



Clinical Protocol Summary

Evaluation of the TULSA-PRO MRI-Guided Transurethral Ultrasound Prostate Ablation Device in Patients with Localized Prostate Cancer: a Prospective, Single-Arm, Pivotal Clinical Study

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Protocol Synopsis

Protocol Title	Evaluation of the TULSA-PRO MRI-guided transurethral ultrasound prostate ablation device in patients with localized prostate cancer
Protocol Number	GCP-10100
Study Design	Prospective, multi-center, single-arm study
Sample Size	Part I - 110 patients target (115 treated) Part II - 35 patient (from US sites only)
Study Period	Estimated recruitment period: 6-12 months Follow-up and analysis of primary endpoints: 12 months Interim analysis of secondary endpoints: 12 months Total study follow-up: 5 years
Study Population	Male, age 45 to 80 years, diagnosed with organ-confined prostate cancer (see eligibility criteria below)
Objective	The primary objective of this study is to further evaluate the safety and efficacy of the MRI-guided TULSA-PRO device intended to ablate prostate tissue of patients with localized, organ-confined prostate cancer
Primary Endpoints	Safety Endpoint: Frequency and severity of all adverse events, categorized according to their attribution. Efficacy Endpoint: Proportion of patients achieving a PSA nadir \leq 25% of the pre-treatment baseline value.
Secondary Endpoints	Erectile Dysfunction Endpoint: Rate of erectile dysfunction, determined by the change from baseline of the proportion of patients with IIEF-5 $<$ 17. Erection Firmness Endpoint: Rate of erection firmness sufficient for penetration, determined by the change from baseline of the proportion of patients with IIEF item 2 \geq 2. Urinary Incontinence Endpoint: Rate of urinary incontinence, determined by the change from baseline of the proportion of patients with EPIC item 5 \geq 1 (one or more pads per day). PSA Nadir Endpoint: Proportion of patients achieving PSA nadir \leq 0.5 ng/ml. PSA Stability Endpoint: Proportion of patients with PSA \leq 0.5 ng/ml at the most recent follow-up visit. Prostate Volume Endpoint: Prostate volume reduction, evaluated on MRI between the treatment day and 12-month follow-up visits.

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	<p>Prostate Biopsy Endpoint: Proportion of patients with negative prostate biopsy at the 12-month follow-up visit, determined by TRUS-guided 10-core biopsy.</p> <p>IPSS Endpoint: Change in International Prostate Symptom Score (IPSS).</p> <p>IIEF Endpoint: Change in International Index of Erectile Function (IIEF-15), and its sub-domains.</p> <p>EPIC Endpoint: Change in Expanded Prostate Cancer Index Composite (EPIC), and its sub-domains.</p> <p>Targeting Accuracy Endpoint: Conformal prostate ablation, measured quantitatively between the target prostate volume and the ablative heating volume on MRI thermometry¹.</p> <p>CE-MRI Endpoint: Conformal prostate ablation, assessed qualitatively by visualizing the peripheral region of enhancement surrounding the non-perfused volume (NPV) on contrast-enhanced (CE)-MRI acquired immediately after treatment.</p> <p>mpMRI Endpoint: Evaluation of prostate MRI using PI-RADS v2, performed at the baseline and 12-month follow-up visits.</p>
<p>DSMC Safety Analysis</p>	<p>Two safety assessments by an independent Data Safety Monitoring Committee (DSMC) will be performed. Study enrolment will continue while data are collected. The DSMC reviews will occur when:</p> <ul style="list-style-type: none"> - First 10 patients complete treatment. If 2 or more of the first 10 patients who have undergone the TULSA-PRO procedure have a documented rectal fistula then the DSMC would recommend stopping the trial. - First 10 patients complete 1-month follow-up visit. If $\geq 10\%$ of all patients who have undergone the TULSA-PRO procedure at the time of the DSMC analysis have a documented rectal fistula, then the DSMB would recommend stopping the trial.
<p>Eligibility Criteria</p>	<p>Inclusion Criteria</p> <ol style="list-style-type: none"> 1. Male, age 45 to 80 years 2. Biopsy-confirmed adenocarcinoma of the prostate. Biopsy (minimum 10 cores) obtained ≥ 6 weeks and ≤ 6 months before treatment (or at the discretion of PI and approval by the Sponsor). 3. Clinical stage \leq T2b 4.1 Gleason score $\leq 3 + 4$ (Part I only) 4.2 Gleason score 3+4 (Part II only) 5. PSA ≤ 15 ng/ml 6. Eligible for MRI [Form GCP-10131] 7. Eligible for general anesthesia (ASA category ≤ 3) 8. Prostate volume ≤ 90 cc, on Baseline MRI 9. Prostate size ≤ 5.0 cm in sagittal length, and ≤ 6.0 cm in axial diameter, on Baseline MRI 10. Life expectancy ≥ 10 years 11. No calcifications in the planned ultrasound beam path, or at the discretion of the investigator with approval from the Sponsor.

