Study of an Enhanced Lithotripsy System (ELS) in the Treatment of Urinary Stone Disease (STONES)

Protocol Number: 2018-01
Version 2.0

Dated July 10, 2019

Protocol Signature Page

Investigator's statement

I agree to conduct this clinical investigation in accordance with the design and specific provisions of this protocol; modifications to the study are acceptable only with a mutually agreed upon protocol amendment as approved by the sponsor and ethics review board. I agree to await ethics review board approval of the protocol and informed consent before initiating the study, to obtain consent from participants prior to their enrollment in the study, to collect and record data as required by the protocol and electronic case report forms, and to maintain study documents for the period of time required.

Confidential

This document contains confidential information belonging to Applaud Medical Inc, except as may be otherwise agreed to in writing, by accepting or reviewing these materials, I agree to hold such information in confidence and not to disclose it to others (except where required by applicable law), nor use it for unauthorized purposes.

Investigator's signature	Date of signature

Contents

PROTOCOL SYNOPSIS:

Title	Study of an Enhanced Lithotripsy System (ELS) in the Treatment of Urinary Stone Disease (STONES)
Protocol ID	2018-01
Study Device	Enhanced Lithotripsy System (ELS™)
Indications for Use Statement	Fragmentation of urinary stones in the renal pelvis and ureter (upper, middle, and lower ureter)
Study Design	Prospective, single-arm, multi-center safety and efficacy trial
Purpose	The purpose of this study is to demonstrate the safety and performance of ELS in participants with a urinary stone within the renal pelvis and/or ureter
Study Population	Participants who are diagnosed with a stone in the renal pelvis or ureter and who meet the inclusion/exclusion criteria
Inclusion Criteria	1. Male or female aged ≥ 18 years 2. Provides written informed consent 3. Understands and accepts the study requirements 4. One urinary stone eligible for treatment (minimum) that is: a) apparent on a computed tomography (CT) scan within 14 days prior to study enrollment b) located within the renal pelvis or ureter c) is ≥ 3 mm in all dimensions d) is ≤ 10 mm in maximum dimension and has area <56 mm^2 as estimated by pre-procedure CT 5. Participants with two or more stones in one or both kidneys are admissible and must meet the following inclusion criteria: a) Number of stones (> 3 mm) present on treated side is 2 or less b) Untreated stones must not be anticipated to require treatment within 30 days of enrollment, as determined by the investigator
Exclusion Criteria	1. Age less than 18 years of age or over 75 years of age 2. Diagnosis of radiolucent stones 3. History of cystinuria 4. Urine pH below 5.5 5. Current untreated urinary tract infection 6. Pregnancy 7. Vulnerable individuals (mentally disabled, physically disabled, prisoner, etc.) 8. Enrollment in another research study or previous participation within 30 days of enrollment.

	9. Participant has planned general anesthesia during index procedure with American Society of Anesthesiologists (ASA) physical classification level of 3 or greater 10. Known sensitivity to possible medications used before, during, or after the ELS procedure, including but not limited to the following: sedative agents, general anaesthetics, topical anaesthetics, and opioid analgesics 11. Coagulation abnormality or taking prescription anticoagulants that cannot be stopped during treatment. Aspirin usage will be discontinued at least 7 days prior to enrollment at the discretion of the attending physician 12. Mobility issues - unable to comfortably lie still for up to 120 minutes or unable to roll from back to side 13. Known hypersensitivity to conductivity gel 14. Body mass index (BMI) ≥ 35 unless anticipated skin to stone distance (anticipated distance from site of ELS treatment head to stone per pre-operative CT) is < 135 mm 15. Implanted spinal cord neurostimulator intrathecal pump or any device that may interfere with energy transmission 16. Participant has open wounds, lesions, dermatitis, or ischemic tissues in the treatment area 17. Participant has had a major surgery that removed tissue around the spinal cord (e.g. a laminectomy) within the treatment area 18. Participant will undergo treatment of a stone located in the distal ureter and has previous hernia repair or surgical mesh implanted in the inguinal/hypogastric regions
Sample Size	Up to 75 participants will be enrolled to achieve approximately 58 participants that are evaluable for the primary endpoint
Enrollment period/Timeline	February 2019 through January 2020 (11 months)
Number of sites	Up to eight sites. Participating countries include Australia and New Zealand
Follow-up Schedule and Study Procedures	Participants require follow-up through 90 (± 21) days after their last ELS procedure with interim visits at Day 1, 2, 3, 7 (± 1), 14 (± 4) and 30 (± 4) days <u>Pre-procedure testing (minimum):</u> a. Urinalysis b. Urine culture c. Serum creatinine d. Computed Tomography (CT) scan (non-contrast) within the last 14 days showing location, radiodensity and size of stone e. Assessment of pain medication intake f. Pain assessment g. An x-ray KUB is recommended if participant is suspected to have radiolucent stones and CT scout film is not available or suitable for use

	<u>During Procedure (up to 2 ELS treatments):</u> Cystoscopy with local anaesthesia and light or moderate sedation or light general anaesthesia (investigator's discretion), placement of ureteral catheter, periodic fluoroscopic and/or diagnostic ultrasound imaging (at investigator's discretion), intraluminal ureteral placement of ELS Acoustic Enhancer material and administration of acoustic energy. Multiple repetitions of ELS Acoustic Enhancer placement-insonation cycle will be performed <u>Follow-up:</u> 1, 2, 3, 7 days (telephone follow-up): Assess pain and pain medications, evaluate for AEs 14 (± 4) days (on site exam): KUB X-ray and ultrasound; physical exam; assess pain and pain medications; urine culture; evaluate for AEs; Assess for eligibility for 2nd ELS Treatment (i.e. treated stone/fragment is ≥ 3 mm and subject remains eligible per I/E criteria) 30 (± 4) days after last ELS procedure: CT scan (non-contrast) to evaluate stone status; physical exam; assess pain and pain medications; evaluate for AEs; serum creatinine; Assess for eligibility for 2nd ELS Treatment Treatment 2 (if necessary): Repeat ELS treatment if subject meets eligibility criteria (i.e. treated stone/fragment is ≥ 3 mm and subject remains eligible per I/E criteria). If performed, repeat Day 1, 2, 3, 7, 14 & 30 Follow-Up visits 90 (± 21) days: physical exam; serum creatinine; evaluate for AEs and record medications; renal-bladder ultrasound for safety assessment
Primary Endpoint	Treatment success: Proportion of study participants who, after up to 2 ELS treatments, have a complete absence of stones or with any residual fragments measuring less than 3 mm in the largest dimension as assessed by follow-up imaging through 30 day follow-up after last ELS procedure
Secondary Endpoints	• Proportion of participants with Serious Device and/or Serious Procedure-Related AEs from initial ELS Treatment through 30 days following last ELS treatment • Proportion of participants with Serious Device and/or Serious Procedure-Related AEs from initial ELS Treatment through 90 days following last ELS treatment • All AEs & SAEs from initial ELS Treatment through 30 days following last ELS treatment • All AEs & SAEs from initial ELS Treatment through 90 days following last ELS treatment • Participant satisfaction at 30 day follow-up following last ELS treatment
Other Observations	• Pain scores will be assessed using a validated pain scale, summarized and tabulated by visit, including subgroups of

	participants with pain versus no pain at baseline, and grouped by pain medication usage • Use and quantity of pain medication for managing stone-associated pain, including timing and type of medication, will be tabulated • The anaesthesia regimen used during ELS procedures (e.g. general/local) will be tabulated • Procedural data will be tabulated • Length of hospital stay will be tabulated • Stones and stone fragments recovered through post-ELS treatment urine straining will be characterized for chemical composition
Study Success Criteria	The observed treatment success rate as defined in the proposed study will be assessed against a literature reference rate of 63.96% to evaluate similarity of the study outcomes to published performance. The relevant hypothesis test will be conducted by computing the 95% exact confidence interval on the study success rate. Note: this is a reference rate that was derived from the AUA Guidelines (2016) and is based upon treatment of stones less than or equal to 10 mm within the ureter by shockwave lithotripsy

