UROTRONIC

ROBUST I Pilot Study

Re-Establishing Flow Via Drug Coated Balloon For The Treatment Of Urethral Stricture Disease

Statistical Analysis Plan (SAP)

August 11, 2017

NCT03014726

[redacted]

Approvals

The undersigned have reviewed this document and agree with its contents.

Document Revision History

Revision	Date	Author	Description of Changes
A	[redacted]		Initial Release

Table of Content

1. INTRODUCTION

This document outlines the detailed statistical methods for the data collected within the scope of Protocol # DSC016 Rev F, ROBUST I Pilot Study, "Re-Establishing Flow via Drug Coated Balloon for The Treatment of Urethral Structure Disease." The purpose of this plan is to provide a framework within which answers if the study objectives can be achieved via statistically appropriate analytical methods. Specifically, the SAP has the following purpose: To prospectively (a priori) outline the types of analyses and presentations of data that will form the basis for conclusions to be reached that will answer the study objectives outlined in the protocol, and to explain in detail how the data will be handled and analyzed, adhering to commonly accepted standards and practices of biostatistical analyses in the medical industry. Results obtained from the analyses outlined in this document will be the basis of the Clinical Study Report for this study.

2. STUDY OBJECTIVE(S)

The study is designed to determine the safety and effectiveness for drug-coated balloon (DCB) in the treatment of urethral stricture disease in adult males.

3. STUDY DESIGN

This is a prospective, non-randomized, open label, single arm, multi-center pilot study, focusing on male subjects with single urethral stricture. The stricture may occur at the anterior urethra or bladder neck contracture.

Subjects will be followed up post-treatment at 5 days, 14 days, 30 days, 90 days, 180 days and 365 days, and then annually for up to 5 years. The annual follow-up after the first year is optional.

Table 3-1: Study Visit Schedule

	Baseline	**Intra-Procedure**	**Pre-Discharge**	**5 d**	**14 d**	**30 d**	**3 Mth**	**6 & 12 Mth**	**Annually for up to 5 yrs**	**Unscheduled Visit**
Compliance Window	-30 days	NA	NA	± 1 day	± 2 days	± 5 days	± 14 days	± 30 days	± 60 days	NA
Physical Examination	√				√	√	√	√	√	√
Medication Usage Review	√	√	√	√	√	√	√	√		√
Antibiotic	√ (pre-procedure)		√							
Blood analysis (Complete blood cell count (CBC), Blood urea nitrogen (BUN), Serum creatinine)	√		√	√						

	Baseline	Intra-Procedure	Pre-Discharge	5 d	14 d	30 d	3 Mth	6 & 12 Mth	Annually for up to 5 yrs	Unscheduled Visit
Compliance Window	-30 days	NA	NA	± 1 day	± 2 days	± 5 days	± 14 days	± 30 days	± 60 days	NA
Alanine aminotransferase (ALT)	√			√						
Urine Analysis (sugar, protein, WBC/RBC, Bacteria (UTI))	√ Within 7 days of procedure				√	√	√			√
Urine collection (drug analysis)	√		√ (2^{nd} Void)	√	√	√				
Blood collection (drug analysis)	√ [1]		√ [1] (multiple samples in 24 hrs)	√ [1]						
Review Protected Sexual Activities			√	√	√	√	√ [3]	√ [3] (6 mths only)		
Semen Evaluation	√ (sperm quality)				√ (sperm and drug)	√ (sperm and drug)		√ (6 months for sperm only)		
USS	√									
Mundy PROM	√				√	√	√	√	√	√
IPSS, IIEF	√				√	√	√	√	√	√
VAS Pain score	√		√	√	√	√				
Qmax	√				√	√	√	√	√	√
PVR	√				√	√	√	√	√	√
Urethrogram	√ Record	√ [4] Record					√ Record	√ Record		
Cystoscopy	√ Record							√ Record (16F cystoscope)		√ Record

	Baseline	Intra-Procedure	Pre-Discharge	5 d	14 d	30 d	3 Mth	6 & 12 Mth	Annually for up to 5 yrs	Unscheduled Visit
Compliance Window	-30 days	NA	NA	± 1 day	± 2 days	± 5 days	± 14 days	± 30 days	± 60 days	NA
14F Rubber catheter urethral Lumen evaluation								√ (If 16F scope failed to pass)		
Subject Satisfaction Questionnaire							√	√		
AE Review	√		√	√ [2]	√	√	√	√	√	√

Note

1 – For the PK test, a total of 8 blood samples will be collected /patient. It requires patients to stay in the hospital overnight for blood draws at 0 , 1, 3, 5, 10, 24 hrs post-procedurely. The blood draws at baseline and 5 days follow-up will be done accordingly, but no hospital stay is required.