¹ Conformal prostate ablation is measured using the Dice Similarity Coefficient (DSC), linear accuracy and precision, and volumetric over-/under-heating of the target prostate volume

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	<p>Exclusion Criteria</p> <ol style="list-style-type: none"> 1. Evidence (including Baseline MRI and bone scan) of extracapsular extension, sphincter involvement, seminal vesicle invasion, lymph node invasion or metastases 2. Suspected tumour on Baseline MRI within 3 mm of the prostatic urethra, or in the prostate apex within 3 mm from the sphincter plane 3. Prior definitive treatment of prostate cancer 4. Prior transurethral resection of the prostate (TURP) 5. Use of 5-alpha reductase inhibitors (5-ARIs) or hormone therapy within 3 months prior to the baseline visit. Baseline PSA must be established after a minimum of 3 months following 5-ARIs discontinuation. Additionally, use of 5-ARIs is not permitted following treatment during the study follow-up period. 6. Prostate calcifications > 1 cm in largest diameter, on Baseline Ultrasound 7. Cysts > 1 cm in largest diameter, on Baseline MRI 8. Bleeding disorder (International Normalized Ratio (INR) > ULN and partial thromboplastin time (PTT) > ULN) 9. Abnormal coagulation and current anticoagulant therapy. Patients whose anticoagulation therapy can be temporarily reversed within 7 days prior to treatment are eligible. Platelet inhibitors (ie: ASA) and heparin are not exclusion criteria. 10. Acute unresolved Urinary Tract Infection (UTI) 11. Interest in future fertility 12. History of any other malignancy other than skin cancer, or low grade bladder cancer² which has been completely resected, within the previous 2 years. Patients that have had curative treatment of a previous malignancy and no recurrence of that malignancy within the past 2 years will be allowed. 13. Patients with peripheral arterial disease with intermittent claudication or Leriche Syndrome (i.e. claudication of the buttocks or perineum) 14. Patients with diabetes who have evidence of complications from their diabetes, such as end organ sequelae of diabetes (ie: severe peripheral vascular disease, diabetic retinopathy), or Hemoglobin A1c > 7%. 15. History of any major rectal or pelvic surgery or radiotherapy 16. History of ulcerative colitis or other chronic inflammatory conditions affecting rectum (includes rectal fistula, anal stenosis) 17. Documented clinical prostatitis requiring therapy within 6 months prior to Treatment 18. History of urethral and bladder outlet disorders, including urethral stricture disease, urethral diverticulae, bladder neck contracture, urethral fistulae, urethral stenting, urethral sling, urethroplasty or chronic indwelling urethral catheter 19. Patients with artificial urinary sphincter or any penile implant 20. Severe neurogenic bladder 21. Untreated bladder stones 22. History of acute urinary retention within the last 12 months 23. Active untreated gross hematuria for any cause
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² Study subjects with previous history of low grade bladder cancer that has been completely resected within the previous 2 years will be allowed to undergo surveillance cystoscopy, as scheduled, except for a period of 1 month after the study treatment or within 1 week of any study visit.

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	<ol style="list-style-type: none"> 24. Post Void Residual (PVR) bladder volume > 250 mL, confirmed on repeat evaluation 25. Obstructing median lobe enlarged out of proportion to the rest of the prostate and protruding significantly into the bladder, sometimes referred to as “ball valve” median lobe, determined on Baseline MRI 26. Any prostate related investigational therapy within 6 months of Visit 1 27. History of Parkinson’s disease or multiple sclerosis 28. History of drug abuse 29. Known infectious disease including HIV positivity or AIDS-related illness, HBV and HCV 30. Current unilateral or bilateral hydronephrosis 31. Allergy or contraindications to administration of the GI anti-spasmodic drug: <ol style="list-style-type: none"> a. Patients in the USA: Glucagon Contraindications: Pheochromocytoma (adrenal gland tumour), chronic hypoglycemia, insulin releasing tumour, hypersensitivity to glucagon, allergy to glucagon, lactose or glycerin. b. Patients in Canada and Europe: Buscopan (Hyoscine) Contraindications: Porphyria/Myasthenia Gravis, Heart attack within the last 6 months, poorly controlled angina requiring medication, heart failure not controlled with medication, hypersensitivity to hyoscine butylbromide, or atropinics. 32. Contraindications to administration of gadolinium-based MRI contrast agent (e.g. Magnevist), such as chronic, severe kidney disease (glomerular filtration rate (GFR) <30 mL/min/1.73m²), acute kidney injury, history of Sickle Cell Disease, history of anemia (low red blood cell count), or intolerance/allergy to the contrast agent 33. Other severe, acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or study drug administration, or may interfere with the interpretation of study results, which in the judgment of the investigator would make the patient inappropriate for entry into this study.
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2. Study Schedule

