The RELIEF Ureteral Stent – Assessment of Retrograde Urinary Reflux

Protocol Number: 809792

Principal Investigator: Seth Bechis, MD, MS

IDE Number: N/A (device is FDA approved)

Sponsor: The Ureteral Stent Company

Funded by: The Ureteral Stent Company

Version Number: 1.1

24 July 2024

Summary of Changes from Previous Version:

Affected Section(s)	Summary of Revisions Made	Rationale

Table of Contents

1 PROTOCOL SUMMARY

Leave blank. Text should be included under the relevant subheadings below.

1.1 SYNOPSIS

Title: The RELIEF Ureteral Stent vs. Standard DJ Stent – Assessment of Retrograde Urinary Reflux
Study Description: Assessment of retrograde urine reflux after placement of the RELIEF® Ureteral Stent using cystography after contrast gravity-filling of the bladder and assigning a urinary reflux grade. Randomized controlled trial for evaluation of the stent placement and the adequacy of short-term drainage (defined as the presence of the stent in the ureter and the lack of surgical or other intervention to treat symptoms associated with the stent itself on the stented side during the first 48 hours).
Primary Objective: Assessment of retrograde urine reflux after placement of a ureteral stent using cystography after contrast gravity-filling of the bladder and assigning a urinary reflux grade based on standard scoring.
Secondary Objectives: Assessment of stent symptoms (incidence, relationship to device, severity) attributed to the ureteral stent; Reporting the Ureteral Stent Symptoms Questionnaire (USSQ) before stent placement, after placement at day 3, prior to removal and post removal; Visualization of distal coil floating in bladder (Y/N) after stent placement
Primary Endpoint: Study success defined as adequate short-term drainage defined as the presence of the stent in the ureter and the lack of surgical or other intervention to treat symptoms associated with the stent itself on the stented side during the first 48 hours [Day 0-2] following placement.
Secondary Endpoints: USSQ Scale (Ureteral Stent Symptoms Questionnaire) [Time Frame: Day 3 as endpoint, Unplanned hospital visits or doctor visits related to the stent, Medication use

Description of Sites/Facilities Enrolling Participants: UC San Diego
Description of Study Intervention: Randomized Controlled Trial
Study Duration: 1 year
Participant Duration: 1 year

1.2 SCHEMA

See section 1.3

1.3 SCHEDULE OF ACTIVITIES (SOA)

Procedures	Screening/Enrollment Day -90 to -1	Stent Placement (Day 0)	Post-Stenting, Visit 1 (Day 1)	Follow up Phone call (Day 3)	Stent Removal (Day 7-10)	2-days Post Stent Removal (Day 9-12)
Informed consent	X					
Demographics	X					
Medication Review	X	X	X	X	X	X
Randomization		X				
Ureteral Stent Symptoms Questionnaire			X	X	X	X
RELIEF Ureteral Stent or DJ Stent		X (placement per standard of care)		X (removal per standard of care)		
Intraoperative Post Stent Photo		X			X	
Adverse event review and evaluation		X	X	X	X	X
Clinical Usability Survey		X				

2 INTRODUCTION

2.1 STUDY RATIONALE

Traditional ureteral stents are commonly used in practice to relieve renal obstruction or as a scaffold to promote healing after endoscopic or open/ laparoscopic surgeries involving the ureter [1]. However, morbidities can be associated with placing these stents such as pain or irritative bladder symptoms, which are felt in part to be due to urinary reflux up the stent. The RELIEF stent has the potential to improve urinary symptoms due to its unique structural design, which allows the ureteral orifice to close naturally and reduce the reflux of urine back into the kidney. This study seeks to assess whether the RELIEF stent has less reflux and, therefore, less irritative symptoms.

2.2 BACKGROUND

The most commonly reported symptoms include urgency, urinary frequency, dysuria, incontinence, hematuria, suprapubic discomfort, fever due to urinary tract infections and flank pain and they can occur in up to 80% of stented patients. Sometimes, the symptoms are poorly tolerated and can negatively affect the patient's quality of life [2, 3].