2 – Pain /discomfort after the procedure is common and to be expected. Steps can be taken to minimize or eliminate pain /discomfort. It is at physician's discretion, whether the pain /discomfort is an adverse event, or a normal healing process.

3 – Review may be eliminated depending on the results of drug analysis from first 5 subjects. If so, a notice will be given to the study sites by Sponsor.

4 – Recorded Fluroscopy/urethrogram required before any intervention, during predil, post dil, during DCB, after DCB (fluoroscopy only)

3.1. TREATMENT(S)

All subjects will be treated with drug-coated balloon (DCB) according to the following flow chart. See Protocol for further details.

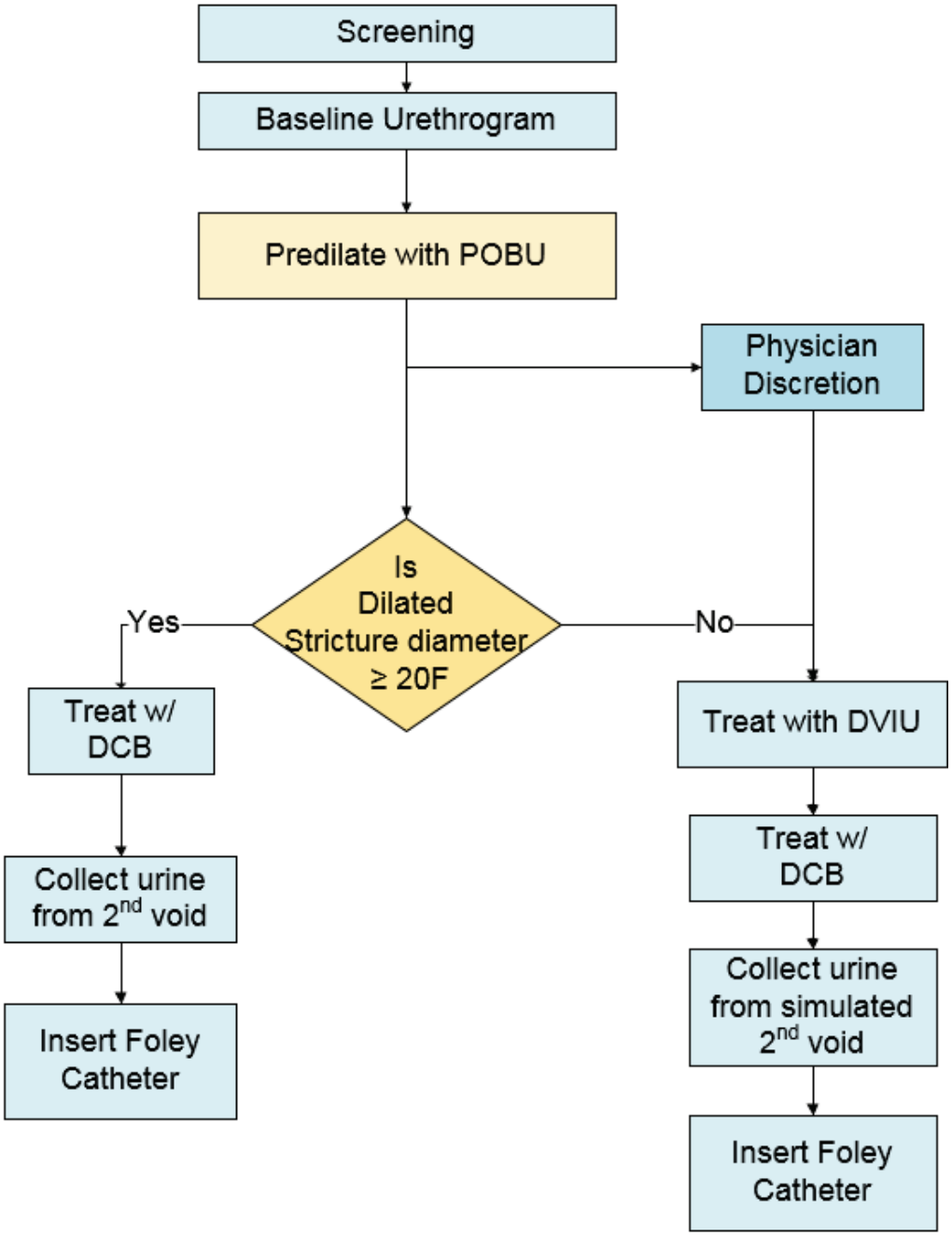

Figure 3-1: Treatment Flow Chart

3.2. SUBJECT ENROLLMENT

Up to 50 subjects will be enrolled and treated with the device at up to 5 clinical sites. Only subjects who meet the inclusion/exclusion criteria will be eligible to be enrolled and participate in the study.

A subject is considered enrolled if he:

- Meets all the inclusion criteria
- Does not meet ANY exclusion criteria
- Provided informed consent
- Had the investigational device introduced

3.2.1. INCLUSION CRITERIA

1. Male subjects ≥ 18 years' old
2. Visual confirmation of stricture via cystoscopy or urethrogram
3. Single lesion anterior urethral stricture or bladder neck contracture, less than or equal to 2.0 cm
4. One to three (1-3) prior diagnosis and treatment of the same stricture (including self-catheterization) including DVIU (Direct Vision Internal Urethrotomy), but no prior urethroplasty
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 13 or higher
7. Lumen diameter <12F by urethrogram
8. Able to complete validated questionnaire independently
9. Qmax <10 ml/sec or completely unable to void due to severity of stricture and has a suprapubic cystostomy tube in place

3.2.2. EXCLUSION CRITERIA

1. Strictures greater than 2.0 cm long.
2. Subjects that have more than 1 stricture.
3. Sensitivity to paclitaxel or on medication that may have negative interaction with paclitaxel
4. Subjects who have a suprapubic catheter
5. Previous urethroplasty within the anterior urethra
6. Stricture due to bacterial urethritis or untreated gonorrhea
7. Stricture dilated or incised within the last 3 months
8. Presence of local adverse factors, including abnormal prostate making catheterization difficult, urethral false passage or fistula.