Visit No	Visit Type	Window Allowance	Office Visit, Lab Tests & Patient Forms	Imaging
0	Screening	Biopsy ≥ 6 weeks and ≤ 6 months before treatment (or at the discretion of PI and approval by the Sponsor)	<ul style="list-style-type: none"> - PSA³ - Prostate biopsy (min. 10 cores) <i>(Can use previous documented results)</i> - Informed Consent Form (ICF) - Economic Data Collection⁷ 	<ul style="list-style-type: none"> - Baseline Prostate MRI evaluated for malignant lesions using PI-RADS v2, and to assess prostate size, cysts⁴, extracapsular extension, sphincter involvement, seminal vesicle invasion, lymph node invasion and metastases
1	Eligibility & Baseline	≤ 6 weeks before treatment	<ul style="list-style-type: none"> - Inclusion, exclusion assessment - Medical history - Physical Examination - PSA³ <i>(Screening PSA can be used as Baseline PSA, at the discretion of the PI and if acquired within 3 months prior to treatment)</i> - Urine Culture - Blood and Urine analysis - Uroflowmetry/PVR volume - Concomitant medication - Adverse Events - Quality of life questionnaire - Demographics questionnaire - Pre-treatment bowel preparation instructions given to patient - Economic Data Collection⁷ 	<ul style="list-style-type: none"> - Baseline Prostate Ultrasound⁵ to assess calcifications - Baseline Bone Scan to assess metastases, only if patient has clinical stage T2 and PSA > 10 ng/ml - MRI, Ultrasound and Bone Scan ≤ 6 months before treatment - If performed after the biopsy, MRI and Ultrasound must be > 6 weeks after biopsy - Can use previously documented results
2	Treatment	≤ 6 weeks after baseline visit	<ul style="list-style-type: none"> - PSA³ - Supra-pubic catheter placement - Overnight admission at discretion of PI - Concomitant medication - Adverse events - Economic Data Collection⁷ 	<ul style="list-style-type: none"> - Prostate MRI for planning and treatment

³ Activities and procedures that can elevate PSA levels must be avoided prior to any study related PSA test. For example, PSA should be obtained prior to any Digital Rectal Exam (DRE), cystoscopy or biopsy. Additionally, patients should be instructed to avoid vigorous exercise, riding a bicycle, sexual activity and ejaculation for at least 48 hours prior to any scheduled study related PSA test.

⁴ At the discretion of the PI, the assessment of prostate cysts may be done by Ultrasound instead of MRI.

⁵ At the discretion of the PI, the Baseline Prostate Ultrasound to assess calcifications may be replaced by a Computer Tomography (CT) imaging exam.

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Visit No	Visit Type	Window Allowance	Office Visit, Lab Tests & Patient Forms	Imaging
3	Catheter Removal	Between 1 and 4 weeks	<ul style="list-style-type: none"> - Catheter removal at the discretion of the PI and following clamping for 24 hours to verify ability to void - Concomitant medication - Adverse events - Economic Data Collection⁷ 	
4	1-month follow-up	5 weeks ± 1 week	<ul style="list-style-type: none"> - Physical examination - PSA³ - Blood and Urine analysis - Concomitant medication - Adverse events - QOL questionnaire - Economic Data Collection⁷ 	
5	3-month follow-up	3 months ± 2 weeks	<p>Note: Visit may be performed by telephone and mail⁶</p> <ul style="list-style-type: none"> - Concomitant medication (<i>may be performed by telephone</i>) - Adverse events (<i>may be performed by telephone</i>) - QOL questionnaire (<i>may be performed by mail or telephone</i>) - PSA³ (<i>may be performed at local clinic</i>) - Physical examination (<i>if visit occurs in person</i>) - Economic Data Collection⁷ 	
6	6-month follow-up	6 months ± 1 month	<ul style="list-style-type: none"> - Physical examination - PSA³ - Concomitant medication - Adverse events - QOL questionnaire - Economic Data Collection⁷ 	

⁶ If there are no significant ongoing adverse events at the 1-month visit, then this visit may be performed by telephone and mail, at the discretion of the PI.

⁷ Economic data are costs associated with the patients' involvement in the study. This can include the procedure and labs etc. that are done at every visit which are documented in de-identified UB-04 Forms provided by the site. Economic data collection is optional for the patient and will only be collected if the patient signs the optional portion of the consent form.

