Minimally Invasive Prostatic Vapor Ablation - Multicenter, Single Arm Study for the Treatment of BPH in Large Prostates (Rezūm XL)

Protocol No. 3034-001 Rev 05

Approvals: Signatures on File

Authored by:	Andrea Stone		
	Clinical Program Manager	Signature	Date
Reviewed by:	Kevin Hagelin		
	Clinical Program Manager	Signature	Date
	Cindy B. Ogden		
	Director, Clinical Operations	Signature	Date
	Sara Petrie		
	Quality & Regulatory	Signature	Date

Revision History

Revision	Date	Description
01	October 2016	Initial IDE submission
02	December 2016	1. Inclusion/Exclusion Criterion Changes: a. Changed Exclusion #14 b. Combined Exclusion numbers 29, 30, 31, 32, 33, and 34. c. Added Exclusion #33 2. Modified section 9.1 to eliminate washout and introduced wash in period 3. Modified section 9.5.1 to allow subjects to continue to stay on BPH medications after the procedure under the physician's discretion up to 3 months.
03	November 2017	1. Increased sample size from 40 to 88 subjects 2. Moved the 4 week follow-up visit to a 6 week follow-up visit 3. Increased active sites from 6 to 7 4. Lowered Inclusion PVR to 300ml 5. Exclusion Criteria updated and sorted into body system categories 6. Modified Primary Efficacy Endpoint Responder rate from 40% to 50% per the request of the FDA 7. Added Primary Safety Endpoint per the request of the FDA. 8. Added Ancillary Endpoint A6: PGI-I Questionnaire 9. Updated list of abbreviations per protocol changes 10. Added a Retroperitoneal Ultrasound at baseline, 2 weeks (if abnormal blood draw) and 6 weeks. 11. Section 11.2 Urodynamics: Defined "poor detrusor muscle function 12. Added Section 11.7: Retroperitoneal Ultrasound defining the parameters of the imaging 13. Added Section 14.3 and 14.3.1 Defining that Tissue Blanching, Edema and Erythema in the urethral lining and prostatic tissue are anticipated thermal therapy effects. 14. Added Section 14.10 Independent Review of Retroperitoneal Ultrasound (renal and bladder) 15. Clarified section 9.3.3 that the stopping rule pertains to 6 weeks post procedure among the first 20 subjects 16. Defined "intervention" in section 9.3.3 17. Added the requirement of a flexible cystoscopy post procedure in section 10.4.2 18. Modified Table 10-2 to include post procedure flexible cystoscopy, addition of Abdominal and Pelvic Exam, CT scan and urine culture at 2 and 6 weeks

		19. Section 11.7 removed wording of perforation and fistula assessment through retroperitoneal ultrasound 20. Added Section 11.8 Genitourinary Perforation and Fistula Formation to assess perforation and fistula assessment at the 2 and 6 week visits through Abdominal and Pelvic exams, urine culture and CT scan if necessary 21. Section 12.2 added Grade 4 hydronephrosis to the primary safety endpoint list 22. Section 14.0 Definition of Adverse Events – clarified all adverse events will be reported 23. Updated the potentially anticipated adverse event list in section 14.4 24. Section 19.1 Clinical Events Committee – clarified all AEs and SAEs should be reported and adjudicated
04	February 2018	1. Added Grade 2 Hydronephrosis as exclusionary criteria #17 2. Modified Prostate cancer testing exclusionary criteria eliminating MRI and PSA Velocity parameter language 3. Modified Primary Safety Endpoint from Grade 4 to Grade 2 Hydronephrosis 4. Clarified section 9.3.3 definition of stopping rule to include the words “hospitalization” and “bladder” 5. Table 10-1 eliminating MRI and PSA velocity parameter language 6. Modified footer #4 in Table 10-2 to include “other exams deemed necessary” 7. Modified Section 10.6 to clarify subjects whom discontinue BPH medications post procedure and resume prior to their 6 month follow-up will be a treatment failure 8. Added language in section 11.8 to allow other evaluations deemed necessary to rule out perforations of the GI or GU 9. Section 12.4.2 Secondary Endpoint S2 performance goal was changed from 5.4 to 6.0 10. Updated 24 month data in Table 8-2 11. Modified exclusion criteria#18 by removing PSA > 10ng/ml unless prostate cancer is ruled out by biopsy

05	October 2018	1. Change US site total from 6 to 10. Totaling 11 active US and AUS sites. 2. Remove baseline interval of PGI-I test 3. Changed Sponsor name and contact information from NxThera to NxThera, a Boston Scientific Company due to company acquisition 4. Addition of mandatory UA prior to procedure 5. Standardization of antibiotics pre and post catheterization removal 6. Addition of scale of Severity of Adverse Events

Minimally Invasive Prostatic Vapor Ablation - Multicenter, Single Arm Study for the Treatment of BPH in Large Prostates (Rezūm XL)

CLINICAL STUDY PROTOCOL:

3034-001 Revision 05

October 2018

SPONSOR:

NxThera, a Boston Scientific Company
10700 Bren Rd. W
Minnetonka, MN 55343

This study will be conducted in compliance with the protocol and applicable regulatory requirements.

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Protocol Signature Page

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October 2018

I have read this protocol and agree to adhere to the requirements. I will provide copies of this protocol and all pertinent information to the study personnel under my supervision and my hospital Ethics Committee/Institutional Review Board (EC/IRB). I will discuss this material with them and ensure they are fully informed regarding the conduct of the study according to this protocol, applicable regulatory requirements, and hospital EC/IRB requirements.

I agree to and understand the material presented in this protocol, and must not publicly disclose in any manner the design, results, or conclusions of this investigation without prior written consent of NxThera, a Boston Scientific Company.

_____
Clinical Site Name

_____ _____
Site Principal Investigator Signature **Date**

_____
Site Principal Investigator Printed Name

Table of Contents

1 Protocol synopsis

Title:	Minimally Invasive Prostatic Vapor Ablation - Multicenter, Single Arm Study for the Treatment of BPH in Large Prostates (Rezūm XL).
Purpose:	To evaluate the safety and efficacy of the Rezūm System and assess its effect on urinary symptoms secondary to Benign Prostatic Hyperplasia in patients with prostate sizes >80cm^3 and ≤150 cm^3
Study Design:	This study is a prospective, non-randomized clinical trial of subjects with benign prostatic hypertrophy (BPH).
Enrollment:	A sample size of 88 enrolled and treated subjects is planned.
Follow-up:	Follow-up visits required post-procedure: 2 weeks, 6 weeks, 3 months, 6 months, and 12 months. In addition, subjects will be followed annually thereafter for 3 years.
Clinical Sites:	Up to 11 sites (10 United States and 1 Australia)
Inclusion Criteria:	1. Male subjects ≥ 50 years of age who have symptomatic BPH. 2. International Prostate Symptom Score (IPSS) score ≥ 13. 3. Peak urinary flow rate (Qmax): ≥ 5ml/sec to ≤ 12 ml/sec with minimum voided volume of ≥ 125 ml. 4. Post-void residual (PVR) ≤300 ml. 5. Prostate volume >80 cm^3 to ≤150 cm^3
Exclusion Criteria:	**<u>Urology</u>** 1. Any prior invasive prostate intervention (e.g., "Radiofrequency" thermotherapy, balloon, microwave thermotherapy, "Prostatic Urethral Lift", "Transurethral Resection", or laser) or other surgical interventions of the prostate. 2. Undergone a prostate biopsy within 60 days prior to the scheduled treatment date or has an imminent need for surgery. 3. Verified acute bacterial prostatitis within last 12 months documented by culture. 4. Active or history of epididymitis within the past 3 months. 5. Urethral strictures, bladder neck contracture, unusual anatomy or muscle spasms that would prevent the introduction and use of the Rezūm device. 6. Diagnosed bladder, urethral or ureteral stones or active stone passage in the past 6 months, provided that stones that are known to be in the kidney and have been stable for a period exceeding 3 months are permissible. 7. Subject interested in maintaining fertility. 8. Use of the following medications where the dose is not stable (stable dose defined as the same medication and dose in the last three months): a. Beta-blockers; b. Anticonvulsants; c. Antispasmodics; d. Antihistamines; e. Alpha blockers for BPH and anticholinergics or cholinergics; f. Type II, 5-alpha reductase inhibitor (e.g., finasteride (Proscar, Propecia)); g. Dual 5-alpha reductase inhibitor (e.g., dutasteride (Avodart));

h. Estrogen, drug-producing androgen suppression, or anabolic steroids;
i. PD5 Inhibitors (e.g., Viagra, Levitra or Cialis)

9. Subjects who have had an incidence of spontaneous urinary retention either treated with indwelling transurethral catheter or suprapubic catheter 6 months prior to baseline. A provoked episode now resolved is still admissible
10. Evidence of atonic neurogenic bladder evaluated by a baseline urodynamic assessment.
11. Visible hematuria with subject urine sample without a known contributing factor.
12. Presence of a penile implant or stent(s) in the urethra or prostate
13. Active urinary tract infection by culture within 7 days of treatment or two documented independent urinary tract infections of any type in the past 6 months.

Gastroenterology

14. Previous pelvic irradiation or radical pelvic surgery.
15. Previous rectal surgery (other than hemorrhoidectomy) or known history of rectal disease.

Nephrology

16. Compromised renal function defined as serum creatinine > 2.0 mg/dl.
17. Hydronephrosis (Grade 2 or higher).

Oncology

18. Prostate cancer testing:
    If PSA is > 2.5 ng/ml and ≤ 10 ng/ml with free PSA <25%, prostate cancer for the subject must be/had been ruled out through a negative biopsy prior to enrollment
    - Males 50-59 years - PSA is >2.5 ng/ml and ≤10 ng/ml with free PSA <25%,
    - Males 60+ years - PSA is >4 ng/ml and ≤10 ng/ml, with free PSA <25%
19. History of confirmed malignancy or cancer of the prostate or bladder; however, high grade prostatic intraepithelial "PIN" is acceptable.
20. History of cancer in non-genitourinary system that is not considered cured (except basal cell or squamous cell carcinoma of the skin). A potential participant is considered cured if there has been no evidence of cancer within five years of enrollment.

Cardiology

21. History of clinically significant congestive heart failure (i.e., NYHA Class III and IV).
22. Cardiac arrhythmias that are not controlled by medication and/or medical device.
23. An episode of unstable angina pectoris, a myocardial infarction, transient ischemic attack, or a cerebrovascular accident within the past six months.

	Pulmonology 24. History of significant respiratory disease where hospitalization for the disease is required. **Hematology** 25. Diagnosed or suspected bleeding disorder, or coagulopathies. 26. Use of antiplatelet or anticoagulant medication except low dose aspirin (<100mg/day) within 10 days prior to treatment. **Endocrinology** 27. History of diabetes not controlled by a stable dose of medication over the past three months, provided that patients with a hemoglobin A1c <8.0% are allowed. **Immunology** 28. History of immunosuppressive conditions (e.g., AIDS, post-transplant). **Neurology** 29. Any cognitive or psychiatric condition that interferes with or precludes direct and accurate communication with the study investigator regarding the study or affect the ability to complete the study quality of life questionnaires. 30. Diagnosed or suspected primary neurologic conditions such as multiple sclerosis or Parkinson's disease or other neurological diseases known to affect bladder function, sphincter function or poor detrusor muscle function (< 25% of accepted and established nomograms). **General** 31. Currently enrolled in any other pre-approval investigational study in the US (does not apply to long-term post-market studies unless these studies might clinically interfere with the current study endpoints (e.g., limit use of study-required medication, etc.). 32. Any significant medical history that would pose an unreasonable risk or make the subject unsuitable for the study. 33. Inability to provide a legally effective "Informed Consent Form" and/or comply with all the required follow-up requirements.
Primary Endpoints:	**Primary Efficacy Endpoint** The proportion of the intent-to-treat (ITT) analysis population that responds to therapy must be statistically significantly greater than 50%. A responder is defined as a subject who has an IPSS improvement ≥ 30% post-treatment compared to baseline. **Primary Safety Endpoint – Post Procedure Device Related Serious Complications:** Demonstration that the composite rate of post procedure device related serious complications in treated subjects is statistically significantly less than 12% at 6 months. These composite device-related serious complications for this endpoint are defined as: • Perforation of the rectum or GI tract • Formation of fistula between the rectum and urethra • Permanent damage to the bladder, trigone or ureteral orifices requiring intervention • Grade 2 hydronephrosis

Secondary and Ancillary Endpoints:	Secondary Endpoint S1: Device-related retention catheterization rate
	Secondary Endpoint S2: Absolute IPSS improvement at 6 Months
	Secondary Endpoint S3: Percent Responder at 1 year
	Secondary Endpoint S4: Percent Responder at 2 years
	Secondary Endpoint S5 Percent Responder at 3 years
	Ancillary Endpoint A1: Additional Responder Analyses
	Ancillary Endpoint A2: Change in Qmax and PVR
	Ancillary Endpoint A3: Change in Sexual Function
	Ancillary Endpoint A4: Change in Quality of Life
	Ancillary Endpoint A5: Procedure Parameters
	Ancillary Endpoint A6: PGI-I Questionnaire
	Ancillary Endpoint A7: Rezūm II Comparisons
Principal Investigator:	Henry Woo, MD Professor of Surgery Sydney Adventist Hospital Clinical School University of Sydney P.O. Box 5017, Wahroonga, NSW, 2076. Australia
Sponsor, Study and Data Management:	NxThera, a Boston Scientific Company 10700 Bren Rd. W Minnetonka, MN 55343 Tel: 800-328-3881
Study Monitors:	**US Monitoring:** IMARC Research Inc. 22560 Lunn Road Strongsville, OH 44149 **AUS Monitoring:** TBD

2 List of Abbreviations and Phrases

AE	Adverse Event
AUASI	American Urological Association Symptom Index
AUR	Acute Urinary Retention
AUR	Acute Urinary Retention
BCI	Bladder Contractility Index
BOOI	Bladder Outlet Obstruction Index
BPH	Benign Prostatic Hyperplasia; also known as Benign Prostatic Hypertrophy
BPHII	BPH Impact Index
BUN	Blood Urea Nitrogen
CEC	Clinical Events Committee
CRF	Case Report Form
CV	Curricula Vitae
DRE	Digital Rectal Exam
DU	Detrusor Underactivity
EC	Ethics Committee
ED	Erectile Dysfunction
EF	Erectile Function
FDA	Food and Drug Administration
GCP	Good Clinical Practices
HIFU	High Intensity Focused Ultrasound
HIPAA	Health Insurance Portability and Accountability Act
HoLAP	Holmium Laser
ICF	Informed Consent Form
ICS	International Continence Society
ICSmaleIS	International Continence Society Male Incontinence Scale
ID	Identification Code
IDE	Investigational Device Exemption
IIEF	International Index of Erectile Function
IFU	Instructions For Use
IPP	Intravesical Prostatic Protrusion
IPSS	International Prostate Symptom Score
IRB	Institutional Review Board
LUTS	Lower Urinary Tract Symptoms
MCID	Minimal Clinically Important Difference
MSHQ-EjD	Male Sexual Health Questionnaire – Ejaculatory Dysfunction
MRI	Magnetic Resonance Imaging
NSAID	Non-Steroidal Anti Inflammatory Drug
OAB-q SF	Over Active Bladder Questionnaire Short Form

PAE	Prostate Artery Embolization
PGI-I	Patient Global Impression of Improvement (PGI-I)
PIN	Prostatic Intraepithelial Neoplasia
PSA	Prostate Specific Antigen

3 Introduction and Background

3.1 Scope of the Problem

BPH is a histologic diagnosis that refers to the proliferation of smooth muscle and epithelial tissue cells within the prostatic transition zone. BPH is a common chronic medical condition often associated with progressive development of lower urinary tract symptoms (LUTS), a troublesome and threatening ailment in the aging male. The bother factor of the symptoms associated with LUTS/BPH increase in severity proportional to age [1 2]. The incidence of BPH increases from 40% among males between the ages of 50 and 60 years to 90% among males older than 80 years of age [3]. The healthcare costs for BPH are within the ten most prominent and most expensive diseases in men over 50 years of age in the US [4]; surgical treatments for BPH rank amongst the highest of the Medicare reimbursement categories. The global prevalence of LUTS/BPH, the impact of BPH on patients and their partners, and the economic burden of this condition has confirmed the need for appropriate medical care [1, 5-8].

Traditionally, the primary objective of treatment has been to alleviate bothersome LUTS that result from the prostatic enlargement. Pharmaceutical treatment focuses on altering disease progression and preventing physiologic symptoms associated with BPH/LUTS. Pharmacologic classes employed include alpha-adrenergic antagonists (alpha-blockers), 5-alpha reductase inhibitors (5-ARIs) and antimuscarinic agents. Choosing the correct medical treatment for BPH symptoms is complex and ever-changing. Many men begin medical therapy but have inadequate improvement in their symptoms and quality of life, or experience undesirable side-effects that lead to discontinuation. Increasingly, men do not want to commit to a lifetime pharmaceutical treatment often with multiple drugs. Pharmaceutical agents are costly when used for long periods of time, and for some patients, particularly in older men, compliance with medications becomes an issue.

While TURP (mono- and bi-polar) procedures have historically been termed the “gold standard” surgical procedure for BPH, the most common indications for TURP have shifted considerably over the past decade. TURP previously was utilized to achieve improved voiding symptoms, but without formal objective quantification. The indication for TURP today is more likely to be moderate-to-severe voiding symptoms attributed to BPH where the patient is or has become refractory to medical therapies. Other aggressive treatments for severe BPH include laser vaporization or thermotherapy (e.g., tissue ablation). With the availability of a variety of new well-studied treatments, most men are reluctant to undergo a major surgical procedure to treat BPH with its inherent surgical risks and potential deterioration in sexual function.

Minimally invasive treatments allow urologists to introduce other treatment modalities into the treatment continuum between medical management and more invasive surgical approaches. Early on, these new technologies were embraced with excitement; however, many of these minimally invasive BPH treatments did not live up to the initial expectations, which often were based on a small case series clinical trials where the patients were followed for short durations and without adequate control groups to evaluate the clinical outcomes data. Recent minimally invasive treatment clinical studies (Rezūm and PUL) have conducted rigorous randomized controlled studies, following the patients out to five (5) years post-treatment.

Examples of less invasive treatments include prostatic urethral expanders (mechanical shaping procedures) or prostatic urethral stent [9]; PUL [10], TUMT and TUNA. TUMT and TUNA

thermotherapy (ablation) procedures utilize the *conduction* of thermal energy to deliver heat therapies. As a result of certain limitations and tolerability of these minimally invasive treatments for BPH, traditional TUMT and TUNA procedures have not been widely adopted within the urologic community. A perspective of BPH management is provided in both the USA and European literature ([11, 12].

CONVECTIVE WATER VAPOR ENERGY (WAVE™) technology (Rezūm System, NxThera, a Boston Scientific Company) is a minimally invasive, radiofrequency (RF) energy-based thermal treatment designed to *convectively* deliver sterile water vapor, or steam thermal energy, to ablate targeted prostate tissue with site-specific treatments confined within the transition zone (or the hyperplastic central zone tissue of median lobes) in men with moderate-to-severe BPH. The principles of this WAVE technology and effective ablation of human prostatic adenomas have been validated by histological and radiographic studies of the Rezūm System to treat BPH using gadolinium-enhanced MRIs and clinical trials including a multicenter randomized, controlled design study [13-18].

The Rezūm System clinical application presented for expanded study in this protocol delivers a rapid, thermal ablation treatment that mitigates the symptoms of BPH with an excellent safety profile. Convective water vapor energy ablation of prostate adenomas produces statistically significant and clinically meaningful improvements of LUTS often within 2 weeks of treatment. Clinical efficacy data to-date has demonstrated durable improvements in BPH symptoms out to 24 months, including IPSS, Qmax, QoL, decreased incontinence episodes, and preserved sexual function. Treated subjects will be evaluated yearly up to 3 years post-treatment. The Rezūm procedure is most often performed in an office setting with oral medication and/or a prostate block for intra-procedure pain management. The Rezūm System minimally invasive treatment is an attractive alternative for a broad range of patients with symptomatic BPH, including those with a median lobe, and provides a first-line BPH treatment option for those patients who have failed medical management or who cannot or do not want to pursue medical management to treat their BPH.

4 Proposed Intended Use

The Rezūm System is intended to relieve symptoms, obstructions, and reduce prostate tissue associated with BPH, and indicated for men ≥ 50 years of age with a prostate volume ≥ 30 cm^3 and ≤ 150 cm^3. The Rezūm System is also indicated for the treatment of prostates with hyperplasia of the central zone and/or a median lobe.

