

A Prospective Study to Evaluate the Safety and Effectiveness of Steerable Ureteroscopic Renal Evacuation (SURE) using the CVAC® Set

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STUDY PROTOCOL

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 clinical investigation shall not begin until the required approvals from the Ethics Committee.

Study Design

This is a prospective, single-arm study to assess safety and efficacy of a novel steerable ureteral catheter system, the CVAC® Set ("CVAC"), for the treatment of urinary stones. The Steerable Ureteral Renal Evacuation (SURE) with CVAC will combine standard ureteroscopic procedure including standard laser lithotripsy with steerable ureteroscopic vacuum aspiration of the stone debris and dust. The baseline and post-op day (POD) 1 and POD 30 non-contrast CT (NCCT) images utilized to determine the efficacy endpoints will be reviewed by independent radiologist(s).

Sample Size

40 Subjects (not to exceed 50 subjects)

Primary Endpoint

The primary efficacy endpoint is the stone clearance, defined as percent reduction in stone volume, at POD 1 on NCCT by independent reviewer(s).

Secondary Endpoints

The secondary endpoints are listed below.

- Stone clearance at POD 30
- Stone Free Rate (SFR) at POD 1 and POD 30
- Residual stone volume at POD 1 and POD 30

Safety Analysis

Adverse Events (AEs) will be reported and compiled throughout the study. Evaluations will be made for the incidence of device and procedure related AEs and Investigator(s) will determine Unanticipated Adverse Device Effects (UADEs) and Serious Adverse Events (SAEs).

Investigator Survey

Each treating Investigator will complete an Investigator survey. The survey will include Likert Scale questions and is designed to assess the Investigator's satisfaction with the safety, efficacy, reliability and ergonomics of CVAC and the surgical procedure. The survey may also include device performance feedback, procedural suggestions, training feedback, and any additional customer concern or dissatisfaction during or after the use of CVAC.

ENROLLMENT, INCLUSION AND EXCLUSION CRITERIA

Subject Screening/Baseline/Informed Consent

Subjects meeting inclusion criteria and none of the exclusion criteria will be eligible for enrollment. The informed consent will be obtained from the subjects prior to enrollment.

Inclusion Criteria

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

- ≥ 18 years of age;
- Candidate for ureteroscopy with laser lithotripsy;
- Total renal stone burden of 7 mm - 30 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;
- 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 and have agreed to the IRB approved informed consent form (ICF).

Exclusion Criteria

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

- Significant morbidities that in the opinion of the Investigator, could represent an increased peri-operative risk for the subject;
- Challenging renal anatomy that does not allow for initiation of SURE;
- 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 urinary diversion;
- Ureteral ipsilateral stricture, untreated;
- Ureteral stricture, untreated (not to include “tight” ureter);
- Ipsilateral impacted ureteral stone (not to include proximal ureter or ureteropelvic junction “UPJ” stones);
- Medullary sponge kidney;
- Renal insufficiency requiring dialysis at the time of screening;
- Bleeding diathesis (anticoagulants that cannot be discontinued); and
- Any subjects with intraoperative complications, i.e., ureteral trauma, prior to introduction of CVAC®

STUDY DURATION

The anticipated study start date is July 2023. The study will continue until the last subject completes 30-day non-contrast CT (NCCT) or is withdrawn from the study. The anticipated study close-out date is December 2024.

BACKGROUND AND STUDY RATIONALE

Ureteroscopy (URS) is a common endoscopic procedure to remove kidney stones from the kidney with reported stone-free rates of 55-80%. [1] Ureteroscopic stone procedure involves either or combination of lasering stones with dusting technique (assumes spontaneous passage) or lasering stone followed by stone basketing (active removal). Active retrieval with basketing can lead to excessive procedural times and may leave smaller stone fragments behind, leading to high residual stone burden. Residual stones are problematic since they can lead to stone events such as need for ancillary post-operative procedures, emergency department visits, renal colic, hospital admission, and can act as a nidus for new stone formation.

