



The ProVIDE Study

Clinical Investigation Plan

Protocol Number: CIP 002 Rev 04

NCT Number: NCT05186740

Product: ProVee Urethral Expander System

Protocol Ref: CIP 002

IDE Study Sponsor: ProVerum Inc.

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Statement of Confidentiality:

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The ProVIDE Study Clinical Investigation Plan

Investigational site number: _____

I, the undersigned, have read and understand the protocol specified above and agree on its content. I agree to perform and conduct the study as described in the clinical investigation plan and in accordance with the relevant parts of the ICH Guidelines for Good Clinical Practice (GCP), applicable United States (US) Code of Federal Regulations (CFR) including but not limited to 45 CFR Part 46, 21 CFR parts 812, 50, 54, 56, the International Standard ISO 14155 (Clinical Investigation of Medical Devices for Human Subjects), ethical principles that have their origins in the Declaration of Helsinki, and pertinent individual country laws and regulations. In addition, when applicable, I agree to enlist sub-investigators who also agree to perform and conduct the study as described in the protocol.

Principal Investigator (Print Name): _____

Principal Investigator (Signature): _____ Date : _____

Sponsor (Signature): _____ Date : _____

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1.0 Protocol Summary

1.1. Study Synopsis

Title	ProVIDE Study
Protocol Number	[REDACTED]
Investigational Device	ProVee Urethral Expander System (the 'ProVee device')
Device Description	[REDACTED] [REDACTED] [REDACTED]
Sponsor	ProVerum Inc.
Global Principal Investigator	[REDACTED]
Study Design	<p>This is a prospective, multi-center, randomized, double-blind, sham-controlled study to evaluate the safety, performance, and effectiveness of the ProVee Urethral Expander System (Investigational Device) when used in subjects with symptomatic urinary obstruction related to benign prostatic hyperplasia (BPH). Subjects are assigned to their treatment arm using an unbalanced (2 ProVee:1 Sham) randomization stratified by Investigational Site. Subjects randomized to the ProVee Treatment Arm will receive treatment in the Operating Room (OR), clinical office, or in an out-patient treatment room, with local anesthesia, conscious sedation, spinal block and/or with general anesthesia, per the Investigator's discretion.</p> <p>[REDACTED] [REDACTED] [REDACTED] [REDACTED]. As with the Treatment Arm, Subjects randomized to the Control Arm will undergo the sham procedure in the Operating Room (OR), clinical office, or in an out-patient</p>

	<p>treatment room, with local, spinal block, sedation and/or with general anesthesia, per the Investigator's discretion. Blinding procedures shall be in place.</p> <p>All subjects are followed for 3 months until the co-primary effectiveness endpoints are evaluated. After their 3-month visit, all subjects will be unblinded to their treatment assignment. Subjects assigned to the ProVee Treatment Arm will continue to be followed up to 60 months post implantation. Following unblinding, subjects assigned to the Control Arm (Sham) may elect to be treated with the ProVee Urethral Expander System (crossover to the active treatment). After being treated, Crossover Subjects will be followed using the same schedule used with the ProVee Treatment Arm. Control Arm subjects choosing not to receive the ProVee Treatment will be exited from the study. From 12 months onward, the Crossover Cohort shall be analyzed with the Treatment Arm Cohort in the assessment of long-term safety and effectiveness.</p>
Study Objective	To evaluate the safety and effectiveness of the ProVee Urethral Expander System in subjects with lower urinary tract symptoms secondary to Benign Prostatic Hyperplasia (BPH)
Sample Size	A total of 225 subjects (150 ProVee subjects and 75 Sham subjects) will be enrolled and treated.
Study Centers	Maximum of twenty two (22) sites with up to eighteen (18) in the US and up to four (4) OUS. [REDACTED] [REDACTED].
Target Enrolment	The enrolment period is estimated to be 12 months. Follow-up time period is 60 months. The study duration is estimated to be 72 months.
Patient Population	Male subjects who are 45 years and older with lower urinary tract symptoms (LUTS) related to symptomatic benign prostatic hyperplasia (BPH).
Eligibility Criteria	<p><u>Inclusion</u></p> <ol style="list-style-type: none"> 1. Males \geq 45 years of age 2. IPSS of \geq 13, IPSS V/S \geq 1 at baseline assessment 3. Prostate volume of \geq 30 cc and \leq 80 cc

<p>4. Prostatic urethral L2 lengths \geq 3.75cm by TRUS</p> <p>5. Failed, intolerant, or subject choice to not take a medication regimen for the treatment of LUTS</p> <p><u>Exclusion</u></p> <p>1. Void volume \leq 125 ml; $Q_{max} \geq$ 12ml/s; PVR $>$ 250 ml</p> <p>2. Obstructive median lobe defined by EITHER $>$10mm protrusion on sagittal mid-prostate plane as measured by TRUS OR an obstructive median lobe seen on cystoscopy e.g., 'ball valve'</p> <p>3. High bladder neck, with the absence of lateral lobe encroachment indicating a high likelihood of primary bladder neck obstruction</p> <p>4. Anatomy that would prevent the apices of the ProVee from engaging with the lateral lobes e.g., high degree of bladder neck angulation such that the anterior bladder neck is not visible</p> <p>5. Acute urinary retention</p> <p>6. Known immunosuppression</p> <p>7. History of or suspected prostate or bladder cancer</p> <p>8. Baseline PSA $>$ 10 ng/mL or confirmed or suspected prostate cancer (Subjects with a PSA level above 2.5 ng/mL, or age specific, or local reference ranges should have prostate cancer excluded to the Investigator's satisfaction, including a SOC biopsy if indicated).</p> <p>9. Recent urinary tract stones OR widespread calcifications on the prostatic urethral wall, within 3 months of index procedure</p> <p>10. A history of prostatitis within the last two years</p> <p>11. Active or history of epididymitis within the past 3 months</p> <p>12. Neurogenic bladder and/or sphincter abnormalities due to Parkinson's disease, multiple sclerosis, cerebral vascular accident, diabetes</p> <p>13. History of urinary retention within 12 months of baseline assessment</p> <p>14. Requiring self-catheterization to void</p> <p>15. An active urinary tract infection (UTI) at time of index procedure</p> <p>16. Gross haematuria, within 3 months of index procedure</p> <p>17. Subjects with known allergy to nickel or titanium</p> <p>18. Life expectancy estimated to be less than 60 months</p>

Exclusion

1. Void volume \leq 125 ml; $Q_{max} \geq$ 12ml/s; PVR $>$ 250 ml

2. Obstructive median lobe defined by EITHER $>$ 10mm protrusion on sagittal mid-prostate plane as measured by TRUS OR an obstructive median lobe seen on cystoscopy e.g., 'ball valve'

3. High bladder neck, with the absence of lateral lobe encroachment indicating a high likelihood of primary bladder neck obstruction

4. Anatomy that would prevent the apices of the ProVee from engaging with the lateral lobes e.g., high degree of bladder neck angulation such that the anterior bladder neck is not visible

5. Acute urinary retention

6. Known immunosuppression

7. History of or suspected prostate or bladder cancer

8. Baseline PSA $>$ 10 ng/mL or confirmed or suspected prostate cancer (Subjects with a PSA level above 2.5 ng/mL, or age specific, or local reference ranges should have prostate cancer excluded to the Investigator's satisfaction, including a SOC biopsy if indicated).

