain Severity by Self-Report in Clinical and Health Services Research. *Spine*. 200;25(24):3140-51.

The standard IPSS is self-administered and will be completed at baseline and at each in-office follow-up visit beginning with the 30-Day Visit.

9.3.2 IPSS (Acute)

The acute IPSS is the same as the standard IPSS except that the questions refer to the subject's condition in the past week instead of the past month. This questionnaire will be completed by the subject at the 14-Day follow-up visit.

9.3.3 BPH Impact Index

The BPH Impact Index is a self-administered questionnaire that measures the impact of BPH symptoms on the subjects' quality of life. The questionnaire assesses physical discomfort, anxiety/worry, bothersome, and effect on activities of daily living.

The BPH Impact Index will be completed at baseline and at each follow-up visit beginning with the 30-Day Visit.

9.3.4 International Index of Erectile Function

The International Index of Erectile Function (IIEF) is a standardized, validated, self-administered questionnaire that is used to assess the subject's erectile function. The Sexual Health Inventory for Men (SHIM) is part of the IIEF and consist of 5 questions. This is sometimes called IIEF-5 and is used as a diagnostic test for erectile dysfunction and impotence.

The standard IIEF will be administered at baseline and at each follow-up visit beginning with the 30-Day Visit.

9.3.5 EQ-5D

EQ-5D™ is a standardized instrument for use as a measure of health outcome. EQ-5D-5L is a self-reported generic preference-based measure of health, developed by the EuroQol Group. The instrument can be applied to, and has been shown to be valid for, a wide range of health conditions. The EQ-5D has been used in many studies as a way of capturing the health-related quality of life of patients, trial participants and the general public.

The EQ-5D will be administered at baseline and at each follow-up visit beginning with the 30-Day Visit.

9.3.6 MSHQ-EjD

MSHQ-EjD is the four-item version of Male Sexual Health Questionnaire (MSHQ) to assess ejaculatory dysfunction (EjD). It is a self-reported questionnaire that contains three ejaculatory function items and one ejaculation bother item.

The MSHQ-EjD will be administered at baseline and at each follow-up visit beginning with the 3-Month Visit.

9.3.7 Subject Pain Questionnaire

The Visual Analog Scale (VAS) pain score (1 to 10 scale) will be used to assess the subject's pain. The person administering the questionnaire should explain to the subject that the pain being assessed is limited to urological and pelvic pain including pain associated with urinating and/or bowel movements.

The pain scale will be administered at baseline, post-procedure while the subject is in recovery, following Foley removal and at the 14-Day, 30-Day and 3-Month Visits.

9.3.8 Subject Satisfaction Questionnaire

This questionnaire is specific to the Urotronic DCB procedure on the treatment of moderate-to-severe LUTS/BPH and will assess subject blinding and measure overall satisfaction with the procedure, recommendation of treatment to friends/family and if the subject would undergo the treatment again if symptoms were to recur within 1 year.

The Subject Satisfaction Questionnaire will be self-administered at the 3-Month and 12-Month Visits.

9.4 Blood Analysis

Complete Blood Count (CBC):

- CBC includes hemoglobin, hematocrit, platelets, RBC and WBC

Comprehensive Metabolic Panel (CMP):

- Glucose, HbA1c (as appropriate), calcium, protein (albumin, total protein), electrolytes (bicarbonate, chloride, sodium, potassium), kidney (creatinine, blood urea nitrogen [BUN]), liver (alkaline phosphatase [ALP], alanine amino transferase [ALT], aspartate amino transferase [AST], bilirubin)

Prostate Specific Antigen (PSA)

9.5 Dipstick Urine Analysis

A urine dipstick analysis must be performed at the baseline visit and at each follow up visit starting at the 14 Day Follow-up. A more sensitive test (e.g. microscopy) may be performed in lieu of a dipstick test. The Baseline measurement must be performed within 14 days prior to treatment. Samples taken for this test must be taken at least seven (7) days following discontinuation of all antibiotics. Subjects need to have a negative urine analysis prior to the study index procedure. Data collected should include, at minimum:

- Glucose
- Protein
- Leukocytes
- Blood
- Nitrite

9.5.1 Urine culture

A urine culture needs to be performed within 14 days prior to treatment. Samples taken for this test must be taken at least seven (7) days following discontinuation of all antibiotics. Subjects need to have a negative urine culture prior to the study index procedure. Urine cultures will be performed during follow up only if indicated.

9.6 Uroflowmetry

Subjects will be asked to hydrate and refrain from voiding for two hours prior to each uroflowmetry. Hydration may be achieved by asking the subject to drink 2 or more cups of non-caffeinated fluids.

A bladder scan is recommended to be performed prior to voiding to ensure the subject has a bladder volume of at least 250 ml.

Outcomes will be recorded for each qualified void on the CRFs and the strip recordings collected. Voiding data will be obtained with the subjects in the standing or sitting position, voiding into the uroflow instrumentation. The uroflow meter will provide the following information:

- Voided volume (≥150 ml required for a valid test)
- Peak flow rate (Qmax), averaged over an approximately 2-second interval if an artifact is noted
- Voiding time

If the voided volume is less than 150 ml, the test must be repeated at least once. If the voided volume is still less than 150 ml, the test with the highest voided volume will be used.

Uroflow must be performed before cystoscopy or at least 14 days after cystoscopy, when applicable.

9.6.1 Peak Flow Rate (Qmax) Measurement

Most uroflow equipment will automatically identify the peak flow rate of a voiding pattern, however this may result in spurious, non-physiologically relevant readings if a sudden spike is captured (e.g. due to bumping equipment, etc.). The recommendation for determining the Qmax reading is to have an Investigator review the readout and apply the 2-second rule to improve consistency if an artifact is noted. The Investigator's reading of the peak flow rate should be documented on the uroflow readout.

9.6.2 Post Void Residual Urine Volume

Following uroflowmetry, residual urine volume in the bladder shall be assessed by either bladder scanner ultrasound or catheterization. The same method must be used pre- and post-treatment.

9.7 Cystoscopy

A screening cystoscopy will be performed to confirm the presence of obstructive BPH, to estimate the BPH severity, and identify any significant contribution of the median lobe to obstruction.

Flexible or rigid cystoscope will be used to facilitate the DCB procedure.

A cystoscopy will also be performed at the 6-Month follow-up visit concentrating on the prostatic urethra.

9.8 TRUS

Transrectal Ultrasonography (TRUS) at baseline is required to determine the prostate size and to measure any intravesical prostatic protrusion (IPP).

