NeoTract® UroLift® System

Executive Summary of the MedLift Study

Study Title: Median Lobe Prostatic UroLift Procedure

Protocol Number: **CP00001 Rev C**

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Sponsored by:

NeoTract®, Inc.
4473 Willow Rd., Suite 100
Pleasanton, CA 94588

Telephone:
925-401-0700

PROTOCOL SUMMARY

Study Title:	**Median Lobe Prostatic UroLift Procedure**
Study Objectives:	Evaluate the safety and effectiveness of the UroLift® System when used in symptomatic benign prostatic hyperplasia (BPH) subjects with an enlarged median lobe.
Study Design:	Prospective, multicenter, non-blinded, single arm (non-randomized) study.
Sample Size:	A total of no more than 48 subjects (minimum of 40) will be enrolled.
Subject Population:	Males age of 50 years or older diagnosed with symptomatic benign prostatic hyperplasia (BPH).
Number of Centers:	A maximum of 10 investigational sites located in the US
Clinical Indication:	The UroLift System is indicated for the procedure of symptoms due to urinary outflow obstruction secondary to benign prostatic hyperplasia (BPH) in men over the age of 50.
Effectiveness Endpoint:	At 6 months, the 95% lower confidence limit of the mean percent improvement in IPSS over baseline for the UroLift system must be ≥25%. The Lower 95% confidence Limit, determined using bootstrap method is 50.8%.
Safety Endpoint:	The composite observed rate of post-procedure device related serious complications less than or equal to 15% at 3 months. Composite device related serious complications for this endpoint are 1) De Novo (new) severe urinary retention lasting more than 21 consecutive days post procedure, 2) Device related formation of fistula between the rectum and urethra, and 3) perforation of the rectum or GI tract, 4) damage to ureter or ureteral orifices 5) damage to the trigone requiring surgical repair or 6) *de novo*, sustained erectile dysfunction.
Additional Assessments:	Over the 12 month follow-up period, lower urinary tract symptoms (LUTS), quality of life (QOL), recovery, uroflowmetry, PVR, proportion of subjects who experience de novo sustained erectile dysfunction and anejaculation through 12 months, number of subjects with encrusted implants, patient satisfaction and adverse events severity and relatedness will be assessed.

ENROLLMENT CRITERIA

Inclusion Criteria

Subjects enrolled in this clinical study must meet all of the following criteria.

1. Male gender
2. Diagnosis of symptomatic BPH
3. Age ≥ 50 years
4. International Prostate Symptom Score (IPSS) ≥ 13
5. Peak urine flow rate ≤ 12 ml/sec on a voided volume ≥ 125 ml
6. Prostate volume ≥ 30 cc to ≤ 80 cc per ultrasound
7. Prostate Length measurement of ≥30 and ≤80 mm
8. Enlarged median lobe contributing to obstruction of the prostate

Exclusion Criteria

Subjects will be excluded from the study if any of the following conditions apply.

1. Current urinary retention
2. Post void residual (PVR) urine > 250 mL
3. Active urinary tract infection at time of procedure
4. Previous BPH surgical procedure
5. Urethral conditions that may prevent insertion and delivery of device system into bladder (i.e. urethral strictures, meatal stenosis, bladder neck contracture)
6. Previous pelvic surgery (i.e. incontinence sling, trauma repair, penile implants, artificial sphincter) or irradiation
7. History of neurogenic or atonic bladder
8. Stress urinary incontinence
9. Biopsy of the prostate within the past 6 weeks
10. Life expectancy estimated to be less than 5 years
11. History of prostate or bladder cancer
12. Prostate-Specific Antigen (PSA) level above the age specific reference ranges, unless prostate cancer has been excluded to the satisfaction of the investigator.
13. Current gross hematuria
14. Known coagulopathies or subject on anticoagulants or antiplatelets other than aspirin ≤ 100 mg (unless antiplatelets are withheld minimum 3 days prior to procedure)
15. Use of the following medications pre-screening (uroflow, questionnaires)
    - Within 4 months of baseline assessment: estrogen, any drug producing androgen suppression, or anabolic steroids (excluding topical testosterone)
    - Within 3 months of baseline assessment: 5-alpha-reductase inhibitors
    - Within 2 weeks of baseline assessment:
        - alpha-blockers, androgens (topical are acceptable), gonadotropin-releasing hormonal analogs, anticholinergics or cholinergic medication
        - phenylephrine, pseudoephedrine, or imipramine medications
    - Within 1 week of baseline assessment, unless documented on stable dose for ≥ 6 months: beta blockers, antidepressants, anticonvulsants, and antispasmodics
16. Calculus urinary within the prior 3 months
17. Prostatitis requiring treatment (antibiotics) within the last year
18. Other co-morbidities that could impact the study results such as:
    - severe cardiac arrhythmias uncontrolled by medications or pacemaker
    - congestive heart failure NYHA III or IV
    - history of uncontrolled diabetes mellitus
    - significant respiratory disease in which hospitalization may be required
    - known immunosuppression (i.e. AIDS, post-transplant, undergoing chemotherapy)
19. Desire to maintain fertility post procedure
20. Unable or unwilling to complete all required questionnaires and follow up assessments (e.g. lives out of area)
21. Unable or unwilling to sign informed consent form
22. Currently enrolled in any other investigational clinical research trial that has not completed the primary endpoint.

