Utilizing Holmium Laser for FURS Renal Stone Lithotripsy Comparing Stone Breaking vs. Stone Dusting Settings

Clinical Study Protocol

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

Study Number: LUM-SBU-VP-15-01

Protocol Revision: A

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Sponsor Name: Lumenis, Ltd.

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STATEMENT OF CONFIDENTIALITY

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Study Synopsis

Study Title	Utilizing Holmium Laser for FURS Renal Stone Lithotripsy Comparing Stone Breaking vs. Stone Dusting Settings	
Protocol No:	LUM-SBU-VP-15-01	
Device Name:	Lumenis Pulse 120H Holmium Laser system	
Design	Prospective, randomized, single center	
Planned Study period	**Initiation**: January 2016	**Final Report**: May 2016
Objective	**Primary:** Demonstrate the efficiency of stone dusting Vs stone breaking of the P120H holmium laser and 200 DFL ball tip fibers **Secondary:** Demonstrate the usability and safety of stone dusting	
Study population	Twenty (20) subjects presenting with a renal stone and candidates for FURS	
Main Inclusion Criteria	• Subject will be older than 18 years of age • Subject was diagnosed with renal calculi between 0.8 to 2 cm in size • Subject is a candidate for FURS procedure • Subject is willing and has signed the Informed Consent Form	
Main Exclusion Criteria	• Underwent previous PCNL or FURS in current kidney • Need to perform concomitant procedure, other than FURS	
Investigational Treatment and study course	A single FURS procedure will be performed with either high or low frequency holmium laser lithotripsy. Subjects will be randomized during enrollment to receive treatment with one of the two parameter sets. Follow up sessions: • Day of discharge • One month follow-up	
Criteria for Evaluation (endpoints)	Primary Endpoints: • Procedure time • Usage of alternative stone extracting devices • Catheterization time • Time to hospital discharge • Stone clearance based on 1 month follow-up imaging data Secondary Endpoints: • Intraoperative Complications – based on Modified Clavien Classification • Visibility during procedure • Occurrence of retropulsion that interferes with procedure • Ability to reach fragments during the procedure • Fiber flexibility with scope deflection- any damage to fiber • Fiber durability- deflection without losing energy/ efficiency • Damage to scope	

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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, 2]. Its wavelength of 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 [3].

Holmium laser energy is emitted using flexible hard core fibers of varying diameters to the target tissue. The flexibility of the fibers enables reaching and treating areas that otherwise would have been hard or impossible to reach.

The most common use of the holmium laser is for the fragmentation of urinary tract calculi (stones). Using rigid and flexible endoscopies the holmium fiber can be manipulated to reach stones located within the lower and upper regions of the urinary tract, including the renal pelvis [4, 7]. Once placed in the correct location the holmium laser is capable of fragmenting any type of stone. Comparison of this technique to external energy sources such as extracorporeal shockwave energy shows a clearly significant difference in stone fragmentation, favoring laser lithotripsy both for the absolute ability to fragment stones and the required number of sessions for complete removal [5]. Complications are minimal and transient [5]. Holmium laser lithotripsy has recently also been shown to be a safe and effective method for the management of large renal stones (2-3 cm) [6]. When the laser is combined with suction, large renal stone removal surgery can also be safe and effective, while decreasing the total operative time [13].

Due to its flexibility advantage, holmium lithotripsy is mostly described as the modality of choice for retrograde ureteroscopic fragmentation of ureteral stones and small renal stones. During these procedures low power settings (low energy and frequency) are commonly used, due to the retropulsion effect of the holmium laser on the stone that prolong the lithotripsy process. These low power settings limit the fragmentation efficacy of the laser.

Several methods to overcome retropulsion have been shown in in-vitro testing, including reduced energy per pulse used at higher frequencies and longer pulse duration [8, 9, 10]. The use of high

frequency (40-80Hz) at low energy settings (0.2-0.5) has been suggested to enable fragmenting the stone into very fine particles (dust) that are washed out spontaneously. The use of decreased energy per pulse minimizes retropulsion, whereas the use of high frequency enables the application of the same accumulated energy to the stone, thus leading to similar lithotripsy. The application of these parameters in a clinical scenario has been limited, but explorative studies have shown that the use of stone dusting settings with high frequency & low energy can reduce operative time while demonstrating excellent clearance of renal stones at one month post procedure [14]

1.2 Rationale for Evaluation

The Lumenis Pulse P120H enables a wide range of working parameters that include use of high frequency at low energy. The use of the “stone dusting” set of parameters versus the commonly used “stone breaking” parameters may aid the physician in completing the procedure in a shorter period of time. The high frequency may reduce procedure time due to the ability to quickly fragment the stone, the resultant smaller stone fragments that can be washed out without the need for additional extraction procedures and the reduction of the retropulsion effect that necessitates repositioning of the flexible ureteroscope and fiber thus adding additional time to the procedure.

