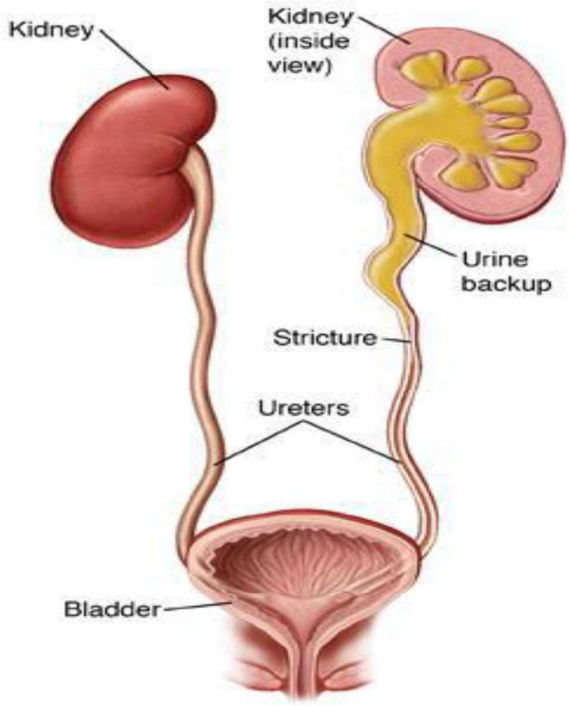

Figure 1 View of the human ureter, identifying a ureteric stricture[Error! Bookmark not defined.]

According to a study published in 2012, 1 in 11 Americans suffer from kidney stones.[3] Common causes of ureteral strictures are procedures used to treat kidney stone disease such as ureteroscopy and lithotripsy. Ureteral strictures occurred in 1.5% to 3% of patients undergoing these procedures.[4–6] Another major cause of ureteral strictures is a result of renal transplants and renal transplantation surgeries. Approximately 3.4% to 5.5% of patients who received a kidney transplant had a ureteral stricture post renal transplantation.[7–9]

2. INVESTIGATIONAL DEVICE DESCRIPTION

The investigational device used in this investigation is the Optilume® Ureteric Drug Coated Balloon (Optilume DCB, Urotronic Inc.).

The Optilume DCB is a flexible cystoscope-compatible balloon catheter with a dual lumen shaft, radiopaque marker bands, and a drug coating on the balloon portion. The dual lumen shaft allows the

catheter to have both a through lumen for guidewires, fluid flushing, etc. as well as an inflation lumen for inflating the balloon catheter to the desired pressure and diameter.

The catheter shaft is a dual lumen PEBAX 7233 extrusion that is thermally bonded to a semi-compliant Grilamid L25 MED Nylon 12 Natural balloon. The catheter distal tip (balloon end) is a tapered atraumatic tip made from 6333 PEBAX. The catheter shaft is 0.038" (0.97mm) guidewire compatible and the balloon-shaft assembly is sized such that it can be placed through the working channel of a flexible cystoscope.

The proximal end of the device consists of a polycarbonate Y-luer that has a guidewire irrigation lumen and a luer style inflation lumen. Next to the Y-luer, a PEBAX 4533 strain relief is used to reduce stress on the luer-shaft transition during the procedure.

A polytetrafluoroethylene balloon protector sheath is placed over the balloon to protect it prior to placing the balloon catheter into a high-density polyethylene hoop. The single-use disposable device is then packaged in a Tyvek pouch and sterilized using ethylene oxide (EtO). After sterilization, the Tyvek pouch is sealed in a foil pouch with a desiccant pack and then placed in a labeled shelf box carton.

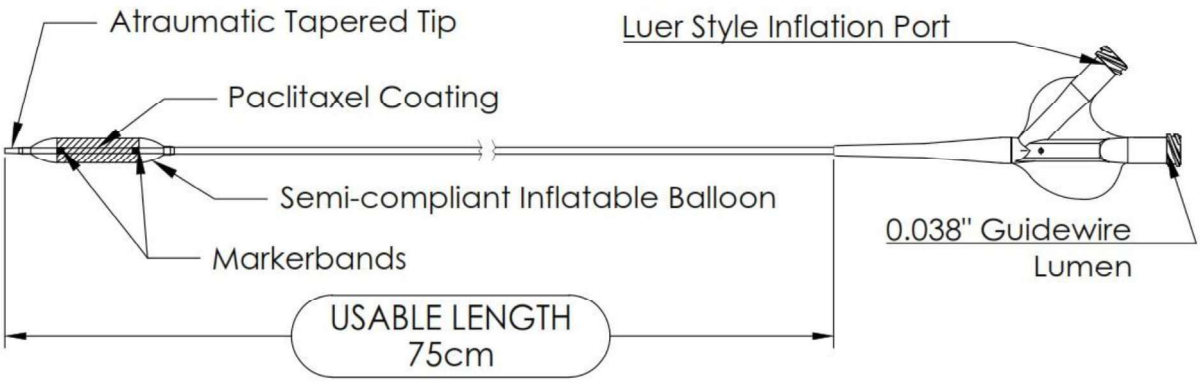

Figure 2-1. Optilume DCB

The Optilume DCB comes in a range of balloon sizes. Refer to the Instructions for Use (IFU) for a complete listing.