Shao et al have studied the relationship between bladder filling and the renal pelvic pressure (RPP) in stented patients, which revealed that RPP increases mildly during bladder filling and dramatically during voiding, indicating the occurrence of urinary reflux. As a result, the authors encouraged early removal of the stents [4]. Another study showed that patients with stents whose distal coils cross the midline are at higher risk of post-stenting morbidities [5].

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

There is a potential risk of loss of confidentiality of data. Every effort will be made to keep the patients' information confidential.

The study participants may feel uncomfortable while addressing some of the questions in the pain questionnaire. They may refuse to answer any of these questions. They may stop their participation in this study at any time.

The standard of care surgical risks and risks with either of the stents should have been reviewed with their surgeon.

Patients who participate in this research study will not get to select the type of stent they will receive.

The principal investigator for this research project has determined and verified that all imaging scans prescribed for this project would typically be performed as part of the standard medical care required to adequately monitor the participant's current illness. If they are especially concerned with radiation exposure, or they have had a lot of x-rays or imaging scans already, they should discuss this with the principal investigator for this project, Dr. Bechis, or their regular doctor.

2.3.2 KNOWN POTENTIAL BENEFITS

There is potential direct benefit for the patients assigned to the RELIEF stent group as we suspect it will provide relief from discomfort during recovery after ureteroscopy. The knowledge to be gained from this research is whether the Relief stent reduces urinary reflux and decreases postoperative pain and discomfort for patients who undergo kidney stone surgery and stent placement. If the Relief stent provides improvement in symptoms, this will improve patient care and comfort.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

The group of investigators, including the principal investigator, and the research support staff will monitor for adverse events. Data will be reviewed quarterly to ensure it is accurate, complete, and its collection complies with the protocol. There will also be a continual assessment of the risks and benefits.

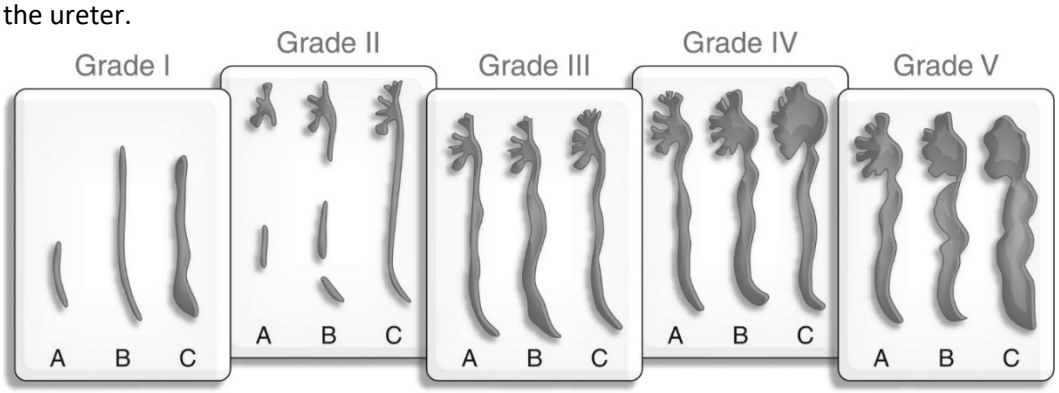
Furthermore, Case report forms will be generated for each subject and completed by the investigator or study coordinator. The investigator or study coordinator will countersign each form. After the case report forms for a visit are completed, the research coordinator will enter a limited set of data into a Redcap data management system. Original case report forms will be securely maintained at the clinical sites. Completed copies of the case report forms will be sent to the research coordinator where they will be stored on a secure hard drive. Subjects will be asked to report any adverse events to the study coordinator or physician. All adverse events will be reported on a standardized form that will elicit the number and specify the type of tests used, therapy (or therapies) used, and clinical visits (office, ER and hospitalization) required until the event is resolved.

3 OBJECTIVES AND ENDPOINTS

We hypothesize that the RELIEF stent will offer the same function as a traditional stent with the added benefits of 1) prevention of urinary reflux and 2) reduction of irritative bladder symptoms.