The 200 DFL fiber demonstrated high performances in terms of flexibility, efficiency and durability especially in high repetition rates. This fiber is considered to be Lumenis’s optimal solution for stone treatment in flexible ureteroscopy thus will be utilized in both procedures.

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 Fiber

Slimline end-firing silica fibers are standard fibers used for laser lithotripsy procedures, to deliver laser energy from the system to the treatment site. The new 200 DFL flexible fiber is specially designed with a ball tip to facilitate fiber introduction through a fully deflected ureteroscope. The Slimline 200 micron fiber is single use, supplied ethylene oxide sterile.

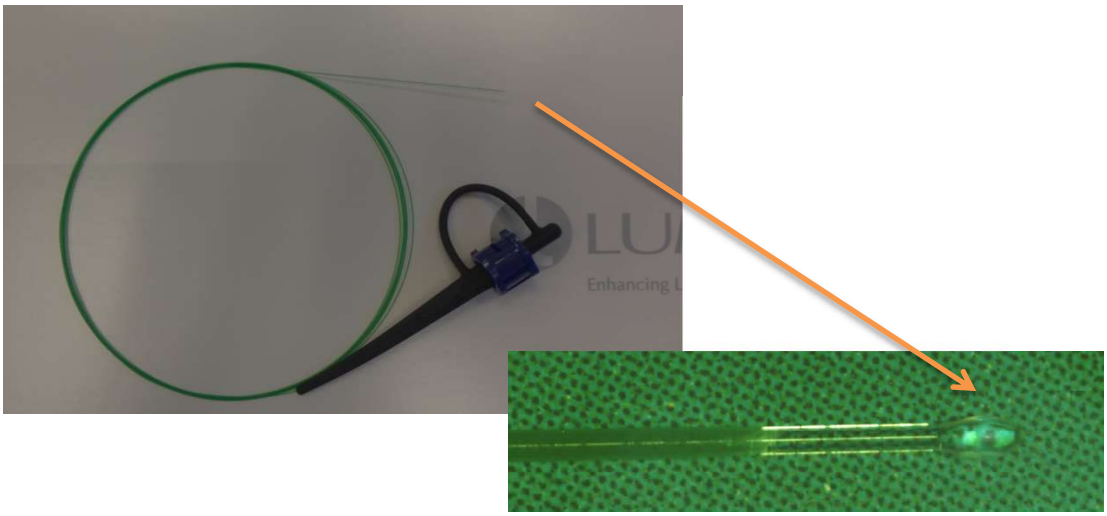

Figure 1 - 200 micron fiber with ball tip

3 Study Design

This is a randomized, two arms, prospective, single center study. Subjects will undergo a single flexible ureteroscopic renal surgery (FURS) procedure for a kidney stone as part of this study, using the study device. Follow up visits are scheduled for the day of release from the hospital and at 1 month post procedure. Additional treatment sessions, if required, will be at the discretion of the investigator, as part of the site standard of practice. Additional treatment sessions will not be included in this study.

4 Study Objectives

4.1 Primary

Demonstrate the efficiency of stone dusting Vs stone breaking of the P120H holmium laser and 200 DFL ball tip fibers

4.2 Secondary

Demonstrate the usability and safety of stone dusting

5 Outcome Measures

5.1 Primary Endpoints

- Procedure time
- Usage of alternative stone extracting devices
- Catheterization time
- Time to hospital discharge
- Stone clearance based on 1 month follow-up imaging data

5.2 Secondary Performance Endpoints

- Intraoperative Complications – based on Modified Clavien Classification
- Visibility during procedure
- Occurrence of retropulsion that interferes with procedure
- Ability to reach fragments during the procedure
- Fiber flexibility with scope deflection- any damage to fiber
- Fiber durability- deflection without losing energy/ efficiency
- Damage to scope

5.3 Safety

Incidence and severity of adverse events will be based on the modified Clavien classification system [12]

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 one 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

6.2.1.1 Subject will be older than 18 years of age

6.2.1.2 Subject was diagnosed with renal calculi meeting the following criteria:

- Largest stone measures no more than 2cm on a single diameter and is no less than 0.8cm as defined by X-ray or CT.
- Accumulative stone burden (addition of all stone diameters) is no more than 2.5cm.