9.9 Semen Analysis

Semen analyses will be evaluated in subjects enrolled in the PK cohort at baseline, 30 days, 3 months and 6 months post-procedure.

The semen will be analyzed by the site's local laboratory for sperm quality:

- Sperm density or concentration
- Total number (Sperm count)
- Motility
- Progressive motility
- Morphology

9.10 Remote Assessments

If a subject is not able to return for an in-person follow-up visit, the site should collect as much information as possible remotely by calling the subject. The site should attempt to conduct the following:

- Follow-up on any ongoing adverse events
- Determine if the subject has experienced any new adverse events since the previous visit
- Determine if there have been any changes to the medications since the previous visit
- Review protected sexual activities, if applicable
- Ask the subject to complete the applicable study questionnaires
    - Mail or email the study questionnaires to the subject to complete and return. If that is not possible, the site may fill out the questionnaires by asking the subject the questions over the phone and noting on the questionnaires that they were completed over the phone

A Protocol Deviation must be completed to document any protocol-required assessments that were not completed at the visit.

10 STATISTICAL CONSIDERATIONS

This section summarizes the main statistical considerations for the data analysis. Statistical details including plans for subgroup analyses, poolability, handling of missing data and control of the type I error for secondary endpoints are provided in a standalone Statistical Analysis Plan (SAP).

10.1 **Primary Efficacy Endpoint Analysis**

Subjects will be randomized in a 2:1 ratio to Test:Control. Randomization will be stratified by IPSS severity at baseline. The number of subjects randomized at an individual site in the randomization arm may not exceed 25% of the total randomized study sample size (n=37).

To meet the primary efficacy endpoint, the observed improvement in IPSS (π) at 12 months post-treatment in the Test arm must be at least 25% greater than that of the Control arm at 3 months:

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

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

Where:

$\pi_{Test,12}$ = Mean reduction in IPSS from baseline for the Test arm at 12 months

$\pi_{Control,3}$= Mean reduction in IPSS from baseline for the Control arm at 3 months

The statistical hypothesis test for the primary efficacy endpoint will be based on a two-sample t-test at a one-sided 0.025 alpha level (equivalent to a two-sided 0.05 alpha level).

10.2 **Primary Safety Endpoint Analysis**

The Primary Safety Endpoint will be analyzed with descriptive statistics and nominal 95% confidence interval. There will be no formal statistical hypothesis test.

A major device-related serious complication is defined as any of the following events through 12 months:

- Device-related rectal fistula or 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
- Device-related urethra or prostatic capsule rupture requiring surgical intervention

10.3 **Secondary Endpoint Analyses**

Secondary endpoints will be tested against the corresponding null hypotheses using a sequential gatekeeping strategy to control the type I error rate. Significance of the secondary endpoints will be based on sequential testing of the endpoints, proceeding in the order listed, until a non-significant result is reached at which time no further claims of significance will be made. Significance will only be claimed if success for the hypothesis test for the primary endpoint is achieved. Each test will be performed at a one-sided 0.025 alpha level.

10.4 **Ancillary Endpoint Analyses**

For those endpoints without a specified hypothesis test, descriptive statistics will be used in reporting outcomes. Continuous variables will be summarized with means or medians and standard deviations. Adverse Events, protocol deviations, and device malfunctions will be summarized with descriptive statistics.

10.5 **Sample Size Justification**

Sample size for the Randomization arm of the study is based on the Primary Efficacy Endpoint using the following assumptions:

- Statistical power of 90%
- One-sided 0.025 alpha
- 2:1 randomization allocation (treatment : control)
- A common standard deviation of 7
- Mean improvement in the Control arm of 6 points and mean improvement in the Test arm of 12.5 points
- 10% loss of follow-up rate

Based on these assumptions, a sample size of 132 evaluable subjects (88 Test and 44 Control) provides approximately 90% power. Assuming a 10% loss of follow-up rate, the randomization sample size is 147 (approximately 98 Test and 49 Control). With the 15 subjects in the PK arm, the total number of subjects required is 162 randomized/treated subjects (147+15). It should be noted that more than 162 subjects will be need to be consented (i.e. enrolled) to reach this total of 147 randomized and 15 PK subjects.

10.6 **Study Success Criteria**

For the study to be declared a success, the Primary Efficacy Endpoint and Secondary Endpoint 1 must be met without any safety concerns.

10.7 **Analysis Populations**

All subjects enrolled in the study, including those withdrawn from the study or lost to follow up, will be accounted for and documented. The primary endpoint analysis and secondary endpoints will be analyzed using the Intent To Treat (ITT) population, under which all randomized subjects will be included for the analysis, regardless of whether or not the subject received the randomized treatment.

In addition, the analyses will be completed on an As Treated (AT) basis (i.e. based on treatment actually received) and a Per Protocol (PP) basis. The PP analysis population will exclude subjects with the following significant protocol violations:

- Subject's rights are violated or did not give consent and subject data was requested to be excluded by IRB/REB
- Subject has a confirmed diagnosis of urethral stricture, bladder neck contracture at the time of treatment that would confound study results

- Subject had UTI at the time of treatment
- Subject had radiation of the pelvic region
- Subject had a previous surgery for BPH
- Subject did not complete wash out of drugs
- Subject had bladder or sphincter dysfunctions or anything else that would confound the results
- Subject had a psychiatric or cognitive disorder that prevents him from adequately answering the study questionnaires
- Subjects who are unblinded before the Primary Endpoint evaluation as required by the cohort

10.8 Handling of Missing Data

10.8.1 For the Primary Efficacy Endpoint and Secondary Endpoints S1

Subjects who withdraw due to adverse events, lack of effectiveness, or who initiate alternative BPH therapies will be considered as having no improvement in IPSS score. For subjects that have missing data for the primary efficacy endpoint, data will be imputed via multiple imputation as described in the SAP.

10.8.2 For the Primary Efficacy Endpoint

Unless there is evidence of occurrence of a primary safety endpoint event, subjects with missing data for the primary safety endpoint are presumed to not have experienced a primary safety endpoint event.

11 DEFINITION OF ADVERSE EVENT(S)

For purposes of this study, an adverse event (AE) is defined as any adverse change from the subject's baseline medical condition(s) occurring during the course of the study. For the purpose of AE documentation, the start of the course of the study is defined as the day of the study index procedure. All AE's will be recorded on an Adverse Event CRF whether considered procedure-related or not, and will be classified as described in Section 11.5.