SCREENING ACTIVITY TIME PERIODS

Activity	Time Frame	Special Considerations
Flexible Cystoscopy	Within 6 months	Cystoscopy performed outside of study, within 6 months of index procedure, can be used to qualify for enrollment, provided eligibility morphology was determined, (enlarged median lobe.). If not all data collected with recording prior, there will also be a pre-procedure cystoscopy. This procedure, with video recording, will capture additional anatomical details and assist in implant planning.
TRUS or Pelvic Ultrasound	Within 6 months	Ultrasound performed outside of the study, within 6 months of screening, can be used to qualify enrollment, provided eligibility morphology (e.g. enlarged median lobe, Intravesical Prostatic Protrusion, etc.) and image are documented. In all cases, the image and data must be entered into EDC prior to index procedure.
Medical History	Within 30 days	
Uroflowmetry	Within 30 days	Either before cystoscopy or > 1wk after cystoscopy. Must be obtained after med washout
PVR	Within 30 days	Must be obtained after med washout
PSA	Within 6 months	
Urinalysis, Urine Culture & Sensitivity	Within 30 days	
Questionnaires	Within 30 days	Either before cystoscopy or > 1wk after cystoscopy. Must be obtained after med washout
Medications	**Medication washout timeframe**	**Caveats**
1) Estrogen, any drug producing androgen suppression, or anabolic steroids	1) 4 months prior to uroflow studies & questionnaires	
2) 5-alpha-reductase inhibitors	2) 3 months prior to uroflow studies & questionnaires	2) Subjects should remain off 5ARIs for the duration of the study, unless clinically required.
3) Alpha-blockers	3) 2 weeks prior to uroflow studies & questionnaires	3) Subjects should remain off alpha blockers for the duration of the study, unless clinically required.
4) Phenylephrine, pseudoephedrine, imipramine, anticholinergic or cholinergic medication	4) 2 weeks prior to uroflow studies & questionnaires	
5) Beta blockers, antidepressants, anticonvulsants, and antispasmodics	5) 1 week prior to questionnaires	5) Unless documented on stable dose for ≥ 6 months, in which case the drug should not be altered or discontinued for entrance into or throughout the course of the study; unless otherwise deemed necessary for patient care.
6) Anticoagulants or antiplatelets other than aspirin ≤ 100 mg	6) 3 days prior to procedure	

SUMMARY OF PROCEDURES

Tests and Assessments	Screening	Procedure Through Hospital Release	1 Month (± 7 days)	3 Months (± 14 days)	6 Months (± 30 days)	12 Months (± 30 days)
Questionnaires						
Urinary Symptoms	X		X	X	X	X
Sexual Function that includes MSHQ-EjD Sexual function, Anejaculation Function, IIEF	X		X	X	X	X
Incontinence Severity Index	X		X	X	X	X
Dysuria	X		X	X	X	X
Hematuria	X		X	X	X	X
Quality of Recovery VAS			X			
Pain VAS	X		X	X	X	X
Patient Satisfaction			X	X	X	X
Medical History	X		X	X	X	X
Sexual Function Assessment	X		X	X	X	X
Uroflowmetry[1]	X		X	X	X	X
PVR	X		X	X	X	X
PSA	X					
UA	X		X	X	X	
Urine Culture and Sensitivity	X		X	X	X	
TRUS or Pelvic Ultrasound[1]	X					
Flexible Cystoscopy[1]	X[2]	X[2]			X	
DRE		X[3]				
Catheterization		X	X	X		
Concomitant Medications	X	X	X[4]	X[4]	X[4]	X[4]
Adverse Events		X	X	X	X	X
Intervention Review		X	X	X	X	X

