PROCEPT BioRobotics

Official Title: The WATER Study
Waterjet **A**blation **T**herapy for **E**ndoscopic **R**esection of prostate tissue
Clinical Investigational Protocol

NCT Number: NCT02505919

Document Date: 12-Apr-2016

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The WATER Study

Waterjet Ablation Therapy for Endoscopic Resection of prostate tissue

Protocol Number: **TP0038**

Version Number: **G**

Date: **12 April, 2016**

Device: **AQUABEAM® System**

Sponsor: **PROCEPT BioRobotics Corporation**
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Redwood City, CA 94065, USA

Geographical regions: **United States, European Union, Australia and New Zealand**

Protocol Revision Number	Protocol Revision Date
Rev. A	29 April, 2015
Rev. B	30 June, 2015
Rev. C	24 July, 2015
Rev. D	6 October, 2015
Rev. E	7 January, 2016
Rev. F	28 March, 2016
Rev. G	12 April 2016

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1 GENERAL STUDY INFORMATION

1.1 Study Acknowledgement/Confidentiality

By signing this Protocol, the Investigator(s) acknowledges and agrees:

The WATER study will be conducted according to the EC/IRB approved protocol and in accordance with 21 CFR 50, 54, 56, 812 , ISO 14155 (if relevant to the site's geography) and any other applicable regulations. The Protocol contains all necessary details for conducting the study. The Investigator will conduct this study as detailed herein, in compliance with The World Medical Association Declaration of Helsinki (59th WMA General Assembly, Seoul, October 2008) and the applicable regulatory requirements, and will make every reasonable effort to complete the study within the time designated.

The Protocol and all relevant information on the device relating to pre-clinical and prior clinical experience will be made available to all Investigators, nurses and other personnel who participate in conducting this study. The Investigator will discuss this material with them to ensure that they are fully informed regarding the device and the conduct of the study.

The Investigator(s) indicate they have reviewed the protocol and assure no deviations to the protocol are made without prior written agreement from the sponsor, except when necessary to eliminate an immediate hazard(s) to the study subjects. The Investigators will report to the EC/IRB and the sponsor any changes in the research activity and all unanticipated problems involving risk to the study subjects.

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The sponsor and trial participants (including the principal investigator) agree to the terms outlined in the attached Clinical Trial Agreement.

Study Role	Signature	Date
Sponsor/Designee		
Principal Investigator		
Co-Investigator		
Co-Investigator		
Co-Investigator		

1.2 Investigational Summary

Title:	The WATER Study: WATER – **W**aterjet **A**blation **T**herapy for **E**ndoscopic **R**esection of prostate tissue
Design:	A prospective multicenter randomized blinded study comparing Aquablation of the prostate with the AQUABEAM System with standard transurethral resection of the prostate (TURP) for the treatment of lower urinary tract symptoms (LUTS). The primary endpoints for safety and effectiveness will be measured at 3 and 6 months, respectively, and subjects will be followed out to 3 years to collect long-term clinical data. The trial will utilize a group sequential design with a single interim look and will incorporate a sample size re-estimation at the time of the interim look based on the promise for superiority on the primary effectiveness endpoint.
Randomization Scheme:	2:1 randomization (Aquablation:TURP)
Investigational Device Name:	AQUABEAM® System
Device Description and Intended Use:	PROCEPT BioRobotics has developed the AQUABEAM, a personalized image-guided tissue removal system that utilizes proprietary heat-free high-velocity waterjet technology to resect and remove the targeted tissue. The AQUABEAM System is intended for the resection and removal of prostate tissue in males suffering from lower urinary tract symptoms (LUTS).
Primary Objective:	Compare safety and effectiveness of the AQUABEAM System and TURP in the treatment of benign prostatic hyperplasia (BPH) in men 45 to 80 years of age
Primary Safety Endpoint:	The primary safety endpoint is the proportion of subjects with adverse events classified as Clavien-Dindo Grade 2 or higher or any grade 1 event resulting in persistent disability (e.g. ejaculatory disorder or erectile dysfunction) evidenced through 3 months post treatment. The Aquablation group will be declared to be non-inferior to TURP if it can be established that the difference is within the non-inferiority margin of $\delta = 0.10$. If non-inferiority is established, a test for superiority will be conducted. If it can be established that the difference is greater than 0, superiority will also be claimed.
Primary Effectiveness Endpoint:	The primary effectiveness endpoint is the IPSS change from baseline to 6 months. Aquablation will be declared non-inferior to TURP if the change score is non-inferior using a non-inferiority margin of 4.7 points. If non-inferiority is established, a test for superiority will be conducted. If it can be established that the difference is greater than 0, superiority will also be claimed.
Overall Study Success Criterion	Both Primary Safety and Primary Effectiveness Endpoints must be met in order to consider the study a success.
Additional Endpoints:	The following is a list of secondary endpoints intended to support product labeling: • Reoperation or re-intervention within 6 months • Evaluation of the proportion of sexually active subjects reporting a worsening of sexual function through 6 months on either the IIEF-15 or the MSHQ-EjD questionnaires • Evaluation of the proportion of subjects meeting a composite of serious device or procedure related events defined as Major Adverse Urologic Events (MAUE) through 6 months • Length of hospital stay (days) in the treatment groups • Length of operative time (minutes) in the treatment groups • Length of resection time (minutes) in the treatment groups Additional endpoints will be tested as outlined in the protocol below.
Enrollment:	Between 177 and 270 male subjects (118 to 180 Aquablation:59 to 90 TURP) age 45 to 80 and presenting with an IPSS ≥ 12 will be randomized and blinded to treatment. Up to an additional 60 subjects (up to 3 per site) may be enrolled and treated as training or roll-in subjects to familiarize the operator with the AQUABEAM System prior to randomization. To ensure that every study site enrolls a reasonable number of randomized study subjects, Investigators will be given permission to treat their roll-ins and begin to randomize subjects once a minimum of 5 fully eligible subjects have been enrolled.

Clinical Sites:	Up to 20 clinical study sites in the United States, European Union, Australia and New Zealand. Individual centers will be limited to enroll up to 15% of the overall population in the trial, unless written pre-approval is obtained from the sponsor.
Inclusion Criteria	1. Subject has diagnosis of lower urinary tract symptoms due to benign prostatic enlargement causing bladder outlet obstruction 2. Subject is willing to be randomized 3. Subject is mentally capable and willing to sign a study-specific informed consent form 4. Subject is willing and able to comply with all study requirements 5. Clinical investigator has documented in the subject's medical record that in his/her judgment the subject is a surgical candidate for either the Aquablation or the TURP procedure and may be randomized into either arm 6. Age from 45 through 80 years 7. Subject has medical record documentation of a prostate volume between 30mL and 80mL (inclusive) by transrectal ultrasound (TRUS) (If TRUS testing documentation is available from less than 180 days prior to the informed consent date and the prostate volume is between 30mL and 80mL, it may be used for the inclusion/exclusion criteria) 8. Subject has an IPSS score greater than or equal to 12 measured at the baseline visit 9. Subject has medical record documentation of a maximum urinary flow rate (Qmax) less than 15mL/s (If uroflow testing documentation is available within 90 days prior to the informed consent date, and the sample is greater than or equal to 125mL, and the Qmax is less than 15mL/s it may be used for the inclusion/exclusion criteria) 10. Subject has a serum creatinine that is within the normal range for the laboratory at the study center (or documentation of clinical insignificance in the subject's medical record by the investigator if outside the normal range) and measured ≤ 30 days prior to the date of surgery 11. History of inadequate response, contraindication, or refusal to medical therapy
Exclusion Criteria	1. BMI ≥ 42 2. History of prostate cancer or current/suspected bladder cancer 3. Prostate cancer should be ruled out before participation to the satisfaction of the investigator if PSA is above acceptable thresholds 4. Subjects with a history of actively treated bladder cancer within the past two (2) years 5. Neurogenic bladder as confirmed by urodynamics or other neurological disorder that affects bladder function 6. Diagnosis of polyneuropathy 7. Bladder calculus or clinically significant bladder diverticulum (e.g., pouch size >20% of full bladder size) 8. Active infection, including urinary tract infection 9. Prostatitis treated with antibiotics within 1 year of enrollment 10. Diagnosis of or has received treatment for chronic prostatitis or chronic pelvic pain syndrome (e.g. nonbacterial chronic prostatitis) 11. Ever been diagnosed with a urethral stricture, meatal stenosis, or bladder neck contracture 12. Subject has damage to external urinary sphincter 13. Subject has diagnosis of stress urinary incontinence that requires treatment or daily pad or device use 14. PVR > 300 mL 15. Urinary retention at time of enrollment or subject has been catheterized in the 14 days prior to the surgical procedure 16. Subject has a history of intermittent self-catheterization 17. Previous prostate surgery or history of other lower urinary tract surgery such as e.g. urinary diversion, artificial urinary sphincter or penile prosthesis 18. Subjects on anticoagulants (if medication cannot be stopped before and after procedure) or known coagulopathy (except aspirin below 100mg/d) 19. Any severe illness that would prevent complete study participation or confound study results

	20. Serious concurrent medical conditions such as heart disease (e.g., myocardial infarction within 30 days prior to the date of informed consent, congestive heart failure – NYHA IV), pulmonary disease or uncontrolled diabetes 21. Has had an open heart surgery, or cardiac arrest < 180 days prior to the date of informed consent 22. Participants using systemic immune-suppressants including corticosteroids; unable to withhold non-steroidal anti-inflammatory agents (NSAIDs, including aspirin) for 3-5 days prior to treatment except for low dose aspirin (e.g. less than or equal to 100mg) 23. Known illicit substance abuse 24. Participants using anticholinergics specifically for bladder problems. Use of medications with anticholinergic properties is allowable provided the patient does not have documented adverse urinary side effects from these medications. 25. Dementia or psychiatric condition that prevents the participant from completing required follow up 26. Contraindication to general or spinal anesthesia 27. Subject is classified as American Society of Anesthesiologists (ASA) III or higher 28. Previous pelvic radiotherapy 29. Participating in another investigational study that could affect responses to the study device 30. Subject has any other disease or condition(s) that would interfere with completion of the study and follow up assessments, would increase risks of the procedure, or in the judgment of the investigator would potentially interfere with compliance to this study or would adversely affect outcomes 31. Subject is unwilling to accept a transfusion should one be required
Follow up Schedule:	Post-operative through catheter removal, One (1) week, One (1), three (3), six (6), twelve (12), twenty four (24), and thirty six (36) months post procedure
Principal Investigator	Dr. Claus Roehrborn Co-Principal Investigator UT Southwestern Medical Dallas, Texas, USA Dr. Peter Gilling Co-Principal Investigator Tauranga Urology Research Limited Tauranga, New Zealand
Administration	PROCEPT BioRobotics is the study sponsor. The study will be conducted under an approved IDE from the FDA according to 21 CFR 812, according to ISO 14155 (if relevant to the site's geography) and other applicable regulations. Data will be monitored by PROCEPT personnel or designates. Data from this study will be used to support regulatory submissions and medical publications

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2 CLINICAL INVESTIGATIONAL PLAN

2.1 Background

Benign prostatic hyperplasia (BPH), or enlargement of the prostate due to benign growth of glandular tissue, is a very common disease of older men. Prostatic tissue may compress the urethral canal, causing partial or sometimes complete obstruction of the prostatic urethra, which interferes with the normal flow of urine. Symptoms of BPH include urinary hesitancy, frequent urination, dysuria, increased risk of urinary tract infections and urinary retention.

Therapy for BPH includes medication and various surgical approaches. While medication is first-line therapy, many men do not have adequate responses to treatment. Surgical approaches include transurethral resection of the prostate (TURP) and other less invasive approaches such as transurethral microwave thermotherapy (TUMT) or transurethral needle ablation (TUNA). TURP involves invasive removal of prostate tissue using electrocautery and/or sharp dissection. While TURP remains the gold standard for treatment, it carries risks, including bleeding, clot retention/colic, bladder wall injury, hyponatremia (water intoxication), bladder neck contracture, urinary incontinence, retrograde ejaculation, and erectile dysfunction. Additional techniques using lasers or electrocautery that either ablate or enucleate the adenomatous tissues have been developed to improve the efficiency and reduce the morbidity of TURP.

PROCEPT BioRobotics has developed the AQUABEAM System, utilizing a high-velocity saline jet designed to selectively cut prostatic glandular tissue, a minimally invasive surgical procedure dubbed Aquablation. The AQUABEAM System is currently under clinical investigation for the treatment of lower urinary tract symptoms associated with benign prostatic hyperplasia (BPH).

High-pressure water jet technology was originally used in industry to cut metal, ceramic, wood, and glass. In recent years, however it has been adapted to dissect parenchymal tissues in animal as well as human models. The technique was first described for liver resection, first in dogs and subsequently humans for selective dissection of liver parenchyma, leaving bile ducts and blood vessels untouched [1], [2] Further experience demonstrated the feasibility of this technology for open and laparoscopic resection of a wide range of parenchymal organs such as the brain, kidney and lungs [3], [4], [5], [6]. More recently, similar hydrodissection and waterjet technology have been used to show safety and efficacy in the transurethral setting, being utilized for resection of bladder tumors [7]. These previous investigations have determined the safety and efficacy of utilizing a high pressure waterjet for dissection of parenchymal tissue and one can reasonably conclude the technique can be applied to prostatic tissue

Ablation of prostate adenoma, as opposed to cutting, has also previously been shown to be safe and effective in the setting of benign prostatic hyperplasia. Various forms of lasers have been utilized in prostatic ablation, with varying results [8]. Thermoablation techniques have also been utilized for prostatic ablation, again showing safety and efficacy and with varying results in outcome measures [9]. These techniques help pave the path to future technologies involving prostate ablation, including water jet dissection, by evaluating where those technologies have succeeded and where they need improvement.

To date, 57 subjects (New Zealand, Australia and India) have been successfully treated with the AQUABEAM System.