GLOSSARY OF ABBREVIATIONS:

ABBREVIATION	TERM
AE	Adverse Event
ASA	American Society of Anaesthesiologists
ASADE	Anticipated Serious Adverse Device Effect
BMI	Body Mass Index
CIP	Clinical Investigation Plan
CIRF	Clinically Insignificant Remaining Fragments
CT	Computed Tomography
DMP	Data Management Plan
EC	Ethics Committee
eCRF	Electronic Case Report Form
ELS	Enhanced Lithotripsy System
SWL	Shock Wave Lithotripsy
IFU	Instructions for Use
IRB	Institutional Review Board
ISO	International Organization for Standardization
KUB	Kidney, ureter & bladder
PNL	Percutaneous Nephrolithotomy
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SWL	Shockwave Lithotripsy
TGA	Therapeutic Goods Administration
UADE	Unanticipated Adverse Device Effect
USADE	Unanticipated Serious Adverse Device Effect
URS	Ureteroscopy

1. INTRODUCTION

1.1 Background Information

Urinary stone disease is a prominent and growing public health priority, both in the U.S. and globally [1], [2]. Lifetime prevalence of urinary stones is approximately 1 in 11 in the U.S. general population [1], with rates of emergency department visits for urinary stone disease more than doubling in the past twenty-five years [3]. Some one-half of patients with previous urinary stones experience a recurrence within 10 years [2], [4]. Stone disease is associated with significant morbidity: many stones require surgical intervention, while those that pass without surgery routinely take many weeks to do so, a period of debilitating pain and the risk, among others, of life-threatening sepsis from stone-associated obstruction [5], [6].

Stones typically form in the renal collecting system (as kidney stones), with onset of severe—and frequently excruciating—flank pain and other symptoms triggered by one or more stones passing from the kidney into the ureter and being retained at a narrowing such as the ureteropelvic junction, over the iliac vessels, or at the ureteric meatus [5]. Imaging-based diagnosis of urinary stones is typically by non-contrast CT, although ultrasound can be effective as a radiation-sparing diagnostic imaging modality [7]. Clinical management of ureteric stones includes observation, typically with pain management; observation with medical expulsive therapy; and surgical exposure of ureter and endoscopic stone removal (ureterolithotomy); factors including ureteral anatomy and degree of obstruction; symptom severity and symptom manageability through pain medication; occurrence of infection or other comorbidities; and stone size, composition, and location are taken into account in physician-patient decision making around the urgency of surgical intervention and evaluating among possible surgical intervention options [5], [8].

Current mainstream minimally invasive surgical interventions for ureteric stones—primarily shockwave lithotripsy (SWL), ureteroscopy (URS) with or without laser lithotripsy, and percutaneous nephrolithotomy (PCNL)—can be effective in shortening the time required for many patients to become stone-free, while at the same time having significant drawbacks. PCNL, the most invasive of the mainstream non-open-surgery methods, is associated with risk of injury to organs nearby the kidney and ureter including the lung, liver, spleen and bowel and has been reported to have a 4% transfusion rate [9]. URS almost invariably entails general anesthesia, with its associated risks for the patient as well as its implications for healthcare system cost and need for potentially scarce operating theatre infrastructure; the ureteral manipulation in URS, moreover, is associated with long recovery times and significant post-operative pain as well as risk of urinary stricture and other complications [6], [10]. These downsides of URS are counterbalanced by the procedure having generally high efficacy even after only a single treatment [11], although recent studies have noted that, for patients with stones larger than 5 mm, some 40-55% in fact have residual fragments 30 days after URS with laser lithotripsy [12], [13].

SWL avoids both PCNL's percutaneous access and URS's ureteral manipulation, allowing it to be performed without general anesthesia and conferring further advantages—potentially significant ones—in minimizing recovery time [14], [15]. SWL's noninvasiveness is conducive to multiple treatments of a single stone over the course of several weeks without undue patient burden; the widely cited SWL treatment success rate of 64% [11], [16]

reflects as many as three sequential SWL treatments. SWL is associated with rates of gross hematuria around 20% and reports of significant intra- and post-operative pain from the large (up to 3000) number of intense shockwaves administered to the patient by the SWL system's treatment head [8], [17], [18], partially offsetting the advantages associated with SWL's noninvasiveness. Taking into account the many and varied trade-offs with both URS and SWL, guidelines committees in the U.S., Europe, and elsewhere have generally elected to continue to recommend both as suitable first-line surgical interventions for most stone patients [6], [11].

For patients for whom immediate surgical intervention is not an absolute imperative, the prospect of achieving stone-free status quickly through URS or SWL is evaluated against the risks and costs of these interventions. Compelling intermediate options between surgical intervention (by URS or SWL) and watchful waiting with pain management are highly prized by urologists, patients and other healthcare system stakeholders, but have remained elusive. Therapeutic regimens referred to as medical expulsive therapy (MET), typically incorporating the α-adrenoceptor antagonist Tamsulosin and the calcium channel stabilizer nifedipine (a) can be used with the intention of increasing the likelihood of, and shortening the time from symptom onset until, spontaneous stone passage [6], [11]. Accumulating evidence from recent large-scale clinical trials, however, increasingly suggests that current mainstream MET regimens have little effect for most patients [19], [20].

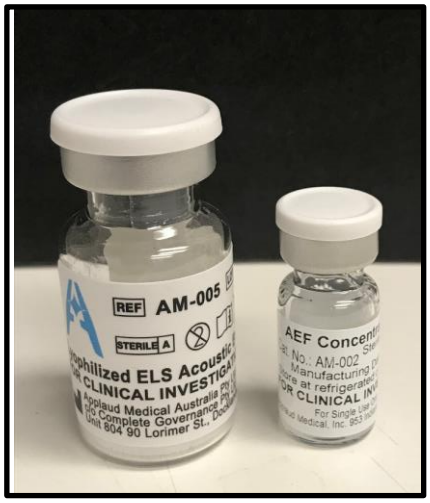
The Enhanced Lithotripsy System is intended as a compelling new option for helping ureteral stone patients become stone-free quickly, comfortably, and safely. Taking into account the shared reliance among ELS and SWL on an extracorporeal acoustic energy source and other key similarities between the two procedures, SWL is considered to be the closest benchmark treatment option for ELS. The AUA Endourological Society Guideline for Surgical Management of Stones [11] has formed the basis of Applaud Medical's clinical evaluation plan and is an important reference for understanding performance. The European Association of Urology (EAU) Urolithiasis Guidelines Panel has published a thorough review of the state of the art to inform urologists and facilitate evidence-based clinical management [6]. These two important guidelines can be referenced for the current state of the art for urinary stone treatment.

It should be noted that the above-referenced 64% SWL treatment success estimate includes multiple studies with mixed imaging modalities and heterogeneous residual fragment size thresholds.