5 Device Description

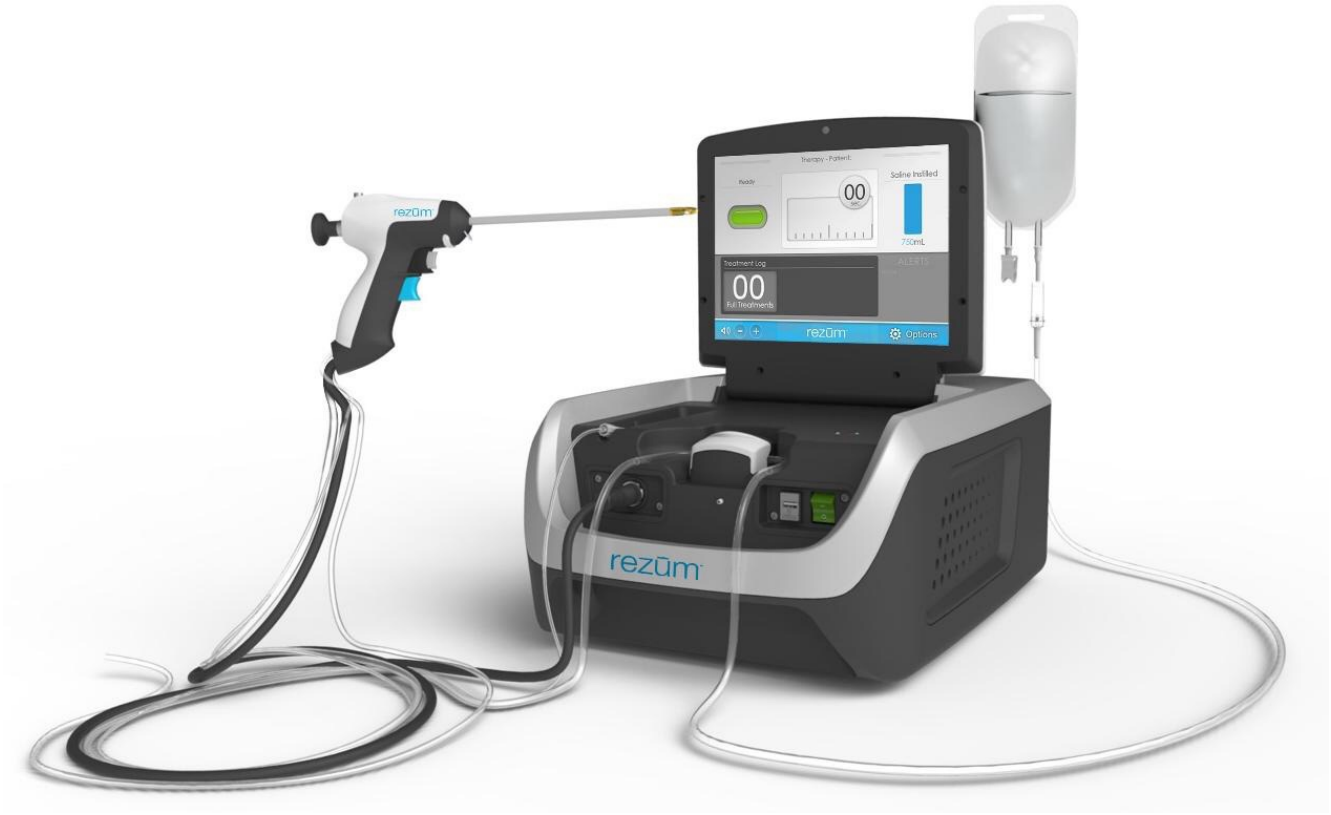


FIGURE 5-1: SCHEMATIC OF THE REZŪM SYSTEM

NxThera, a Boston Scientific Company's Rezūm System consists of the following major components (Figure 5-1):

- Generator
- Sterile disposable Delivery Device

The Generator is capital equipment that is reusable and is non-sterile. The Generator does not come in contact with the subject. The full description of the Generator, warnings and precautions are provided in the Instructions for Use (IFU).

The shaft of the Delivery Device is 20F in circumference and can accommodate a 4mm 30º rigid cystoscopic lens. Saline fluid is flushed through the Delivery Device during the procedure to allow for visualization and to protect the urethra from injury during treatment.

5.1 Principles of Operation

The basic principle of the Rezūm System is to deliver a controlled amount of sterile water vapor directly into the hyperplastic tissue in the transition zone of the prostate using a transurethral approach as shown in Figure 5-2. The stored thermal energy in the vapor is transferred directly onto the cell membranes as

the vapor condenses and releases the heat of condensation, causing cell death. In addition, this thermal energy transfer collapses the vasculature within the treatment zone, resulting in a bloodless procedure. NxThera, a Boston Scientific Company hypothesizes that the alpha adrenergic nerves and receptors are also destroyed in the process. Saline flush runs during vapor delivery to protect and preserve the urethra. Collectively, the treatment immediately compromises or eliminates the contractile capability of the smooth muscle tissue, and over time, the necrotic tissue is naturally resorbed by the body through the immune system response, thereby relieving the BPH symptoms. A summary of the procedure is provided below.

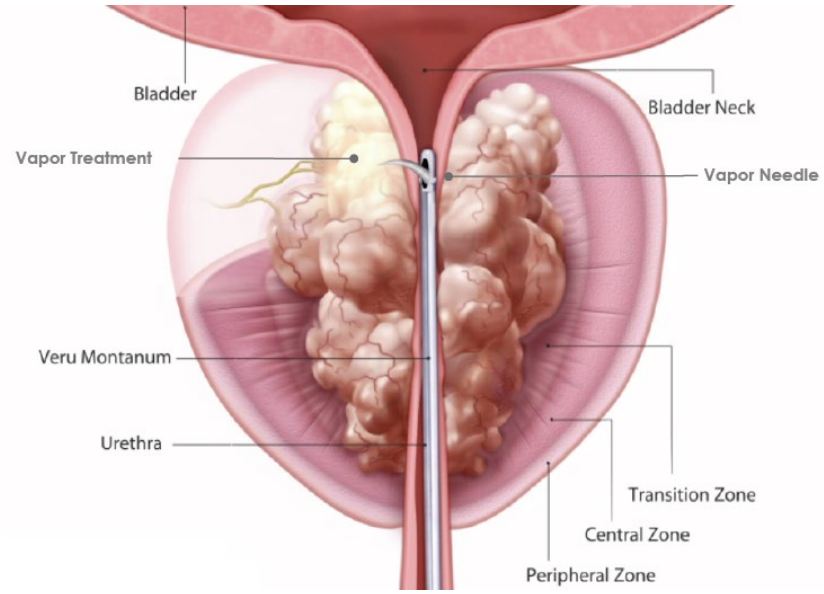


FIGURE 5-2: TRANSURETHRAL TREATMENT WITH THE REZŪM SYSTEM

The Rezūm System treatment summary provided below is only intended as an overview, and the procedure descriptions in the IFU should be followed at all times.

1. The water vapor is created by an inductive coil heating element in the Rezūm Delivery Device. The flow of vapor is controlled by delivering defined levels of RF energy and sterile water flow controlled by the Generator into the inductive coil heating element.
2. The Rezūm Delivery Device is inserted using a standard transurethral approach (Figure 4.2). A standard 4mm, 30°, rigid cystoscopic lens is inserted into the Delivery Device, thereby allowing the Delivery Device to be advanced and positioned under direct visualization within the prostatic urethra. The verumontanum and bladder neck/bladder serve as the anatomic markers to delineate the boundaries of the transition zone area of the prostate to be treated.
3. Standard saline flush is used to both visualize and irrigate the urethra during navigation and during delivery of the vapor treatments (thereby keeping the urethral tissue cool).
4. Using direct visualization, the treating physician positions the distal tip of the Delivery Device lateral at a ~ 90 degree angle against the wall of the urethra within the prostate at the initial point of the targeted treatment area.

5. The physician deploys the needle with the Delivery Device through the wall of the urethra and into the prostate tissue.
6. The physician then activates and holds the Vapor Activation Button, thereby delivering vapor into the transition zone through 3 sets of 4 vapor emitter holes spaced 120° apart located near the tip of the vapor needle. The total length of vapor needle that can penetrate the prostate tissue is fixed at 10 mm. The time of each vapor delivery is predetermined (less than 10 seconds) for each therapeutic treatment/dose.
7. After each treatment, the vapor needle is retracted, and the physician repositions the Delivery Device and deploys the vapor needle at the next targeted treatment location. The number and location of each treatment during a Rezūm procedure are described in the IFU. In this study, the number of treatments delivered in each lobe of the prostate will be documented in the CRF.

6 Study Rationale

6.1 Overview: Spectrum of Therapeutic Options for LUTS/BPH

BPH disease management for individual patients depends on diagnostic testing, monitoring, assessing the prognosis of disease progression, treatment planning and the prediction of treatment outcome based on the severity of the patient's LUTS. The patient should be informed of all available and acceptable treatment alternatives applicable to his clinical condition, as well as the related benefits, risks and costs of each modality to actively participate in the shared decision-making process. The table presents and lists in progressive order from least to most invasive treatment modalities available for LUTS/BPH.

Spectrum of Therapeutic Options for LUTS/BPH
Conservative treatment - Watchful Waiting (regular observation without treatment)
Medical therapies
α_1-adrenoreceptor antagonists (for treating signs or symptoms of BPH)
5α-reductase inhibitors (for treating benign prostatic enlargement due to BPH)
Antimuscarinic agents (for treating OAB/storage symptoms)
Phosphodiesterase-type 5 inhibitors (for treating signs or symptoms of BPH with or without erectile dysfunction)
Vasopressin analogues (for treating nocturnal polyuria)
Combination therapy: α_1-blocker + 5α-reductase inhibitors α_1-blocker + anticholinergics
Complementary and Alternative Medicines
Minimally invasive therapies
Electromagnetic energy thermal ablation
Radiofrequency (RF) Transurethral Needle Ablation (TUNA) Systems
Prostiva – a conductive RF-induced transurethral needle ablation
Rezūm System – a convective RF-induced water vapor energy thermal therapy

Microwave-induced transurethral thermotherapy (TUMT) – a conductive thermotherapy
High intensity focused ultrasound (HIFU) therapy
Interstitial laser coagulation
Mechanical reshaping
Prostate urethral lift (PUL)
Prostatic stent placement
Water jet ablation
Balloon dilation
Histotripsy – cavitation to create mechanical non-thermal destruction
Surgical therapies
Open prostatectomy
HoLAP -transurethral holmium laser ablation of the prostate
PVP - photoselective vaporization of the prostate
TUIP -transurethral incision of the prostate
TUVP - transurethral vaporization of the prostate
TURP - transurethral resection of the prostate, monopolar and bipolar
Other emerging therapies
PAE - prostate artery embolization
Intraprostatic botulinum toxin injection

6.2 Points of Consideration Related to Therapeutic Options

Complementary and Alternative Medicines: An absence of objective scientific evidence for dietary supplements or combination phyto-therapeutic agents and other nonconventional therapies suggests no recommendation for these agents.

Pharmacological Management: A variety of single drugs or combination drugs typically represent the first-line of treatment option for bothersome BPH. Many men initiate medical therapy, but have inadequate improvement in their symptoms and quality of life and many times experience undesirable side-effects including hypotension, dizziness, retrograde ejaculation, hormonal effects such as breast tenderness, etc. that lead to discontinuation. In addition, this population often includes men who are taking drugs to manage other health issues (e.g., hypertension, erectile dysfunction), and must deal with the side effects of different combination drug therapies. These BPH drugs often are costly and require lifetime use. Increasingly, men do not want to commit to lifetime pharmaceutical treatment with multiple drugs.

Thermal Ablation: The direct or indirect application of electromagnetic energy to thermally ablate tissue include microwave and radiofrequency systems. Both TUMT and the original TUNA systems utilized heat transfer by conduction to thermally ablate tissue, which required treatment times of 30 minutes or more in order to deposit the amount of energy required to optimize the tissue temperature gradient to produce necrosis [19]. These systems are clinically indicated to treat small-to-moderate size prostate glands of up to 50 cm^3. Clinical studies of these conductive thermal ablation approaches demonstrated the lack of durability, and high rates of retreatment. In addition, patient selection criteria regarding

prostate size and the ability to treat median lobes were negative attributes preventing their widespread adoption [11, 12]. The Rezūm System is a "next generation" RF TUNA system which convectively delivers thermal energy in the form of vapor, or steam, to rapidly and uniformly ablate prostate tissue to treat BPH, including median lobes, without the durability and retreatment issues reported for the first generation thermal ablation systems.

Mechanical Reshaping: Prostatic stents have a limited role in the treatment for moderate-to-severe LUTS. They are primarily used as an alternative to catheterization especially in elderly men, often prior to surgery, but have poor tolerability due to misplacement, migration and exacerbation of symptoms resulting from encrustation. When prostatic stents fail they can be problematic to remove. A different mechanical reshaping approach is the PUL system. In a PUL procedure, multiple small, permanent suture implants are delivered with cystoscopic guidance to retract or compress the protruding lateral lobes causing the obstruction. In PUL studies, prostates of up to 100 cm^3 were reported treated with up to 11 implants.

Surgical Interventions: Surgical procedures to treat BPH typically are offered as a treatment alternative for patients with moderate-to-severe LUTS, patients who developed acute urinary retention or other BPH-related complications and patients with large prostate glands (≥80 cm^3). Surgical procedures are the most invasive option for BPH management and generally patients will have failed medical therapies before proceeding with surgical procedure. Transurethral resection (TURP) is considered the gold standard surgical procedure, although various alternatives such as bipolar TURP, laser vaporization and laser enucleation also are options; all have undesirable peri-operative and post-operative morbidities including retrograde ejaculation and erectile dysfunction.

For the reasons outlined above, we plan further study of the Rezūm System utilizing Water Vapor Energy (WAVE™) technology, a minimally invasive, RF thermal energy-based treatment, designed to convectively deliver sterile water vapor for targeted ablation limited to the transition zone, median lobe or elevated central zone in men with clinical BPH, and having a prostate size ≥80cm^3. The Rezūm System therapy provides clinicians with an efficacious and safe option in the continuum between medical management and surgical approaches. Results have been documented in a multicenter randomized, controlled trial (RCT) [16, 17].

6.3 Rationale for Treatment of Large Prostates

In prostates ranging from 80-150 cm^3, the obstruction causing the BPH results from hyperplasia of the transition zone (lateral lobes) and central zone, and often includes a median lobe (central zone tissue) and/or transition zone tissue that protrude into the bladder (e.g., intravesical protrusions). Currently available BPH treatment options for patients with large prostates that are unresponsive to oral medications are TURP, laser or simple, open prostatectomy. For patients who are not eligible for surgery, treatment options include intermittent catheterization, possible prostatic urethral stents and perhaps prostate incision. Because the Rezūm System is able to ablate 1.5 to 2.0 cm^3 of prostate tissue with each treatment, irrespective of tissue location, larger prostates can be treated by selecting the location of each treatment and determining the number of treatments to be delivered in a procedure based on each patient's individual anatomy.

Since the Rezūm device was cleared to be utilized in the U.S. and in Europe, urologists have, on their own volition, successfully treated patients with prostates >80 cm^3 and have been developing treatment algorithms and vapor needle placement on their own, without guidance from NxThera, a Boston Scientific Company.

The focus of this clinical study is to evaluate the safety and efficacy, using the Rezūm System to treat BPH in men with prostates >80 cm^3 and ≤150 cm^3 evaluating the results in improvements in LUTS symptoms (IPSS) over a 6-month period. The prior Rezūm RCT included men with moderate-to-severe LUTS with prostates 30 cm^3 to 80 cm^3, as measured by TRUS. As the size of prostates with nodular hyperplasia can range from 50 cm^3 to 200 cm^3, a trial of safety and efficacy in men with larger prostates is desirable. This study will allow the systematic study of the treatment algorithm (e.g., placement and number of treatments, and post-treatment catheterization) to optimize the outcome of using the Rezūm System to treat BPH in men with very large prostates.

7 Risk-Benefit Analysis

7.1 Risk Analysis

Complications and risks that exist for the other thermal ablation treatments of the prostate to treat BPH also exist for using the Rezūm System. The types of anticipated adverse events (AEs) which occur as a result of a BPH procedure with the Rezūm System have been documented in previous clinical trials of the Rezūm System including a randomized controlled clinical trial (RCT) [14, 16, 17]. The major risks and symptoms commonly associated with these types of thermal treatments are described below. A more extensive list of other types of AEs that could occur are provided in Section 14.

- **Pain:** Peri- and post-procedure pain as a result of a thermal ablation procedure may occur with the Rezūm treatment. Pain scores were transiently elevated during the procedure, but comparable to the pain reported from the rigid cystoscopy used in the control subjects. Other minimally invasive treatments report persistent pain up to 3 months. In the Rezūm RCT, post-procedure pelvic pain/discomfort from the Rezūm treatment was reported by only 2.9% (4/136) subjects [16].

- **Bleeding:** Subjects could experience bleeding from the introduction of the Rezūm System transurethral Delivery Device that incorporates a standard 4 mm, 30° endoscopic cystoscopy lens. The shaft of the Delivery Device is approximately 20F, comparable to the size of a rigid cystoscope. Gross hematuria possibly/probably related to the procedure was reported in 2.2% (3/136) subjects in the RCT of the Rezūm System [16]. The circumference of the Rezūm Delivery Device vapor needle is only 18 gauge which minimizes the risk of bleeding at the site of each vapor needle deployment. The vapor delivered into the prostate tissue at the tip of the Delivery Device vapor needle is 103°C, which causes instantaneous destruction of tissue cell membranes, and the collapse and closure of blood vessels in the targeted treatment areas. As a result, minimal, if any, bleeding is observed at the site of the vapor needle deployment for each treatment.

- **Infection / Fever:** Prostate tissue ablated with the water vapor thermal therapy could become infected or a consequential urinary tract infection (UTI) could occur. If infection is suspected or detected, appropriate diagnostic (urine culture) and therapeutic measures should be taken. If a

question of sepsis exists, a urine and blood culture should be performed and other aggressive evaluations and treatments made. To mitigate these risks, all devices are supplied sterile and the procedure is performed under conditions approved for cystoscopy procedures. Antibiotics and NSAIDs are recommended pre- and post-procedure. In the Rezūm RCT, of the 136 treated subjects who received thermal therapy in the treatment arm, fever was reported in 0.7% (1/136) and UTI (culture proven) in 1.5% (2/136) of the subjects [16].

- **Perforation:** With the Rezūm System treatment, tissue ablation occurs following deployment of the vapor needle delivery of water vapor during each 9-second treatment. When water is heated into vapor, it expands by 1,700 times. Because the vapor mass is physically less dense than the densified tissue membranes that separate each zone of compartment of the prostate (surgical capsules or pseudocapsules, true outer capsule of the prostate, urethra, bladder neck and external sphincter), the vapor remains within each targeted treatment area (e.g., transition zone or central zone) when injected into the prostate. No thermal effects occur outside of the prostate or in the peripheral zone when the transition zone or central zone is targeted. Although perforation of the prostate or adjacent bladder/rectum could occur as a result of user error in placement of the delivery sheath and vapor needle, this risk is remote. This potential risk is mitigated by the device design; the total length of the vapor needle that is deployed from the Delivery Device that penetrates prostate tissue has a fixed length of 10.25 mm. Urologists participating in clinical trials or in clinical practice receive training in the endoscopic procedure and proper use of the Delivery Device. There have been no reports of perforation in any clinical trial experience or commercial experience with the Rezūm System.

- **Ejaculatory and Erectile Dysfunction:** Potential side-effects of minimally invasive, including thermal ablation procedures to treat BPH include ejaculatory and/or erectile dysfunction. A sterile saline flush irrigation to enhance visualization and cool the surface of the urethra is used during the procedure to minimize urethral tissue ablation and potential side effects. While these side effects also could occur with the Rezūm System procedure, the data from the Rezūm clinical studies in Section 8 below demonstrated minimal risk. In the RCT of the Rezūm System, including 136 men treated with thermal therapy, no treatment or device-related de novo ED was reported during in the 12-month follow-up of subjects in this trial [17].

- **Incontinence:** Incontinence has been reported to occur after certain minimally-invasive procedures resulting from injury or damage to the urinary sphincter muscle or nerves. The Rezūm System Delivery Device and procedure are designed to limit treatment to tissue within the prostatic urethra, between the verumontanum and the bladder neck. In the Rezūm RCT, incontinence was assessed pre-treatment and at months 1, 3, 6 and 12 after treatment with two questionnaires, OAB-q SF, ICS male IS-SF. *De novo* urge urinary incontinence was reported as an AE in a single subject (0.7%, 1/136). Significant and durable improvements over 12 months were documented, including over-active bladder bother (OAB-q SF) improvement of 45%, and incontinence (ICS male IS-SF) improvement of 25% as compared to baseline ($P<0.0001$).

- **Urinary retention:** Acute urinary retention (AUR) is a common side effect of BPH treatments post-procedure. This urinary retention can be attributed to swelling or sloughing of the tissue secondary to the ablative injury of tissue, and may require the use of a urinary catheter. Retention also may be caused by clot formation within the urethra as a result of bleeding from the procedure.

The reported incidences of retention from BPH treatments generally are acute and short-lived and typically resolve once tissue healing is complete. In the Rezūm System RCT, of the 136 subjects who received thermal therapy, 4.4% (6/136) experienced acute urinary retention [16].

- **Tissue expulsion:** Small pieces of coagulated tissue could potentially slough off after thermal therapy for BPH and possibly cause partial obstruction or even urinary retention. This tissue is usually expelled during urination. This sloughing process may continue for a few months post-procedure depending on the rate of healing. While this is a natural phenomenon, it may cause anxiety and be a nidus for infection.

- Significant **blood pressure elevation** has been reported in other BPH therapies and may occur during treatment. A combination of very short treatment times (e.g., <10 seconds) and the fact that the Rezūm System treatment does not involve the direct application of electromagnetic energy to the prostate tissue mitigates the risk of any clinically significant spike in blood pressure in connection with the procedure. No reports of a significant blood pressure increase have been observed in any clinical trial experience with the Rezūm System.

- Lower urinary tract symptoms present at baseline in BPH subjects may worsen or persist. These symptoms include but are not limited to the following:
    - Dysuria
    - Frequency
    - Urgency
    - Nocturia
    - Acute urinary retention
    - Incontinence
    - Sensation of not emptying bladder completely
    - Urethral stricture
    - Urethritis
    - Irritative urinary symptom
    - Urethral injury causing false passage or adhesion
    - Urinary clot retention
    - Chronic pain in the pelvic area
    - Bladder spasm
    - Hematuria with or without clot in urethra
    - Discharge or cloudy urine
    - Discharge of tissue material during urination
    - Scarring of the urethral system
    - Urinary tract infection

- Other less frequent but potential risks reported with minimally invasive BPH treatments may include:
    - Abscess
    - Damage to bladder floor, trigone, and sphincter
    - Rectal and perineal findings
    - Flu-like symptoms
    - Hematospermia

- Epididymitis
- Flank pain
- Blood loss (> 500 ml)

The full list of anticipated adverse events is provided in Section 14.4. Risks for subjects in this study may be similar to those for subjects being treated with commercially available devices delivering thermal therapy such as the Urologix Prostiva RF device, the AMS Laserscope Greenlight HPS device, the Urologix Targis device, and newer generations of these devices or other TUMT devices.

To minimize the likelihood or severity of these potential risks, clinical investigators will undergo training in the use of the Rezūm System and subjects will be screened and evaluated for medical histories or conditions that may compromise successful operation or performance of the device. The entire procedure will be conducted under the guidance of the "Rezūm System Instructions for Use." The Rezūm device has undergone extensive risk analysis, testing and is designed with a number of safeguards built into the device to mitigate any serious risks.