Primary Objectives:

- Assessment of retrograde urine reflux after placement of a ureteral stent using cystography after contrast gravity-filling of the bladder and assigning a urinary reflux grade based on the following standardized scoring system:
  - Grade I: urine refluxes into the ureter only.
  - Grade II: urine refluxes into the ureter and up to the kidney without dilation.
  - Grade III: urine refluxes into the ureter and kidney and causes mild dilation.
  - Grade IV: urine refluxes into ureter and kidney and causes dilation without twisting of the ureter.
  - Grade V: urine refluxes into ureter and kidney and causes significant dilation with twisting of the ureter.



- Evaluation of the stent placement and the adequacy of short-term drainage (defined as the presence of the stent in the ureter and the lack of surgical or other intervention to treat symptoms associated with the stent itself on the stented side during the first 48 hours).

Secondary Objectives:

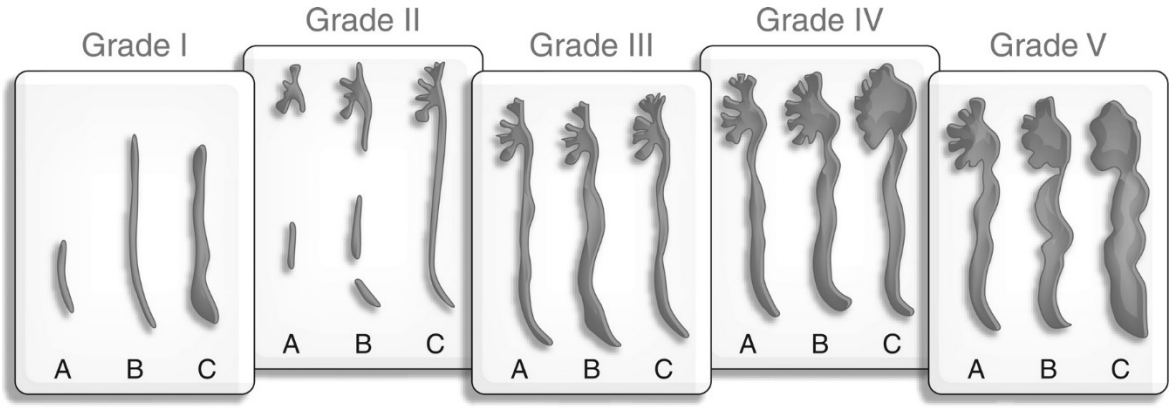
- Assessment of pain or irritative symptoms attributed to the ureteral stent as well as unplanned return visits to ED, OR, or clinic.
- Reporting the Ureteral Stent Symptoms Questionnaire (USSQ) before stent placement, after placement at day 3, prior to removal and post removal.
- Visualization of distal coil floating in bladder (Y/N), after stent placement.

Study Endpoints:

1- Primary effectiveness endpoint:

- Study success defined as adequate short-term drainage defined as the presence of the stent in the ureter and the lack of surgical or other intervention to treat symptoms associated with the stent itself on the stented side during the first 48 hours [Day 0-2] following placement.
- [Note: In some cases, the ureteral stent may not be sufficient to relieve pain (not associated with stent specifically) and alternative surgical treatment may be warranted. In these cases, patient data will be captured but non-device related cause captured as reason for subject stenting termination.]
- Assessment of retrograde urine reflux after placement of the ureteral stent, as determined by the visualization of urine in the distal ureter to the kidney using cystography after contrast gravity-filling of the bladder and assigning a urinary reflux grade based on:
  - Grade I: urine refluxes into the ureter only.
  - Grade II: urine refluxes into the ureter and up to the kidney without dilation.

- Grade III: urine refluxes into the ureter and kidney and causes mild dilation.
- Grade IV: urine refluxes into ureter and kidney and causes dilation without twisting of the ureter.
- Grade V: urine refluxes into ureter and kidney and causes significant dilation with twisting of the ureter.



- Visualization of distal coil in bladder, after stent placement. Document placement using a cystoscope.

2- Primary safety endpoint:
Assessment of pain or irritative symptoms (incidence, severity) attributed to the ureteral stent as well as unplanned return visits to ED, OR, or clinic.