2.2 AquaBeam System Pre-Clinical Experience

PROCEPT conducted acute and chronic animal studies to assess the safety and efficacy of the AQUABEAM System in a canine model.

Eight (8) non castrated male dogs (2 Acute and 6 chronic) were successfully treated through a previously created perineal urethrostomy. The Aquablation procedure successfully ablated the adenomatous elements while preserving the collagenous structures. There was no active bleeding in any of the dogs during or

after the Aquablation procedure. Five of the six dogs that underwent survival study survived up to the 6-week mark. Complications included two dogs with infections, which were successfully treated with antibiotics, a false passage created during catheter placement and two bladder neck perforations (from mechanical insertion). Histological evaluations at 6 weeks revealed a normal cellular architecture and full re-epithelialization of the treatment cavity [10].

In addition to animal studies, the AQUABEAM System has been tested on the bench to assess the general performance characteristics. The characteristics include dimensional, visual, bond strength, software and functional. The functional testing was conducted on a specially created bench model to simulate performance characteristics of prostate tissue resection. The bench model used parameters found in medical literature and feedback from clinicians. The AQUABEAM System met these pre-clinical testing requirements, as well.

2.3 AquaBeam System Clinical Experience

The AQUABEAM System is currently under clinical investigation for the treatment of lower urinary tract symptoms associated with benign prostatic hyperplasia (BPH). To date, 57 subjects (New Zealand, Australia [11] [12] and India [13] have been successfully treated with the AQUABEAM System. One subject experienced a recurrence of symptoms at 3 months and underwent a second procedure resulting in a total of 58 procedures to treat 57 subjects. Moreover, another subject experienced a recurrence of symptoms at 5 days and underwent a TURP procedure.

In the 57 subjects enrolled and treated, there were no reported device related serious adverse events occurring in any of the 58 procedures performed. In the India and New Zealand/Australia studies, procedure success was defined as successful resection and removal of prostate tissue from the target site, yielding an observable increase in the prostatic urethral opening after treatment with the AQUABEAM System. In all 58 treatments, 100% (58 of 58) procedures achieved the definition of procedural success.

Although the pilot studies were not powered to demonstrate effectiveness of the AQUABEAM System, when compared to baseline symptoms and quality of life effectiveness measures, subjects treated with the AQUABEAM System exhibited a clinically and very highly statistically significant improvement ($p<0.0001$) for all measures of effectiveness (IPSS, Qmax, QOL, and PVR) through the APS study 6-month follow up interval and ABS study 3-month follow up interval. A comparison of the available follow up results to the original baseline scores is presented in **Figures 1-3** for the APS and ABS studies, respectively.

Figure 1 India, New Zealand and Australia APS Study 6-month Follow-up Results on 34 matched Subjects

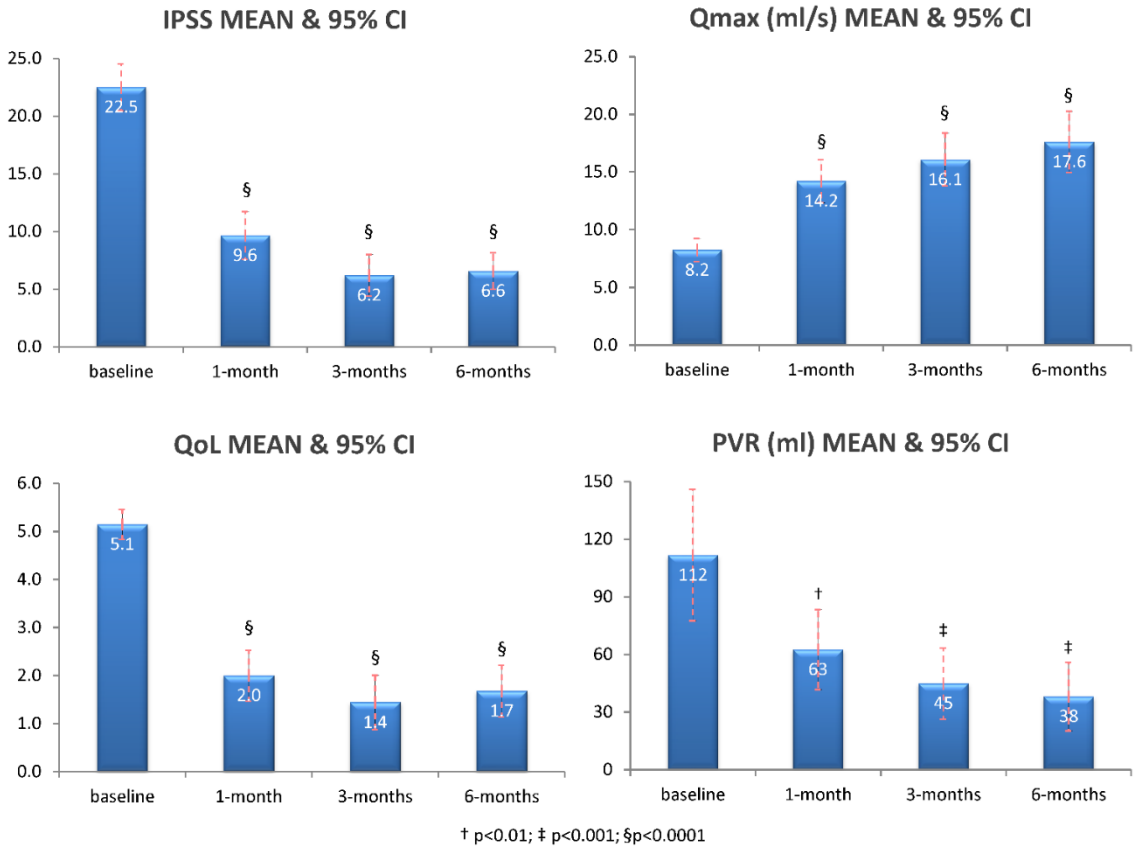
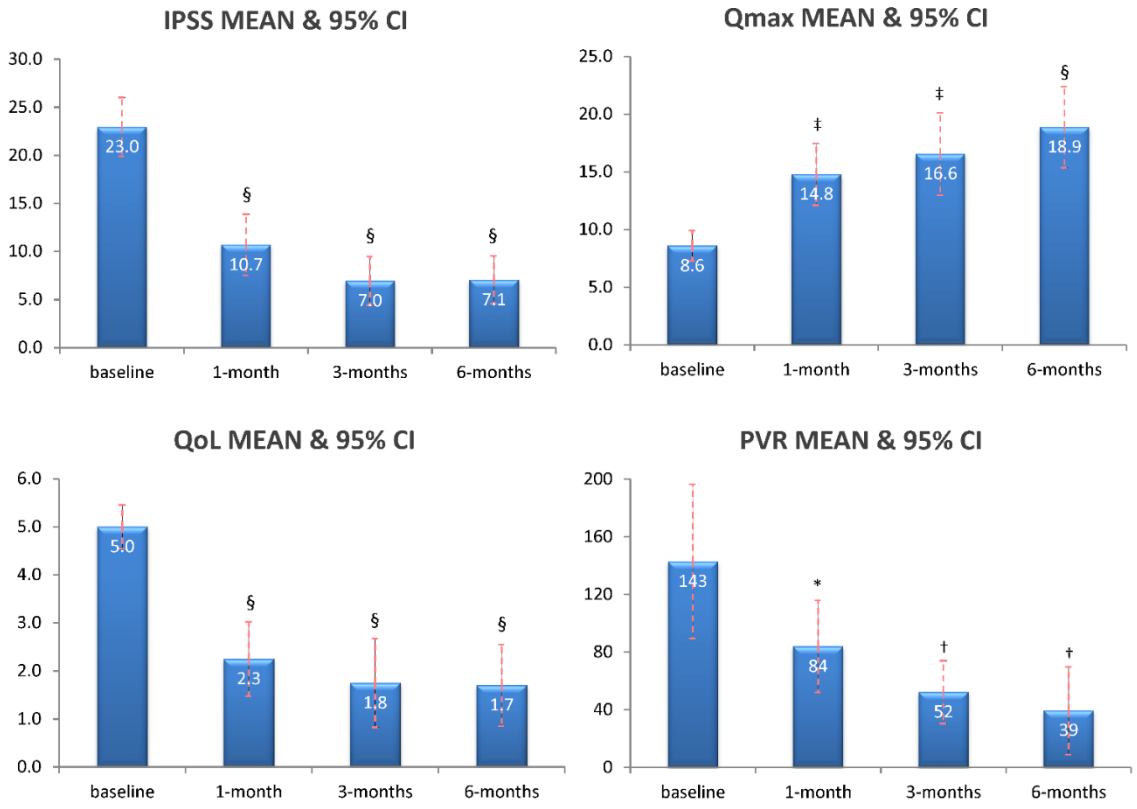
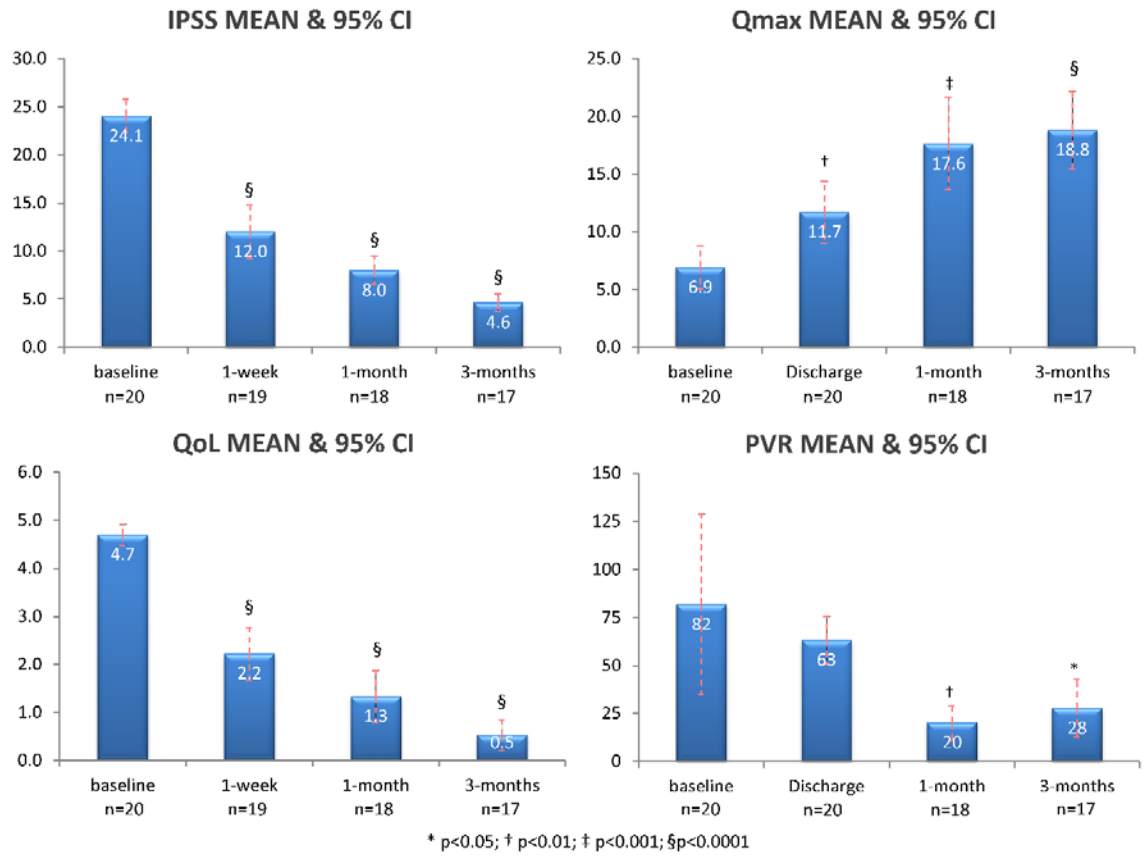


Figure 2 Phase 2 Results - New Zealand and Australia APS Study 6-month Follow-up Results on 20 matched Subjects



* p<0.05; † p<0.01; ‡ p<0.001; §p<0.0001

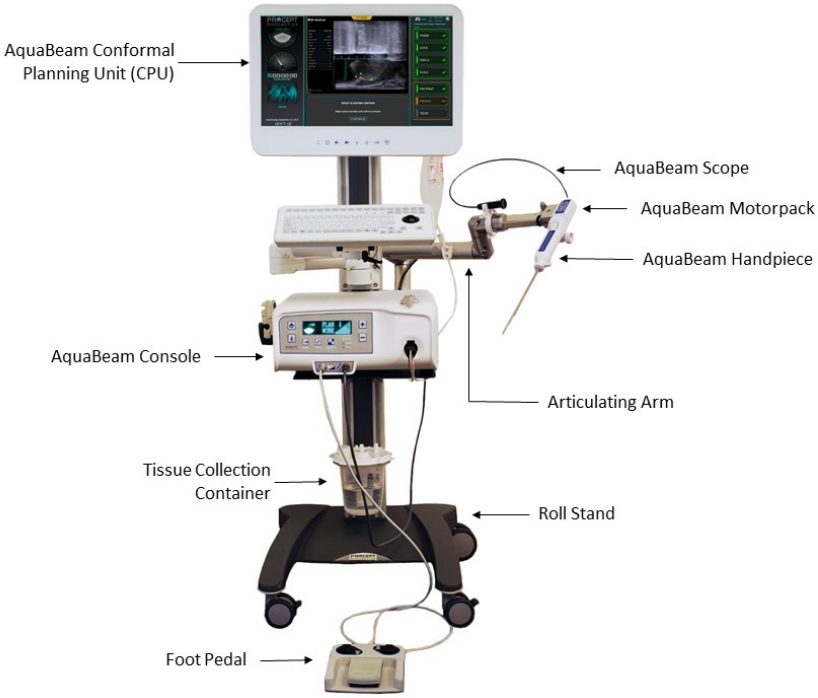
Figure 3 India ABS Study 3-month Follow-up Results on 20 Subjects