7.2 Benefit Analysis

The Rezūm System is designed to provide relief from LUTS associated with BPH. The potential benefits of thermal ablation therapy with the Rezūm System are presented in comparison with other minimally invasive thermal treatment procedures for BPH including, but not limited to, conventional Prostiva RF, TUMT, and laser treatments.

Previous Rezūm clinical trials (FIM/pilot and RCT) included subjects with moderate to severe symptoms (IPSS ≥13), with prostates in volumes of 30 to 80 cm^3. The data obtained from this current study will be used to further document the efficacy and safety of the Rezūm System in men with prostates >80 cm^3. Participants in the study could directly benefit as well as others in the future. In the recent clinical experience after FDA Clearance of the Rezūm System, approximately 7% of 7,300 men who considered the option of a minimally invasive treatment with the Rezūm System presented with prostate volumes of 80 cm^3 or larger.

Potential Benefits of the Rezūm System thermal therapy

- **Attractive alternative for a broad range of patients with symptomatic BPH:** Appropriate for men with moderate-to-severe LUTS/BPH.

- **An in-office or out-patient procedure:** Can be performed using oral medications or local prostate block for pain management.

- **Shorter treatment times:** Rezūm System treatments typically can be completed in less than 7 minutes of actual procedure time. In past studies, the hyperplastic tissue in the transition and central zones of the prostate have been treated with an average of 4.5 water vapor injections, each for 9-seconds in duration; when present, median lobe treatments average 1.6 water vapor injections. In contrast, Prostiva RF and TUMT treatment times range from 20 to 65 minutes; laser treatment times range from 20 minutes to 3 hours.

- **Targeted and uniformity of ablative effect:** The Rezūm System vapor ablation technology convectively delivers heat thermal energy in the form of sterile water vapor created using RF energy, to physically transfer the vapor through the tissue interstices. This convective heat transfer involves virtually no discernible thermal gradient with the treatment zone as seen with conductive heat transfer technologies (e.g., Prostiva RF, TUMT).

- **Ability to treat median lobes:** A major feature of the Rezūm System therapy is the ability to treat central zones and median lobes, when present. This is a limitation for the majority of other minimally invasive thermal treatment, with the exception of the Prostiva RF device.

- **Rapid improvements of LUTS/BPH:** Rezūm clinical studies have demonstrated clinically significant improvements in BPH symptoms as soon as two weeks post-treatment. Rezūm clinical studies also have demonstrated statistically significant improvements in symptoms, flow rate, QoL and decreased incontinence episodes at 1 and 3 months post-treatment.

- **Durable improvements of LUTS/BPH:** Rezūm clinical studies have demonstrated sustained improvements documented for at 6, 12 and 24 months post-treatment (FIM/pilot and RCT results).

- **Sexual function is preserved:** RCT results have shown that LUTS and flow rate improvements are achieved after treatment with the Rezūm System and that erectile and ejaculatory function are preserved [17]. No de novo erectile dysfunction (ED) occurred in the Rezūm RCT. Clinically meaningful improvement in erectile function also occurred in 27% of sexually active men including those with moderate to severe ED.

- **Lower risk of adverse events:** Including some of the following:
  - ***No eschar formation*:** Because water vapor ablation involves the mass transfer of wet thermal energy, the treated tissue is not desiccated, and therefore, the tissue does not char or carbonize as seen with the Prostiva RF device.

  - ***Bleeding at treatment sites negligible*:** The thermal energy released when vapor phase shifts, or condenses, causes almost instantaneous destruction of tissue cell membranes, and collapses and closes blood vessels in the targeted treatment areas, minimizing or eliminating any significant bleeding at the treatment site(s) [13].

Note: A standard for assessing outcomes related to management of LUTS for BPH, both in clinical practice and clinical research trials, also is paramount for evaluating the benefits and risks of a minimally invasive BPH treatment procedure, including the costs of treatment, patient compliance and durability of beneficial effects. The current and most widely employed tool is the International Prostate Symptom Score (IPSS), a validated, self-administered questionnaire to quantify a patient's LUTS with domain scores for severity of seven lower urinary tract symptoms (LUTS); three storage symptoms (frequency, nocturia, urgency) and four voiding/irritative symptoms (feeling of incomplete emptying, intermittency, straining, and a weak stream). One additional quality of life (QoL) question assesses the degree of bother associated with the seven symptoms of BPH. A three-point improvement in the AUA-SI/IPSS is considered clinically meaningful. More recently, a 25% or greater improvement over baseline standard has been used to define a "responder." This questionnaire often is referenced in differentiating outcomes of various treatment options for BPH.

8 Summary of Prior Clinical Experience

8.1 Rezūm Pilot Study

The Rezūm pilot study, a prospective, non-randomized, open label study was conducted in 3 international centers in the Dominican Republic, Czech Republic and Sweden utilizing convective water vapor thermal energy (WAVE technology, Rezūm System) to treat LUTS associated with BPH [14]. The optimized energy dose of 208 calories had been determined in the first series of 15 of the 65 subjects treated. The safety and efficacy of the treatment with the Rezūm System was confirmed in this study and validated the principles of this thermotherapy. The AEs reported by subjects in this study were typical of endoscopic procedures and transient. Clinically and statistically significant improvements in IPSS, QoL, and Qmax were observed within 1 month post-procedure and sustained through 24 months after treatment. Results were comparable to outcomes reported for other minimally invasive therapies (Prostiva RF, TUMT). The study design and results are summarized below:

TABLE 8-1: BASELINE DEMOGRAPHICS AND CHARACTERISITICS

Characteristic	Mean (SD, Range)	N
Age, years	66.6 (7.7, 50- 90)	65
Prostate volume, cc	48.6 (20.5, 20 - 110)	65
PSA, ng/mL	3.9 (4.2, 0.2 - 20)	65
IPSS – all subjects	21.6 (5.5, 13- 35)	65
LUTS severity, n (%) [Range] Moderate (IPSS ≤18) [13-18] Severe (IPSS >19) [19-34]	 21/65 (32.3%) 44/65 (67.7%)	65
QoL (question 8 of IPSS)	4.3 (1.1, 0- 6)	65
BPHII	6.8 (2.8, 0- 13)	64
Qmax, mL/s	7.9 (3.2, 1.4 - 15)	65
PVR, mL	92.4 (77.3, 0- 300)	63
Ethnicity, n (%)		65
Caucasian	46/65 (70.8%)	
Black or African Origin	2/65 (3.1%)	
Hispanic or Latino	17/65 (26.2%)	
History of ED, n (%)	24/50 (48.0%)	50
History of Retrograde Ejaculation	4/50 (8.0%)	50
IIEF-15 – all subjects Total score range 0-75)	34.4 (25.4, 5 - 73)	61
IIEF-EF, severity score (range), n (%) Normal (≥26-30) Mild (17 ≤ IIEF-EF ≤25) Moderate (11 ≤ IIEF-EF ≤16) Severe (1 ≤ IIEF-EF ≤ 10)	 19/64 (29.7%) 9/64 (14.1%) 5/64 (7.8%) 31/64 (48.4%)	64
IIEF Question 9 (score range 0 -5) "When you had sexual stimulation or intercourse, how often did you ejaculate?"		
Continuous (all subjects' scores)	2.2 (2.3, 0 - 5)	65
No sexual stimulation	29/65 (44.6%)	
Almost never or never	2/65 (3.1%)	

A few times (much less than ½ the time)	6/65 (9.2%)	
Sometimes (about half the time)	2/65 (3.1%)	
Most times (much more than ½ the time)	5/65 (7.7%)	
Almost always or always	21/65 (32.3%)	
MSQH-EjD Function (score range 0-15)	5.9 (4.8, 1- 13)	14†
MSQH-EjD Bother (score range 0 – 5)	2.3 (2.3, 0- 5)	14†
†Questionnaire administered at only one study center; the other 2 centers utilized IIEF question 9 to access ejaculatory function.		

8.1.1 Rezūm Pilot Study: Subjects and Procedures

A total of 65 men with moderate to severe LUTS due to BPH and requiring intervention were enrolled. Eligibility criteria; ≥45 years old with IPSS ≥13, maximum flow rate (Qmax) ≤15mL/s with a voided volume ≥125 mL, a post-void residual volume (PVR) <300 mL, and a prostate 20 - 120 cc. Exclusion criteria; confirmed or suspected prostate or bladder cancer, active UTI or bacterial prostatitis within the last year. An appropriate wash-out period was required for antihistamines, antispasmodics, α-blockers, androgens, gonadotropin-releasing hormone analogs, 5α-reductase inhibitors, and use of antidepressants, anticholinergics, anticonvulsants, ß-blockers (unless with documented evidence of a stable dosing). Assessments included IPSS, Qmax, QoL, PVR, PSA, IIEF-EF, MSHQ-EjD and adverse events at week 1, and 1, 3, 6, 12 and 24 months post-procedure. After the procedure, gadolinium-enhanced MRIs were performed on 59 of the 65 subjects after the week 1, and 1, 3 and 6 month evaluations in order to confirm and characterize ablation of the adenomas and resorption of the treated tissue.

8.1.2 Rezūm Pilot Study: IPSS, Quality of Life and Qmax

Water vapor thermal therapy resulted in clinically and statistically significant improvements in IPSS, QoL, BPHII throughout the course of the 2-year follow-up in these subjects (Table 8-2). IPSS change from baseline was the primary effectiveness outcome measure. Significant reductions in IPSS were achieved as early as 1 month, $p<0.001$. Further improvements were noted at 3 months with a mean -13.4 points decrease. These improved symptom scores were durable throughout 24 months, $p<0.001$.

Analysis of the IPSS composite categories for both irritative and obstruction symptom domains showed significant and durable improvements throughout assessments over 2 years. The mean collective irritative symptom scores were decreased by 61% at 12 months and 56% at 24 months, the mean obstructive symptoms by 69% at 12 and 24 months, $p<0.001$ (data not shown).

Qmax increased significantly from 8.1 (SD ± 3.1) mL/s at baseline to 12.7 (6.3) mL/s at 12 months ($p<0.001$); improved peak flow rate was sustained at 11.9 (6.2) mL/s at 24 months. Improvements in urinary symptoms were commensurate with >50% improvements in quality of life measures (QoL of IPSS and BPHII) over 24 months of follow-up, $p<0.5$ - <0.001.

TABLE 8-2: CHANGES IN IPSS, QOL, BPHII AND QMAX AFTER THERMAL THERAPY

Outcome measure	1 Week	1 Month	3 Months	6 months	12 months	24 months
IPSS						
N (paired values)		64	62	62	58	43
Baseline		21.6 (5.5)	21.7 (5.5)	21.6 (5.6)	21.7 (5.7)	21.7 ± 5.3
Follow-up		14.8 (8.4)	8.3 (5.8)	8.5 (7.0)	9.2 (6.5)	9.6 ± 6.5
Change		-6.8 (10.0)	-13.4 (7.6)	-13.1 (8.6)	-12.5 (7.6)	-12.1 ± 7.9
P Value		<0.001	<0.001	<0.001	<0.001	<0.001
QoL						
N (paired values)	64	64	62	62	58	43
Baseline	4.3 (1.1)	4.3 (1.1)	4.3 (1.1)	4.3 (1.1)	4.4 (1.1)	4.4 (1.2)
Follow-up	3.6 (1.8)	2.9 (1.8)	1.5 (1.4)	1.6 (1.6)	1.7 (1.4)	1.8 (1.4)
Change	-0.8 (1.8)	-1.5 (2.0)	-2.8 (1.6)	-2.7 (2.0)	-2.7 (1.6)	-2.6 (1.7)
P Value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
BPHII						
N (paired values)		62	61	59	56	42
Baseline		6.8 (2.9)	6.8 (2.9)	6.8 (2.9)	6.9 (2.8)	7.1 (2.7)
Follow-up		5.5 (3.6)	2.2 (2.4)	2.0 (2.6)	2.0 (2.3)	2.3 (2.5)
Change		-1.2 (4.4)	-4.7 (3.2)	-4.8 (3.7)	-4.9 (3.0)	-4.8 (3.5)
P Value		0.034	<0.001	<0.001	<0.001	<0.001
Qmax (mL/s)						
N (paired values)	61	63	61	60	57	41
Baseline	8.1 (3.1)	7.9 (3.2)	8.1 (3.2)	8.0 (3.1)	8.1 (3.3)	8.3 (2.9)
Follow-up	7.6 (3.9)	9.9 (3.9)	12.8 (6.4)	12.3 (5.3)	12.7 (6.3)	11.9 (6.2)
Change	-0.5 (4.2)	2.0 (4.5)	4.7 (6.4)	4.3 (5.5)	4.6 (6.4)	3.7 (6.6)
P Value	0.989	<0.001	<0.001	<0.001	<0.001	0.001

8.1.3 Rezūm Pilot Study: IPSS outcomes based on severity of LUTS

The IPSS changes after Rezūm thermal therapy also were evaluated based on severity of LUTS, moderate (IPSS ≤18) or severe (IPSS ≥19). Figure 8-1 shows that subjects with either moderate or severe symptoms achieved significantly improved scores ($p < 0.05$ to < 0.0001). At baseline, a total of 68% of participants had severe symptoms. Notably in this subgroup urinary symptom scores decreased a mean 37% relative to baseline at 1 month (-9.3 points), and further decreased a mean 65% (-15.8 points), 60% (-14.5 points) at 6 and 12 months, respectively, and were durable through 24 months, a 54 % decrease (-13.4 points). Subjects with moderate symptoms had mean score decreases of 46% (-7.6 points) from 3 to 12 months, and a sustained mean decrease of 54% (-8.8 points) at 24 months. As the Rezūm System will be an attractive minimally invasive treatment for patients with moderate to severe symptoms, the documented success of the Rezūm thermal therapy to treat patients at the upper end of the spectrum of BPH severity is of significance.

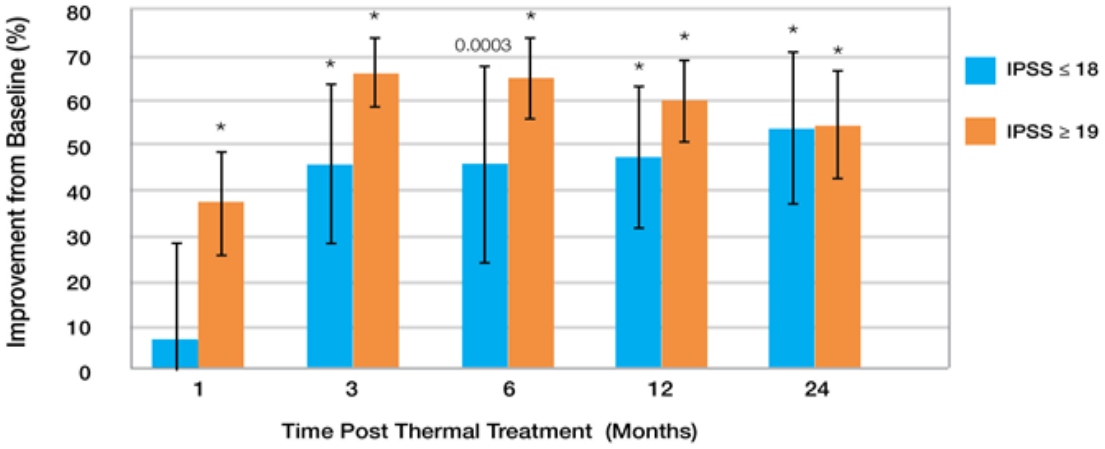


Figure 8-1: **Improvements in IPSS in subjects with moderate and severe LUTS**

8.1.4 Rezūm Pilot Study: Criteria to define "responders" based on IPSS changes

Based on criteria used to define IPSS responders in individual subjects, 72.6% of subjects had ≥50% decrease in their symptom scores at 3 months after Rezūm thermal therapy. This response level exceeds what is considered the threshold described as a clinically meaningful response of ≥25% often used to define a "responder" in drug trials for LUTS/BPH. Improvement in symptom scores ≥50% were observed in over >60% of subjects throughout 24 months post-procedure (Table 8-3). Responses relative to a ≥3 point and ≥5 decrease in IPSS were shown in 93% and 79.1% of subjects at 24 months, respectively. An IPSS change of ≥ 3 points is accepted as being clinically meaningful by the American Urological Association [11].

TABLE 8-3: PROPORTION OF SUBJECTS WITH IPSS IMROVEMENTS

Post treatment	**IPSS Change from Baseline n/N (% of subjects)**	
	≥25%	**≥50%**
3 Months	53/62 (85.5%)	45/62 (72.6%)
6 Months	55/63 (87.3%)	46/63 (73.0%)
1 Year	48/58 (82.8%)	39/58 (67.2%)
2 Years	36/43 (83.7%)	26/43 (60.5%)
	≥3 Points	**≥5 Points**
3 Months	56/62 (90.3%)	51/62 (82.3%)
6 Months	57/63 (90.5%)	53/63 (84.1%)
1 Year	51/58 (87.9%)	47/58 (81.0%)
2 Years	40/43 (93.0%)	34/43 (79.1%)

8.1.5 Rezūm Pilot Study: MRI Imaging to evaluate the physical effects of thermal ablation

Gadolinium-enhanced MRIs, with corresponding 3-dimentional volumetric renderings were used to characterize the ablative lesions, and tissue resorption, as a result of the convective water vapor thermal therapy procedures. Of the 65 men in the pilot study, 59 consented to undergo MRI evaluations after their week 1, and 1, 3 and 6 month post-procedure assessments. Outcomes for 44 subjects have been reported [15]. A single of water vapor treatment resulted in a mean ablative lesion size of 1.7 cm^3. This lesion volume compares with a mean of 4.8 cm^3 per lobe when more than one treatment per lateral lobe was delivered. For prostates lobes treated with more than one water vapor treatment, the gadolinium defects coalesced, evidencing contiguous ablative lesions with tissue resorption occurring over time. In the Mynderse et al. report, as few as a mean of 2 water vapor treatments (range 1-4) per lateral lobe resulted in a mean 38% reduction (-13.8 cm^3) in transition zone volume at 6 months, as compared to baseline 1-week images [15]. The tissue lesions remained within the targeted treatment zone without compromising the integrity of the bladder, rectum, or urinary sphincter. The gadolinium images showed a significant resolution of ablated tissue by 3 months (91.5%) and nearly complete resolution of the ablated tissue by 6 months (95%). Prostate volumes assessed by MRI were significantly decreased at all time points, $p<0.001$ [15]. The volume was reduced 24% at month 3 and 30% at month 6. Prostate volumes measured with TRUS showed a mean decrease of 11% at 12 months ($p<0.001$). In another complementary histological study of excised adenomas in men scheduled for TURP, a distinct demarcation was observed between nonviable treated (ablated) tissue and untreated prostate [13].

8.1.6 Rezūm Pilot Study: Sexual function

A history of erectile dysfunction (ED) was reported by 48% (24/50) of subjects. Erectile function (IIEF-EF) scores were normal (≥26 - 30) for 29.7% (19/64 subjects, whereas 48.4% (31/64) had severe erectile dysfunction (IIEF-EF ≤10). No clinically significant changes in sexual function were observed over the 2-year assessments.

8.1.7 Rezūm Pilot Study: Safety

Mild-to-moderate transient AEs, typically Clavien-Dindo Class I or II, occurred in a portion of the subjects including urinary retention, dysuria, urgency, hematospermia and suspected UTI and resolved within a few days to 4 weeks. The total of 125 events in 45 subjects related to the device/procedure included many anticipated AEs that can occur after rigid cystoscopy. Most AEs (75%) were reported within the first 30 days after the procedure. A total of 14 unrelated, serious AEs were reported in 10 subjects. One subject with persistent LUTS adjudicated as device/procedure related, Clavien-Dindo Grade IIIb, had a median lobe which was not treated. This subject elected to undergo a TURP at 42 days post-procedure. No late occurring adverse events were reported in the 12 to 24 month follow-up including no treatment-related de novo ED.

TABLE 8-4: ADJUDICATED ADVERSE EVENTS

Adverse Event	Events N	Subjects n	%	0-1 mos n	>1-3 mos n	>3-12 mos n	>12-24 mos n
Related SAE	3	1	1.5	1	0	0	0
Unrelated SAE	14	10	15.4	4	1	6	3
Non-serious related AEs	124						
Urinary retention	24	22	33.8	21	2	1	0
Dysuria	14	14	21.5	9	4	1	0
Urinary urgency	14	13	20.0	10	4	0	0
UTI-suspected	13	13	20.0	8	4	1	0
Hematuria	10	9	13.8	10	0	0	0
Poor stream	10	9	13.8	6	3	1	0
Pain/discomfort, other	7	7	10.8	5	2	0	0
Nocturia	6	5	7.7	5	1	0	0
Urinary frequency	5	4	6.2	4	1	0	0
Urethral secretion, without hematuria or stones	3	3	4.6	2	0	1	0
Fever	3	3	4.6	3	0	0	0
Terminal dribbling	2	2	3.1	1	0	1	0
Scrotal pain/discomfort	2	2	3.1	1	1	0	0
Urinary incontinence, urge	2	1	1.5	1	0	0	0

8.1.8 Rezūm Pilot Study: Conclusion

This is the first study of a technology utilizing RF energy to create water vapor, or steam, to convectively deliver targeted, precise thermal energy. This minimally invasive therapeutic option provided clinically significant improvement in LUTS symptoms, urinary flow and quality of life for subjects with symptomatic BPH; responses were durable throughout 24 months follow-up. The tissue ablation and resolution observations with the MRI and histological studies explain and substantiate the commensurate rapid and significant improvements in LUTS after WAVE therapy shown in this open label pilot study [13-15] and the subsequent RCT [16,17].

8.2 Rezūm II Pivotal Study

In the Rezūm II study, a prospective randomized, single-blind, RCT, subjects were treated at 15 participating clinical investigational sites in the United States utilizing RF convective water vapor thermal energy (Rezūm System) in a transurethral approach to treat LUTS associated with BPH [16, 17]. The Rezūm treatments provided rapid improvements within 2 weeks after the procedure. The clinical efficacy and safety outcomes were durable over 12 months with significant and clinically meaningful improved symptoms, flow rate, QoL, decreased incontinence episodes and preserved sexual function. Procedures were performed in an office or ambulatory surgery center setting using oral pain medication, prostate block or conscious sedation. The Rezūm therapy was found to be applicable to treating hyperplastic prostate in each of the transition zone and central zone/median lobe. The study design and results are summarized below.