9. Recent urinary tract stones OR widespread calcifications on the prostatic urethral wall, within 3 months of index procedure

10. A history of prostatitis within the last two years

11. Active or history of epididymitis within the past 3 months

12. Neurogenic bladder and/or sphincter abnormalities due to Parkinson's disease, multiple sclerosis, cerebral vascular accident, diabetes

13. History of urinary retention within 12 months of baseline assessment

14. Requiring self-catheterization to void

15. An active urinary tract infection (UTI) at time of index procedure

16. Gross haematuria, within 3 months of index procedure

17. Subjects with known allergy to nickel or titanium

18. Life expectancy estimated to be less than 60 months

	<ol style="list-style-type: none"> 19. Taking androgens, unless eugonadal state for at least 3 months or greater with a stable dosage for at least 2 months as documented by the Investigator 20. Use of 5-alpha-reductase inhibitors (e.g., dutasteride, finasteride) within 6 months of baseline assessment 21. Use of Phenylephrine / Pseudoephedrine within 24 hours of baseline assessment 22. Use of alpha-blockers (e.g., Terazosin, Doxazosin, Alfuzosin, Tamsulosin) within 2 weeks of baseline assessment 23. Use of estrogen or drug-producing androgen suppression (e.g. gonadotropin-releasing hormonal analogues) within 1 year of baseline assessment 24. Use of antihistamines, anticonvulsants, and antispasmodics within 1 week of baseline assessment unless there is documented evidence that the patient was on the same drug dose for at least 6 months with a stable voiding pattern (the drug dose should not be altered or discontinued for entrance into or throughout the study) 25. Use of anticholinergics or cholinergic medication within 2 weeks of baseline assessment 26. Use of beta-blockers where the dose is not stable. (Stable dose is defined as having the same medication and dose in the last 6 months) 27. Use of Phosphodiesterase-5 Enzyme Inhibitors in doses for BPH within 2 weeks of baseline assessment 28. Current treatment with anticoagulants (e.g., coumadin or enoxaparin) or antiplatelet medications other than aspirin (e.g., clopidogrel, or alternative and ASA). Patient unable to stop taking anticoagulants and/or antiplatelets within 3 days prior to the procedure or coumadin at least 5 days prior to the procedure. Low dose aspirin \leq100mg/day not prohibited 29. Future fertility concerns 30. Previous prostate surgery, balloon dilatation, stent implantation, laser prostatectomy, hyperthermia, or any other invasive treatment to the prostate; including penile implants 31. Previous pelvic irradiation or radical pelvic surgery 32. Previous rectal surgery (other than hemorrhoidectomy) or known history of rectal disease
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	<p>33. Urethral strictures, bladder neck contracture, or other potentially confounding bladder pathology</p> <p>34. Urethral pathologies that may prevent insertion of Delivery System</p> <p>35. Uncontrolled diabetes mellitus including Hgb AIC >8%</p> <p>36. Overactive bladder (OAB) requiring treatment by OAB medication</p> <p>37. Urinary incontinence</p> <p>38. Patients taking tri-cyclic antidepressants.</p> <p>39. Compromised renal function (i.e., serum creatinine >1.8 mg/dl or upper tract disease)</p> <p>40. Hepatic disorder, bleeding disorders or metabolic impairment that might confound the results of the study or have a risk to subject per investigator's opinion</p> <p>41. Any major comorbidities or presence of unstable conditions, e.g., uncontrolled HTN, NYHA Class III or IV, cardiac arrhythmias that are not controlled by medication/medical device, myocardial infarction within the past 6 months, COPD with FEV₁ <50, renal illness that might prevent study completion or would confound study results</p> <p>42. Vulnerable populations such as incarcerated or institutionalized adults, inmates, patients with physical, psychological (such as developmentally delayed adults), or medical impairment that might, in the judgment of the Investigator, prevent study completion or comprehension, or may confound study results (including patient questionnaires)</p> <p>43. History or current medical condition that would result in an unacceptable patient risk if that subject were to be included in the study</p> <p>44. Any subject that is currently enrolled in another ongoing investigational study.</p>
Visit Schedule	<ul style="list-style-type: none"> • [REDACTED] • [REDACTED] • [REDACTED] • [REDACTED] • [REDACTED] • [REDACTED]



	<ul style="list-style-type: none">● [REDACTED]● [REDACTED]● [REDACTED]● [REDACTED]● [REDACTED]● [REDACTED]
Analysis Population:	Screening (enrolled), intent-to-treat, per protocol basis and completed cases
Primary Endpoints	<p>Primary Safety Endpoints</p> <ol style="list-style-type: none">1. <i>Adverse Events</i> (time frame: procedure to 12 months) Rate of device or procedure related serious adverse events through 12-months.2. <i>Need for urinary catheterization</i> (time frame: >7 days post procedure) The rate of extended post-operative urinary catheterization (> 7 days from treatment) for inability to void among patients treated with the ProVee device. <p>Primary Effectiveness Endpoints</p> <ol style="list-style-type: none">1. <i>Reduction in BPH Symptoms compared to Sham</i> (time frame: procedure to 3 months) The ProVee Treatment Group will be considered superior to the Sham Treatment Group when the mean 3-month improvement from baseline score for the IPSS symptom questionnaire demonstrates a minimum statistical margin of 25% compared to mean improvement from baseline for the Sham Treatment Group alone.2. <i>Symptoms Improvement</i> (time frame: Procedure to 12 months) The mean percent change in IPSS in the treatment arm is at least 30% improvement over the patient's pre-treatment baseline score.
Secondary Endpoints	[REDACTED] [REDACTED] [REDACTED] [REDACTED]

A horizontal bar chart with 10 categories on the y-axis and sample counts on the x-axis. Category 0 has the highest count (1000). Categories 1, 3, 5, 7, and 9 have lower counts, with category 5 having the fewest (~100).

Category	Sample Count
0	1000
1	~250
2	1000
3	~250
4	1000
5	~100
6	1000
7	~250
8	1000
9	1000

	[REDACTED]

1.2. Patient Flow Chart and Schedule of Activities

The patient flow chart is provided in Figure 1 and the schedule of study activities in contained in Table 1.

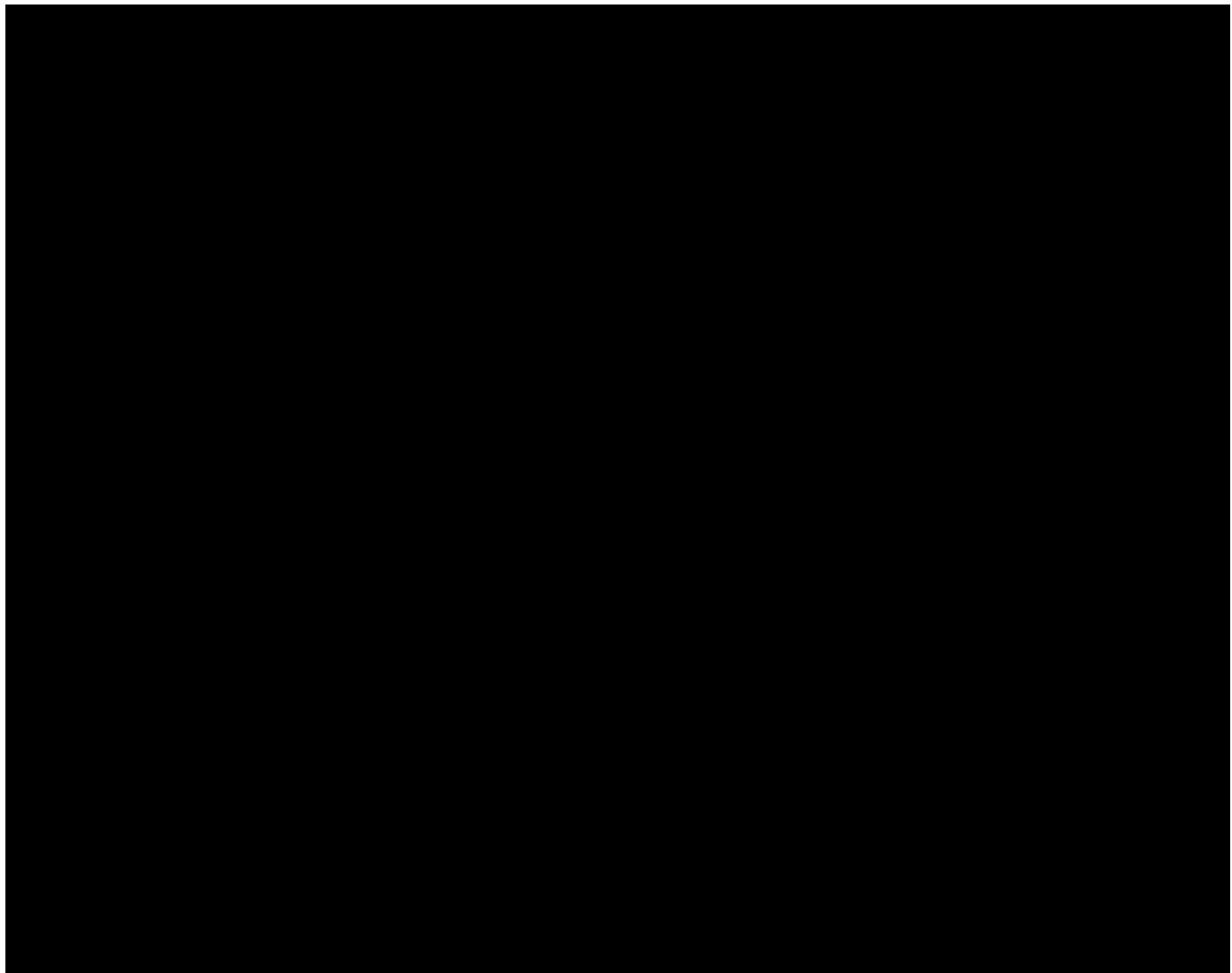
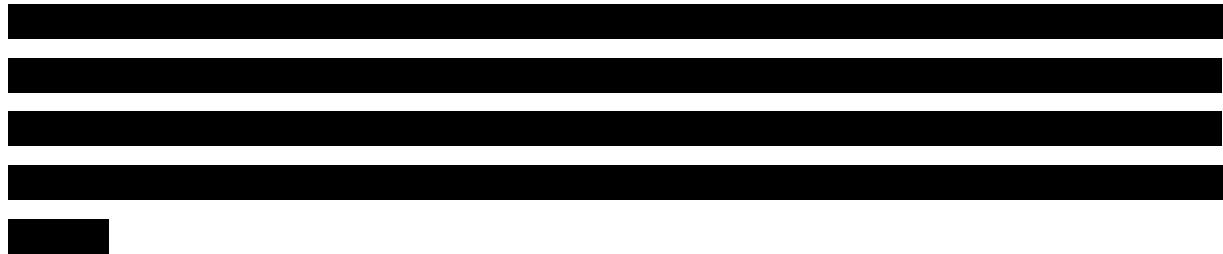


