Ablation efficacy of contact side firing fiber in predefined settings for treating BPH

Clinical Study Protocol

Study Device: **Lumenis pulse P120H Holmium Laser System**

Study Number: LUM-SBU-VP-15-02

Protocol Revision: B

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Sponsor Name: Lumenis, Ltd.

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Study Synopsis

Study Title	Ablation efficacy of contact side firing fiber in predefined settings for treating BPH	
Protocol No:	LUM-SBU-VP-15-02	
Device Name:	Lumenis Pulse 120H Holmium Laser system	
Design	Prospective, single arm, single center	
Planned Study period	**Initiation**: January 2016	**Final Report**: August 2016
Objectives	**Primary:** To explore Vaporization efficacy and safety when treating PBH with the contact side firing fiber with recommended settings **Secondary:** To demonstrate the usability of BPH treatment with the combined tools Xpeeda+ Pulse 120H	
Study population	Twenty (20) subjects presenting with a hyperplasia enlarged prostate and candidates for surgery	
Main Inclusion Criteria	• Subject will be older than 18 years of age • Subject was diagnosed with enlarged prostate of ≥ 30 gr volume • Subject is a candidate for surgery treatment • Subject is willing and has signed the Informed Consent Form • AUA score ≥ 12 • Qmax <15 mL/s	
Main Exclusion Criteria	• Need to perform concomitant procedure, other than prostate vaporization • PVR > 300mL • Current Urine retention and Pdet <40 cm H20 • Documented or suspected prostate cancer and / or bladder cancer • Neurogenic bladder disorder / neurogenic voiding dysfunction • Urethral strictures • Previous prostatic, bladder neck, or urethral surgery • Known history of spinal cord injury • Urogenital trauma • Bladder neck stricture • Evidence of urinary tract infection • History of chronic prostatitis	
Investigational Treatment and study course	Following enrollment, each subject will undergo a single treatment for ablation of the prostate. Following treatment subjects will be required to return for follow-up visits at 1 and 3 months. Follow up sessions: • Peri-procedure and day of discharge • One month post-surgery • 3 months post-surgery	

Criteria for Evaluation (endpoints)	Primary Endpoints:
	• Efficacy
	  • Ablation time
	  • Ablation rate calculated as: Prostate volume measured using pre and post treatment (3 month) TRUS images/ procedure time
	  • Ablation efficacy calculated as: Prostate volume measured using pre and post treatment (3 month) TRUS/ energy used
	• Safety:
	Intraoperative complications
	  • Complications according to Clavien scale
	  • Conversion to TURP to maintain hemostasis (procedure completed with laser)
	  • Conversion to TURP to complete procedure
	  • Capsule perforation
	  • Blood loss (blood transfusion, pre and post-operative hemoglobin and hematocrit)
	2. Perioperative complications
	  • Urinary Retention
	  • Haematuria
	  • Dysuria
	  • Infection
	  • Urge incontinence
	  • Stress incontinence
	  • Erectile Dysfunction (International Score as compared to baseline)
	  • Re-catheterization
	  • Readmission for secondary operation
	
	Secondary Endpoint:
	• Usability:
	  • Visibility during procedure- subjective assessment
	  • No. of fibers used during procedure
	  • Catheterization time
	  • Hospital stay duration
	  • IPSS QOL (follow-up visits as compared to baseline)
	  • QMax ml/s (follow-up visits as compared to baseline)
	  • PVR (follow-up visits as compared to baseline)
	  • PSA (follow-up visits as compared to baseline)
	  • AUA (follow-up visits as compared to baseline)

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1 Introduction

1.1 Background

The Lumenis Holmium Laser System family has been used for more than a decade for many procedures and specialties requiring excision, incision, ablation, and vaporization of tissue.

The holmium:yittrium–aluminum–garnet (Ho:YAG) laser, known as the holmium laser, is a very commonly used laser in urological surgery [1, **Error! Reference source not found.**]. Its wavelength f 2,120 nm is very near the absorption peak of water (1,910 nm). As a result, it can be used for soft tissue-based applications as well as stone fragmentation. Since soft tissue is comprised primarily of water, the holmium laser energy is effective for excision, incision, ablation, and vaporization when in direct contact with soft tissue, and for coagulation when a few millimeters from soft tissue. If fired directly onto mucosa, the laser has an effective penetration depth of 300– 400 micron, thus limiting the collateral injury during tissue-based applications. Additionally, stones (both urinary and gastrointestinal) contain sufficient amount of water that can absorb laser energy leading to their fragmentation, thus facilitating their removal [**Error! Reference source not found.**].