Therefore, methods to maximize stone clearance are vital to ureteroscopic stone treatment and ultimately improving patient outcomes. The concept of a steerable vacuum device advances today's ureteroscopic stone surgery and could minimize residual stone burden post-op compared to dusting alone. A novel endoscopic system that combines the capability of standard ureteroscope with irrigation and aspiration has the potential to optimize the procedural outcome.

CVAC® SET

Indications for Use

The CVAC® Set (CVAC Aspiration System and CVAC Image Processor) is intended to establish a conduit during endoscopic urological procedures for the treatment and removal of urinary stones (kidney stones, fragments, and dust). The CVAC Aspiration System is a sterile, single use, steerable ureteral catheter system with integrated vision, irrigation and aspiration. The CVAC Image System is a video processor that is used for clinical image processing.

Irrigation and aspiration of kidney stones and stone dust is accomplished with the dedicated irrigation and vacuum channels of CVAC. The CVAC Set can be used with additional accessories to perform various diagnostic and therapeutic procedures. [2]

Device Description

The CVAC Set builds on the first-generation CVAC device, originally called K-VAC and evaluated in a pilot randomized controlled study conducted at Muljibhai Patel Urological Hospital (MPUH) in 2019. [3] The first-generation CVAC is a steerable irrigation-aspiration catheter designed to assist in the removal of kidney stone fragments and stone dust after standard lithotripsy procedures. This device is currently marketed in the U.S. as the CVAC Aspiration System (first-generation CVAC).

The first-generation CVAC operates with external fluoroscopic guidance for placement. It uses saline irrigation and a hospital vacuum to flush out and remove kidney stones from the renal pelvis and calyces. A separate ureteroscope is used to localize stones and for laser lithotripsy prior to the use of the first-generation CVAC.

The CVAC[®] Set is a second-generation CVAC that integrates direct vision into the steerable irrigation-aspiration catheter design. The CVAC Set includes two main components: the sterile, disposable CVAC Aspiration System and the reusable CVAC Image Processor. The second-generation CVAC provides direct visualization throughout the procedure and obviates the need for a separate ureteroscope for the procedure.

STUDY PROCEDURE OVERVIEW

Endpoints

Stone clearance, stone free rate and residual stone volume will be determined by independent radiologist review of NCCT data captured at POD 1 and POD 30.

Operative Treatment

The site research coordinator or other designated study personnel will be present during each of the operative procedures to collect the operative data. The data may include:

- Laser lithotripsy: setting and time
- Image & video capture: redacted images and videos of the endoscope and fluoroscopy tower. Video of Investigator interface may also be captured; no identifiable subject images will be collected.

Discharge and Post-operative Course

Subjects should be discharged with the site's standard of care post-operative instructions for URS, including tamsulosin unless contraindicated. The subjects will receive verbal instructions regarding stent removal, returning to clinic if appropriate, and the requirements of the POD 1 and POD 30 non-contrast CT imaging.

Follow-up Visits

Non-contrast CT (NCCT) [≤ 2 millimeter cuts] will be performed to evaluate the stone clearance, residual stone volume, and stone-free status at the POD 1 and POD 30.

Unscheduled Visits

If a subject has an Unscheduled Visit (clinic visit, ED visit, hospitalization or retreatment) following the index procedure, the designated study staff should try to collect any information available pertaining to the subject's follow up from the index procedure or new stone events.

TREATMENT OF URETERAL STONES

Concomitant treatment of the ureteral stones will be allowed at the time of the index procedure and the procedural details will be documented. Data collected on the ureteral stone treatment will be analyzed separately for effectiveness and safety analyses.

TREATMENT OF CONTRALATERAL KIDNEY

Treatment of the contralateral kidney is allowed at the time of the index procedure and the procedural details including baseline and POD 1 and POD 30 NCCT will be recorded. Data collected on contralateral kidney stone treatments will be analyzed separately for effectiveness and safety analyses.

CT ANALYSIS

Baseline, POD 1, and POD 30 NCCT images will be evaluated, and the following parameters reported for renal stones:

- Stone clearance
- Residual stone volume
- Stone free status – yes, no; where stone free is defined as
 - zero residual fragments,
 - no stones > 2mm, and
 - no stones > 4mm
- Stone location
- Stone dimensions
- Hydronephrosis
- Hydroureter

Any Unscheduled Visit CT will also be reviewed by an independent radiologist(s).