Any adverse changes occurring between the time the subject is enrolled (i.e. consented) and the day of the study index procedure will be captured on the Medical History CRF.

Pre-existing conditions will not be reported as an AE unless there is an adverse change in that condition. Any AE which resolved and then recurred will be reported as a separate AE.

An AE may be volunteered spontaneously by the subject or discovered as a result of questioning or physical examination by an investigator or study staff.

11.1 Treatment Related Symptoms

The Urotronic DCB procedure is designed to alleviate the moderate-to-severe LUTS/BPH. Subjects to be treated have moderate-to-severe LUTS/BPH prior to treatment. These symptoms are expected to continue and may even worsen slightly prior to improvement as part of the healing process. Other

expected acute but transient symptoms from the treatment are dysuria, hematuria, and acute urinary retention as the tissue heals.

Worsening or new onset LUTS, dysuria or non-obstructive hematuria that occur and resolve within 14 days of treatment that do not require intervention (other than initial catheterization, prophylactic antibiotic, anti-inflammatory medication, and pain medication) will not be considered an AE as these are expected and part of the healing process. However, all aggressively treated symptoms will be recorded in the CRF. Intervention as it relates to hematuria includes but is not limited to, hospitalization, the need to irrigate the bladder and urethra, or the need for transfusion therapy.

Common urinary symptoms will be considered an AE if any of the following occur:

a. Worsening or new onset LUTS requiring intervention or persisting beyond 14 days post treatment
b. Worsening or new onset LUTS requiring hospitalization or intervention other than the use of catheterization, one standard course of antibiotic, anti-inflammatory and/or pain medication
c. Hematuria that requires irrigation or is obstructive (post-discharge)
d. Urinary tract infection defined as $>10^5$ CFU/mL of a single organism plus symptoms localized to bladder
e. Urinary retention after index procedure healing
f. If new onset LUTS recurs after the same symptom is resolved and is considered clinically significant or requiring re-catheterization.

11.2 **Urinary Retention and Catheterization**

A catheterization that occurs within 24 hours of a prior catheterization will be considered to be the same catheterization event.

All catheterizations and cystoscopies will be recorded in the CRF.

While catheterization in and of itself is not an AE, the reason for catheterization must be evaluated for purposes of determining an AE.

11.3 **Acute Urinary Retention Definition**

Acute urinary retention is the lack of ability to urinate. It typically has to be treated with a catheter to avoid serious complications of the bladder and/or kidney.

11.4 **Obstructive LUTS**

Obstructive LUTS has some symptoms similar to Urinary Retention. Obstructive LUTS is usually a chronic condition and is sometimes referred to as chronic urinary retention. Symptoms of obstructive LUTS are:

- Poor stream
- Hesitancy
- Terminal dribbling

- Incomplete voiding
- Overflow incontinence (occurs in chronic retention)

11.5 **Reporting and Classification of AEs**

Adverse events should be classified according to their underlying cause, if known (e.g., fever resulting from infection should be reported as "infection"). Symptoms related to a diagnosis should not be reported as separate AEs. In the above example, fever is a symptom caused by infection and should be reported as infection only.

Concomitant AEs that are unrelated (in the clinician's judgment) should be reported as separate events.

AE determination is based on three levels of evidence:

Level 1 – final diagnosis

Level 2 – signs

Level 3 – symptoms

Every effort should be made to collect Level 1 evidence of any AE. If an AE has all three levels of evidence, the AE should be reported only once at the highest level of severity, which is the final diagnosis (Level 1). A single AE should not be reported as multiple AEs based on separate symptoms and signs.

In cases where a diagnosis is not possible, AE determination should be based on the next highest level of evidence (i.e., Level 2: signs), followed by symptoms (Level 3), if symptoms are all that are available to the investigator.

A corrective action (e.g. catheterization) itself is not an AE but the reason of the catheterization may be an AE. The AE determination always should be based on the reason that a corrective action was taken. Note: there may be multiple signs or symptoms representing only one AE. Figure 11-1 below is an AE determination and outcome flowchart.

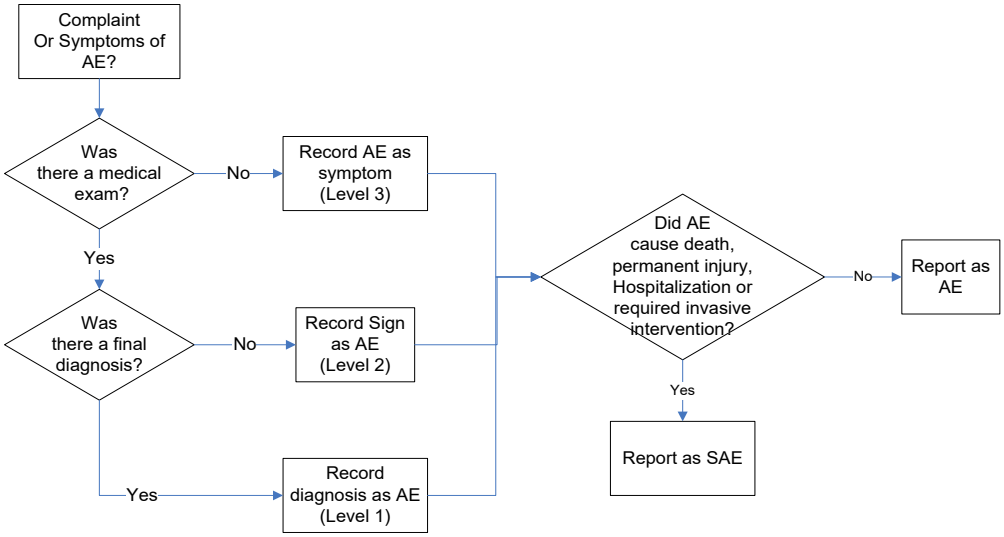

Figure 11-1: AE Determination and Outcome Flowchart

Example 1 (Diagnosis): prostatitis often has dysuria, urinary frequency, nocturia, difficult urination, pain in the groin, pelvic area or genitals, painful ejaculation, and sometimes, flu-like symptoms such as fever and chills. If the diagnosis can be established, prostatitis should be the name of the AE and the other symptoms should be included in the event description.

Example 2 (Diagnosis): Urinary tract infection (UTI) often has dysuria, urinary frequency, urinary urgency, and hematuria. If the diagnosis of UTI can be established, the name of the AE should be UTI and the other symptoms should be included in the event description.