8.2.1 Rezūm II Study: Subjects and Procedures

Participants were men ≥50 years old with an IPSS ≥13, maximum flow rate of >5 ml/sec to <15 ml/sec with a minimum voided volume of 125 ml, and a prostate volume of 30-80 cm^3 as measured by TRUS.

Excluded were subjects with a PVR greater than 250 ml, PSA greater than 2.5ng/ml with a free PSA less than 25% (unless prostate cancer was ruled out by biopsy), any active UTI within 7 days or two independent infections within the last 6 months. An appropriate wash-out period was required for subjects taking antihistamines, antispasmodics, α-blockers, androgens, gonadotropin-releasing hormone analogs, 5α-reductase inhibitors, as well as antidepressants, anticholinergics, anticonvulsants, ß-blockers (unless with documented evidence of a stable dosing).

A total of 197 subjects were stratified by IPSS severity and randomized 2:1 and received either the Rezūm thermal therapy (136) or a control procedure (61). The control procedure was rigid cystoscopy with simulated active treatment sounds which closely replicated the experiences of the Rezūm thermal treatment procedure. The primary endpoint compared IPSS reduction at 3 months versus baseline between the active treatment and the control arms.

After completing their 3-month follow-up, and up to 6 months following the original procedure date, subjects in the control arm had the option to receive the Rezūm thermal therapy or no treatment. Those subjects who chose an alternative therapy were exited from the study. Any subject who received the thermal therapy (active or crossover) will have annual follow-up evaluations for 5 years. Assessments included subject self-administered questionnaires completed pre-procedure and at follow-up visits: IPSS; QoL instruments (QoL from IPSS, BPHII); sexual function (IIEF-15, MSHQ-EjD); incontinence (OAB-q SF, ICS male IS-SF). Uroflowmetry was repeated at 4 weeks, 3, 6, 12 and 24 months.

TABLE 8-5: BASELINE CHARACTERISTICS FOR ENROLLED SUBJECTS

	Thermal Treatment Mean (SD)	Control Mean (SD)	p Value
Age, years	63.0 (7.1)	62.9 (7.0)	0.914
Body mass index (kg/m^2)	28.7 (4.4)	28.1 (5.0)	0.363
Prostate volume (cc)	45.8 (13.0)	44.5 (13.3)	0.525
Prostate specific antigen (ng/ml)	2.1 (1.5)	2.0 (1.6)	0.695
IPSS	22.0 (4.8)	21.9 (4.7)	0.857
Qmax (ml/sec)	9.9 (2.3)	10.4 (2.1)	0.187
PVR (ml)	82.0 (51.5)	85.5 (51.6)	0.658
IPSS QoL score	4.4 (1.1)	4.4 (1.1)	0.800
BPH Impact Index	6.3 (2.8)	6.2 (2.9)	0.817
ICS male score	4.4 (2.8)	4.6 (2.3)	0.764
IIEF-Erectile function domain score	17.2 (10.3)	16.5 (9.8)	0.693
MSQH-EjD: Ejaculatory dysfunction score	7.8 (4.1)	9.0 (3.8)	0.050
OAB-q SF Bother scale	39.6 (18.0)	39.9 (18.3)	0.906
OAB-q SF HRQL	64.5 (20.0)	66.7 (16.9)	0.470

8.2.2 Rezūm II Study: Comparison of Thermal Therapy and Control Arms at 3 Months

The primary effectiveness endpoint for the treatment group was achieved at 3 months with IPSS reduced by 50%, as compared with a 20% reduction in IPSS for the control group ($p<0.0001$). Other outcomes

for the treatment group, including the Qmax, QoL and BHP II, were significantly improved (p<0.0001) in comparison to the control group. Treatment effects were sustained at 24 months (presented in Figure 8-3).

No clinically significant changes in sexual function were observed between the treatment group and the control group.

Subjects in the treatment group had a significant improvement in OAB-q SF scores for overactive bladder bother and impact on life (p<0.0001) (data not shown). The total ICS male incontinence score decreased significantly from baseline (mean 4.40 ± 2.86) to 3 months and through to 24 months (mean 3.0 ± 2.6; paired t test p-<0.0001) (data not shown).

TABLE 8-6: COMPARISONS OF MEAN CHANGES AT 3 MONTHS

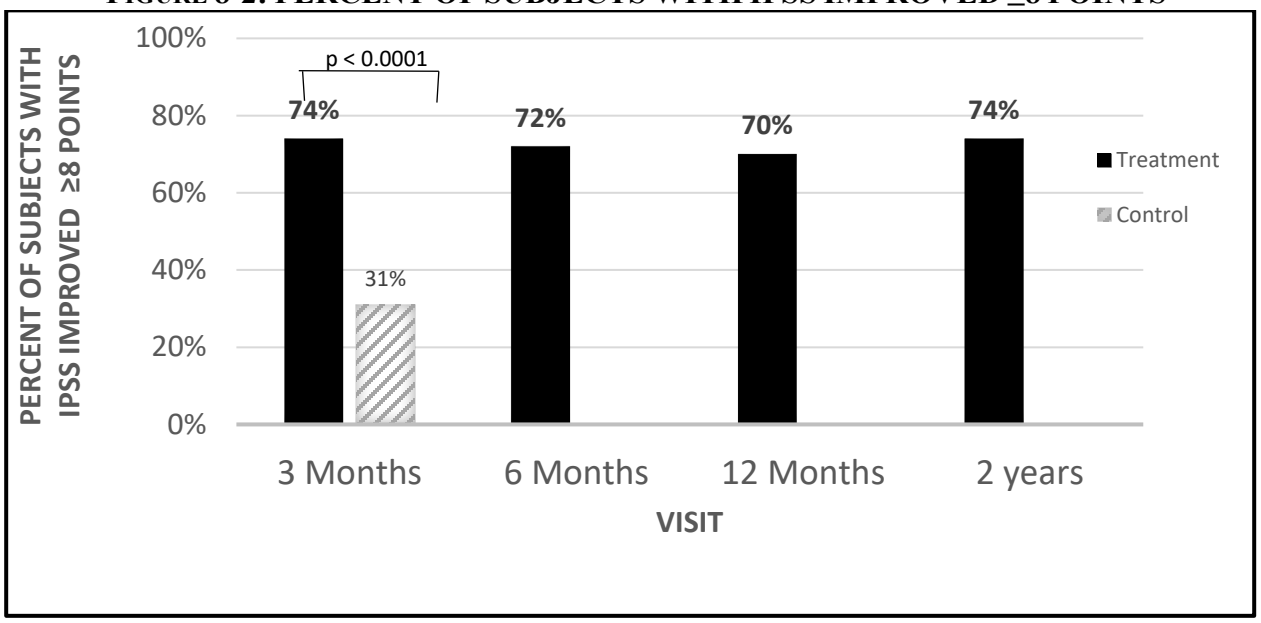
Outcome Measure	Thermal Therapy ITT Group (N=136) Mean ± SD			Control ITT Group (N=61) Mean ± SD			P *
	Baseline	3 Months	Change	Baseline	3 Months	Change	
IPSS	22.0 ± 4.8 (136)	10.8 ± 6.5 (136)	-11.2 ± 7.6	21.9 ± 4.7 (61)	17.5 ± 7.6 (61)	-4.3 ± 6.9	<0.0001
Qmax	9.9 ± 2.3 (136)	16.1 ± 7.3 (133)	6.2 ± 7.1	10.4 ± 2.1 (61)	10.8 ± 4.0 (61)	0.5 ± 4.2	<0.0001
QoL of IPSS	4.4 ± 1.1 (136)	2.3 ± 1.5 (134)	-2.1 ± 1.6	4.4 ± 1.1 (61)	3.5 ± 1.5 (61)	-0.9 ± 1.5	<0.0001
BPHII	6.3 ± 2.8 (136)	2.9 ± 2.9 (134)	-3.4 ± 3.5	6.2 ± 2.9 (61)	4.7 ± 3.5 (61)	-1.5 ± 3.0	0.0003
IIEF-EF	22.6 ± 7.4 (91)	22.7 ± 8.4 (90)	0.1 ± 7.4	21.2 ± 8.3 (40)	21.0 ± 9.1 (40)	-0.3 ± 5.6	0.795
MSHQ-EjD Function	9.3 ± 3.1 (91)	9.7 ± 4.5 (90)	0.3 ± 4.3	9.8 ± 3.6 (40)	9.6 ± 4.3 (40)	-0.2 ± 3.2	0.443
MSHQ-EjD Bother	2.2 ± 1.7 (91)	1.8 ± 1.7 (90)	-0.4 ± 1.9	2.0 ± 1.7 (40)	1.8 ± 1.8 (40)	-0.2 ± 1.9	0.623

**P* value using a two sample t-test comparing mean ± SD changes in the treatment arm and control arms for IPSS, Qmax, QoL, BPHII; ITT= intent to treat analysis.

8.2.3 Rezūm II Study: IPSS as Primary Endpoint

An improvement in IPSS of 8 points or greater was documented in 74% of subjects in the treatment group versus 31% in the control group at 3 months; the outcome was sustained at 24 months as shown in Figure 8-2. An 8-point or greater improvement is considered a "marked improvement".

FIGURE 8-2: PERCENT OF SUBJECTS WITH IPSS IMPROVED ≥8 POINTS



Subjects in the treatment group with either moderate (IPSS ≤ 18) or severe (IPSS ≥19) symptoms had improved scores (p=0.0297 to <0.001) in comparison to the control group (Table 8-7). Notable were subjects with IPSS ≥19 that had mean IPSS improvements of 14.2 ± 7.3 points at 6 months, 13.5 ± 6.9 points at 12 months and 13.0 ± 7.0 at 24 months. Thermal therapy treatments resulted in IPSS reductions as early as 2 weeks after the procedure (p=0.0006), further improving at three months with an average of decrease of 50% or greater (p<0.0001), and sustained through 24 months.

TABLE 8-7: OUTCOMES STRATIFIED BY IPSS SEVERITY: RESPONDERS WITH AT LEAST 30% SCORE IMPROVEMENTS AT 3 MONTHS

Baseline IPSS Strata Mean [Min- Max]	Thermal Therapy Group % (n/total N)	Control Group % (n/total N)	p-Value (1-sded Z test)
IPSS – all scores	77.9 (106/136)	34.4 (21/61)	<0.0001
IPSS ≤18 17 [13-18]	59.5 (22/37)	31.3 (5/16)	0.0297
IPSS ≥19 24 [19-34]	84.9 (84/99)	35.6 (16/45)	<0.0001

8.2.4 Rezūm II Study: Treatment effects durable throughout 24 months

Significant differences (p<0.05) in outcomes between the thermal therapy group and control group († at ≤3 months), as well as in the treatment group through 24 months versus baseline (*) are shown in Figure 8-3. This data highlights the rapid improvements in IPSS, Qmax and QoL evident before 1 month after thermal treatment, which improvements sustained through 24 months. No significant differences in erectile function (IIEF-EF) or ejaculatory function (MSHQ-EjD function) occurred

between the treatment and control arms. The presence of a median lobe was not a significant factor in predicting a change in IPSS.

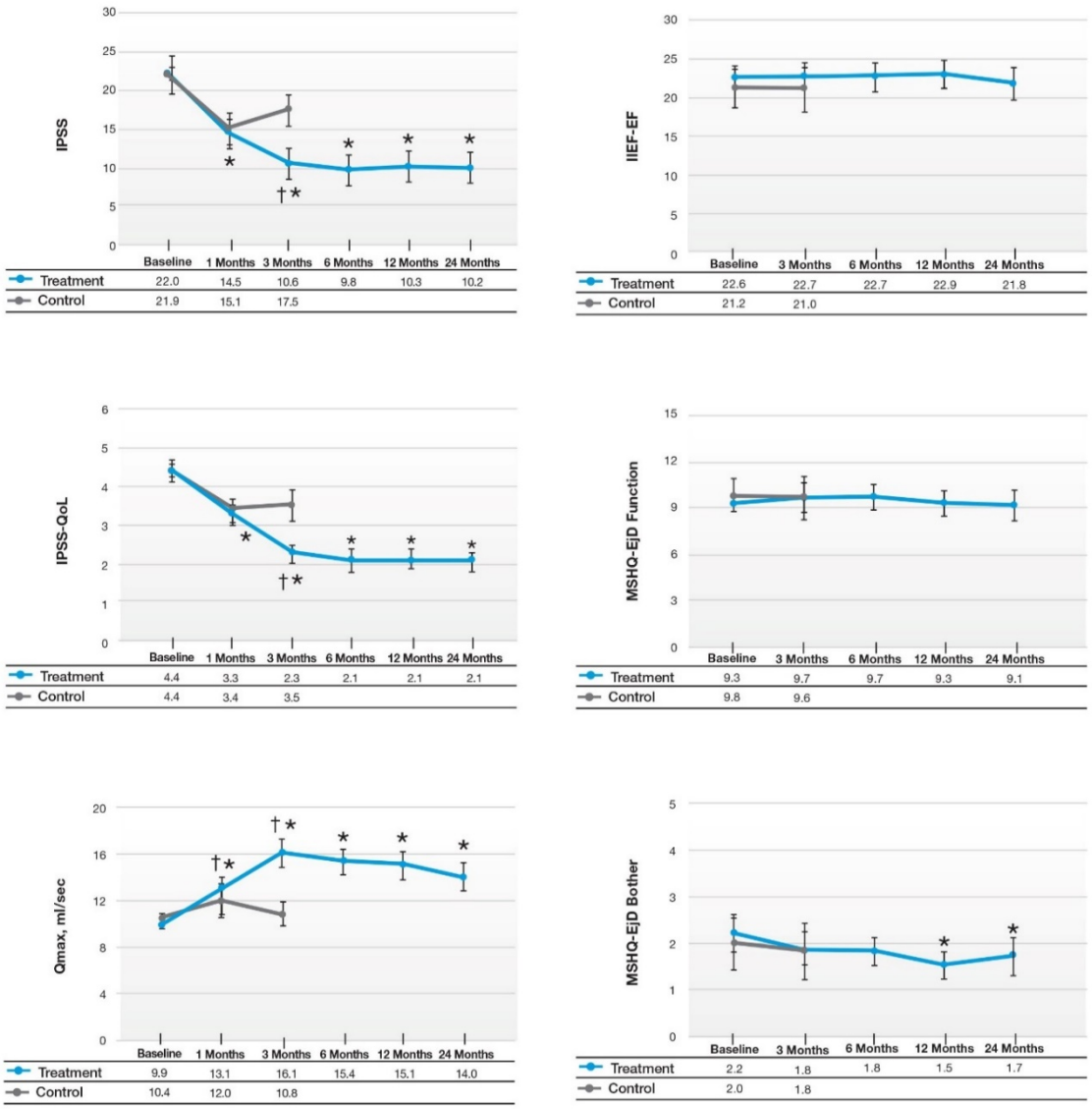


Figure 8-3: TREATMENT EFFECTS OVER 24 MONTHS

8.2.5 Rezūm II Study: Sexual function

A prior history of erectile dysfunction (ED) was documented in 52% of treatment subjects and 54% of control subjects (P = 0.801), and a spectrum of decrease-to-absence of ejaculation in 26% in the treatment subjects and 18% in the control subjects (P = 0.237). As shown in Figure 8-3 no significant differences in erectile function (IIEF-EF) or ejaculatory function (MSHQ-EjD function) occurred between the active and control arms in the blinded 3 months of study, or in the treatment arm throughout 24 months.

The impact of changes in IIEF-EF was evaluated using the criterion of minimum clinically important differences (MCID) in erectile function (EF) described by Rosen et al, which represents the amount of change in the EF domain needed to be clinically meaningful to subjects [20]. For each EF severity category, the MCID would require a minimal EF score increase of 2 for men with mild ED, an increase of 5 for men with moderate ED, and 7 for men with severe ED. Changes in IIEF-EF also were analyzed relative to the baseline severity of LUTS, either moderate or severe IPSS. The MCID helps to define responses to interventions benefitting EF. Its use in the Rezūm pivotal trial is the first use of this assessment in a non-pharmacological intervention study related to ED. At 3 months after thermal therapy, 32% of subjects achieved MCIDs in EF scores as did 27% of subjects at 1 year and 23% at 2 years, including those with moderate to severe ED (Table 8-8).

TABLE 8-8: MIMIMAL CLINICALLY IMPORTANT DIFFERENCES (MCID) IN IIEF-EF CHANGES

IIEF-EF Baseline Severity	Month 3 (N = 90 sexually active) MCID Increase			Month 12 (N= 77 sexually active) MCID Increase			Month 24 (N= 71 sexually active) MCID Increase		
	n/N	Mean ± SD	Range	n/N	Mean ± SD	Range	n/N	Mean ± SD	Range
Severe (1-10)	2/7	12.5 ± 4.9	9-16	2/3	11.5 ± 3.5	9-14	1/4	20.0 ± NA	20-20
Moderate (11-16)	9/15	10.1 ± 4.6	5-17	6/13	11.2 ± 4.4	7-18	5/11	10.0 ± 3.9	6-15
Mild (17- ≤ 25)	18/68	4.0 ± 2.2	2-10	13/61	5.3 ± 2.8	2-12	10/56	5.4 ± 3.3	2-11
Improved Scores, n (%)	29/90 (32)			21/77 (27)			16/71 (23)		

8.2.6 Rezūm II Study: Median Lobe Treatment

A total of 42 of 135 (31.1%) treatment subjects had a median lobe or elevated bladder neck from central zone hyperplasia, of which 30 were treated at the discretion of the physician. Median lobes received an average of 1.6 water vapor injections. Subjects without a median lobe, and subjects with median lobes that were treated, experienced similar improvements in symptom scores (p=0.33) and flow rates (p=0.52). Eleven of 61 (18%) control subjects had a median lobe.

8.2.7 Rezūm II Study: Procedural pain management and catheterization

Investigators used varying combinations of pain and anxiety management during procedures based on their clinical judgment and standard of practice. Of the 196 subjects, 135 (68.9%) received oral sedation only, 41 (20.9%) had a prostate block, and 20 (10.2%) received conscious IV sedation.

Catheterization immediately post-procedure was performed at the discretion of the treating physician, frequently done to avoid effects of inflammation and swelling that might occur. A total of 90.4% (122/135) of treatment subjects were catheterized for a mean 3.4 ± 3.2 days. Of these catheterizations, 68% (83/122) were discretionary and 32% (39/122) were due to an unsuccessful voiding trial immediately following the procedure. In the control group, 19.7% (12/61) of subjects were catheterized for a mean 0.9 ± 0.8 days.

Subjects reported that time to resume usual activities after discharge, typically after removal of the catheter, was a median of 4 (0-90) days for the treatment group and 1 (0-15) day for the control group.

8.2.8 Rezūm II Study: Safety assessments

No perioperative adverse events occurred. Two treatment subjects had three SAEs adjudicated as procedure-related (Table 8-9). One subject had de novo extended urinary retention due to undiagnosed intravesical lobe protrusion and subsequently had a simple (open) prostatectomy. The second subject had nausea and vomiting due to an allergic reaction to alprazolam and was hospitalized overnight for observation. Other non-serious related AEs included post-procedure dysuria, hematuria, frequency and urgency, hematospermia and UTI. AEs were of mild-to-moderate severity and most resolved within 3 weeks.

Subjects' self-reports of modest decreases in ejaculatory volume occurred in 6 men (4.4% of 136), reported within 17 to 44 days after treatment in 4 subjects and after 5 and 7 months, respectively, in 2 subjects. Of these 6 subjects, 3 had a history of EjD. Anejaculation was self-reported in 4 men (2.9%), occurring within 6 to 61 days after treatment. These events are not reflected in the MSHQ-EjD scores. The presence of a median lobe did not have an impact on the profile of adverse events related to sexual function, specifically ejaculation effects in the 30 subjects who received thermal therapy. No treatment or device-related de novo ED was reported during the 12 month period after treatment

TABLE 8-9: ADJUDICATED ADVERSE EVENTS

Adverse Event	Treatment (n=136) 0-3 Months		Control (n=61) 0-3 Months		Treatment (n=134) >3-12 Months		Treatment (n=117) >12-24 Months	
	No. Events	No. Subjects (%)	No. Events	No. Subjects (%)	No. Events	No. Subjects (%)	No. Events	No. Subjects (%)
Serious AEs	**8**	**7 (5.1%)**	**0**	**0 (0.0%)**	**11**	**9 (6.7%)**	**2**	**2 (1.7%)**
Related Serious AEs	**3**	**2 (1.5%)**	**0**	**0 (0.0%)**	**0**	**0 (0.0%)**	**0**	**0 (0.0%)**
Nausea	1	1 (0.7%)	1	1 (1.6%)	0	0 (0.0%)	0	0 (0.0%)
Vomiting	1	1 (0.7%)	1	1 (1.6%)	0	0 (0.0%)	0	0 (0.0%)
Urinary Retention	1	1 (0.7%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)
Non-Serious AEs	**164**	**59 (43.4%)**	**26**	**14 (23.0%)**	**50**	**28 (20.9%)**	**45**	**26 (22.2%)**
Related Non-Serious AEs	**138**	**52 (38.2%)**	**11**	**6 (9.8%)**	**9**	**8 (6.0%)**	**0**	**0 (0.0%)**
Dysuria	23	23 (16.9%)	1	1 (1.6%)	1	1 (0.7%)	0	0 (0.0%)
Hematuria, Gross	16	16 (11.8%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)
Hematospermia	10	10 (7.4%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)
Urinary Frequency	8	8 (5.9%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)
Urinary Urgency	8	8 (5.9%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)
UTI, Suspected	6	5 (3.7%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)
Urinary Retention	5	5 (3.7%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)
Epididymitis	4	4 (2.9%)	1	1 (1.6%)	0	0 (0.0%)	0	0 (0.0%)
Anejaculation	4	4 (2.9%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)
Pain/Discomfort, Pelvic	4	4 (2.9%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)
UTI, Culture Proven	4	4 (2.9%)	0	0 (0.0%)	0	0 (0.0%)	0	0 (0.0%)
Decrease in Ejaculatory Volume	3	3 (2.2%)	0	0 (0.0%)	2	2 (1.5%)	0	0 (0.0%)

8.2.9 Rezūm II Study: Conclusion

The convective water vapor energy ablation of prostate adenomas with the Rezūm System demonstrated statistically significant and clinically meaningful improvements in the symptoms for LUTS due to BPH as early as within 2 weeks after treatment. The clinical efficacy and safety were durable over 24 months with improved symptoms, flow rate, QoL, decreased incontinence episodes and preserved sexual function. These results support the application of WAVE technology as a safe and effective minimally invasive therapeutic alternative for symptomatic BPH without compromising sexual function including treatment of patients with a median lobe.