6.2.1.3 Subject is a candidate for FURS procedure

6.2.1.4 Subject is willing and has signed the Informed Consent Form

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

6.2.2 Exclusion Criteria

6.2.2.1 Subject has undergone a previous treatment for stones in the same kidney

6.2.2.2 Subject requires another, concomitant procedure, other than FURS, to be performed during this treatment session.
6.2.2.3 Female subject is pregnant
6.2.2.4 Concomitant anticoagulant medication that cannot be suspended during surgery

7 Study Procedures

7.1 Study duration and timelines

For each subject the duration of the study will be of 1 month. 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 a follow-up visit at 1 month 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 8-10 weeks from study initiation.

7.2 Study Measures

- Various assessments will be performed throughout the study at different time-points as detailed in Intraoperative Complications – based on Modified Clavien Classification

Table 1.

7.2.1 Objective Measures

7.2.1.1 Blood workup: including CBC & BMP
7.2.1.2 Urine workup: including urine analysis and urine culture (if applicable)
7.2.1.3 Renal stone size and location will be performed using Computer Tomography
7.2.1.4 All imaging verifying the diagnosis, pre-intervention images, intra-operative (during laser activation) images, immediate post-operative and follow-up images and relevant fluoroscopy and CT 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.

7.2.1.5 Stone clearance status will be confirmed one month post discharge using non contrast abdominal Computed tomography (for Radioluscent calculus) or KUB X-ray combined with kidneys and bladder Ultrasound imaging (for radiopaque calculus).

7.2.2 Investigator Subjective Assessments

7.2.2.1 Procedure Questionnaire will record subjective usability parameters such as ability to maintain fiber durability and deflection, retorpulsion and visibility impairment and resolution (due to bleeding or other disturbances), subjective assessment of lithotripsy efficiency, aspiration and combined procedures.

- Intraoperative Complications – based on Modified Clavien Classification

Table 1 – Assessments time-points

Assessment		Performed During Visit		
	Baseline (Pre-operative)	**Perioperative**	**Hospital discharge**	**1 month follow-up**
Subject assessment (ICF, medical history, demographics, inclusion/exclusion evaluation)	X			
Imaging	X (CT and / or X-ray)			X (CT and / or X-ray)
Blood analysis (CBC & BMP) and urine analysis	X		X	X
Urine culture (if applicable)	X			X
Physician Subjective Procedure questionnaire		X		
Adverse Event Assessment		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.
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 and photographs.

7.3.3 Subject randomization

Allocation of the treatment parameters used during the procedure will be performed using study randomized envelopes. The sponsor will provide the site with sealed envelopes containing “stone breaking” or “stone dusting” treatment parameters. Randomization will be divided into two groups of patients (1-10 and 11-20) with randomization ratio of 1:1 in each group. The randomization list will take into consideration additional subjects that will be required to replace subjects that have dropped from the study. If any subject drops out from the study and is replaced by another subject randomization will continue as per the original randomization scheme (this new subject will not receive the randomization of the subject that was replaced).

7.4 Pre-treatment evaluation

The following examinations are included in the standard of practice for subjects with renal calculi 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).
- Stones sizes and locations measured using the most resent X-ray or abdominal Computed Tomography imaging performed.

7.5 FURS 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 FURS procedures.

7.5.2 Preoperative antibiotics

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

7.5.3 Retrograde guide introduction

The subject will be placed in the dorsal lithotomy position. A cystoscope will then be inserted through the urethra into the bladder. If a prior ureteral stent is present the vesicle end of the ureteral stent will be removed outside the external urethral meatus, a guidewire will be inserted through its lumen up to the renal pelvis (under fluoroscopy). A ureteral catheter will then be used to perform retrograde pyelography under fluoroscopy. If no previous stenting was performed ureteral catheterization of the treated side will be performed and guide introduction to the kidney will be performed under fluoroscopy through the ureteral meatus as commonly performed.
This part of the procedure is complete when at least one guidewire is left in place. This guidewire will remain throughout the procedure as a safety measure.

7.5.4 Ureteral dilation and access sheath

If ureteral dilation is needed, mainly when ureteral stenting wasn't performed prior to the surgery, it will be performed using consecutive ureteral dilators or ureteral balloon dilator per standard hospital practice.
Introduction of a ureteral access sheath will be introduced per standard hospital practice.