Example 3 (Sign): Hematuria may lead to other symptoms, such as dysuria, pain in flank and back, in addition to blood in the urine. A blood clot may obstruct the urethra and lead to urinary retention. A disease diagnosis is preferred but a diagnosis may not be possible. In this case, the name of the AE should be hematuria with clot retention and the other symptoms should be included in the event description.

The AEs in the study may be further coded by Medical Dictionary for Regulatory Activities (MedDRA) and graded according to Common Terminology Criteria for Adverse Events (CTCAE) for the purpose of regulatory reporting or publication.

11.6 **Potential Anticipated Adverse Events**

Potential anticipated adverse events are those that may occur in association with a BPH treatment or procedure, including those AEs listed below or reported in the literature associated with surgical or minimally invasive obstructive BPH procedures:

<u>Procedural Risks</u>

- Adverse reaction to the drug coating
- Sepsis and infection

- Fever
- Perforation of urethra
- Perforation of bladder
- Splitting of the prostate capsule
- Urinary symptoms and adverse events including:
    - Dysuria
    - Frequency
    - Urgency
    - Nocturia
    - Acute urinary retention (not due to clot)
    - Acute urinary retention (due to clot)
    - Acute urinary retention (due to clogged Foley catheter)
    - Chronic urinary retention
    - Incontinence
    - Sensation of not emptying bladder completely
    - Urethritis
    - Urethral injury causing false passage or adhesion
    - Chronic pain in the pelvic area
    - Bladder spasm
    - Urethrorrhagia or Hematuria with or without clot in urethra
    - Discharge or cloudy urine
    - Discharge of tissue material during urination
    - Scarring of the urethral system
    - Urinary tract infection
    - Urethral Stricture
- Abscess (prostatic, bladder, scrotal)
- Bladder problems or damage (reduced bladder sensation, spasms, bladder neck contracture, bladder neck stenosis, bladder fistula)
- Bladder perforation or rupture
- Damage to the urethral system
- Worsening of LUTS/BPH
- Seroma
- Kidney compromise or failure
- Reproductive system disturbances such as infertility and/or miscarriages
- Prostate abnormalities and damage
- Device embolization or separation (defined as a separation of the device or parts of the device such that it cannot be removed from the body by withdrawing the device but requires another method to retrieve the device)

Other Pelvic Health Risks

- Unmasking of incontinence – underlying stress or urge incontinence may be unmasked and symptoms of incontinence controlled previously by the BPH may be evident
- Rectal incontinence
- Rectal damage
- Rectal fistula
- Rectal stenosis
- Rectal, perineal findings
- Anal irritation
- Elevated PSA
- Nerve damage
- Weakness or numbness
- Abdominal or low back pain
- Flu-like symptoms
- Hematospermia
- Epididymitis
- Erectile dysfunction
- Retrograde ejaculation or ejaculatory dysfunction
- Pressure sensation
- Prostatitis
- Cancer - the risk of cancer due to chromosomal damage is unknown

Other potential non-pelvic anticipated adverse events that may occur in this subject population are:

- Blood pressure change during therapy
- Arrhythmia
- Flank pain
- Blood loss (> 500 ml)
- Adverse reaction to medication and anesthesia as listed in the labeling
- Low blood pressure (hypotension)
- High blood pressure (hypertension)
- Fainting, dizziness, or blurred vision (vasovagal reaction, syncope)
- Allergic reaction
- Fatigue
- Dyspnea
- Confusion
- Memory loss
- Swelling or bruising (edema, hematoma)
- Aneurysm – thoracic and cranial

- Low back pain
- Pneumonia
- Collapsed lung
- Pulmonary embolism
- Pneumothorax
- Upper respiratory disease
- Cough
- Sore throat
- Apnea
- Coughing up blood (hemoptysis)
- Choking (aspiration)
- Venous thrombosis
- Myocardial infarction, angina, ischemia
- Cardiac arrhythmia
- Stroke or transient ischemic attack
- Brain damage
- Headache
- Depression
- Perforation of or damage to the gastrointestinal tract
- Abdominal pain
- Constipation
- Nausea or vomiting
- Fetal risk
- Adverse reaction to medication

Drug Risks

Adverse reaction to the paclitaxel and symptoms observed derived primarily from IV infusion studies of the drug in treating cancer subjects include:

- Chromosomal abnormalities and the risk of cancer
- Fetal harm when a pregnant woman is exposed
- Anaphylaxis and hypersensitivity with paclitaxel
- Inhibition of the healing of the urethra post procedure
- Myelosuppression including: neutropenia, leukopenia, thrombocytopenia, anemia
- Arrhythmia
- Peripheral neuropathy
- Myalgia or Arthralgia
- Alopecia
- Hypotension

- Nausea, vomiting or diarrhea
- Elevated bilirubin, ALP and AST
- Potential effect on the liver and kidneys is unknown and have not been studied

The amount of the paclitaxel delivered locally during the Optilume DCB procedure is much lower than a single dose of systemic chemotherapy provided to cancer patients and the drug appears to be essentially remain localized in the prostate and urethra.

11.7 **Definition of Serious Adverse Event(s)**

An adverse event is considered to be a serious adverse event (SAE) when the subject outcome is any of the following:

- Death
- Life-threatening
- In-patient hospitalization or prolongation of an existing hospitalization
- Persistent or significant disability/incapacity
    - Substantial disruption of a person's ability to conduct normal life functions, i.e. the adverse event resulted in a significant, persistent or permanent change, impairment, damage or disruption in the subject's body function/structure including chronic diseases, physical activities and/or quality of life
- Congenital anomaly or birth defect
- Required medical or surgical intervention to prevent permanent impairment of a body function or damage to a body structure
- Important medical event
    - If the AE does not fit the other outcomes, but the event may jeopardize the health of the subject or require medical or surgical intervention (treatment) to prevent one of the outcomes listed above

An SAE may or may not be related to the study procedure.

Note: A planned hospitalization for a pre-existing condition, or a procedure required by the protocol without serious deterioration in health, is not considered a serious adverse event.

11.8 **Unanticipated Adverse Device Effect(s) (UADE)**

An unanticipated adverse device effect (UADE) is any serious adverse effect on the health or safety of a subject, any life-threatening problem or death caused by, or associated with a device, if such effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan (e.g., ICF, Study Protocol, Instructions for Use (IFU), publications, etc.), or

any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

If an unanticipated adverse effect associated with the investigational device occurs, the investigator shall notify the Sponsor and the IRB/REB as soon as possible.