Delivery of holmium laser energy to the target tissue is commonly performed by emitting the energy through flexible hard core fibers of varying diameters. The flexibility of the fibers enables reaching and treating areas that otherwise would have been hard or impossible to reach. Fibers used for soft tissue procedures deliver the laser energy to the desired location by either emitting the laser beam forward (end-fire) enabling excision or to the side (side-firing) used mainly for ablation of tissue.

Benign Prostate Hyperplasia (BPH) endourologic surgery can be performed by either excision of the prostate tissue (Holmium Laser Enucleation of the Prostate – HoLEP) or ablation of the prostate tissue (Holmium Laser Ablation of the Prostate – HoLAP). During the HoLAP procedure, a channel is created within the prostatic fossa to relieve the patient of symptoms secondary to BPH. Side-firing fiber is used to systematically remove superficial layers of the prostate tissue until a cavity is formed. Depending on the prostate volume, this can be a time consuming procedure.

Ablation efficiency during the HoLAP procedure is limited by the laser system output power, transmission loss and the effectiveness of the energy applied to the tissue. The current Lumenis Pules p120H can deliver up to 120W with commonly used energy per pulse of 2-3J at frequencies ranging from 60-30 Hz, accordingly. In order to increase the effective energy per pulse that affects the tissue, any water based interface gap between the fiber and the tissue should be reduced to a minimum. This enables maximum energy to be absorbed directly by the water content of the tissue, leading to ablation. Therefore, using the fiber in direct contact with the tissue during ablation is considered an advantage, particularly in procedures requiring high ablation rate, such as HoLAP.

In order to increase the efficiency of the HoLAP procedures Lumenis has developed several side firing fibers that can be used in contact with the tissue to maximize the laser tissue effect and increase the

ablation efficiency of the holmium laser. Together with the powerful tool of the pulse p120H Lumenis offer an efficient and safe combination for HoLAP procedure

This study is intended to quantify the ablation efficiency and the safety of the Xpeeda fiber together with defined settings of the pulse 120H.

1.1 Rationale for Evaluation

The Lumenis Pulse P120H enables a wide range of working parameters that include use of high frequency at low energy. The usage of predefined set of parameters for vaporization and coagulations may aid the physician in completing the procedure in a relative short period of time, investing less time and energy with no complications. The combination of side firing fiber together with the pulse 120H is expected to show an effective tool to treat BPH.

2 Device Description

2.1 Laser System – Lumenis Pulse P120H Holmium Laser

The Lumenis Pulse P120H is a high pulsed solid-state laser used for Urology procedures, worldwide. Importantly, both intended use and indications for use claims as well as underlying laser technology are similar to the marketed product. The activated laser is based on a flash lamp excited, Ho:YAG rod. The Ho:YAG rod derived photons are guided into the attached delivery system fiber. The system delivers a second, low powered laser in the visible wavelength spectrum of 650nm that enables aiming the high, invisible laser energy to the desired location.

2.2 Fibers

Xpeeda side firing silica fibers are improved fibers used for laser procedures, to deliver laser energy from the system to the treatment site. The Xpeeda fibers deliver energy directly to the tissue, due to the ability to use it in contact with the tissue during the entire procedure. Xpeeda fibers were design to withstand the high power laser emission of the Lumenis Pulse120H. The Xpeeda fiber is single use, supplied ethylene oxide sterile.

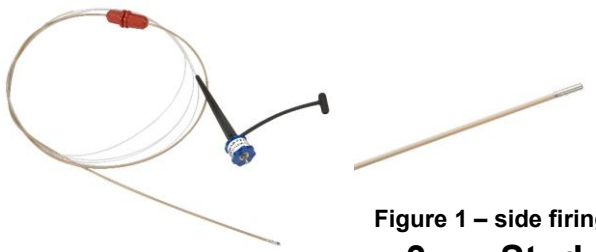

Figure 1 – side firing Xpeeda fiber

3 Study Design

This is a one arms, prospective, single center study. Subjects will undergo a single treatment for ablation of the prostate using the study device. Follow up visits are scheduled for the day of release

from the hospital and at 1 and 3 months post procedure. Additional treatment sessions, if required, will be at the discretion of the investigator, as part of the site standard of practice. Additional sessions will not be included in this study.

