OPTILUME®

URETHRAL DRUG COATED BALLOON CATHETER

Caution: Federal law restricts this device to sale by or on the order of a physician

1111-003 Rev B

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1 DEVICE DESCRIPTION

1.1 Balloon Catheter

Optilume® Urethral Drug Coated Balloon (Optilume DCB) Catheter is a 0.038” (0.97 mm) over-the-wire (OTW) guidewire compatible catheter with a dual lumen design and a tapered, atraumatic tip. The Optilume DCB is used to exert radial force to dilate narrow urethral segments (strictures). The distal end of the catheter has a semi-compliant inflatable balloon that is coated with a proprietary coating containing the active pharmaceutical paclitaxel. The drug coating covers the working length of the balloon body. The device has two radiopaque marker bands that indicate the working length of the balloon where the drug coating is applied. The drug coated balloon is covered with a protective sheath that is discarded prior to use.

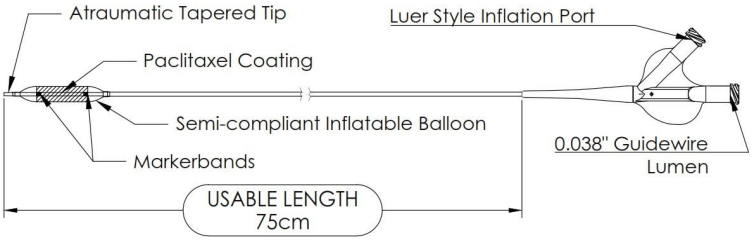

Figure 1-1. Optilume DCB Design

The device is sterilized using ethylene oxide in a Tyvek pouch. Post sterilization the sterile, pouched catheter is sealed in a foil pouch with desiccant and placed within a single unit carton.

1.2 Available Sizes and Nominal Paclitaxel Dose

The Optilume DCB device sizes and catalogue numbers are provided in Table 1-1. The 18F-30F (6-10mm) balloon diameters are flexible cystoscope compatible. The drug coating consists of the active pharmaceutical ingredient paclitaxel and excipients. The drug coating covers the working length of the balloon component of the catheter. The drug coating is evenly distributed across the balloon surface at a concentration of 3.5 µg/mm2. The drug coating is released from the balloon and transferred to the urothelium during balloon inflation.

Table 1-1: Optilume® DCB Available Sizes and Paclitaxel Dose

Catalogue Number	Diameter	Length	Rated Burst Pressure (RBP)	Paclitaxel Dose (µg)
1110-06030B	18F / 6mm	30 mm	12 atm	1,979
1110-06050B	18F / 6mm	50 mm	12 atm	3,299
1110-08030B	24F / 8mm	30 mm	12 atm	2,639
1110-08050B	24F / 8mm	50 mm	12 atm	4,398
1110-10030B	30F / 10mm	30 mm	10 atm	3,299
1110-10050B	30F / 10mm	50 mm	10 atm	5,498
1110-12030B [1]	36F / 12mm	30 mm	8 atm	3,958
1110-12050B [1]	36F / 12mm	50 mm	8 atm	6,597
[1] – These DCB sizes are not compatible with flexible cystoscopes.				

2 INDICATIONS FOR USE

The Optilume Urethral Drug Coated Balloon is used to treat patients with obstructive urinary symptoms associated with anterior urethral stricture. It is designed to be used in adult males for urethral strictures of ≤3 cm in length.

3 CONTRAINDICATIONS

The Optilume Urethral Drug Coated Balloon is contraindicated for use:

- in patients with known hypersensitivity to paclitaxel or structurally related compounds, and
- in patients with urologic implants such as penile implants or artificial urinary sphincters.

4 WARNINGS

- The Optilume DCB is supplied STERILE for single use only. Do not reprocess or re-sterilize. Reprocessing and re-sterilizing could increase the risk of patient infection and risk of compromised device performance.
- The foil pouch and the outer surface of the inner Tyvek pouch are NON-STERILE. The CONTENTS of the inner Tyvek pouch are STERILE.
- Do not use this device if there is an active infection in the urinary tract (UTI). Infection must be resolved before treating the stricture with the Optilume DCB.
- Do not use after the “Use By” date.
- Men should abstain from sex or use barrier contraception (wear a condom) for 30 days post treatment to avoid exposure of sexual partner to paclitaxel. Paclitaxel may still be present at very low levels after 30 days, see Section 12.1.9.
- The Optilume DCB contains paclitaxel, a known genotoxic aneugen. Because paclitaxel may be present in semen after treatment with the Optilume DCB (Section 12.1.9), men with partners of child-bearing potential should use highly effective contraceptive and avoid fathering children until at least 6 months after treatment with the Optilume DCB. Paclitaxel was detectable in semen in 60% (9/15), 39% (5/13) and 8.3% (1/12) of subjects at 1 month, 3 months, and 6 months post-treatment, respectively.
- Maximum paclitaxel concentrations in semen were 17.6, 3.5, and 0.9 ng/mL at 1 month, 3 month and 6 months, respectively, while group mean (SD) paclitaxel concentrations in semen at those same timepoints were 3.0 (4.9), 0.5 (1.0), and 0.1 (0.2) ng/mL. Mean paclitaxel semen concentrations approached the lower limit of quantitation (0.1 ng/mL) at 6 months post-treatment. The risks associated with these paclitaxel concentrations in semen are unknown. The effect of treatment with the Optilume DCB on sperm and spermatogenesis is also unknown.
- Do not manipulate the Optilume DCB in an inflated state. Aspirate (deflate) the balloon completely before gently removing the device from the urethra.
- If resistance is encountered at any time during the insertion or withdrawal of the device do not force passage. Resistance may cause damage to device or urethra.
- The impact of multiple treatments with the Optilume DCB for the same stricture has not been extensively studied. Multiple treatments of the same stricture will increase exposure to paclitaxel, the risks associated with this are currently unknown.

5 PRECAUTIONS

- Carefully inspect the Optilume DCB and package prior to use. Do not use the catheter if it is damaged or if the size, shape, or condition is unsuitable for the intended procedure. Use immediately once the foil pouch has been opened.
- Use dry sterile gloves or dry gauze pads to handle the Optilume DCB prior to use. Care should be taken to minimize contact with the coated balloon portion of the device.
- Never inflate the Optilume DCB outside the body or prior to reaching the target stricture as it may disrupt the coating integrity. Preparation of the device should be done with the balloon still within the balloon protector to avoid inflating the balloon.
- Do not immerse or wipe the balloon section of the Optilume DCB with any fluid as the integrity of the drug coating may be damaged or compromised. Replace any Optilume DCB where the balloon has come into contact with fluids prior to use.
- Prior to use of the Optilume DCB, physicians should read and understand the instructions for use. Failure to follow the indications, contraindications, restrictions, warnings, and precautions may result in complications.
- The Optilume DCB should be manipulated under direct visualization via cystoscopy or high-quality fluoroscopic observation during use.
- Monitor for signs of anaphylaxis or hypersensitivity to paclitaxel
- Never use air or any gaseous medium to inflate the Optilume DCB.
- The Optilume DCB should be used only by physicians who are experienced and knowledgeable in the clinical and technical aspects of urethral balloon dilatation.
- The Optilume DCB should not be inflated in excess of the rated burst pressure (RBP). See Table 1-1 or individual device labeling for the listed RBP for each balloon size. To ensure proper regulation of balloon pressure, use of a balloon inflation device with pressure gauge is recommended.
- Do not attempt to pass the Optilume DCB through a smaller French size cystoscope than indicated on the label.
- Do not attempt to pass the 36F (12mm) diameter Optilume DCB through the working channel of a flexible cystoscope.
- The working length of the balloon must cover the entire target stricture length. See Section 11.2 for device sizing instructions.
- For proper drug transfer to the urothelium, allow the coating to hydrate in the urethra for a minimum of 60 seconds prior to inflation and maintain inflation of the Optilume DCB for a minimum of 5 minutes.
- If the product has a failure prior to or during inflation, replace the Optilume DCB and repeat the procedure. If failure is after achieving inflation to RBP, do not replace the device as sufficient dilation and drug transfer has been accomplished.
- After use, this product may be a potential biohazard. Handle and dispose of in accordance with accepted medical practice and applicable local regulations.
- No long-term studies have been performed to evaluate the carcinogenic potential of the Optilume DCB.

6 DRUG INFORMATION

6.1 Mechanism of Action

The Optilume DCB coating contains paclitaxel, an anti-mitotic pharmaceutical agent that specifically binds to and stabilizes microtubules. Paclitaxel has been reported to inhibit smooth muscle cell and fibroblast proliferation and migration as well as secretion of extracellular matrix. The combination of these effects may result in the inhibition of urothelium hyperplasia/scar tissue formation and therefore stricture recurrence.

6.2 Drug Interactions

Formal drug interaction studies have not been conducted for the Optilume DCB. The respective instructions for use for all drugs used in conjunction with the Optilume DCB should be consulted for interactions with paclitaxel. Consideration should be given to the potential for systemic and local drug interactions in the urethra in a patient who is taking a drug with known interactions with paclitaxel or when deciding to initiate drug therapy in a patient who has been treated with the Optilume DCB. The metabolism of paclitaxel is catalyzed by cytochrome P450 isoenzymes CYP2C8 and CYP3A4 and it is a substrate of P-glycoprotein. Potential drug interactions may occur with any drug that affects these isoenzymes. In the absence of formal drug interaction studies, caution should be exercised when administering paclitaxel.

6.3 Carcinogenicity, Genotoxicity and Reproductive Toxicology

The Optilume DCB contains paclitaxel, a known aneugen. Because paclitaxel may be present in semen after treatment with the Optilume DCB (Section 12.1.9), men with partners of child-bearing potential should use highly effective contraceptive and avoid fathering children until at least 6 months after treatment with the Optilume DCB. Paclitaxel was detectable in semen in 60% (9/15), 39% (5/13) and 8.3% (1/12) of subjects at 1 month, 3 months, and 6 months post-treatment, respectively.

