A Prospective, Randomized Study to Evaluate the Safety and Effectiveness of Steerable Ureteroscopic Renal Evacuation (SURE) using the CVAC® Aspiration System Compared to Basketing for the Removal of Renal Calculi Following Ureteroscopic Laser Lithotripsy

ASPIRE Study

(ASPiration to Improve Renal Calculi Removal Effectiveness)

Short Study Title:

Comparison of laser lithotripsy with and without Steerable Ureteroscopic Renal Evacuation (SURE)

Protocol: CP00001
Revision: E
ClinicalTrials.gov Identifier: NCT04519294

Study Sponsor	Calyxo, Inc. 4473 Willow Rd., Suite 100 Pleasanton, CA 94588 Telephone: 925-526-5900
Study Principal Investigator	Brian R. Matlaga, MD, MPH Professor of Urology Johns Hopkins University School of Medicine 600 North Wolfe Street / Park 221 Baltimore, Maryland 21287 bmatlag1@jhmi.edu

This investigational study was designed and will be conducted, recorded, and reported in compliance with the principles of Good Clinical Practice (GCP) Guidelines and the International Organization for Standardization (ISO) 14155, as well as in accordance with all national, state, and local laws of the appropriate regulatory authorities and the Declaration of Helsinki 2013. The following signature verifies that the investigational plan presented in the protocol is clearly understood and agreed upon.

_____ _____

Site Investigator Signature Date

_____

Site Investigator Name (please print or type)

1.0 PROTOCOL SYNOPSIS

STUDY TITLE

A Prospective, Randomized Study to Evaluate the Safety and Effectiveness of Steerable Ureteroscopic Renal Evacuation (SURE) using the CVAC® Aspiration System Compared to Basketing for the Removal of Renal Calculi Following Ureteroscopic Laser Lithotripsy

SAMPLE SIZE

Sample size is based on the stone free rate (SFR) where stone free status is defined as zero residual fragments at 30 days observed on non-contrast CT (NCCT) by blinded central reviewer(s). Sample size determination was performed assuming the SFR_{CVAC} = SFR_B = 25%.A sample size of N=116 (58 per group using 1:1 randomization) produces at least 80% power to reject the non-inferiority null hypothesis assuming a one-sided α=0.05 normal approximation test.

PRIMARY ENDPOINT

The primary efficacy endpoint is the SFR, where stone free status is defined as zero residual fragments at 30 days observed on non-contrast CT (NCCT) by blinded central reviewer(s). The SFR is calculated by determining the number of subjects in each treatment arm with a stone free status of 'yes' and dividing that by the total number of subjects treated in the respective treatment arm.

SECONDARY ENDPOINTS

The secondary endpoints are listed below. Regardless of if the primary effectiveness non-inferiority hypothesis test passes, each of the secondary endpoints listed below will be tested using 0.05 Type I Error rate.

- SFR where stone free status is no stones > 2mm;
- SFR where stone free status is no stones > 4mm;
- Percent reduction in stone volume (i.e., stone clearance rate) at 30 days;
- Residual stone volume at 30 days;
- Rate of subjects with device and procedure related safety events through 90 days;
- Stone events (SE) defined as subject reported passage of a stone confirmed by documented evidence (e.g. photo of stone or stone submitted to site study staff) or any recurrent stone related symptom(s) requiring clinic or ED visit, hospitalization or additional interventions attributable to residual fragments through 6 months [6, 7]; and,
- Stone events through 24 months.

SAFETY ANALYSIS

Adverse events (AEs) will be reported and compiled throughout the study with on-going review by the Sponsor in conjunction with an independent Medical Monitor. Because this is a post-market evaluation, events meeting the definition of product feedback, complaints or reportable events will be handled per

the Sponsor's Product Monitoring SOP. [8] Evaluations will be made for the incidence of device and procedure related AEs, unanticipated adverse device effects (UADEs) and serious adverse events (SAEs). The following safety parameters will be evaluated in the final study analyses and compared between treatment arms:

- The incidence of all AEs (overall, unanticipated, anticipated, relationship, and serious) to the treatment and control arms
- The incidence of SAEs by relationship (stone events, device related, procedure related or systemic)

Tables will summarize both event counts and per subject incidence. Event counts will be summarized by time interval and severity. The AE rate and safety profile will be compared between groups.

SUBJECT SCREENING/BASELINE

Subjects meeting all inclusion criteria and none of the exclusion criteria will be eligible for enrollment. Prior to initiating any study related procedure or change in medical care, the subject will undergo informed consent and must sign the current Institutional Review Board (IRB) approved Informed Consent Form (ICF).