1.2 Introduction to Enhanced Lithotripsy System (ELS)

The ELS is a medical device system designed to be used to treat urinary stone patients in minimally invasive surgical procedures. As illustrated in Figure 1, the ELS comprises the ELS Console and ELS Acoustic Enhancer. The ELS console includes the ELS treatment head, which connects to the main console body through a cable and is designed to emit a beam of low-intensity acoustic energy in the ultrasound range of the acoustic energy spectrum. ELS Acoustic Enhancer is a single-use component supplied in vials and designed to be placed in the patient's urine via a ureteral catheter. As discussed in further detail below, the acoustic energy beam emanating from the face of the ELS treatment head mechanically energizes microparticles contained within ELS Acoustic Enhancer, causing the microparticles to emit

ELS Console, including base and treatment head



ELS Acoustic Enhancer

Figure 1: Components of the Enhanced Lithotripsy System (ELS). At left, the ELS Console, including the base unit and treatment head. At right, the two supplied forms of ELS Acoustic Enhancer.

short-range shockwaves that progressively erode, pit and fragment the stone. While neither the energy beam nor the microparticles by themselves have any significant effect on a urinary stone, the combination of the two is designed to reduce a stone (or stones) to dust and small fragments easily passed by the patient through urination in a procedure lasting less than an hour.

Refer to Section 3.0 for a more in-depth description and also refer to the IFU for technical details and procedure for operation.

Unlike other urinary stone interventions requiring sedation or general anaesthesia, the ELS treatment requires only numbing of the tip of the urethra, making it easily performed in diverse clinical settings. When compared to current available treatment options for ureteric colic and stone disease, ELS offers benefits when compared to available interventional treatment options (SWL and URS, refer to Table 1).

Table 1: Benefits of ELS as compared to select mainstream current surgical interventions for ureteral stones

Treatment Benefit	SWL	URS	ELS
Spares patients acute renal and extrarenal injury from intense shockwaves	–	✓	✓
No need for stenting for swelling associated with ureteral manipulation	✓	–	✓
No need for general anaesthesia	✓	–	✓
No real-time visualization required	–	–	✓
Small size of the device facilitates transport from one treatment room to another	–	–	✓

2. RATIONALE FOR CURRENT STUDY

2.1 Study objective

The objective of this study is to quantify the safety and performance of ELS in participants with a urinary stone within the renal pelvis and/or ureter.

2.2 Study rationale

Applaud Medical will leverage the data generated from this confirmatory study for premarket marketing applications and the overall clinical evaluation of the ELS within the specified indication. This study introduces minor changes to the design of ELS and refinements of the IFU which were determined from the experience gained from the ongoing multi-center, prospective feasibility clinical study in Australia (Protocol number 2017-03) that includes a broader patient population than the proposed study. This study also introduces a performance-based primary endpoint to prospectively test the statistical hypothesis that the treatment success rate meets a performance goal.

Previous studies, including ELS 2017-03 and studies in India, have successfully established the safe use of ELS, as demonstrated by a 0% rate of device-related serious adverse events (0 events from 13 participants). Refer to the Investigator's Brochure for a comprehensive review of information Applaud Medical has to support the use of ELS.

3. Device Description

3.1 Enhanced Lithotripsy System

The ELS Console

The ELS Console is a precision-engineered unit designed to produce an acoustic energy beam that can be directed toward the affected portion of the upper urinary tract of a patient with a urinary stone. The console body encloses a sophisticated amplifier module along with other subsystems, such as a power supply, as well as user interface. Cabled into the ELS console body is an oblong component with a flat face designed to be positioned against the skin of a patient's lower back or inguinal region. This ELS console component is referred to as the ELS Treatment Head.

Figure 2: ELS Console: front and side views. The console includes a treatment head designed to direct a beam of low-intensity acoustic energy directed toward the affected kidney or ureter from an application site on the body surface.

The ELS console is tabletop size, measuring 28cm x 26cm x 21 cm, and weighs 3.4 kg. The user interface includes a high-visibility touchscreen, a large physical button for engaging the acoustic energy beam, and a circumferential multicolor light band. The system also includes a foot pedal that can be used during the procedure at the user's discretion. Front- and side-view photos of the ELS console are shown in Figure 2.

The ELS treatment head resembles, in some ways, a standard diagnostic ultrasound probe. As in a diagnostic ultrasound probe, the skin-contacting surface is designed to vibrate in the ultrasonic regime of the acoustic energy spectrum. While most diagnostic ultrasound is in the frequency range from 1 MHz to 20 MHz, the vibrations in the ELS treatment head face are at a slightly lower frequency, around 500 kHz, still well above the upper end of the audible range at 20 kHz. The treatment head connects by a cable to the ELS console base unit.

The vibration of the face of the ELS treatment head during a procedure is precisely engineered so that when the treatment head is positioned against the patient's skin, the acoustic energy passing into the patient is beam-like in form, maintaining approximately the treatment head's cross-section as it passes through the patient's anatomy (Figure 3). This type of acoustic energy is referred to as a *quasi-collimated beam*. The shape of the beam is designed to facilitate insonating the affected portion of the patient's upper urinary tract with treatment head positioning based only on the urologist's examination of pre-operative scans along with reference to bony landmarks and other superficial anatomical features. As will be further described below, the frequency of the acoustic energy is designed to optimally energize microparticles within ELS Acoustic Enhancer.

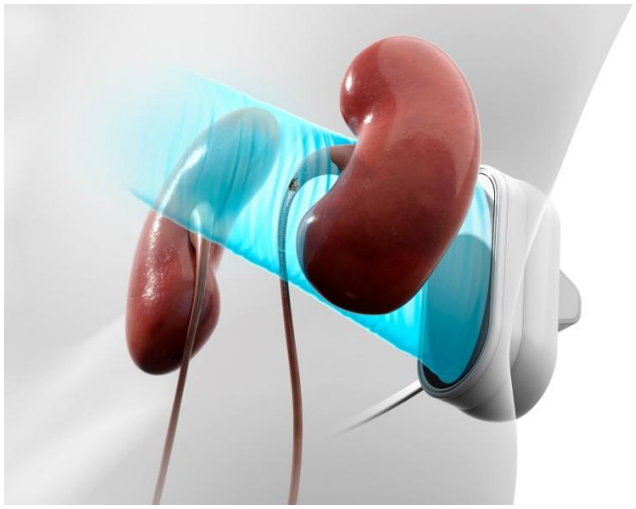


Figure 3: The ELS treatment head produces a quasi-collimated beam of acoustic energy, facilitating insonation of the affected portion of the patient's upper urinary tract without real-time imaging.

ELS Acoustic Enhancer

ELS Acoustic Enhancer is a liquid containing micron-scale particles within a matrix consisting mostly of water. The presence of the particles gives Acoustic Enhancer a milky appearance Figure 4, although the particles are sufficiently small and sparse as to have a minimal effect on viscosity; Acoustic Enhancer's viscosity is similar to that of water alone. As will also be further described below, to use Acoustic Enhancer in a urinary stone procedure, multiple small volumes of Acoustic Enhancer are placed in the patient's urine over the course of the procedure. Whereas the low intensity of the acoustic energy beam produced by the ELS treatment head precludes its having a significant effect on stones by itself, the energy beam can energize ELS Acoustic Enhancer microparticles in a way that brings about erosion, pitting and fragmentation. Acoustic Enhancer's comparatively low viscosity facilitates the placement of Acoustic Enhancer in the patient's urine by attaching a syringe to a cystoscopically positioned 5 Fr catheter.

Figure 4: ELS Acoustic Enhancer, drawn up into a syringe and ready for placement in the affected ureter.

Each Acoustic Enhancer microparticle has a perfluoroalkane gas core with a lipid shell. Acoustic Enhancer lipids closely resembling naturally occurring lung surfactants, while perfluoroalkane gases are routinely used as tamponades in surgery to correct retinal detachment. The microparticle lipid shell has also been engineered to mimic certain structures in the naturally occurring category of molecules known as pyrophosphates. Collectively, the design of the microparticle structure confers two key functions: a capacity to dramatically expand and contract in response to changes in the local pressure environment and a tendency to accumulate on the surfaces of urinary stones containing biomineralized calcium.