Maximum paclitaxel concentrations in semen were 17.6, 3.5, and 0.9 ng/mL at 1 month, 3 month and 6 months, respectively, while group mean (SD) paclitaxel concentrations in semen at those same timepoints were 3.0 (4.9), 0.5 (1.0), and 0.1 (0.2) ng/mL. Mean paclitaxel semen concentrations approached the lower limit of quantitation (0.1 ng/mL) at 6 months post-treatment. The risks associated with these paclitaxel concentrations in semen are unknown.

6.4 Vascular Paclitaxel Coated Device Meta-Analysis

A meta-analysis of randomized, controlled trials for the use of paclitaxel coated devices in treating patients with peripheral arterial disease (PAD) was published by Katsanos et. al in 2018.1 This analysis suggested the possibility of an increased risk of mortality resulting from the use of paclitaxel-coated vascular devices. This higher risk of death was observed at time points at least two years after treatment with the paclitaxel-containing devices. The presence and magnitude of the late mortality risk should be interpreted with caution because of multiple limitations in the available data, including wide confidence intervals due to a small sample size, pooling of studies of different paclitaxel-coated devices that were not intended to be combined, substantial amounts of missing study data, no clear evidence of a paclitaxel dose effect on mortality, and no identified pathophysiologic mechanism for the late deaths.

In January 2021, Nordanstig and colleagues published interim results of a large, randomized national registry trial evaluating paclitaxel coated devices against uncoated control devices that showed no significant increase in mortality for paclitaxel coated devices

through a median of 2.5 years follow-up.2 These results compliment published outcomes from large national health insurance databases in the US and Germany showing no increase in mortality risk with the use of paclitaxel coated devices. Longer term follow-up through 5 years is ongoing for these studies.

Patients receiving the Optilume DCB will be treated with a paclitaxel-coated balloon for a different condition (stricture) in a different part of the body (the urethra). Unlike the cardiovascular application, the drug is deposited on the urethra and not in the blood, although a small amount of drug can diffuse through the urethra into the blood. The mortality rate in the ROBUST series of trials evaluating the Optilume DCB was 0.6 deaths per 100 patient follow-up years, which is no different than the expected rate of mortality for men in this age group.

7 POTENTIAL ADVERSE EFFECTS

The potential adverse effects of the Optilume DCB related to mechanical dilation are similar to urethral balloon dilation catheter and include but not limited to the following:

- Dissection of the urethra
- Perforation of the urethra
- Hematuria
- Inflammation
- Infection
- Recurrence of the stricture
- Detachment of a component of the catheter
- Bothersome urinary symptoms or painful urination

1 Katsanos K, Spiliopoulos S, Kitrou P, Krokidis M, Karnabatidis D. Risk of death following application of paclitaxel-coated balloons and stents in the femoropopliteal artery of the leg: a systematic review and meta-analysis of randomized controlled trials. J Am Heart Assoc. 2018;7(24):e011245

2 Nordanstig J, James S, Andersson M, Andersson M, Danielsson P, Gillgren P, et al. Mortality with paclitaxel-coated devices in peripheral artery disease. N Engl J Med. 2020;383(26):2538-46

- Genital or pelvic pain

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

- Allergic reaction
- Alopecia
- Anemia
- Gastrointestinal symptoms
- Hematological dyscrasia (including leucopenia, neutropenia, thrombocytopenia)
- Hepatic enzyme changes
- Myalgia/athralgia
- Myelosuppression
- Peripheral neuropathy

8 HOW SUPPLIED

The Optilume DCB catheter is supplied STERILE for single use only (ethylene oxide sterilization). The Optilume DCB is in a double pouch packaging system (foil and Tyvek pouches) contained within a single unit box.

9 STORAGE

The Optilume DCB should be stored at room temperature in a dry location in its original packaging. The device should be used prior to the “Use by” date on the packaging.

10 RECOMMENDED ITEMS

Prepare the following items using sterile technique:

- 0.038” or smaller guidewire (flexible tip)
- Flexible or rigid cystoscope
- Sterile saline or sterile water for irrigation
- Inflation device manometer and ≥20cc capacity
- Three-way stopcock to connect the inflation device to the catheter. Alternatively, the inflation device can be directly connected to the catheter.
- Contrast media NOTE: Optional for use with fluoroscopic guided procedures

11 DIRECTIONS FOR USE

11.1 Peri Procedural Medication

It is recommended that physicians follow the American Urologic Association (AUA) guidelines for pre-procedure medications and preparation for an endoscopic procedure, including the administration of a pre-procedure antibiotic as appropriate. Oral NSAIDs are also recommended to be given prior to the procedure.

If a urinary tract infection (UTI) is present, it is recommended that the patient be treated with antibiotics until the infection is resolved before the treatment procedure.

11.2 Device Size Selection

Pre-operative or intra-operative retrograde urethrogram (RUG) or voiding cystourethrography (VCUG) is recommended to identify stricture location, stricture length, and degree of lumen narrowing to inform device size selection. Recommended device diameter selection may depend on anatomic location of the urethral stricture, however for strictures in both the penile and bulbar urethra select an Optilume DCB balloon length that is slightly longer than the stricture length to be treated. The balloon length must extend approximately 0.5-1 cm beyond the stricture on both sides to ensure full coverage of the treated area with the drug coating.

11.2.1 Bulbar Urethral Stricture Device Sizing

For strictures in the bulbar urethra, it is recommended to select a balloon diameter that is slightly larger than the distal healthy urethra diameter. Do not to oversize the Optilume DCB by more than 30% relative to the distal healthy urethra. The majority of bulbar strictures evaluated in the ROBUST III clinical program utilized a 30F Optilume DCB.

Table 11-1: Bulbar Urethra Balloon Sizing Guide

Distal Healthy Urethra Diameter	Optilume® DCB Size	
	Stricture Length ≤ 1.5 cm	Stricture Length 1.5 cm – 3 cm
<19F	18F (6mm) x 30 mm	18F (6mm) x 50 mm
19F – 23F	24F (8mm) x 30 mm	24F (8mm) x 50 mm
24F – 30F	30F (10mm) x 30 mm	30F (10mm) x 50 mm
> 30F	36F (12mm) x 30 mm	36F (12mm) x 50 mm

11.2.2 Penile Urethral Strictures

For urethral strictures in the penile or pendulous urethra, it is recommended to select the balloon diameter that most closely matches the distal healthy urethra diameter. Size selection for penile strictures evaluated in the ROBUST III clinical study were roughly split between 24F and 30F Optilume DCB. Urotronic does not recommend using the 36F diameter Optilume DCB in the penile urethra.

Table 11-2: Penile Urethra Balloon Sizing Guide

Health Distal Urethral Diameter	Optilume® DCB Size	
	Stricture Length ≤ 1.5cm	Stricture Length 1.5 - 3cm
<22F	18F (6mm) x 30 mm	18F (6mm) x 50 mm
22F – 27F	24F (8mm) x 30 mm	24F (8mm) x 50 mm
>27F	30F (10mm) x 30 mm	30F (10mm) x 50 mm

11.3 Balloon Preparation

1. Open the sterile inflation device package and remove the inflation device and 3-way stopcock. If use of a 3-way stopcock is desired, connect the stopcock to the inflation device.

   NOTE: Use of a 3-way stopcock is optional, if the inflation device has a male luer connection it can be directly connected to the female luer hub on the catheter.

2. Fill the inflation device half-way with sterile saline and attach to the Optilume DCB

   It is recommended that the balloon remain covered with the balloon protector sheath during preparation.

3. With the inflation device pointing downwards, draw back plunger to aspirate air from the balloon. Hold until no air bubbles can be seen coming out of the saline in the inflation device. Disconnect the inflation device and purge air from the inflation device, reattach and repeat as needed to until no air is left in the balloon.

4. With catheter preparation complete, disconnect the inflation device.

5. If using fluoroscopy fill the inflation device with a 1:1 normal saline-contrast mixture, otherwise fill will sterile saline.

6. Attach inflation device to the stopcock or the female luer hub on the balloon catheter and pull vacuum on the inflation device.

11.4 Optilume DCB Insertion and Dilation

1. With aid of a cystoscope and utilizing saline irrigation, position a 0.038" guidewire across the stricture with the flexible tip coiled in the bladder.
2. Remove the protective sheath from the tip of the Optilume DCB.

Caution: *Care should be exercised when passing a balloon coated with paclitaxel through any cystoscope system. Minimize excessive handling and do not touch the balloon. Do not wipe the balloon with dry, wet or lubricated gauze, or any solvent which could damage the integrity of the drug coated balloon.*

3. For 18-30F (6-10mm) balloon diameters, place the Optilume DCB catheter over the guidewire and advance through the working channel of a flexible or rigid cystoscope. Alternately, all balloon diameters may be placed by positioning the guidewire and Optilume DCB side by side with the cystoscope.

Caution: *Side by side positioning must be used for the 36F Optilume DCBs as they are not compatible with the working channel of a flexible cystoscope.*

Caution: *Do not advance the guidewire or the Optilume DCB if resistance is met without first determining the cause of resistance and taking appropriate action to correct.*

4. Position the Optilume DCB across the stricture with the cystoscope placed distal to the balloon (away from the bladder) to visualize the proper placement of the balloon across the stricture. Leave the balloon in position uninflated for a minimum of 1 minute prior to inflation to adequately hydrate the drug coating prior to inflation. Alternatively, the position the Optilume DCB with fluoroscopy by using the radiopaque markers demarking the working length of the balloon.
5. Inflate the balloon to the rated burst pressure (RBP) using the inflation device. Maintain pressure for a minimum of 5 minutes, or until desired dilation is achieved.