3- Secondary endpoint:
- USSQ Scale (Ureteral Stent Symptoms Questionnaire) [Time Frame: Day 3 as endpoint
- Unplanned hospital visits or doctor visits related to the stent
- Medication use endpoint:
  - Physicians can prescribe standard medications such as alpha blocker (Tamsulosin), Anticholinergic (Oxybutynin), phenazopyridine (Pyridium), ibuprofen and Tylenol prn pain for the duration of the stent plus 1 day (post stent removal) (Document on CRF)
  - Requests for “breakthrough” pain medication (narcotics) would be at the request of the patient post procedure (not to be given as a standard dose). (Document on CRF)
  - Patients to keep medication diary in situations where patients are not taking medications as prescribed
  - Use of medication (amount and type of medication) will be analyzed between the RELIEF stent and DJ Stent groups, including calculation of cost of medications between 2 groups

4 STUDY DESIGN

4.1 OVERALL DESIGN

Allocation: Randomized 1:1 RELIEF stent vs. DJ Stent
Endpoint Classification: Comparison Study
Intervention Model: Two Group Assignment
Masking: Open Label
Primary Purpose: Treatment

Patients will undergo their scheduled ureteroscopy with laser lithotripsy and ureteral stent placement per standard of care methods.

Screening/Enrollment:

- Patients will be screened for eligibility
- If eligible, patients will be enrolled in the study through signing of the Informed Consent Form
- Medical charts will be reviewed, demographics will be collected, and medications will be reviewed prior to surgery

Day 0 (Stent Placement)

- Patients will be randomized to one of two study groups (Relief stent vs DJ stent)
- Medical charts will be reviewed and medications will be reviewed prior to surgery
- Stent will be placed per standard of care
- A intraoperative photo of the stent will be taken to confirm placement

Post-stent Follow-Up:

- Post-operatively complete Ureteral Stent Satisfaction Questionnaire (USSQ) surveys at day 1, day 3, day of stent removal, and 2 days post stent removal (note day of removal) (between 7-10 days in normal practice (even up to 14 days):
- Medications will be tracked on the CRF at day 1, day 3, day of stent removal, and 2 days post stent removal
- Day 1 (12-30 hours after stenting procedure), subject will be evaluated by study personnel for acceptable procedural outcome.
- Document any unplanned hospital visits or doctor visits related to the stent
  Day 1, Day 3, Day of stent removal (i.e., Day 7-10), and 2 days post stent removal, subject will be evaluated by study personnel for ongoing tolerability and stent performance (e.g., drainage) in person or by phone.
- Direct or remote evaluation will be documented. If unusual levels of pain or other potentially serious complications are suspected, the subject will be brought in for Clinician evaluation.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

We seek to compare the Relief stent to our currently used ureteral stent to determine if it offers improved clinical outcomes. To this end, patients will be randomized to receive either the Relief stent or the standard stent and the prospectively collected data will be analyzed and compared. At our target enrollment of 50 patients (25 patients in each arm), a power analysis for our primary endpoint (differences in incidence of retrograde urine reflux between randomized study arms) determined that our study will be sufficiently powered (80%) to detect a moderate effect size (w = 0.4) at an alpha level of 0.05.

4.3 END OF STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed all phases of the study including the last visit or the last scheduled procedure shown in the Schedule of Activities (SoA), Section 1.3.

The end of the study is defined as completion of the last visit or procedure shown in the SoA in the trial globally.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

To be eligible to participate in this study, an individual must meet all the following criteria:

1. Has capacity to consent
2. Stated willingness to comply with all study procedures and availability for the duration of the study
3. Persons, 18 years of age or older
4. Male or female subjects with confirmed ureteral and/or renal stones or strictures documented via abdomen X-ray KUB (kidney ureter bladder) or CT (computed tomography)

5.2 EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Distal ureteral obstruction where suture portion of stent may be placed
2. Urinary reflux (assessed by pre-stent cystogram)
3. Pregnancy or lactation
4. Patients requiring bilateral surgical stone management procedure
5. Infected stones
6. Patients where 24cm or 26cm stent lengths are not suitable
7. Ureteral structure in distal third of ureter
8. Intraoperative exclusion: based on urologist's discretion, if trauma has been induced to the distal ureter due to ureteroscopy maneuvers, exclude these patients

5.3 LIFESTYLE CONSIDERATIONS

N/A

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently randomly assigned to the study intervention or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this trial (screen failure) because of a stent contraindication may be rescreened. Rescreened participants should be assigned the same participant number as for the initial screening.