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Visit No	Visit Type	Window Allowance	Office Visit, Lab Tests & Patient Forms	Imaging
7	12-month follow-up	12 months ± 1 month	<ul style="list-style-type: none"> - Physical examination - Transrectal Ultrasound (TRUS) guided 10-core prostate biopsy - PSA³ (<i>prior to biopsy</i>) - Uroflowmetry/PVR volume (<i>prior to biopsy</i>) - Concomitant medication - Adverse events - QOL questionnaire - Economic Data Collection⁷ 	<ul style="list-style-type: none"> - Follow-up Prostate MRI evaluated using PI-RADS v2 (<i>prior to biopsy</i>)
8	2-year follow-up	24 months ± 2 months	<ul style="list-style-type: none"> - Physical examination - PSA³ - Concomitant medication - Adverse events - QOL questionnaire - Economic Data Collection⁷ 	
9	3-year follow-up	36 months ± 2 months	<ul style="list-style-type: none"> - Physical examination - PSA³ - Concomitant medication - Adverse events - QOL questionnaire - Economic Data Collection⁷ 	
10	4-year follow-up	48 months ± 2 months	<ul style="list-style-type: none"> - Physical examination - PSA³ - Concomitant medication - Adverse events - QOL questionnaire - Economic Data Collection⁷ 	
11	5-year follow-up	60 months ± 2 months	<ul style="list-style-type: none"> - Physical examination - PSA³ - Concomitant medication - Adverse events - QOL questionnaire - Economic Data Collection⁷ 	

3.0 Purpose of the Investigation

The purpose of this Pivotal clinical study is to establish the safety and effectiveness of the TULSA-PRO for accurate and precise ablation of the prostate gland, with reduced safety margins and in a larger prostate cancer population.

3.1 Work to Date

Computer simulations

Initial feasibility of using MRI-TULSA for whole-gland prostate ablation has been evaluated extensively in computer simulations, including ultrasound device requirements, MRI thermometry specifications, treatment delivery feedback control algorithms and treatment planning strategies [Chopra *et al* 2005, Chopra *et al* 2006, Burtnyk *et al* 2009, Kobelevskiy *et al* 2009, Burtnyk *et al* 2010a, Burtnyk *et al* 2010b, N’Djin *et al* 2012a, DOC-10444, DOC-10450, DOC-10455, DOC-10456]. Most recently, the computer simulations were validated with the clinical Phase I data, and were used to support the pivotal trial treatment parameters [DOC-10699, DOC-10718].

Experiments in tissue-mimicking gel phantoms

Using a prototype system, the feasibility, accuracy and precision of heating tissue to thermal ablation using a transurethral ultrasound device under MRI-guidance has been investigated in tissue-mimicking gel phantoms [Tang *et al* 2007, Burtnyk *et al* 2010b, N’Djin *et al* 2012b]. Experiments in tissue-mimicking gel phantoms are a key component of development, verification and validation of the PMI TULSA-PRO, including refinement of the MRI protocol, system validation and clinical site qualification.

Pre-clinical experiments in the canine prostate model

Several in-vivo experiments have been performed in the canine prostate model to evaluate the ability of MRI-TULSA to treat the prostate under realistic clinical conditions including dynamic changes in blood flow and ultrasound attenuation during treatment [Boyes *et al* 2007, Chopra *et al* 2008, Chopra *et al* 2009, Chopra *et al* 2010, Siddiqui *et al* 2010, PMI-10129, Burtnyk *et al* 2015].

These studies have established the ability to accurately generate thermal patterns in-vivo that conform to target volumes within about 1 mm using closed-loop temperature feedback control in under 30 min. Comprehensive histological analysis of the canine prostate tissue after treatment has also revealed the close relationship (≤ 3 mm) between acute 100% cell kill, 55°C target temperature on MRI thermometry and the peripheral region of enhancement surrounding the NPV on post-treatment CE-MRI.

Table 1: Summary of number and type of pre-clinical and clinical studies.

Phase	Year	MRI-TULSA System	MRI System	Number of Subjects
Pre-clinical canine	2006 - 2009	Sunnybrook prototype	GE 1.5T	13 canines, acute 4 canines, delayed 48 hours
Pre-clinical canine	2010	PMI TULSA-PRO prototype	GE 1.5T	10 canines, acute 2 canines, delayed 7 days 2 canines, delayed 14 days
Pre-clinical canine	2012	PMI TULSA-PRO	Siemens 3T	8 canines, delayed 28 days

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Phase 0 clinical	2009	Sunnybrook prototype	GE 1.5T	8 patients, “treat-and-resect”
Phase 0 clinical	2012	Sunnybrook prototype	Philips 3T	4 patients, “treat-and-resect”
Phase I clinical	2013 - 2015	PMI TULSA-PRO	Siemens 3T	30 patients with 12-month follow-up

Phase 0 “treat-and-resect” clinical studies

Using the Sunnybrook prototype system, Dr. Laurence Klotz, Chief of Urology, and Dr. Rajiv Chopra, MRI physicist, led two Ethics Committee (EC)-approved Phase 0 academic “treat-and-resect” clinical studies of MRI-TULSA [Chopra *et al* 2012, Colquhoun *et al* 2011, Ramsay *et al* 2017]. All twelve patients across both studies underwent a radical prostatectomy immediately following MRI-TULSA, with acute whole-mount histological evaluation of the ablation zone correlated to MRI temperature measurements. All patients had organ-confined prostate cancer with Gleason score ≤ 7 and PSA ≤ 15 ng/ml.