Caution: *DO NOT exceed RBP of the balloon. RBP for each balloon size is provided on the Tyvek pouch label and in Table 1-1 of this document. Inflation in excess of RBP may cause the balloon to rupture.*

Caution: *Inflation devices are capable of attaining very high pressures with minimal effort. The use of an inflation device with a pressure gauge is highly recommended to optimize dilatation force to yield the urethral stricture and allow drug penetration into the urothelium.*

11.5 Deflation and Removal

1. Deflate balloon by applying vacuum to the balloon with the inflation device. When the balloon is completely deflated, withdraw guidewire and Optilume DCB slowly. If slight resistance is felt when the balloon is being removed, gently rotate the catheter to help the balloon fold around the catheter shaft and facilitate withdrawal.

Caution: *If resistance is encountered when removing the guidewire and/or Optilume DCB through a cystoscope, STOP and remove them together as a single unit to prevent damage to the guidewire, catheter or patient anatomy.*

2. If the product has a failure prior to inflation or during inflation at a pressure less than RBP, replace Optilume DCB and inflate per above instructions. If the failure is after inflation to RBP, do not repeat the Optilume DCB procedure as sufficient dilation and drug transfer has been accomplished.

3. Insert a 12-14 Fr lubricious Foley catheter and leave in place for a minimum of 2 days or per standard of care, whichever is greater.

12 SUMMARY OF CLINICAL STUDIES

The safety and effectiveness of the Optilume DCB is derived from the ROBUST clinical program, which is comprised of three studies. These studies are:

- ROBUST-I First-in Man Study
- ROBUST-II Early Feasibility Study
- ROBUST-III Pivotal Randomized study

12.1 ROBUST III Pivotal Study

12.1.1 Objective

The objective of the ROBUST III study was to evaluate the safety and effectiveness of the Optilume DCB as compared to standard-of-care (SOC) endoscopic management of recurrent anterior urethral strictures.

12.1.2 Study Design

The ROBUST III study is a prospective, 2:1 randomized, multicenter, single blind trial comparing the Optilume DCB against SOC endoscopic management of recurrent anterior urethral strictures. Eligibility criteria are shown below.

Inclusion Criteria

1. Male subjects ≥ 18 years old
2. Visual confirmation of stricture via cystoscopy or urethrogram
3. Single, tandem or diffuse anterior urethral stricture(s), less than or equal to 3.0 cm total length measured by retrograde urethrogram. (Stricture length is defined as the distance between the most distal edge of the stricture to the most proximal edge of the stricture).
4. Two or more prior dilation treatments of the same stricture, including DVIU (Direct Vision Internal Urethrotomy). Note: Catheterization is not considered a dilation treatment.
5. Significant symptoms of stricture such as frequency of urination, dysuria, urgency hematuria, slow flow, feeling of incomplete emptying, recurrent UTI's.
6. IPSS score of 11 or higher (assumed to be "35" if suprapubic catheter is present)
7. Lumen diameter ≤12F by urethrogram
8. Qmax <15 ml/sec (assumed to be "0" if suprapubic catheter is present)
9. Guidewire must be able to cross the lesion

Exclusion Criteria

1. Subjects with diffuse stricture length, greater than 3.0 cm in total length. (Stric ture length is defined as the distance between the most distal edge of the stric ture to the most proximal edge of the stricture).
2. Subjects with a history of hypersensitivity reactions to TAXOL, on medication that may have negative interaction with paclitaxel, with solid tumors who have a baseline neutrophil counts of <1500 cells/mm3 or subjects with AIDS-related Kaposi's sarcoma with baseline neutrophil counts of <1000 cells/mm3.

3. Subjects who had an indwelling suprapubic catheter longer than 3 months total prior to enrollment.
4. Previous urethroplasty within the anterior urethra.
5. Stricture dilated or incised within the last six (6) weeks (urethral catheterization is not considered dilation).
6. Presence of local adverse factors, including abnormal prostate making catheter ization difficult, urethral false passage or fistula.
7. Presence of signs of obstructive voiding symptoms not directly attributable to the stricture at the discretion of the physician.
8. Diagnosis of untreated and unresolved BPH or BNC.
9. Untreated stress urinary incontinence (SUI).
10. History of diagnosed radiation cystitis.
11. Diagnosis of carcinoma of the urethra, bladder or prostate within the last 2 years.
12. Active kindey, bladder, urethral or ureteral stone passage in the last six (6) weeks or concern of stone passage in the next 6 weeks at the discretion of the investigator.
13. Diagnosis of chronic renal failure and treatment with hemodialysis.
14. New diagnosis of OAB (overactive bladder) within the last 6 months.
15. Use of alpha blockers, OAB (Overactive Bladder) medication, anticonvulsants (drugs that prevent or reduce the severity and frequency of seizures), and anti spasmodics where the dose is not stable. (Stable dose is defined as having the same medication and dose in the last six months.)
16. Dependence on Botox (onabotulinumtoxinA) in urinary system.
17. Presence of an artificial urinary sphincter, slings or stent(s) in the urethra or prostate.
18. Known neurogenic bladder, sphincter abnormalities, or poor detrusor muscle function
19. Diagnosed with Lichen Sclerosus, or stricture due to balanitis xerotica obliterans (BXO).
20. Previous hypospadias repair.
21. 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 two years of enrollment.
22. Any cognitive or psychiatric condition that interferes with or precludes direct and accurate communication with the study investigator regarding the study or affect the ability to complete the study quality of life questionnaires.
23. Unwilling to use protected sex for 30 days' post treatment.
24. Unwilling to abstain or use protected sex for 90 days' post treatment if sexual partner is of child-bearing potential.
25. Inability to provide Informed Consent Form (ICF) and/or comply with all the required follow-up requirements

26. Participation in other pre-market studies or treatment with an investigational drug or device. Long-term follow-up or post market study of an approved device is allowed.
27. Current active infection in the urinary system.
28. Current uncontrolled diabetes (hemoglobin A1c > 8.0%) or evidence of poor wound healing due to diabetes
29. Diagnosed or suspected primary neurologic conditions such as multiple sclerosis or Parkinson's disease or other neurological diseases known to affect bladder function, sphincter function or poor detrusor muscle function.
30. Visible hematuria in subject's urine sample without known contributing factor.
31. Invisible hematuria (or significant microscopic hematuria, i.e., hematuria of ≥ 3 RBC's/HPF) that may be caused by a clinically significant disease unless it is attributed to the urethral stricture disease or other causes which are benign and not requiring treatment.

Follow-up visits were completed at the time of Foley removal (2-5 days), 30 days, 3 months, 6 months, and 12 months post-treatment. Subjects were blinded to treatment received through primary follow-up of 6 months. Long term follow-up is planned yearly through 5 years for subjects receiving the Optilume DCB.

Subjects randomized to SOC endoscopic management were allowed to cross over to receive the Optilume DCB prior to the close of the 12-month follow-up window if stricture recurrence was confirmed by recurrent lower urinary tract symptoms (LUTS) and urethral diameter <12F measured by urethrogram. Subjects crossing over to receive the Optilume DCB will be followed according to the standard follow-up schedule through 5 years, beginning on the date Optilume DCB treatment was received.

Clinical assessments during follow up included:

- International Prostate Symptom Score (IPSS) questionnaire
- International Index of Erectile Function (IIEF) questionnaire
- Visual Analogue Scale (VAS) for Pain (Procedure through 30 days)
- Uroflowmetry, including peak urinary flow rate (Qmax) and post-void residual (PVR)
- Laboratory testing
- Physical exam

Primary Efficacy Endpoint: The primary efficacy endpoint was defined as the proportion of subjects free from stricture recurrence at 6 months, which was defined as the ability to pass a 16F flexible cystoscope or 14F rubber catheter through the treated area.

The statistical hypothesis test for the primary efficacy endpoint was based on a two-sample continuity corrected Chi-square test at the two-sided 0.05 alpha level (equivalent to a one-sided 0.025 alpha level). For the trial to be successful, the statistical evaluation for the resolution of the stricture at 6 months of the Optilume arm will be statistically compared to the Control arm.

$$Ho: Pt \leq Pc$$

$$Ha: Pt > Pc$$

Where Pt is the stricture free rate at 6 months in the Optilume arm and PC is the stricture free rate at 6 months in the Control arm.

Primary Safety Endpoint: The primary safety endpoint is defined as a composite of pre-defined device or procedure related serious complications through 3 months post-treatment. The proportion of subjects experiencing a serious device or procedure related event of the following types will be reported:

- Formation of rectal fistula.
- Unresolved de novo stress urinary incontinence (requiring ≥ 1 pad per day).
- Urethral rupture or burst.

The primary safety endpoint was analyzed with descriptive statistics and nominal 95% confidence intervals.

Hypothesis tested secondary endpoints:

- Time to treatment failure through 6 months
- Change in Qmax at 6 months
- Responder Rate at 12 months (A responder is defined as subjects with an improvement of ≥50% from baseline in IPSS score.)

Ancillary endpoints:

- Change in IPSS over time
- Percent responder over time
- Qmax, PVR over time
- Rate of acute urinary retention through 6 months
- Freedom from repeat intervention over time
- Change in erectile function

The primary analysis set was intention-to-treat (ITT). The ITT set was comprised of all subjects who were enrolled and randomized to receive either the Optilume DCB or SOC endoscopic management. Primary and hypothesis tested secondary endpoints employed multiple imputation for handling missing data.