2.1. Drug Coating

The Optilume DCB coating consists of the active pharmaceutical ingredient (API) 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/mm^2. The drug coating is released from the balloon and transferred to the urothelium during balloon inflation.

2.2. Mechanism of Action

The primary mode of action is mechanical dilation of the ureteric stricture. The dilation is a result of uniform outward radial pressure of the balloon on the ureter wall. At the time of dilation, paclitaxel is transferred from the balloon to the ureter wall. The drug limits excessive cellular proliferation and fibrotic scar tissue generation at the location of the stricture to maintain ureter lumen patency.

2.3. Investigational Device Intended Purpose and Indication

The investigational device is intended for treatment of strictures within the urinary tract. The investigational indication for the device is the following: The Optilume Ureteric Drug Coated Balloon is indicated for the treatment of adult patients with benign ureteric strictures up to 4cm in length.

2.4. Training Requirements

Investigators using the DCB during this clinical investigation must have training and experience in endoscopic procedures within the ureters. Training specific to the study will be provided by the sponsor and must be completed prior to use within this clinical investigation.

3. CLINICAL INVESTIGATION DESIGN RATIONALE

3.1. Drug-Coated Balloons in the Ureter

The concept of using a drug-coated balloon (DCB) for treating ureteric strictures has been studied in humans previously. Kallidonis et al[10] evaluated the clinical efficacy and safety of DCB dilation for the management of non-malignant ureteral strictures in a single-center pilot study using the Lutonix® DCB in Greece. Twenty-five patients with benign ureteral strictures related to uretero-enteric anastomosis (n = 13); lithiasis (n = 5), post-surgical complications (iatrogenic n = 5), transplanted kidney (n = 1) and post-radiotherapy (n = 1) were included. Following passage of the guidewire, predilatation was performed using 5 to 8 mm high-pressure balloon catheter. A 5 or 6F DCB was then dilated across the lesion for up to 4 minutes, and the dilation was repeated up to a total of 3 times at 6 or 7 atmospheres based on the manufacturer's recommendation. Mean lesion length was 40 ± 28.5 mm. Mean follow up was 36 ± 10.46 months. Strictures were located in the upper ureter (12%), lower ureter (32%), ureterovesical anastomosis (4%), and uretero-enteric anastomosis (52%) levels. Radiological success was defined as

no sign of ipsilateral hydronephrosis or improvement of existing residual dilatation based on CT or Tc-99 m DTPA renogram. The overall radiological success at 1-year follow-up was 88% (22/25 patients). A total of 32% (8/25 patients) required additional dilation to maintain ureteral patency, and the overall failure rate at 1-year follow up was 12% (3/25 patients). The only complication reported was one case of febrile urinary tract infection (acute pyelonephritis) in a female patient.

3.2. Optilume Urethral DCB Evidence

The Optilume Urethral DCB has the same design as the investigational device for ENDURE 1. It is also a paclitaxel-coated balloon and is currently FDA approved for the treatment of anterior urethral strictures in men. There is extensive evidence supporting the effectiveness of the Optilume Urethral DCB in treating strictures within the urinary tract. The following sections summarize the data available from the ROBUST I, II, and III studies for the Optilume Urethral DCB.

3.2.1. ROBUST I

ROBUST I was 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. Subjects were followed through 5 years post treatment.

The primary efficacy endpoint was improvement in IPSS at 90 days follow-up.

- A subject's DCB treatment was considered to be successful if their IPSS was less than or equal to 11 at the 90-day follow-up.
- Treatment failure was defined by
  - IPSS score of greater than 11 at the 90-day follow-up, or
  - if a subject had a second DCB treatment (retreatment), or
  - if a subject exited the study early due to treatment failure (IPSS >11 without cystoscopically confirmed anatomical success at the time of exit or receiving additional stricture treatment with an alternative therapy).

Primary Efficacy Performance Goal: Recurrence < 0.5 as defined by an IPSS score of less than or equal to 11. The performance goal was met if the upper limit of the one-sided 95% confidence interval for recurrence is less than 50%.

Table 1 shows that the pre-defined primary efficacy endpoint was met at 90 days follow-up.

Table 1 Subjects with IPSS Greater than 11 (Failures) at 90 Days

Variables	Days post-procedure	n/N, (proportion), [upper limit of one-sided 95%CI]	P-value
• IPSS Score > 11; or • If retreated by DCB; or • If exited study due to treatment failure	90 days[2]	8/51, (0.157), [0.265]	<0.001

[1] Primary Efficacy Performance Goal: Recurrence < 0.5. Performance goal is met if the upper limit of the one-sided 95% confidence interval for recurrence is less than 50%.