2.4 Study Device Description –AQUABEAM System

PROCEPT BioRobotics' product is called the AQUABEAM System (**Figure 4**), which is intended for use in Aquablation – image-guided waterjet tissue resection – in patients suffering from lower urinary tract symptoms resulting from BPH. The System is comprised of nine main components along with accessories. The actual treatment with the AQUABEAM System is referred to as Aquablation. The main components are as follows:

Figure 4 AQUABEAM System

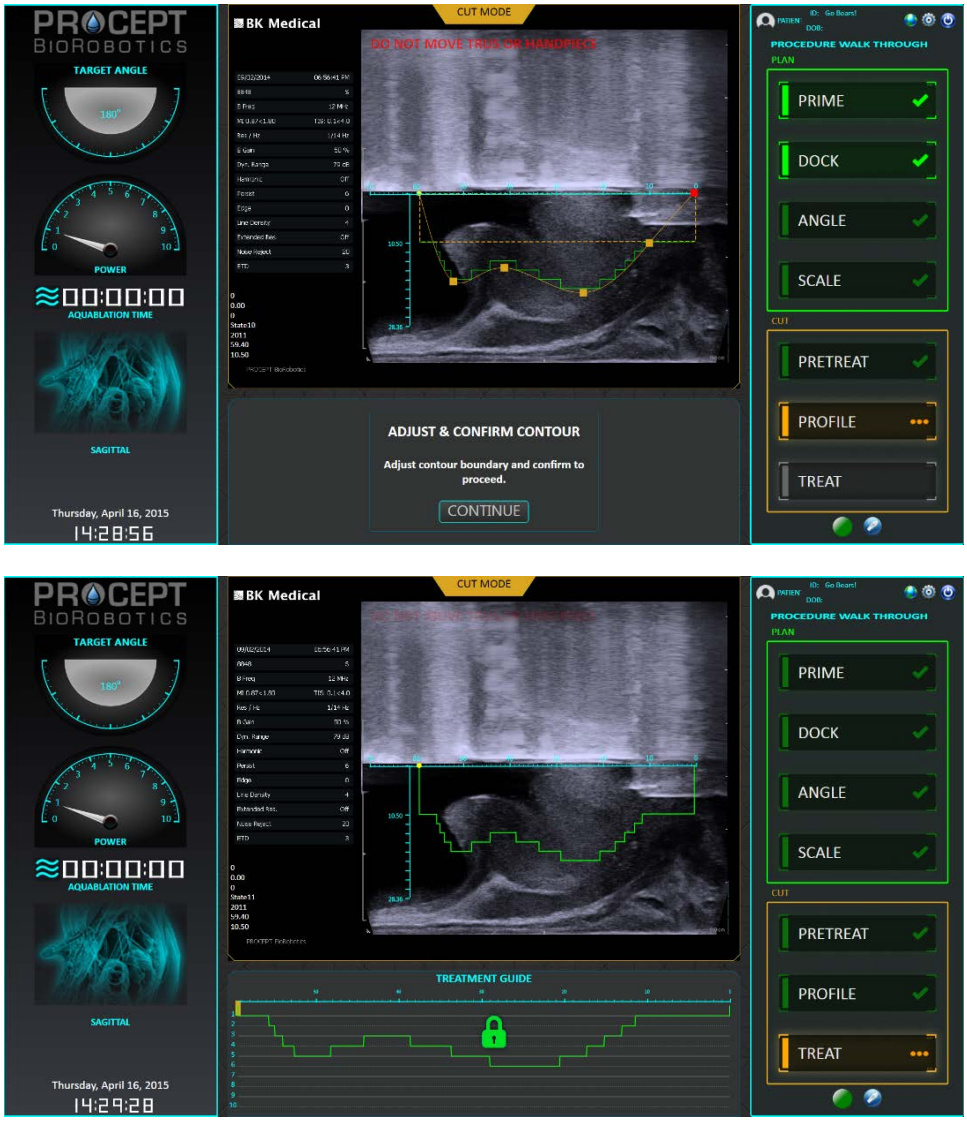


- ***AquaBeam Conformal Planning Unit:***

Live transrectal ultrasound (TRUS) video is imported into and displayed by the AQUABEAM Conformal Planning Unit (CPU) allowing the operator to map the contour of the prostate. The prostatic capsule, verumontanum and bladder are visualized allowing the operating Investigator to identify key anatomical markers, to optimize position of the AQUABEAM Handpiece and select the target area for treatment.

The planned parameters are downloaded to the AQUABEAM Console and Aquablation treatment can be initiated. During Aquablation treatment, the operating Investigator will utilize the AQUABEAM CPU (see **Figure 5**) to monitor the progress of resection. At any point in time the operating Investigator can pause Aquablation treatment and make real-time adjustments to the target area as appropriate.

Figure 5 Representations of User Interface of the AQUABEAM CPU

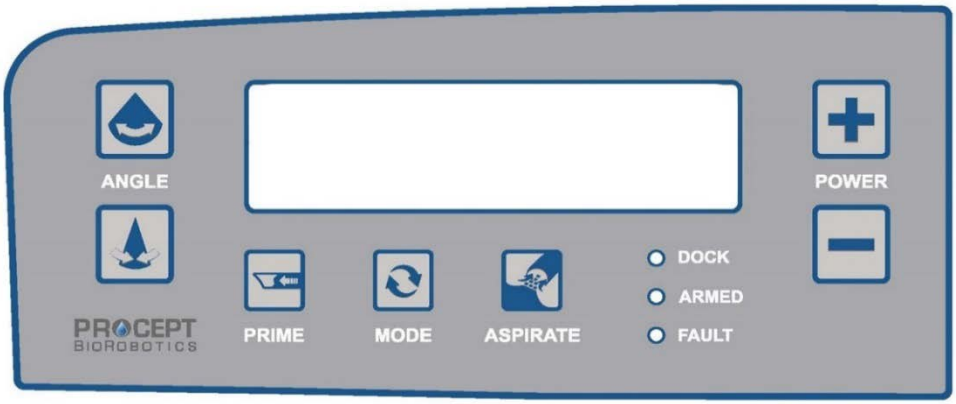


(Refer to User Manual for current configuration of the CPU interface)

- ***AquaBeam® Console:***

Prior to initiation of treatment, the AQUABEAM Console (see **Figure 6**) is attached to the AQUABEAM Handpiece which provides the conduit of saline fluid connection to be used in the subject treatment. The AQUABEAM Console generates the saline pressure allowing controlled resection of the prostate tissue in accordance with the AQUABEAM CPU measurements. During the administration of the saline, the AQUABEAM Console controls the movement of the probe (rotation and translation). In addition, the console utilizes a peristaltic pump that assists in evacuation of saline from the bladder and prostatic urethra.

Figure 6 Representations of the AQUABEAM Console

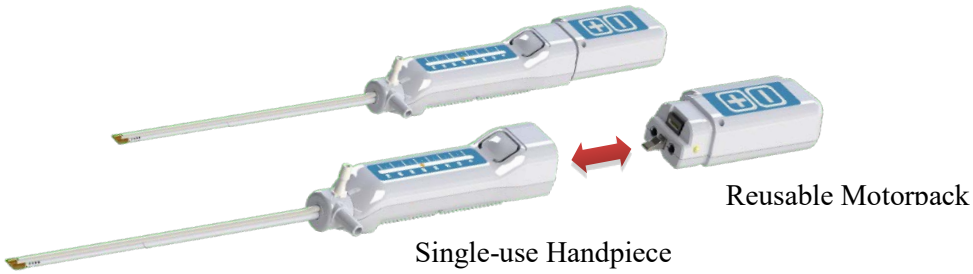


(Refer to User Manual for current configuration of the Console)

- ***AquaBeam Handpiece:***

The AQUABEAM Handpiece (see **Figure 7**) is a sterile single use medical device and is connected to the AQUABEAM Console via a reusable motorpack (see **Figure 7**). The AQUABEAM Handpiece is compatible with the AQUABEAM Scope (see **Figure 8**) which is inserted into the central lumen of the AQUABEAM Handpiece, enabling live cystoscopic visualization of the prostatic urethra prior, during, and after Aquablation treatment.

Figure 7 Representations of the AQUABEAM Handpiece and Motorpack



(Refer to User Manual for current configurations of Handpiece and Motorpack)

The tip of the AQUABEAM Handpiece is inserted transurethrally into the subject and advanced through the prostatic urethra into the bladder. Using both live TRUS and cystoscopic guidance, the operating Investigator positions the tip of the AQUABEAM Handpiece to the desired location within the prostate. Upon initiation of treatment, the AQUABEAM Handpiece delivers a high-velocity sterile saline stream perpendicular relative to the Handpiece probe. The Aquablation is designed for the resection of both median and lateral lobes, on small and large prostates during surgical procedures.

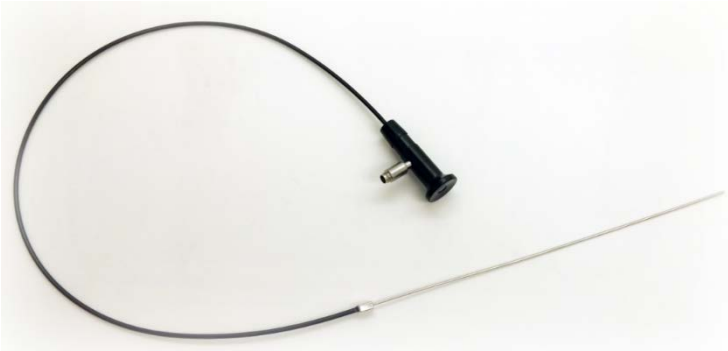
The Handpiece follows the prescribed treatment plan and precisely resects the prostate tissue in accordance with the contour preset during the TRUS planning phase. It is anticipated that Aquablation treatment will take < 10 minutes to perform and the operating Investigator may utilize electrocautery to address residual bleeding following treatment. The patient is then catheterized, sent to recovery. Typically the catheter is removed within 12-48 hours post-treatment according to the Investigator's discretion.

- ***AquaBeam Scope:***

The AQUABEAM Scope (see **Figure 8**) is inserted into the Handpiece and offers live cystoscopic visualization of the prostatic urethra prior, during, and after Aquablation treatment.

The AQUABEAM Scope is reusable and needs to be sterilized prior to each procedure. Please refer to the AQUABEAM Scope IFU for reprocessing instructions.

Figure 8 Representation of the AQUABEAM Scope



(Refer to User Manual for current configuration of Scope)

All operating investigators shall receive both didactic and practicum training on the proper use of the AQUABEAM System prior to subject enrollment. For the specifics on the operating instructions please refer to the AQUABEAM System instructions for Use/User Manual.

2.5 Indications for Use

The AQUABEAM System is intended for the resection and removal of prostate tissue in males suffering from lower urinary tract symptoms.

2.6 Overall Design

Prospective, multicenter, multinational, 2:1 randomized, double-blinded controlled trial. Both the follow-up study staff and participating subject are blinded to treatment (see section on blinding below). The trial will utilize a group sequential design with a single interim look and will incorporate a sample size re-estimation at the time of the interim look based on the promise for superiority on the primary effectiveness endpoint.

2.7 Study Objectives

Compare safety and effectiveness of the AQUABEAM System and Transurethral Resection of the Prostate (TURP) in the treatment of benign prostatic hyperplasia (BPH) in men 45 to 80 years of age.

2.8 Study Duration

Each subject is followed for 36 months (3 years) postoperatively. Enrollment is expected to take up to 12 months. Total study duration from first subject enrolled to last subject completing the prescribed follow up is 48 months.

2.9 Number of Sites

Up to twenty (20) sites will participate. Up to 15 sites may be from the US. All sites will undergo training in use of the study device prior to use.

2.10 Sample Size

Between 177 and 270 subjects will be enrolled, randomized and blinded (118 to 180 AQUABEAM:59 to 90 TURP). The study has an interim sample size calculation. An additional 60 roll-in subjects may be enrolled and treated prior to randomization to allow the investigators to become familiar with the AQUABEAM System.

The total maximum sample size proposed, including the roll-in cases, is 330 subjects.

2.11 Study Population

The target patient population is subjects with symptomatic BPH who have not responded adequately to standard medical therapy. To participate, a subject must meet all inclusion criteria and none of the exclusion criteria listed in Table 1.