Table 1: ProVIDE Study Schedule of Activities for Consented Subjects

2.0 Introduction



2.1. Study Rationale

Benign prostatic hyperplasia (BPH) refers to the non-malignant proliferation of smooth muscle and epithelial cells within the prostatic transition zone resulting in an enlargement of the prostate gland. It is estimated to occur in more than 50% of men in their 60s, growing to 90% of men in their 80s, and is the fourth most common diagnosed disease in men above 50 years old, ranking behind coronary artery disease, hypertension and type 2 diabetes¹. Patients often present with lower urinary tract symptoms (LUTS), secondary to BPH. These symptoms, which include urgency, frequency, retention of urine, difficulty in voiding/emptying of the bladder and problems following urination such as post void dribbling, have a major impact on quality of life and require treatment¹⁻³.

The main goal of BPH treatment is to alleviate LUTS in order to improve the patient's quality of life, options are drug therapy or surgical intervention.

- **Drug Therapy** - Whilst there is no pharmacological cure for BPH, drug therapy is often the first line treatment option and is used to manage symptoms by either shrinking the prostate (5-alpha reductase inhibitors) or relaxing muscles surrounding the prostate (alpha blockers). In some instances, patients may be prescribed a combination of both drugs (CombiRx)³. While medication can provide relief for some men, limited efficacy⁴ and negative side effects contribute to poor compliance, with up to 82% of men electing to discontinue drug therapy within one year⁵.
- **Surgical Intervention** – Traditionally, surgical intervention has involved removal of the obstructing tissue from the prostate gland typically via resection. Whilst invasive, this Transurethral Resection of the Prostate (TURP) and surgical equivalents are considered to

be the cornerstone of LUTS surgical treatment delivering durable outcomes as shown by studies with a follow-up of 8-22 years⁶. Despite generally providing longer lasting symptomatic relief, less than 3% of BPH patients elect to undergo resective surgery due to the potential side effects, such as urinary incontinence, erectile dysfunction and ejaculatory dysfunction, associated with the procedures⁶. More recently Minimally Invasive Surgical Therapies (MISTs) are recommended for the treatment of LUTS. These non-resective procedures re-shape the prostate by means of a medical device and offer patients a treatment solution with greater efficacy than medication and fewer complications than resective surgery^{6,7}.

[REDACTED]

[REDACTED]

[REDACTED]

2.2. Background

2.2.1. *Benign Prostatic Hyperplasia (BPH)*

Benign prostatic hyperplasia is a histologic diagnosis that refers to the proliferation of smooth muscle and epithelial cells within the prostatic transition zone. In clinical BPH abnormal prostate anatomy will result from the excessive proliferation, resulting in a varying degree of benign prostatic obstruction (BPO) and benign prostatic enlargement (BPE)¹.

It is the lower urinary tract symptoms (LUTS), secondary to BPH, due to BPO and BPE that are a common problem among men with a major impact on quality of life (QoL), and substantial economic burden. Symptoms increase in frequency and severity with age and include symptoms prior to urination related to frequency, urgency, retention of urine and difficulty voiding/emptying of the bladder and problems following urination related to post void dribbling^{1,3}.

2.2.2. *Current Treatment Options*

[REDACTED]

[REDACTED]

[REDACTED]
[REDACTED] .

2.2.3. Drug Therapy

The two main class of medications are α 1Adrenoceptor antagonists (α 1-blockers) and 5α -reductase inhibitors (5-ARIs):

- α 1-blockers aim to inhibit the effect of endogenously released noradrenaline on smooth muscle cells in the prostate and thereby reduce prostate tone and bladder outlet obstruction.
- 5α -reductase inhibitors reduce levels of dihydrotestosterone (DHT) inducing apoptosis of prostate epithelial cells leading to a reduction in prostate size.

[REDACTED]
[REDACTED]
[REDACTED] [REDACTED]
[REDACTED]
[REDACTED]

2.2.4. BPH Surgery

Surgical treatment of symptomatic BPH has classically involved removal of the obstructing adenomatous tissue from the prostate gland typically via Transurethral Resection of the Prostate (TURP) using monopolar electroconductivity where tissue is cored out with a heated wire loop, simultaneously cutting and cauterizing the tissue. In addition to TURP there are a variety of modifications and alternatives technologies that all involve tissue resection or ablation. These procedures include bipolar TURP (BTURP), water vapor thermal therapy known as transurethral vaporisation of the prostate (TUV), laser enucleation and resection of the prostate using holmium laser(HoLEP), thulium:yttrium-aluminium-garnet laser(Tm:YAG) or a Photoselective Vaporization of the Prostate (PVP) Greenlight laser.

[REDACTED]

[REDACTED]

[REDACTED] . [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED] [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

In response to the limitations of drug therapy and surgical intervention, a number of minimally invasive surgical therapies (MIST) have been developed to treat LUTS^{6,7}. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED] [REDACTED]

[REDACTED] [REDACTED]

[REDACTED] [REDACTED]

2.2.5. ProVee Urethral Expander System

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

2.2.6. Design Verification and Biocompatibility Studies

2.2.7. Clinical Experience (First in Man)

2.3. Risk/Benefit Assessment

To evaluate device related risk, ProVerum performed a risk analysis in accordance with the harmonized European standard ISO 14971 “*Medical Devices – Application of Risk Management to Medical Devices*”.

2.3.1. Known Potential Risks

Risk associated with the use of a minimally invasive devices such as the ProVee device include but are not limited to:

- Dysuria
- Haematuria
- Urge Incontinence
- Urinary Calculus
- Pain Pelvic and/ or with Ejaculation
- Acute Urinary Retention
- Urinary Tract Infection
- Urinary Incontinence
- Micturition Urgency
- Pollakiuria
- Nocturia
- Temporary Prostatic Urethral Inflammation

- Urethral Stricture

2.3.2. Known Potential Benefits

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

2.3.3. Assessment Of Potential Risks And Benefits

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

3.0 Objectives And Endpoints

3.1. Study Objective

To evaluate the safety and effectiveness of the ProVee Device in subjects with lower urinary tract symptoms secondary to Benign Prostatic Hyperplasia (BPH). The primary endpoints are defined in section 3.2 and the secondary endpoints are specified in section 3.3.