7.6 FURS procedure

A flexible ureteroscope will be inserted over a guidewire to the kidney, with or without a ureteral access sheath, as needed. Renoscopy will then be performed and all calculi will be localized.

7.6.1 Fiber introduction

After the stones are visualized, the 200 DFL fiber is introduces through the scope (either partially deflected or fully deflected, till visible in the end of scope.

7.6.2 Lithotripsy

Lithotripsy will be performed using the Lumenis Pulse 120H holmium laser system and the 200 DFL ball tip fiber using the suggested parameter range sets listed below. The treatment set used will be predefined according to the treatment group the subject was randomized to.

Task	Group I (stone breaking)	Group II (stone dusting)
Energy per pulse	1 - 2.0 J	0.2 - 0.5 J
Frequency	10 – 30 Hz	70 – 80 Hz
Maximum power possible	40 W*	40 W*

- Do not exceed the maximum 40W energy

7.6.3 Stone clearance

In all stages of the procedure, stone fragments extraction may be assisted, if needed by the use of baskets, forceps or saline flushing. Use of such accessories will be recorded.

At the end of stone fragmentation procedure, the renal pelvis will be inspected again and a “stone-free status” will be determined by the surgeon. Remnant fragments of 1 mm will be included under the “stone-free status” category. Complete stone clearance will be confirmed by intraoperative fluoroscopy. Finally, the ureter will also be inspected ureteroscopically and fluoroscopically with the administration of contrast medium to detect possible urine extravagation and remnant stone fragments.

7.6.4 Stent placement

A double-J ureter catheter may be introduced, per standard hospital practice.

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 following the procedure for a follow-up visit to assess stone clearance 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. Continuous variables will be compared between the two groups using independent samples Student's t-test or Mann-Whitney U test. A p-value < 0.05 will be considered as significant.

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 [12].

8.2 Interim analysis

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. Treatment safety and both primary and secondary endpoints will be analyzed following the completion of all study subjects follow-up period.

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:

1. led to death,
2. led to serious deterioration in the health of the subject, that either resulted in
   - 2.1. a life-threatening illness or injury, or
   - 2.2. a permanent impairment of a body structure or a body function, or
   - 2.3. in-patient or prolonged hospitalization, or
   - 2.4. medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,
3. 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 lithotripsy 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 FURS procedure performed as part of this study and as established in the literature are noted below [11]. These complications are related to FURS, whether or not lithotripsy is performed, and regardless of the method that is used for either removal or fragmentation of the stone.

- Intraoperative complications: bleeding, perforation of the ureter or renal pelvis wall, ureteral avulsion, subcapsular hematoma
- Postoperative complications: urinary tract infection, hydronephrosis, colic pain, ureteral strictures, steinstrasse

9.3.2 Anticipated Device Related Adverse Events

The potential risks related to the system may include: kidney perforation, lacerations and hematomas. 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 fragmentation of upper renal stones has been shown to be safe and effective with a very low rate of complications [77].

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 200 micron fiber with flexible ureteroscopes.

9.3.3 Anticipated Benefits

Holmium laser energy has been shown to be able to fragment any stone composition. Due to the flexibility of the delivery device (fiber) any location in the kidney collecting system can be reached. Combining these advantages with the ability to fragment the stone into particles that will wash out naturally and do not require retrieval, as well as increased efficiency due to reduced movement of the stone during the procedure may lead to reduced procedure time and procedure complications as compared to the commonly used parameters used for lithotripsy.

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/her 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.

- Eligibility Form
- Pre-treatment Evaluation Form
    - Demographic
    - General medical history
    - Specific medical history
- Randomization Form
- Treatment information form
- Post Treatment Information Forms (follow-up forms)
- Subjective assessment Forms
- Adverse Event Form
- Study completion Form

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. The device along with associated delivery and accessories are not to be used for other non-research subjects during the conduct of the evaluation.

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.
- Clinical photographs stored on CD-ROM or similar electronic media.
- 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

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12 Abbreviations and Terms

PCNL	Percutaneous Nephrolithotomy
FURS	Flexible ureteroscopic renal surgery
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
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**
Subject assessment (ICF, medical history, demographics, inclusion/exclusion evaluation)	X			
Imaging	X (CT and / or X-ray)			X (CT and / or X-ray)
Blood analysis (CBC & BMP) and urine analysis	X		X	X
Urine culture (if applicable)	X			X
Physician Subjective Procedure questionnaire		X		
Adverse Event Assessment		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 _____