[1]All subject Uroflow strip chart recordings, Ultrasound images and cystoscopy videos collected in the study will be forwarded to NeoTract

[2] Any cysto performed w/in 6 months can be used for screening if median lobe is identified. Index UroLift procedure to involve pre-procedure and post-procedure flexible cysto. Pre-procedure to record and confirm anatomy, plan implants; post-procedure to record outcome, ensure proper placement

[3] Performed to rule out rectum implantation

[4] Relevant medications only: BPH/LUTS; Sexual Function; GU; Prostate Cancer

STATISTICAL ANALYSIS

Primary Hypotheses

For the trial to be successful, the statistical evaluation of primary effectiveness endpoint must result in a rejection of the null hypothesis (H_0) in favor of the alternative hypothesis (H_1).

Primary Effectiveness Endpoint: UroLift system compared to an Objective Performance Goal (OPG) at 6 months post treatment:

Let $\delta\mu_p$ equal the expected percent change in IPSS scores from baseline at 6 months. The null and alternative hypotheses are as follows:

$$H_0: \ \delta\mu_p \leq 25\%$$

$$H_1: \ \delta\mu_p \geq 25\%$$

Sample Size Estimate

From a practical perspective, the sample size estimate can be based on the number of expected subjects that could have been included in the UroLift pivotal trial (L.I.F.T.) had subjects with median lobe been allowed to enroll. To statistically corroborate the sample size estimate, an evaluation of the IPSS response in the L.I.F.T. treatment arm at 6 months was evaluated. Taking this value and applying a lower confidence bound, the estimated mean IPSS response for this study was determined.

For a one-sided 95% confidence interval, based on a t-test, the sample size estimate was calculated.

Intention to Treat Group

The main analyses, including endpoints, will be performed on the "intent-to-treat (ITT)" group. All subjects who are enrolled will be included in the intention to treat analysis. With the ITT analysis, primary outcome data from subjects retreated with either the UroLift System or with any other surgical procedure will be censored the day after the alternative procedure. Additionally, subjects that start on alpha blockers or 5ARI medications specifically for the treatment of BPH, and use then consistently will have their results censored the day after starting this medication. Consistent usage is defined any medication use for more than 60 days.

The IIT population is used for efficacy analyses.

Safety Group

Any safety analysis, outside of safety endpoint, will be performed on the "Safety Group". All data will be included through exit, unless a non-UroLift BPH surgical procedure (e.g. TURP, Laser, HOLEP) is performed. In these cases, follow-up safety data will be censored on the day of the alternative procedure.

Evaluation of Primary Effectiveness Hypothesis

If the lower limit of the one-sided 95% confidence interval for mean IPSS percentage change for the UroLift system at 6 months is greater than or equal to 25%, then the null hypothesis will be rejected in favor of the alternative hypothesis. (The lower 95% confidence limit, determined using bootstrap method is 50.8%.)

Subjects who have missing IPSS data due to lost to follow-up will have the percent change from baseline at 6 months value imputed using the MCMC (Markov Chain Monte Carlo) multiple imputation method. Partially completed IPSS questionnaires will also be considered missing. The lower bound of the one-sided 95% confidence interval will be constructed using the mean and standard error from the MCMC method.

Evaluation of Safety Endpoint

The composite observed rate of post-procedure device related serious complications less than or equal to 15% at 3 months. Composite device related serious complications for this endpoint are 1) de Novo (new) severe urinary retention lasting more than 21 consecutive days post procedure, 2) formation of fistula between the rectum and urethra, and 3) perforation of the rectum or GI tract, 4) damage to ureter or ureteral orifices 5) damage to the trigone requiring surgical repair or 6) de novo, sustained erectile dysfunction.

The CEC will determine if any adverse events reported through 3 months post-index procedure qualify to meet the 6 elements of the composite safety endpoint. The observed rate of the six serious complications must be less than or equal to 15% for the trial to be successful.

Analysis of Success Measures

For subjects treated with the UroLift System, the procedure will be considered successful if the post-procedure cystoscopy exhibits an increase in the urethral opening post-procedure and the subject is free of device/procedure related serious adverse events immediately post-procedure. Independent of whether or not the procedure was successful, all subjects will be included in the ITT analysis of the primary endpoints.