Table 1. Study eligibility criteria

Inclusion Criteria	Exclusion Criteria
1. Subject has diagnosis of lower urinary tract symptoms due to benign prostatic enlargement causing bladder outlet obstruction 2. Subject is willing to be randomized 3. Subject is mentally capable and willing to sign a study-specific informed consent form 4. Subject is willing and able to comply with all study requirements 5. Clinical investigator has documented in the subject's medical record that in his/her judgment the subject is a surgical candidate for either the Aquablation or the TURP procedure and may be randomized into either arm 6. Age from 45 through 80 years 7. Subject has medical record documentation of a prostate volume between 30mL and 80mL (inclusive) by transrectal ultrasound (TRUS) (If TRUS testing documentation is available from less than 180 days prior to the informed consent date and the prostate volume is between 30mL and 80mL, it may be used for the inclusion/exclusion criteria) 8. Subject has an IPSS score greater than or equal to 12 measured at the baseline visit 9. Subject has medical record documentation of a maximum urinary flow rate (Qmax) less than 15mL/s (If uroflow testing documentation is available within 90 days prior to the informed consent date, and the sample is greater than or equal to 125mL, and the Qmax is less than 15mL/s it may be used for the inclusion/exclusion criteria) 10. Subject has a serum creatinine that is within the normal range for the laboratory at the study center (or documentation of clinical insignificance in the subject's medical record by the investigator if outside the normal range) and measured ≤ 30 days prior to the date of surgery 11. History of inadequate response, contraindication, or refusal to medical therapy	1. BMI ≥ 42 2. History of prostate cancer or current/suspected bladder cancer 3. Prostate cancer should be ruled out before participation to the satisfaction of the investigator if PSA is above acceptable thresholds 4. Subjects with a history of actively treated bladder cancer within the past two (2) years 5. Neurogenic bladder as confirmed by urodynamics or other neurological disorder that affects bladder function 6. Diagnosis of polyneuropathy 7. Bladder calculus or clinically significant bladder diverticulum (e.g., pouch size >20% of full bladder size) 8. Active infection, including urinary tract infection 9. Prostatitis treated with antibiotics within 1 year of enrollment 10. Diagnosis of or has received treatment for chronic prostatitis or chronic pelvic pain syndrome (e.g. nonbacterial chronic prostatitis) 11. Ever been diagnosed with a urethral stricture, meatal stenosis, or bladder neck contracture 12. Subject has damage to external urinary sphincter 13. Subject has diagnosis of stress urinary incontinence that requires treatment or daily pad or device use 14. PVR > 300 mL 15. Urinary retention at time of enrollment or subject has been catheterized in the 14 days prior to the surgical procedure 16. Subject has a history of intermittent self-catheterization 17. Previous prostate surgery or history of other lower urinary tract surgery such as e.g. urinary diversion, artificial urinary sphincter or penile prosthesis 18. Subjects on anticoagulants (if medication cannot be stopped before and after procedure) or known coagulopathy (except aspirin below 100mg/d) 19. Any severe illness that would prevent complete study participation or confound study results 20. Serious concurrent medical conditions such as heart disease (e.g., myocardial infarction within 30 days prior to the date of informed consent, congestive heart failure – NYHA IV), pulmonary disease or uncontrolled diabetes

	21. Has had an open heart surgery, or cardiac arrest < 180 days prior to the date of informed consent 22. Participants using systematic immune-suppressants including corticosteroids; unable to withhold non-steroidal anti-inflammatory agents (NSAIDs, including aspirin) for 3-5 days prior to treatment except for low dose aspirin (e.g. less than or equal to 100mg) 23. Known illicit substance abuse 24. Participants using anticholinergics specifically for bladder problems. Use of medications with anticholinergic properties is allowable provided the patient does not have documented adverse urinary side effects from these medications. 25. Dementia or psychiatric condition that prevents the participant from completing required follow up 26. Contraindication to general or spinal anesthesia 27. Subject is classified as American Society of Anesthesiologists (ASA) III or higher 28. Previous pelvic radiotherapy 29. Participating in another investigational study that could affect responses to the study device 30. Subject has any other disease or condition(s) that would interfere with completion of the study and follow up assessments, would increase risks of the procedure, or in the judgment of the investigator would potentially interfere with compliance to this study or would adversely affect outcomes 31. Subject is unwilling to accept a transfusion should one be required

2.12 Screening and Enrollment

Potential study participants will undergo screening in the investigator's clinic. A patient must sign a study-specific, IRB- or ethics committee (EC)-approved informed consent form prior to any testing for eligibility that goes beyond standard care. For the purposes of this protocol, "patient" refers to a patient who is a candidate for the study but has not yet met all eligibility criteria. When a patient has signed the study-specific informed consent form and has met all eligibility criteria, he is considered a study subject. Basic information regarding patients who fail screening will be recorded in the screen failure log.

To ensure that every study site is able to randomize a reasonable number of subjects, Investigators will be given permission to treat their roll-ins and begin to randomize subjects once a minimum of 5 fully eligible subjects have been enrolled.

During the screening process, each patient will be tracked with a screening number. Once a patient is enrolled, he is assigned a study subject number.

2.13 Baseline Evaluation

A subject who appears to meet study eligibility criteria will undergo a baseline assessment consisting of medical history focusing on urinary signs and symptoms. Assessment will also include preoperative vital signs, medical history, concomitant medications; BPH symptom assessment, prostate volume measurement; blood serum analysis including PSA; urinalysis and uroflowmetry. See **Table 2** for complete schedule of assessments for all visits.

2.14 Roll-in Phase

Prior to subject randomization, each operating investigator shall go through a didactic review of the clinical protocol and AQUABEAM System. The first few subjects (as determined by the study sponsor) will not be randomized but rather be treated with AQUABEAM. Upon completion of the roll-in phase, the operating Investigator will be certified by the Sponsor and can commence participation in the randomized portion of the study.

2.15 Randomization

Subjects will be prospectively randomized into one of two treatment groups. Randomization must occur prior to surgery and only after the subject provides written informed consent, completes all baseline procedures and meets the requirements of the study inclusion and exclusion criteria. Randomization should be performed as closely as possible to the point of surgery to minimize the incidence of dropout prior to treatment.

Subjects will be randomly assigned on a two to one (2:1) basis to either the treatment group (Aquablation) or the control group (TURP). Randomization will be stratified by baseline IPSS score (<20 and ≥20) and study site. Permuted block randomization will be performed within strata. To minimize the opportunity for the sequence to be predicted, the block size will be variable and randomly chosen from small multiples of 3 (i.e. 3 or 6). The randomization schedules for all strata will be generated in advance by the contracted study statistician using a computerized random number generator. Investigational sites will not have access to the randomization schedules. Any investigator who is found to tamper with the randomization scheme will be immediately terminated from the study and his/her study site data removed from analysis; patients at such sites treated under the protocol will be followed for an additional 3 months for safety purposes only.

Administration of randomization assignments will be accomplished using a web-based electronic data system. Treatment assignment is made only after verification of proper informed consent execution and study eligibility. The study coordinator or a designee will obtain the randomization assignment per the provided randomization instructions. A copy of the randomization assignment will be maintained in the subject's file.

A subject is not randomized until the randomization assignment has been dispensed by the randomization system. Once a randomization assignment is dispensed, the subject is considered randomized. If, between the time of randomization and the beginning of surgery, the subject becomes ineligible or withdraws, the subject is still considered randomized. The reason for failure to treat will be recorded in the subject's study records. If a subject becomes ineligible or withdraws prior to the initiation of surgery or is found to be ineligible at the time of surgery, the subject will be removed from the primary analysis population as no treatment was performed (and therefore post-treatment data would not be available).

2.16 Blinding

This is a double-blinded study as both the follow-up study staff (blinded coordinator and blinded investigator who perform all follow-up assessments) and patient are blinded to treatment. The treating physician is not blinded to treatment. All sites will provide two staff member teams: unblinded team (investigator and coordinator) and blinded team (investigator and coordinator).

The investigator providing study treatment cannot be blinded to the device because of system-specific requirements for use. To preserve study blinding as much as possible within the imposed ethical constraints, study personnel who are unblinded will refrain from administration of any scheduled subject assessments (e.g., questionnaires) after treatment.

All efforts will be made to maintain the study blind throughout the trial until each subject's trial participation is complete. The following describes the measures being taken to maintain the study blind.

a) Subjects: Subjects will not be told their randomization assignment by any site study personnel involved in the trial and will receive the same care throughout the trial. Efforts will be made to ensure subjects are not unblinded during the study procedure.

b) The site should not disclose the randomization assignment to the subject until after the subject's participation in the study is complete or at the counsel of the Data Monitoring Committee (DMC). Blinding of subjects will help to prevent bias due to subjects dropping out because of non-compliance with the randomization (e.g. do not want to be in the control group) or inherently favoring the treatment product.

c) Randomization Assignment: Each site will randomize subjects using the electronic data base. After the appropriate information is entered into the electronic case report form (eCRF), the randomization function will be activated and the assignment made (Treatment or Control). This randomization process is performed by the unblinded team as closely as possible to the point of surgery to minimize the incidence of dropout prior to treatment.

d) Site Study Personnel: There are two designated teams at each site: blinded and unblinded.

Blinded Team Responsibilities. The **blinded team** is responsible for administering all subject testing and care beginning at the 1 week phone call and to the end of each subject's participation. The blinded team will have access to all eCRFs, except for the eCRFs for randomization and those used to collect data related to the procedure, device and adverse events prior to hospital discharge. The blinded team is particularly responsible for:

1. Scheduling routine follow-up care/visits for all study subjects
2. Performing follow-up visits and assessments
3. Entering study data for all study visits occurring after the 1-week phone call.

Unblinded team responsibilities. The **unblinded team** is responsible for those activities and documentation related to the procedure, including randomization, the selection and use of the device used at time of procedure, and recording the procedure and device study data in the eCRFs and device accountability log. The Sponsor will work with each individual site to determine the documentation needed in the subject's medical records (e.g. procedure notes) to protect the study blind. The Study Coordinator on the unblinded team remains unblinded to the subject treatment assignment and is particularly responsible for:

1. Obtaining randomization from EDC system prior to procedure
2. Ensuring appropriate devices are available on procedure day
3. Completing Device Accountability Log by recording the provided lot and/or serial number information
4. EDC entry for all data pertaining to treatment assignment, procedure information and information regarding discharge after the procedure
5. EDC entry for all AEs occurring prior to hospital discharge

2.17 Surgical Procedure

The surgical procedure should take place within 90 days of initial subject evaluation for participation in the study.

2.18 Preoperative Instructions

Subjects must avoid taking non-steroidal anti-inflammatory agents (NSAIDs, including aspirin) for 3-5 days prior to treatment except for low dose aspirin (e.g., less than or equal to 100mg).

2.19 Anesthesia

All surgical procedures will be performed under general or spinal anesthesia. For subjects undergoing spinal anesthesia, special measures will be taken to preserve blinding:

- Headphones with music
- Cover eyes with an opaque mask

Note that subjects receiving spinal anesthesia are typically sedated, making the likelihood of unblinding low. Such measures are typically not necessary for patients undergoing general anesthesia. However, the unblinded study team should ensure that the patient does not see study devices or sponsor personnel both prior to and after the procedure, which could result in unblinding.

2.20 Evaluation Prior to Device Use

The Investigator will perform a standard assessment of the prostatic urethra and urinary bladder by cystoscopy and transrectal ultrasound (TRUS) to confirm the subject continues to meet all enrollment criteria. Should the investigator find any conditions that exclude the subject (e.g., bladder cancer, diverticula, urethral strictures, bladder calculus, meatal stenosis, bladder neck contracture, etc.), the subject will receive clinical care according to standard practice and will exit the study 30 days after the scheduled study index procedure. For these subjects, the 30-day period is for safety assessment only. These subjects will not count towards the study's total sample size as no study-related treatment was provided and no follow-up data are expected. During TRUS, the investigator will also measure various distances in the bladder to calculate prostate volume. Finally, using the TRUS image, the operating Investigator will identify the bladder neck and the verumontanum and roadmap the contour of the prostate to be resected on the AQUABEAM CPU. This preplanning is then programmed into the AQUABEAM Console which will later drive both the angle and depth of the AQUABEAM waterjet achieving the desired contour established during the planning stage.

2.21 AquaBeam Device Use

A brief description is provided below. The study investigator will be trained in device use through didactic, practicum training and through proctoring. Complete details on the preparation and use of the AQUABEAM System can be found in the device's instructions for use and user manual documents. Should any device defect or malfunction be noticed at any point, whether prior to, during, or after a procedure, this defect or malfunction should be recorded on the Device Malfunction CRF that is provided for this study.

Insertion. The 24F AQUABEAM Handpiece probe is inserted into the prostatic urethra similar to a rigid cystoscope.

Imaging. The AQUABEAM System incorporates real-time visualization utilizing cystoscopy. The cystoscopy is used in conjunction with live Transrectal Ultrasound (TRUS) imaging to allow the operating Investigator to identify anatomical features and boundaries as well as to monitor the position of the Handpiece probe tip during planning and treatment.

Anchoring. Upon completion of cystoscopic visualization, the Handpiece is docked to the motorpack, which is secured to the articulating arm. Upon attachment, the Handpiece is rigidly fixated to prevent movement during Aquablation.

Planning. The Investigator plans the Aquablation treatment zone using the computer monitor called the AQUABEAM Conformal Planning Unit (CPU). Using real-time TRUS to visualize the contour of the prostate, the Investigator first selects the angle of resection. This is followed by a pre-treatment of the prostate to finalize the location of the treatment zone and calculate the tissue depth guides. Finally, the Investigator adjusts the boundaries of treatment by defining the treatment contour along the length of the prostate to conform to the shape of the prostate adenoma. The boundaries serve as a tissue depth guide to help maintain the treatment within the targeted zone.

Treatment. The Investigator depresses the foot pedal to initiate the high velocity saline stream application. Starting at the base of the prostate, the resection continues towards the apex while the saline and ablated tissue are actively suctioned from the prostate into a container for post-procedure tissue analysis. At any point during the procedure, the Investigator can pause the treatment by releasing the foot pedal. Using buttons on the Motorpack or on the Console, the Investigator can manually adjust the resection depths in real-time as the procedure is monitored on both live ultrasound and cystoscopy. Aquablation stops upon reaching the planned treatment endpoint (next to the verumontanum).

For the specific instructions on the pre-procedure planning and actual operation of the AQUABEAM System, please refer to the AQUABEAM System Instructions for Use and User Manual.

Analysis of Excised Tissue. At the direction of the investigator, histopathology of the excised tissue may be performed. The study sponsor will be allowed access to either an H&E slide for each subject or the high-definition photographs of the tissue slides.

Handpiece Removal. When the procedure is complete, saline is turned off and the Handpiece/Motorpack is undocked from the Articulating Arm. The Investigator endoscopically can view the treatment zone by manually guiding the Handpiece within the prostate in a similar manner to a cystoscope. After post-procedural cystoscopy is complete, the Handpiece is removed from the urethra and the AQUABEAM System is powered off.

Cauterization of remaining tissue. Upon completion of Aquablation, the AQUABEAM Handpiece is removed from the subject and, if deemed necessary by the Investigator, a resectoscope is subsequently inserted to perform cautery. The resectoscope must have a coagulation-specific bipolar or monopolar electrode installed and utilize coagulation (COAG) mode on the RF generator only. Cutting/vaporization (CUT) mode shall not be used.

2.22 Transurethral Resection of the Prostate (TURP)

The TURP may be performed according to the local logistics and customs. The goal is that the procedure be done in the way that is typical and routine for the respective institution and research site to assure that the outcomes are in line with those expected in general from a TURP procedure.