Phase I clinical trial

Most recently, MRI-TULSA was evaluated in a single-arm, prospective Phase I clinical study sponsored by PMI to determine the safety and feasibility of the TULSA-PRO in patients with localized prostate cancer [Chin *et al* 2016, Clinical Protocol DOC-10246, FDA IDE G130103, Health Canada ITA 199241, Eudamed No. CIV-13-04-010681]. Patient enrolment spanned March 2013 to March 2014 at three trial sites: Dr. Joseph Chin at Western University (UWO), London Health Sciences Center, London ON, Canada; Dr. Heinz-Peter Schlemmer at the German Cancer Research Center (DKFZ), Heidelberg, Germany; and Dr. James Relle at William Beaumont Health System, Royal Oak MI, USA.

A total of thirty patients underwent prostate ablation with the TULSA-PRO. All patients had biopsy-proven low-/intermediate-risk prostate cancer with clinical stage T1c – T2a, PSA ≤ 10 ng/ml, Gleason score ≤ 6 (USA and Germany) $\leq 3+4$ (Canada), and no prior treatment of their prostate. Primary endpoints were safety (frequency and severity of adverse events) and feasibility (conformal thermal ablation on MRI thermometry and CE-MRI). Clinical follow-up included serial PSA, QOL questionnaires (IPSS, erectile function domain of the IIEF-15, and bowel habits domain of the UCLA-PCI-SF), 12-month prostate biopsy, cystoscopy and MRI.

Only 2 of 22 patients who underwent 3-year biopsy experienced histological upgrading with respect to their 12-month biopsy (GCP-10281).

Biochemical recurrence (Phoenix criteria of 2 ng/ml above nadir) occurred in 10 patients, with an estimated 5-year biochemical recurrence-free survival of 61%. At 5-year follow up, median (IQR) PSA decreased from 5.8 ng/mL to a post-treatment nadir of 0.26 ng/mL in patients free of salvage therapy. PSA remained stable at 1 years and at 5 years. Among the 10 men who underwent post-TULSA salvage, PSA decreased 82% from 6.1 ng/ml to nadir of 0.80 ng/ml (GCP-10281). The estimated 5-year salvage-free survival was 67%. The estimated five-year disease-specific survival was 100%, with overall survival of 97% and metastasis-free survival of 97% (Nair et al 2020).

Adverse Events (AE) were evaluated according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4. There were no intraoperative complications, no rectal injury or fistula, and no severe

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urinary incontinence. There were no Grade 4 or higher AE, and only one attributable Grade 3 AE (epididymitis in 1 patient, resolved with IV-antibiotics). Treatment-emergent Grade 2 erectile dysfunction managed with medication was experienced by 10/30 (33%) subjects, ongoing at the final visit in 4/16 (25%) men who completed 5-year follow-up. There were no cases of Grade 3 erectile dysfunction requiring surgical intervention. Most patients experienced some type of rapidly resolving Grade 2 genitourinary event within the first month of treatment such as urinary retention (5 men, resolved with catheterization), urgency (5 men, resolved with medication), bladder spasm (4 men, resolved with medication), or obstructive micturition (3 men, resolved with catheterization). At five years, 2 men continued to have Grade 2 GU complications: lower urinary tract symptoms managed with medication. Gastrointestinal events were limited to 5 Grade 1 events of bloating, constipation, or rectal pain that resolved on their own in the first month [GCP-10281].

Median (IQR) ultrasound treatment time was 36 (26–44) min and prostate volume 44 (38–48) cc. Spatial accuracy and precision of thermal ablation was 0.1 ± 1.3 mm, with the conformal NPV confirmed on CE-MRI after treatment. Median PSA decreased 87% from 5.8 (3.8–8.0) ng/ml to 0.8 (0.5–1.1) ng/ml at 1 month, remaining stable at 0.8 (0.6–1.1) ng/ml to 12 months. IPSS and UCLA-PCI-SF bowel habits domain scores returned to baseline values by 3 months, remaining stable to 12 months. At 3 months, Median (IQR) IPSS was stable from baseline through 5-year follow-up (Nair et al 2020). IIEF-15 erectile function domain scores and erections sufficient for penetration (IIEF question 2 ≥ 2) recovered by one year and declined thereafter, likely due to the advanced age of this cohort. UCLA-PCI-SF bowel function and bowel bother scores were unchanged.

The results of the Phase I study demonstrate that MRI-TULSA is a safe and feasible procedure for the accurate and precise conformal ablation of prostate tissue. The PMI TULSA-PRO system provides accurate treatment planning, real-time thermal dosimetry and precise control of prostate ablation, with a well-tolerated side-effect profile. The results of this study are sufficiently compelling to justify further study of the TULSA-PRO in a Pivotal clinical trial with a larger prostate cancer patient population and reduced safety margins.

4.0 Investigational Study Endpoints and Objectives

4.1 Primary Objectives and Endpoints

The primary objective of this study is to further evaluate the safety and effectiveness of the MRI-guided TULSA-PRO device intended to ablate prostate tissue of patients with localized, organ-confined prostate cancer.