9. Presence of signs of obstructive voiding symptoms not directly attributable to the stricture such as BPH at the discretion of the clinical investigator
10. Previous radical prostatectomy
11. Previous pelvic radiation
12. Diagnosed kidney, bladder, urethral or ureteral stones or active stone passage in the past 6 months.
13. Diagnosed with chronic renal failure unless under hemodialysis or has a serum creatinine level greater than 2 mg/dL
14. Use of alpha blockers, beta blockers, OAB (Overactive Bladder) medication, anticonvulsants (drugs that prevent or reduce the severity and frequency of seizures), and antispasmodics where the dose is not stable. (Stable dose is defined as having the same medication and dose in the last six months.)
15. Use of Botox (onabotulinumtoxinA) in urinary system within the last 12 months

16. Presence of a penile implant, artificial urinary sphincter, or stent(s) in the urethra or prostate
17. Known neurogenic bladder, sphincter abnormalities, or poor detrusor muscle function
18. Diagnosed with Lichen Sclerosus, or previous hypospadias repair
19. History within the last 5 years of carcinoma of the bladder or prostate
20. History of cancer in non-genitourinary system, which is not considered, cured (except basal cell or squamous cell carcinoma of the skin). A potential participant is considered cured if there has been no evidence of cancer within five years of randomization
21. 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
22. Unwilling to use protected sex for ≥30 days post treatment
23. Inability to provide legally effective Informed Consent Form (ICF) and/or comply with all of the required follow-up requirements
24. Participation in other pre-market studies
25. Stricture due to balanitis xerotica obliterans (BXO)

3.3. PRIMARY ENDPOINTS AND DEFINITIONS

3.3.1 Primary Efficacy Endpoint: Improvement in IPSS (International Prostate Symptoms Score)

For this study, improvement of IPSS is chosen as the primary efficacy endpoint. Subjects entering this study is very obstructive with poor quality of life. IPSS is a questionnaire that addresses the global quality of life related to their lower urinary tract symptoms (LUTS). The presence of stricture greatly affects the subject's quality of health and LUTS. Therefore, it is a relevant efficacy endpoint.