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

The study intervention is placement of the RELIEF Ureteral Stent, and the control product is the Ascerta stent by Boston Scientific. Placement of the stent is described in section 4 of the protocol.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 ACQUISITION AND ACCOUNTABILITY

The Relief stent is provided from the company at no charge. The control stent is our current standard stent (Ascerta by Boston Scientific) which is available in stock. Both will be kept in an OR storage location, and the Relief stent will have a notice that it is for research purposes and not to be used outside of this study and without instruction by the study PI and coordinator.

6.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

Both the Relief stent and control stent are supplied in standard sterile packaging.

6.2.3 PRODUCT STORAGE AND STABILITY

The stents will be stored in the usual location where Urology disposable products are kept.

6.2.4 PREPARATION

No preparation is required.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Patients will be randomized to receive either the Relief stent or the standard ureteral stent. The randomization sequence will be computer-generated, and patients will be randomly allocated based on this sequence.

6.4 STUDY INTERVENTION COMPLIANCE

There will be three questionnaires completed by subjects at multiple different timepoints which will ensure study invention compliance.

6.5 CONCOMITANT THERAPY

N/A

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

Discontinuation from having the stent placed for the expected duration of 7-14 days does not mean discontinuation from the study, and remaining study procedures should be completed as indicated by the study protocol. If a clinically significant finding is identified (including, but not limited to changes from baseline) after enrollment, the investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an adverse event (AE).

The data to be collected at the time of study intervention discontinuation will include the following:

- Detailed reason for early or late stent removal

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request.
An investigator may discontinue or withdraw a participant from the study for the following reasons:

- Pregnancy
- Significant study intervention non-compliance
- If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation

The reason for participant discontinuation or withdrawal from the study will be recorded on the Withdrawal Case Report Form (CRF). Research participants who sign the informed consent form and are randomized but do not receive the study intervention may be replaced. Research participants who sign the informed consent form, and are randomized and receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study, will not be replaced.

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she fails to return for 3 scheduled visits and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 EFFICACY ASSESSMENTS

The primary objective of the study is to assess whether the Relief stent causes reflux of urine. This will be assessed using a standardized grading system described previously. The additional objective of evaluating adequacy of short-term drainage uses the following definition: presence of stent in the ureter and lack of surgical or other intervention to treat symptoms associated with the stent itself during the first 48 hours. This will be determined during the phone interview or in person visit with the patient on

days 1 and 3 as well as by questionnaire. Medications used will be tracked on the research form per the timeline at days 1, 3, 7-10.

Screening will occur in the clinics to identify patients with stone disease who meet eligibility requirements and who require surgical treatment for their stones.

Patients who are deemed clinically suitable and choose to participate will be screened utilizing the EMR for recruitment. The urology provider will first determine if they are interested in participating in the research study and upon agreement, a study team member or research coordinator will introduce the study details and initiate a consent interview. If eligible, these patients will be approached during pre-surgical preoperative clinic visits by the research team to further explain the study and further address any of their questions and get their consent. Patients will be free to leave the study without any impact or influence on their clinical care or management at any point should they desire to do so.