12.1.3 Subject Allocation

The study started enrollment on October 25th, 2018, completed enrollment in the randomized cohort on June 10th, 2020, and closed enrollment on December 11th, 2020. A total of 141 subjects were enrolled at 22 investigational sites, 127 in the randomized cohort (Optilume n=79, Control n=48) and 14 in the pharmacokinetics sub-study. A single subject participated in the pharmacokinetic sub-study as part of the protocol defined cross-over procedure, giving a total of 15 evaluable subjects for pharmacokinetic parameters.

Figure 12-1 provides an overview of subject allocation over the duration of the study.

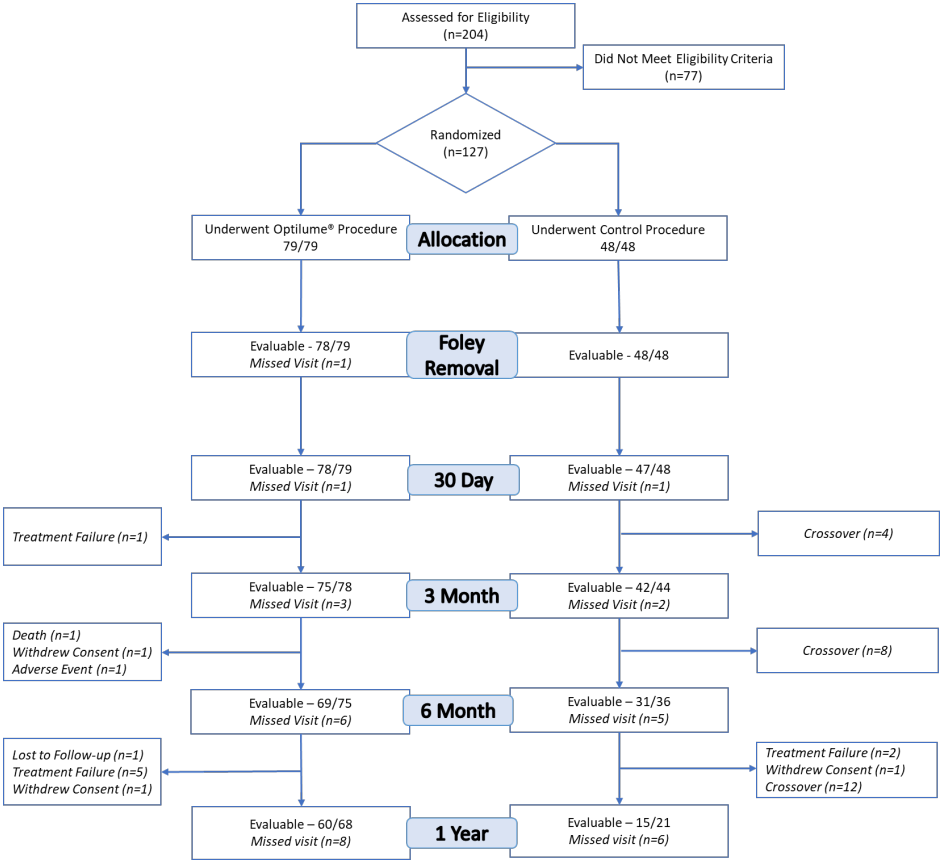

Figure 12-1. Subject Allocation

12.1.4 Subject Demographics and Stricture Characteristics

A total of 127 subjects were randomized in a 2:1 fashion to the Optilume DCB arm or standard-of-care Control arm. Subject demographics and baseline characteristics were well matched between arms and are summarized in **Table 12-1**.

Table 12-1. Baseline Demographics and Medical History

Characteristic	Control	Optilume DCB	p-value[1]
Demographics			
Age	60.6 ± 16.0 (48)	58.7 ± 15.5 (79)	0.500
Race			0.838
American Indian or Alaska Native	1/48 (2.1%)	0/78 (0.0%)	
Asian	2/48 (4.2%)	3/78 (3.8%)	
Black or African American	6/48 (12.5%)	9/78 (11.5%)	
Native Hawaiian or Pacific Islander	0/48 (0.0%)	1/78 (1.3%)	
White	39/48 (81.3%)	65/78 (83.3%)	
Ethnicity			0.673
Hispanic or Latino	3/48 (6.3%)	3/78 (3.8%)	
Not Hispanic or Latino	45/48 (93.8%)	75/78 (96.2%)	
BMI	28.9 ± 6.9 (48)	30.5 ± 6.7 (77)	0.206
Medical History / Risk Factors			
LUTS Presentation			>0.999
Dysuria	18/48 (37.5%)	36/79 (45.6%)	
Frequency	34/48 (70.8%)	63/79 (79.7%)	
Hematuria	12/48 (25.4%)	10/79 (12.7%)	
Hesitancy	29/48 (60.4%)	38/79 (48.1%)	
Incomplete Voiding	35/48 (72.9%)	57/79 (72.2%)	
Nocturia	41/48 (85.4%)	58/79 (73.4%)	
Pelvic Pain	3/48 (6.3%)	3/79 (3.8%)	
Poor Stream	43/48 (89.6%)	70/79 (88.6%)	
Retention	24/48 (50.0%)	27/79 (34.2%)	
Terminal dribbling	23/48 (47.9%)	33/79 (41.8%)	
Urgency	33/48 (68.8%)	54/79 (68.4%)	
Urinary Incontinence	4/48 (8.3%)	2/79 (2.5%)	0.198
Prior Pelvic Radiation	6/48 (12.5%)	9/79 (11.4%)	>0.999
Genitourinary History	33/47 (70.2%)	57/79 (72.2%)	0.837
Bacterial Prostatitis	3/48 (6.3%)	3/79 (3.8%)	
Benign Prostatic Hyperplasia	14/48 (29.2%)	25/79 (31.6%)	
Bladder Neck Contracture	1/48 (2.1%)	1/79 (1.3%)	
Bladder Stones	2/48 (4.2%)	4/79 (5.1%)	
Cystitis	1/48 (2.1%)	4/79 (5.1%)	
Fistula of Rectum	0/48 (0.0%)	1/79 (1.3%)	
Inflammatory Bowel Disease	0/48 (0.0%)	1/79 (1.3%)	
Kidney Stone	7/48 (14.6%)	15/79 (19.0%)	
Muscle Spasms	2/48 (4.2%)	0/79 (0.0%)	
Other	21/48 (43.8%)	31/79 (39.2%)	
Overactive Bladder	3/48 (6.3%)	8/79 (10.1%)	
Prostate Cancer	5/48 (10.4%)	8/79 (10.1%)	
Unusual Bladder Anatomy	0/48 (0.0%)	1/79 (1.3%)	
Urinary Tract Infection(s)	17/48 (35.4%)	27/79 (34.2%)	

[1]p-values based on unpaired t-test for continuous variables and Fisher's exact test for categorical variables.

Stricture characteristics were similar between arms and are summarized in **Table 12-2**.

Table 12-2. Baseline Stricture Characteristics

Stricture Characteristics	Category	Control n/N (%)	Optilume DCB n/N (%)	p-value
Urethral Stricture Etiology	Iatrogenic	16/47 (34.0%)	21/78 (26.9%)	0.566
	Idiopathic	22/47 (46.8%)	42/78 (53.8%)	
	Inflammatory	2/47 (4.3%)	1/78 (1.3%)	
	Traumatic	7/47 (14.9%)	14/78 (17.9%)	
Retention (luminal obliteration)	Obliterated / Near Obliterated	17/47 (36.2%)	26/79 (32.9%)	0.846
	Patent Urethra	30/47 (63.8%)	53/79 (67.1%)	
Anatomic Location	Bulbar	45/47 (95.7%)	71/79 (89.9%)	0.319
	Penile	2/47 (4.3%)	8/79 (10.1%)	
Stricture Length (cm)	n Mean ± SD	47 1.72 ± 0.73	78 1.63 ± 0.76	0.528
Diameter of Urethra at Stricture (mm)		47 2.33 ± 0.88	78 2.46 ± 0.96	0.470
Diameter of Heathy Urethra at Normal (mm)		48 8.97 ± 2.19	78 9.52 ± 2.33	0.195
Number of Prior Dilations	n Mean ± SD Median Min, Max	48 4.3* ± 7.5 3.0 1, 53	79 3.2 ± 1.7 3.0 2, 10	0.321
	≥5 prior Dilations	10/48 (20.8%)	13/79 (16.5%)	0.636

*Data includes single subject with 53 prior dilations.

12.1.5 Device Sizes Used in the Study

A total of 129 devices were opened or used during 125 procedures. This includes 83 devices opened/used in the randomized cohort, 32 devices used during crossover procedures, and 14 devices used in the pharmacokinetic cohort. Four devices experienced device deficiencies (3 balloon burst and 1 balloon leak) and were replaced, and one was opened but not used (wrong size opened). The device deficiencies did not lead to adverse events. Table 12-3 summarizes the device sizes used in the study.

Table 12-3. Device Sizes Used.

Balloon Diameter	Balloon Length	
	30 mm	50 mm
18F (6 mm)	0	0
24F (8 mm)	2	6
30F (10 mm)	33	83
36F (12 mm)	2	2

12.1.6 Primary Safety and Efficacy Endpoints

Primary Safety Endpoint

The primary safety endpoint was the proportion of subjects experiencing a composite of a serious device or procedure related fistula formation, unresolved de novo stress urinary incontinence, or urethral rupture or burst through 3 months post-procedure. No subjects experienced a primary safety endpoint event through 3 months post-treatment as adjudicated by the independent Clinical Events Committee (CEC).