As part of the safety assessment, special attention will be made to determine the rates of erectile dysfunction, erection firmness sufficient for penetration and urinary incontinence, evaluated specifically using the corresponding secondary endpoints.

- **Safety Endpoint:** Frequency and severity of all adverse events will be evaluated by attribution.
- **Efficacy Endpoint:** Prostate ablation efficacy will be evaluated using the proportion of patients achieving a PSA nadir $\leq 25\%$ of the pre-treatment baseline value.

4.2 Secondary Objectives and Endpoints

There are multiple secondary objectives of this study designed to examine in more detail the safety and effectiveness of the TULSA-PRO device, as well as its impact on patient quality of life. Additional secondary imaging endpoints evaluate the spatial accuracy and precision of prostate ablation using TUSLA-PRO device, as well as changes observed on diagnostic prostate MRI.

- **Erectile Dysfunction Endpoint:** Rate of erectile dysfunction, determined by the change from baseline of the proportion of patients with IIEF-5 < 17.
- **Erection Firmness Endpoint:** Rate of erection firmness sufficient for penetration, determined by the change from baseline of the proportion of patients with IIEF item 2 \geq 2.
- **Urinary Incontinence Endpoint:** Rate of urinary incontinence, determined by the change from baseline of the proportion of patients with EPIC item 5 \geq 1 (one or more pads per day).
- **PSA Nadir Endpoint:** Proportion of patients achieving PSA nadir \leq 0.5 ng/ml.
- **PSA Stability Endpoint:** Proportion of patients with PSA \leq 0.5 ng/ml at the most recent follow-up visit.
- **Prostate Volume Endpoint:** Prostate volume reduction, evaluated on MRI between the treatment day and 12-month follow-up visits.
- **Prostate Biopsy Endpoint:** Proportion of patients with negative prostate biopsy at the 12-month follow-up visit, determined by TRUS-guided 10-core biopsy.
- **IPSS Endpoint:** Change in International Prostate Symptom Score (IPSS), between the baseline and most recent follow-up visit.
- **IIEF Endpoint:** Change in the Erectile Function, Orgasmic Function, Sexual Desire, Intercourse Satisfaction and Overall Satisfaction domains of the International Index of Erectile Function (IIEF-15), between the baseline and most recent follow-up visit.
- **EPIC Endpoint:** Change in Urinary, Bowel, Sexual and Hormonal domains of the Expanded Prostate Cancer Index Composite (EPIC), between the baseline and most recent follow-up visit.
- **Targeting Accuracy Endpoint:** Conformal prostate ablation, measured quantitatively between the target prostate volume and the target temperature isotherm on MRI thermometry acquired during the TULSA-PRO procedure, and described using three measures of targeting accuracy:
 - Dice Similarity Coefficient (DSC – unitless from 0 to 1), is a statistical validation metric to measure the degree of spatial overlap between two regions [Dice 1945].
 - Over- and under-targeted volumes (outside the target volume \pm ½ voxel margin), representing the amount of tissue \geq target temperature outside the target volume and < target temperature inside the target volume, respectively. The over- and under-targeted volumes are expressed in absolute cc, and as a % of the target volume.
 - Linear targeting in mm, representing the spatial accuracy (average) and precision (standard deviation) of the TULSA-PRO to heat the target boundary to the target temperature.
- **CE-MRI Endpoint:** Conformal prostate ablation, assessed qualitatively by visualizing the peripheral region of enhancement surrounding the non-perfused volume (NPV) on contrast-enhanced (CE)-MRI acquired immediately after treatment.
- **mpMRI Endpoint:** Characterize the effect of the TULSA-PRO ablation on diagnostic multi-parametric prostate MRI (mpMRI), determined using PI-RADS v2 performed at the Baseline and 12-month follow-up visits.

4.3 Economic Data Collection

Profound Medical Inc., would also like to collect individual patient-level economic data in order to create a TULSA cost model for reimbursement purposes. Economic data include the costs and expenses associated with the patient's participation in the study, including the treatment day and follow-up care. Data will be collected using UB-04 forms provided by each site who has consented, enrolled and treated patients under this protocol (Protocol Rev D). This portion of the study is optional and all anonymized UB-04s will be collected from the site only if the patient provides their consent. Data collected will not be published and is for information purposes only.

5.0 Statistical Considerations

5.1 Study Hypothesis and Sample Size

It is hypothesized that the use of the TULSA-PRO MRI-guided transurethral ultrasound prostate ablation device for ablation of prostate tissue in patients with localized organ-confined prostate cancer would be deemed not clinically interesting if 50% of patients or less had a reduction in PSA \geq 75% (PSA nadir \leq 25% of the pre-treatment baseline value). Conversely, the use of the TULSA-PRO MRI-guided transurethral ultrasound prostate ablation device for ablation of prostate tissue in patients with localized organ-confined prostate cancer would be deemed clinically of interest if this rate was greater than 50%. Therefore, using a one-sided, $\alpha=0.025$ exact test for a single proportion, one would achieve at least 80% statistical power to distinguish between $H_0: p \leq 50\%$ versus $H_a: p > 50\%$ with 90 total patients (calculated using nQuery Advisor version 7.0), where the performance goal for the success proportion is 50% and it is expected that $p=65\%$.