DEVICE ACCOUNTABILITY

All CVAC® systems utilized at the site will be tracked. The site is responsible for maintaining accountability and disposition of all study devices used in this clinical study by documenting the lot numbers and expiration date of the product used during each procedure.

SOURCE DOCUMENTS

Original documents, data, and records may include the following: hospital records, clinical and office charts, laboratory notes/reports, recorded data from automated instruments, and source document worksheets.

DATABASE

The Sponsor will utilize a password protected database to collect and store the clinical study data. Every effort will be made to secure data in a de-identified manner.

SAFETY ASSESSMENTS

Safety Oversight

As with any surgical procedure, there is a risk of Adverse Events (AEs) and complications associated with cystoscopy and ureteroscopy. Potential complications include, but are not limited to sepsis, bleeding, and injury to ureter.

Adverse Events (AEs) will be compiled throughout the study. Evaluations will be made for the incidence of stone events, device and procedure related AEs, incidence of Unanticipated Adverse Device Effects (UADEs) and incidence of Serious Adverse Events (SAEs). AEs will be classified by seriousness, relatedness to the device, relatedness to the study procedure, and whether they were anticipated or not. AEs will be categorized by Clavien-Dindo classification by the Investigator.

Stone events (SE) defined as subject reported passage of a stone or any recurrent stone related symptom(s) requiring clinic or ED visit, hospitalization, or additional interventions attributable to residual fragments.

STATISTICAL ANALYSIS

Categorical variables will be summarized using relative frequencies and percentages. Continuous variables will be summarized using mean \pm standard deviation, median, and minimum and maximum. All statistical analyses will be performed using Stata version 17.0.

TRAINING

The training of study personnel will be the responsibility of Calyxo, Inc. Training will cover topics such as study device, study protocol, surgical technique, and data collection

APPENDIX I: ADVERSE EVENT (AE) REPORTING

The Adverse Events (AEs) will be reported according to MPUH's IRB reporting requirements and the study protocol.

EVENT DEFINITIONS

ADVERSE EVENT (AE)

An adverse event (AE) is any untoward medical occurrence in a subject administered a study device or procedure, which does not necessarily have a causal relationship with the treatment.

SERIOUS ADVERSE EVENT (SAE)

A Serious Adverse Event (SAE) is defined as an AE which leads to:

- Death;
- Serious deterioration in the health of the subject, that resulted in:
 - Life-threatening illness or injury, or
 - Permanent impairment of a body structure or a body function, or
 - In-patient hospitalization or prolongation of existing hospitalization, or
 - Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function.

NOTE: Planned hospitalization, including overnight stay following index procedure, for a pre-existing condition without serious deterioration in health, is not considered a SAE.

UNANTICIPATED ADVERSE DEVICE EFFECT (UADE)

An UADE is any serious adverse effect on health or safety or any life-threatening problem or death caused by or related to the device

EVENT CATEGORIES

The Investigator will make the following assessments regarding the nature of the event:

- Event relationship (device related, procedure related or systemic);
- Event severity (mild, moderate or severe);
- If the event was anticipated or unanticipated; and,
- Clavien-Dindo Classification, when applicable to grade post-operative complications.

EVENT RELATIONSHIP***DEVICE-RELATED ADVERSE EVENT***

The event follows a reasonable probability that the event was the result of a breakdown or malfunction of the device during index procedure.

PROCEDURE RELATED ADVERSE EVENT

The event follows a reasonable probability that the event was the result of the index procedure and was the cause of an abnormal reaction of the subject.

SYSTEMIC (NON-DEVICE RELATED) ADVERSE EVENT

The event follows a reasonable probability that the event is related to other factors such as the subject's condition, other therapeutic interventions, or concomitant medications and has no timely relationship to the SURE procedure with CVAC®.

EVENT SEVERITY

There are three (3) categories of severity for an AE, SAE, or UADE as defined below:

- Mild: causing no limitation of usual activity, an experience that is usually transient, and requires no special treatment or intervention;
- Moderate: causing some limitation of usual activity, an experience that is alleviated with simple therapeutic treatments;
- Severe: causing inability to carry out usual activity, an experience that requires therapeutic intervention.