Table 12-4. Primary Safety Endpoint Results

Endpoint	Control n/N (%)	Optilume DCB n/N (%)
Serious device or procedure related complication through 3 months post-treatment	0/48 (0.0%)	0/79 (0.0%)
Formation of Fistula	*0/48 (0.0%)*	*0/79 (0.0%)*
Unresolved De Novo Stress Urinary Incontinence	*0/48 (0.0%)*	*0/79 (0.0%)*
Urethra Rupture or Burst	*0/48 (0.0%)*	*0/79 (0.0%)*

Primary Efficacy Endpoint

The primary efficacy endpoint was a comparison of the rate of subjects free from stricture recurrence through 6 months post-procedure. This endpoint was evaluated by the ability to pass a 16F flexible cystoscope or a 14F rubber catheter through the treated area at 6 months post-treatment. If a 16F scope was unable to pass, a 14F rubber catheter was attempted. If at least one of the stated instruments was able to pass through the treated area, the subject was considered a success for this endpoint. If neither instrument could pass through the treated area, the subject was considered a failure. Any subjects who have a second dilation procedure, pursue surgical intervention, or otherwise seek alternative treatment for the target stricture prior to the close of the 6-month visit window are considered treatment failures for the primary analysis.

Subjects crossing over from the Control arm to receive treatment Optilume DCB or any subject in either arm receiving alternative therapy prior to 240 days (6-month window +30d) were considered a failure for this endpoint. The difference between arms was estimated using multiple imputation for missing values. The primary endpoint was met, with an estimated difference of 44.4% between groups at 6 months ($p<0.0001$).

Table 12-5. Primary Efficacy Endpoint – ITT, Multiple Imputation

Variable	Difference [95% CI]
Stricture free defined as the ability to pass a 16Fr flexible cystoscope or a 14Fr rubber catheter at 6 months post-treatment	44.4% [27.6% – 61.1%]
P-value	<0.0001
P-value is based on two-sample continuity corrected Chi-square test utilizing a weighted Z-score.	

A Complete Case assessment was conducted as a further sensitivity analysis, utilizing only observed values to calculate the difference between arms (i.e. no imputation of missing outcomes). The observed difference between arms was 47.8%, which is consistent with the estimated difference from the primary analysis. The primary efficacy endpoint was 74.6% in the Optilume DCB arm and 26.8% in the standard-of-care Control arm. The Optilume DCB showed statistical superiority to standard-of-care endoscopic management in maintaining freedom from stricture recurrence through 6 months post-treatment ($p<0.001$).

Table 12-6. Primary Efficacy Endpoint Results (Complete Case)

Endpoint	Control (n=48)	Optilume DCB (n=79)	Difference [95% CI]	p-value
Proportion of Subjects Stricture Free	26.8% (11/41)	74.6% (50/67)	47.8% [28.7% – 66.9%]	<0.0001

P-value is based on two-sample continuity corrected Chi-square test.

A total of 19 subjects are missing the primary endpoint assessment in the randomized cohort. The rate of missing primary endpoint data was balanced between arms, with 12 (15.2%) in the Treatment arm and 7 (14.6%) in the Control arm. Five (5) subjects missed their 6-month visit due to COVID concerns, 6 subjects had their 6-month visit done remotely due to site or government COVID policy, 4 subjects withdrew from the study prior to the 6-month visit, and 4 subjects missed their 6 month visit for reasons not known to be directly related to COVID.

12.1.7 Hypothesis Tested Secondary Endpoints

Time to Treatment Failure

A hypothesis tested time-to-event analysis comparing time to treatment failure was conducted. Treatment failure was defined as a subject receiving additional treatment of the study stricture or subject having been confirmed to have stricture recurrence (unable to pass 16F cystoscope or 14F catheter) through 240 days post-procedure. The Optilume DCB was superior to standard-of-care in time to treatment failure (p<0.0001).

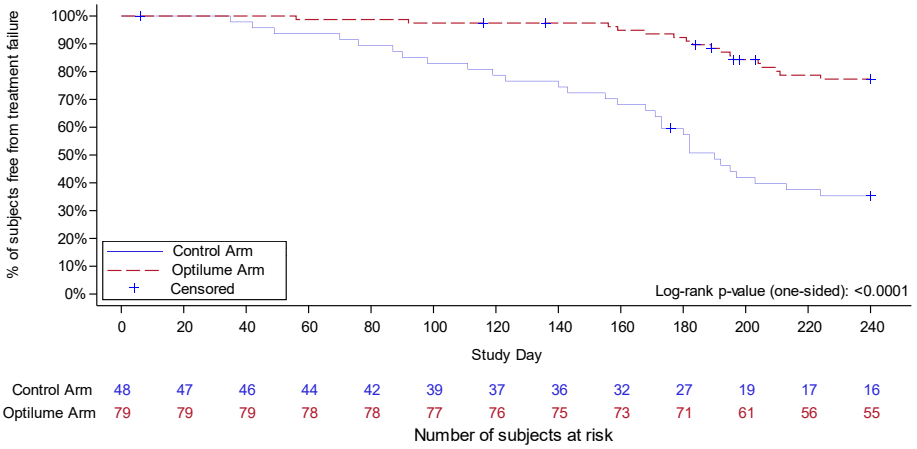

Figure 12-2. Kaplan-Meier Plot of Freedom from Treatment Failure Through 6 Months

Change in Qmax at 6 Months

The change in Qmax at 6 months post-treatment was compared between arms. The Optilume DCB showed a significantly higher increase in Qmax at 6 months compared to Control, with a point estimate for the difference between arms of +4.78 mL/sec favoring the Optilume arm (p=0.0031). Missing data were imputed via multiple imputation.

Table 12-7. Change in Qmax at 6 Months (ITT, Multiple Imputation)

Variable	Point Estimate of Difference [90% CI]
Change in Qmax	+4.78 [1.94, 7.61]
P-value (one-sided)	0.0031
P-value is based on independent samples t-test.	

Percent Responder at 12 Months (IPSS)

The rate of therapeutic responders, defined as subjects with an improvement of ≥50% from baseline in IPSS score, in the Optilume arm was compared against a performance goal of 50%. Subjects experiencing a treatment failure (failure to pass 16F cystoscope/14F catheter or repeat treatment) were considered failures for this endpoint, while responder status for subjects missing IPSS scores at 1 year was imputed using multiple imputation with a linear regression model.

The point estimate of the responder rate at 12 months utilizing the multiple imputation approach was 59.6%, with the lower bound of the 90% confidence interval of 49.9% not meeting the pre-specified performance goal of 50% (p=0.051).

Table 12-8. Responder Rate at 12 Months (ITT, Multiple Imputation)

Endpoint	Optilume DCB (N=79)
IPSS improvement of ≥ 50% from baseline at 1 Year	
% (90% CI)	59.6% (49.9%, 69.3%)
P-value	0.0514

12.1.8 Ancillary Endpoints

Change in IPSS Over Time

Table 12-9. provides the change in International Prostate Symptom Scores (IPSS) scores for both arms using a Failure Carried Forward analysis. Failure Carried Forward is a data analysis method which carries forward the worst value observed during follow-up for those who experienced treatment failure.

Table 12-9. IPSS Over Time (Failure Carried Forward)

Study Arm	Baseline	30-Day	3-Month	6-Month	1-Year
Control					
n	47	47	45	43	42
Mean ± SD	22.8 ± 6.97	9.5 ± 7.40	12.4 ± 9.17	15.4 ± 9. 57	19.9 ± 7.46
Median	22.0	7.0	11.0	14.0	18.5
Min, Max	11, 35	1, 35	0, 35	1, 35	7, 35
Optilume DCB					
n	79	78	74	71	67
Mean ± SD	22.0 ± 6.78	7.6 ± 5.70	7.4 ± 5.76	8.3 ± 6.15	9.0 ± 7.12
Median	22.0	6.0	6.0	8.0	8.0
Min, Max	11, 35	0, 26	0, 24	0, 26	0, 26

Percent Responder Over Time

Table 12-10 provides the percent responder over time using the failure carried forward analysis. An International Prostate Symptom Scores (IPSS) responder is defined as a subject with a ≥50% improvement in IPSS.

Table 12-10. IPSS Responder (≥50% Improvement) Over Time (Failure Carried Forward)

Study Arm	30-Day	3-Month	6-Month	1-Year
Control				
n/N (%)	28/47 (59.6%)	21/45 (46.7%)	12/43 (27.9%)	1/42 (2.4%)
90% CI	46.5%, 71.7%	33.8%, 59.9%	17.0%, 41.3%	0.1%, 10.8%
Optilume DCB				
n/N (%)	57/78 (73.1%)	56/74 (75.7%)	50/71 (70.4%)	39/67 (58.2%)
90% CI	63.6%, 81.2%	66.1%, 83.6%	60.3%, 79.2%	47.4%, 68.4%
Confidence intervals (CI) are estimated using the Clopper-Pearson (exact) approach. .				

Peak Flow Rate (Qmax) Over Time

Table 12-11 provides the peak flow rate (Qmax) values for both groups using the failure carried forward analysis.

Table 12-11. Peak Flow Rate Over Time (Failure Carried Forward)

Study Arm	Baseline	30-Day	3-Month	6-Month	1-Year
Control					
n	47	44	39	44	41
Mean ± SD	7.4 ± 3.5	15.8 ± 8.5	13.3 ± 9.3	11.1 ± 7.6	7.6 ± 4.0
Median	7.9	14.8	11.4	9.9	7.5
Min, Max	0.0, 14.5	1.3, 38.5	0.0, 41.9	0.0, 31.2	0.0, 14.8
Optilume DCB					
n	78	75	71	67	65
Mean ± SD	7.6 ± 3.4	18.3 ± 9.1	18.6 ± 10.9	16.6 ± 8.9	15.5 ± 9.0
Median	7.2	17.4	15.1	15.0	13.5
Min, Max	0.0, 14.9	1.6, 44.4	1.6, 54.0	1.6, 48.5	1.6, 48.8

Post Void Residual (PVR) Urine Volume

Table 12-12 provides the PVR for both groups using the failure carried forward analysis.