3.2. Primary Endpoints

3.2.1. Primary Safety Endpoint

1. *Adverse Events* (time frame: procedure to 12 months)

Rate of device or procedure related serious adverse events through 12-months.

2. *Need for urinary catheterization* (time frame: >7 days post procedure)

The rate of extended post-operative urinary catheterization (> 7 days from treatment) for inability to void among patients treated with the ProVee Device.

3.2.2. Primary Effectiveness Endpoints

1. *Reduction in BPH Symptoms compared to Sham (time frame: procedure to 3 months)*

The ProVee Treatment Arm will be considered superior to the Sham Treatment Arm when the mean 3-month improvement from baseline score for the IPSS symptom questionnaire demonstrates a minimum statistical margin of 25% compared to mean improvement from baseline for the Sham Treatment Arm alone.

2. *Symptoms Improvement (time frame: Procedure to 12 months)*

The mean percent change in IPSS in the treatment arm is at least 30% improvement over the patient's pre-treatment baseline score.

3.3. Secondary Safety Endpoints

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

6. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

4.0 Study Design

4.1. Overall Design

This is a prospective, multi-center, 2:1 randomized, double-blind, sham-controlled study to evaluate the safety, performance, and effectiveness of the ProVee Device (Investigational Device) when used in subjects with symptomatic urinary obstruction related to benign prostatic hyperplasia (BPH).

The primary endpoints will be assessed up to the 1 year follow-up. To assess the long term safety and effectiveness, all subjects randomized to the treatment arm will be monitored for adverse events and continued assessment through 5 years post procedure.

4.2. Cohort Description

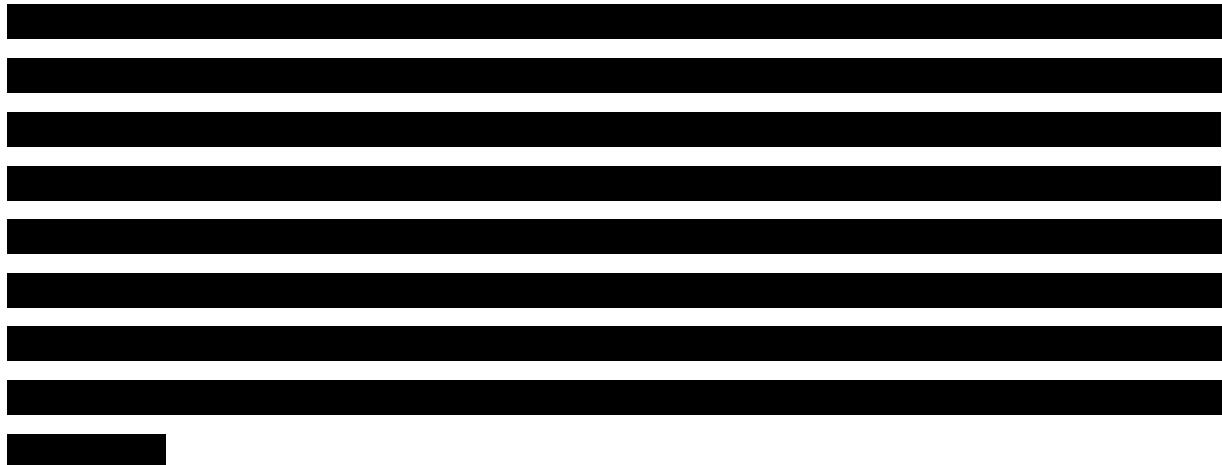
The study design has 2:1 randomization (Investigational Device: Sham Procedure) stratified by Investigational Sites. As a result, the study includes 3 subject cohorts – Sham Treatment Group (Control Arm), ProVee Treatment Group (Investigational Arm) and Cross-Over Arm. The subject will be blinded as to whether he is in the control or treatment group. Unblinding will occur at 3 months post procedure after follow-up assessments are completed.

4.2.1. *Sham Treatment Group (Control Arm)*

[REDACTED]

[REDACTED]

[REDACTED]



Following unblinding after the 3-month visit, subjects assigned to the Control Arm (sham procedure) may elect to be treated with the ProVee Device (crossover to treatment). Refer to section 4.2.3 for further details. The subjects choosing not to crossover and receive the ProVee Device will be exited from the study.

4.2.2. ProVee Treatment Group (Investigational Arm)

The ProVee Treatment Group subjects will receive the ProVee Device. All subjects in the ProVee Treatment Group will be followed at a minimum of 5 years per the assessment schedule (**Table 7**).

4.2.3. Cross Over Group

Specific to the Control Arm, after unblinding, upon completion of the 3 month follow-up assessments, qualifying subjects who are willing to comply with the required follow-up can be offered treatment with the ProVee Device if they meet the retreatment or crossover enrollment criteria specified in 6.9. After being treated, Crossover Subjects will be followed using the same schedule used with the ProVee Treatment Arm. From 12 months onward, the Crossover Cohort shall be analyzed with the Treatment Arm Cohort in the assessment of long-term safety and effectiveness. Control Arm subjects choosing not to receive the ProVee Device will be exited from the study.

5.0 Study Population

The patient population is male subjects who are 45 years and older with lower urinary tract symptoms (LUTS) related to symptomatic benign prostatic hyperplasia (BPH).

5.1. Inclusion Criteria

1. Males \geq 45 years of age
2. IPSS of \geq 13, IPSS V/S \geq 1 at baseline assessment
3. Prostate volume of \geq 30 cc and \leq 80 cc
4. Prostatic urethral L2 lengths \geq 3.75cm by TRUS
5. Failed, intolerant, or subject choice to not take a medication regimen for the treatment of LUTS

5.2. Exclusion Criteria

1. Void volume \leq 125 ml; $Q_{max} \geq 12\text{ml/s}$; PVR > 250 ml
2. Obstructive median lobe defined by EITHER $>10\text{mm}$ protrusion on sagittal mid-prostate plane as measured by TRUS OR an obstructive median lobe seen on cystoscopy e.g., ‘ball valve’
3. High bladder neck, with the absence of lateral lobe encroachment indicating a high likelihood of primary bladder neck obstruction
4. Anatomy that would prevent the apices of the ProVee from engaging with the lateral lobes e.g., high degree of bladder neck angulation such that the anterior bladder neck is not visible
5. Acute urinary retention
6. Known immunosuppression
7. History of or suspected prostate or bladder cancer
8. Baseline PSA $> 10 \text{ ng/mL}$ or confirmed or suspected prostate cancer (Subjects with a PSA level above 2.5 ng/mL , or age specific, or local reference ranges should have prostate cancer excluded to the Investigator's satisfaction, including a SOC biopsy if indicated).