Either a bipolar or a monopolar TURP is acceptable. Irrigation solutions therefore may be either 0.9% saline, Glycine, Sorbitol, Mannitol or other solutions that are customarily used to avoid TURP syndrome.

It is expected that the Investigator will use a continuous flow resectoscope of any brand, and that the irrigation fluid is preferably warmed to body temperature.

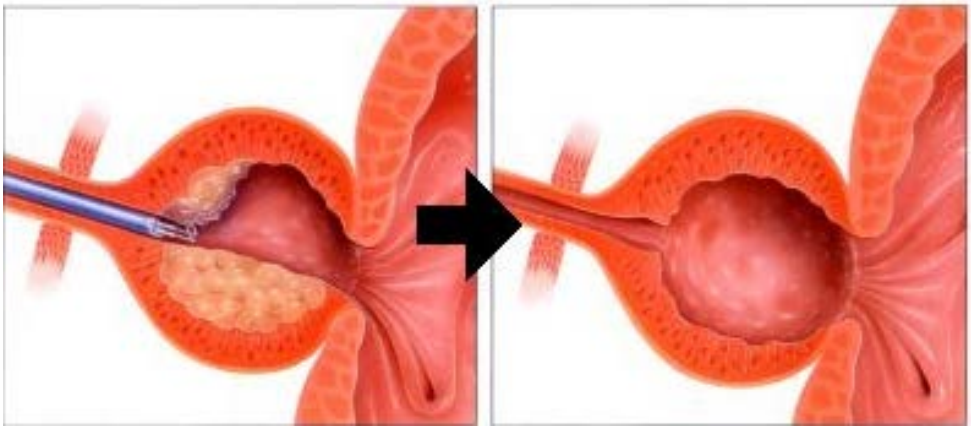
There are many basic techniques described for the performance of a complete TURP (Nesbit, Mauermayer, etc.). While the precise technique and sequence of steps is not relevant it is important to note that the goal should be a complete and thorough TURP and not a channel or limited TURP.

It is expected that any intravesical or middle lobe be resected in its entirety; the lateral lobes are resected starting at the bladder neck and ending parallel to the verumontanum respecting the external sphincter, down to the level of the so-called surgical capsule, which is recognized as the fibrous prostate tissue that surrounds the granular prostatic adenoma.

While some Investigators prefer to start at 6 o'clock and work upward on the lateral lobes, others may prefer to start anteriorly at 12 o'clock and work downward. The handling of the bladder neck is left to the discretion of the Investigator as long as a substantial opening of the bladder neck is achieved as is typical for the final appearance of a completed TURP (as shown in **Figure 9**).

The handling of the catheter is also left to the individual Investigator's usual practice. In most cases a three way catheter would be inserted and connected to continued irrigation for either a few hours or overnight using 0.9% saline. In most cases it is anticipated that the catheter would be removed in the morning with a voiding trial.

Figure 9 Final Appearance of Completed TURP



2.23 Device Malfunction

Investigators will record any device malfunctions for either AquaBeam or TURP devices on specific CRFs. If an Aquabeam device malfunctions, investigators will notify the sponsor within 24 hours and complete a device observation eCRF. The device/component experiencing the malfunction will be returned to the sponsor for evaluation. If a TURP device fails, the investigator should complete a similar CRF and notify the manufacturer of the TURP device according to 21 CFR 803.30 or relevant non-US regulation.

2.24 Post-Procedure Management

Post-procedure care is defined as care provided to the subject during the period starting after the procedure to hospital discharge. Post-procedure care is overseen by the **unblinded investigator**. Data collection relevant to post-procedure care is entered by the **unblinded coordinator**.

The subject will be managed post-operatively as per standard practices. A Foley catheter is not required, though it can be placed at any point postoperatively if urinary retention occurs. Prior to hospital discharge, a **blinded team** member meets the subject and arranges for study-related follow-up. If the catheter is not removed prior to discharge, an additional catheter removal visit is required; this visit is conducted by the **unblinded investigator** and can occur at any time within 72 hours after discharge.

2.25 Care Handoff

After hospital discharge, care is handed off to the **blinded study team** (blinded investigator and blinded coordinator). The blinded team provides study-related care to each subject from the 1 week phone call to the subject's final study visit. The blinded team will evaluate and document all adverse events (AEs) in subjects occurring after hospital discharge. If, however, the subject experiences an AE that requires invasive urologic management, this care is handled by the **unblinded team** and any documentation for this AE is completed by the **unblinded team**. Once the event has resolved, care is handed back to the **blinded team**. The blinded team will not be able to see AEs entered by the unblinded team.

2.26 Follow-Up Evaluations

The subject will have a phone visit specific to the study at 7 days (+/- 3 days) and follow-up clinic visits at 1 month (+/- 5 days), at 3 months (+/- 10 days), at 6 months (+/- 30 days), at 12 months (+/- 60 days), at 24 months (+/- 60 days) and at 36 months (+/- 60 days). At each clinic visit, the subject will undergo medical evaluation, completion of symptom scores, uroflow and assessment of adverse events. The 36-month visit is the final visit. All follow-up scheduled evaluations are performed by the **blinded team**.

2.27 Competing Studies

In the event where a study center is participating in similar and competing research studies with the same or similar subject populations, the Investigator must provide documentation on the methods the center is using to minimize selection bias when allocating subjects for the WATER Study.

2.28 Unscheduled Visits

Any subject may be seen for any reason in the investigator's clinic. The reason for unscheduled visits (including adverse event assessment and/or surgical treatment) will be documented accordingly on CRFs.[1]

[1] Unscheduled visits to investigators from other specialties (e.g., cardiologist visit for heart problem) do not need to be documented unless there is a new adverse event (in which case an AE CRF should be completed).

2.29 Study Assessments

The schedule of assessments is shown in **Table 2**. Details of selected assessments are provided below:

Table 2. Schedule of Assessments

Evaluation	Baseline w/in 90 days of Tx	Tx	Post-Op	Follow-Up Clinic Visits					
				1 wk (+/-3 days) (phone)	1 mon (+/-5 days)	3 mon (+/-10 days)	6 mon (+/-30 days)	12,24,36 mon (+/- 60 days)	unscheduled
Medical history	X								
Vital Signs /Urological Examination	X				X[7] (vital signs only)				
PSA	X						X	X	
Serum Blood Test for CBC and electrolytes	X		X[4]						
Urine for M/C/S	X	X[1]							X[6]
Qmax and PVR	X				X	X	X	X	
Cystourethroscopy	X (within 3 months)	X[2]							
Urodynamics (at selected sites)	X (within 6 months)						X		
Pain NRS and Dysuria Score		X[3]	X[5]	X	X	X			
Incontinence Severity Index	X		X[5]	X	X	X	X		
Blinding Questionnaire			X	X	X	X	X	X	
IPSS, EQ-5D, IIEF-15, MSHQ-EjD, WPAI:US	X			X	X	X	X	X	X
TRUS	X (within 6 months)	X				X			
DRE	X					X			
Concomitant Medication	X	X	X	X	X	X	X	X	X
Concomitant Procedure			X	X	X	X	X	X	X
Procedure information		X							
Adverse events		X	X	X	X	X	X	X	X

[1] Urine dipstick analysis to be done within 72 hours prior to procedure
[2] Rigid cystoscopy is required
[3] To be assessed immediately prior to the procedure
[4] Done in the recovery room
[5] To be completed post-catheter removal
[6] If clinically indicated
[7] If subject has intraoperative or postoperative cardiovascular event

Medical history. During the baseline assessment, the investigator or coordinator will record details of medical history as they relate to BPH.

Vital Signs / Urological examination. At baseline the investigator will measure vital signs and perform a focused urological examination and document any preoperative abnormalities. Vital signs will be collected at the 1-month visit if the subject had an intraoperative or post-operative cardiovascular adverse event.

Serum Blood Test. A blood sample will be collected to measure PSA, complete blood count (CBC) and electrolytes (to include at least levels of sodium, blood urea nitrogen and creatinine). Test timing is shown in the schedule of assessments. A urine sample may be collected at any unscheduled visits if clinically indicated.

Urine for M/C/S. A mid-stream urine sample will be collected at baseline, and repeated within 72 hours prior to the procedure to exclude current urinary tract infection. M/C/S is also collected (if indicated clinically) during any unscheduled visit.

DRE. Digital rectal examination (DRE) will be performed to assess the prostate for size and the presence of nodular or hard tissue.

TRUS. Transrectal ultrasound (TRUS) shall be performed to assess eligibility for prostate volume, length, transverse width, anterior/posterior width and general condition of the prostate. Presence of a middle or intravesical lobe should be documented by sagittal images. The investigator will estimate prostate volume using standard methods (length × width × height × $\pi/6$).

Uroflow. At baseline and each follow-up visit, the subject will undergo measurement of urinary flow rate (Qmax) and post-void residual volume (PVR). For a uroflow test to be valid, the voided volume must be ≥ 125 ml. The subject can repeat the test if necessary.

Urodynamics. Detrusor pressure (PDet@Qmax) will be measured at selected sites. Sites should follow the methods outlined in Chapple [14].

Cystoscopy. At baseline, cystoscopic examination will be performed to assess the bladder for presence of cancer, trabeculation and positioning of the ureteric orifices and the urethra for evidence of stricture (including bladder neck contracture) and prostatic lobe formation (both lateral and medial). Baseline historical cystoscopy will be accepted if the following 2 conditions are met: 1) Baseline cystoscopy was performed and recorded by the study investigator(s) within 90 days of treatment, and 2) The cystoscopy report includes sufficient information for the monitor to source verify all the related inclusion/exclusion criteria, including findings on the area of the bladder neck.

Blinding Questionnaire. A method of assessing subjects knowledge of procedure awareness.

Pain Severity Assessment (NRS) and Dysuria Score. A method of measuring post-operative pain and pain on micturition.

International Prostate Symptom Score (IPSS). IPSS is a validated measure of urinary dysfunction due to BPH [14]. Subjects will complete an IPSS form at baseline and at each follow-up visit.

EuroQol Group 5-Dimension Self-Report Questionnaire (EQ-5D). EQ-5D [15] is a validated instrument that measures health-related quality of life in five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. It also includes the EQ-VAS which is used to measure the individual's global self-rated health status. Subjects will complete an EQ-5D form at baseline and at each follow-up visit.

International Index of Erectile Function Questionnaire (IIEF-15). IIEF-15 [16] is a validated, fifteen-item questionnaire designed to diagnose the presence and severity of erectile dysfunction. Subjects will complete an IIEF-15 form at baseline and at each follow-up visit.

Male Sexual Health Questionnaire to assess Ejaculatory Dysfunction (MSHQ-EjD). MSHQ-EjD [17] is a validated, four-item questionnaire that assesses ejaculatory function and related distress or bother. Subjects will complete a MSHQ-EjD form at baseline and at each clinic visit.

Incontinence Severity Index (ISI). ISI [18] is a validated means of assessing incontinence and will assist in isolating *de novo* incontinence rather than preexisting incontinence secondary to Bladder Outlet Obstruction.

WPAI: US: is a validated six-item questionnaire that assess the effect of urinary symptoms on a subject's ability to work and perform regular activities

Concomitant Medications. All medications will be recorded on a rolling log. See Concomitant Medications below.

Concomitant Procedures. All urologic procedures that occur during follow-up will be recorded on a rolling log.

2.30 Adverse events.

The occurrence of all adverse events will be documented in all study subjects throughout the study treatment and follow-up period. AE information (start and stop date, description of event, severity, relatedness to the treatment procedure, the device itself or other study-related procedures) will be assessed and recorded on CRFs. Whether an AE meets the definition for serious adverse event will be determined by the study investigator and sponsor using the ISO 14155 definition (**Table 3**). All events consistent with an SAE must be reported to the Sponsor within 24 hours of awareness of the event. Relatedness of the AE to the surgical procedure or the study device itself will be judged by the investigator according to **Table 4**.

The classification of surgical complications shall be done per **Table 5**. Note that persistent ejaculatory or erectile dysfunction, the need for re-catheterization after postoperative day 3, and urinary incontinence related to surgery are considered to be surgical complications.

Table 3. Adverse event definitions (ISO 14155).

Term	Definition
Adverse event* (AE)	Any untoward medical occurrence, unintended disease, or injury, or untoward clinical signs in subjects, whether or not related to the investigational medical device
Serious adverse event* (SAE)	An adverse event that: a). led to a death, b). led to a serious deterioration in the health of the subject that either resulted in 1). a life-threatening illness or injury, or 2). a permanent impairment of a body structure or a body function, or 3). in-patient or prolonged hospitalization, or 4). medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function NOTE: Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration, is not considered a serious adverse event.
Adverse device effect (ADE)	An adverse event related to the use of an investigational medical device. This term includes any event resulting from insufficient or inadequate instructions for use, operation, or any malfunction, any event resulting from use error or from intentional misuse of the investigational medical device
Serious adverse device effect (SADE)	An adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event
Unanticipated Adverse Device Effect (UADE)	A serious adverse effect which by its nature, incidence, severity or outcome has not been identified in the current version of risk analysis report.

*Note that these definitions do not imply a relationship between the adverse event and the study device.

Table 4. Adverse event relatedness categories.

Term	Definition
Unrelated	No evidence that AE related to treatment procedure or device
Unlikely	While the AE could be due to a procedure or device, an alternative explanation is highly likely.
Possibly	AE is plausibly related to treatment procedure or device but an alternative explanation is more likely
Probably	AE likely to be related to treatment procedure or device even though alternative explanations are possible
Definitely	AE almost certainly related to treatment procedure or device

Table 5. Classification of surgical complications according to the modified Clavien-Dindo grading system [19].

Grade	Definition
Grade 1	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions. Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgetics, diuretics and electrolytes and physiotherapy. This grade also includes wound infections opened at the bedside.†
Grade 2	Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included.*
Grade 3	Requiring surgical, endoscopic or radiological intervention.
Grade 3a	Intervention not under general anesthesia.
Grade 3b	Intervention under general anesthesia.
Grade 4	Life-threatening complication (including CNS complications: brain haemorrhage, ischaemic stroke, subarachnoid bleeding, but excluding transient ischaemic attacks) requiring IC/ICU management.
Grade 4a	Single organ dysfunction (including dialysis).
Grade 4b	Multi-organ dysfunction.
Grade 5	Death of a subject.