4 Study Objectives

4.1 Primary

To explore Vaporization efficacy and safety when treating PBH with the contact side firing fiber with recommended settings

4.2 Secondary

Demonstrate the usability of BPH treatment with the combined tools Xpeeda fiber+ Lumenis Pulse 120H system

5 Outcome Measures

5.1 Primary Endpoints:

5.1.1 Efficacy

- Ablation time
- Ablation rate calculated as: Prostate volume measured using pre and post treatment (3 month) TRUS / procedure time
- Ablation efficacy calculated as: Prostate volume measured using pretreatment and post treatment (3 month) TRUS / energy used

5.1.2 Safety:

5.1.2.1 Intraoperative complications

- Complications according to Clavien scale
- Conversion to TURP to maintain hemostasis (procedure completed with laser)
- Conversion to TURP to complete procedure
- Capsule perforation
- Blood loss (blood transfusion, pre and post-operative hemoglobin and hematocrit)

5.1.2.2 2. Perioperative complications

- Urinary Retention
- Haematuria
- Dysuria
- Infection
- Urge incontinence
- Stress incontinence
- Erectile Dysfunction (International Score as compared to baseline)

- Re-catheterization
- Readmission for secondary operation

5.2 Secondary Endpoint:

5.2.1 Usability:

- Visibility during procedure
- No. of fibers used during procedure
- Catheterization time
- Hospital stay duration
- IPSS QOL (follow-up visits as compared to baseline)
- QMax ml/s (follow-up visits as compared to baseline)
- PVR (follow-up visits as compared to baseline)
- PSA (follow-up visits as compared to baseline)
- AUA score (follow-up visits as compared to baseline)

6 Patient Population

6.1 Source and Sample Size

Subjects shall be selected by the physician within his patient population. One (1) site will participate in this study and will treat twenty (20) subjects. Enrolled subjects that did not complete the full course of the study will be discarded from performance analysis if they have not returned for the 1 and/or 3 month follow-up visits.

6.2 Eligibility

Each subject will be evaluated by the Investigator to assess his suitability for entry into this study according to the following criteria:

6.2.1 Inclusion Criteria

- Subject will be older than 18 years of age
- Subject was diagnosed with enlarged prostate of ≥ 30 gr volume
- Subject is a candidate for surgery treatment
- Subject is willing and has signed the Informed Consent Form
- AUA score ≥ 12
- Qmax <15 mL/s

Any of the following will exclude the subject from the study:

6.2.2 Exclusion Criteria

- Need to perform concomitant procedure, other than prostate vaporization
- PVR > 300mL
- Current Urine retention and Pdet <40 cm H20

- Documented or suspected prostate cancer and / or bladder cancer
- Neurogenic bladder disorder / neurogenic voiding dysfunction
- Urethral strictures
- Previous prostatic, bladder neck, or urethral surgery
- Known history of spinal cord injury
- Urogenital trauma
- Bladder neck stricture
- Evidence of urinary tract infection
- History of chronic prostatitis

7 Study Procedures

7.1 Study duration and timelines

For each subject the duration of the study will be of 3 months. Subjects may remain hospitalized following surgery, based on physician's discretion. Subjects will be followed at the day of their discharge from the hospital. Each subject will return for follow-up visits at 1 and 3 months following the treatment procedure at which time they will have completed their participation in the study.

It is expected that enrollment of all study subjects at the site will occur within 12-16 weeks from study initiation.

7.2 Study Measures

7.2.1.1 Various assessments will be performed throughout the study at different time-points as detailed in fiber positioning, vaporization control and ability to successfully complete the procedure.

Table 1.

7.2.2 Objective Measures

7.2.2.1 Blood workup: including CBC, BMP, & PSA

7.2.2.2 Urine workup: including urine analysis, and urine culture if applicable

7.2.2.3 BPH volume will be performed using trans-rectal ultrasound prior to the procedure.

All imaging verifying the diagnosis, pre-intervention images, intra-operative (during laser activation) images, immediate post-operative and follow-up images will be recorded on electronic media for documentation, further analysis and data recording.

Subject anonymity will be assured for all images by deleting any ID detail. Only the code for the Case Number in the study will appear on the records being transferred to the sponsor.