CLAVIEN-DINDO CLASSIFICATION

The Clavien-Dindo classification system for complications is a validated method that is used to grade post-operative complications encountered following endoscopic stone surgery.

TABLE 3: CLAVIEN-DINDO CLASSIFICATION TABLE

GRADE	DEFINITION
GRADE I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions
GRADE II	Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgesics, diuretics, electrolytes, and physiotherapy. This grade also includes wound infections opened at the bedside
GRADE III	Requesting surgical, endoscopic, or radiological intervention
Grade IIIa	Intervention not under general anesthesia
Grade IIIb	Intervention under general anesthesia
GRADE IV	Life-threatening complication (including CNS complications)* requiring IC/ICU management
Grade IVa	Single organ dysfunction (including dialysis)
Grade IVb	Multiorgan dysfunction
GRADE V	Death of a patient

*Brain hemorrhage, ischemic stroke, subarachnoidal bleeding, but excluding transient ischemic attacks.

CNS, central nervous system; IC, intermediate care; ICU, intensive care unit.

APPENDIX II: ADVERSE EVENT LISTING

Anticipated Events Related to URS, laser lithotripsy and stent placement

The following is a list of AEs that have been reported in the medical literature as complications following ureteroscopy with laser lithotripsy and placement of a ureteral stent. These AEs include, but are not limited to: [4, 5] [6, 7, 8, 9, 10, 11, 12]

- Basket inversion;
- Bleeding;
- Bleeding requiring blood transfusion;
- Conversion to open procedure;
- Delayed bleeding requiring angio-embolization;
- Discomfort;
- Edema;
- Entrapment;
- Fever;
- Hematoma;
- Hematuria;
- Hemorrhage;
- Hydronephrosis;
- Inability to disengage from irretrievable object
- Increased radiation exposure;
- Infected urine fluid reabsorption;
- Infection;
- Injury to adjacent organs including colon, lung, liver, spleen
- Loss of kidney;
- Moderate or severe stent pain
- Nephrostomy tube placement;
- Other injury to the urethra, bladder, ureter or kidney;
- Pain;
- Perforation;
- Recurrent stone formation;
- Renal backflow;
- Renal failure;
- Residual stones or stone fragments;
- Sepsis or Systemic Inflammatory Reaction Syndrome (SIRS);
- Staged or repeat procedure;
- Stone push-up;
- Stone migration into the ureteral wall
- Tissue injury caused by temperature rise at the laser site;
- Urinoma;
- Ureteral avulsion;
- Ureteral lesions;
- Ureteral perforation;
- Ureteral reflux;
- Ureteral stent placement;
- Ureteral stricture; or
- Urosepsis.

Anticipated Events Related to SURE Procedure with CVAC

Inclusive of the above anticipated events for ureteroscopy, the following is a list of AEs that could potentially occur as a result of the SURE procedure using the CVAC® Set: [13]

- Allergic reaction;
- Perforation, puncture, bleeding and/or hematuria, ureteral avulsion;
- Damage to ureter or kidney;
- Device is ineffective, subject does not get effectively treated and all stones are not removed;
- Discomfort, pain, inflammation, infection and/or fever;
- Electrolyte imbalance or excess fluid absorption from over irrigation.
- Excessive fluoroscopy exposure to subject or staff;
- Extra-mural displacement of stone(s) outside collecting system;

- Inability to remove device necessitating open procedure;
- Prolonged procedure;
- Retained foreign body (device);
- Sepsis or Systemic Inflammatory Reaction Syndrome (SIRS); or
- Ureteral obstruction (post device inflammation or stone obstruction).

Anticipated Events Related to General Anesthesia

Lastly, the following AEs can occur as a result of general anesthesia to complete the above procedures:

- Cardiac events;
- Acute myocardial infarction;
- Deep vein thrombosis;
- Pulmonary embolism;
- Cerebrovascular accident;
- Stroke;
- Pneumonia; or,
- Death.

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