Following completion of the initial study enrolment (Part I), 48% of patients treated (55 of 115) were from US sites. In efforts to achieve a study population with majority of American patients, we will target 35 total patients from up to 4 clinical sites within the United States in Part II of the study enrolment.

5.2 Study Population

The population used to evaluate the study primary endpoints (safety and effectiveness) will be the modified intent-to-treat (mITT) group. The mITT group consists of all subjects who meet the eligibility criteria, have a valid and signed informed consent form, and have received treatment⁷ with the TULSA-PRO device according to this clinical protocol. The population used to evaluate the study secondary endpoints will be the per protocol (PP) group, except for the Prostate Biopsy Endpoint which will use the mITT group. The PP group will be defined as all subjects who are part of the mITT group and have completed the 12-month follow-up visit. Any subject who is included in the mITT group but not the PP group will be described, including the reasons for exclusion.

A patient who withdraws before TULSA-PRO treatment delivery will not be included in the mITT group, and will be replaced by enrolling an additional patient. If a patient withdraws from the study after

⁷ Subjects who receive *any* treatment (ultrasound delivery) with the TULSA-PRO device, even if the therapy is not complete, will be considered to have received treatment with the TULSA-PRO device.

treatment delivery, they will be accounted for in the mITT group, regardless of the reason for their withdrawal.

5.3 Outcome Data and Analysis

Analysis of the study primary endpoints will be performed using data up to the 12-month follow-up visits. A formal interim analysis of secondary endpoints will also occur using data up to the 12-month follow-up visits.

Below is a summary of the data analysis methods used to evaluate the outcome of the clinical trial.

Demography and baseline characteristics

Demographic and baseline laboratory results will be summarized using descriptive statistics for all subjects.

Primary Endpoint Analyses

The primary efficacy outcome will be the proportion of patients achieving a PSA nadir $\leq 25\%$ of the pre-treatment baseline value, representing a clinically meaningful reduction in PSA of at least 75% and clear evidence of effective prostate ablation. Given a maximum pre-treatment baseline PSA of 15 ng/ml, a reduction of at least 75% would result in a post-treatment PSA less than 4 ng/ml, which is clinically significant. Adverse events will be summarized using descriptive statistics, primarily the frequency and proportion of events. Given subjectivity in defining erectile dysfunction and urinary incontinence, these outcomes will be quantified and reported using the IIEF and EPIC questionnaires.

Secondary Endpoint Analyses

All secondary endpoints will be described using summary and descriptive statistics, in tables, lists and figures, and 95% confidence intervals will be constructed for select endpoints of interest. Three analyses of the Prostate Biopsy Endpoint will be performed, as described below in Section 0. Although PI-RADS v2 is not specifically designed for post-treatment assessment, it will be used with the additional criteria of areas of scar (defined as T2 dark) or fluid (based on T2 bright, DWI no restriction, and DCE-MRI non-enhancing) assumed to be cancer free.

Missing Data

All reasonable methods will be used to try to minimize missing data, however, some missing data is expected to occur. Except for PSA, IIEF-5, IIEF item 2, EPIC item 5 and Prostate Biopsy, no interpolation of missing data will occur, and endpoints will be assessed using the mITT and PP populations as described above.

Missing PSA data will be interpolated using the Last Value Carried Forward (LVCF) method, where missing values are replaced by the last measured PSA value. Similarly, missing IIEF-5, IIEF item 2 and EPIC item 5 data will be interpolated using the LVCF method, but only in regards to the Erectile Dysfunction Endpoint, Erection Firmness Endpoint and Urinary Incontinence Endpoint. Missing quality of life data will not be interpolated for analysis of the IPSS, IIEF and EPIC endpoints.

6.0 Investigational Study Plan

6.1 Study Design

This study is a prospective, multi-center, single arm clinical trial evaluating the TULSA-PRO MRI-guided transurethral ultrasound prostate ablation device for prostate ablation in patients with localized, organ-confined prostate cancer. Men diagnosed with biopsy-proven, organ-confined, low- to intermediate-risk prostate cancer will be eligible for participation in this study, provided they have not received prior treatment of their prostate cancer. Subjects must satisfy all inclusion and none of the exclusion criteria and provide a signed written informed consent prior to their participation in the study.

6.2 Overview of Study Periods and Visits

Each subject will participate in eleven patient visits, categorized into four study periods. Clinical management of the subjects will be in accordance with standard of care (SOC) at the discretion of the Principal Investigator (PI) or their designee. When applicable, CRF sections will be completed based on source documentation collected. Results of additional clinically-indicated procedures acquired outside of the scheduled study follow-up will be recorded on the Unplanned Study Visit CRF.