Table 12-12. Post Void Residual Volume Over Time (Failure Carried Forward)

Study Arm	Baseline	30-Day	3-Month	6-Month	1-Year
Control					
n	46	45	41	44	42
Mean ± SD	133.8 ± 155.1	79.1 ± 87.3	113.4 ± 124.2	141.4 ± 194.1	181.5 ± 201.7
Median	76.0	43.0	59.0	90.5	128.0
Min, Max	0, 703	0, 402	0, 467	0, 999	0, 999
Optilume DCB					
n	77	75	70	67	66
Mean ± SD	109.8 ± 116.9	75.6 ± 86.2	103.4 ± 134.4	73.1 ± 117.7	94.6 ± 121.8
Median	60.0	39.0	54.0	30.0	50.5
Min, Max	0, 557	0, 378	0, 650	0, 634	0, 546

Rate of Acute Urinary Retention Through 6 Months

The rate of acute urinary retention (AUR) events requiring catheterization that occurred prior to the close of the 6-month window was evaluated using the ITT population.

Table 12-13. Rate of Acute Urinary Retention Requiring Catheterization Through 6 Months (ITT)

Endpoint	Control	Optilume DCB	Difference (95% CI)
Rate of acute urinary retention requiring catheterization by 6 months	3/48 (6.3%)	1/79 (1.3%)	-5.0% (-22.7%, 12.9%)
Confidence Intervals (CI) for the difference are estimated using the exact approach.			

Freedom from Repeat Intervention Over Time

Repeat intervention in this study included repeated dilation of the study stricture with sounds, balloon dilation (including crossover treatment with Optilume DCB), Direct Visual Internal Urethrotomy (DVIU), and urethroplasty. Kaplan-Meier estimates of freedom from repeat intervention was 83.2% in the Optilume arm compared to 21.7% in the Control arm. In this analysis, completed using the ITT population, subjects were censored at the time of their last visit or at 395 days, whichever is earliest. Censoring these subjects at the date of the snapshot or 395 days results in point estimates of 86.3% for Optilume and 23.1% for Control.

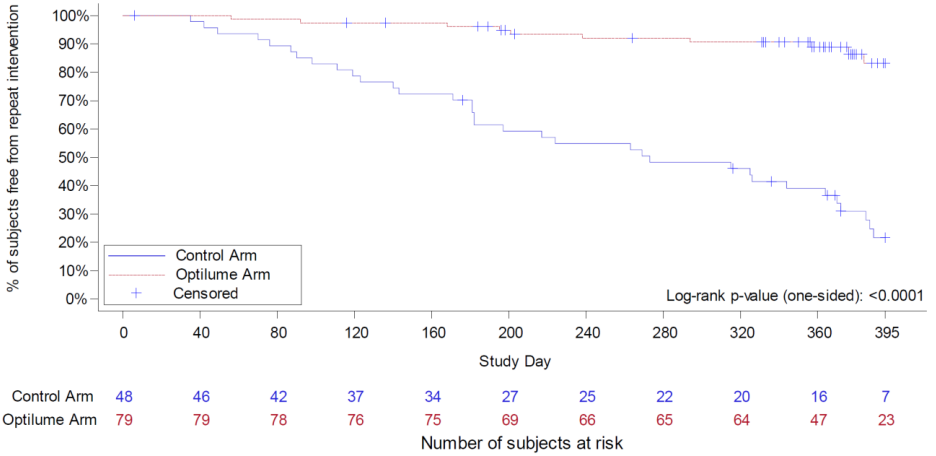

Figure 12-3. Kaplan Meier Curve for Freedom from Repeat Intervention (ITT)

Change in Erectile Function

The impact of study treatment of erectile function was assessed utilizing the International Index for Erectile Function (IIEF) questionnaire. The IIEF is a validated 5-part, 15 item questionnaire that evaluates erectile function, orgasmic function, sexual desire, intercourse satisfaction, and overall satisfaction. The 'Overall Satisfaction' (OS) score ranges from 2-10, with higher scores indicating higher satisfaction. Using the Complete Case analysis, there was no change in the OS score from baseline to 1 year follow-up for either arm, indicating there is no impact on patient reported sexual function by either the Optilume DCB or standard of care endoscopic treatments.

12.1.9 Pharmacokinetic Sub-Study

A sub-study including 15 non-randomized subjects was conducted to determine the pharmacokinetic profile of paclitaxel in blood (plasma), urine, and semen after treatment with the Optilume DCB. Determination of plasma paclitaxel concentration was evaluated immediately after completion of the procedure, at 1, 3, and 5 hours, and at

Foley removal, 30 days, 3 months, and 6 months post-procedure. Urine paclitaxel concentration was evaluated immediately post-procedure, at Foley removal, and at 30 days, 3 months, and 6 months. Semen paclitaxel concentration was evaluated at 30 days, 3 months, and 6 months post-procedure. Clinical follow-up without additional pharmacokinetic sampling will continue through 5 years post-procedure.

A summary of pharmacokinetic parameters, including maximum concentration (Cmax) and time to maximum concentration (Tmax) for plasma is in Table 12-14. Paclitaxel concentration over time in urine and semen can be found in Table 12-15 and Table 12-16, respectively. On average, paclitaxel concentration in plasma fell below the limit of quantitation of the method (0.10 ng/mL or 0.1 part per billion) by 5 hours post-procedure, while average paclitaxel concentration in urine fell below the limit of quantitation by 30 days. The average paclitaxel concentration in semen was near the limit of quantitation (0.12 ng/mL) by 6 months.

Table 12-14. Summary of Plasma Pharmacokinetic Parameters

Parameter	Plasma
C_{max} (ng/mL)	
n	15
Mean	0.12 ± 0.15
Min, Max	<0.10, 0.52
T_{max} (hr)	
n	15
Median	0.25 ± 0.96
Min, Max	0.25, 3

Table 12-15. Paclitaxel concentration over time in urine.

Measure	Urine Concentration (ng/mL)					
	Baseline	0hr	Foley Removal	30 Days	3 Months	6 Months
Mean ± St Dev	<0.1 ± 0.0	414.4 ± 484.8	13.8 ± 14.6	<0.1 ± 0.0	<0.1 ± 0.0	<0.1 ± 0.0
Median	<0.1	231.0	11.1	<0.1	<0.1	<0.1
Max, Min	<0.1	1940, 46.4	54.4, 0.9	0.18, <0.1	<0.1	<0.1
Subjects with Measurable Amt	0/15 (0.0%)	15/15 (100.0%)	15/15 (100.0%)	4/15 (26.7%)	0/15 (0.0%)	0/14 (0.0%)

Table 12-16. Paclitaxel concentration over time in semen.

Measure	Semen Concentration (ng/mL)			
	Baseline	30 Days	3 Months	6 Months
Mean ± St Dev	<0.10 ± 0.00	2.99 ± 4.88	0.48 ± 0.98	0.12 ± 0.23
Median	<0.10	0.27	<0.10	<0.10
Max, Min	<0.10	17.60, <0.10	3.45, <0.10	0.85, <0.10
Subjects with Measurable Amt	0/14 (0.0%)	9/15 (60.0%)	5/13 (38.5%)	1/12 (8.3%)

12.1.10 Adverse Events

A total of 240 adverse events have been reported in 92 subjects in the randomized cohort, a summary can be found in Table 12-17. The most common events adjudicated by the Clinical Events Committee (CEC) as being 'Possibly', 'Probably', or 'Definitely' related to the Optilume DCB and/or the procedure included post-operative hematuria (11.4%), dysuria (6.3%), and urinary tract infection (6.3%). Adverse event rates and types were generally well matched between arms, with the Optilume arm showing a trend toward higher rates of post-procedure hematuria and dysuria. These events were all mild in nature, and generally resolved within 30 days of onset.

Table 12-17. Adverse Events by Category for the Randomized Cohort.

Event Types	Control		Optilume DCB	
	Events	Subjects	Events	Subjects
Any Adverse Events	**89**	**39/48 (81.3%)**	**151**	**53/79 (67.1%)**
Serious Adverse Events	*8*	*8/48 (16.7%)*	*10*	*9/79 (11.4%)*
Non-serious Adverse Event	*81*	*38/48 (79.2%)*	*141*	*53/79 (67.1%)*
Treatment Related Adverse Events	**14**	**9/48 (18.8%)**	**47**	**31/79 (39.2%)**
Device Related	*5*	*4/48 (8.3%)*	*35*	*28/79 (35.4%)*
Procedure Related	*9*	*5/48 (10.4%)*	*12*	*10/79 (12.7%)*

A summary of events adjudicated by the CEC as related to the device or procedure can be found in Table 12-18.