9. Recent urinary tract stones OR widespread calcifications on the prostatic urethral wall, within 3 months of index procedure
10. A history of prostatitis within the last two years
11. Active or history of epididymitis within the past 3 months
12. Neurogenic bladder and/or sphincter abnormalities due to Parkinson's disease, multiple sclerosis, cerebral vascular accident, diabetes'
13. History of urinary retention within 12 months of baseline assessment
14. Requiring self-catheterization to void
15. An active urinary tract infection (UTI) at time of index procedure
16. Gross haematuria, within 3 months of index procedure
17. Subjects with known allergy to nickel or titanium
18. Life expectancy estimated to be less than 60 months
19. Taking androgens, unless eugonadal state for at least 3 months or greater with a stable dosage for at least 2 months as documented by the Investigator
20. Use of 5-alpha-reductase inhibitors (e.g., dutasteride, finasteride) within 6 months of baseline assessment
21. Use of Phenylephrine / Pseudoephedrine within 24 hours of baseline assessment
22. Use of alpha-blockers (e.g., Terazosin, Doxazosin, Alfuzosin, Tamsulosin) within 2 weeks of baseline assessment
23. Use of estrogen or drug-producing androgen suppression (e.g. gonadotropin-releasing hormonal analogues) within 1 year of baseline assessment
24. Use of antihistamines, anticonvulsants, and antispasmodics within 1 week of baseline assessment unless there is documented evidence that the patient was on the same drug dose for at least 6 months with a stable voiding pattern (the drug dose should not be altered or discontinued for entrance into or throughout the study)
25. Use of anticholinergics or cholinergic medication within 2 weeks of baseline assessment
26. Use of beta-blockers where the dose is not stable. (Stable dose is defined as having the same medication and dose in the last 6 months)
27. Use of Phosphodiesterase-5 Enzyme Inhibitors in doses for BPH within 2 weeks of baseline assessment

28. Current treatment with anticoagulants (e.g., warfarin or enoxaparin) or antiplatelet medications other than aspirin (e.g., clopidogrel, or alternative and ASA). Patient unable to stop taking antiplatelet and/or antiplatelets within 3 days prior to the procedure or warfarin at least 5 days prior to the procedure. Low dose aspirin \leq 100mg/day not prohibited
29. Future fertility concerns
30. Previous prostate surgery, balloon dilatation, stent implantation, laser prostatectomy, hyperthermia, or any other invasive treatment to the prostate; including penile implants
31. Previous pelvic irradiation or radical pelvic surgery
32. Previous rectal surgery (other than hemorrhoidectomy) or known history of rectal disease
33. Urethral strictures, bladder neck contracture, or other potentially confounding bladder pathology
34. Urethral pathologies that may prevent insertion of Delivery System
35. Uncontrolled diabetes mellitus including Hgb AIC $>$ 8%
36. Overactive bladder (OAB) requiring treatment by OAB medication
37. Urinary incontinence
38. Patients taking tri-cyclic antidepressants.
39. Compromised renal function (i.e., serum creatinine $>$ 1.8 mg/dl or upper tract disease)
40. Hepatic disorder, bleeding disorders or metabolic impairment that might confound the results of the study or have a risk to subject per investigator's opinion
41. Any major comorbidities or presence of unstable conditions, e.g., uncontrolled HTN, NYHA Class III or IV, cardiac arrhythmias that are not controlled by medication/medical device, myocardial infarction within the past 6 months, COPD with FEV₁ $<$ 50, renal illness that might prevent study completion or would confound study results
42. Vulnerable populations such as incarcerated or institutionalized adults, inmates, patients with physical, psychological (such as developmentally delayed adults), or medical impairment that might, in the judgment of the Investigator, prevent study completion or comprehension, or may confound study results (including patient questionnaires)
43. History or current medical condition that would result in an unacceptable patient risk if that subject were to be included in the study
44. Any subject that is currently enrolled in another ongoing investigational study.

5.3. Strategies For Recruitment And Retention

A series of seven horizontal black bars of varying lengths, decreasing in length from left to right. The bars are positioned at different vertical intervals, creating a stepped effect. The first bar is the longest, followed by a shorter one, then a longer one, then a shorter one, then a very long one, then a shorter one, and finally a very long one on the far right.

5.4. Screen Failures

A series of ten horizontal black bars of varying lengths, decreasing in length from left to right. The bars are evenly spaced and extend across the width of the frame.

6.0 Study Assessments And Procedures

6.1. Informed Consent

The subject will be given and asked to read and sign the approved Informed Consent Form (ICF). The subject is entitled to a minimum of twenty-four (24) hours to review the ICF. The subject is entitled to take the ICF home to discuss with a relative, friend or their local doctor. If the subject

is interested, an appointment to return to the clinic to meet with the investigator and staff will be arranged.

The Investigator and/or delegate must fully explain to the subject all aspects of the study that are relevant to the decision of participation in the study. Any questions will be addressed and if they wish to proceed, the subject's informed consent is documented by means of a written, signed, and dated ICF prior to the start of the study. Subjects who do not have decision making capacity to consent will be excluded from the Study.

Subject enrolment occurs at the time of ICF execution. Once the subject has completed the informed consent procedure and signed the ICF, the Investigator or delegated Study research staff can complete the screening process with the subject. Every subject that signs a ICF will be considered enrolled in the Study. If a subject has provided consent and completed screening, and for any reason does not complete the assessment phases, the subject will be exited from the Study. Any subjects that screen fail prior treatment with the investigational device or sham control device, will not be counted in the data analysis.

The eCRF for each subject will document that informed consent was obtained prior to participation in the Study. The original signed consent forms must remain in each subject's Study file and must be available for verification by Study monitors at any time. Medical records will also retain and scan an original ICF.

6.2. Screening Assessment

[REDACTED]

Table 2: Pre-Treatment Procedures

6.2.1. Discontinuation of BPH-LUTS Medication

A thick black rectangular redaction box covers the bottom portion of the page content, obscuring several lines of text.

Table 3: Discontinuation of BPH-LUTS Medication

6.3. Study Randomization

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

6.4. Index Procedure (Treatment)

[REDACTED]

6.5. Post-procedure / Discharge

[REDACTED]

- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]

- [REDACTED]
- [REDACTED]

6.6. Performance of Assessments and Procedures

6.6.1. *Questionnaires*

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10 of 10

6.6.3. *Uroflowmetry*

[REDACTED]

[REDACTED]

[REDACTED] [REDACTED]

[REDACTED]

6.6.4. *TRUS*

[REDACTED]

[REDACTED]

and/or the median lobe is protrudes ≥ 8 mm on sagittal mid-[REDACTED]

[REDACTED]

[REDACTED] a prostate volume of ≥ 30 cc and ≤ 80 cc and the exclusion

[REDACTED]

[REDACTED]

6.6.5. *Blood Tests*

[REDACTED].

6.6.6. *Urinalysis*

[REDACTED]

6.6.7. *Medical History and Physical Exam*

[REDACTED].

6.6.8. *Adverse Event Assessment*

[REDACTED]

[REDACTED]

[REDACTED]

6.6.9. Assessment of Concomitant Medications

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

6.7. Follow-up Assessments

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

6.8. Study Follow-up Timepoints

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]



6.8.1. 1-Month (± 7 days) Follow-up

- [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

- [REDACTED]

- [REDACTED]

- [REDACTED]

6.8.2. 3-month (± 14 days) Follow-up

- [REDACTED]

[REDACTED]

[REDACTED]

- [REDACTED]

[REDACTED]

[REDACTED]

- [REDACTED]

- [REDACTED]

- [REDACTED]

- [REDACTED]

[REDACTED]

[REDACTED]



- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]

6.8.3. 6-month (\pm 1 month) Follow-up

- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
 - [REDACTED]
 - [REDACTED]
 - [REDACTED]
 - [REDACTED]
 - [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]