The Sponsor will investigate the event and notify the authorities and IRB/REB and all other participating IRBs/REBs and investigators. Should the Sponsor determine that an unanticipated adverse device effect presents an unreasonable risk to all participating subjects, the Sponsor will suspend the clinical investigation and notify all participating investigators, IRBs/REBs and country regulatory bodies.

11.9 Reporting of all Adverse Events

The signs, symptoms and sequelae of an underlying AE should not be reported as separate AEs.

All AEs must be recorded on a CRF. All AEs also must be described by (a) duration (start and resolution dates); (b) severity; (c) relationship to the study device and study procedure; (d) action taken to resolve the event; (e) outcome of the event; and (f) whether or not such event is considered to have been serious and (g) whether the event meets the definition of a UADE. Additional information, such as procedural notes, treatment notes, or a signed clinical summary, may be required as supporting documentation for the reported AE.

During the study, all AEs must be reported to the Sponsor within the period outlined in Table 14-1. All deaths should also be reported on the End of Study CRF. A copy of the subject's death records, medical records for the events that led to the subject's death, and a death certificate (if available) should be provided.

11.10 Relationship of AEs to the Device and Procedure

A description of how an AE relates to the study device and to the study procedure will be reported on the Adverse Event CRF and be determined by the Investigator using the following definitions:

- ***Definite*:** The AE follows a reasonable temporal sequence from the time of the index procedure, which includes AEs that occur during the index procedure or during the follow-up period.
- ***Probable***: The AE follows a reasonable temporal sequence from the time of the index procedure, and the possibility can be excluded that factors other than the index procedure, such as underlying disease, concomitant drugs, or concurrent treatment caused the AE.
- ***Possible***: The AE follows a reasonable temporal sequence from the time of the index procedure and the possibility of index procedure involvement cannot be excluded. However, other factors such as underlying disease, concomitant medications, or concurrent treatment are presumable.

- ***Unlikely***: The AE has an improbable temporal sequence from the time of the index procedure, or such AE can be reasonably explained by other factors, including underlying disease, concomitant medication, or concurrent treatment.
- ***Not related***: The AE has no temporal sequence from the time of the index procedure, or it can be explained by other factors, including underlying disease, concomitant medication, or concurrent treatment.

Adverse events will be reviewed and adjudicated by the Clinical Events Committee (CEC) as described in Section 14.1.

11.11 **Adverse Event Severity**

A description of the severity of the adverse event will be reported on the Adverse Event CRF and be determined by the Investigator using the following definitions:

- ***Mild:*** An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities
- ***Moderate:*** An event that causes discomfort sufficient to interfere with normal everyday activities, non-invasive intervention may be indicated
- ***Severe:*** An event that prevents normal everyday activities or is incapacitating; invasive intervention may be indicated

NOTE: The term 'Severe' does not necessarily equate to 'Serious' when determining if an event is a Serious Adverse Event. Please refer to Section 11.7 for the definition of a Serious Adverse Event.

11.12 **Device Failures, Malfunctions and Near Incidents**

Device failures or malfunctions will be reported to the Sponsor by the clinical sites. If the failure or malfunction results in negative clinical sequelae, the event shall be reported to the Sponsor within two (2) working days after the Investigator becomes aware of the device-related adverse event and reported to the IRB/REB (if required) within the IRB/REB required timeframe. The malfunctioning investigational device involved in the incident should be returned to the Sponsor for evaluation.

12 TRAINING

The Sponsor will be responsible for training of appropriate clinical site study personnel. To ensure proper procedural technique, uniform data collection and protocol compliance, the Sponsor will present a formal training session to personnel at each study site. At this training session, the study protocol, techniques for the identification of eligible subjects, instructions on data collection, study blinding procedures, schedules for follow-up, and regulatory requirements will be reviewed.

13 DATA MANAGEMENT

13.1 Study Database and Electronic Case Report Forms

All required clinical data will be collected and compiled on web-based, standardized, electronic Case Report Forms (eCRFs).

The eCRFs are designed to accommodate the specific features of the study design. Modification of the eCRF will only be made if deemed necessary by the Sponsor and/or appropriate regulatory body. Appropriate quality control measures will be established to ensure accurate and complete transfer of information from the study documentation to the study database.

13.2 Subject Identification

Subjects that provide informed consent will be assigned a unique identification code (ID) using the format "6XX-YYY" where:

6XX = Institution Number, assigned by the Sponsor to each study site

YYY = Enrollment Number, assigned by the institution as each subject is enrolled in the study

The subject ID will be used to track subject information throughout the study.

13.3 Central Database

All study documentation will be collected and compiled in a central database. Appropriate quality control measures will be established to ensure accurate and complete transfer of information from the study documentation to the central database.

14 STUDY RESPONSIBILITIES AND MANAGEMENT

14.1 Clinical Events Committee

An independent Clinical Events Committee (CEC) will be utilized for this study. The CEC will be responsible for adjudicating the CTCAE severity, seriousness and relatedness of all adverse events occurring during the study period. The CEC will also adjudicate whether the event qualifies as a primary safety endpoint event. A charter will be completed for the CEC outlining membership, duties and functions.

The CEC will be made up of a minimum of two clinicians with expertise in urology and one clinician with expertise in cardiology. All members of the CEC will be blinded to the subjects' treatment and the primary results of the study. The CEC will meet regularly to review and adjudicate all adverse events. The committee will also review and rule on all deaths that occur throughout the study.

14.2 Data Monitoring Committee

An independent Data Monitoring Committee (DMC) will be utilized for this study. The DMC will be responsible for the oversight and safety monitoring of the study. A charter will be completed for the DMC outlining membership, duties, functions and meeting frequencies.

The DMC will be comprised of leading experts in urology, cardiology and biostatistics who are not participating in the study and have no affiliation with the Sponsor. All members of the DMC will be unblinded to the subjects' treatment and the primary results of the study. The DMC will review accumulating safety data during the enrollment phase of the study to monitor for incidence of serious adverse events that would warrant modification or termination of the study.