7.2.2.4 BPH treatment will be confirmed and three months post discharge using trans rectal ultrasound.

7.2.2.5 Investigator Subjective Assessments

7.2.2.6 Procedure Questionnaire will record subjective usability parameters including visibility impairment and resolution (due to bleeding or other disturbances), fiber positioning, vaporization control and ability to successfully complete the procedure.

Table 1 – Assessments time-points:

Assessment		**Performed During Visit**			
	Baseline (Pre-operative)	**Perioperative**	**Hospital discharge**	**1 month follow-up**	**3 month follow-up**
Subject assessment (ICF, medical history, demographics, inclusion/exclusion evaluation)	X				
Trans Rectal Ultrasound	X				X
Post Void Residual Ultrasound	X			X	X
Q-Max Uroflow	X			X	X
Urodynamic Evaluation	X				
Blood analysis (CBC, BMP & PSA) & urine analysis	X	X (CBC)			X
Urine culture (if applicable)	X				X
Erectile Dysfunction	X				X
Subject Questionnaires (AUA, QoL)	X			X	X
Physician Subjective Procedure Questionnaire		X			
Adverse Event Assessment		X	X	X	X

7.3 Screening Procedures

7.3.1 Subject Enrollment

1. During the first visit, the investigator will screen the subject for eligibility to participate in the clinical study using the Inclusion & Exclusion criteria. During screening, the study physician will review the subject's medical history to ensure that the subject meets the study criteria.
2. If the subject has met the preliminary study eligibility criteria, the study physician will obtain an informed consent from the subject, clearly indicating his/her understanding of the procedure, requirements and risks involved with study participation and other applicable treatment options. It will be understood that no compensation will be payed to the subjects for participating in the clinical study.
3. The subject will be enrolled to the study and the treatment will be scheduled.

7.3.2 Subject Identification

At enrollment, each subject will receive an identifying number that will include a consecutive serial number. The subject identification number and the subject initials will be used to identify the subject during the entire study and will be entered in the subject's CRF for each treatment.

7.4 Pre-treatment evaluation

The following examinations are included in the standard of practice for subjects with PBH and may have been performed prior to the subject enrollment. Medical history as well as measurements that were completed prior to study enrollment will be used as baseline data for the study.
A complete history and physical examination and total duration of the patient's symptoms:
Blood and urine tests including urinalysis, urine cultures, complete blood count (CBC), BMP & PSA, BPH volume and other analysis measured using the most recent trans rectal ultrasound performed.

7.5 BPH treatment pre-operative preparations (according to hospital routine of care)

7.5.1 Anesthesia

The subject will be put under regional (spinal) anesthesia or general anesthesia, per standard hospital practice for BPH procedures.

7.5.2 Preoperative antibiotics

The subject will be given intravenous preoperative antibiotics per standard hospital practice.

7.6 Procedure

7.6.1 Cystoscopy and Fiber introduction

The subject will be placed in dorsal lithotomy position. A 21 F cystoscope will be inserted through the urethra and the entire lower tract will be inspected to assess the degree of obstruction and to rule out presence of urethral stricture, bladder neck contracture or unexpected bladder pathology (tumors, stones).

The Xpeeda laser fiber will be introduced through the cystoscope and vaporization of the prostate is initiated (settings: frequency-60Hz, energy 2J, power-120W).

7.6.2 Vaporization

Initially, a bladder neck groove is performed at the 5 o'clock and 7 o'clock positions with direct light contact with the tissue. If a significant median lobe is present, this will be vaporized between the 2 grooves.

Following this, the lateral lobes of the prostate will be vaporized from 1 o'clock to 5 o'clock, and from 11 o'clock to 7 o'clock positions. Next, the roof tissues will be vaporized from the level of the bladder neck to the level of the veru montanum if necessary. Lastly, apical tissues will be vaporized with care to avoid ablation of the veru montanum and external sphincter. Coagulation will be utilized as necessary (settings: frequency-20Hz, power-20W)

At the end of the procedure, the entire lower tract will be inspected to assure an open channel and rule out any significant bleeding. A 22F catheter will be inserted – traction and continuous bladder irrigation can be utilized as necessary

7.7 Follow - up Regimen

Each subject will be evaluated by the physician post the procedure as per standard of care to assess subject wellness. Subjects will be released from the hospital per the hospital standard practice. Each subject will return one month and 3 months following the procedure for a follow-up visits to assess prostate condition and subject well-being. Evaluations during each of these visits will be performed as described in Table 1. Additional unscheduled visits or examinations performed that are not part of the standard of care will be recorded in a dedicated Case Report Form (CRF).