6.8.4. 12-month (\pm 1 month) Follow-up

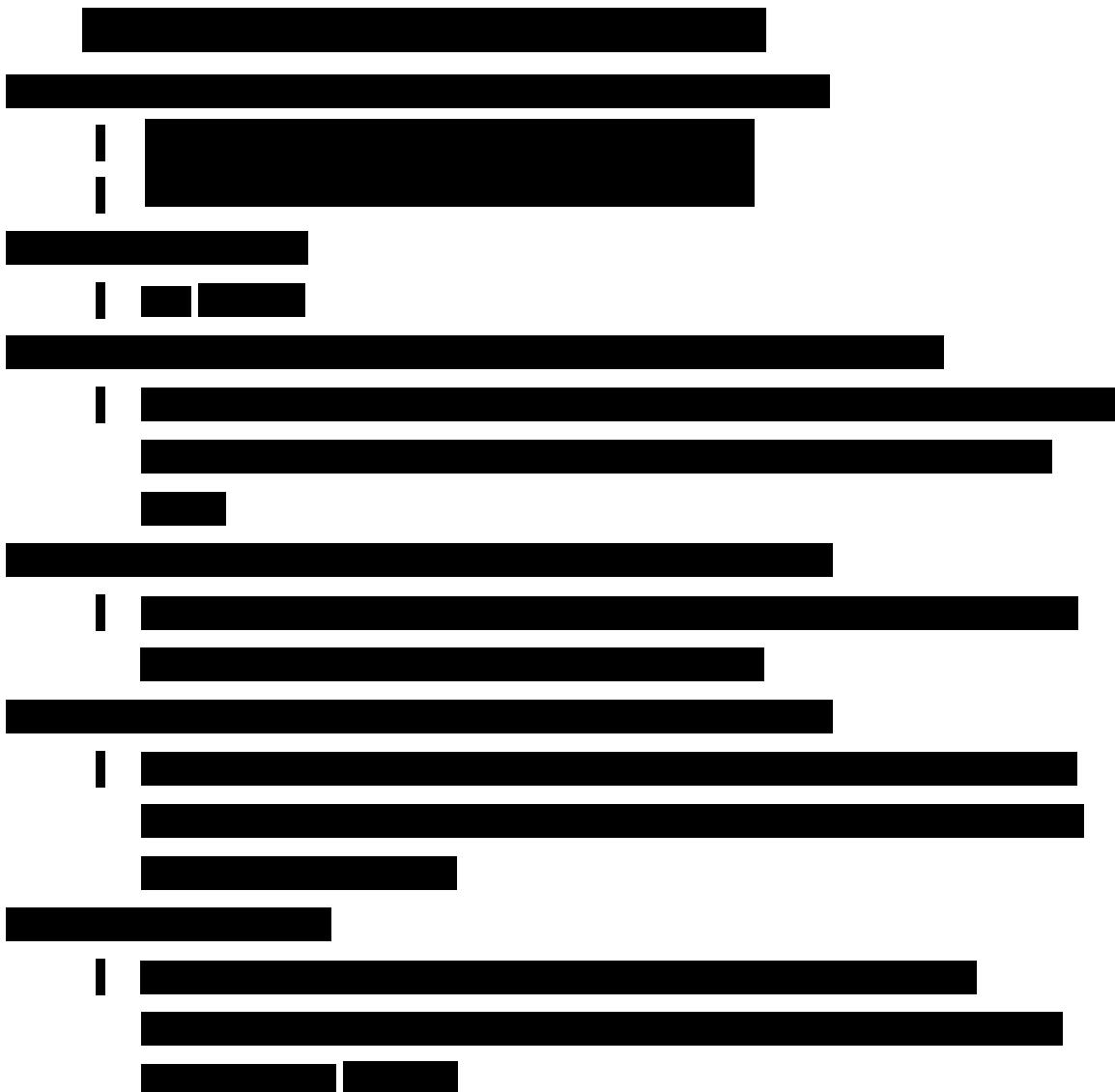
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
 - [REDACTED]
 - [REDACTED]
 - [REDACTED]
 - [REDACTED]
 - [REDACTED]

- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]

6.8.5. 2-year (\pm 1 month) to 5-year (\pm 1 month) Follow-up

6.9. Cross Over following 3 month Follow-up

A series of seven horizontal black bars of varying lengths, decreasing from left to right. The first bar is the longest, followed by a shorter one, then a very long one, then a medium one, then two more short ones, and finally the shortest one on the far right.



The Inclusion and Exclusion criteria for cross over eligibility are as follow:

Inclusion

1. Males ≥ 45 years of age
2. Failed, intolerant, or subject choice to not take a medication regimen for the treatment of LUTS

² Sham procedure will not count as a prostate surgery under this exclusion definition. Other prostate surgery will result in exclusion from crossover

Exclusion

1. Acute urinary retention
2. Known immunosuppression
3. History of or suspected prostate or bladder cancer
4. Baseline PSA > 10 ng/mL or confirmed or suspected prostate cancer (Subjects with a PSA level above 2.5 ng/mL, or age specific, or local reference ranges should have prostate cancer excluded to the Investigator's satisfaction, including a SOC biopsy if indicated).
5. Recent urinary tract stones OR widespread calcifications on the prostatic urethral wall, within 3 months of baseline assessment
6. A history of prostatitis within the last two years
7. Active or history of epididymitis within the past 3 months
8. Neurogenic bladder and/or sphincter abnormalities due to Parkinson's disease, multiple sclerosis, cerebral vascular accident, diabetes
9. History of urinary retention within 12 months of baseline assessment
10. Requiring self-catheterization to void
11. An active urinary tract infection (UTI) at time of index procedure
12. Gross haematuria, within 3 months of baseline assessment
13. Subjects with known allergy to nickel or titanium
14. Life expectancy estimated to be less than 60 months
15. Taking androgens, unless eugonadal state for at least 3 months or greater with a stable dosage for at least 2 months as documented by the Investigator
16. Use of 5-alpha-reductase inhibitors (e.g., dutasteride, finasteride) within 6 months of baseline assessment
17. Use of Phenylephrine / Pseudoephedrine within 24 hours of baseline assessment
18. Use of alpha-blockers (e.g., Terazosin, Doxazosin, Alfuzosin, Tamsulosin) within 4 weeks

of baseline assessment

19. Use of estrogen or drug-producing androgen suppression (e.g. gonadotropin-releasing hormonal analogues) within 1 year of baseline assessment
20. Use of antihistamines, anticonvulsants, and antispasmodics within 1 week of baseline assessment unless there is documented evidence that the patient was on the same drug dose for at least 6 months with a stable voiding pattern (the drug dose should not be altered or discontinued for entrance into or throughout the study)
21. Use of anticholinergics or cholinergic medication within 2 weeks of baseline assessment
22. Use of beta-blockers where the dose is not stable. (Stable dose is defined as having the same medication and dose in the last 6 months)
23. Use of Phosphodiesterase-5 Enzyme Inhibitors in doses for BPH within 2 weeks of baseline assessment
24. Current treatment with anticoagulants (e.g., warfarin or enoxaparin) or antiplatelet medications other than aspirin (e.g., clopidogrel, or alternative and ASA). Patient unable to stop taking antiplatelet/ASA within 7 days prior to the procedure or warfarin at least 5 days prior to the procedure. ASA <100mg/day not prohibited
25. Future fertility concerns

26. Previous pelvic irradiation or radical pelvic surgery
27. Previous rectal surgery (other than hemorrhoidectomy) or known history of rectal disease
28. Urethral strictures, bladder neck contracture, or other potentially confounding bladder pathology
29. Urethral pathologies that may prevent insertion of delivery system
30. Uncontrolled diabetes mellitus including Hgb AIC >8%
31. Overactive bladder (OAB) requiring treatment by OAB medication
32. Urinary incontinence
33. Patients taking tri-cyclic antidepressants.
34. Compromised renal function (i.e., serum creatinine >1.8 mg/dl or upper tract disease)

35. Hepatic disorder, bleeding disorders or metabolic impairment that might confound the results of the study or have a risk to subject per investigator's opinion
36. Any major comorbidities or presence of unstable conditions, e.g., uncontrolled HTN, NYHA Class III or IV, cardiac arrhythmias that are not controlled by medication/medical device, myocardial infarction within the past 6 months, COPD with FEV₁ <50, renal illness that might prevent study completion or would confound study results
37. Vulnerable populations such as incarcerated or institutionalized adults, inmates, patients with physical, psychological (such as developmentally delayed adults), or medical impairment that might, in the judgment of the Investigator, prevent study completion or comprehension, or may confound study results (including patient questionnaires)
38. History or current medical condition that would result in an unacceptable patient risk if that subject were to be included in the study
39. Any subject that is currently enrolled in another ongoing investigational study.

For cross over subjects sites should aim to schedule the ProVee placement procedure within 30-days, and not later than 90 days, after the 3-month follow-up.

6.10. Subject Retreatment

A series of horizontal black bars of varying lengths, with a small bar at the top and a large bar at the bottom.

6.11. End Of Study Definition

A study subject is considered to have completed the study if he/she has completed all phases of the study including the last follow up assessment as shown in Table 1. The end of the study is defined as completion of the last follow up assessment in the study. Once this has occurred, the declaration of the end of study will be submitted to the IRB/IEC, as required. Following this, the Sponsor will advise the study sites on the procedures for closing the study.