INCLUSION AND EXCLUSION CRITERIA

Inclusion Criteria

Subjects must meet ALL the following criteria to be eligible for study enrollment:

- ≥ 18 years of age;
- Candidate for ureteroscopy with holmium laser lithotripsy;
- Total renal stone burden of 7 mm - 20 mm as measured by the sum of the longest dimension from the axial, coronal or sagittal view (whichever is longest) of each stone on CT within 90 days before the index procedure;
- At least one renal stone ≥ 7mm as measured by the longest diameter from the axial, coronal or sagittal view (whichever is longest) on CT within 90 days before the index procedure;
- Be willing and able to return for and respond to all study-related follow up procedures; and,
- Have been informed of the nature of the study, agreeing to its requirements, and have signed the IRB approved ICF.

Exclusion Criteria

Subjects may not enroll if they meet ANY of the following criteria:

General Comorbidities:

- BMI ≥ 45;
- Known coagulopathies or subject on anticoagulants/antiplatelets other than aspirin ≤ 81 mg that cannot be discontinued perioperatively;
- Subjects requiring intermittent self-catheterization;
- Subjects with significant morbidities such as American Society of Anesthesiologists (ASA) score [9] of ≥ 4, severe spinal cord injuries, severe cardiopulmonary insufficiency, uncontrolled diabetes, neurological disorders, bedbound, anticipated life expectancy less than 5 years, or any other comorbidity, that in the opinion of the Investigator, could represent an increased peri-operative risk for the subject;

Medical History:

- Previous pelvic radiation;
- Ipsilateral partial nephrectomy within 6 months prior to index procedure;
- History of ipsilateral ureteral reimplantation or ureteral reconstruction;
- Simple or radical prostatectomy within 6 months prior to index procedure;
- History of cystectomy;
- History of calyceal diverticula stone;
- History of cystine stone formation;
- History of renal donation or transplant;
- Any other previous pelvic surgical treatment that could put the subject at greater procedural complication risk or technical difficulty;

Anatomical:

- Ureteral ipsilateral stricture, untreated;
- Ureteral stricture, untreated (not to include "tight" ureter);
- Any other bladder, ureteral or kidney congenital genitourinary abnormalities (e.g. Horseshoe kidney, ipsilateral duplicated or partially duplicated collecting system, ipsilateral ectopic kidney, cross-fused ectopia, solitary kidney, etc.) preventing the ability to render the subject stone free;

Renal Exclusions:

- Nephrocalcinosis;
- Renal tubular acidosis;
- Medullary sponge kidney;
- Renal insufficiency as defined as an estimated glomerular filtration rate (GFR) <30 ml/min/1.73m^2 or dialysis at the time of screening;
- More than three (3) UTI in the last 6 months, which may indicate infection stones, or preoperative/operative assessment of investigator indicates presence of infection stones;
- Bilateral disease where contralateral treatment is anticipated or scheduled to occur prior to completion of the 30 day post-op CT study assessment;
- Any procedure within the urinary tract within 2 weeks of index procedure, except the following:
    - treatment of ureteral calculi,
    - ureteral stent placement,
    - ureteral stent removal,
    - Foley catheter removal.
- Presence of intraparenchymal kidney stone(s) determined by pre-operative CT;
- Nephrostomy tube in place within 72 hours of start of index procedure;

Intraoperative Exclusions:

- Indwelling urinary catheter (IUC), generally referred to as a "Foley" or suprapubic catheter, at the time of index procedure;
- Visual (endoscopic) evidence of infection, struvite stone, stone embedded in the parenchyma, or any other stone determined to be inaccessible or preventing the ability to render the subject stone free;
- Ureteral perforations associated with stent or treatment of a ureteral stone occurring in the same surgical setting and prior to commencement of the index procedure;
- Inability to place 12/14 French ureteral access sheath required for treatment of renal stones during index procedure;

- Impacted ureteral calculi (e.g. adherence to wall, unable to pass guidewire, or wall is edematous) per assessment of treating investigator;

General/Other Exclusions:

- Have participated in any other clinical trial within the last 3 months, and/or plans to participate in any other investigational or invasive clinical trial during this study;
- If female, be pregnant, breast-feeding, or if childbearing age, is not using contraception between screening and 90 days post-op;
- Subject has current or recent history of substance abuse (e.g. recreational drugs, narcotics, or alcohol) requiring intervention;
- Is a prisoner or ward of the state; or,
- Is unable to meet the treatment and follow up protocol requirements.