*Note that the need for medications related to BPH (e.g., alpha blockers) is likely related to lack of effectiveness (not safety) and is not considered to meet criteria for a Grade 2 event.
†This includes the following: persistent ejaculatory dysfunction, erectile dysfunction or urinary incontinence and urinary retention requiring re-catheterization after 3 days post-procedure. Note that bladder catheterization itself is considered a Clavien-Dindo Grade 1 event.

2.31 Concomitant Medications

Many patients with BPH take medications for symptom control (e.g., alpha blockers, prostaglandin inhibitors, phosphodiesterase inhibitors, etc.). These medications are known to affect BPH symptom scores and marked changes in medication use could contribute to bias in assessing effect sizes. The consent form will note that changes in medications for BPH should be limited during the study's follow-up period. Concomitant medications are captured using the Concomitant Medication log in the study's EDC system.

The blinded investigator:

- Will remind the patient that changes to BPH-related medications should be minimized.
- Will not increase doses of BPH-related medications unless there is marked subject bother. If the dose of any BPH-related medication is increased, reason for increase will be recorded in the medication log.
- Will not start any new BPH-related medication unless there is marked subject bother. Reason for starting a new medication will be recorded in the medication log.
- May reduce the dose of BPH-related medications if the subject experiences drug side effects (e.g., orthostatic hypotension). Reason for decreasing the dose should be documented in the medication log.

2.32 Subject Termination or Withdrawal

Subjects may be terminated or withdrawn from the study for the following reasons:

- Voluntary withdrawal: the subject voluntarily chooses not to further participate in the study. In this case, the site will ask the subject whether he consents to having a telephone call at 12 months after treatment to assess safety and effectiveness outcomes.
- Subject death.
- Adverse event preventing study participation.
- Loss to follow-up (see below)
- At the discretion of the Principal Investigator, or where the ongoing participation of the subject involves a risk greater than perceived benefit.
- The Sponsor may terminate the study at any time.

If a subject withdraws, the site coordinator will complete a withdrawal CRF page.

2.33 Loss to Follow-Up

A subject will be considered "lost to follow up" and terminated from the study when they can no longer be reached by study staff and have missed study visits. The site must notify the sponsor of subject status and consult with them regarding discontinuation of any study subject prior to ceasing all attempts to contact subject. A subject may only be categorized as LTF if the following is true:

- Failure to complete two consecutive follow up visits (unless the missed visit is the last study visit).
- Documentation of three unsuccessful attempts by the Investigator or his/her designee to contact the subject or next of kin.

2.34 Missed Visits/Subject Accountability

Missing data within this subject cohort is expected to occur at a low rate. All efforts will be used to prevent any data from not being captured. The sites will be instructed to identify and obtain contact information for the primary care giver for the subject. Complete site training and regular monitoring will also help to minimize missing data.

In the clinical study report, the number and proportion of subjects who had each follow-up visit will be presented. Subjects who withdraw from the study will be tabulated with the reasons for the withdrawal.

2.35 Study Termination

The sponsor has the right to discontinue the study at any time for any reason.

2.36 Study Exit

The subject's participation in the study is considered complete at the end of the 36-month visit or if the subject withdraws from the study. A study exit form shall be completed.

3 STUDY ENDPOINTS

3.1 Primary Safety Endpoint

The primary safety endpoint is the proportion of subjects with adverse events rated as probably or definitely related to the study procedure classified as Clavien-Dindo Grade 2 or higher or any Grade 1 event resulting in persistent disability (e.g. ejaculatory disorder or erectile dysfunction) evidenced through 3 months post treatment. Note that the Clavien-Dindo classification scheme is for grading postoperative complications not events that reflect lack of effective treatment.

The Aquablation group will be declared to be non-inferior to TURP if it can be established that the difference in rates is statistically within the non-inferiority margin of $\delta = 0.10$ (see Statistical Analysis below). If non-inferiority is established, a test for superiority will be conducted. If it can be established that the difference is statistically greater than 0, superiority will also be claimed.

3.2 Primary Effectiveness Endpoint

The primary effectiveness endpoint is the IPSS change score from baseline to 6 months. A non-inferiority comparison will be performed using a non-inferiority margin of 4.7 points. If non-inferiority is established, a test for superiority will be conducted. If it can be established that the difference is greater than 0, superiority will also be claimed. Adjustment for interim analysis is described below.

3.3 Additional Endpoint Assessments

The following is a list of secondary endpoints intended to support product labeling. Statistical details are provided in another section.

- Reoperation or re-intervention within 6 months. Reoperation means any surgical procedure on the lower urinary tract to treat problems potentially related to BPH. Re-intervention means any invasive procedure (e.g., cystoscopy) to evaluate problems potentially related to BPH. Re-intervention excludes TRUS and urodynamics evaluations required by the study during follow-up.
- Evaluation of the proportion of sexually active subjects reporting a worsening of sexual function through 6 months on either the IIEF-15 or the MSHQ-EjD questionnaires
- Evaluation of the proportion of subjects meeting a composite of serious device or procedure related events defined as MAUE through 6 months
- Length of hospital stay (days) in the treatment groups
- Length of operative time (minutes) in the treatment groups, defined as time from pre-treatment visualization to insertion of indwelling catheter (IDC).
- Length of resection time (minutes) in the treatment groups, defined as start of first pedal activation to end of last pedal use for either Aquablation or TURP.

The following objectives are pre-specified but are not intended to support product labeling:

- Evaluation of proportion of subjects with Clavien-Dindo classification of Grade 2 or higher or any Grade 1 with persistent disability (e.g. ejaculatory disorder or erectile dysfunction) at 30 days, 6 months, and 1 year
- Evaluation of the proportion of subjects with Dysuria through 30 days
- Duration of catheterization (hours)
- Change in hemoglobin (gm/dl) at discharge from baseline
- Reoperation or Re-intervention within 30 days, 12 months, 24 months and 36 months

- Changes in the proportion of subjects using medications for BPH symptoms at month 6. An additional analysis of change in total daily dose of BPH-specific medications (e.g., alpha blockers, prostaglandin inhibitors, phosphodiesterase inhibitors, etc.) at month 6 will be performed.
- IPSS score at baseline, and 7 days, 1, 3, 6, 12, 24 and 36 months
- IPSS-QoL at baseline, and 7 days, 1, 3, 6, 12, 24 and 36 months
- Qmax at baseline, 1, 3, 6, 12, 24 and 36 months
- PVR at baseline, 1, 3, 6, 12, 24 and 36 months
- Outcome of device/procedure related serious adverse events
- Pain & dysuria score at post-op, 7, 30 days, and 3 months
- EQ-5D at baseline, and 7 days, 1, 3, 6, 12, 24 and 36 months
- ISI at baseline, at post-op, 7 days, 1, 3, and 6 months
- IIEF-15 at baseline, and 7 days, 1, 3, 6, 12, 24 and 36 months
- MSHQ-EjD at baseline, 7 days, 1, 3, 6, 12, 24 and 36 months
- WPAI:US at baseline, 7 days, 1, 3, 6, 12, 24 and 36 months
- Pdet@Qmax at baseline and 6 months
- Change in categorization, by treatment group, of subjects from obstructed to unobstructed or unobstructed to obstructed. The determination of "obstructed" and "unobstructed" is based on Chapple [20]
- Use of cautery immediately post Aquablation. Cautery use will be assessed as minutes from cautery start to stop and total amount of "on time".
- Number of subjects in whom re-catheterization was needed between discharge after the index procedure and month 3. Re-catheterization is defined as the need to place a urinary catheter in the bladder for symptoms related to BPH. This excludes re-catheterization for study purposes or for purposes unrelated to LUTS.
- Amount of irrigation fluid used intraoperatively (liters)
- Number of subjects in whom postoperative irrigation started
- Amount of Fluid used postoperatively (liters)
- Duration of postoperative irrigation (hours)
- Subset analyses of the following variables by treatment and baseline IPSS scores of < 20 and ≥ 20, as well as by treatment and baseline prostate size of < 45g and ≥ 45g:
- IPSS score at baselines, and 7 days, 1, 3, 6, 12, 24 and 36 months
- IPSS-QoL at baseline, and 7 days, 1, 3, 6, 12, 24 and 36 months
- Qmax at baseline, 1, 3, 6, 12, 24 and 36 months
- PVR at baseline, 1, 3, 6, 12, 24 and 36 months
- Operative time (minutes)
- Resection time (minutes)
- Evaluation of proportion of subjects with Clavien-Dindo classification of Grade 2 or higher or any Grade 1 with persistent disability (e.g. ejaculatory disorder or erectile dysfunction) at 30 days, 3 months, 6 months, and 1 year

4 STATISTICAL CONSIDERATIONS

4.1 Primary Statistical Objective

The primary objective of this study is to demonstrate non-inferiority in the safety and effectiveness of the Aquablation and TURP in the treatment of BPH in men 45 - 80 years of age. Both the primary safety and primary effectiveness endpoints must be met in order to consider the Study a success.

4.2 Primary Effectiveness Endpoint Calculation

The primary effectiveness hypothesis a non-inferiority comparison of the mean change in IPSS score from baseline to 6 months across groups using a non-inferiority margin of 4.7 points. This type of comparison is consistent with FDA guidance [14].

For the primary effectiveness endpoint, the null hypothesis is that the mean IPSS change score for Aquablation is inferior to that for TURP, using a non-inferiority margin of 4.7 points.

The alternative hypothesis is that the mean IPSS change score for Aquablation is non-inferior to TURP, using a non-inferiority margin of 4.7 points.

These hypothesis statements are written as follows:

$$H_O: \mu_C - \mu_T <= -\delta$$

$$H_A: \mu_C - \mu_T > -\delta$$

where μ_T and μ_C represent the mean changes in IPSS (from baseline to 6 months) for the treatment and control groups, respectively. Negative changes from baseline represent patient improvement under this design. The pre-specified non-inferiority margin (δ) is 4.7 points. The hypothesis will be tested with one-sided overall type I error controlled at 0.025 using an O'Brien-Fleming-type spending function to account for possible early stopping with a single interim analysis when all subjects are through 3 months of follow-up.

Aquablation will be declared non-inferior to TURP if it can be established that the difference in change in IPSS score between the two groups is within the non-inferiority margin of $\delta = 4.7$ points. If non-inferiority is established, a test for superiority will be conducted. If it can be established that the mean difference is statistically greater than 0 points (i.e. $\mu T > \mu C$), superiority will also be claimed.

Justification for 4.7 point Non-Inferiority Margin (NIM): As outlined in the BPH guidance document,[2] for non-inferiority studies, the hypothesis should incorporate a non-inferiority delta level that reflects a maximum tolerable difference that is "clinically insignificant" (i.e., "not clinically meaningful") in the analysis of the primary endpoint. Larger values of the non-inferiority delta level are usually supported by demonstrating significant benefits in the safety of the investigational device. In addition, the draft FDA guidance for non-inferiority trials advises that the non-inferiority margin must be no larger than the entire assumed treatment effect of the active control (i.e. TURP) and should reasonably rule out an effect in a placebo arm had there been one [20].

Barry et al[3], further corroborated by Roehrborn et al[4], evaluated the minimum change from baseline in symptom score required for patient perception on benefit and demonstrated that the magnitude of improvement in symptom score required for patient perception of change was correlated with the subjects baseline score. Subjects with a higher score at baseline require a greater decrease in symptom score to obtain the same level of satisfaction when compared to subjects with a lower symptom score at baseline (Table 6 below).

[2] http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm223664.pdf
[3] Barry, MJ, Willifred WO, Chang Y, et al., **Benign prostatic hyperplasia specific health status measures in clinical research: How much change in the American Urological Association Symptom Index and the Benign Prostatic Hyperplasia Impact Index is perceptible to patients**. J Urol, 1995, 154:1770-1774.
[4] Roehrborn, Claus G.; Wilson, Timothy H.; Black, Libby K. **Quantifying the Contribution of symptom improvement to satisfaction of men with moderate to severe benign prostatic hyperplasia : 4-year data from the CombAT trial.** Journal of Urology, 2012. Vol. 187, No. 5, p. 1732-1738.

TABLE 6: Mean absolute changes in AUA symptom and BPH impact index scores for each level of self-rated global improvement for subjects with lower versus higher baseline scores[2]

Pt Assessment of Improvement	***Mean Absolute Change +/- SEM (No Patients) in AUA Symptom Index***	
	Lower Baseline Scores*	***Higher Baseline Scores****
Marked	-7.4 ± 0.29 (183)	-16.3 ± 0.76 (40)
Moderate	-4.0 ± 0.29 (227)	-8.7 ± 0.62 *(70)*
Slight	-1.9 ± 0.29 (252)	-6.1 ± *0.54* (95)
None	-0.2 ± *0.35* (184)	-2.0 ± 0.62 (69)
Worse	+3.3 ± 1.09 (17)	+1.2 ± 1.79 (7)

*** Lower baseline score 8 to 19 points, higher baseline score *20* to 35 points.**

Given that this perception of meaningful change is variable relative to baseline IPSS, the appropriate NIM for the WATER trial is derived from the expected baseline of the study population and the data from the Barry study regarding Mean Absolute Change in AUA Symptom Index required for slight improvement (lower baseline scores 8-19 points, AUA-SI change of 1.9 points; higher baseline scores 20-35 points, AUA-SI change of 6.1 points). Data available from prior studies (Procept and other BPH device trials) supports that a reasonably conservative estimate of distribution of subjects between the lower baseline scores (12-19) and higher baseline scores (20 and above) is 33% lower baseline and 67% higher baseline. Applying this distribution of baseline symptom score to the data from Barry et al, we calculate the appropriate NIM for the WATER study to be 4.7 points (1/3*1.9 + 2/3*6.1).