8 Study Analysis Plan

8.1 Study Analysis

The results of the study: subject demographics, baseline assessments, treatment parameters, treatment evaluations and follow-up assessments will be summarized and descriptive analysis will be performed. Adverse events reported will be listed, documenting course, outcome, severity, and possible relationship to the treatment. The modified Clavien classification will be used to evaluate severity of Adverse Events [2].

8.2 Interim report

Interim analysis of the immediate post-operative data will be performed after at least 10 subjects underwent surgery in order to assess the immediate study results. If applicable, most of the study endpoint analysis will be performed for the initial 10 patients including ablation duration, safety parameters and secondary end-points (if applicable according to follow-up scheduled). Treatment

safety and adverse events report, durations and all endpoints will be analyzed following the completion of all study subjects follow-up period and summarized in the final report.

9 Adverse Events (AE)

9.1 Adverse Events Definitions

9.1.1 Adverse Event

Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device

9.1.2 Adverse Device Effect

Adverse event related to the use of an investigational medical device. Adverse Device Effect can be an anticipated serious adverse Device Effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report or unanticipated if it has not been identified in the risk analysis report.

9.1.3 Serious Adverse Events

NOTE: The term serious is not synonymous with severity, which may be used to describe the intensity of an event experienced by the subject. An AE that does not meet any of the below criteria will be classified as non-serious.

A serious adverse event is any event that:

4. led to death,
5. led to serious deterioration in the health of the subject, that either resulted in:
    - 5.1. a life-threatening illness or injury, or
    - 5.2. a permanent impairment of a body structure or a body function, or
    - 5.3. in-patient or prolonged hospitalization, or
    - 5.4. medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,
6. led to foetal distress, foetal death or a congenital abnormality or birth defect

Any adverse events or complications reported by the patient or observed by the physician that occur during or after treatment with the device will be recorded in the medical record or source document and on the dedicated Case Report Form. The investigator will determine if the AEs are device related or procedure related. This assessment shall include the onset date, resolution date, severity, seriousness, frequency, additional treatment required and outcome.

Each adverse event should be assessed according to the following criteria:

9.1.4 Classification

9.1.4.1 Severity (based on Clavien classification)

Each adverse event should be assessed for its severity, or the intensity of an event experienced by the subject.

- **Mild**: Awareness of a sign or symptom that does not interfere with the subject's activity or is transient resolved without treatment and has no sequelae.
- **Moderate**: May interfere with the subject's usual activity and require additional intervention and/or treatment, and may have additional sequelae.
- **Severe**: Significant discomfort to the subject and/or interferes with the subject's activity. Additional intervention and or treatment are necessary. Additional sequelae occur. Severe is used to describe the intensity of an event experienced by the subject.

9.1.4.2 Relationship of AE to the Device

Each adverse event should be assessed for its relationship to the device or procedure as identified as follows:

- **Device**: This category should be restricted to adverse events directly attributable to the vaporization procedure
- **Procedure:** This category should be restricted to adverse events inherent to the procedure irrespective of the fiber performance.

Use the following categories for assigning the certainty of the relationship:

- **Definitely Related:** An AE is definitely related if it is obvious, certain or there is little doubt regarding the relationship
- **Possibly Related:** An AE is possibly related if it is capable of being related but relatively unlikely.
- **Not Related:** An AE is not related if it is determined that there is no plausible association.
- **Unknown:** Use this term if there is insufficient information to determine if the AE is related to the device or procedure.

9.1.4.3 Pre-existing Conditions

A pre-existing condition should not be reported as an adverse event unless there has been a substantial increase in severity or frequency of problems, which has not been attributed to natural history.

9.1.4.4 Diagnosis

There should be an attempt to report a "diagnosis" rather than the individual signs, symptoms and abnormal laboratory values associated with the diagnosis. However, a diagnosis should be reported only if, in the Investigator's judgment, it is relatively certain (i.e., definite or possible). Otherwise individual signs, symptoms and abnormal laboratory values should be reported as the adverse events.

9.2 Reporting

9.2.1 Adverse Events (AE) and Severe Adverse Events (SAE) Reporting

All serious adverse events, whether or not deemed expected or device-related, must be reported to the clinical monitor immediately or within 24 hours of knowledge by telephone (see below). A written report must follow within five (5) working days and is to include a full description of the event and sequence. If the Lumenis monitor cannot be reached, the site personnel will directly contact the Lumenis Communication Center (USA) at +1-877-586-3647.