ENROLLMENT AND RANDOMIZATION

Study subjects will be enrolled and randomized to treatment intraoperatively. If a subject requires treatment of ureteral calculi, treatment of the ureteral stones should be completed prior to randomization. If ureteral perforation(s) occur as a result of a stent or the treatment of ureteral calculi prior to randomization, the subject should not be enrolled or randomized.

Once all ureteral stones are treated, eligibility has been confirmed based on successful placement of the ureteral access sheath and visual inspection of the collecting system and kidney stones via retrograde pyelogram, the subject is ready for enrollment. At that time, subjects will be randomized intraoperatively with a 1:1 ratio of test-to-control subjects. The subject is considered enrolled into the study at the time of randomization just prior to commencement of lithotripsy of the renal stones.

OPERATIVE TREATMENT

The site research clinical coordinator or other designated study personnel will be present in the surgical suite during each of the operative procedures to confirm final eligibility criteria, perform randomization and collect the operative data required for eDC entry detailed further in the sections that follow.

Laser Lithotripsy: Once a subject is randomized, the Investigator should adhere to the assigned method of stone removal. The goal of all index procedures is rigorous removal of stones and fragments to actively render the subject stone free. Basketing is allowed as an adjunct to SURE procedures in order to render the subject stone free. Ureteroscopic laser lithotripsy should be performed per physician preference given the assigned mechanism of removal, stone location and composition, and the best interest of the patient. The laser settings can therefore be adjusted as needed to accommodate the method of removal, stone location, and the stone composition. To provide homogeneity in lithotripsy methodology, 30 watt lasers are excluded from use in the study procedures.

Stent Placement & Removal: At the conclusion of the stone removal procedure, retrograde pyelogram will be performed prior to placement of the ureteral stent to assess any damage to the kidney or ureter. The post-operative stent will be placed and should remain for a minimum of three (3) days and removed thereafter at the Investigator's discretion. Subjects should be advised not to self-remove the stent; the stent should be removed in clinic at the post-op visit.

STUDY PROCEDURE OVERVIEW

Clinic and telephone follow-up visits will occur at the following time points after the index procedure: post-op, 30 days, 3 months, 6 months, 12 months, 18 months and 24 months. The assessments performed at each of the follow-up time points are summarized in the study procedure overview below.

Table 1: ASPIRE Study Procedure Overview

Test or Procedure	Screening/ Baseline (-30 days)	Operative/ Discharge (Day 0)	Post-Op	30 days (-10/+20 days)	3 months (± 14 days)	6 months (± 14 days)	12 months (± 45 days)	18 months (± 45 days)	24 months (± 60 days)	Unscheduled Visit
	Clinic	OR	Clinic	Phone + CT	Phone	Phone	Phone	Phone	Phone	Clinic or Phone
Informed consent	X									
Demographics	X									
Medical History	X									
Non-contrast CT[1]	X[2]			X						C
KUB x-ray or KUB US[1]	C									C
Physical Exam	X									
Labs[4]	X									C
UA, culture[4]	X									C
Pregnancy Test[5]	X									
Con. Medications	X	X	X	X	X	X	X	X	X	X
Randomization		X[3]								
Procedure Timing, Image/Video		X								C
Retrograde Pyelogram		X								
Investigator Survey		X								
UB-04 & EOB Capture[6]		X								X
Stent Removal[7]			X							
Patient Reported Outcomes	X			X	X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X	X	X	X
Stone Events			X	X	X	X	X	X	X	X

KEY: "X" = required procedure; "C" = procedure not required, but images and/or results captured if performed

[1] If NCCT, KUB or KUB/US are performed per standard of care or out of clinical necessity at or in between any clinic visit, results will be captured as a part of study

[2] Captured ≤ 90 days prior to index treatment date; refer to image acquisition protocol for CT acquisition parameters

[3] Roll-in training subjects will not be randomized and automatically assigned to CVAC®