Table 12-18. Device/Procedure Related Adverse Events by MedDRA System Organ Class and Preferred Term

System Organ Class / Preferred Term	Control		Optilume DCB	
	Events	Subjects (N=48)	Events	Subjects (N=79)
Renal and Urinary Disorders	5	4/48 (8.3%)	19	16/79 (20.3%)
Dysuria	0	0/48 (0.0%)	5	5/79 (6.3%)
Bladder Spasm	2	1/48 (2.1%)	2	2/79 (2.5%)
Hematuria	0	0/48 (0.0%)	3	3/79 (3.8%)
Urethral Stenosis	1	1/48 (2.1%)	1	1/79 (1.3%)
Urinary Incontinence	0	0/48 (0.0%)	2	2/79 (2.5%)
Urinary Retention	0	0/48 (0.0%)	2	2/79 (2.5%)
Urine Flow Decreased	1	1/48 (2.1%)	1	1/79 (1.3%)
Lower Urinary Tract Symptoms	1	1/48 (2.1%)	0	0/79 (0.0%)
Terminal Dribbling	0	0/48 (0.0%)	1	1/79 (1.3%)
Urethral Hemorrhage	0	0/48 (0.0%)	1	1/79 (1.3%)
Urethritis	0	0/48 (0.0%)	1	1/79 (1.3%)
Injury, Poisoning and Procedural Complications	3	2/48 (4.2%)	11	11/79 (13.9%)
Post Procedural Hematuria	0	0/48 (0.0%)	9	9/79 (11.4%)
Medical Device Site Extravasation	1	1/48 (2.1%)	1	1/79 (1.3%)
Anaesthetic Complication Pulmonary	1	1/48 (2.1%)	0	0/79 (0.0%)
Catheter Site Irritation	1	1/48 (2.1%)	0	0/79 (0.0%)
Urinary Retention Postoperative	0	0/48 (0.0%)	1	1/79 (1.3%)
Infections and Infestations	2	2/48 (4.2%)	7	6/79 (7.6%)
Urinary Tract Infection	1	1/48 (2.1%)	5	5/79 (6.3%)
Bacteriuria	0	0/48 (0.0%)	2	2/79 (2.5%)
Sepsis	1	1/48 (2.1%)	0	0/79 (0.0%)
Reproductive System and Breast Disorders	1	1/48 (2.1%)	6	5/79 (6.3%)
Prostatitis	0	0/48 (0.0%)	2	2/79 (2.5%)
Testicular Pain	1	1/48 (2.1%)	1	1/79 (1.3%)
Pelvic Pain	0	0/48 (0.0%)	1	1/79 (1.3%)

Penile Pain	0	0/48 (0.0%)	1	1/79 (1.3%)
Perineal Pain	0	0/48 (0.0%)	1	1/79 (1.3%)
General Disorders, Administration Site Conditions	2	2/48 (4.2%)	0	0/79 (0.0%)
Fatigue	1	1/48 (2.1%)	0	0/79 (0.0%)
Pyrexia	1	1/48 (2.1%)	0	0/79 (0.0%)
Investigations	0	0/48 (0.0%)	2	1/79 (1.3%)
Alanine Aminotransferase Increased	0	0/48 (0.0%)	1	1/79 (1.3%)
Aspartate Aminotransferase Increased	0	0/48 (0.0%)	1	1/79 (1.3%)
Musculoskeletal & Connective Tissue Disorders	1	1/48 (2.1%)	0	0/79 (0.0%)
Back Pain	1	1/48 (2.1%)	0	0/79 (0.0%)
Respiratory, Thoracic and Mediastinal Disorders	0	0/48 (0.0%)	1	1/79 (1.3%)
Pneumonia Aspiration	0	0/48 (0.0%)	1	1/79 (1.3%)
Vascular Disorders	0	0/48 (0.0%)	1	1/79 (1.3%)
Hypertension	0	0/48 (0.0%)	1	1/79 (1.3%)

12.1.11 Serious Adverse Events

A summary of all serious adverse events (SAE) categorized by MedDRA version 23.0 System Organ Class and Preferred Term (PT) is given in Table 12-19. An SAE was defined as any untoward medical occurrence that results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, requires medical/surgical intervention to prevent life-threatening illness or injury or to prevent permanent impairment of a body structure or function, or a congenital anomaly or birth defect.

Serious adverse events were generally infrequent, with no single event type having a significantly higher rate in either arm. Each arm had two events deemed to be 'Possibly', 'Probably', or 'Definitely' related to the treatment. These events included complications related to aspiration during anesthesia (one in each arm) and post-procedural UTI/sepsis requiring hospitalization for IV antibiotics (one in each arm).

Table 12-19. Summary of Serious Adverse Events

System Organ Class/ Preferred Term	Control		Optilume DCB	
	Events	Subjects (N=48)	Events	Subjects (N=79)
Cardiac Disorders	**1**	**1/48 (2.1%)**	**0**	**0/79 (0.0%)**
Bradycardia	*1*	*1/48 (2.1%)*	*0*	*0/79 (0.0%)*
Gastrointestinal Disorders	**0**	**0/48 (0.0%)**	**2**	**2/79 (2.5%)**
Intestinal Infarction	*0*	*0/48 (0.0%)*	*1*	*1/79 (1.3%)*
Abdominal Pain	*0*	*0/48 (0.0%)*	*1*	*1/79 (1.3%)*
General Disorders and Administration Site Conditions	**0**	**0/48 (0.0%)**	**1**	**1/79 (1.3%)**
Non-Cardiac Chest Pain	*0*	*0/48 (0.0%)*	*1*	*1/79 (1.3%)*
Infections and Infestations	**2**	**2/48 (4.2%)**	**2**	**2/79 (2.5%)**
COVID-19	*0*	*0/48 (0.0%)*	*1*	*1/79 (1.3%)*
COVID-19 Pneumonia	*1*	*1/48 (2.1%)*	*0*	*0/79 (0.0%)*
Sepsis	*1*	*1/48 (2.1%)*	*0*	*0/79 (0.0%)*
Urinary Tract Infection	*0*	*0/48 (0.0%)*	*1*	*1/79 (1.3%)*

System Organ Class/ Preferred Term	Control		Optilume DCB	
	Events	Subjects (N=48)	Events	Subjects (N=79)
Injury, Poisoning and Procedural Complications	**1**	**1/48 (2.1%)**	**0**	**0/79 (0.0%)**
Anesthetic Complication Pulmonary	*1*	*1/48 (2.1%)*	*0*	*0/79 (0.0%)*
Nervous System Disorders	**2**	**2/48 (4.2%)**	**0**	**0/79 (0.0%)**
Intracranial Aneurysm	*1*	*1/48 (2.1%)*	*0*	*0/79 (0.0%)*
Thalamus Hemorrhage	*1*	*1/48 (2.1%)*	*0*	*0/79 (0.0%)*
Renal and Urinary Disorders	**2**	**2/48 (4.2%)**	**1**	**1/79 (1.3%)**
Urinary Retention	*2*	*2/48 (4.2%)*	*0*	*0/79 (0.0%)*
Urethral Cancer	*0*	*0/48 (0.0%)*	*1*	*1/79 (1.3%)*
Respiratory, Thoracic, Mediastinal Disorders	**0**	**0/48 (0.0%)**	**3**	**3/79 (3.8%)**
Pulmonary Embolism	*0*	*0/48 (0.0%)*	*1*	*1/79 (1.3%)*
Lung Adenocarcinoma	*0*	*0/48 (0.0%)*	*1*	*1/79 (1.3%)*
Pneumonia Aspiration	*0*	*0/48 (0.0%)*	*1*	*1/79 (1.3%)*
Surgical and Medical Procedures	**0**	**0/48 (0.0%)**	**1**	**1/79 (1.3%)**
Colectomy	*0*	*0/48 (0.0%)*	*1*	*1/79 (1.3%)*
Total	**8**	**8/48 (16.7%)**	**10**	**9/79 (11.4%)**

12.1.12 Crossover Cohort

Baseline characteristics for the Crossover cohort were generally similar to the randomized cohort with the notable exception being that subjects had an average number of prior treatments of 5.9 compared to 3.2 in the randomized Optilume arm. Excluding the single subject with 60 prior dilations the average falls to 4 prior dilations in the Crossover cohort, which as expected is 1 more than the average in the randomized cohort (i.e. addition of index Control procedure).

Procedure characteristics for the Crossover cohort are similar to the Randomized cohort, with most subjects (87%, 28/32) receiving pre-dilation with an uncoated balloon. Similar to the randomized cohort most subjects (91%, 29/32) received a 30F diameter DCB.

12.1.12.1 Primary Efficacy Endpoint – Stricture Free Rate at 6 Months

The ability to pass a 16F flexible cystoscope or 14F rubber catheter was evaluated at 6 months post crossover to treatment with the Optilume DCB. The proportion of subjects with anatomical success in the Crossover cohort was comparable to that in the Randomized cohort (59.3% [16/27] vs 74.6% [50/67]).

12.1.12.2 Secondary Efficacy Endpoint – Time to Treatment Failure

The time to treatment failure (ULT failure, repeat treatment) was compared for crossover subjects after their randomized therapy (Control) to the time to treatment failure after receiving the Optilume DCB. Overall, stricture recurrence occurred more quickly after Control therapy as compared to after Optilume DCB therapy within individual subjects receiving both.

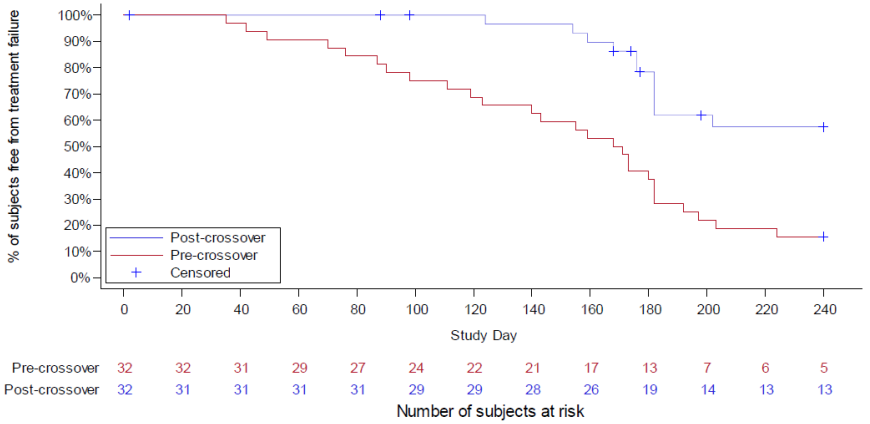

Figure 12-4. Time to Treatment Failure for Crossover Subjects Receiving Initial (Control) Therapy and Optilume DCB

The change in Qmax at 6 months and responder rate at 12 months were not measured for the crossover cohort.