ELS Acoustic Enhancer is supplied in vials in one of two product forms: a liquid formulation referred to as ELS Acoustic Enhancer Concentrate (AM-002) and a lyophilized formulation referred to as Lyophilized ELS Acoustic Enhancer (AM-005). ELS Acoustic Enhancer material is prepared at the clinical site immediately prior to use through dilution and mixing of the supplied product. See the Appendix of the IFU for preparation instructions of the ELS Acoustic Enhancer material.

3.2 Device Accountability

All investigational product will be labelled as being for Clinical Investigational Use Only. Device accountability will be maintained on a dedicated log at the site of product storage including the date and quantities of ELS components received, dispensed and returned. Information regarding the specific identification numbers for ELS components used are to be recorded onto the appropriate eCRF for each study participant undergoing the treatment procedure throughout the course of the study. Only an appropriately qualified person may dispense the study device to participants in the study. The study device is to be used in accordance with

the protocol under the direct supervision of the study investigator. Components of the ELS must be stored and used per the instructions given in the IFU.

All supplies are to be returned to the sponsor or designee as soon as practical upon request by the sponsor or designee or upon completion of the study. ELS accounting procedures must be completed before the study is considered terminated.

4. STUDY DESIGN

4.1 Study Design

This study is a prospective, single-arm, multicentre confirmatory study.

4.2 Number of Participants

A total of up to 75 participants presenting with urinary stones and meeting the inclusion/exclusion criteria will be recruited for this study. This will include male and female participants with urinary stone disease.

4.3 Eligibility Criteria

4.3.1 Inclusion Criteria

1. Participant is ≥ 18 years
2. Participants has voluntarily signed/dated the informed consent form.
3. Participant understands and accepts the study requirements.
4. Participant has one urinary stone eligible for treatment (minimum) that is:
    a. apparent on a computed tomography (CT) scan within 14 days prior to study enrollment,
    b. located within the renal pelvis or ureter,
    and,
    c. is ≥ 3 mm in all dimensions
    d. is ≤ 10 mm in maximum dimension and has area <56 mm^2, as estimated by pre-procedure CT (area calculation: product of mathematical constant pi and the square of the radius for a stone appearing approximately circular on CT; product of long dimension and short dimension for a stone appearing oblong on CT)
5. Participants with additional stone(s) in one or both kidneys are admissible and must meet the following inclusion criteria:
    a. Number of stones (≥3 mm) present on treated side is 2 or less
    b. Untreated stones must not be anticipated to require treatment within 30 days of enrollment, as determined by the investigator

4.3.2 Exclusion Criteria

1. Participant is less than 18 years of age or over 75 years of age

2. Participant is diagnosed with radiolucent stones
3. Participant has history of cystinuria
4. Participant has urine pH below 5.5
5. Participant has an untreated urinary tract infection
6. Participant is pregnant
7. Participant is a vulnerable individual (mentally disabled, physically disabled, prisoner, etc.)
8. Participant is enrolled in another research study or has previous participation within 30 days of enrollment.
9. Participant has planned general anesthesia during index procedure with American Society of Anesthesiologists (ASA) physical classification level of 3 or greater.
10. Participant has known sensitivity to possible medications used before, during, or after the ELS procedure, including but not limited to the following: sedative agents, general anaesthetics, topical anaesthetics, and opioid analgesics.
11. Participant has coagulation abnormality or taking prescription anticoagulants that cannot be stopped during treatment. Aspirin (ASA) usage will be discontinued at least 7 days prior to enrollment at the discretion of the attending physician.
12. Participant has mobility issues and is unable to comfortably lie still for up to 120 minutes or unable to roll from back to side.
13. Participant has known hypersensitivity to conductivity gel.
14. Participant has body mass index (BMI) ≥ 35 unless anticipated skin to stone distance (anticipated distance from site of ELS treatment head to stone per pre-operative CT) is < 135 mm.
15. Participant has an implanted spinal cord neurostimulator, intrathecal pump or any device that may interfere with energy transmission
16. Participant has open wounds, lesions, dermatitis, or ischemic tissues in the treatment area.
17. Participant has had a major surgery that removed tissue around the spinal cord (e.g. a laminectomy) within the treatment area.
18. Participant will undergo treatment of a stone located in the distal ureter and has previous hernia repair or surgical mesh implanted in the inguinal/hypogastric regions.

4.4 Screening and Enrollment Procedures

4.4.1 Eligibility review

Patients presenting with urinary stone disease will be screened for this study. Initial eligibility criteria for the study will be determined by the investigator based upon review of their medical history, presentation and diagnostic imaging. If the participant appears to meet the study criteria, then the investigator will explain the investigational treatment, provide information regarding the potential risks and benefits, explain the follow-up requirements and obtain written informed consent per the informed consent process.

4.4.2 Informed consent process

The investigator, or authorised designee, is responsible for obtaining written informed consent from each participant using the IRB/EC approved consent form prior to initiation of any study specific assessments or procedures.

Potential study participants will be given adequate time to review the consent form, ask questions, and consider their options before being asked to sign the form. Informed consent shall be obtained under circumstances that minimise the possibility of coercion or undue influence. The information that is given to the participant shall be in language understandable to the participant. The participant will not be led to believe that they are waiving their rights as a study participant or the liability of the sponsor or investigator.

Study participants will be informed that the sponsor and regulatory authorities will have access to personally identifying information for the purposes of monitoring data against source documentation. However, all data stored and presented by the sponsor will be de-identified. The participant will be asked to sign one copy of the informed consent form. The original, signed document remains at the investigational site and a copy (or second signed original) is given to the participant.

If new information regarding the investigational device becomes available and/or the clinical investigational plan (CIP) changes and the information can significantly affect a participant's future health and medical care, participants will be informed of the information and may be asked to sign a revised informed consent form.

Any modification to the study sample informed consent form made by the Investigational Site must be approved by the sponsor and the IRB/EC before use. Each Investigational Site will provide the sponsor with a copy of the EC approved consent forms.

4.4.3 Screening assessments

Refer to Section 6.1 for screening assessments.

4.4.4 Point of enrollment

Enrollment is defined as that time when the participant signs the informed consent form and is then eligible to begin screening assessments. Participants who fail to meet screening assessment requirements (see Section 6.1) will be counted as a screen failure and will not be treated with the ELS. Screen failures will be documented at the site on a screening log.

Each enrolled study participant will be assigned a unique participant identification number at the time of enrollment. This participant identification number will be retained throughout the study. Investigational site will keep a log that notes the participant’s name and corresponding participant identification number. All electronic case report forms (eCRFs) will be tracked, evaluated, and stored using only the participant ID number. No personal identifying information will be included on the eCRFs.

4.5 Participant Withdrawal or Discontinuation

Study participants may withdraw from the study at any time at their request and may also be discontinued at the physician's discretion or for other event/s related to the participant's health or welfare, including study participants' non-compliance with pre-study requirements. Participation in the study will cease immediately if the study participant requests to be terminated from the study.

5. STUDY ENDPOINTS

5.1 Primary Endpoint

Treatment success: Proportion of study participants who are successfully treated following up to 2 ELS treatments [defined as absence of stones or with remaining fragments of less than 3 mm on the largest dimension by follow-up imaging through 30 day visit after last ELS procedure].