14.3 **Investigator Responsibilities**

Each investigator is responsible for ensuring the investigation is conducted according to all signed agreements, the study protocol, IRB/REB requirements, and applicable laws and regulations. Also, Investigators may not begin enrollment until Sponsor or its designee receives and approves (when necessary) the following documents:

- Signed Investigator Agreement
- Financial disclosure forms for all participating investigators
- IRB/REB roster
- IRB/REB protocol and ICF approvals
- Investigators' current curricula vitae (CV)
- Signed Site Delegation Log

It is acceptable for Investigators to delegate one or more of the study functions to an associate or Co- or Sub-Investigator, or a trained Study Coordinator; however, the Principal Investigator remains responsible for the proper conduct of the clinical investigation, including obtaining and documenting proper study informed consent, collecting all required data, submitting accurate and complete CRFs, etc.

At each study site, appropriate procedures must be followed to maintain subject confidentiality according to appropriate local regulations. Each site may have its own internal procedures or requirements for use and release of subject medical information in research studies. Each Investigator is responsible for obtaining appropriate approvals, consents, or releases of medical information as dictated by their relevant subject privacy laws.

The study is not transferable to other sites attended by the Investigator unless prior approval is obtained from the appropriate IRB/REB and the Sponsor.

14.3.1 Confidentiality

All information and data sent to the Sponsor concerning subjects or their participation in this study will be considered confidential according to the country's patient confidentiality regulations. Data used in the analysis and reporting of this evaluation will be used in a manner without identifiable reference to the subject. Investigators will consent to visits by Sponsor's staff and its authorized representatives, as well as by the FDA or local governmental body, to review the study subjects' medical records, including any test or laboratory data that might have been recorded on diagnostic test media (e.g., cystograms).

14.3.2 Amending the Investigational Study Protocol

Neither any Investigator nor the Sponsor will modify the Investigational Protocol without first obtaining concurrence of the other in writing. All changes to the Investigational Protocol must be submitted to the FDA and IRB/REB for review and approval unless the changes do not affect the subject's safety or the integrity of the data (e.g. administrative changes). Any change that would require alteration to the ICF must receive approval from the applicable IRB/REB prior to implementation. Following approval, any Investigational Protocol amendment must be distributed to all protocol recipients at the site.

14.3.3 Protocol Deviations

A protocol deviation/violation is generally an unplanned digression from the protocol that is not implemented or intended as a systematic change. An investigator failed to perform tests or examinations as required by the protocol or failures on the part of study subjects to complete scheduled visits as required by the protocol, would be considered protocol deviations. These type of deviations are reported to the Sponsor and in accordance with the IRB/REB policy.

A Protocol Deviation CRF must be completed by the site for each study protocol deviation (e.g., failure to obtain informed consent, randomizing or treating a subject who does not meet inclusion / exclusion criteria, not performing required testing, missed follow-up window, etc.). Those deviations from the protocol that occur due to limitations related to the COVID-19 pandemic should be reported with the type of deviation describing how the specific activity failed to follow protocol specified requirements and the reason for deviation describing how COVID-19 impacted the ability to perform the specific activity.

An Investigator must notify the Sponsor and the reviewing IRB/REB of any deviation from the Study Protocol that was done to protect the life or physical well-being of a subject. Such notice should be given as soon as possible, but no later than five (5) working days after the emergency occurred.

14.3.4 Protocol Deviation Notification/Approval to IRB/REB/Sponsor before Implementation

A protocol deviation may be a limited prospective exception to the protocol (e.g. agreement between Sponsor and Investigator to randomize a single subject who does not meet all inclusion/exclusion criteria due to out of window historical data). This type of deviation initiated by the clinical Investigator must be reviewed and approved by the IRB/REB and the Sponsor prior to implementation. These types of deviations are only approved if they do not impact data integrity or put subjects at unreasonable risk.

14.3.5 Site Noncompliance and Nonperformance

Repeat serious protocol deviations will be closely monitored. If excessive deviations or a failure to reduce deviations are noted, the Sponsor reserves the right to suspend study enrollment at that site until a sufficient system is in place at the site to reduce further deviations.

14.3.6 Device Accountability

Urotronic's sham catheters, pre-dilation balloon catheters and Optilume BPH Prostatic Drug Coated Balloon Dilation Catheters allocated for investigational site use will be stored in a secured area at room temperature until use. Each site will be responsible for tracking the receipt and disposition of all investigational devices. All unused sham, pre-dilation and DCB catheters must be returned to the Sponsor at the end of the study.

The Investigator must ensure the device is used only in accordance with the protocol and current IFU. The Investigator must maintain records that document device delivery to the study site, inventory at the site and administration to subjects. This record should include dates, quantities, model and lot numbers (if applicable) and the unique subject ID assigned to study subjects. The Investigator should maintain records that document which device(s) the subject received according to the protocol and assigned randomization. In the case where a device has failed, the Investigator must make every possible effort to return the device to the Sponsor.

14.4 Subject Enrollment Process

All study candidates, after pre-procedure screening, must appropriately consent to participate in the study, as administrated by qualified study site personnel using an IRB/REB and Sponsor-approved informed consent form (ICF) prior to beginning any aspect of the study procedure or tests that are not standard of care for the site. Investigational sites will be required to document the consent process within each enrolled subject's medical record. Administering the questionnaires can be done prior to signing the ICF if those questionnaires are collected as standard of care at the site, the questionnaires are consistent with the IRB/REB approved versions of the questionnaire, and are collected within the time specified.

Timely communication by each site is critical to avoid over enrolling when the enrollment is close to the end. When enrollment is close to the end, the following procedures will be implemented:

- Before the subject signs the study ICF, the study site must confirm the availability of an enrollment slot. A phone call to the Sponsor is the preferred method.
- Immediately after the procedure, the study site must inform the Sponsor of the subject's eligibility and the completion of the procedure. A phone call to the Sponsor is the preferred method.

14.5 Institutional Review Board (IRB)/Research Ethics Board (REB)

Investigators must submit the study protocol to their respective Institutional Review Board (IRB)/ Research Ethics Board (REB) and obtain the IRB's/REB's written approval before being allowed to conduct and participate in the study. Each Investigator is responsible for fulfilling any conditions of approval imposed by their respective IRB/REB, such as regular reporting, study timing, etc. Investigators will provide the Sponsor or its designee with copies of such approvals and reports.

14.6 **Informed Consent Form (ICF)**

The Sponsor will provide a template informed consent form (ICF) to each study site for IRB/REB submission. The template may be modified to suit the requirements of the individual study site but the Sponsor must pre-approve all changes to the ICF prior to initial submission to the IRB/REB.