12.1.12.3 Ancillary Efficacy Endpoints

Ancillary results for the crossover cohort were consistent with the pivotal study cohort.

12.2 Summary of Supplemental Clinical Information

12.2.1 ROBUST Clinical Program

A high level summary of study design, attributes of the strictures treated, and outcomes for each of the trials in the ROBUST clinical program can be found in Table 12-20.

Table 12-20. Study Design and Stricture Attribute for ROBUST Clinical Program

	ROBUST-I	ROBUST-II	ROBUST III
Study design	Single Arm	Single Arm	Randomized
Number of sites	Four (4) in Latin America	Five (5) in the U.S.	22 in the U.S. and Canada
Number enrolled	53	16	79 (Optilume Arm)
Stricture Attributes	Length: 0.9cm ± 0.5cm (53) *Proportion ≥2cm:* 1/53 (1.9%) Prior Dilations: 1.7 ± 0.8 (53) *Proportion with ≥2:* 43% Anatomical location *Bulbar:* 53/53 (100%) *Penile:* 0/53 (0%) Etiology	Length: 2.1cm ± 0.7cm (16) *Proportion ≥2cm:* 13/16 (81.3%) Prior Dilations: 4.1 ± 4.9 (16) *Proportion with ≥2:* 100% Anatomical location *Bulbar:* 16/16 (100%) *Penile:* 0/16 (0%)	Length: 1.6cm ± 0.8cm (79) *Proportion ≥2cm:* 36/79 (45.6%) Prior Dilations: 3.2 ± 1.6 (79) *Proportion with ≥2:* 100% Anatomical location *Bulbar:* 71/79 (89.9%) *Penile:* 8/79 (10.1%)

	ROBUST-I	ROBUST-II	ROBUST III
	Idiopathic: 2/53 (3.8%) *Iatrogenic: 24/53 (45.3%)* *Traumatic: 27/53 (50.9%)* *Inflammatory: 0/53 (0.0%)* Retention at Baseline: 27/53 (50.9%) Pre-dilation: 53/53 (100%) Prior Radiation: 0/53 (0.0%)	Etiology *Idiopathic: 11/16 (68.8%)* *Iatrogenic: 2/16 (12.5%)* *Traumatic: 3/16 (18.8%)* *Inflammatory: 0/16 (0.0%)* Retention at Baseline: 1/16 (6.3%) Pre-dilation: 7/16 (43.8%) Prior Radiation: 0/16 (0.0%)	Etiology *Idiopathic: 42/78 (53.8%)* *Iatrogenic: 21/78 (26.9%)* *Traumatic: 14/78 (17.9%)* *Inflammatory: 1/78 (1.3%)* Retention at Baseline: 26/79 (32.9%) Pre-dilation: 79/79 (100%) Prior Radiation: 9/79 (11.4%)
Stricture-free rate [a]	6 months: 75% (36/48) 1 year: 77% (36/47)	6 months: 73% (11/15)	6 /months: 75% (50/67)
Average IPSS (As Observed)	Baseline: 25.2 ± 4.5 (n=53) 3 months: 6.1 ± 7.6 (n=51) 6 months: 4.6 ± 5.2 (n=45) 1 year: 4.5 ± 3.9 (n=40) 2 years: 6.9 ± 7.7 (n=38) 3 years: 5.5 ± 6.9 (n=33)	Baseline: 18.4 ± 4.9 (n=16) 3 months: 7.5 ± 6.4 (n=16) 6 months: 7.0 ± 6.7 (n=14) 1 year: 6.0 ± 6.1 (n=9)	Baseline: 22.0 ± 6.8 (n=79) 3 months: 7.2 ± 5.5 (n=73) 6 months: 7.8 ± 5.6 (n=69)
Most Common AEs Reported	UTI – 10.8% Stricture Recurrence – 9.8% Urinary Retention (acute or chronic) – 8.2% Dysuria – 7.2% Hematuria (perioperative) – 6.2% Hematuria (post-30 days) – 5.7%		

12.2.2 ROBUST I Study

ROBUST I is a prospective, multicenter, single arm study evaluating the safety and efficacy of the Optilume DCB in recurrent anterior urethral strictures. A total of 53 subjects were enrolled at 4 investigational centers in Panama and the Dominican Republic. Key eligibility criteria included anterior urethral strictures ≤2 cm in length with 1-3 prior dilations. Subjects with prior urethroplasty, Lichen Sclerosis, penile implants or artificial urinary sphincters, and prior pelvic radiation were excluded. Follow up is planned through 5 years post-treatment.

Study strictures were an average of 0.9cm in length, with an average of 1.7 prior dilations. Subject follow-up is complete through 3 years. Subjects experienced immediate and sustained functional and symptomatic improvement as measured by the IPSS questionnaire, Patient Reported Outcome Measure (PROM) questionnaire, and Qmax. Freedom from stricture recurrence was measured by the ability to pass a 16F flexible cystoscope and was 75% (36/48) at 6 months and 77% (36/47) at 12 months. Freedom from repeat intervention was 77% (33/43) at 3 years.

Table 12-21: ROBUST I Efficacy Results

Measure	Baseline	3 Months	6 Months	1 Year	2 Years	3 Years
IPSS	25.2 ± 4.5 (53)	6.1 ± 7.6 (51)	4.6 ± 5.2 (45)	4.5 ± 3.9 (40)	6.9 ± 7.7 (38)	5.5 ± 6.9 (33)
IPSS QoL	4.9 ± 0.9 (53)	0.8 ± 1.3 (51)	0.7 ± 0.9 (45)	0.7 ± 0.9 (40)	0.9 ± 1.5 (38)	0.7 ± 1.2 (33)
Qmax (mL/sec)	5.0 ± 2.6 (46)	22.2 ± 12.5 (51)	19.8 ± 10.8 (45)	20.1 ± 10.0 (39)	17.5 ± 10.4 (38)	15.1 ± 8.3 (33)
Measure	**Baseline**	**3 Months**	**6 Months**	**1 Year**	**2 Years**	**3 Years**
PVR (mL)	141.4 ± 105.1 (43)	36.5 ± 37.7 (51)	30.0 ± 42.8 (45)	24.6 ± 32.1 (39)	45.5 ± 49.5 (38)	50.2 ± 62.5 (33)

The primary safety endpoint was a composite of device and procedure-related serious complications at 3 months including urethral formation of fistula, de novo severe urinary retention last >14 days, unresolved de novo stress urinary incontinence, and urethra rupture or burst. None of the subjects experienced such an event (0/53, 0.0%). Treatment related complications were mild and consisted of common events experienced after urological procedures such as post-procedural hematuria, urinary tract infection, and dysuria.

12.2.3 ROBUST II Study

ROBUST II is a prospective, multicenter, single arm study evaluating the safety and early feasibility of the Optilume DCB. Subject follow-up is complete through 2 years. A total of 16 subjects were enrolled at 5 investigational centres. Key eligibility criteria were similar to ROBUST I with the exception of allowing stricture length up to 3cm and requiring a minimum of 2 prior endoscopic treatments of the stricture.

Study strictures were an average of 2.1cm in length and had an average of 4.1 prior dilations. Freedom from stricture recurrence at 6 months was 73% (11/15).

Table 12-22: ROBUST-II Efficacy Results

Measure	Baseline	3 Months	6 Months	1 Year	2 Years
IPSS	18.4 ± 4.9 (16)	7.5 ± 6.4 (16)	7.0 ± 6.7 (14)	6.0 ± 6.1 (9)	4.2 ± 4.1 (9)
IPSS QoL	4.4 ± 1.3 (16)	1.8 ± 1.8 (16)	1.6 ± 1.5 (14)	1.4 ± 1.5 (9)	1.2 ± 1.2 (9)
Qmax (mL/sec)	6.9 ± 3.7 (16)	18.9 ± 16.4 (15)	17.5 ± 9.4 (13)	20.8 ± 9.1 (9)	25.4 ± 26.1 (8)
PVR (mL)	187.1 ± 227.1 (16)	79.3 ± 80.3 (15)	64.1 ± 40.2 (13)	66.4 ± 57.5 (9)	65.5 ± 79.3 (8)

No subject met the primary safety composite endpoint of urethral formation of fistula, new strictures requiring intervention, unresolved de novo stress urinary incontinence, and urethra rupture or burst at 3 months.

13 WARRANTY

Urotronic warrants that reasonable care has been used in the design and manufacture of this product. This warranty is in lieu of and excludes all other warranties not expressly set forth herein, whether express or implied by operation of law or otherwise, including, but not limited to, any implied warranties for a particular purpose. Handling, storage, cleaning and sterilization of this device as well as other factors relating to the patient, diagnosis, treatment, surgical procedures and other matters beyond Urotronic's control directly affect the device and the results obtained from its use. Urotronic's obligation under this warranty is limited to the repair or replacement of this device and Urotronic shall not be liable for any incidental or consequential loss, damage or expense directly or indirectly arising from the use of this device. Urotronic assumes no liability with respect to devices reused, reprocessed or re-sterilized and makes no warranties, express or implied, including but not limited for a particular purpose, with respect to such devices.

14 SYMBOLS USED IN THE DEVICE LABELS

	Quantity of 1 per box
	Caution: Federal law restricts this device to sale by or on the order of a physician.
	Indicates the date when the medical device was manufactured.
	Do not resterilize
	Do not re-use
	Do not use if package is damaged
	Fragile
	Use-by date
	Keep away from sunlight
	Keep Dry
	Manufacturer
	Does not contain latex
	Temperature limit 15°C - 30°C
	Caution: Consult instructions for use
	Sterilized using ethylene oxide
	Single sterile barrier system
	Single sterile barrier system with protective packaging outside
	Medical Device
	Unique Device Identifier
	Contains a medicinal substance

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