- i. Pre-Study Baseline
 - Screening: Initial patient assessment for study qualification
 - Study Visit 1: Subject eligibility and baseline assessment
- ii. MRI-TULSA Procedure
 - Study Visit 2: Treatment delivery with the TULSA-PRO device
- iii. Follow-up Procedures
 - The purpose of each visit and clinical lab tests are outlined in the “Study Schedule”.

6.3 Study Completion

Subjects will have completed the study once they have completed their 5-year follow-up visit. Subjects who have undergone the prostate ablation treatment and who withdraw from the study prior to the 12-month follow-up will be asked to complete prostate MRI and biopsy.

The study primary endpoints will be complete once the 110th subject has undergone treatment and completes the 12-month follow-up visit. A formal interim analysis of the secondary endpoints will be performed once the 110th subject has undergone prostate ablation treatment and completes the 12-month follow-up visit.

Actual enrolment of the first phase was 115 patients. With the addition of a second enrolment phase of 35 patients, the study will be complete once the last patient (150th subject) has undergone treatment and completes the 5-year follow-up visit.

An independent steering committee (Data and Safety Monitoring Committee, DSMC) will be established to review the study outcome. A minimum of two safety assessments by the DSMC will be performed. Study enrolment will continue while data are collected and reviewed.

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The first DSMC review will occur after the first cohort of ten subjects complete treatment. A complete review of the study including all results to date and adverse events, if any, will be completed to assess the safety of the TULSA-PRO procedure. The review will also include patients who have decided to withdraw from the study. If two or more of the first ten patients who have undergone the TULSA-PRO procedure (mITT group) have a documented rectal fistula then the DSMC would recommend stopping the trial.

The second DSMC review will occur after the first cohort of ten subjects complete their 1-month follow-up visit. A complete review of the study including all results to date and adverse events, if any, will be completed to assess the safety of the TULSA-PRO procedure. The review will also include patients who have decided to withdraw from the study. If $\geq 10\%$ of all patients who have undergone the TULSA-PRO procedure (mITT group) at the time of the DSMC analysis have a documented rectal fistula, then the DSMC would recommend stopping the trial.

6.4 Anticipated Duration of the Clinical Investigation

Once subject enrolment begins, it is expected that at least twenty procedures will be conducted per month using the TULSA-PRO. The primary endpoints of the study are intended to be completed 12 months after the last patient has undergone the prostate ablation treatment.

Upon completion of the initial enrolment phase, a total of 115 patients were treated. A second enrolment phase consisting of 35 patients will be initiated at selected clinical sites within the United States. Once all sites have initiated subject enrolment, it is expected that at least 2-3 TULSA treatments will be conducted per month allowing total enrolment to be completed in less than 12 months.

7.0 Investigational Site Training

Profound Medical Inc. (PMI) will provide investigational site training prior to study initiation. Training topics will include but are not limited to device usability, Good Clinical Practice (GCP), AE reporting, study details and procedures, study documentation, informed consent, and CRF completion. All clinically significant changes from baseline will be followed until resolution or stabilization as determined by the Principal Investigator (PI) or their designee.

8.0 Records and Reports

8.1 Data handling and record-keeping

All records and reports related to the investigation of PAD-105 will be maintained as per ICH Guidance E6: Good Clinical Practice.

8.2 Record maintenance and retention

The investigator-sponsor will retain the specified records and reports for up to 2 years after the marketing application is approved for the investigational device or PMI will inform the investigator when the documents are no longer needed.

8.3 Device Accountability

It is the responsibility of the investigator to ensure that a current record of investigational device (product) disposition is maintained at each study site where investigational device is inventoried and disposed. Records and logs will be verified during site monitoring visits.

Upon completion of the study, all unused investigational device and supply must be returned to PMI.

9.0 Adverse Event (AE) Recording/Reporting

The procedure, “GCP-10039 – Investigational Regulatory Reporting” outlines AE or SAE assessment and country specific reporting timelines. The Principal Investigator(s) will be trained on the procedure to ensure that the reporting requirements are understood and will be followed throughout the trial period.

Sponsor Contact for AE Reporting:

Attn: Mathieu Burtnyk

Phone: 647 476 1350 x408

Email: mburtnyk@profoundmedical.com

10. Site Monitoring Procedures

Independent monitoring of the clinical study for adherence to the clinical protocol will be conducted periodically by qualified staff.

Representatives of PMI must be allowed to visit all study site locations periodically to assess the data quality and study integrity. On site they will review study records and directly compare them with source documents, discuss the conduct of the study with the investigator, and verify that the facilities remain acceptable. Certain CRF pages and/or electronic files may serve as source documents.

In addition, the study may be evaluated by PMI Internal auditors and government inspectors who must be allowed access to CRFs, source documents, other study files, and study facilities. PMI audit reports will be kept confidential.

The investigator must notify PMI immediately of any inspections scheduled by regulatory authorities, and promptly forward copies of inspection reports to PMI.

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