[2] 90-day follow-up, a total of fifty one (51) subjects were evaluable at the 3 month follow-up:

- Fifty one (51) subjects had an IPSS score available at the 90-day follow-up, of which eight (8) had an IPSS score >11.
- Two (2) subjects missed the 3-month visit and were excluded from the analysis. These subjects were eventually considered lost to follow-up.

Furthermore, the same efficacy performance goal was also met at 6-Month, 1-Year, 2-Year, 3-Year, and 4-year post-procedure follow-ups, Table 2.

Table 2 Subjects with IPSS Greater than 11 (Failures) During Long-Term Follow-Up

Variables	Time	n/N, (proportion), [upper limit of one-sided 95%CI]
• IPSS Score > 11 at FU; or • if retreated by DCB; or • if exited study due to treatment failure	6 Months	9/50, (0.18), [0.293]
	1-Year	10/48, (0.21), [0.328]
	2-Year	16/47, (0.34), [0.470]
	3-Year	15/43 (0.35), [0.485]
	4-Year	12/41 (0.29), [0.431]
	5-Year[a]	20/43 (0.47) [0.614]

[a] Two subjects who missed the 4-year visit were evaluable for the 5-year timepoint.

All subjects are planned to receive treatment with the Optilume DCB. There are no comparator devices for this clinical investigation.

6.3. Subjects

This clinical investigation is intended to include adults suffering from ureteric strictures. The following sections describe the specific inclusion and exclusion criteria for participation.

6.3.1.Inclusion Criteria

All the following criteria must be met to be included in the clinical investigation:

1. Age 18 years or older
2. Single lesion ureteric or uretero-enteric stricture less than or equal to 4.0 cm in length[a]
3. Two functioning kidneys

6.3.2.Exclusion Criteria

None of the following criteria can be met to be included in the clinical investigation:

1. Treatment of the target ureter with incision or balloon dilation within 3 months of the study treatment
2. Subjects with more than one ureteric stricture
3. Subjects with target stricture in bifid or duplicated ureter
4. Known sensitivity to paclitaxel or on medication that may have negative interaction with paclitaxel
5. Ureteric stricture caused by extrinsic compression of the ureter
6. Unable to endoscopically access target stricture for any reason
7. Existing stones in the ipsilateral kidney or ureter (except for asymptomatic kidney stones) that are in close proximity to the target ureteric stricture
8. Chronic renal failure treated with dialysis
9. eGFR <30 mL/min/1.73m^2
10. Kidney function ≤ 25% of split function on the side with target stricture as measured by functional renogram

[a] This includes any strictures along the ureter, UPJ obstruction, UVJ obstruction, uretero-enteric, or reimplant strictures.

11. Kidney function ≤35% of split function on the side opposite target stricture as measured by functional renogram or other significant pathology or impairment that may impact renal function
12. Life expectancy less than 12 months
13. Women who are pregnant or breastfeeding
14. Women of child-bearing potential planning to get pregnant in the next year or are unwilling to use contraception over the next 12 months
15. Males unwilling to abstain or use protected sex for 30 days post treatment
16. Males unwilling to use highly effective contraception for6 months post treatment if sexual partner(s) are of child-bearing potential
17. Inability to provide legally effective informed consent
18. Unwilling or unable to meet protocol follow-up requirements
19. Participation in any interventional clinical investigation of a medical device, drug, or biologic (excluding registries) that may confound the results of the trial
20. Active systemic or urinary tract infection
21. Active malignancy in the abdomen or pelvis, or any malignancy considered considerable risk for metastasizing to the abdomen or pelvis over the next 12 months
22. Uncontrolled diabetes defined as hemoglobin A1C ≥ 8% at baseline
23. Unable to come off antiplatelet or anticoagulation medication prior to treatment to prevent bleeding complications at the discretion of the investigator
24. Any other condition that may confound the results of the trial or presents an unacceptable risk for any study-related procedure
25. Individuals who are unable to fully understand all aspects of the investigation that are relevant to the decision to participate, or who could be manipulated or unduly influenced as a result of a compromised position, expectation of benefits or fear of retaliatory response
26. Presence of any condition that precludes administration of furosemide during renograms
27. Unable to tolerate contrast related to required study procedures or imaging.

6.3.3.Total expected duration of the clinical investigation.

The total duration of the clinical investigation is expected to be about six years.

6.3.4.Expected duration of each subject's participation.

Each subject is expected to participate in the study for approximately five years and three months.

6.3.5.Number of subjects required to be included in the clinical investigation.

Up to 60 subjects will be enrolled in the clinical investigation.

6.3.6.Estimated time needed to select this number (i.e. enrolment period).

The enrollment period is expected to last about nine months.

7. CLINICAL INVESTIGATION PROCEDURES

The following sections describe the procedures for the ENDURE 1 clinical investigation. The table below summarizes study procedures and follow up.