If an anticipated adverse event occurs at any time during or after the use of the study device, the Investigator must report it to Lumenis. If the anticipated adverse event, in the opinion of Lumenis or the Investigator, is likely to affect the safety of the subjects or the conduct of the study, the IRB/ethic committee will be notified of the effect as required by the authorized representative.

The Investigator shall report to the EC and regulatory authorities serious adverse events and device deficiencies that could have led to a serious adverse device effect, if required by the national regulations or by the EC.

9.3 Risk/ Benefit Analysis

9.3.1 Anticipated Procedure Related Adverse Events

Anticipated adverse events that are related to the BPH Vaporization procedure performed as part of this study and as established in the literature are noted below [**Error! Reference source not found.**]. hese complications are related to BPH Vaporization, whether or not ablation is performed, and regardless of the method that is used for either removal or the adenoma.

- Intraoperative complications: bleeding, prostate capsular perforation, infection and different risks due to the anesthesia
- Postoperative complications: Dysuria, hematuria, urge incontinence, urinary retention, urgency, infection

9.3.2 Anticipated Device Related Adverse Events

The potential risks related to the system may include prostate capsule perforation and beelding. Nevertheless, this modified system is based on the previous marketed family of Ho:YAG lasers that is already largely used in the clinical arena, and for the same indications. The use of Ho:YAG for ablation of the prostate adenoma has been shown to be safe and effective with a very low rate of complications [**Error! Reference source not found.Error! Reference source not found.**].

Finally, the modified system underwent a thorough series of pre- clinical verification and validation testing to ascertain its maintained safety and performance as well as the safe and effective use of the Xpeeda fibers.

9.3.3 Anticipated Benefits

The Holmium laser has been shown to be able to vaporize soft tissues and in particularly prostate adenoma diagnosed as BPH. Duo to the high-energy power of the Lumenis pulse 120H and the usage of side firing fiber this tissue can be ablated quite easily. The Xpeeda fiber was design to work in full contact with the tissue thus delivering maximum energy for efficient vaporization. Bleeding control is successfully utilized with the holmium laser and the specific settings of the Lumenis pulse 120H. Using fiber defocusing or wider pulse size (predefined settings designed for the double puddle of the device) will minimize intraoperative complications. Moreover, the vaporization efficacy of the pulse 120H may lead to reduced procedure time and postoperative complications, including readmission as compared to the other commonly used parameters and devices for BPH treatment.

10 Administrative Procedures

10.1 Investigator Selection

The investigator must be of good standing as an investigator and knowledgeable in relevant areas of clinical research to ensure adherence to the requirements of the protocol, including the protection of human subjects. Other site personnel must have appropriate research experience and infrastructure to ensure adherence to the protocol and enrollment of sufficient numbers of evaluable subjects. The curriculum vitae (CV) of the Investigator will be maintained in the Sponsor files as documentation of previous medical training, and federal databases will be searched to ensure that the investigator and/or the site are not prohibited from engaging in federally sponsored clinical research. The Principal Investigator will sign the signature page of this protocol, agreeing to comply with all applicable government regulations and the requirements of this study.

10.2 IRB / Ethical Committee Approval

This clinical study will be conducted according to all applicable regulations under the Medical Device Directive and in accordance with the ICH Good Clinical Practice and local laws and regulations relevant to the use of medical devices.

An Ethical Committee (EC or IRB) will approve the clinical study protocol prior to study initiation. Approval will be indicated in writing with reference to the final protocol number and date.
Details regarding the IRB / EC 's constitution including the names of its members, their qualifications and what function they perform on the board (e.g., chairman, specialist, lay-member) will be made available to enable Lumenis and the Investigator to conform to regulations governing research on experimental devices.

10.3 Informed Consent

Prior to the procedure, the Investigator or his delegate must explain to each subject (or the subject's legally authorized representative) the nature of the study, its purpose, expected duration, and the benefits and risks of study participation. After this explanation and before entering the study, the subject (or legally authorized representative) must voluntarily sign and date the IRB (EC) -approved Informed Consent form.