9 Rezūm XL Clinical Study Design

This is a prospective, multicenter, single arm clinical trial designed to evaluate the safety of the Rezūm System in treating subjects with symptomatic BPH for prostate sizes >80cm^3 and ≤150 cm^3.

A total of 88 subjects will be enrolled in the study. After the completion of the 6-month follow-up evaluation a responder analysis will be completed based on baseline IPSS (responder) at 6 months post-procedure.

Subjects with signed informed consents and who meet all the inclusion and none of the exclusion criteria will be enrolled to receive convective water vapor ablation treatments using the Rezūm System.

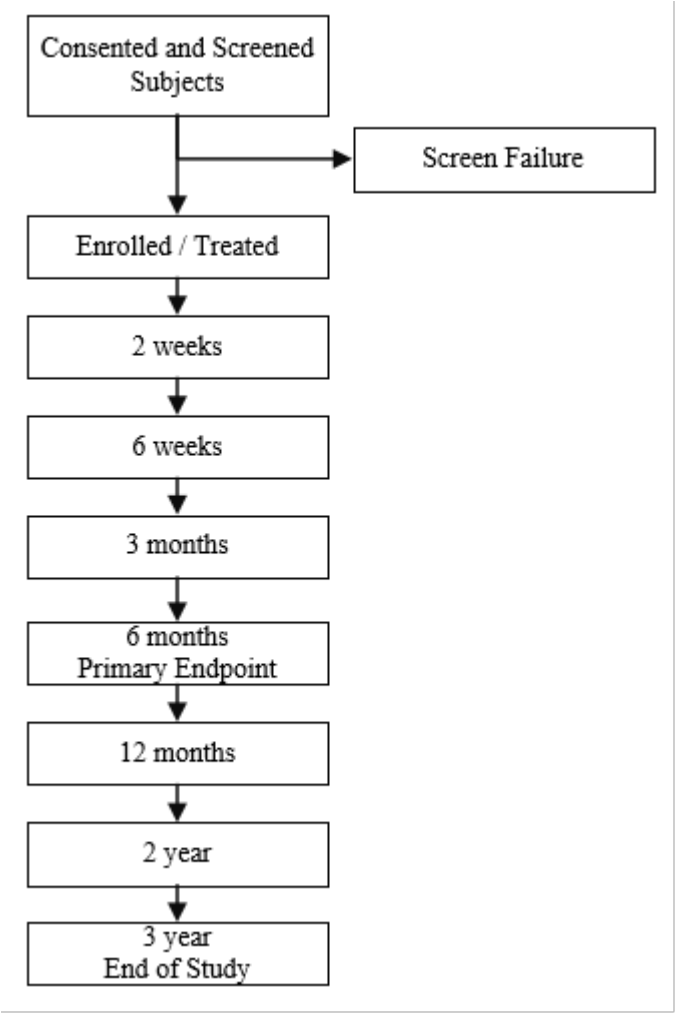


FIGURE 9-1: STUDY DESIGN FLOW CHART

9.1 Screening and Enrollment

Subjects who give written informed consents to undergo screening procedures will be considered screened subjects. These subjects will undergo a series of baseline screening evaluations. The subjects will be required to meet all inclusion/exclusion criteria prior to enrollment.

Test results that are within the timeframes specified in this protocol may be used. Research coordinators will review questionnaires for completeness only. If a question is left unanswered or is un-interpretable, the coordinator will return the questionnaire to the subject to complete or for clarification at the time of the visit.

Subjects meeting all study inclusion/exclusion criteria after their baseline evaluation will be enrolled upon insertion of the Rezūm delivery device at the time of the Rezūm procedure. Only enrolled subjects constitute the ITT analysis population and will be considered evaluable. Those subjects who do not meet inclusion/exclusion criteria after the screening or baseline evaluation will be counted as screen failures and will be withdrawn from the study provided any screening evaluation related AEs occurring during baseline testing have been resolved.

To access long-term efficacy, all subjects receiving the Rezūm treatment will be monitored for AEs and IPSS assessment for 3 years post procedure.

9.2 Investigational Sites, Sample Size and Study Duration

The study will have up to 11 sites activated. If non-US sites are recruited into the study, a maximum of 1 site outside of the US will be allowed in the study. This non-US sites will be from Australia. A site is considered authorized to enroll subjects after IRB/EC approval(s) are received, all training has occurred, and the study-specific regulatory documents are completed. A site will be considered one of the 11 clinical investigation sites if it is active, which is defined as having subject(s) enrolled. Sites who are authorized to enroll subjects, but do not enroll any subjects, may be replaced and will thereafter not be considered as one of the 11 clinical investigation sites. No one site may enroll more than 33% of the total study sample size.

The maximum size of the study will not exceed 88 subjects. The estimated study duration is 4 years, comprised of 6 months for enrollment, 3 years of follow-up, and 6 months to complete data collection / analysis and compile the final study report.

9.3 Study Objective and Endpoints

The purpose of the study is to determine the safety and efficacy of the Rezūm System in prostate sizes $>80cm^3$ and $\leq 150\ cm^3$. Data from this study will be used to support the expanded indication labeling application for the device in the U.S. and other countries. The endpoints studied to meet these objectives are described below.

9.3.1 Primary Efficacy Endpoint

For the primary efficacy endpoint to be met, the proportion of the modified intention-to-treat analysis population that responds to therapy must be statistically significantly greater than 50%. A responder is defined as a subject who has an IPSS improvement $\geq$ 30% post-treatment compared to baseline.

9.3.2 Primary Safety Endpoint – Post Procedure Device Related Serious Complications

For the primary safety endpoint to be met, the proportion of the treated analysis population that experiences a safety composite event must be statistically significantly less than 12%.

These composite device-related serious complications for this endpoint are defined as:

- Perforation of the rectum or GI tract
- Formation of fistula between the rectum and urethra
- Permanent damage to the bladder, trigone or ureteral orifices requiring intervention
- Grade 2 hydronephrosis

9.3.3 Safety Monitoring Early Stopping Rule

An early stopping rule is instituted in the study to monitor the rate of steam-related injury.

This early stopping rule is intended to provide a higher degree of sensitivity to steam-related injury and earlier time-frame than is provided by the primary safety endpoint composite which includes a wider spectrum of adverse events and a longer time period of 6-months post-procedure.

If 2 patients experience a post-procedure CEC-determined device-related steam-related injury requiring intervention within the first 20 subjects treated with Rezūm, the early 6 week post procedure stopping rule is triggered. A threshold of 2 patients with an event out of the first 20 subjects is an observed event rate of 10%.

For the study stopping rule "Intervention" is defined as any surgical procedure or hospitalization performed to remedy or correct a potential permanent damage to the bladder, trigone or ureteral orifices, perforation of the rectum or GI tract, or formation of fistula between the rectum and urethra or bladder.

Irrigation of clot retention or necrotic tissue obstruction is allowed, if medically necessary, and should be reported as an adverse event but will not be counted toward the stopping rule.

9.3.4 Secondary Endpoints

The following secondary endpoints will be statistically assessed to provide additional characterization of the Rezūm System in the treatment of obstructive BPH. Secondary endpoint S2 with prespecified hypotheses and well-controlled Type I error will be used to and to support potential labeling claims. Refer to Section 12.4 for further details.

- Secondary Endpoint S1: Device-related retention catheterization rate
- Secondary Endpoint S2: Absolute IPSS improvement at 6 months
- Secondary Endpoint S3: Percent Responder at 1 year
- Secondary Endpoint S4: Percent Responders at 2 years
- Secondary Endpoint S5: Percent Responders at 3 years

9.3.5 Ancillary Endpoints

The following ancillary endpoints are to provide additional characterizations of the safety and effectiveness of the Rezūm System in the treatment of obstructive BPH. Refer to Section 12.5 for further details.

- Ancillary Endpoint A1: Additional Responder Analyses
- Ancillary Endpoint A2: Change in Qmax and PVR
- Ancillary Endpoint A3: Change in Sexual Function
- Ancillary Endpoint A4: Change in Quality of Life
- Ancillary Endpoint A5: Procedure Parameters
- Ancillary Endpoint A6: PGI-I Questionnaire
- Ancillary Endpoint A7: Rezūm II Comparisons

9.4 Subject Selection

To be eligible for enrollment in the study, subjects must meet all of the inclusion criteria and none of the exclusion criteria.

9.4.1 Inclusion Criteria

1. Male subjects $\geq$ 50 years of age who have symptomatic BPH.
2. International Prostate Symptom Score (IPSS) score $\geq$ 13.
3. Peak urinary flow rate (Qmax): $\geq$ 5ml/sec to $\leq$ 12 ml/sec with minimum voided volume of $\geq$ 125 ml.

4. Post-void residual (PVR) ≤300 ml.
5. Prostate volume >80 cm^3 to ≤150 cm^3

9.4.2 Exclusion Criteria

Urology

1. Any prior invasive prostate intervention (e.g., "Radiofrequency" thermotherapy, balloon, microwave thermotherapy, "Prostatic Urethral Lift", "Transurethral Resection", or laser) or other surgical interventions of the prostate.
2. Undergone a prostate biopsy within 60 days prior to the scheduled treatment date or has an imminent need for surgery.
3. Verified acute bacterial prostatitis within last 12 months documented by culture.
4. Active or history of epididymitis within the past 3 months.
5. Urethral strictures, bladder neck contracture, unusual anatomy or muscle spasms that would prevent the introduction and use of the Rezūm device.
6. Diagnosed bladder, urethral or ureteral stones or active stone passage in the past 6 months, provided that stones that are known to be in the kidney and have been stable for a period exceeding 3 months are permissible.
7. Subject interested in maintaining fertility.
8. Use of the following medications where the dose is not stable (stable dose defined as the same medication and dose in the last three months):
    a. Beta-blockers;
    b. Anticonvulsants;
    c. Antispasmodics;
    d. Antihistamines;
    e. Alpha blockers for BPH and anticholinergics or cholinergics;
    f. Type II, 5-alpha reductase inhibitor (e.g., finasteride (Proscar, Propecia));
    g. Dual 5-alpha reductase inhibitor (e.g., dutasteride (Avodart));
    h. Estrogen, drug-producing androgen suppression, or anabolic steroids;
    i. PD5 Inhibitors (e.g., Viagra, Levitra or Cialis)
9. Subjects who have had an incidence of spontaneous urinary retention either treated with indwelling transurethral catheter or suprapubic catheter 6 months prior to baseline. A provoked episode now resolved is still admissible.
10. Evidence of atonic neurogenic bladder evaluated by a baseline urodynamic assessment.
11. Visible hematuria with subject urine sample without a known contributing factor.
12. Presence of a penile implant or stent(s) in the urethra or prostate.
13. Active urinary tract infection by culture within 7 days of treatment or two documented independent urinary tract infections of any type in the past 6 months.

Gastroenterology

14. Previous pelvic irradiation or radical pelvic surgery.
15. Previous rectal surgery (other than hemorrhoidectomy) or known history of rectal disease.

Nephrology

16. Compromised renal function defined as serum creatinine > 2.0 mg/dl.
17. Hydronephrosis (Grade 2 or higher).

Oncology

18. Prostate cancer testing:
    If PSA is > 2.5 ng/ml and ≤ 10 ng/ml with free PSA <25%, prostate cancer for the subject must be/had been ruled out through a negative biopsy prior to enrollment.
    - Males 50-59 years - PSA is >2.5 ng/ml and ≤10 ng/ml with free PSA <25%,
    - Males 60+ years - PSA is >4 ng/ml and ≤10 ng/ml, with free PSA <25%
19. History of confirmed malignancy or cancer of the prostate or bladder; however, high grade prostatic intraepithelial "PIN" is acceptable.
20. History of cancer in non-genitourinary system that is not considered cured (except basal cell or squamous cell carcinoma of the skin). A potential participant is considered cured if there has been no evidence of cancer within five years of enrollment.

Cardiology

21. History of clinically significant congestive heart failure (i.e., NYHA Class III and IV).
22. Cardiac arrhythmias that are not controlled by medication and/or medical device.
23. An episode of unstable angina pectoris, a myocardial infarction, transient ischemic attack, or a cerebrovascular accident within the past six months.

Pulmonology

24. History of significant respiratory disease where hospitalization for the disease is required.

Hematology

25. Diagnosed or suspected bleeding disorder, or coagulopathies.
26. Use of antiplatelet or anticoagulation medication except for low dose aspirin (<100mg/day) within 10 days prior to treatment.

Endocrinology

27. History of diabetes not controlled by a stable dose of medication over the past three months, provided that patients with a hemoglobin A1c <8.0% are allowed.

Immunology

28. History of immunosuppressive conditions (e.g., AIDS, post-transplant).

Neurology

29. Any cognitive or psychiatric condition that interferes with or precludes direct and accurate communication with the study investigator regarding the study or affect the ability to complete the study quality of life questionnaires.
30. Diagnosed or suspected primary neurologic conditions such as multiple sclerosis or Parkinson's disease or other neurological diseases known to affect bladder function, sphincter function or poor detrusor muscle function (<25% of accepted and established nomograms).

General

31. Currently enrolled in any other pre-approval investigational study in the US (does not apply to long-term post-market studies unless these studies might clinically interfere with the current study endpoints (e.g., limit use of study-required medications, etc.)
32. Any significant medical history that would pose an unreasonable risk or make the subject unsuitable for the study.
33. Inability to provide a legally effective "Informed Consent Form" and/or comply with all of the required follow-up requirements.

9.5 Site Selection

Sites will be selected based on the availability of the subject pool to be included in the study and the sites' ability to perform the research in compliance with FDA IDE regulations and guidelines.

The sites and physicians are required to comply with the FDA's IDE regulations (the definition of subject enrollment is per this protocol). In addition, the sites must be able to comply with any country-specific requirements as well as other requirements specified by their respective IRB or EC.

9.6 Physician Selection

Physicians selected must have experience in performing cystoscopies, treating BPH subjects and/or other male urological therapies. Selected physicians will be trained through the commercial training program in the use of the Rezūm System prior to enrolling subjects. The primary investigator will ensure that only trained sub-investigators who satisfy the physician selection criteria can perform any part of the study interventional procedure.

Healthcare professionals or site staff that assist or perform the follow-up evaluations are not required to be trained on the use of the Rezūm System, but must be delegated and trained to perform the follow-up visit procedures.

10 Study Procedures

10.1 Pre Screening, Screening, and Baseline

An investigational site may pre-screen potential subjects by reviewing medical records to identify the study population. Once identified, these subjects can be approached for the study and consented. The site may not initiate any study-specific (non-standard of care) procedures without first obtaining an informed consent.

All baseline testing and evaluations must be done as close to the time of treatment as possible and repeated if needed. Any required procedures that were performed before obtaining an informed consent as part of the standard of care may be used in lieu of the study tests as described in Table 10-1.

The following evaluations will be completed for all study candidates. Evaluations performed within the screening window may be acceptable. The required baseline evaluations are shown below:

TABLE 10-1: SCREENING EVALUATIONS CONDITIONS

Evaluations	Accepted interval prior to procedure (unless specified otherwise)	Condition
TRUS	Within 6 months of consent	Evaluation is complete and adequately documented in report for assessment.
TAUS	Within 6 months of consent	Evaluation is complete and adequately documented in report for assessment.

Evaluations	Accepted interval prior to procedure (unless specified otherwise)	Condition
Retroperitoneal ultrasound (renal and bladder)	Within 6 months of consent	Evaluation is complete and adequately documented in report for assessment.
Digital rectal exam (DRE)	Within 30 days	Evaluation is complete and adequately documented in report for assessment.
PSA level	Within 180 days of consent	**Males 50-59** – If PSA is >2.5 ng/ml and <10 ng/ml with free PSA <25% **Males 60+** - If PSA is >4 ng/ml and ≤10 ng/ml, with free PSA <25%
Prostate biopsy for cancer	Within 12 months	For men with a history of elevated PSA (defined above by age), prostate cancer must be ruled out by a negative biopsy.
Medical history	Within 30 days	Evaluation is complete and adequately documented in report for assessment.
Physical exam evaluation	Within 30 days	Evaluation is complete and adequately documented in report for assessment.
Uroflowmetry • Voided volume (must be ≥ 125 mL or test must be repeated for all the uroflow tests) • Voiding time • Peak flow rate (Qmax)[1] • Average flow rate	Within 60 days	Must be performed before cystoscopy or ≥14 days after cystoscopy and no evidence of UTI.
Post-void residual urine volume (PVR; may be measured by either ultrasound or catheterization but the same method must be used pre- and post-treatment)	Within 60 days of treatment	Must be performed before cystoscopy or ≥14 days after cystoscopy and no evidence of UTI. The PVR method used during screening must be the same as that used in the follow-up tests.
Blood analysis • Complete blood cell count (CBC) • Blood urea nitrogen (BUN) • Blood sugar • Serum creatinine	Within 30 days	
Urine analysis • Sugar • Protein • WBC/RBC • Bacteria	Within 30 days	

Evaluations	Accepted interval prior to procedure (unless specified otherwise)	Condition
Urine culture for infection only if infection is suspected		Must have documented negative infection before enrolling and before taking the IPSS at baseline.
Urodynamic Testing	Within 60 days	The Urodynamic guidelines provided by the study sponsor must be used by all participating sites.
Subject questionnaires • International Prostate Symptoms Score (IPSS) – Standard • BPH Impact Index (BPHII) • MSHQ-EjD • International Index of Erectile Function (IIEF) • EQ-5D-5L • Pain Scale	Within 30 days	
Screening flexible cystoscopy (recorded)	Within 60 days	
Current or prior (up to 6 months) medication consumption	Prior to enrollment	A list of current and prior medication is required to determine the need for wash in and stability of dose.
Note: [1]Due to the variability of the uroflow study, only whole numbers for Qmax will be used. Fractions will be rounded to the nearest whole number following conventional rounding rules.		

10.2 Subject Enrollment

Only subjects who meet all the inclusion and none of the exclusion criteria will be eligible to be enrolled and participate in the study. A subject will be considered officially enrolled only if the subject has signed an informed consent, meets all the inclusion and none of the exclusion criteria and at the time of the Rezūm Delivery device insertion into the urethra.

10.3 Concomitant Therapy

Therapy (medication and non-medication therapies) not restricted by a protocol requirement may be used during the study for the treatment or prevention of disease or to maintain good health. However, the subjects should not take concomitant medications that affect the BPH symptoms except for the stable dose at baseline out to the 3 month follow-up visit.

10.4 Summary of Study Procedure

The treatment for the study may be performed in an office, outpatient, ambulatory surgical, or hospital setting.

10.4.1 Peri-Procedural Medication

A 5-day course of oral antibiotic is recommended to be started up to 2 days prior to the procedure and completed after the procedure. An oral NSAID also may be given prior to the procedure.

Immediately pre-procedure, a urine analysis must be completed to verify no new active urinary infections have arose between screening and treatment.

There are three main pain medication protocol options used with the Rezūm procedure. Conscious sedation, a prostate block or oral medication. The first option is conscious sedation (propofol) and it may be done in clinic, an ambulatory setting, outpatient or hospital setting (per physician's recommendation). The second option is to use a local anesthesia in the form of a prostate block given 5-10 minutes before the procedure. The third option is oral medication, which includes an anti-anxiety medication (e.g., Valium or Xanax) and an oral analgesic (e.g. hydrocodone or oxycodone) given at least 45 minutes prior to the procedure. The physician has the discretion to prescribe anti-pain or other medications typically used during the rigid cystoscope procedures. If administered, the use of these medications will be recorded in the case report form.

It is recommended that a bolus of lidocaine gel is injected into the urethra 10 minutes prior to beginning the Rezūm procedure. In general, the Rezūm procedure approach is similar to a rigid cystoscopy. Therefore, the same type of medication/anesthetic used with rigid cystoscopy procedures is recommended for the Rezūm procedure. If administered, the use of an anesthetic or sedative will be recorded in the case report form.

10.4.2 Rezūm Treatment

The objective of the treatment is to create contiguous, overlapping lesions running parallel to the natural slope of the urethra. Both pre-procedure cystoscopy and TRUS help to "map" or plan the ideal treatment. The total number of treatments in each lobe of the prostate is determined by the length of the hypertrophied prostatic tissue and can be customized to the configuration of the gland including the median lobe.

The Rezūm System should be prepared per the Instructions for Use. A compatible 4 mm, 30º, 30cm cystoscopy lens is inserted into the Rezūm Delivery Device and the cystoscopy camera and light source is attached to the Delivery Device, allowing the visual images to be viewed on a monitor. The distal tip of the Delivery Device is coated with a lidocaine gel or equivalent water soluble gel to lubricate the device prior to insertion into the urethra.

The Rezūm procedure is performed with the patient in the dorsal lithotomy position and the treatment device is inserted into the urethra. Confirmation of the contours of the prostate and planned disbursement of thermal lesions as derived from the baseline cystoscopy is recommended. Examination of the bladder and specifically the ureteral orifices is important, particularly in the event that median lobe tissue has elevated the orifice. Treatment begins with the needle tip visually positioned and inserted beginning approximately 1 cm distal to the bladder neck. It is suggested to complete all treatments on one side of the gland in order take advantage of the latent heat from prior treatments on that side, and then proceed to treat tissue on the contralateral side of the gland.

Multiple thermal treatments are delivered with the retractable vapor needle that penetrates a fixed 10.25 mm into the prostatic tissue. Each treatment delivers approximately 208 calories of thermal energy by converting 0.42 mL of sterile water into vapor thermal energy with the application of RF current to the inductive coil within the device. The treatment needle has a total of 12 small emitter holes spaced around its tip at 120° intervals to allow circumferential dispersion of thermal energy to create an approximate 1.5 to 2.0-cm lesion that remains confined within the anatomical zones of the prostate. A continuous saline (room temperature) flush irrigation through the device lumen enhances visualization and cools the urethral surface to preserve the urethral lining.