5.2 Secondary Endpoints

- Proportion of participants with Serious Device and/or Serious Procedure-Related AEs from initial ELS Treatment through 30 days following last ELS treatment.
- Proportion of participants with Serious Device and/or Serious Procedure-Related AEs from initial ELS Treatment through 90 days following last ELS treatment.
- All AEs & SAEs from initial ELS Treatment through 30 days following last ELS treatment
- All AEs & SAEs from initial ELS Treatment through 90 days following last ELS treatment
- Participant satisfaction at 30 day follow-up following last ELS treatment

5.3 Other Observations

- Pain scores will be summarized and tabulated by visit, including subgroups of participants with pain versus no pain at baseline.
- Use and quantity of pain medication for managing stone-associated pain will be characterized by timing and type of medication.
- Proportion of participants who underwent various anaesthesia regimens (e.g. general/local)
- Procedural data will be tabulated
- Length of hospital stay
- Stones that are retained will be characterized

6. STUDY VISIT SCHEDULE AND PROCEDURES

6.1 Screening

Screening for this study includes the following assessments. Refer to the Schedule of Assessments Table 2: Schedule of Events.

- Participants will undergo a CT scan within 14 days of the ELS procedure to estimate the approximate stone size (in mm), radiodensity and location (e.g. renal pelvis, distal ureter). Investigators should perform additional imaging prior to ELS treatment, particularly if symptoms have changed or if a participant is in the process of ureteral stone passage, because a change in stone position may influence treatment approach. This additional imaging can include KUB x-ray, renal/bladder US, or CT depending on investigator's discretion. If CT imaging is performed more than once, the CT imaging that occurs just prior to the first ELS procedure will be counted as baseline.
- The scout film acquired during the baseline CT is recommended to be used to document radiopacity for participants suspected with radiolucent stone(s). A KUB x-ray may be performed if the scout film is not available for this purpose.
- Participants will undergo a physical exam and medical history.
- For women of child-bearing age, participants will undergo a pregnancy test (if necessary).
- Participants will undergo a urinalysis and urine culture.
- Serum creatinine will be collected to review renal function.
- Prior to treatment, participant usage of pain medication (type, dose and frequency) will be documented, whether such pain medications were prescribed in connection with the scheduled study procedure or otherwise.
- Prior to treatment, participant usage of anticoagulants (type, dose and frequency) will be documented.
- Within 1 day of the ELS Treatment, study participants will also be asked to complete a pain questionnaire (pain score). The pain questionnaire may be completed on the same day as ELS Treatment before the treatment takes place.

6.2 Study Visits

Refer to Table 2: Schedule of Events.

6.2.1 ELS Treatment

The investigator and designated co-investigator(s) will be trained to the IFU before performing the investigational procedure (ELS treatment). Refer to the IFU for a complete description of the ELS treatment procedures.

ELS Treatment is expected to take between around 30 minutes and around 60 minutes, depending on stone size. Additional time may be required before and after treatment. The procedure will be performed using local anaesthesia and light or moderate sedation, or a light general anaesthesia as per investigator discretion, local regulations and standard clinical practice. During treatment, study participants will be monitored for clinically significant dysrhythmia (i.e. cardiac arrhythmia seen on ECG) herein defined as any alteration in cardiac rate and/or rhythm that necessitates directed intervention including the administration of antiarrhythmic agents, cardioversion, defibrillation, and/or physical manipulations such as vagal maneuvers.

The ELS treatment steps are described in detail within the IFU. Investigators are trained to the IFU before ELS Treatment.

At investigator's discretion or as directed by IFU, fluoroscopic or diagnostic ultrasound imaging may be used. Imaging that is used to document status of the stone, urinary tract, an adverse event or device deficiency shall be recorded and collected by research staff.

Upon completion of ELS Treatment, remove the 5 Fr catheter and initiate standard retrograde pyelogram recovery and discharge procedures.

AEs will be recorded.

6.2.2 Discharge

Study participants will follow the site-specific discharge procedure.

Study participants will be educated on methods for straining and collecting stone fragments. Following the procedure, they will be given a jug and sieve for straining their urine, an instruction sheet and a collection kit. They will be advised how to filter their urine, dry any collected stone fragments and store these fragments until directed to take back to their next clinic or doctor's appointment.

6.2.3 Follow-up at Days 1, 2 and 3

On Day 1, Day 2 and Day 3 post-procedure, follow-up visits will be conducted by phone (at a minimum).

- AEs since last observation will be documented (see Adverse Events section).
- Ensure participant is collecting any stone fragments obtained through urine straining.
- Ask about usage of pain medications (type, dose and frequency), whether such pain medications were prescribed in connection with the procedure or otherwise.
- Complete pain questionnaire (pain score) on Days 1, 2 and 3

6.2.4 Follow-up at Day 7 (7 days +/- 1 day after each ELS procedure)

Day 7 follow-up will be conducted by phone.

- Document any reported AEs since last observation was performed (see Adverse Events section below).
- Ensure participant is collecting any stone fragments obtained through urine straining.
- Ask about usage of pain medications (type, dose and frequency), whether such pain medications were prescribed in connection with the procedure or otherwise.
- Complete pain questionnaire (pain score).

6.2.5 Follow-up at Day 14 (14 days +/- 4 days after each ELS procedure)

- The participant will undergo a physical examination.
- The following imaging will be performed to observe the status of the ureter and stone:
    - Collect a KUB X-ray
    - Perform a renal bladder ultrasound to evaluate status of ureter and stone or residual fragments (if any).

  Per investigator discretion, a low-dose, non-contrast CT to evaluate status of ureter and stone or residual fragments (if any) may be performed instead of the combination of X-ray and ultrasound.

- Document any reported AEs since last observation was performed (see Adverse Events section below).
- Collect and label any stone fragments obtained by the participant through urine straining.
- Urinalysis, including urine culture
- Ask about usage of pain medications (type, dose and frequency), whether such pain medications were prescribed in connection with the procedure or otherwise.
- Complete pain questionnaire (pain score).
- ELS Treatment eligibility will be assessed by the investigator If the remaining stone size is 3 mm or more in any dimension, the participant is eligible for one additional ELS Procedure. Refer to Section 6.2.8.

6.2.6 30-day follow-up (30 +/- 4 days after each ELS procedure)

- Participants will undergo a low-dose non-contrast CT scan to assess ureter, stone (residual fragment) size, location and radiodensity (if stone/fragment present).
- Conduct an on-site follow-up after the last ELS treatment: 1) 30 days after first ELS treatment, if first treatment was successful, or 2) 30 days after second ELS treatment, if a second treatment was performed.
- Conduct focused physical exam
- Serum creatinine to assess renal function
- Document any reported AEs since last visit (see Adverse Events section below).
- Complete pain questionnaire (pain score) and document any pain medications
- ELS Treatment eligibility will be assessed by the investigator If the remaining stone size is 3 mm or more in any dimension, the participant is eligible for one additional ELS Procedure. Refer to Section 6.2.8.

6.2.7 90-day follow-up (90 +/- 21 days after last ELS procedure)

Conduct an on-site follow-up after the last ELS treatment.

- Conduct focused physical exam
- Serum creatinine to assess renal function
- Perform diagnostic renal-bladder ultrasound to assess ureter.
- Document any reported AEs since last visit (see Adverse Events section below).
- Document concomitant medications

6.2.8 Study Exit

- Complete study exit form

6.3 Additional ELS Procedure

6.3.1 Eligibility

The participant may require an additional ELS Treatment of the urinary stone to meet the treatment success definition. Participants are eligible for retreatment if he or she meets the eligibility criteria (Section 4.3). The eligibility assessment will be performed at the Day 14 Follow-up and may be confirmed at the Day 30 Follow-up CT scan. The investigator shall document the circumstances that lead to participants that are eligible for an additional ELS

Treatment but decline, or based upon the investigator's discretion, are not suitable for an additional ELS Treatment.