With the end of the study being declared, no more prospective subject data will be collected, and sites must cooperate addressing any data queries regarding existing data to allow for data lock, and analysis.

6.12. Adverse Events And Serious Adverse Events

Once a patient is randomized, all AEs must be reported for follow-up period (as designated for treatment, control or crossover arms). All AEs irrespective of their relatedness to the device and/or procedure which occur throughout the duration of the study shall be reported. The Investigator will monitor the occurrence of adverse events for each subject during the course of the study. All adverse events reported by the subject, observed by the Investigator, or documented in medical records will be documented on the Adverse Event Case Report Forms (CRFs), whether believed by the Investigator to be related or unrelated to the investigational device. All pre-existing medical conditions will be recorded in the subject's medical record and/or baseline CRFs. Beginning with subject enrollment, any new event that was not present at baseline, or worsening of a pre-existing condition, is considered an adverse event.

[REDACTED]

[REDACTED]

6.12.1. Definition Of Adverse Events (AE)

Adverse Events are defined as any undesirable treatment emergent signs or symptoms.

6.12.2. Adverse Device Effect (ADE)

An Adverse Device Effect is defined as any AE that is considered device-related. All ADEs are further classified as anticipated or unanticipated.

6.12.3. Anticipated Adverse Device Effect (AADE)

An Anticipated Adverse Device Effect is defined as any undesirable health related experience occurring to a subject whether or not it is considered related to the investigational product or drug regimen prescribed as part of the protocol, predefined in the protocol and/or Instruction for Use (IFU) that is identified or worsens during a clinical study.

6.12.4. Unanticipated Adverse Device Effect (UADE)

Unanticipated Adverse Device Effect is defined as any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, the Device, if that effect was not previously identified in nature, severity, or degree of incidence (frequency) in the investigational plan, subject informed consent, IFU, or any other unanticipated serious problem associated with a device that relates to the rights, welfare and safety of the subject.

6.12.5. Serious Adverse Event (SAE)

Serious Adverse Events are a subset of Adverse Events and are defined as an event which leads to:

1. Death due to any cause
2. Life-threatening condition
3. Results in persistent or significant disability/incapacity
4. Requires in-patient hospitalization or prolonged hospitalization.
5. Is an important medical event that may not result in death, be life-threatening, or require hospitalization but may be considered serious when, based upon appropriate medical judgment, may jeopardize the subject and/or may require intervention to prevent one of the outcomes listed in this definition

6.12.6. Classification Of An Adverse Event

[REDACTED]

6.12.7. Adverse Event Reporting

[REDACTED]

6.12.8. Reporting of Device Failures and Malfunctions

[REDACTED]



6.12.9. Reporting Timelines

Event	Report Timeframe to Sponsor	Report Timeframe to IRB / EC
Adverse Events - (Regardless of Device or Procedure Relationship)	eCRFs to be completed promptly	According to the reporting requirements of the local IRB/EC
Serious Adverse Events	Within 24 hours of site knowledge of the event	According to the reporting requirements of the local IRB/EC
Unanticipated Adverse Device Events	Within 24 hours of site knowledge of the event	According to the reporting requirements of the local IRB/EC, but no later than 10 days per FDA guidelines, after the site learns of the event
Device Failures / Malfunction	Within 24 hours of site knowledge of the failure / malfunction	According to the reporting requirements of the local IRB/EC

ProVerum will take any necessary steps to investigate all Unanticipated Adverse Device Events (UADEs) and will be responsible for notifying the US FDA, all other participating IRBs/EC and all investigators within ten (10) working days after ProVerum first received notice of the UADE.

7.0 Preparation/Handling/Storage/Accountability

7.1. Acquisition And Accountability

a) [REDACTED]

For more information, contact the Office of the Vice President for Research and Economic Development at 319-335-1111 or research@uiowa.edu.

ANSWER

7.2. Formulation, Appearance, Packaging, And Labeling

A series of 12 horizontal black bars of varying lengths, decreasing in length from top to bottom. The bars are evenly spaced and extend across the width of the frame.

7.3. Product Storage And Stability

A horizontal bar chart consisting of four solid black bars of increasing height from left to right. The bars are separated by small gaps and are set against a white background.



[REDACTED]

[REDACTED]

[REDACTED]

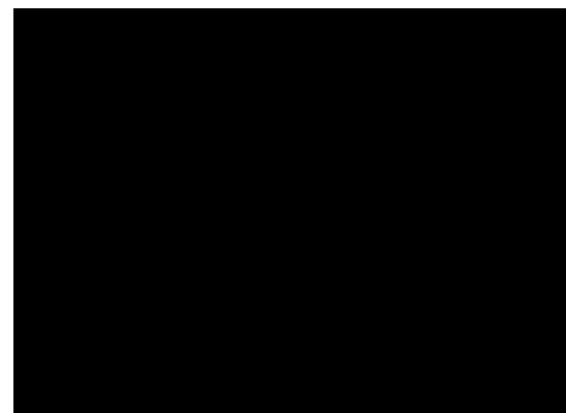
[REDACTED]

7.4. Preparation

[REDACTED]



Implant Positioning



Expander Deployment



11.	[REDACTED]
	[REDACTED]
	[REDACTED]
	[REDACTED]
	[REDACTED]
Post Expander Deployment	
14.	[REDACTED]
	[REDACTED]
	[REDACTED]
	[REDACTED]
	[REDACTED]

8.0 Measures To Minimize Bias: Randomization And Blinding

The following measures are in place to minimize bias during the study:

8.1.1. *Subject screening*

[REDACTED]

8.1.2. *Subject randomization*

8.1.3. *Study Blinding*

A series of 20 horizontal black bars of varying lengths, arranged vertically. The bars are of uniform thickness and are set against a white background. The lengths of the bars decrease from top to bottom, creating a visual gradient. The first bar is the longest, followed by a short bar, then a long bar, and so on, ending with the shortest bar at the bottom.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED].

8.2. Study Intervention Compliance

The study will be conducted in accordance with the Declaration of Helsinki, International Conference on Harmonization Good Clinical Practice (ICH GCP), ISO 14155, applicable United States (US) Code of Federal Regulations (CFR) including but not limited to 21 CFR parts 812, 50, 54, 56 and the pertinent individual country laws and regulations. The study will comply with local national legislations and requirements regarding Institutional Review Boards (IRB) / Ethics Committees (EC). The study may only begin once authorizations have been granted by the FDA, EC and IRB for the Clinical Investigational Plan, informed consent form and other adjunctive material. Treatment refusals will be minimized by careful and thoughtful informed consent. Loss to follow up will be minimized through regular and routine follow-up with subjects.

8.3. Concomitant Therapy

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

9.0 Study Intervention Discontinuation And Participant Discontinuation/Withdrawal

9.1. Participant Discontinuation/Withdrawal From The Study

A subject is free to withdraw from participation in the study at any time upon request and for any reason without prejudice to his or her future medical care by the physician or the institution. The subject shall notify the Investigator of the request to withdraw in writing. Study withdrawal by a subject is the withdrawal of consent from further participation in the study. A subject who withdraws consent after enrollment will be evaluated to the time of withdrawal. Withdrawal of consent precludes any further study-related treatment or data collection. At a minimum, every effort shall be made to document subject outcome at the time of withdrawal including a review of adverse events that may have occurred since the last follow-up visit.

An investigator may discontinue or withdraw a subject from the study if the Investigator feels the subject can no longer fully comply with the requirements of the study or based on his/her medical judgement. Every effort shall be made to document at the time of withdrawal any adverse events that have occurred since the last follow-up visit.

The reason for subject or investigator discontinuation or withdrawal from the study will be recorded on the eCRF.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

9.2. Lost To Follow-Up

The Investigator will encourage subjects to return for all required follow-up visits. If a subject refuses to return for follow-up visits, the Investigator shall make every effort to obtain the subject's vital status. In the event of subject death, a death certificate or autopsy report shall be obtained to confirm the cause of death and recorded on the eCRF.