The prostate adenoma in the transition and central zones can be targeted. Any intravesical prostatic protrusions of either lateral or median lobes may be injected starting 1 cm from the proximal edge of the protrusion. Prior to treating the median lobe treatments angle the treatment needle at 45 degrees medially into the tissue. The treatment needle should be retracted after each treatment and repositioned in approximately 1-cm increments distal from the previous site to the end of the prostatic tissue just proximal to the verumontanum.

Upon removal of the Rezūm delivery device, a flexible cystoscope will be inserted into the subject's urethra to conduct an immediate post procedure (recorded) inspection of the bladder, trigone and ureteral orifices. Any incidences of bladder, trigone or ureteral orifice injury which should be visible as blanching, erythema, or other trauma immediately post-procedure should be reported and documented as an adverse event.

10.5 Follow-up

10.5.1 Prior to Discharge

There is potential for transient acute urinary retention occurring after any transurethral BPH procedure – the reported incidence ranges from 6.8% after a TURP, to a high of 23% after a treatment with the Prostiva RF device. Given subjects with prostates ≥80 cm^3 are likely to receive a larger number of treatments (than with smaller prostates), including treatments of intravesical protrusions right at the bladder neck, it is required that each subject have an indwelling Foley catheter for a minimum of 7 days post the Rezūm procedure before attempting a voiding trial. A 16-French catheter is recommended. The incidence of urinary retention in the Rezūm II pivotal trial for prostates ≥30 to 80 gms was 4.4%.

The subjects should continue to stay on his BPH medication after the procedure under the physician's direction up to 3 months post procedure.

Antibiotics prior to catheter removal (7-10 days post procedure) is required. Physicians are required to onboard antibiotics 2 days prior to catheter removal and continue antibiotics for 3 days post catheter removal. The types of antibiotics to be prescribed will be left to physician discretion and potential resistance.

10.5.2 Post Treatment Care

During the post-treatment period, investigators will follow the current AUA guidelines in managing their subjects for the detection of prostate cancer in addition to the evaluations required by this protocol.

10.5.3 Scheduled Follow-up Evaluations

The following evaluations will be completed at each visit as indicated in Table 10-2. For the subset of subjects who agree to endoscopic evaluations, an examination will be performed at their 6 month visit after all the questionnaires have been answered.

TABLE 10-2: SCHEDULE OF VISITS

	Baseline Pre-Op	Intra Procedure	Discharge	Cath Removal	2 weeks	6 weeks	3 months	6 months	12 months	Annually to 3 years	Unscheduled
Compliance window				**Min. 7 days post**	**± 2 days**	**± 7 days**	**± 7days**	**± 30 days**	**± 30 days**	**± 60 days**	
Physical Exam	√			**Voiding Trial and, if appropriate, Indwelling Catheter removal***	√	√	√	√	√	√	
Medical History	√										
Blood Analysis (CBC, BUN, Blood Sugar, Serum Creatinine)	√				√						
Urine Analysis (Sugar, Protein, WBC/RBC, Bacteria)	√	√			√	√					
Abdominal and Pelvic Exam					√	√					
Uroflow (Qmax + PVR)	√					√	√	√	√	√	
Urodynamics Assessment	√								√ **(optional)**		
IPSS (Standard)	√					√	√	√	√	√	
IPSS (Acute)					√						
Additional Questionnaires: • IIEF • MSHQ-EjD • BPHII • EQ-5D-5L	√					√	√	√	√	√	
PGI-I QoL						√	√	√	√	√	
Resumption to Activities questionnaire					√	√[1]					
Subject satisfaction questionnaire								√	√	√	
Prostate specific antigen (PSA)	√						√	√	√	√	
Intravesical Protrusion (TAUS)	√							√	√	√	

	Baseline Pre-Op	Intra Procedure	Discharge	Cath Removal	2 weeks	6 weeks	3 months	6 months	12 months	Annually to 3 years	Unscheduled
Prostate volume (TRUS)	√							√	√	√	
Retroperitoneal ultrasound (renal and bladder)	√				√[3]	√					
Digital Rectal Exam (DRE)	√						√	√	√	√	
Rezūm Procedure		√									
Subject pain scale	√		√		√	√	√	√			
Adverse event(s) review		√			√	√	√	√	√	√	√
Medication(s) used	√	√	√		√	√	√	√	√	√	√
Flexible Cystoscopy (recorded)	√[2]	√[2]						√[2]			
CT Scan (Intravenous rectal and oral contrast)					√[4] If needed	√[4] If needed					

[1]If subjects have not resumed to activities by 2 weeks, a repeat of the Resume to Activities Questionnaire should be done at the 6 week follow-up
[2]Videos to be reviewed by CEC to assess integrity to the bladder, trigone, or ureteral orifices
[3]Only required if subject's BUN and/or Creatinine level is abnormal from their baseline assessment
[4]Only required if subject answers "yes" to abnormalities in the abdominal and pelvic exam questions AND they have a positive infection identified from the urine culture then a CT Scan, or other exams deemed necessary are to be ordered.

10.5.4 Unscheduled Follow-up Visits

If subjects are seen for unscheduled/interim visits because of an AE, appropriate Case Report Form(s), including the AE CRF, will be completed, if applicable. At the investigator's discretion, some of the evaluations and tests may be repeated, if indicated. Sponsor requests that if any additional tests or procedures listed within this protocol are performed during an unscheduled visit the investigator provide the results on the Unscheduled Visit CRF.

10.6 Alternate BPH Treatments

Subjects who opt for alternate BPH treatments within 6 months of their treatment will be considered to have failed the treatment for the primary efficacy analysis. Additionally, subjects whom discontinue their BPH medication 3 months post-procedure and then resume prior to the 6 month visit will be considered a treatment failure. Alternate treatments include BPH medications (only if given to treat BPH symptoms), PUL, Prostiva RF, TURP, TUMT, laser, etc. Refer to Statistical Analysis Plan (CLP 3034-002) for missing data handing instructions.

10.7 Multiple IPSS Responses

If a subject has multiple IPSS baseline responses, the last baseline value prior to the procedure will be used in the analysis.

If a subject has multiple post-baseline IPSS responses within the same time visit window period, the average results will be used for the subject in all analyses unless there is scientific valid reason(s) to exclude one or more of the responses.

10.8 Follow-up Procedures

10.8.1 Lost to Follow-up

If a subject fails to comply with follow-up evaluations, the investigational site must make at least three attempts to contact the subject. Each attempt to contact the subject and the method used (e.g., telephone contact, registered letter) must be documented in the subject's records.

If a subject misses one of the follow-up evaluations, but is present at the subsequent follow-up, the subject can be readmitted into the study and queried retrospectively for basic information (e.g., AEs); however, the missed evaluation must be documented on a Protocol Deviation CRF. The IPSS and other questionnaires will be collected prospectively only.

10.8.2 Subject Withdrawal from Study

10.8.2.1 Voluntary Withdrawal

A subject may voluntarily withdraw from the study at any time. If a subject officially withdraws from the study, the investigator must ensure that the reason for the withdrawal is documented. If the subject has any device and/or procedure related AEs, the investigator should continue contact

with the subject until the resolution of the AE(s), if possible. Data from these subjects will be included in the analysis up to the point of each subject's withdrawal.

10.8.2.2 Data Withdrawal Due to Exclusion Criteria

A subject's data may be excluded from the analysis if the subject is later found not to meet one or more major exclusion criteria. The major exclusion criteria that would cause the withdrawal of the subjects' data are:

- Failure to obtain an informed consent prior to treatment;
- Subject has a baseline IPSS score of <13;
- Subject had an evidence of an atonic neurogenic bladder evaluated by a urodynamic assessment;
- Subject had a urethra contracture or stricture;
- Subject had a psychiatric condition that prevents him from adequately answering the study questionnaires;
- Subject had a neuromuscular disorder that will confound the results; or
- Subject has a prostate volume outside of the >80 cm^3 to ≤150 cm^3 range.

The decision to exclude the subject's data from analysis will be decided by the CEC.

10.8.2.3 Involuntary Withdrawal

A subject also may be withdrawn by the investigator if the subject's participation in the study will have a negative effect on the safety of the subject. Data obtained up to the date of the subject's withdrawal will be included in the study, if applicable.

10.8.2.4 End of Study

Subjects may exit the study at the end of the study (i.e., the study is discontinued by the Sponsor) or when the subject has completed the 3-year follow-up visit, whichever comes first, unless the subject opted to undergo an alternative BPH treatment. Subjects who receive an alternative BPH treatment will exit the study after the 6 months follow-up evaluation.

An End of Study CRF will be completed at the time the study is completed, discontinued, or lost to follow-up for each subject.

11 Subject Evaluation Description

11.1 Subject Questionnaires

All questionnaires are self-administered and will be completed at baseline (if applicable) and at the required follow-up visit. Questionnaires completed at baseline will be compared to those completed at follow-up visits to assess the effect of treatment. The major instruments and assessments administered are described in this section.

11.1.1 IPSS (Standard)

The IPSS contains the well-validated, highly reliable and responsive American Urological Association symptom score (AUA-SI) assessment to identify the severity of BPH symptoms. The first seven questions in the IPSS address frequency, nocturia, weak urinary stream, hesitancy, intermittence, incomplete emptying, and urgency, and scored on a 6-point scale (0 to 5). Patients are asked to respond relative to the statement of "During the last month or so how often have you had……" (each symptom category) - Not at all, Less than 1 time in 5, Less than 1/2 the time, About 1/2 the time, More than 1/2 the time or Almost always. Although there are no standard recommendations for grading patients with mild, moderate, or severe symptoms, patients can be generally classified as follows: 0-7 mildly symptomatic, 8-19 moderately symptomatic, and 20-35 severely symptomatic.

The IPSS also includes the following eighth question that is designed to assess the degree of "bother" associated with the subject's urinary symptoms: "If you were to spend the rest of your life with your urinary condition just the way it is now, how would you feel about that?" Answers range from "delighted" to "terrible" (0-6). This question correlates well with the overall BPH symptom score and summarizes the impact of urologic symptoms on quality of life.

The standard IPSS will be administered at baseline and at each follow-up visit, except the two and four week follow-up.

11.1.2 International Prostate Symptom Score (Acute)

The acute IPSS is the same as the standard IPSS except that the questions refer to the subject's condition in the past week instead of the past month. This IPSS will be administered at the 2 week follow-up visit and if indicated, at unscheduled visits.

11.1.3 BPH Impact Index

The BPHII was developed for use in conjunction with the IPSS for men experiencing "lower urinary tract symptoms" (LUTS). The BPHII contains four questions designed to assess the level of physical discomfort, worry, how bothersome the symptoms are, and the level of interference with the subject's daily activities, each scored on a scale from 0-4.

11.1.4 International Index of Erectile Function

The IIEF is a standardized 15-question, validated, multi-dimensional, self-administrated questionnaire has been found to be useful in the clinical assessment of erectile dysfunction. A score of 0-5 is awarded to each of the 15 questions that examine the 4 main domains of male sexual function: erectile function (Q1,2,3,4,5,15), orgasmic function (Q 9,10), sexual desire (Q 11,12),

intercourse satisfaction (Q 6,7,8) plus overall satisfaction domain(Q 13,14). Question responses are relative to performance over the past 4 weeks. The IIEF-15 total score is the sum of the ordinal responses to the 5 domains.

11.1.5 Male Sexual Health Questionnaire Short Form

The MSHQ-EjD Short Form is an abridged version of the 25-item MSHQ. It is a standardized 4-item, validated, self-administrated questionnaire used to assess ejaculation dysfunction. Patient responses are relative to performance "in the past month" related to ejaculatory function in 3 domains (frequency, force, volume) and an independent ejaculatory bother domain.

11.1.6 Eq-5D-5L

The EQ-5D-5L consists of 2 pages – descriptive system (page 1) and the EQ Visual Analogue scale (EQ VAS) (page 2). The descriptive system comprises 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) with each dimension having 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The EQ VAS records the respondent's self-rated health on a 20cm vertical, visual analogue scale with endpoints labelled 'the best health you can imagine' and 'the worst health you can imagine'.

11.1.7 Patient Global Impression of Improvement (PGI-I)

The PGI-I is a single question transition scale asking the patient to rate their urinary tract condition now, as compared with how it was prior to beginning treatment on a scale from "1-Very much better" to "7- Very much worse".

11.1.8 Subject Pain Questionnaire

Pre- and post-procedure pain will be evaluated using a standardized pain questionnaire.

11.1.9 Resumption to Activities

An assessment of when a subject resumed his normal activities after the Rezūm procedure will be evaluated.

11.1.10 Subject Satisfaction Questionnaire

The Subject Satisfaction Questionnaire queries the subjects about their impressions of the treatment.

11.2 Urodynamics

Urodynamic testing evaluates how well the bladder, sphincters, and urethra are storing and releasing urine. Urodynamic tests focus on the bladder's ability to hold urine and empty steadily and completely. Urodynamic tests also can show whether the bladder is having involuntary contractions that cause urine leakage.

Within the study, all subjects will undergo baseline urodynamic testing to evaluate the bladders function and efficiency. The voiding pressure-flow study helps assess two critical factors related to the bladder, bladder neck and prostate: detrusor activity (normal vs. impaired) and outlet resistance (obstructed vs. unobstructed). Poor detrusor muscle function is defined as any subject with bladder outlet obstruction, calculated from the urodynamic tracings, accompanied by

impaired detrusor underactivity who fall below the 25th percentile of accepted and established nomograms.

Procedure: A repeat free uroflowmetry procedure is performed and the patient is placed in lithotomy position to insert a 6 or 7 French dual lumen urodynamics catheter. Air charged (T-Doc) urodynamic catheters will be used for reliability of testing and standardized for all study centers. Using a large syringe, the bladder will be emptied to obtain an accurate post-void residual urine volume (this sample may be utilized for urinalysis per protocol). A 10-French rectal balloon catheter, to monitor abdominal pressure, will be placed 10 cm above the internal rectal sphincter.

During the filling phase of the cystometrogram, it is important to assess the sensory response of the patient. The technician will instruct the subject in the following steps:

- **First Sensation**: When is the first sense of bladder filling?
- **First Desir**e: When is the first desire to void, such as when the subject might consider pulling off the highway at the next available service station?
- **Strong Desire**: When is the definite desire to find the next restroom?

It is usually easier to leave the patient in the lithotomy position during the filling phase.

The emptying pressure-flow measurement should be performed in the subject's preferred position--standing or sitting. It is vital to make sure all the pressure monitors are functioning properly and usually a "cough test" will demonstrate this function. It is often preferred to allow the subject to void in private for best pelvic relaxation. It is vitally important that complete confidence exists in the registering of both abdominal, detrusor and uroflow catheters, transducers and computer tracings. If there is any question about any of these factors, the urodynamic study should be repeated after correcting any defects.

The urodynamic voiding pressure-flow study makes a precise diagnosis of obstruction in men and assumes the outcome of prostate tissue reduction and consequent LUTS will improve when obstruction is documented. It is difficult to diagnose obstruction in the face of detrusor underactivity (DU). Impaired contractility results from long-term obstruction and BOOI must be at least 40 cm H_2O to be able to confirm adequate contractility of the bladder [21]. An International Continence Society (ICS) nomogram can exclude obstructed patients who have impaired contractility. This requires clinical judgment in selecting patients for treatment, but typically reduced compliance of the bladder is improved after treatment of the BPH.

The bladder outlet obstruction index (BOOI) is calculated from the urodynamic tracings. $P_{det}=P_{ves}-P_{abd}$**; BOOI =** P_{det} Q_{max} **--** $2Q_{max}$ **[cm H2O]**

Bladder contractility index (BCI) is calculated: $P_{det}Qmax + 5(Qmax)$. This value is greater than 150 in a strong contracting bladder, 100-150 in normal bladder, and less than 100 in a weak bladder. This corresponds to the ICS nomogram.

All tracings will be submitted for analysis by an independent reviewer.

11.3 Uroflowmetry

Recommendations of the International Incontinence Society (ICS) Good Urodynamics Practices protocol will be used for this study.

Subjects will be asked to hydrate and refrain from voiding for two hours. Hydration may be achieved by asking the subject to drink 2 or more cups of non-caffeinated fluids.

General Instructions for Uroflowmetry:

- It is preferred that the measurements be performed in the standing position. All subsequent measures should be performed in the same position as was used for the baseline assessment.
- Men should have a sense of bladder fullness and express a desire to void prior to micturition testing.
- Fullness of the bladder will be assessed by ultrasound; urine volume must be from ≥250 to ≤550 mL prior to uroflow determination.
- Uroflowmetry will be performed using a standard calibrated flowmeter.
- Recording will start at initiation of voiding
- Parameters will be calculated by the flowmeter, and the printout of the record will be photocopied and retained.
- Uroflowmetry results will be considered valid only if the pre-void total bladder volume (assess by ultrasound) was ≥250 to ≤550 mL and the voided volume was ≥125 mL.
- Retests will be allowed only in the event of small voided volume (<125 mL) or uroflowmeter malfunction.

Adequate privacy should be provided and patients should be asked to void when they feel a ‘‘normal’’ desire to void. Patients should be asked if their voiding was representative of their usual voiding and their view should be documented.

To qualify for entry into the study the following measurements must be achieved:

- Voided volume (≥125 ml required to be eligible for the study);
- Peak flow rate, Qmax (≥ 5ml/sec to < 12 ml/sec to qualify) averaged over a 2 second interval;
- Average flow rate;
- Voiding time.

11.3.1 Peak Flow Rate (Qmax) Measurement

The recommendation for determining Qmax is to apply the 2 second-rule to improve consistency, which avoids artifacts in the reading.

11.3.2 Post Void Residual Urine Volume

Following uroflowmetry, residual urine volume in the bladder will be assessed by bladder scanner ultrasound. It is recommended that PVR be obtained with urodynamic testing catheter after voiding just prior to the urodynamic pressure-flow study.

Voiding efficiency (VE) is calculated to determine percentage of bladder emptying in relation to bladder filling volume: VE = (voided volume/bladder capacity) x 100%.

All tracings and printouts of uroflowmetry and post-void ultrasound shall be submitted to an independent reviewer for reading, calculations and entry into the case report form. Multiple data points can be reported from noninvasive uroflowmetry. These include the following:

- Voided volume (VV in milliliters)
- Flow rate (Qmax in milliliters per second)
- Maximum flow rate (Qmax in milliliters per second)
- Average flow rate (Qave in milliliters per second)
- Voiding time (total time during micturition in seconds)
- Flow time (the time during which flow occurred in seconds)
- Time to maximum flow (onset of flow to Qmax in seconds)

Interpretation of Uroflowmetry Data

- Baseline uroflowmetry data will be interpreted by the principal investigator to assess subject eligibility (Inclusion criteria 3 and exclusionary criterion 10);
- Data for all protocol required follow-up visits thereafter will be read by an independent reviewer;
- All efficacy analyses will be performed using the independent reviewer's assessments.

11.4 Flexible Cystoscopy

A screening flexible cystoscopy will be performed to check for the integrity of the bladder, urethral abnormalities, strictures, prostatic urethral configuration, presence of median lobe within the bladder, and to gauge how much of the prostate protrudes into the bladder (defined as intravesical prostatic protrusion). It is recommended that all air bubbles be expelled to assure quality video monitoring.

A post-treatment flexible cystoscopy will be performed immediately post procedure and at the 6-month follow-up visit after other evaluations are completed. All cystoscopies are to be video-recorded and forwarded to the sponsor. A copy of these recordings will be provided to the Clinical Events Committee (CEC) for a review of potential Adverse Events.

11.5 Digital Rectal Exam

A digital rectal exam (DRE) will be used to screen for malignant prostate tissue.

11.6 Transabdominal and Transrectal Ultrasound

The primary purpose of ultrasound imaging in this study is to determine prostate size and the presence of any intravesical prostatic protrusion. There is a very high correlation between an IPP with bladder outlet obstruction (BOO). Studies of transabdominal (TAUS) and transrectal (TRUS) ultrasound [22-24] show three grades of distance between the tip of prostatic intrusion and base of the bladder.

These grades correlate very well with PSA and degree of LUTS due to BPH:

- ≤ 5mm is grade I,
- >5 to 10mm is grade II, and

- >10mm is grade III

The lobar anatomy has been well demonstrated utilizing resolution of 3-T MRI imaging [25].

The TAUS will be performed with approximately 150 mLs of urine in the bladder. Bladder wall thickness also can be described and combined with flexible cystoscopy observation. The distance from the tip of the prostatic protrusion to the circumscribed base of the bladder is measured in millimeters.

A TRUS will be used to assess the prostate volume, prostatic urethral length and transverse width and general condition of the prostatic tissue. This will be performed at baseline and at different post-treatment follow-ups. To ensure reliable within-subject measurements of the prostate, TRUS will be standardized. Key elements of TRUS standardization include, but are not limited to:

- Ultrasound equipment and transducer and probe configuration recorded for each examination;
- All configurations (bi-plane, multi-plane, and end-fire probes) are acceptable, provided no change of equipment will take place during study;
- Lateral decubitus position is the preferred patient positioning for TRUS measurement.

The following views are required:

- Transverse view at base of prostate,
- Transverse view at mid-gland,
- Transverse view distal third or apex,
- Longitudinal view mid-plane,
- Longitudinal view right side approximately 30-45 degrees from midline, and
- Longitudinal view left side approximately 30-45 degrees from midline.

Prostate volumes will be determined by the following formula: $\pi/6 \times$ (transverse diameter $\times$ anteroposterior diameter $\times$ cephalocaudal diameter).

Hardcopies of these images will be obtained by thermal printer (and then photocopied) or otherwise retained.

All TAUS results will be submitted for analysis by an independent reviewer.

Interpretation of TRUS measurements

- Baseline TRUS data will be interpreted by the principal investigator to assess subject eligibility (Inclusion criteria 5).
- TRUS data for all protocol required follow-up visits thereafter will be read by an independent reviewer.
- All efficacy analyses will be performed using the independent reviewer's assessments.