10.4 Subject Withdrawal/Dropouts

The subjects will be advised in the written Informed Consent form that they have the right to withdraw from the study at any time without prejudice, and may be withdrawn at the Investigator's/Lumenis' discretion at any time. In the event that a subject drops out of the study or is withdrawn from the study, the Exit/Termination CRF should be completed. On the withdrawal page, the Investigator should record the date of the withdrawal, the person who initiated withdrawal and the reason for withdrawal.

Reasonable effort should be made to contact any subject lost to follow-up during the course of the study in order to complete assessments and retrieve any outstanding data and study supplies. The records of subjects who terminate prior to completing the study will be retained and the reason for termination will be documented.

The following are possible reasons for subject dropout/withdrawal:

- Adverse event that would prevent subject compliance with the protocol;
- Subject withdrawal of consent;

However, every effort should be made to see that subject is followed for the remainder of the study even if subject is unable or unwilling to comply with the protocol.

10.5 Case Report Forms/Data Collection

The Investigator is responsible for completely and accurately recording study data in the appropriate sections of the CRFs provided by Lumenis. The CRFs must be signed by the Investigator or by his/her authorized person as designated in a note to file.

The monitor will ensure the quality of data recording at each investigational site by comparison to supporting source documents during periodic site visits. Adherence to proper recording of information as well as assuring that corrections are being made will also be addressed during these periodic visits.

Data will be recorded on the following CRFs. Where data is not located in the subject's source file, the CRF will be the source for this data.

10.6 Required Documentation

Prior to starting the clinical study, the following documents must be submitted or returned to Lumenis by the Investigator:

- Signed Clinical Trial Acknowledgement for the protocol
- Signed Clinical Evaluation Agreement
- Curriculum vitae of the Principal Investigator
- Signed Financial Disclosure Statement for each investigator
- Written approval from the Ethical Committee of both the protocol and informed consent form

10.7 Subject's Financial Compensation

Subjects participating in this study will not be compensated for participating in this study.

10.8 Device Use/Accountability

The evaluation site personnel will maintain records of the model and serial number of the device (if appropriate) used for each treatment during the conduct of the study. The device along with the associated delivery and accessories are to be maintained by the research sponsor with reasonable care being taken by the Investigators and facility to prevent damage to, or unauthorized use of the equipment.

10.9 Training Requirements

PI and all study personnel are well familiar with the procedure and device operation including all related tools and equipment. No training or additional instructions are required prior to study initiation.

10.10 Modification of Protocol

The protocol may be amended with the agreement of the sponsor and upon notification of and approval by the IRB / EC.

Investigators should review the contents of this protocol. Subsequent alterations should only be made in writing in conjunction with the sponsor.

Medically significant amendments to the protocol (e.g., changes that increase the risk or the inconveniences for the patient, inclusion of new categories of patients, significant modifications to the study device, etc.) must be approved by the local IRB / EC prior to implementation and authorized representative, as applicable.

10.11 Data Retention/Archiving Data

The Investigator must keep the following documents in a secure place for at least 2 years after the last clearance of a marketing application or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product.

- A signed copy of the final protocol and amendments.
- Copies of the subjects' evaluation forms, data clarification forms and any associated subject-related raw data or where applicable, authorized copies of raw data.
- The subjects' signed Informed Consent forms.

10.12 Site Monitoring

The study monitors are designated as agents of Lumenis and are assigned to oversee the conduct and progress of the study and to be the principal communication link between Lumenis and investigator. The study monitors will be involved in monitoring of sites and records, to ensure continued compliance with the protocol and adequacy of the investigator and the facility to carry out the study.

The study will be monitored by representatives of Lumenis Medical, Ltd. by telephone, in writing and during on-site visits. At a minimum, site visits will be scheduled prior to the initiation of the study, and at the end of the study. The purpose of site visits will be to ensure compliance with the investigational plan, to ensure appropriate use of investigational devices, and to inspect and retrieve study data.