10.0 Statistical Considerations

10.1. Study Success

[REDACTED]

[REDACTED]

[REDACTED]

10.2. Analysis Cohorts

Different groups of subjects, or Analysis Cohorts, will be identified depending on the type and extent of analysis being performed.

10.2.1. Screening Cohort (Enrolled)

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

10.2.2. Safety/Intent-to-Treat (ITT) Cohort

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

10.2.3. Per-Protocol Cohort

[REDACTED]

[REDACTED]

10.2.4. Cohort for Procedure Success Endpoints

[REDACTED]

10.2.5. Cohort for Primary and Secondary Effectiveness Endpoints

[REDACTED]
[REDACTED].

10.2.6. Cohort for Safety Endpoints

[REDACTED]

10.3. Derived Data

[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

10.4. Statistical Methods

[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

10.5. Handling of Dropouts and Missing Data

Every effort will be made to collect all data points in the study. The sponsor plans to minimize the amount of missing data by appropriate management of the prospective clinical trial, proper screening of study subjects, and training of participating investigators, monitors and study coordinators. Specific details regarding handling of missing data are included in ProVIDE Statistical Analysis Plan.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

All other endpoints will be analyzed “as-is” without any special data imputation methods used to replace missing data.

10.6. Poolability

A series of 20 horizontal black bars of varying lengths, starting with a short bar and ending with a very long bar. The bars are arranged vertically, with the first bar being the shortest and the last bar being the longest. The bars are black on a white background.

³ Meinert, C. (1986). *Clinical Trials: Design, Conduct, and Analysis*. Oxford University Press, New York.
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10.7. Sensitivity Analyses

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10.8. Subgroup Analyses

- [REDACTED]
- [REDACTED]

10.9. Sample Size Determination

[REDACTED]

[REDACTED]

[REDACTED]

■ β [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED] [REDACTED]

[REDACTED]

[REDACTED]

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[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED] β [REDACTED]

[REDACTED]

10.10. Power to Pass Both Co-Primary Objectives Simultaneously

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED].

10.11. Sample Size Justification – Safety

[REDACTED]

[REDACTED]

[REDACTED]

11.0 Supporting Documentation And Operational Considerations

11.1. Regulatory, Ethical, And Study Oversight Considerations

The study will be conducted in accordance with International Conference on Harmonization Good Clinical Practice (ICH GCP), ISO 14155-2020, applicable United States (US) Code of Federal Regulations (CFR) including but not limited to 21 CFR parts 812, 50, 54, 56 and applicable local regulations for OUS sites. This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practice and applicable regulatory requirements.

11.1.1. IRB/ EC Information

The protocol, informed consent document, and relevant supporting information will be submitted to the IRB/EC for review and be approved before the study is initiated. In addition, any subject recruitment materials will be approved by the IRB/EC prior to use. The study will be conducted in accordance with the regulations of the United States Food and Drug Administration (FDA) as described in 21 CFR 50 and 56, applicable laws and the IRB/EC requirements.

The Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor, and documented approval from the Institutional Review Board (IRB)/Ethics Committee (EC), except where necessary to eliminate an immediate hazard(s) to the study participants. All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB/EC for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB/EC before the changes are implemented to the study. All changes to the consent form will be IRB/EC approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

11.1.2. Informed Consent Process

The principles of informed consent described in FDA Regulations (21 CFR Part 50) must be followed. The background of the proposed study and the potential benefits and risks shall be carefully explained to the subject. Before undergoing protocol required assessments the subject or their legal representative must give witnessed written consent to participate in the study using the informed consent form approved by the clinical site's IRB/EC. A copy of the signed consent form shall be given to the subject, an original shall be filed in the subject's medical record, and a copy maintained with the site's research documentation. The informed consent form is written in compliance with the current Health Insurance Portability and Accountability Act (HIPAA) regulations.

11.1.3. Confidentiality And Privacy

All information and data sent to the Sponsor, and its authorized representatives, concerning subjects or their participation in this study will be considered confidential. All data used in the analysis and reporting of this evaluation will be used in a manner without identifiable reference to the study subject.

11.1.4. Safety Oversight

[REDACTED]

[REDACTED]

[REDACTED]

11.1.5. Clinical Monitoring

The responsibilities of the clinical monitors include ensuring that IRB/EC approval is obtained prior to initiating the study, investigators understand and comply with the investigational plan, all subject consent forms are properly completed, Case Report Forms are accurate and supported by appropriate source verified documents, and all reports are filed in accordance with the protocol and the appropriate regulations. If a monitor finds that an investigator is not complying with the executed study agreements, the investigational plan, Government regulations, or the requirements of the reviewing IRB/EC, prompt action will be taken to secure compliance. In addition, shipment of the device may be stopped or the participation of the investigator may be terminated (21 CFR 812.46).

Clinical monitors may also be responsible for assessing the adequacy of the facilities, training, and technical support.



11.1.6. Data Handling And Record Keeping

Investigators will be trained on the appropriate records to maintain and reports to file. ProVerum Ltd. will maintain records relating to the clinical investigation and file the reports within the appropriate timeframes in accordance with 21 CFR 812, Subpart G.

A thick black horizontal bar, likely a redacted section of text.

11.1.7. Protocol Amendments

11.1.8. Emergency Actions

A horizontal bar chart consisting of four solid black bars of increasing width from left to right. The bars are positioned against a white background.

11.1.9. Financial Disclosure

All investigators must provide the study Sponsor with documentation of financial interest related to ProVerum Ltd. Investigator's will need to complete a Financial Disclosure in compliance with 21CFR 54 and send it to the study Sponsor during the approval process of the site and upon study close-out.

11.1.10. Publication And Data Sharing Policy

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

11.2. Abbreviations

Abbreviation	Explanation
AADE	Anticipated Adverse Device Effect
ADE	Adverse Device Effect
AEs	Adverse Events
AUA	American Urological Association
BPE	benign prostatic enlargement
BPH	Benign Prostatic Hyperplasia
BPO	benign Prostatic Obstruction
CEC	Clinical Events Committee
CFR	Code of Federal Regulations
CONSORT	Consolidated Standards of Reporting Trials
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Forms
DHT	Dihydrotestosterone
DSMB	Data Safety Monitoring Board
EAU	European Association of Urology
eCRF	Electronic Case Report Form

Abbreviation	Explanation
ED	Erectile Dysfunction
EDC	Electronic Data Capture
EO	Ethylene Oxide
FDA	Food and Drug Administration
FIM	First-in-Man
FPS-R	Faces Pain Scale-Revised Questionnaire
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HIPAA	Health Insurance Portability and Accountability Act
HREC	Human Research Ethics Committee
ICF	Informed Consent Form
ID	Internal Diameter
IFU	Instructions for Use
IIEF	International Index of Erectile Function
IPSS	The International Prostate Symptom Score
IRB	Institutional Review Board
IRT	Interactive Response Technology



Abbreviation	Explanation
ISO	International Standards Organisation
LUTS	Lower Urinary Tract Symptoms
MIST	Minimally Invasive Surgical Therapies
MSHQ-EjD	Male Sexual Health Questionnaire – Ejaculatory Domain
OAB	Overactive bladder
OD	Outer Diameter
OR	Operating Room
PI	Principal Investigator
PIC	Subject Implant Card
PMH	Past Medical History
PVP	Photoselective Vaporization of the Prostate
PVR	Post Void Residual
Q_{\max}	Maximum urinary flow rate
QoL	Quality of life
RE	Retrograde Ejaculation
SAE	Serious Adverse Event

Abbreviation	Explanation
TRUS	Transrectal ultrasound
UADE	Unanticipated Adverse Device Effect
UTI	Urinary Tract Infection

11.3. Protocol Amendment History

Revision	Date Issue	Summary of Changes
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED]
[REDACTED]	[REDACTED]	[REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED]
[REDACTED]	[REDACTED]	[REDACTED] [REDACTED] [REDACTED]
[REDACTED]	[REDACTED]	[REDACTED] [REDACTED]

12.0 Study Definitions

[REDACTED]

[REDACTED].

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