11.7 Retroperitoneal Ultrasound (Renal and Bladder)

A retroperitoneal ultrasound of the abdomen and pelvis will be performed to assess the patients' urinary tract integrity at pre-procedure baseline, 2 weeks (as applicable) and again at their 6 week follow-up appointment. These retroperitoneal ultrasound imaging studies will be used to determine the study's satisfaction of the primary safety endpoint, in particular the presence of permanent damage to the bladder, trigone, or ureteral orifices. The written request for sonographic examination will include sufficient information directing the examiner to allow for appropriate performance of the ultrasound focusing on the primary safety endpoint criteria listed above. Retroperitoneal ultrasound guidelines (urinary tract and bowel):

Kidney Assessment

- Kidney examination should include transverse and long-axis (sagittal or coronal) views
- Assessment of the cortices and renal pelvises should be made
- The maximum length of each kidney should be recorded
- For vascular kidney examination, Doppler ultrasound can be utilized to assess renal arterial and venous patency and suspected renal artery stenosis
- The kidneys and perirenal regions should be assessed for abnormalities
- Measurements should be taken of any abnormalities

Bladder Assessment

- For examination of the complete urinary tract, transverse and longitudinal (sagittal or coronal) images of the distended urinary bladder should be included if possible
- Abnormalities of the bladder wall or lumen should be noted

Bowel Assessment

- Evaluation of the bowel for wall thickening, dilatation, muscular hypertrophy, masses, vascularity, and other abnormalities can be made
- Identification of bowel perforations or fistulas should be reported

Any site reported abnormalities present on the 2 week (if abnormal BUN or Creatinine) or 6-week ultrasound that were not present at baseline will be reviewed as potential device-related serious complications and a final adjudication will be made by the Clinical Events Committee. The retroperitoneal ultrasound will be used in conjunction with TRUS to adjudicate the potential complications.

11.8 Genitourinary Perforation and Assessment of Fistula Formation

A urine culture and an abdominal & pelvic exam will be conducted at the 2 and 6 week follow- up visit to assess for potential perforation of the rectum or GI tract; or fistula formation between the urethra and rectum.

The patients also will be asked the following questions:

1) Are you passing gas (air) in your urine? Checking for pneumaturia

2) Are you seeing any fresh blood in your stool or when you wipe? Checking for hematochezia
3) Are you seeing any urine coming from your rectum? Checking for recto-urethral fistulas

If a patient answers yes to any of the three questions, and the patient's urine culture is positive for infection, then the patient will undergo an intravenous rectal and oral contrast CT exam, or any other evaluation method deemed necessary if clinical suspicion exists, to rule out perforation of the GI or GU tracts and/or fistula formation.

12 Statistical Considerations

12.1 Sample Size Justification

For the trial to be successful, the primary efficacy endpoint must be adequately powered.

For the primary efficacy endpoint to be met, the proportion of the ITT analysis population that responds to therapy must be statistically significantly greater than 50%. A responder is defined as a subject who has an IPSS improvement $\geq$30% post-treatment, as compared to baseline.
The required sample size for this endpoint was calculated based on the following assumptions:

- One-sample exact binomial hypothesis test of proportions,
- Type 1 error of 0.025, one sided,
- Statistical power of 90%, and
- Population responder rate of at least 67.5%.

The responder rate in the Rezūm II trial was 77.9% (106/136). A population rate of at least 67.5% is selected as a conservative assumption for the responder rate in the Rezūm XL trial based on the lower bound of a two-sided 99% confidence interval for the responder rate in the Rezūm II trial. Based on these assumptions, a sample size of at least 88 intention-to-treat subjects is required for analysis.

Additional subjects may be screened since some subjects that consent may exit the study without being enrolled (e.g. due to withdrawal of consent or not meeting eligibility criteria).

12.2 Primary Safety Endpoint - Post Procedure Device Related Serious Complications:

This safety endpoint will be to demonstrate that the composite rate of post procedure device related serious complications at 6 months is acceptably low.

The following hypothesis will be tested in a one-sided exact binomial test at the 5% significance level.

H_o: $P_{Rezūm6} \geq 12\%$

H_1: $P_{Rezūm6} < 12\%$

Where:

$P_{Rezūm6}$ is the proportion of subjects experiencing one or more safety composite events within 6 months post-procedure. The safety endpoint is a composite of the four types of events listed below.

Device-related serious complications for this endpoint are defined as:

- Device perforation of the rectum or GI tract
- Device related formation of fistula between the rectum and urethra
- Permanent damage to the bladder, trigone or ureteral orifices requiring intervention
- Grade 2 hydronephrosis

The adverse events listed above will be adjudicated by the clinical events committee (CEC) for this endpoint. With a sample size of 88 subjects, a performance goal of 12% requires that no more than 5 subjects (5.7%) experience a device-related serious complication in order for this endpoint to be met.

12.3 Primary Efficacy Endpoint

This efficacy endpoint will be to demonstrate that the responder rate is greater than 50% at 6 months. The following hypothesis will be tested in a one-sided exact binomial test at the 2.5% significance level.

H_o: $P_{Rezūm6} \leq 50\%$

H_1: $P_{Rezūm6} > 50\%$

Where:

$P_{Rezūm6}$ is the proportion of subjects in which IPSS improves by at least 30% at 6 months

The performance goal of 50% is derived based on clinical relevance and ensuring response greater than historical sham responder rate. The sham arm of the Rezūm II study showed an approximately 35% responder rate for the sham arm at 3 months. The performance goal adds a 15% margin to the historical sham responder rate.

To further minimize the likelihood of a placebo effect, the endpoint is evaluated at 6 months instead of 3 months, as any placebo effect is expected to be less at 6 months compared to 3 months. The performance goal is conservative since the historical control responder rate would likely have been lower at 6 months than at 3 months.

With the proposed sample size of 88 patients, and based on a one sided type 1 error of 0.025, with a composite event rate of no more than 3.4%.

12.4 Secondary Endpoints

The secondary endpoints include an assessment of IPSS on a continuous scale and additional responder analyses at different follow up time points. All secondary endpoints will be analyzed based on the treated analysis population consisting of subjects treated with the Rezūm System.

For all secondary endpoints based on IPSS scores, treated subjects who chose alternate treatments other than the assigned treatment prior to the end of the endpoint's follow-up period will be considered failures and their baseline value will be used as their imputed follow-up IPSS score for the secondary endpoint analysis.

12.4.1 Secondary Endpoint S1: Device-related retention catheterization rate

This safety endpoint will be to characterize the rate of post procedure device-related serious retention catheterizations at 6 months.

Device-related serious catheterizations for this endpoint are defined as:

- De novo acute severe urinary retention lasting more than 30 cumulative days post treatment

Catheterizations will be adjudicated by the clinical events committee (CEC) for this endpoint.

12.4.2 Secondary Endpoint S2: Absolute IPSS improvement at 6 months

The following hypothesis will be tested in a one-sided one-sample *t*-test at the 2.5% significance level.

H_o: $\mu_{Rezum6} \leq 6.0$

H_1: $\mu_{Rezum6} > 6.0$

Where:

μ_{Rezum6} is the mean IPSS improvement at 6 months

The performance goal of a 6.0 point average improvement in IPSS score is derived based on clinical relevance and ensuring response greater than historical sham mean improvement. In the previously conducted Rezūm II study, observed mean improvement in the sham arm at 3 months was 4.3 points. The Rezūm II study required the treatment arm mean to exceed 125% of the mean sham improvement. In order to ensure clinical relevance, an additional 15% is added to the Rezūm II criteria. The minimum performance goal of 6.0 equals 140% of the historical sham mean improvement.

Statistical significance will be claimed when the alternate hypothesis of the secondary endpoint is met based on a one sided type 1 error of 0.025.

If the final number of treated subjects is 88 and the standard deviation of the improvement in IPSS score is 8 points, then the mean improvement in IPSS score at 6 months must be at least 7.1 in order to pass the hypothesis test and conclude that the mean IPSS improvement is statistically significantly greater than 6.0 points.

12.4.3 Secondary Endpoint S3: Percent Responder at 1 year

This efficacy endpoint will be to characterize the responder rate at 1 year in all subjects treated with the Rezūm System. The endpoint is defined the same as the primary objective, but will be evaluated at 1 year of follow-up.

12.4.4 Secondary Endpoint S4: Percent Responder at 2 years

This efficacy endpoint will be to characterize the responder rate at 2 years in all subjects treated with the Rezūm System. The endpoint is defined the same as the primary objective, but will be evaluated at 2 years of follow-up.

12.4.5 Secondary Endpoint S5: Percent Responder at 3 years

This efficacy endpoint will be to characterize the responder rate at 3 years in all subjects treated with the Rezūm System. The endpoint is defined the same as the primary objective, but will be evaluated at 3 years of follow-up.

12.5 Ancillary Endpoints

The following ancillary endpoints are to provide additional characterization of the safety and effectiveness of the Rezūm System in the treatment of obstructive BPH.

12.5.1 Ancillary Endpoint A1: Additional Responder Analyses

A responder in this ancillary endpoint is defined as a subject who has an IPSS improvement >8 points post-treatment compared to baseline at each scheduled follow-up time point.

12.5.2 Ancillary Endpoint A2: Change in Qmax and PVR

The A2 efficacy endpoint is the changes in peak urinary flow rate (Qmax) and PVR compared to their baseline values at each scheduled follow-up time point.

12.5.3 Ancillary Endpoint A3: Change in Sexual Function

Changes in sexual function will be assessed using MSHQ-EjD and the IIEF questionnaires for changes in ejaculatory and sexual function.

12.5.4 Ancillary Endpoint A4: Change in Quality of Life

Quality of Life (QoL) changes will be measured using the QoL question in the IPSS and BPH Impact Index (BPHII) and EQ-5D (a standardized instrument for use as a measure of health outcome) assessment and also the average time before subjects was able to resume pre-treatment activity.

12.5.5 Ancillary Endpoint A5: Procedure Parameters

This includes:

- Procedure time
- Treatment time
- Percent of median lobe presented and treated

12.5.6 Ancillary Endpoint A6: PGI-I Questionnaire

This ancillary endpoint characterizes subjects' responses to the PGI-I, a single question transition scale asking the patient to rate their urinary tract condition now as compared with how it was prior to beginning treatment on a 7 point scale.

12.5.7 Ancillary Endpoint A7: Rezūm II Comparisons

This ancillary endpoint characterizes the similarity of outcomes between the 135 treatment arm subjects in the Rezūm II study with prostate sizes ≥30 cm^3 and ≤80 cm^3 treated with Rezūm and the Treatment group of the Rezūm XL study.

Time to first unplanned re-treatment will be compared between the Rezūm XL and Rezūm II subjects over 0-6 months. Additional time intervals may also be analyzed for comparison. The incidence of planned staging of treatment, where additional treatment is planned at the conclusion of the initial treatment procedure will be also be described for the Rezūm XL study.

Adverse event frequencies will be compared between Rezūm XL and Rezūm II subjects over 0-6 months post-procedure. Additional time intervals may also be analyzed for comparison.

12.6 Other Analyses

Adverse events, protocol deviations and device malfunction will be tabulated and included in the analysis. Descriptive statistics will be used in reporting these outcomes.

13 Definition of Study Success

The study will be declared a success if the primary efficacy and safety endpoints are met.

14 Definition of Adverse Event(s)

For purposes of this study, an AE is defined as any adverse change (i.e., *de novo* or preexisting condition) from the subject's baseline medical condition(s) occurring during the course of the study. For the purpose of AE documentation, the start of the study is defined as any time after the treatment has been initiated.

Subjects must be monitored from the start of the study, and throughout the duration of the study, for any and all AEs, including those observed as well as those reported by the subject. All AEs are to be documented by the investigator on the appropriate CRF. All AEs will remain under medical supervision until the Investigator deems the AE to be resolved, returned to baseline or stabilized at a new level no longer requiring medical supervision.

All AEs will be recorded in the CRF whether considered procedure-related or not, and will be classified as described in section 14.7.

Pre-existing conditions will not be reported as an AE unless there is an adverse change in that condition. Any AE which resolves and then recurs will be reported as a separate AE.

An AE may be volunteered spontaneously by the subject or discovered as a result of questioning or physical examination by an investigator or study staff.

14.1 Treatment Related Symptoms

The Rezūm procedure is designed to treat LUTS. Subjects to be treated have moderate-to-severe LUTS prior to treatment. These symptoms are expected to continue and may even worsen slightly prior to improvement as part of the healing process. All reported LUTS will be documented in the CRF. Other expected acute, but transient, worsening of symptoms from the treatment are dysuria, frequency of urination, urgency of urination, urge incontinence, hematuria, slowing of the urinary stream and acute retention as the tissue heals.

The classification of symptoms as an AE will be determined by the CEC.

14.2 Urinary Retention and Obstructive LUTS

14.2.1 Urinary Retention

Urinary retention is the inability to completely empty the bladder and can be acute or chronic.

There are many causations for urinary retention, but BPH in men over the age of 50 account for 53% of the incidence. Neurogenic spinal injury is common, acute prostatitis, medications and pelvic floor disturbance such as urinary external sphincter dyssynergia are other known causes.

Acute urinary retention happens suddenly and lasts only a short time. People with acute urinary retention cannot urinate at all, even though they have a full bladder requiring immediate emergency treatment (i.e., catheterization). Acute urinary retention is an anticipated thermal therapy effect of the Rezūm treatment.

Chronic urinary retention is more insidious and can occur gradually in men with bladder outlet obstruction leading to dysfunctional urinary detrusor with underactivity. This can occur silently over time and can lead to pyelocaliectasis, hydronephrosis with renal insufficiency or failure, bladder and renal calculi and urinary tract infections, occasionally with urosepsis.

14.2.2 Obstructive LUTS

Obstructive LUTS has some symptoms similar to urinary retention. Obstructive LUTS usually is a chronic condition and is sometimes referred to as chronic urinary retention. Symptoms of obstructive LUTS are:

- Poor stream
- Hesitancy
- Terminal dribbling
- Incomplete voiding
- Overflow incontinence (occurs in chronic retention)

14.3 Anticipated Thermal Therapy Effects

14.3.1 Tissue Blanching, Edema and Erythema

Tissue blanching, edema and erythema in the urethral lining and prostatic tissue are anticipated thermal therapy effects from the treatment with the Rezūm delivery system. Any reported symptoms from these anticipated effects will be reported as Adverse Events on the Adverse Event CRF.

14.4 Potential Anticipated Adverse Events

Potential anticipated AEs are those that may occur in association with a BPH treatment or procedure, include those AEs listed below or reported in the literature associated with surgical or minimally invasive BPH procedures:

- Sepsis and infection
- Fever

- Perforation of urethra
- Perforation of adjacent organs including the rectum, bladder and GI tract
- Urinary symptoms and adverse events including:
    - Dysuria
    - Frequency
    - Urgency
    - Nocturia
    - Acute or Chronic urinary retention
    - Incontinence
    - Sensation of not emptying bladder completely
    - Urethral stricture
    - Urethritis
    - Irritative urinary symptom
    - Urethral injury causing false passage or adhesion
    - Urinary clot retention
    - Chronic pain in the pelvic area
    - Bladder spasm
    - Hematuria with or without clot in urethra
    - Discharge or cloudy urine
    - Discharge of tissue material during urination
    - Scarring of the urethral system
    - Urinary tract infection
- Abscess (prostatic, bladder, scrotal)
- Bladder problems or damage (reduced bladder sensation, spasms, bladder neck contracture, bladder neck stenosis, bladder neck mucosal sloughing)
- Bladder perforation or rupture
- Damage to the urethral system
- Prostate seroma
- Kidney compromise or failure
- Hydronephrosis
- Reproductive system disturbances such as infertility
- Prostate abnormalities and damage
- Rectal incontinence
- Rectal damage (including fistulas)
- Rectal stenosis
- Rectal, perineal findings
- Anal irritation
- Elevated PSA
- Nerve damage
- Weakness or numbness
- Abdominal or low back pain
- Flu-like symptoms
- Hematospermia
- Epididymitis

- Blood pressure change during therapy
- Arrhythmia
- Flank pain
- Blood loss (> 500 ml)
- Bowel irritation
- Erectile dysfunction
- Retrograde ejaculation or ejaculatory dysfunction
- Anejaculation
- Pressure sensation
- Prostatitis
- Adverse reaction to medication and anesthesia as listed in the labeling
- Low blood pressure (hypotension)
- High blood pressure (hypertension)
- Fainting, dizziness, or blurred vision (vasovagal reaction, syncope)

Other potential non-pelvic anticipated adverse events that may occur in this subject population are:

- Allergic reaction
- Fatigue
- Dyspnea
- Confusion
- Memory loss
- Swelling or bruising (edema, hematoma)
- Aneurysm – thoracic and cranial
- Low back pain
- Pneumonia
- Collapsed lung
- Pulmonary embolism
- Pneumothorax
- Upper respiratory disease
- Cough
- Sore throat
- Apnea
- Coughing up blood (hemoptysis)
- Choking (aspiration)
- Venous thrombosis
- Myocardial infarction, angina, ischemia
- Cardiac arrhythmia
- Stroke or transient ischemic attack
- Brain damage
- Headache
- Depression
- Perforation of or damage to the gastrointestinal tract
- Abdominal pain

- Constipation
- Nausea or vomiting
- Adverse reaction to medication

14.5 Definition of Serious Adverse Event(s)

An AE is considered to be an SAE if it resulted, or could result in, if not mitigated:

- Death;
- A life-threatening situation;
- Requires the subject to be hospitalized or prolongs an existing hospitalization;
- Persistent or significant disability/incapacity; or,
- Is considered an important medical event.

Important medical events that may not meet one of the above definitions could be considered SAEs if they jeopardize the health of the subject or require surgical intervention to prevent one of the outcomes listed above. An SAE may or may not be related to the study procedure.
Classification of an AE to an SAE will be decided by the CEC.

14.6 Unanticipated Adverse Device Effect(s) (UADE)

A UADE is any serious adverse effect on the health or safety of a subject, any life-threatening problem or death caused by, or associated with a device, if such effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan (e.g., ICF, Study Protocol, Instructions for Use (IFU), publications, etc.), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

If an UADE associated with the investigational device occurs, the investigator shall notify the Sponsor and the IRB/EC as soon as possible.

The Sponsor will investigate the event and notify the FDA and all other participating IRBs/EC and investigators. Should the Sponsor determine that an UADE presents an unreasonable risk to all participating subjects, the Sponsor will suspend the clinical investigation and notify all participating investigators, IRBs/ECs, the FDA, and any other country regulatory bodies.

14.7 Reporting of all Adverse Events

All AEs must be recorded on a CRF. All AEs also must be described by (a) duration (start and resolution dates); (b) adjudication for severity; (c) relationship to the study device; (d) action taken to resolve the event; (e) outcome of the event; and (f) whether or not such event is considered to have been serious (g) determination of single vs recurrent event Additional information, such as procedural notes, treatment notes, or a signed clinical summary, may be required as supporting documentation for the reported AE.

During the study, all deaths must be reported to the Sponsor within the period outlined in Table 17-1. All deaths also should be reported on the End of Study CRF. A copy of the subject's death

records, medical records for the events that led to the subject's death, and a death certificate (if available) should be provided.

14.8 Relationship of AEs to the Rezūm Device

A description of how an AE relates to the study procedure will be reported on the Adverse Event CRF and be determined by the Investigator using the following definitions:

- ***Definite*:** The AE follows a reasonable temporal sequence from the time of the index procedure, which includes AEs that occur during the index procedure or during the follow-up period.
- ***Probable***: The AE follows a reasonable temporal sequence from the time of the index procedure, and the possibility can be excluded that factors other than the index procedure, such as underlying disease, concomitant drugs, or concurrent treatment caused the AE.
- ***Possible***: The AE follows a reasonable temporal sequence from the time of the index procedure and the possibility of index procedure involvement cannot be excluded. However, other factors such as underlying disease, concomitant medications, or concurrent treatment are presumable.
- ***Unlikely***: The AE has an improbable temporal sequence from the time of the index procedure, or such AE can be reasonably explained by other factors, including underlying disease, concomitant medication, or concurrent treatment.
- ***Not related***: The AE has no temporal sequence from the time of the index procedure, or it can be explained by other factors, including underlying disease, concomitant medication, or concurrent treatment.

Those SAEs that are possibly related to the device, the procedure, or the disease state being treated will be reviewed and adjudicated by the CEC. The CEC will review in tabular format all non-device/procedure/disease-related SAEs.

14.9 Degree of Severity of Adverse Events

- ***Mild***: Awareness of the event, but easily tolerated by subject
- ***Moderate***: Discomfort enough to cause interference with usual activity
- ***Severe***: Inability to carry out usual activity

14.10 Device Failures, Malfunctions and Near Incidents

Device failures or malfunctions will be reported to Sponsor by the clinical sites. If the failure or malfunction results in negative clinical sequelae, the event shall be reported to the Sponsor within two (2) working days after the Investigator becomes aware of the device-related adverse event and reported to the IRB/EC (if required) within the IRB/EC required timeframe. The malfunctioning device involved in the incident should be returned to the Sponsor for evaluation.

14.11 Independent Review of Retroperitoneal Ultrasound (renal and bladder)

An independent reviewer will review all baseline, 2 week (if applicable) and 6 week retroperitoneal ultrasounds to assess for any unreported device-related serious complications defined as:

- Device perforation of the rectum or GI tract

- Device related formation of fistula between the rectum and urethra
- Permanent damage to the bladder, trigone or ureteral orifices requiring intervention

If any of the above are noted, a request will be sent to the site to report such event. Copies of the retroperitoneal ultrasound will be available for the CEC if they deem necessary.

15 Training

The Sponsor will be responsible for training appropriate clinical site study personnel. All physicians proctored by the Sponsor, as well as other trained physicians, must have completed the commercial training program. To ensure proper procedural technique, uniform data collection and protocol compliance, the Sponsor will present a formal training session to personnel at each study site. At this training session the Sponsor will review the study protocol, techniques for the identification of eligible subjects, instructions on data collection, schedules for follow-up assessments, and regulatory requirements.

16 Data Management

16.1 Subject Identification

Subjects who successfully pass the screening tests and wish to participate in the study will be assigned a unique identification code (ID) using the format "XXX-YYY" where:

XXX = Institution Number, assigned by the Sponsor to each study site
YYY = Enrollment Number, assigned by the institution as each subject is enrolled in the study

In addition to the ID, each subject's initials will be used as an identifier included on documentation submitted to the Sponsor.