A subject's DCB treatment is considered to be successful if their IPSS 11 or lower.

Rationale for this endpoint
Stricture affects flow which in turns cause LUTS and reduce the patients quality of life. Patients with an IPSS score between 8-19 are considered to have moderate LUTS. Heyns and Marais (2002)[1]showed IPSS provides a quantitative estimate of subjective symptoms, including Qmax. Additional studies have shown a clear inverse correlation of severity of urethral stricture and Qmax. Therefore for the subjects in this study with severe strictures and multiple failed treatments, IPSS of 11 or lower can be considered successful with significant improvement in the quality of life.

3.3.2 Primary Safety Endpoint: Rate of Treatment Related Serious Complication

This safety endpoint is defined as a composite device related serious complications at 90 days. Device related is defined to include both device and procedure related.

- Device related formation of fistula
- Device related de novo severe urinary retention lasting > 14 consecutive days' post-treatment.
- Device related unresolved de novo stress urinary incontinence (requiring >1 pad/day) at 90 days or earlier
- Urethra rupture or burst

[1] Heyns CF and Marais Dc (2002) "Prospective Evaluation Of The American Urological Association Symptom Index And Peak Urinary Flow Rate For The Followup Of Men With Known Urethral Stricture Disease" J of Urology, pp 2051-2055

3.4. SECONDARY ENDPOINTS

3.4.1 S1: Stricture Recurrence Rate

The definition of stricture recurrence is the urethra lumen being < 14 F with or without recurrence of symptoms at 6 months. The urethra caliber will be measured as follows:

- Passage of a flexible cystoscope to determine ≥ 16 Fr urethral caliber
- If the 16F flexible scope would not pass, then a 14 Fr flexible rubber catheter will be inserted through the treated section

Note: Obstruction symptoms due to BPH (Benign Prostatic Hyperplasia) will not be considered a stricture recurrence.

3.4.2 S2: Improvement LUTS (Lower urinary tract symptoms) Voiding Construct (Mundy PROM) Score (Patient-reported outcome measure)

3.4.4 S3: Change in IIEF (International Index of Erectile Function)

3.4.5 S4: Repeat Treatment Rate

This is defined as repeat surgery or treatment for urethral stricture in the same location of the urethra.

3.4.6 S5: Change in Qmax (Peak Flow Rate) at 3 and 6 months

Assessment of the maximum urinary flow rate during uroflowmetry. The test is only valid if the voided volume is greater than 125ml.

3.4.7 S6: Paclitaxel content in blood, urine and semen

Measurements will be measured by an independent laboratory following GLP regulations.

3.4.8 S7: Stress Urinary Incontinence at <90 days and >90 days

3.5. SAMPLE SIZE CONSIDERATION

The study is powered for the efficacy endpoint of IPSS. According to Heynes (1998), strictures tend to recur at about 50% at 3 months for subjects who had 3 retreatments or more. The study was intended to enroll subjects who had 1-3 prior intervention. However, all subjects enrolled in this study to date had 3 or more retreatments with a number of subject on long term catheterization (personal communication with PI by Dave Perry and documented by emails from PI).

This study is designed to support the claim that the stricture recurrence rate is < 50%. This will be supported if the upper limit of the one-sided 95% confidence interval is less than 50%. Therefore, with a success rate of 75% or greater, 80% statistical power, the required sample size is 23. This study sample size is powered for primary efficacy only.