6.3.2 Scheduling

The additional ELS Treatment is recommended to be performed 30 days (± 14 days) from the index procedure (Day 0). When an additional ELS Treatment is performed, participants will repeat the Day 1, 2, 3, 7, 14 & 30 follow-up visits. The Day 90 Follow-up visit is expected to occur 90 +/- 21 days from the last ELS Treatment.

6.4 Non-ELS Treatment stone interventions

Participants may require intervention other than ELS Treatment to resolve their condition as it relates to their urinary stone(s) selected for ELS Treatment. This study requires one additional ELS Treatment to be performed if needed, as discussed in the section above. These additional stone interventions will be recorded on the appropriate eCRF. Adverse events will be assessed using the definitions in Section 8.1.

6.5 Analysis of collected stone fragments

The collected stone fragments will be characterized by a qualified, central laboratory to determine stone chemical composition. The composition of the stone depends on the substances in the urine causing the stone. It may be made of just one chemical compound or have different chemicals in different layers. The analysis will be done in order to help identify the chemical composition of the stone, which in turn may guide better treatment options for participants with recurrent stone formation.

Table 2: Schedule of Events

Assessment	Screening	ELS Treatment	Days 1,2, and 3 after each ELS procedure	Day 7 (+/- 1) day after each ELS procedure	Day 14 (+/- 4) days after each ELS procedure	Day 30 (+/-4) days after last ELS procedure	Day 90 (+/-21) days after last ELS procedure
Site Visit	✓	✓	By telephone	By telephone	✓	✓	✓
Informed Consent	✓						
Inclusion / Exclusion criteria	✓						
Medical History	✓						
Pregnancy test	✓						
Physical Exam	✓				✓	✓	✓
Serum Creatinine	✓					✓	✓
Urinalysis and urine culture	✓				✓		
CT scan (non-contrast)	✓ (within 14 days of ELS)					✓	
X-ray (KUB)	✓ [1]				✓		
Ultrasound (renal bladder)					✓		✓
2nd ELS Treatment Eligibility					✓[2]	✓[2]	
Participant urine straining, retaining stones for office visit		✓	✓	✓	✓	✓	
AE reporting		✓	✓	✓	✓	✓	✓
Complete Pain Questionnaire	✓ (within 1 day of ELS)		✓	✓	✓	✓	
Concomitant Meds (analgesics, alpha blockers, pain meds etc.)	✓	✓	✓	✓	✓	✓	✓
Complete Participant Satisfaction questionnaire						✓	

1: Recommended for participants suspected of having radiolucent stone(s) if CT scout film not available for use.

2: ELS procedure repeated if CT scan shows stone/fragments of 3mm or more.

7. RISKS AND BENEFITS

7.1 Potential Risks

The potential risks associated with the ELS procedure are expected to be similar or less than those of traditional SWL procedures used to treat urinary stones. Potential adverse events, which may be associated with the ELS and ELS Acoustic Enhancer material, and medications prescribed for use during these procedures include:

- Haematuria
- Pain or discomfort
- Skin redness where the treatment head is held against the body or from the belt that may be used to hold the treatment head in place
- Sensitivity/Tenderness over the treatment area
- Urinary blockage from stone fragmentation
- Bruising of tissue along the path of acoustic energy entering the body
- Urinary tract infection or inflammation
- Fever
- Mild cardiac arrhythmia could result from acoustic energy
- Bruising or damage to the kidneys, or tissue near the kidneys
- Allergic or anaphylactic reaction.
- Differential pressure risks include pressure from backflow of urine in the urinary tract system, and in rare cases rupture in the urinary tract

The procedure is also associated with potential anesthesia risks:

- Reaction to anesthesia
- Bleeding at anesthesia site
- As with any procedure performed with sedation or anaesthesia, there is risk associated that includes heart attack, stroke, and even death.

As with shock wave lithotripsy for urinary stones, the following adverse events may occur while being treated with ELS:

- Common (estimated as greater than 20% of patients)[1]
    - There may be mild bleeding (including blood in the urine) or irritation from the ELS procedure. In rare cases, transfusion may be required to address bleeding.
    - There could be pain associated with the ELS sound wave energy effects and resulting stone fragments, with placement and movement of instruments in the urinary tract, or from other aspects of the procedure.
    - There could be skin redness around where the treatment head was held during the procedure, or irritation or bruising of the skin from the belt used to hold the treatment head in place during the procedure.

[1] Estimated occurrence rates are referenced from FDA, Center for Devices and Radiological Health: Guidance for the Content of Premarket Notifications (510(k)s) for Extracorporeal Shock Wave Lithotripters Indicated for the Fragmentation of Kidney and Ureteral Calculi (August 9, 2000)

- Occasional (estimated as 1-20% of patients)
    - As with any intervention to fragment kidney stones, urinary blockage with a need for alternative treatment may occur. Blockage could be due to stone fragments after the ELS procedure. Also, the stone may be incompletely fragmented, causing urinary tract blockage. – In the case of urinary blockage, an ureteral stent or a tube in the kidney (i.e. nephrostomy tube) may be needed in order to properly relieve the obstruction.
    - There may be bruising of tissue along the path of acoustic energy entering the body through the skin of the lower back.
    - The urinary tract could become infected, or existing urinary tract infection could become worse.
    - There is a possibility of fever.
    - There may be nausea or vomiting associated with administration of anesthesia or other aspects of the ELS procedure.
- Rare (estimated as less than 1% of patients).
    - In rare instances, there could be bruising or damage to the kidneys or tissue near the kidneys, resulting in pain and requiring further treatment. In very rare instances, this could require kidney removal.
    - In rare instances, the acoustic energy could result in mild cardiac arrhythmia (irregular heartbeats).

As with other treatments for urinary stones, sloughed tissue found in or on urinary stones may be released as a result of ELS treatment. In addition, malfunction of the equipment is a possibility and the procedure may need to be rescheduled.

Possible adverse events associated with the placement of the ELS Acoustic Enhancer material in the urinary tract during treatment with the ELS:

The major risk associated with ELS Acoustic Enhancer material is an allergic (less than 1 in a 10,000 patients) or anaphylactic reaction (less than 1 in 20,000 patients). The doctor will be there to address these complications in the unlikely chance that they occur.

The placement of the ELS Acoustic Enhancer follows a standard procedure used in a common diagnostic procedure (retrograde pyelogram). As such, there is a very low risk of adverse events associated with the differential pressures in the urinary tract arising during ELS Acoustic Enhancer placement. Differential pressure risks include pressure from backflow of urine in the urinary tract system, and in rare cases rupture in the urinary tract.

As with any procedures in which cystoscopes and other instruments are inserted into the urinary tract and materials placed using a cystoscope (small tube) into the urinary tract, in very rare cases, portions of the urinary tract could become inflamed or infected. There is also the risk of inadvertently pushing a urinary stone from the urinary tract into the kidney and of ureteral perforation from passage of the ureteral catheter.

Significant new findings that may affect the participant's safety or willingness to continue in the study will be communicated to the study doctors and study participants. An updated informed consent may be administered if appropriate.

7.2 Potential Benefits

ELS achieves cavitation and fragmentation of stones using extracorporeal acoustic energy at significantly lower intensities than that used by SWL systems. This results in the following expected benefits compared to SWL and other existing urinary stone interventions:

- Negligible renal parenchymal damage.
- Minimal or negligible damage to the urothelium.
- Treatment under light or moderate sedation, or light general anaesthesia (at investigator's discretion), rather than heavy sedation or general anaesthesia.
- Respiration and other small movements by the study participant during the ELS procedure should not negatively impact safety or efficacy.

7.3 Mitigation of Risks

Risk to study participants are mitigated in this study by the following:

- All investigations are conducted by investigators who are qualified by training and experience in the treatment of participants with urinary stones and specifically trained in the use of ELS.
- All assessments are procedures performed in the controlled context of a clinical trial.
- Monitoring of the clinical trial to ensure compliance and with a focus on potential safety issues.