[4] To rule out active infection and within 30 days of index procedure

[5] Fertile women only and within 48 hours of index procedure

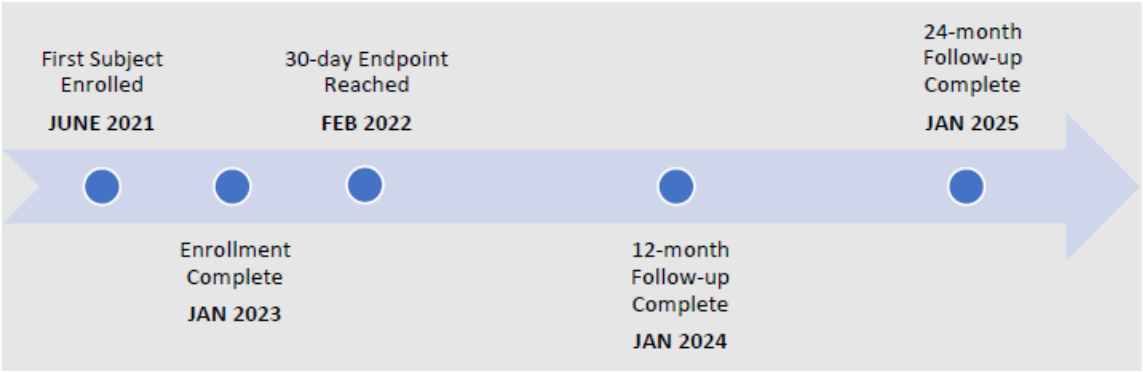
[6] UB-04 and EOB forms are captured for the index procedure and any visits or procedures administered for stone events, reinterventions, retreatments or unscheduled visits.

[7] Stents removed at three (3) or more days following the index procedure. Stents must be removed prior to 30 day CT.

STUDY DURATION

The anticipated study start date is May 2021 followed by approximately 18 months of enrollment. The study will last for 2 years following each subject's ureteroscopy index procedure, until the last subject completes 24-month telephone follow up or is withdrawn from the study. The anticipated study close-out date is January 2025.

Figure 1: ASPIRE Study Timeline*



*All dates are approximate and subject to change.

INVESTIGATOR AND SITE SELECTION

A minimum of 6 and up to a maximum of 15 pre-qualified clinical sites in the United States will be selected for participation in the study. A variety of health-care settings will participate, including large urological practices, universities, and small community clinics with nearby hospital or Ambulatory Surgery Center (ASC) privileges. These sites must demonstrate the following for participation:

- Equipped with suitable medical facilities to fulfill the clinical study requirements.
- Association with and under the guidance of an Institutional Review Board (IRB), which satisfies all the FDA requirements (per 21 CFR Part 56) and conducts meetings on a regular basis.
- Access to 50 hertz Holmium:YAG (Ho:YAG) lasers (as a minimum) for the study lithotripsy procedures and cannot use 30 watt Holmium:YAG.
- Access to an appropriate pool of study candidates and the ability to enroll a minimum of 5 subjects per month per participating Investigator during the study enrollment period.
- Board-certified urologists and are required to demonstrate competency of the SURE procedure using the CVAC® system (minimum of 5 SURE procedures) prior to enrolling subjects.
- Ability to meet the clinical study requirements using dedicated clinical research staff.

Additional site requirements will be assessed during study feasibility meetings or phone calls. Qualified sites will be selected based on the completion of a feasibility questionnaire and site a qualification visit (if required) conducted by Calyxo, Inc. or a designee.

CVAC® ASPIRATION SYSTEM

Indications for Use

The Kalera Vacuum Aspiration Catheter (K-VAC) is used to establish a conduit during endoscopic urological procedures for the treatment of urinary stones. [10]

NOTE: The above intended use was cleared by FDA; the device name has since been changed to CVAC®.

Device Description

The CVAC® Aspiration System is a sterile, single use system consisting of two components, the CVAC® Aspiration Catheter (Catheter) and the CVAC® Introducer (Introducer). The Introducer allows the Catheter to be introduced into the kidney over a standard 0.035" or 0.038" guidewire using standard urological guidewire procedures. This introduction procedure mimics how a flexible ureteroscope is introduced into the kidney. Once the Catheter is in place within the kidney, the Introducer is removed. The CVAC® Catheter is comprised of a control handle at the proximal end connected to the steerable catheter. The control handle has a vacuum port for connection to standard operating room machine suction, a vacuum controller, an irrigation port and a steering control dial that allows the operator to control the angle and direction of the articulating tip at the distal end of the steerable catheter. The outer diameter is 12 Fr, and the working length is 70 cm. The CVAC® catheter has dual concentric lumens that allow for simultaneous irrigation and aspiration and allows for a rapid transition of fluid flow directions within the renal collecting system.

The CVAC® Aspiration System is used to perform the Steerable Ureteroscopic Renal Evacuation (SURE) procedure. The distal end of the CVAC® catheter is steered under fluoroscopic guidance to navigate into each calyx. Stone fragments and dust are evacuated using physician-controlled suction and irrigation. Suction is controlled by the physician using the vacuum controller, and irrigation is accomplished through manual syringe injection of a saline solution.

Figure 2: Overview of the SURE Procedure Using CVAC®