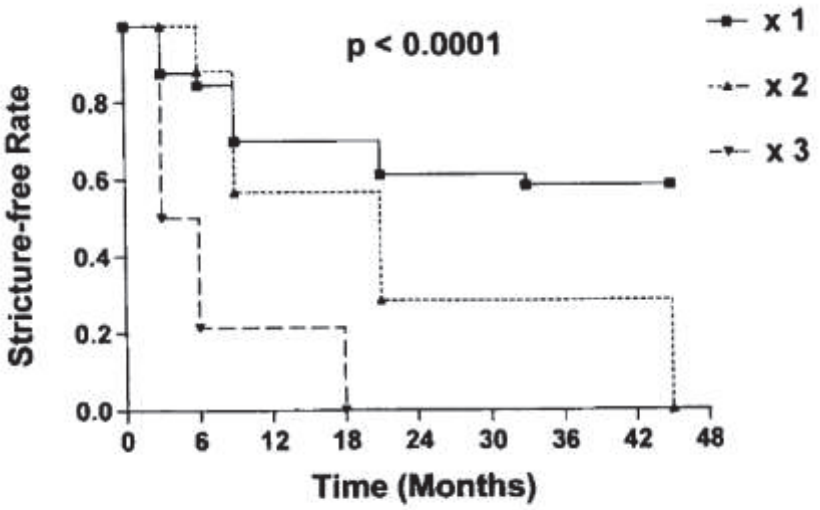

FIG. 2. Stricture-free rate after 1, 2 or 3 times (×1, ×2, ×3) repeated dilation or internal urethrotomy of entire study group, regardless of stricture treatment before randomization.

Figure 3-2: Recurrence Rate From Heynes and Steenkamp 1998[2]

The IPSS of 11 or smaller is used as a surrogate endpoint for successful stricture treatment.

4. ANALYSIS POPULATION

4.1 Analysis population #1 – As Treated

Analysis will be performed on all enrolled patients who received the device.

5. STATISTICAL METHODS OF ANALYSES

5.1. GENERAL CONSIDERATIONS

The data from the study will be tabulated using descriptive analysis. In general, categorical variables will be summarized with the number and percent of subjects with the characteristic. Quantitative variables will be summarized with the mean, median, standard deviation, minimum value and maximum value.

Descriptive analyses of all AEs and urinary symptoms will be provided in the report. In addition, the report will include tabulated results of study deviations and device malfunctions.

5.2. BASELINE CHARACTERISTICS

Baseline characteristics will be summarized using the mean, standard deviation, median and range for continuous characteristics and using counts and percentages for categorical characteristics.

5.3. ANALYSIS OF THE PRIMARY ENDPOINT(S)

The primary efficacy endpoint, IPSS at 3 months, will be estimated and tested using a performance goal of < 50%. The performance goal is considered met if the upper end of the one-sided 95% confidence interval is less than .50.

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[2] C. F. Heyns, J. **W.** Steenkamp, M. **L.** S. De Kock And P. Whitaker (1998) "Treatment Of Male Urethral Strictures: Is Repeated Dilation Or Internal Urethrotomy Useful" J Of Urology Vol 160 Pp 356-358

The null and alternative hypotheses for the primary efficacy endpoints are:

H_0: $p \geq 0.50$

Ha: $p < 0.50$

The primary safety endpoint, rate of device-related serious complications, will reported as descriptive statistics only. The number and percentage of subjects experiencing at least one device-related serious complication will be presented for this endpoint, along with the 95% confidence interval.

5.4. Analysis of the Secondary Endpoint(s)

All secondary endpoints will be summarized. The number and percentage of subjects with the characteristic will be presented for categorical variables. The mean, median, standard deviation, minimum value and maximum value will be presented for quantitative variables. In addition, 95% confidence intervals maybe presented were applicable.

5.5. Analysis of Safety Data

An adverse event (AE) is defined as any adverse change (i.e., de novo or preexisting condition) 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 any time after the treatment has been initiated. See the Protocol for further details on AE and Serious Adverse Event (SAE) classification and

Adverse experiences will be coded using a customized AE coding list based on CTCEA and augmented with study specific custom code. All AEs will be captured from the initiation of treatment through the final visit.
Adverse events will be summarized by presenting:

- The number and percentage of subjects experiencing any AE
- The number and percentage of subjects experiencing any AE by SOC and PT
- The number and percentage of subjects experiencing any SAE
- The number and percentage of subjects experiencing any AE associated with study discontinuation.
- The number and percentage of subjects experiencing any AE related to the study device
- The number and percentage of subjects experiencing any AE according to degree of severity

5.6. Handling of Missing Data

Missing data will be reported. No imputation or other substitution will be made for analysis purposes.

5.7. Visit Windows

Visit windows are assigned to visit time points as follows:

	Baseline	Intra-Procedure	Pre-Discharge	5 days	14 days	30 days	3 Months	6 and 12 Months	Annually for up to 5 years	Unscheduled Visit
Compliance Window	-30 days	NA	NA	± 1 day	± 2 days	± 5 days	± 14 days	± 30 days	± 60 days	NA

5.8. Unscheduled Assessments

Information acquired during unscheduled assessments will be included in the study listings.