16.2 Central Database

All study documentation will be collected and compiled in a central database. Appropriate quality control measures will be established to ensure accurate and complete transfer of information from the study documentation to the central database.

17 Study Responsibilities and Management

The proposed study will be performed in accordance with all requirements set forth in the U.S. regulations, 21 Code of Federal Regulations (CFR) Parts 812, 50, 54, and 56, the World Medical Association Declaration of Helsinki, and any other applicable local laws, regulations, or guidelines in the applicable countries where the study may occur.

17.1 Investigator Responsibilities

Each investigator is responsible for ensuring the investigation is conducted according to all signed agreements, the study protocol, EC/IRB requirements, and applicable laws and regulations. Also,

Investigators may not begin enrollment until Sponsor or its designee receives and approves (when necessary) the following documents:

- Signed Investigator Agreement,
- Financial disclosure forms for all participating investigators,
- EC/IRB roster (or IRB registration no. from the Office of Human Research Protection),
- EC/IRB protocol and ICF approvals,
- Investigators' current curricula vitae (CV), and
- Signed Site Delegation Log.

It is acceptable for Investigators to delegate one or more of the above functions to an associate or Co- or Sub-Investigator, or a trained Study Coordinator; however, the Investigator remains responsible for the proper conduct of the clinical investigation, including obtaining and documenting proper study informed consent, collecting all required data, submitting accurate and complete CRFs, etc.

At each study site, appropriate procedures must be followed to maintain subject confidentiality according to appropriate local regulations (e.g., Health Insurance Portability and Accountability Act (HIPAA) in the U.S.). Each site may have its own internal procedures or requirements for use and release of subject medical information in research studies. Each Investigator is responsible for obtaining appropriate approvals, consents, or releases of medical information as dictated by their relevant subject privacy laws.

The study is not transferable to other sites attended by the Investigator unless prior approval is obtained from the appropriate EC/IRB and the Sponsor.

17.2 Subject Enrollment Process

All study candidates, after pre-procedure screening, must appropriately consent to participate in the study, as administrated by qualified study site personnel using an IRB and Sponsor-approved ICF prior to beginning any aspect of the study procedure or tests that are not standard of care for the site. Investigational sites will be required to document the consent process within each enrolled subjects medical record. Administering the questionnaires can be done prior to signing the ICF. Only subjects who meet the inclusion/exclusion criteria, who signed the study informed consent and completed device insertion will be considered enrolled in the study.

Timely communication by each site is critical to avoid over enrolling when the enrollment is close to the end of each phase. When enrollment is close to the end of each phase, the following procedures may be implemented:

- Before the subject signs the study ICF, the Study Coordinator must confirm the availability of an enrollment slot. A phone call to the Sponsor is the preferred method.
- Immediately after the procedure, the Study Coordinator must inform (phone call or fax or e-mail) the Sponsor to confirm the subject's eligibility and the completion of the procedure. A phone call to the Sponsor is the preferred method.

17.3 Ethics Committee (EC) / Institutional Review Board (IRB)

Investigators must submit the study protocol to their respective EC and/or IRB and obtain the EC's/IRB's written approval before being allowed to conduct and participate in the study. Each Investigator is responsible for fulfilling any conditions of approval imposed by their respective EC/IRB, such as regular reporting, study timing, etc. Investigators will provide the Sponsor or its designee with copies of such approvals and reports.

17.4 Informed Consent Form (ICF)

The Sponsor will provide a template ICF to each study site for EC/IRB submission. The template may be modified to suit the requirements of the individual study site but the Sponsor must pre-approve all changes to the ICF prior to initial submission to the EC/IRB.

Each Investigator or assigned designee must administer this approved ICF to each prospective study subject, and obtain the subject's signature or a legally-approved designee's signature along with the date of consent prior to enrollment in the study. The ICF must be obtained in accordance with the applicable guidelines on 21 CFR 50, 52 and 56, the Declaration of Helsinki, ISO 14155 or local regulations and laws, whichever represents the greater protection of the individual. Subjects must be informed about their right to withdraw from the study at any time and for any reason without sanction, penalty, or loss of benefits to which the subject is otherwise entitled and also be informed that withdrawal from the study will not jeopardize their future medical care. A copy of their signed ICF must be given to each subject enrolled in the study. The institutional standard subject consent form does not replace the Rezūm XL study ICF.

17.5 Case Report Forms (CRFs)

The Sponsor will provide standardized CRFs for each individual subject. The standardized CRFs will be electronic (EDC, 21 CRF Part 11 compliant), and will be used to record study data, and are an integral part of the study and subsequent reports.

The electronic CRFs for individual subjects will be provided by the Sponsor via a web portal. After the data have been monitored and submitted, corrections will be initiated via a data query or DCF to be completed by study site personnel. This DCF also will be done electronically via the web portal. Electronic CRFs must be approved and signed by the Investigator in the appropriate spaces provided using his/her electronic signature.

17.6 Records

Each Investigator must maintain the following accurate, complete, and current records relating to the conduct of the study investigation. The final responsibility for maintaining such records remains with the Investigator. These records include, but are not limited to:

- All signed agreements;
- IRB/EC approval letter(s);
- Signed ICF;
- Records of AEs, including supporting documents;

- Records of protocol deviations, including supporting documents
- Records showing receipt, use and disposition of all devices, including:
  - Date, quantity, model and lot numbers of devices received,
  - Name of person(s) who received, used or disposed of each device,
  - The number of devices returned to the Sponsor and the reason(s) for return;
- All correspondence related to the study;
- Records of each subject's case history, including study-required CRFs, signed ICF, all relevant observations of AEs, the condition of each subject upon entering and during the course of the investigation, relevant medical history, the results of all diagnostic testing, etc.;
- Study personnel visit log;
- Signature authorization and delegation log; and,
- Any other records that applicable regulation requires to be maintained.

17.7 Reports

Table 17-1 lists those reports that are the investigator's responsibility to deliver to the Sponsor. Each study investigator must follow the EC/IRB reporting requirements for their respective site. If applicable regulations or EC/IRB requirements mandate stricter reporting requirements than those listed, the stricter requirements must be followed.

TABLE 17-1: REPORTS REQUIRED FROM INVESTIGATORS TO SPONSOR

Type of Report	Prepared by PI for	Notification Time Frame
UADE	Sponsor, EC/IRB	Within 10 working days of knowledge
Death	Sponsor, EC/IRB	Written reports (e.g., via e-mail) within 48 hours
SAE	Sponsor EC/IRB, if required	Within 10 working days of knowledge Per IRB requirement
Device malfunction with clinical sequelae	Sponsor EC/IRB, if required	Within 48 hours via written communication. Return the device to sponsor within 48 hours.
Serious protocol deviations (e.g., ICF not obtained, to protect the life or physical well-being of a subject in an emergency)	Sponsor EC/IRB, if required	Within 5 working days of knowledge Per IRB requirement
Withdrawal of EC/IRB approval	Sponsor	Within 5 working days of knowledge
Annual progress report	Sponsor, EC/IRB	Annually
Final report	Sponsor, EC/IRB	Within 3 months of study completion or termination
Note: Each IRB/EC may require more stringent reporting requirements that those listed in this table.		

17.8 Sponsor Responsibilities

NxThera, a Boston Scientific Company, is the Sponsor of this study. The Sponsors responsibilities in the study include:

- Selecting the Principal Investigator(s), all clinical investigators and study sites, and other consultants (e.g., monitors) who participate in the study.
- Provide study protocol, device, and GCP training to participating study sites, in quantities sufficient to support study activities, per agreements executed with the study sites.
- Select all qualified clinical Investigators and study sites and other consultants (e.g., the study monitors) who participate in the study.
- Provide financial support to each study site.
- Follow/promote all regulatory standards per appropriate regulations for study sites, core laboratories, and other participants, and ensure compliance by periodically monitoring sites.
- Ensure completion of site monitoring of clinical data at each clinical study site.
- Retain ownership of all clinical data generated in this study, and control the use of the data for appropriate purposes only.
- Review and approve publication of study results in the literature.

17.8.1 Confidentiality

All information and data sent to the Sponsor concerning subjects or their participation in this study will be considered confidential according to HIPAA regulations. Data used in the analysis and reporting of this evaluation will be used in a manner without identifiable reference to the subject. Investigators will consent to visits by Sponsor's staff and its authorized representatives, as well as by the U.S. FDA or any other local governmental body, to review the study subjects' medical records, including any test or laboratory data that might have been recorded on diagnostic test media (e.g., cystograms).

17.8.2 Amending the Investigational Study Protocol

Neither any Investigator nor the Sponsor will modify the Investigational Protocol without first obtaining concurrence of the other in writing. All changes to the Investigational Protocol must be submitted to the EC/IRB for review and approval. Any change that would require alteration to the ICF must receive approval from the applicable EC/IRB prior to implementation. Following approval, any Investigational Protocol amendment must be distributed to all protocol recipients at the site.

17.8.3 Protocol Deviations

A protocol deviation/violation is generally an unplanned excursion from the protocol that is not implemented or intended as a systematic change. An investigator who failed to perform tests or examinations as required by the protocol, or failures on the part of study subjects to complete scheduled visits as required by the protocol, would be considered protocol deviations. These type of deviations are reported to the Sponsor in accordance with the IRB policy.

A Protocol Deviation CRF must be completed by the site for each study protocol deviation (e.g., failure to obtain informed consent, enrolling a subject who does not meet inclusion/exclusion criteria, not performing required testing, missed follow-up window, etc.). An Investigator must notify the Sponsor and the reviewing EC/IRB of any deviation from the Study Protocol that was done to protect the life or physical well-being of a subject. Such notice should be given as soon as possible, but no later than five (5) working days after the event occurred.

17.8.4 Protocol Deviation Notification/Approval to IRB/Sponsor before Implementation

A protocol deviation may be a limited prospective exception to the protocol (e.g., agreement between Sponsor and Investigator to enroll a single subject who does not meet all inclusion/exclusion criteria due to out of window historical data). Deviations initiated by the clinical investigator must be reviewed and approved by the IRB and the Sponsor prior to implementation. This type of deviation can be used for historical data that is out of window due to medication washout or date of screening visit. The objective is to prevent subjects from being subject to repeat and possible invasive testing. These type of deviations are only approved if they do not impact data integrity or put subjects at unreasonable risk.

17.8.5 Site Noncompliance and Nonperformance

Repeat serious protocol deviations will be closely monitored. If excessive deviations or a failure to reduce deviations are noted, the Sponsor reserves the right to suspend study enrollment at that site until a sufficient system is in place at the site to reduce further deviations.

After a site completes all required approvals and training, a site initiation visit will be conducted as a final check of the site readiness. If a site is not able to enroll its first subject 2 months after "Ready to Enroll" status, the Sponsor may elect to terminate the investigational site and allocate the slot to another candidate site.

17.8.6 Device Accountability

Each site will be responsible for tracking the use and disposition of all Rezūm System Delivery Devices and Generators that are opened and or/used on a subject for the trial. Commercial product that is shipped, but not used for this study, will not be accounted on the Device Accountability Log.

18 Study Administration

18.1 Monitoring Procedures

It is the responsibility of the Sponsor to ensure that proper monitoring of this investigation is conducted. Appropriately trained personnel, appointed by the Sponsor, will complete any monitoring that is done. The monitoring will be the responsibility of Sponsor study personnel with an address as listed in the title page of this document. Monitors will ensure that the investigation is conducted in accordance with:

- The signed Investigator's Agreement,
- The Investigational Plan
- Appropriate laws and regulations
- Any conditions of approval imposed by the reviewing EC/IRB and/or other regulatory agencies

The clinical study will be monitored according to the guidelines summarized below. The Sponsor may choose to perform random inspections throughout the study as an element of quality assurance. Investigators shall allow auditing of their clinical investigation procedures.

A study-specific Monitoring Plan is created and implemented to standardize monitoring activities across centers and ensure human subject protection and verify data integrity. The monitors shall receive study specific and SOP training prior to conducting any monitoring visits. Study monitors are selected based on their training, qualifications and experience to monitor the progress of an investigation. Study monitors may be Sponsor's employees or representatives. This study monitoring will include, study initiation, interim, and close out visits. All study monitors will be required to follow the Sponsor's monitoring plan and monitoring SOPs.

The study monitoring will be done by the following Sponsor representative:

US Monitoring:
IMARC Research Inc.
22560 Lunn Road
Strongsville, OH 44149

18.1.1 Monitoring Visits

The following factors will be taken into account when determining the frequency of the monitoring visits: subject accrual rate at each center, total number of subjects enrolled at each center, and Clinical Investigation Plan compliance at each center. It is anticipated each site will be monitored at least once upon the completion of the 6-month follow-up visits for all enrolled subjects at the study site. Monitors will require direct access to subjects' medical records pertinent to the study (and study inclusion criteria), study management documents, regulatory documents and Subject Informed Consent documents, as well as other potential applicable records not listed here.

Monitors may ensure the clinical investigators have and continue to have staff and facilities to conduct the clinical investigation safely and effectively. Monitors may conduct the following monitoring activities throughout the study:

- Verification that the current IRB-approved informed consent was signed and dated by each subject prior to participating in the study required procedures.
- Verification of documentation in the subject's record that informed consent was signed prior to initiation of the study procedures and that a copy of the signed and dated consent was provided to the subject.
- Source documentation verification by reviewing the CRFs against source documentation for accuracy and completeness of information.
- Verification that the IMP is being used according to the CIP, IFU, and all malfunctions/IFU deficiencies are reported, as required.
- Verification that subjects met study enrollment criteria.
- Confirmation that the study is being conducted according to the CIP and applicable regulations.
- Verification that study deviations are documented and reported.
- Verification that the procedures for recording and reporting adverse events to the sponsor are followed.
- Ensuring proper error correction.
- Verification of training documentation of all study personnel participating in study related activities.
- Reviewing all correspondence and regulatory documents, including confirmation of IRB-approved CIP or amendments.
- Resolution of outstanding issues and completion of assigned tasks will be documented by the monitors.

Each monitoring visit will be documented via a monitoring report and follow-up letter. The follow-up visit letter shall be sent to the Investigator to document issues identified, corrective actions and if applicable preventative actions. At subsequent visits the issues resolved shall be documented in this letter to demonstrate resolution.

18.1.2 Study Closure

Study closure is defined as a specific date that is determined by study completion and/or regulatory requirements have been satisfied per the CIP and/or by decision of the Sponsor or FDA. Study closure visits will be conducted at all enrolling clinical sites in order to review record retention requirements with site personnel. A telephone contact may take the place of a study closure visit if appropriate (e.g., low subject enrollment, recent monitoring visit, etc.). Monitoring visits will be conducted by trained monitors and designees. The Monitoring Plan identifies the frequency of monitoring and training requirements of the monitors.

19 Clinical Trial Oversight

19.1 Clinical Events Committee (CEC)

Evaluation and adjudication of safety data (e.g., SAEs, all deaths, etc.) will be performed on an ongoing basis by the CEC. This CEC will be comprised of three independent physician reviewers with an expertise in urology. Members of the CEC will not be participants in the study.

All reported adverse events that are possibly related to the device, the procedure, or disease state being treated will be reviewed and adjudicated by the CEC. The CEC will review in tabular format all non-device/procedure/disease-related events.

20 Study Contact

20.1 Study Principal Investigator

Henry Woo, MD
Professor of Surgery
Sydney Adventist Hospital Clinical School
University of Sydney
P.O. Box 5017, Wahroonga, NSW, 2076. Australia

20.2 Sponsor and Data Management Center

NxThera, a Boston Scientific Company
10700 Bren Rd. W.
Minnetonka, MN 55343
Tel: 800-328-3881

21 Potential Device Change

All design and manufacturing process changes will be performed under the Sponsor's design control process and fully tested to ensure that it meets specifications.

22 Progress Reports

Progress reports will be prepared and submitted to the FDA and other applicable agency annually if required.

23 References

1	Hutchison A, Farmer R, Chapple C et al. Characteristics of patients presenting with LUTS/BPH in six European countries. *Eur Urol* 2006; 50: 555-61

2	Parsons JK, Wilt TJ, Wang PY et al. Progression of lower urinary tract symptoms in older men: a community based study. *J Urol* 2010; 183:1915-20
3	Ackerman SJ, Rein AL, Blute M et al. Cost effectiveness of microwave thermotherapy in patients with BPH: Part I – Methods. *Urology,* 2000; 56: 972-80
4	Fenter TC, Naslund MJ, Shah MB et al. The cost of treating the 10 most prevalent diseases in men 50 years of age or older. *Am J Manag Care* 2006; 12(4 Suppl): S90-8
5	Welch G, Weinger K, Barry MJ. Quality-of-life impact of lower urinary tract symptom severity: results from the Health Professionals Follow-up Study. *Urology* 2002; 59: 245-50
6	Rosen R, Altwein J, Boyle P et al. Lower urinary tract symptoms and male sexual dysfunction: the multinational survey of the aging male (MSAM-7). *Eur Urol* 2003; 44: 637–49
7	Hollingsworth JM, Wei JT. Economic impact of surgical intervention in the treatment of benign prostatic hyperplasia. *Rev Urology* 2006; 8 (Suppl 3); S9-15
8	Speakman M, Kirby R, Doyle S, Ioannu C. Burden of male lower urinary tract symptoms (LUTS) suggestive of benign prostatic hyperplasia (BPH) – focus on the UK. *BJU Int* 2015; 115: 508-19
9	Kapoor R, Liatsikos EN, Badlani G: Endoprostatic stents for management of benign prostatic hyperplasia. *Curr Opin Urol* 2000; 10: 19-22
10	Roehrborn CG, Gange SN, Shore ND et al: The prostatic urethral lift for the treatment of lower urinary symptoms associated with prostate enlargement due to benign prostatic hyperplasia: The L.I.F.T. Study. *J Urol* 2013; 190: 2161-7
11	American Urological Association Guideline. Management of Benign Prostatic Hyperplasia (BPH). Revised March 2010. (http://www.auanet.org/common/pdf/education/clinical-guidance/Benign-Prostatic-Hyperplasia.pdf)
12	European Association of Urology. Guidelines on the management of non-neurogenic male lower urinary tract symptoms (LUTS) including benign prostatic obstruction (BPO). March 2015. (http://uroweb.org/wp-content/uploads/EAU-Guidelines-Non-Neurogenic-Male-LUTS-Guidelines-2015-v2.pdf)
13	Dixon CM, Cedano ER, Mynderse LA, Larson TR. Transurethral convection water vapor as a treatment for lower urinary tract symptomology due to benign prostatic hyperplasia using the Rezūm® system: evaluation of acute ablative capabilities in the human prostate. *Res Rep Urol* 2015;7: 13-8
14	Dixon C, Cedano ER, Pacik D et al. Efficacy and safety of Rezūm system water vapor treatment for lower urinary tract symptoms secondary to benign prostatic hyperplasia. *Urology* 2015; 86: 1042-7
15	Mynderse LA, Hanson D, Robb RA et al. Rezūm system water vapor treatment for lower urinary tract symptoms/benign prostatic hyperplasia: Validation of convective thermal energy transfer and characterization with magnetic resonance imaging and 3-dimensional renderings. *Urology* 2015; 86: 122-7
16	McVary KT, Gange SN, Gittelman MC et al. Minimally invasive prostate convective water vapor energy (WAVE) ablation: A multicenter, randomized,

	controlled study for treatment of lower urinary tract symptoms secondary to benign prostatic hyperplasia. *J Urol* 2016; 195: 1-10
17	McVary KT, Gange SN, Gittelman MC et al. Erectile and ejaculatory function preserved with convective water vapor energy treatment of LUTS secondary to BPH: randomized controlled study. *J Sex Med 2016* (in press)
18	Dixon CM, Cedano ER, Pacik D et al. Two-year results after convective water vapor energy treatment of symptomatic benign prostatic hyperplasia. BJUI (submitted)
19	Bhowmick P, Coad JE, Bhowmick S et al: In vitro assessment of the efficacy of thermal therapy in human benign prostatic hyperplasia. *Int J Hypertherm* 2004; 20: 421-39
20	Rosen RC, Allen KR, Ni X, Araujo AB. Minimal clinically important differences in the erectile function domain of the International Index of Erectile Function Scale. Eur Urol 2011; 60: 1010-16.
21	Oelke M, Rademakers KL, van Koeveringe GA; FORCE Research Group, Maastricht & Hannover. Unravelling detrusor underactivity: Development of a bladder outlet resistance-bladder contractility nomogram for adult male patients with lower urinary tract symptoms. *Neurourol Urodyn* 2015 Jul 31. doi: 10.1002/nau.22841. [Epub ahead of print]
22	Chia, SJ, Heng C, Chan, S.P et al. Correlation of intravesical prostatic protrusion with bladder outlet obstruction. *BJUI* 2003; 91: 371-74.
23	Lee LS, Hong GS, Lim KB et al. Intravesical prostatic protrusion predicts clinical progression of benign prostatic enlargement in patients receiving medical treatment. *Int J o Urol* 2010; 17: 69-74.
24	Park S.C., Lee J.W., Rim J.S. The relationship between intravesical prostatic protrusion and pressure flow study findings in patients with benign prostate obstruction/lower urinary tract symptoms. *Actas Urológicas Españolas* 2012; 36(3): 165-70.
25	Wasserman NF, Spilseth B, Golzarian J et al. Use of MRI for Lobar Classification of Benign Prostatic Hyperplasia: Potential Phenotypic Biomarkers for Research on Treatment Strategies. *AJR Am J Roentgenol* 2015; 205:564-71.
26	Roehrborn CG, Gange SN, Gittelman MC, Goldberg KA, Patel K, Shore ND, Levin RM, Rousseau M, Beahrs JR, Kaminetsky J, Cowan BE, Cantrill CH, Mynderse LA, Ulchaker JC, Larson TR, Dixon CM, McVary KT, Convective Radiofrequency Water Vapor Thermal Therapy with Rezūm System: Durable Two-Year Results of Randomized Controlled and Prospective Crossover Studies for Treatment of Lower Urinary Tract Symptoms due to Benign Prostatic Hyperplasia, The Journal of Urology® (2017), doi: 10.1016/j.juro.2016.12.045.