The treatment effect observed in SHAM controlled trials for other devices is approximately 6 points [21] [22]. In addition, the placebo control arm rates for drug studies range from 2-5 point reduction in symptoms [23]. Provided the lower bound of the one-sided 97.5% confidence interval of the difference between treatment groups exceeds 6 points, we can reasonably rule out the effect that might be associated with a drug placebo or a SHAM procedure. The change in IPSS score from baseline expected with the proposed active control TURP is estimated at 15 points [24], [25], [26], [27]. A symptom improvement of approximately 1.5 points less for PROCEPT with a lower bound of a one-sided 97.5% confidence interval of 4.7 points less for PROCEPT than TURP (e.g. an Aquablation improvement in IPSS of >10 points including the lower bound of the one-sided 97.5% confidence interval) is clinically meaningful and is in line with the treatment effect reported in trials for other approved devices (improvement of 6-13 pts for TUMT and UroLift [21], [22], [28], [29]).

4.3 Primary Safety Endpoint Calculation

The primary safety endpoint will test the proportion of subjects meeting the primary safety endpoint through 3 months post treatment. The hypothesis of interest for the primary safety endpoint is:

$$Ho: P_C - P_T <= -\delta$$

$$Ha: P_C - P_T > -\delta$$

where P_T and P_C represent proportions of treatment and control subjects, respectively, who meet the primary safety endpoint. Analysis of the primary safety hypothesis will be conducted using a z-test of proportions with a pooled variance and continuity correction, using a non-inferiority margin of 10% and a one-sided significance level of 0.025. If non-inferiority is established, a test for superiority at a significance

level of 0.025 will be conducted. If it can be established that the rate difference is statistically greater than 0, superiority will also be claimed.

4.4 Sample Size Considerations and Statistical Analyses

The WATER Study is designed as a prospective, randomized, blinded, controlled trial to demonstrate non-inferiority of the AQUABEAM System to TURP with respect to symptom improvement at 6 months. The WATER Study is designed in accordance with FDA's "Guidance for Non-Clinical and Clinical Investigation of Devices Used for the Treatment of Prostatic Hyperplasia (BPH)," published August 17, 2010.

Subjects will be randomly assigned in a 2:1 ratio to treatment with Aquablation or to treatment with TURP. The Primary Effectiveness Endpoint for this clinical trial is change in IPSS from baseline to 6-month evaluation.

Minimum enrollment (N_{min}) in the WATER trial is 177 subjects (118 Aquablation and 59 TURP) to power at 80% for possible demonstration of superiority for the safety endpoint under an assumption of an endpoint rate of 65% in TURP and 40% in Aquablation, while including a 12% lost to follow-up rate (i.e., 156 evaluable subjects). The primary safety endpoint with 156 subjects evaluable displays over 99% power at a one-sided alpha level of 0.025 to demonstrate non-inferiority within a margin of 10% under an assumption of a true rate of events in the Aquablation group of 40% and expected rate of 65% in the TURP group.

Under an assumption of an effectiveness NIM of 4.7 points and a treatment effect of -1.5 points (i.e., mean change score in Aquablation is 1.5 points lower than TURP) with a standard deviation of 6 points, the sample size of 156 evaluable subjects provides more than 80% power in a test of non-inferiority for the primary effectiveness endpoint.

The trial will utilize a group sequential design with a single interim look and will incorporate a sample size re-estimation (SSR) at the time of the interim look based on promise for superiority on effectiveness. Methods for the SSR have been described in detail [30] [31].

An O'Brien-Fleming (OBF) alpha-spending function will be employed to control for type I error rate on the primary effectiveness endpoint. The maximum enrollment being considered is 270 total enrolled (N_{max} = 1.5 times N_{min}).

An interim analysis incorporating a SSR will take place when all 177 subjects have been enrolled and completed the 3 month evaluation. The analysis will be performed by an independent statistician with a Data Monitoring Committee (DMC) review. Under the enrollment projection, it is assumed that 67% of the subjects will have completed the 6 month assessment at the time of the interim analysis. At this point, the non-inferiority test for primary effectiveness under an OBF alpha-spending function will be computed. Based on this result, the conditional power to claim superiority (CP_{sup}) on the primary effectiveness endpoint will also be computed. The conditional power (CP_{sup}) will be calculated based on the interim results of the primary effectiveness endpoint, with the specific interest of demonstrating superiority. CP_{sup} is defined as the approach that quantifies the statistical power to yield an answer different from that seen at the interim analysis. The data will be partitioned into three zones based on CP_{sup} unfavorable zone (CP_{sup}<40%), promising zone (40%≤CP_{sup}<80%), and favorable zone (CP_{sup}≥80%). The following decision rules outline the possible outcomes of the interim analysis:

(i) If the test for non-inferiority for primary effectiveness under an OBF alpha-spending function fails to reject the null hypothesis, there is no increase in sample size and the submission for the primary analysis will take place when all subjects have completed 6 months follow-up.

(ii) If the test for non-inferiority for primary effectiveness under an OBF alpha-spending function rejects the null hypothesis, and if CP_{sup} <0.4 or ≥0.8, then there is no increase in the sample size and the study will be submitted to FDA based on the outcome from the interim analysis.

(iii) If the test for non-inferiority for primary effectiveness under an OBF alpha-spending function rejects the null hypothesis, and if $0.4 \leq CP_{sup} < 0.8$, then the sample size will be increased by just the right amount such that CP_{sup} is increased to 0.8, under a cap of 270 subjects. The range $0.4 \leq CP_{sup} < 0.8$ is called the promising zone for superiority. Specifically, if CP_{sup} is in its promising zone, this decision rule increases the sample size by the smaller of 270 patients or the number needed to boost CP_{sup} to 0.8.

The testing of the safety endpoint for non-inferiority occurs a single time at the time of submission. All safety data will be complete regardless of the outcome of the sample size adaptation and therefore does not require a type-I error adjustment. If the hypothesis for non-inferiority of the safety endpoint is rejected, a test for superiority of the safety endpoint will take place. A decision tree based on the testing of the effectiveness endpoint is outlined below in Figure 10.

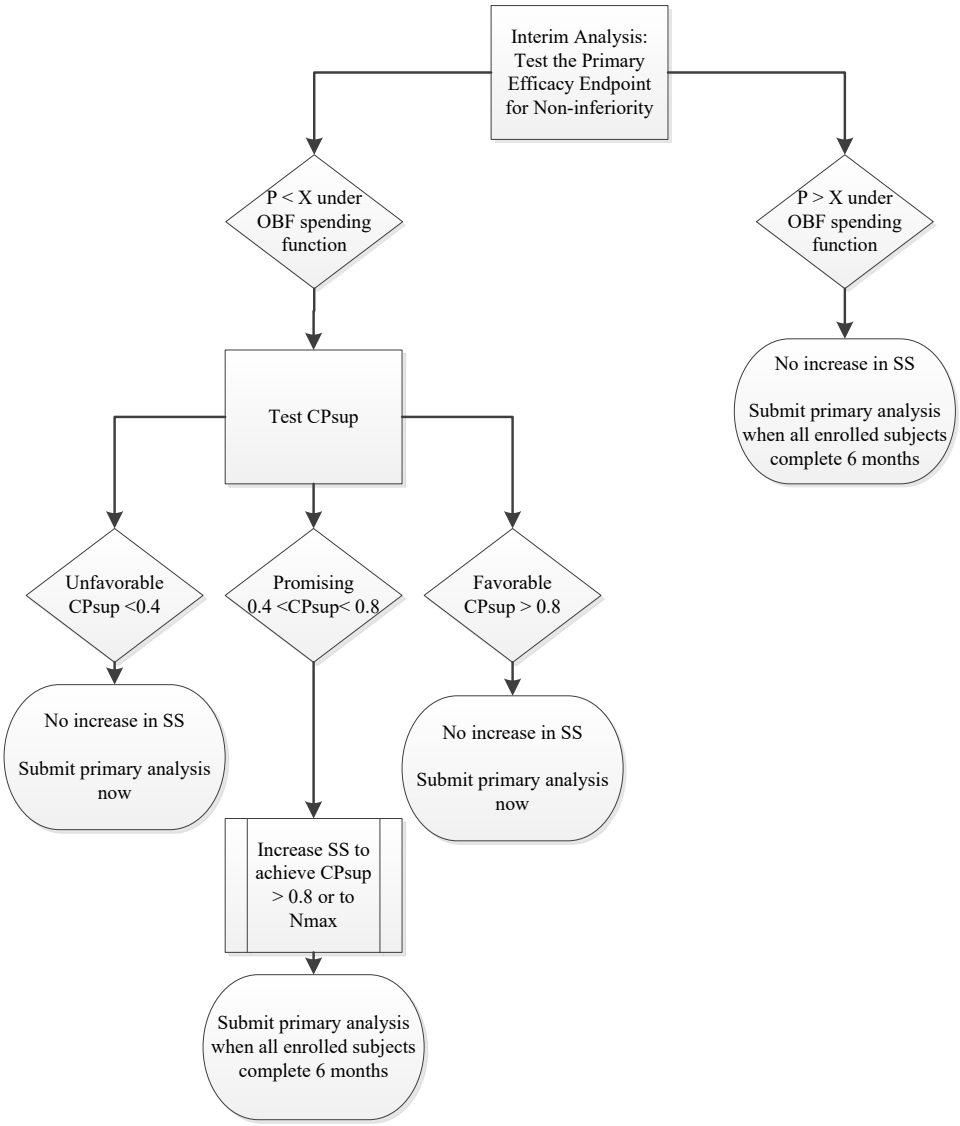


Figure 10: Decision tree for group sequential interim analysis with SSR

A final clinical study report will be produced and submitted when all subjects have completed the 36-month follow-up visit or have exited the study.

Full details of statistical analyses will be outlined in the Statistical Analysis Plan (SAP).

4.5 Study Populations for Analysis

4.5.1 Modified Intent-to-Treat (mITT)

The mITT analysis population includes all randomized subjects in whom an intended intervention is initiated. If a patient is found at the time of the procedure to have a condition that results in study exclusion, this patient does not contribute to the mITT cohort. Subjects will be analyzed according to their randomized group assignment. The mITT population is the primary analysis population for both the primary and secondary endpoints.

4.5.2 Per-protocol (PP)

The per-protocol (PP) population will consist of all mITT subjects that:

1. meet critical study eligibility criteria;
2. have no significant protocol deviations; and
3. have evaluable assessment for the primary study endpoints. The PP population will be used for subset analysis of the primary endpoints.

A significant protocol deviation means non-adherence on the part of the subject or investigator to clinically significant protocol-specific inclusion/exclusion criteria, primary objective variable criteria, and/or GCP guidelines.

4.5.3 Safety

The safety analysis population includes all randomized subjects. Secondary safety endpoints including the summary of adverse events in the trial will be analyzed using this analysis population, divided into groups according to actual treatment received.

4.6 Additional Endpoints

The following secondary objectives are intended to support product labeling. The endpoints will be tested in sequential fashion using the Holms step-down procedure for type-I error rate correction if and only if the primary objective passes according to the non-inferiority criteria outlined above. At the conclusion of the trial, the secondary endpoints intended for product labeling will be ordered sequentially from most significant to least significant. The endpoints will then be tested in order at adjusted levels of significance (i.e. E1: 0.05/k, E2: 0.05/k-1; E3: 0.05/k-2; E4: 0.05/k-3; E5: 0.05/k-4;, where k=number of specified endpoints). Once an endpoint fails, all following endpoints will not be tested. Following is a list of secondary endpoints intended to support product labeling:

- Evaluation of the proportion of subjects requiring re-operation and re-intervention through 6 months. The following hypothesis will be tested:

  $$H: P_C - P_T > -\delta$$

  where P_T and P_C represent proportions of subjects requiring re-operation or re-intervention through 6 months post treatment. The Aquablation group will be declared to be non-inferior to TURP if it can be established that the difference is within the non-inferiority margin of $\delta = 0.10$. The statistical test will be a z-test using pooled variance estimate and no continuity correction. In the case of small counts, an exact procedure will be used. Descriptive statistics and 95% confidence intervals will be calculated.

- Evaluation of the proportion of sexually active subjects reporting a worsening of sexual function through 6 months defined as a decrease of 6 points or more on the IIEF-5 (part of the IIEF-15) or a decrease of 2 points or more on the MSHQ-EjD questionnaires. The following hypothesis will be tested:

  $$Ho: P_T = P_C$$

  $$Ha: P_T < P_C$$

  where P_T and P_C represent proportions of subjects with worsening score on the IIEF-5 and/or the MSHQ-EjD from baseline through 6 months post treatment. The statistical test for superiority will be a z-test using pooled variance estimate and no continuity correction. In the case of small counts, an exact procedure will be used. Descriptive statistics and 95% confidence intervals will be calculated.

- Evaluation of the mean length of hospital stay in the treatment groups. The following hypothesis will be tested:

  $$H: \mu_T - \mu_C > 0$$

  where μt and μc is the average length of stay in days in the treatment and control groups, respectively. Statistical summaries will include means, medians, and standard deviation, as well as 95% confidence intervals. A t-test for superiority will be performed to test the hypothesis that μt is significantly less than μc.

- Evaluation of the mean length of operative time in the treatment groups. The following hypothesis will be tested:

  $$H: \mu_T - \mu_C > 0$$

  where μt and μc is the average operative time in minutes in the treatment and control groups, respectively. Statistical summaries will include means, medians, and standard deviation, as well as 95% confidence intervals. A t-test for superiority will be performed to test the hypothesis that μt is significantly less than μc.

- Evaluation of the mean length of resection time in the treatment groups. The following hypothesis will be tested:

  $$H: \mu_T - \mu_C > 0$$

  where μt and μc is the average operative time in minutes in the treatment and control groups, respectively. Statistical summaries will include means, medians, and standard deviation, as well as 95% confidence intervals. A t-test for superiority will be performed to test the hypothesis that μt is significantly less than μc.