Each Investigator or assigned designee must administer this approved ICF to each prospective study subject, and obtain the subject's signature or a legally-approved designee's signature along with the date of consent prior to any study-specific assessments. The ICF must be obtained in accordance with the applicable guidelines of the Declaration of Helsinki, or local regulations and laws, whichever represents the greater protection of the individual. Subjects must be informed about their right to withdraw from the study at any time and for any reason without sanction, penalty, or loss of benefits to which the subject is otherwise entitled and also be informed that withdrawal from the study will not jeopardize their future medical care. A copy of their signed ICF must be given to each subject enrolled in the study. The institutional standard subject consent form does not replace the study ICF.

14.7 **Case Report Forms (CRFs)**

The Sponsor will provide standardized case report forms (CRFs) for each individual subject. The CRFs will be electronic (EDC, 21 CRF Part 11 compliant), will be used to record study data, and are an integral part of the study and subsequent reports.

The electronic CRFs for individual subjects will be provided by the Sponsor via a web portal. After the data have been monitored and submitted, corrections will be initiated via a data query or Data Clarification Form (DCF) to be completed by study site personnel. This DCF also will be done electronically via the web portal. Electronic CRFs must be approved and signed by the Investigator using his/her electronic signature.

14.8 **Records**

Each Investigator must maintain the following accurate, complete, and current records relating to the conduct of the study investigation. The final responsibility for maintaining such records remains with the Investigator. These records include, but not limited to:

- All signed agreements;
- IRB/REB approval letter(s);
- Signed ICFs;
- Records of AEs, including supporting documents;
- Records of protocol deviations, including supporting documents;
- Records showing receipt, use and disposition of all investigational devices, including:
    - Date, quantity, model and lot numbers of devices received,
    - Name of person(s) who received, used or disposed of each device,

    - The number of devices returned to the Sponsor and the reason(s) for return;
- All correspondence related to the study;
- Records of each subject's case history, including study-required CRFs, signed ICF, all relevant observations of AEs, the condition of each subject upon entering and during the course of the investigation, relevant medical history, the results of all diagnostic testing, etc.;
- Study personnel visit log;
- Signature authorization and delegation log; and,
- Any other records that applicable regulation requires to be maintained.

14.9 **Reports**

Table 14-1 lists those reports that are the investigator's responsibility to deliver to the Sponsor. Each study investigator must follow the IRB/REB reporting requirements for their respective site. If applicable regulations or IRB/REB requirements mandate stricter reporting requirements than those listed, the stricter requirements must be followed.

Table 14-1: Reports Required from Investigators to Sponsor

Type of Report	Prepared by PI for	Notification Time Frame
UADE	Sponsor, IRB/REB	Within 24 hours of knowledge
Death	Sponsor IRB/REB, if required	Written reports (e.g., via e-mail) within 24 hours of knowledge
SAE	Sponsor IRB/REB, if required	Within 24 hours of knowledge Per IRB/REB requirement
Device malfunction with clinical sequelae	Sponsor IRB/REB, if required	Within 48 hours via written communication. Return the device to Sponsor within 48 hours or as requested.
Serious protocol deviations (e.g., ICF not obtained, to protect the	Sponsor	Within 5 working days of knowledge Per IRB/REB requirement

Type of Report	Prepared by PI for	Notification Time Frame
life or physical well-being of a subject in an emergency)	IRB/REB, if required	
Withdrawal of IRB/REB approval	Sponsor	Within 5 working days of knowledge
Progress report	Sponsor, IRB/REB	As required by IRB/REB
Final report	Sponsor, IRB/REB	Within 3 months of study completion or termination
Note: Each IRB/REB may require more stringent reporting requirements that those listed in this table.		

14.10 Sponsor Responsibilities

Urotronic, Inc. is the Sponsor of this study. The Sponsor's responsibilities in the study include:

- Selecting the Principal Investigator(s), all clinical investigators and study sites, and other consultants (e.g., monitors) who participate in the study.
- Provide study protocol, device, and GCP training to participating study sites, in quantities sufficient to support study activities, per agreements executed with the study sites.
- Select all qualified clinical Investigators and study sites and other consultants (e.g., the study monitors) who participate in the study.
- Provide financial support to each study site.
- Follow/promote all regulatory standards per appropriate regulations for study sites, core laboratories, and other participants, and ensure compliance by periodically monitoring sites.
- Ensure completion of site monitoring of clinical data at each clinical study site.
- Retain ownership of all clinical data generated in this study, and control the use of the data for appropriate purposes only.
- Review and approve publication of study results in the literature.

14.10.1 Sponsor Reporting Responsibilities

Table 14-2 lists those reports that are the Sponsor's responsibility and timelines to report to the IRB/REB and FDA. If applicable regulations or IRB/REB and FDA requirements mandate stricter reporting requirements than those listed, the stricter requirements must be followed.

Table 14-2: Sponsor Reporting Responsibilities

Type of Report	Sponsor Reporting Responsibilities	
	Report Prepared For	Reporting Time Frame
Unanticipated Adverse Device Effect (UADE)	Investigators, IRBs/REBs and FDA	**Written** - Within 10 working days from the time the Sponsor first learns of the effect.
Withdrawal of IRB/REB Approval or other action on part of the IRB/REB that affects the study	Investigators, IRBs/REBs and FDA	**Written** – Within 5 working days.
Withdrawal of FDA approval	Investigators and IRBs/REBs	**Written** – Within 5 working days.
Current investigator list	FDA	**Written** – At 6-month intervals. Submit the first list 6 months after FDA approval.
Device Recall	Investigators, IRBs/REBs and FDA	**Written** – Within 30 working days.
Progress Reports	Investigators, IRBs/REBs and FDA	At regular intervals, but in no event less than yearly.
Inappropriate Informed Consent	IRB/REB and FDA	Investigator's report submitted within 5 working days of notification
Study Closure	Investigators, IRBs/REBs and FDA	Within 10 days
Final Report	Investigators, IRBs/REBs and FDA	Significant risk device – Notify FDA within 30 working days of the completion the investigation Final report - within 6 months of study closure.

15 STUDY ADMINISTRATION

15.1 Monitoring Procedures

It is the responsibility of the study Sponsor to ensure that proper monitoring of this investigation is conducted. Appropriately trained personnel, appointed by the study Sponsor, will complete any monitoring that is done. The monitoring will be the responsibility of Sponsor study personnel with

an address as listed in the title page of this document. Monitors will ensure that the investigation is conducted in accordance with:

- The signed Investigator's Agreement
- The Investigational Plan
- Appropriate laws and regulations
- Any conditions of approval imposed by the reviewing IRB/REB and/or other regulatory agencies

The clinical study will be monitored according to the guidelines summarized below. The Sponsor may choose to perform random inspections throughout the study as an element of quality assurance. Investigators shall allow auditing of their clinical investigation procedures.