8. ADVERSE EVENT REPORTING

8.1 Definitions

8.1.1 Adverse Events (AE)

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

Any condition that was recorded as pre-existing is not an AE unless there is a change in the nature, severity or degree of the condition with respect to baseline.

8.1.2 Adverse Device Event (ADE)

Adverse event related to the use of an investigational medical device. This includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device.

8.1.3 Device Deficiencies

Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance.

8.1.4 Serious Adverse Events

An adverse event that:

- led to a death,
- led to a serious deterioration in the health of the participant that resulted in:
    - a life-threatening illness or injury,
    - a permanent impairment of a body structure or a body function,
    - hospitalization or prolongation of existing hospitalization,
    - medical or surgical intervention to prevent permanent impairment to body structure or function,
- led to fetal distress, fetal death, a congenital abnormality, or birth defect.

Note: Planned hospitalisation for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a SAE.

8.1.5 Serious Adverse Device Effect (SADE)

A serious adverse event (SAE) that is related to the device as described in Section 8.2 below.

8.1.6 Unanticipated Serious Adverse Device Effect (USADE)

Any serious adverse effect on health or safety, or any life-threatening problem or death caused by, or associated with a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan. All reported

events will be followed until resolution, stabilization or 90 days after the last participant enrolled has completed the trial, whichever occurs first.

8.2 Adverse Event Relationship

For all collected AEs, the clinician who examines and evaluates the study participant will determine the AE's causality based on temporal relationship and his/her clinical judgment. Anticipated AEs are listed in Section 7.1. The investigator will use the definitions shown in the tables below to assess the relationship of the adverse event to the use of study device, and to assess the relationship of the adverse event to the study procedure. For purposes of this study, "device-related" or "procedure-related" will be defined as adverse events graded "probable" or "highly probable" in their relationship to the study device or procedure.

Table 3: Adverse Event Device Relationship

Relationship	Description
Not Related	• Not associated with device application • Due to an underlying or concurrent illness or effect of another device or drug
Unlikely	little or no temporal relationship to the study device and/or a more likely alternative aetiology exists
Possible	temporal sequence between device application and event is such that the relationship is not unlikely **or** patient's condition or concomitant therapy could have caused the AE
Probable	temporal sequence is relevant **or** event abates upon device application completion/removal **or** event cannot be reasonably explained by the patient's condition
Highly Probable	temporal sequence is relevant **and** event abates upon device application completion/removal or reappearance of the event on repeat device application (rechallenge the system)

Table 4: Adverse Event Study Procedure Relationship

Relationship	Description
Not Related	Not associated with procedure
Unlikely	little or no temporal relationship to the procedure
Possible	temporal sequence between procedure and event is such that the relationship is not unlikely **or** patient's condition or concomitant therapy could have caused the AE
Probable	temporal sequence is relevant **or** event abates upon procedure completion/removal **or** event cannot be reasonably explained by the patient's condition
Highly Probable	temporal sequence is relevant **and** event abates upon procedure completion/removal or reappearance of the event on repeat procedure.

8.3 Assessment and Documentation of Adverse Events

Qualified investigators and research staff will closely and carefully monitor study participants for all anticipated and any unanticipated adverse events. Any adverse event (whether or not related to the investigational device) or device deficiency should be recorded on the appropriate eCRF. All adverse events will be reported from the moment a consented participant has ELS Acoustic Enhancer material enter the body, through to participant study exit. Frequent follow-up visits during the first week following the ELS procedure (at days 1, 2, 3 & 7) and then at days 14, 30 and 90, will enable the investigators and research staff prudent monitoring of participant safety.

Investigational sites will be asked to report the final medical diagnosis as an AE, rather than reporting all signs and symptoms as separate events.

It is the responsibility of the investigator to decide when an adverse event has occurred. Adverse event information will be collected throughout the study. Adverse events will be recorded on the appropriate CRF by the investigator or study coordinator. Event, date of onset, severity, duration, and relationship to the procedure or device will be recorded.

8.4 Serious Adverse Event Reporting

In case of a serious adverse event (whether or not related to the investigational device), or an unanticipated adverse device effect, the investigator should complete the applicable SAE eCRF pages within 24 hours. If the eCRF cannot be completed within 24 hours, the investigator should advise the Sponsor by other means, within 24 hours.

The Sponsor or designates such as the CRO will assist the site with reporting any SAEs to the reviewing ethics committee, according to their requirements and timelines.

In addition, an independent medical advisor will review safety related aspects of the investigation including review of serious adverse events (SAEs) and unanticipated adverse device effects. The medical advisor will be an independent physician not participating as a clinical investigator in the clinical trial who will provide safety oversight for the investigation. For sites in Australia, the Local Sponsor, Five Corners, is responsible for notifying the Therapeutic Goods Administration (TGA) within 7 calendar days of being made aware of all fatal or life threatening, serious and unexpected adverse device events, and within 15 calendar days of being made aware of all other USADEs, with a copy to Applaud Medical Inc.

All SAEs and UADEs must be reported to and reviewed by sponsor and designee as per the table above:

1) Five Corners

Email: AE@fivecorners.com.au

2) Applaud Clinical Affairs:

Applaud Medical, Inc.

Email: clinicalaffairs@applaudmedical.com

NOTE: As applicable, reports must identify participants using the study's unique identifier to protect study participant's confidentiality.

9. MONITORING

Applaud Medical, Inc. or its designee may meet with the investigator prior to the initiation of the study in order to review the adequacy of patient population, facilities, and equipment with respect to the needs of the study, and familiarize investigator with the study protocol.

Applaud Medical, Inc. or its designee will periodically review the data to ensure that the study investigator is in compliance with the protocol and the investigators agreement. Applaud Inc. or its designee will monitor the site to ensure that the completed eCRFs match the medical records and raise queries in the database of any differences.

Applaud Medical, Inc. or designee may meet with investigator at the time enrollment is initiated in order to ensure that the participants are being properly selected, that the methods described in the study are thoroughly understood by the investigator, and that study data are being correctly recorded.

Applaud Medical, Inc. or its designee may visit the clinical site anytime during the course of the study. Additionally, telephone consultation will occur as necessary during the course of the study investigation to ensure proper progress and documentation of the study findings.

10. STATEMENT of COMPLIANCE

An investigator shall conduct the investigation in accordance with the signed agreement with the sponsor, the protocol, local regulations, and any conditions of approval imposed by the ethics committee.

The investigation will be conducted in compliance with the ethical principles that have their origin in the Helsinki Declaration. The investigation will also be conducted in compliance with the Clinical Investigational Plan (CIP), Good Clinical Practice and protection of human participants (21CFR50), ISO 14155: 2011, and regulations of participating countries.

The clinical investigation shall not begin until the required favourable opinion has been obtained from the Ethics Committees, and regulatory authorities. Any additional requirements imposed by the Ethics Committees, IRBs and regulatory authorities shall be followed.