10.13 Termination of Study

Lumenis reserves the right to discontinue the study at any time for administrative or other reasons. Written notice of study termination will be submitted to the investigator in advance of such termination. Termination of a specific site can occur because of (but is not limited to) inadequate data collection, low subject enrollment rate, achievement of the total enrollment, or non-compliance with the protocol or other clinical research requirements

10.14 Reporting Requirements

The investigator must promptly report to Lumenis any withdrawal of IRB / EC approval at the site. Additional reporting requirements include:

- Notify Lumenis' designee and the IRB / EC of any severe adverse device effect, whether anticipated or unanticipated, that occurs during the study as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect. This report is to include a description of the effect, subsequent treatments, clinical outcomes, and outcome diagnoses. If the site personnel are not sure whether an event meets these criteria, they should call the clinical monitor.
- Notify Lumenis or Lumenis's designee and the IRB / EC immediately (within 24 hours) if an emergency situation arises in which the subsequent treatment, in the best interests of the subject, resulted in a deviation from the protocol. This should be followed with written confirmation that describes the emergency action and outcomes, to Lumenis and the IRB / EC within 5 working days.
- Report to the IRB / EC and Lumenis, within 5 working days, the use of the study device without signed informed consent from the subject.
- Report adverse events in accordance with 21 CFR 803.
- Submit regular progress reports to the IRB / EC and Lumenis or Lumenis' designee, as requested by the investigators or IRB/ EC.
- Submitting a final report on the study to the IRB / EC and Lumenis or Lumenis's designee within 3 months after termination or completion of the study.

11 References

1. Elmansy HM, Kotb A, Elhilali MM. Holmium laser enucleation of the prostate: long-term durability of clinical outcomes and complication rates during 10 years of followup. J Urol. 2011 Nov;186(5):1972-6.

2. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of a 6336 patients and results of a survey. Ann Surg 2004;240:205–13
3. Kumar, S. Holmium Laser Ablation of Large Prostate Glands: An Endourologic Alternative to Open Prostatectomy. Journal of Endourology, Vol 21, No. 6, June 2007
4. Barski D, Richter M, Winter C, Arsov C, De Geeter P, Rabenalt R, Albers P. Holmium Laser Ablation of the Prostate (HoLAP): Intermediate term results of 144 patients. World J Urol, 31: 1253-1259, 11Jul2013
5. Brewer S. My Surgical Approach for BPH: A Retrospective of Multiple Options and Current Results.
6. Gravas S, Bachmann A, Reich O, Roehrborn C, Gilling P, De La Rosette J. Critical Review of Lasers in Benign Prostatic Hyperplasia (BPH). BJU International, 107, 1030-1043, 14Sep2010.
7. Tooher R, Sutherland P, Costello A, Gilling P, Rees G, Maddern G. A Systematic Review of Holmium Laser Prostatectomy for Bening Prostatic Hyperplasia. The Journal of Urology, vol. 171, 1773-1781, May 2004.
8. Leo M. Enhanced Prostate Vaporization Using High Power Holmium and Improved Fiber. World Congress of Endourology, submitted 21Jun2015.

12 Abbreviations and Terms

CBC	Cell blood count
AE	Adverse Event
SAE	Serious Adverse Event
BUN	Blood urea nitrogen
CRF	Case Report Form
IRB	Institutional Review Board
EC	Ethical Committee
Ho:YAG	Holmium
CT	Computer Tomography
US	Ultrasound Sonography
Hz	Hertz (frequency unit)
J	Joule (energy unit)
BMP	Basic Metabolic Panel
PSA	Prostate Specific Antigen
W	Watt (power unit)
KUB x-ray	Kidney, ureter, bladder x-ray

13 Appendices

Appendix I
Study Flow Chart

Assessment		Performed During Visit			
	Baseline (Pre-operative)	**Perioperative**	**Hospital discharge**	**1 month follow-up**	**3 month follow-up**
Subject assessment (ICF, medical history, demographics, inclusion/exclusion evaluation)	X				
Trans Rectal Ultrasound	X				X
Post Void Residual Ultrasound	X			X	X
Q-Max Uroflow	X			X	X
Urodynamic Evaluation	X				
Blood analysis (CBC, BMP & PSA) & urine analysis	X	X (CBC)			X
Urine culture (if applicable)	X				X
Erectile Dysfunction	X				X
Subject Questionnaires (AUA, QoL)	X			X	X
Physician Subjective Procedure Questionnaire		X			
Adverse Event Assessment		X	X	X	X

Appendix II
Clinical Trial Acknowledgement

I have read and understand the foregoing protocol, and agree to conduct the clinical trial as outlined herein and in accordance with Good Clinical Practices (ICH-E6) as well as with local and universal regulations pertaining to clinical trials.

Investigator's Signature _____ Date _____

Name _____

Clinic _____

Street Address _____

City, State & Zip Code _____

Country _____

Phone # _____

Fax # _____

E-mail Address _____