A study specific Monitoring Plan is created and implemented to standardize monitoring activities across centers and ensure human subject protection and verify data integrity. The monitors shall receive study specific and SOP training prior to conducting any monitoring visits. Study monitors are selected based on their training, qualifications and experience to monitor the progress of an investigation. Study monitors may be Sponsor's employees or representatives. This study monitoring will include a site qualification, study initiation, interim, and close out visits. Not all sites will require a qualification visit. The reason for waiving the visit (e.g. participation in a previous Urotronic clinical study) will be documented in a Note to File. All study monitors will be required to follow the monitoring plan and monitoring standard operating procedures (SOPs).

The study monitoring will be done by the following Sponsor representative:

Clinlogix, LLC
8 Springhouse Innovation Park, Suite 100
Lower Gwynedd, PA 19002
USA

15.1.1 Monitoring Visit

The following factors will be taken into account when determining the frequency of the monitoring visits: subject accrual rate at each center, total number of subjects enrolled at each center, and Clinical Investigation Plan compliance at each center. Monitors will require direct access to subjects' medical records pertinent to the study (and study inclusion criteria), study management documents, regulatory documents and Subject Informed Consent documents, as well as other potential applicable records not listed here.

Monitors may ensure the clinical investigators have and continue to have staff and facilities to conduct the clinical investigation safely and effectively. Monitors may conduct the following monitoring activities throughout the study:

- Verification that the current IRB/REB-approved informed consent was signed and dated by each subject prior to participating in the study required procedures.

- Verification of documentation in the subject's record that informed consent was signed prior to initiation of the study procedures and that a copy of the signed and dated consent was provided to the subject.
- Source documentation verification by reviewing the CRFs against source documentation for accuracy and completeness of information.
- Verification that the device is being used according to the Clinical Investigation Plan, Instructions for Use and, all malfunctions/ IFU deficiencies are reported, as required.
- Verification that subjects met study entrance criteria.
- Confirmation that the study is being conducted according to the Clinical Investigation Plan and applicable regulations.
- Verification that study deviations are documented and reported.
- Verification that the procedures for recording and reporting adverse events to the Sponsor are followed.
- Ensuring proper error correction.
- Verification of training documentation of all study personnel participating in study related activities.
- Reviewing all correspondence and regulatory documents, including confirmation of IRB/REB-approved Clinical Investigation Plan or amendments.
- Resolution of outstanding issues and completion of assigned tasks will be documented by the monitors.

Each monitoring visit will be documented via a monitoring report and follow-up letter. The follow up visit letter shall be sent to the Investigator to document issues identified, corrective actions and if applicable preventative actions. At subsequent visits the issues resolved shall be documented in this letter to demonstrate resolution.

15.1.2 Study Closure

Study closure is defined as a specific date that is determined by study completion and/or regulatory requirements have been satisfied per the Clinical Investigation Plan (CIP) and/or by decision of the Sponsor or IRB/REB. Study closure visits will be conducted at all enrolling clinical sites in order to review record retention requirements with site personnel. A telephone contact may take the place of a study closure visit if appropriate (e.g., low subject enrollment, recent monitoring visit, etc.)

16 STUDY CONTACT

16.1 **Study Principal Investigator**

Steven A. Kaplan, MD
Professor of Urology
Icahn School of Medicine at Mount Sinai
Director, Benign Urologic Diseases and The Men's Health Program
Mount Sinai Health System

625 Madison Avenue
New York, NY 10022
USA

16.2 **Sponsor**

Urotronic Inc
2495 Xenium Lane N
Minneapolis, MN 55441
USA
info@urotronic.com

16.3 **Data Management**

Libra Medical Inc
8401 73rd Ave N, Suite 63
Brooklyn Park, MN 55428
USA
612-801-6782

17 POTENTIAL DEVICE CHANGE

Future product line extensions or design changes may be introduced into the study based on feedback from investigators. In addition, manufacturing changes may be introduced. All design and manufacturing process changes will be performed under the Sponsor's design control process and fully tested to ensure that it meets specifications. All device changes will be submitted to the FDA for review and approval prior to use in the clinical study. Significant changes that may affect the device safety or performance will be provided to the IRB/REB as a supplemental application.

The device design or process changes will be evaluated to ensure that they continue to meet the product specifications.

18 PUBLICATION POLICY

The data and results from the trial are the sole property of the Sponsor. The Sponsor shall have the right to access and use all data and results generated during the clinical trial. The Investigators will not use the clinical trial/investigation-related data without the written consent of the Sponsor for any other purpose than for clinical trial/investigation completion or for generation of publication material, as referenced in the Clinical Trial Agreement/Investigator Agreement.

The Sponsor acknowledges that the trial's Principal Investigators intend to publish a multi-center publication regarding the clinical trial/investigation results, and numerous secondary publications. The Sponsor must receive any proposed publication and/or presentation materials at least 30 days prior to the proposed date of the presentation or the initial submission of the proposed publication in

order for the materials to be reviewed by the Sponsor in compliance with the Sponsor's publication policy set forth in the Clinical Trial Agreement/Investigator Agreement.

The Sponsor will register the study on the ClinicalTrials.gov website upon approval by an IRB/REB in order to meet the criteria of the International Committee of Medical Journal Editors. Institution(s) and/or Principal Investigator(s) shall not take any action to register the trial.

19 REFERENCES

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[2] Barry MJ, Fowler FJ Jr, O'Leary MP, et al. Measurement committee of the American Urology Association. Med Care. 1995;22:AS145

[3] Vuichoud C and Loughlin KR. Benign prostatic hyperplasia: epidemiology, economics and evaluation. Can J Urol. 2015 (Internal Suppl):1-6

[4] Barry MJ, Fowler FJ Jr, O'Leary MP, et al. Measuring disease-specific health status in men with benign prostatic hyperplasia. Measurement Committee of The American Urological Association. Med Care. 1995 Apr;33(4 Suppl):AS145-55.

[5] McVary KT, Roehrborn CG, Avins AL, et al. Management of benign prostatic hyperplasia (BPH) http://www.auanet.org/guidelines/benign-prostatic-hyperplasia-(2010-reviewed-and-validity-confirmed-2014)