In addition, the principal investigator shall

a) indicate his/her acceptance of the CIP in writing,
b) conduct the clinical investigation in compliance with the CIP,
c) create and maintain source documents throughout the clinical investigation and make them available as requested during monitoring visits or audits,
d) ensure that the investigational device is used solely by authorized users, and in accordance with the CIP and instructions for use,
e) propose to the sponsor any appropriate modification(s) of the CIP or investigational device or of the use of the investigational device
f) refrain from implementing any modifications to the CIP without agreement from the sponsor, Ethics Committee and regulatory authorities, if required,
g) document and explain any deviation from the approved CIP that occurred during the course of the clinical investigation,
h) ensure that an adequate investigation site team and facilities exist and are maintained and documented during the clinical investigation,
i) ensure that maintenance and calibration of the equipment relevant for the assessment of the clinical investigation is appropriately performed and documented, where applicable,
j) ensure the accuracy, completeness, and timeliness of the data reported to the sponsor in the eCRFs and in all required reports,
k) maintain the device accountability records,
l) allow and support the sponsor to perform monitoring and auditing activities,
m) be accessible to the monitor and respond to questions during monitoring visits,
n) allow and support regulatory authorities and the EC when performing auditing activities,
o) ensure that all clinical-investigation-related records are retained as specified in Section 7.4 of ISO 14155:2011, and
p) sign the clinical investigation report.

10.1 Protocol Deviations

The investigator agrees to conduct the investigation in accordance with this protocol. An investigator may not deviate from this Clinical Investigation Plan without first receiving approval in writing from the sponsor and EC, except when necessary to eliminate apparent immediate hazards to a participant.

Deviations will be documented on eCRFs. Investigators will also adhere to procedures for reporting investigation deviations to their EC in accordance with their specific EC reporting policies and procedures.

11. STATISTICAL METHODS

11.1 Population to be analysed

Primary analyses of study data will include available data on all enrolled participants, referred to in International Conference on Harmonization document E9 ("Statistical Principles for Clinical Trials") as the full analysis set. Study enrollment is defined as that time when the participant signs the informed consent form and is then eligible to begin screening assessments. Other study participants will be classified as screen failures.

Study analyses will then be conducted on two distinct cohorts of study participants: an intent-to-treat (ITT) analysis including all enrolled participants and all available data, and a per-protocol (PP) analysis including the subgroup meeting all inclusion and exclusion criteria and for whom treatment was performed according to the study protocol with follow-up through 30 days (or 14 days if no follow-up imaging was required beyond 14 days). Both ITT and PP analyses will be summarized and reported.

11.2 General Considerations

Standard summary statistics will be calculated and reported; for continuous variables, statistics will include means, standard deviations, medians and interquartile ranges. Categorical variables will be summarized as frequencies and percentages.

All p-values will be two-sided, with values less than 0.05 deemed significant.

All statistical analyses will be performed using SAS (version 9.4 or higher, SAS Institute Inc. Cary, NC), R (version 3.2 or higher, R Foundation for Statistical Computing, Vienna, Austria) or other widely accepted statistical or graphical software.

11.3 Primary Endpoint

The study's primary endpoint is treatment success, which is the proportion of study participants who are successfully treated following up to 2 ELS treatments. This is defined as absence of stones or with remaining fragments of less than 3 mm on the largest dimension by follow-up imaging through 30 day visit after last ELS procedure. If ELS Treatment was performed on two stones in one participant, both stones/fragments need to meet the endpoint to be counted as a success.

The study will test the statistical hypothesis that the treatment success rate is not inferior to the performance goal defined using published AUA treatment guidance (64%). Formally, the null and alternative hypotheses are as follows:

H_0: $p < PG$

H_A: $p > PG$

where p is the success rate observed in the prospective study outcomes and PG is the performance goal. The PG in turn is computed as:

$$PG = r - \rho - \Delta,$$

where r is the reference rate, ρ is a correction for differences in treatment success definitions and Δ is the statistical testing margin. These values are further defined as follows:

- r = 64% = 0.64 is the reference rate derived from AUA guidance [13]
- ρ = 4% = 0.04 is a correction factor for the difference between the definition of treatment success in the literature reference and the definition in the study protocol. Specifically, the reference rate is measured after any number of treatments, while the investigational protocol permits at most two treatments before treatment effectiveness is measured.
- Δ = 10% = 0.10 is the statistical testing margin for comparison.

Hence PG = r – ρ – Δ = 64% - 4% - 10% = 50% = 0.50 in the primary endpoint hypothesis testing. The hypothesis test will be performed by comparing the observed success rate to the PG via exact binomial methods, where a lower two-sided 95% exact confidence bound exceeding the PG will constitute rejection of the null hypothesis.

11.4 Secondary Endpoints

The study's secondary endpoints are listed in Section 5.2.

These endpoints, as well as any additional endpoints defined *a priori* in the study protocol or analyzed *post hoc*, will be tabulated and reported descriptively using summary statistics as cited in section 11.2.

Summary tables and listings will be provided for all reported adverse events, as classified by MedDRA system organ class and preferred term, and additionally categorized by seriousness and relatedness. Such summaries will be comprised of the number and percentage of subjects with an adverse event and the total number of such events.

Additionally, a line-item listing of all reported adverse events will be provided.

11.5 Handling of Missing Data

Primary analyses will consist of all available data on enrolled participants, as stated above. Consequently, data will only be absent from analyses of study outcomes in the event that they were not available for collection. Replacement of data via methods such as multiple imputation may be employed when summarizing and reporting study outcomes.

11.6 Sample Size and Power

Sample size and power are predicated on hypothesis testing of the primary endpoint and computed from the *a priori* hypothesis testing previously specified.

- Reference rate: 64%
- Performance Goal = 50% = 0.50
- Estimated ELS performance of 68%

- Desired power: 80%

The required evaluable sample size for a two-sided test at standard alpha of 0.05 was then derived in SAS version 9.4 (SAS Institute, Cary, NC, USA) and found to be 58. Assuming an attrition rate of 30%, 75 patients will be enrolled.

At this planned sample size, the minimal observed success rate required under the above assumptions is 64% (37/58), for which the lower two-sided 95% exact confidence limit is 0.502, just exceeding the PG of 0.50.

11.7 Statistical Analysis Plan

A separate Statistical Analysis Plan will be constructed with additional detail on statistical considerations and content of tables, listings and figures from the various data analyses.

12. DATA MANAGEMENT

12.1 Data Collection

Study data will be collected by electronic Case Report Forms (eCRFs). Data queries and data updates will also be electronic. Source document verification (SDV) will also be electronic in the database. The investigator signature will also be electronic in the database. Each participant will be assigned a unique de-identified ID. All eCRFs for a participant are associated with this de-identified ID.

12.2 Data Storage

The clinical database management system (CDMS) is the electronic data capture (EDC) system Medrio. The Medrio EDC system is developed and hosted by Medrio, Inc. The Medrio EDC system meets CFR 21 part 11 compliance. Study data will be sent to and securely stored in a central location of Medrio's servers for analysis in the Unites States (Dallas Texas, Seattle, Washington, and Washington D.C.)

12.3 Data Confidentiality

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor, and their agents. This confidentiality is extended to cover testing of biological samples in addition to the clinical information relating to study participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The study monitor, other authorized representatives of the sponsor supplying the study device, representatives of the ethics committee may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number.

KUB, ultrasound and/or CT images will be obtained for study evaluation. If published, study participant ID will not be shown.

12.4 Study Record Retention

At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by ethics committee, institutional regulations, and governmental regulations. All study data records shall be retained for a period of time equivalent to the design and expected life of the device, but in no case less than 15 years from the date of release for commercial distribution by the manufacturer. It is recommended to retain the study record at site for a period of 15 years from completion of the study.

13. USE OF DATA AND PUBLICATIONS POLICY

To safeguard the integrity of the study, reports (summary or interim) will not be submitted for publication without prior agreement from Applaud Medical, Inc.

The study will be registered at clinicaltrials.gov prior to enrollment of the first study participant.

Anonymized patient data may be used for publication and presentation purposes. Photos and audio/visual recording of the procedure may be performed at the investigator's discretion. It may be used for professional publication or presentation purposes if the information is anonymized and it is covered by the patient's informed consent."

14. REFERENCES

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