4.7 Handling of Missing Data

All practical monitoring and follow-up steps will be taken to ensure complete and accurate data collection. Missing observations will be described in detail and evaluated for assessment of possible bias.

It is assumed that data will be missing at random. However, to examine this assumption, an analysis will be performed to compare baseline characteristics and symptomatic status (at earlier time points) between those participants with missing data and those who completed the study. Any missing observations will be described in detail and evaluated for assessment of possible bias.

For the primary effectiveness analysis, missing data will be imputed using the method of multiple imputation, with regression models that include relevant baseline covariates and the 3 month IPSS score

(if available). Missing safety outcome data will be imputed using a similar multiple imputation method. A detailed description of the multiple imputation models including the full set of covariates to be used in the imputation model will be outlined in the SAP.

For the primary safety endpoint, a missing data sensitivity analysis will also be performed by comparing analyses using the following approach:

1). Available data only
2). "missing-equals-failure"
3). "missing-equal-success"
4). Last observation carried forward (LOCF)

For the primary effectiveness endpoint, a sensitivity analysis will be performed using:

1). LOCF
2). Same as baseline

In addition, a tipping point analysis will be performed for the primary study endpoints which will allow assessment of sensitivity without need for postulating any missing data mechanism. For the safety tipping point analysis, all possible combinations of missing data from the two arms will be considered, and the point at which significance is no longer achieved will be identified.

The planned sensitivity analyses for the primary outcome in the primary analysis population will be described in further detail in the SAP.

All data collected on safety or adverse events will be reported to the extent it is available, regardless of the active/withdrawn status of participants.

4.8 Pooling of Site Data

The homogeneity of safety and effectiveness results across study sites will be examined and if no statistically significant heterogeneity is found, the results will be pooled. The primary justification for pooling is that study sites will be following the same Protocol, using the same device system, and following the same Instructions for Use/User Manual. Additionally, frequent contact and monitoring of the sites will be performed to ensure that all Study sites are evaluating participants and recording study results in a reliable and reproducible manner. It is not anticipated that any individual study site will dominate the study results. Therefore, it is believed that these procedures will help to ensure that the data from these study sites can be combined and analyzed as if generated at a single site.

To evaluate differences among sites in the study, a summary of important baseline variables, such as demographics, medical history and baseline clinical variables, will be presented by site to allow for easy comparison. Additionally, the summary will provide non-baseline variables by site and by treatment group for comparison of procedure variables and variables related to the primary and secondary endpoints.

For the primary effectiveness endpoint, analysis of variance or other methods will be used to determine heterogeneity of effect sizes across site. For the primary safety endpoint, heterogeneity will be assessed using logistic regression and a site × treatment interaction term or similar test. If evidence of non-poolability is found, baseline and procedural variables found to be different between sites will serve as predictors in a logistic or linear regression that also includes as predictors the treatment assignment, site, and site-by-treatment interaction.

It is also noted that the evaluation of site effect will consider OUS (outside US) versus U.S.-based sites. Thus, another analysis of the site effect will consider the comparison between the results for these two geographical regions in order to determine whether this had an effect on the study findings.

Further explanation on poolability analyses will be described in the SAP.

5 RISK/BENEFIT ANALYSIS

The study protocol has been designed to provide the greatest benefits while assuring the safety of participating subjects by mitigating the occurrence, limiting the severity and ameliorating the effects of any possible adverse events. The following describes the benefits subjects will receive as well as possible adverse events which have been identified as risks and for which subjects will be carefully monitored.

5.1 Benefits

The primary potential benefit of participation is the potential occurrence of successful treatment of BPH using the study device. Additional benefits may be decreased pain, decreased need for urinary catheter postoperatively, and faster overall recovery.

5.2 Risks

Participation in this clinical study may expose the subject to the following potential risks associated with the device and/or the procedure:

- **General or Spinal Anesthesia**

There is a potential risk of developing side effects associated with the use of anesthesia. The risks of anesthesia depend on the type of anesthesia (spinal or general), and agents and/or gases used. The risks of anesthesia include respiratory acidosis and possible respiratory depression or failure, shortness of breath, postoperative pain, hematoma (bleeding around spinal column), spinal infection (meningitis or abscess), nausea and vomiting, dizziness, drowsiness, itching, shivering, liver toxicity, sore throat or damage to throat, teeth, or vocal cords, seizures, stroke (cerebrovascular accident) or temporary loss of normal blood flow to the brain (transient ischemic attack), arrhythmia, tachycardia, trauma to the teeth or tongue, cardiovascular events, and death.

Trained professionals with extensive experience and expertise who routinely administer general anesthesia with moderate sedation to subjects will be responsible for the induction and associated monitoring required for this study. In addition, study subjects will be monitored throughout the recovery period as well after the recovery period.

- **Intraoperative risks from the TURP or Aquablation procedure**

There is a potential risk of bladder perforation or rupture, bleeding, blood vessel damage, capsular perforation, electric shock/burn, fluid overload, embolism, urethral damage causing a false passageway, urethral stricture or adhesions, and puncture of or damage to non-urinary systems.

- **Postoperative risks from the TURP or Aquablation procedure**

After the operation, there is the potential for decrease in kidney function (renal compromise, renal failure), fatigue, fever, headache, infection, abdominal pain, pelvic or buttocks pain, other muscle pain/spasms, numbness, scrotal edema or bruising, penile bruising, trauma or edema, meatal stenosis, edema, hematoma, and swelling, pain, or irritation of the bladder, perineum, prostate, and urethra. Other risks include bladder problems or damage including but not limited to reduced bladder sensation, incontinence, residual urine, bladder distention, spasm, and bladder neck contracture or stenosis. Additional post-operative risks include rectal incontinence or stenosis, urethritis, urine flow decrease, hematuria, transfusion, nocturia,

and urinary symptoms such as dysuria, increased frequency, hesitation, retention, or urgency. There may also be sexual or reproductive side effects such as erectile dysfunction, painful erection, retrograde ejaculation, infertility, decreased potency, impotence, penile disorder or numbness, decrease or loss of sexual desire, and loss of orgasm.

The following are potential risks that are associated with the tests or procedures required as part of the study conduct:

- **Blood draws**

The risks of blood draws include temporary pain and discomfort from the needle stick, and/or tenderness, redness or bruising at the site, bleeding, fainting and lightheadedness. While rare, there is a possibility of infection or a local blood clot.

- **Urodynamic testing**

Risks include temporary, mild irritation of the urethra, and infection.

- **Transrectal Ultrasound (TRUS)**

The risks of TRUS include rectal pain, soreness or bruising, edema, bleeding, perforation, and infection.

- **Cystoscopy**

The risks of cystoscopy include pain, dysuria, damage to the ureteral orifice, perforation or tearing of the urethra, bleeding, and infection.

5.3 Risk Mitigation

Risks during study participation will be minimized by the following:

- Clearly defining the subject inclusion/exclusion criteria.
- The site was chosen because of proven expertise in the field of urological surgery.
- The investigator will receive specific training and instruction in the use of the study device.
- Study subjects undergo intensive monitoring throughout the study by a multidisciplinary team.
- Pre-clinical, in vitro and in vivo testing has been performed in order to optimize the device safety and function.
- Clinical testing in previous human subjects has been performed in order to optimize the device safety and function.

6 STUDY ADMINISTRATION

6.1 Clinical Events Committee

An independent Clinical Events Committee (CEC), consisting of three physicians who are not study Investigators will be utilized for this trial. This CEC will be responsible for the review and adjudication of reported adverse events related to the device or the procedure that occur over the course of the study per the CEC Charter. Additionally, the CEC may adjudicate other events at the request of the Data Monitoring Committee or Sponsor. The CEC adjudicators shall classify (assign relatedness) the above described adverse events based on severity and association to the procedure or other attribution.

Device- or procedure-related events which are associated with the primary safety endpoint analysis will be as adjudicated by the CEC. In the event the CEC differs from the Investigator in classification of events, the resulting CEC adjudication will be used for final analysis and reporting. Any difference between how

the CEC assigns seriousness or relatedness compared to the Investigator will be communicated to the Investigator.

During the review of events, the CEC shall be blinded to the clinical site and study subjects as much as possible. A CEC Charter will be developed prior to the start of study enrollment. The CEC Charter shall include consistent definitions for each type of event and shall outline the review process.

6.2 Data Monitoring Committee

The Data Monitoring Committee (DMC) will consist of a minimum of three (3) members and this group shall also act as the steering committee chartered with advising the sponsor on the design and execution of the study, monitoring the overall implementation of the study, including subject enrollment and protocol compliance, and reviewing final study data.

Membership will include only independent members and therefore will not include a study investigator or a representative from the sponsor. The DMC meetings will consist of open and closed sessions (i.e. "open" denotes sponsor staff present; "closed" denotes without sponsor staff present).

The sponsor or designate will provide the DMC with reports related to subject enrollment, procedural outcome, follow-up visits, adverse events and any other material the DMC may deem necessary to carry out its responsibilities as established at the outset of the committee in the DMC charter. The DMC will assess if early evidence exists for dramatic benefit or harm for subjects while the clinical study is in progress. The DMC will make recommendations to the sponsor concerning continuation, modification or termination of the study.

The DMC will be blinded to both the investigative sites and investigators to minimize bias. The DMC will establish and maintain a Charter detailing specific operating procedures. The DMC will review the proposed interim analysis plan and interim analysis results.

Names and contact information for all DMC members will be on-file at the sponsor and available on request.

6.3 Data Collection/Electronic Case Report Forms (e-CRF)

Case report forms will be used to collect all subject data during the study within the EDC system and are referred to as e-CRFs. The EDC system enables rapid data acquisition and cleaning through extensive data checking and query processing. Monitor visits will be conducted in regular intervals through the study based upon site enrollment rates.

Data will be entered in to a secure EDC system, which allows 21 CFR Part 11 compliance. Subjects follow up visits data will be entered directly by the site with corresponding source documents maintained at the site level.

6.4 Clinical Monitoring

The study will be monitored to ensure that applicable regulations are followed. Written procedures will be established by PROCEPT BioRobotics or their authorized designee to ensure the quality of the study and to ensure that each person involved in the monitoring process carries out the required duties.

Prior to subject enrollment, a study initiation visit will be completed at each investigational site to ensure the following:

- IRB approval has been obtained and documented
- The Investigators and study personnel are appropriately trained and clearly understand the study

- The Investigators and study personnel accept the obligations incurred in undertaking this clinical investigation.

Periodic monitoring visits will be made at all active study sites throughout the clinical study to assure that the Investigator obligations are fulfilled and all applicable regulations and guidelines are followed. These visits will assure that the facilities are still acceptable; the protocol and investigational plan are being followed, the EC/IRB has been notified of approved protocol changes as required, complete records are being maintained, appropriate and timely reports have been made to the Sponsor and the EC/IRB, device and device inventory are controlled and the Investigator is carrying out all agreed activities.

Typically, source-document verification of eCRFs will be done shortly after the eCRFs are completed. A study termination visit will be conducted at the completion of the clinical investigation to ensure that all subject data are properly documented and that all clinical materials are returned to PROCEPT BioRobotics.

If a clinical monitor becomes aware that an Investigator is not complying with the signed Investigator's Agreement, the Investigational Plan, the requirements of 21 CFR 812/ISO 14155 (if relevant) or other applicable regulations, or any conditions of approval imposed by the IRB/EC, PROCEPT BioRobotics will either secure compliance or discontinue shipments of the device to the Investigator and terminate the Investigator's participation in the investigation.

7 STUDY REPORT AND PUBLICATION STRATEGY

7.1 Final Study Report

A Final Study Report will be prepared by PROCEPT BioRobotics with the assistance of the independent safety reviewer, which will be reviewed, approved and signed by the Investigator, and will contain clinical comments based on the data contained in the CRFs.

7.2 Publication Strategy

The study will be registered with www.clinicaltrials.gov, as recommended by the International Committee of Medical Journal Editors.

The Principal Investigator agrees to provide copies of any and all proposed manuscripts to PROCEPT BioRobotics at least 30 days in advance of submitting such proposed manuscripts to a publisher or other third party to evaluate the proposed manuscript for the following purposes:

a) For accuracy and consonance with the study database
b) To ascertain whether confidential information or other proprietary information of PROCEPT BioRobotics (including trade secrets and patent protected materials) is being inappropriately utilized and/or released
c) To provide Principal Investigators with information which may not yet be available to them
d) To provide input from other Investigators and Co-Investigators in the study, if any, regarding the content and conclusions of the proposed manuscripts.

For the avoidance of doubt, PROCEPT BioRobotics may not require any amendments to be made to the clinical data, omissions to be made to it or amendments to the Principal Investigator's interpretation thereof. The decision as to whether to amend the manuscript to include any or all of the opinions or information provided by PROCEPT BioRobotics remains that of the Principal Investigator.

If PROCEPT BioRobotics makes a good faith determination, within such 30-day period, that the publication or presentation would be detrimental to its intellectual property interests, the Principal Investigator shall refrain from submitting such proposed manuscript to a publisher or other third party for

another 365 days or such earlier time that notifies PROCEPT BioRobotics to allow time to file PROCEPT BioRobotics patent applications or take other steps to protect its intellectual property interests.

8 DEFINITIONS

Hematuria Categorized as an Adverse Event – Subjects who require any of the following:

- Extended catheterization beyond 3 days
- Repeat catheterization beyond three days post treatment
- Extended Hospitalization – per hospital standard of care (Serious Adverse Event)
- Blood transfusion (Serious Adverse Event)

Non-Reportable Events - Mild to moderate symptoms that are typically associated with the usual post-operative course including but not limited to dysuria, decreased urinary flow, gross hematuria within 7 days post treatment.

Post Treatment Catheterization Rate – The proportion of participants who are catheterized within 3 days following treatment with the AQUABEAM System.

Urinary Retention Adverse Event – Subjects who present beyond three days post treatment and are unable to void requiring catheterization to resolve their symptoms.

Urinary Incontinence – Subjects who didn't require incontinence pads prior to Aquablation treatment and require more than 1 incontinence pad per day post-treatment.

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