8.2 SAFETY AND OTHER ASSESSMENTS

Case report forms will be generated for each subject and completed by the investigator or study coordinator. The investigator or study coordinator will countersign each form. After the case report forms for a visit are completed, the research coordinator will enter a limited set of data into a data management system. Original case report forms will be securely maintained at the clinical sites. Completed copies of the case report forms will be sent to the research coordinator where they will be stored on a secure hard drive. Subjects will be asked to report any adverse events to the study coordinator or physician. All adverse events will be reported on a standardized form that will elicit the number and specify the type of tests used, therapy (or therapies) used, and clinical visits (office, ER and hospitalization) required until the event is resolved.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS (AE)

The FDA definition of an Adverse event is any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

8.3.3.1 SEVERITY OF EVENT

For adverse events (AEs) not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION

All adverse events (AEs) must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study intervention administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study intervention (DE challenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.
- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
- **Potentially Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.
- **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study intervention) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- **Not Related** – The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

8.3.3.3 EXPECTEDNESS

The study PI and Sponsor will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

8.3.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The study coordinator will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

8.3.5 ADVERSE EVENT REPORTING

The group of investigators, including the principal investigator, and the research support staff will carry out monitoring of all AEs. These will be captured on the appropriate case report form (CRF). Data will be reviewed quarterly to ensure that it is accurate, complete, and that its collection is in compliance with the protocol. There will also be a continual assessment of the risks and benefits.

8.3.6 SERIOUS ADVERSE EVENT REPORTING

The study investigator shall complete an Unanticipated Adverse Device Effect Form and submit to the study sponsor and to the reviewing Institutional Review Board (IRB) as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect. The study sponsor is responsible for conducting an evaluation of an unanticipated adverse device effect and shall report the results of such evaluation to the Food and Drug Administration (FDA) and to all reviewing IRBs and participating investigators within 10 working days after the sponsor first receives notice of the effect. Thereafter, the sponsor shall submit such additional reports concerning the effect as FDA requests.

8.3.7 REPORTING EVENTS TO PARTICIPANTS

N/A

8.3.8 EVENTS OF SPECIAL INTEREST

N/A

8.3.9 REPORTING OF PREGNANCY

N/A

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

This definition could include an unanticipated adverse device effect, 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 or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects (21 CFR 812.3(s)).

8.4.2 UNANTICIPATED PROBLEM REPORTING

The investigator will report unanticipated problems (UPs) to the reviewing Institutional Review Board (IRB). The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are serious adverse events (SAEs) will be reported to the IRB as soon as possible, but in no event later than 10 working days after the investigator first learns of the event.
- Any other UP will be reported to the IRB and to the study sponsor within 3 days of the investigator becoming aware of the problem.

- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and the Office for Human Research Protections (OHRP) within 24 hours of the IRB's receipt of the report of the problem from the investigator.

8.4.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

Cystogram and stent placement are standard urologic procedures. Outcomes from the surgical procedure will be communicated to the patient or their designated family member per standard practice.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

Primary Efficacy Endpoint: presence of reduced ureteral reflux in Relief stent compared to standard ureteral stent.
Comparative statistics will be employed between the two groups. Findings will be reported as the median and interquartile range (IQR) for continuous variables, and percentages and frequencies for categorical variables. To evaluate difference in the incidence of retrograde reflux (primary endpoint: present, absent) and grading between both arms (primary endpoint; Grades I, II, III, IV, V) Chi-square or Fishers exact test will be used as appropriate.

9.2 SAMPLE SIZE DETERMINATION

At our target enrollment of 50 patients (25 patients in each arm), a power analysis for our primary endpoint (differences in incidence of retrograde urine reflux between randomized study arms) determined that our study will be sufficiently power (80%) to detect a moderate effect size (w = 0.4) at an alpha level of 0.05.

9.3 POPULATIONS FOR ANALYSES

To be eligible to participate in this study, an individual must meet all the following criteria:

1. Those who have capacity to consent
2. Stated willingness to comply with all study procedures and availability for the duration of the study
3. 18 years of age and up
4. Male or female subjects with confirmed ureteral and/or renal stones or strictures documented via abdomen X-ray KUB (kidney ureter bladder) or CT (computed tomography)

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

Findings will be reported as the median and interquartile range (IQR) for continuous variables, and percentages and frequencies for categorical variables. To evaluate differences in the incidence of retrograde reflux (Primary endpoint; present, absent) and grading between both arms (Primary endpoint; grades I, II, III, IV, V), chi-square or fishers exact test will be used as appropriate. To analyze USSQ findings between study arms (secondary endpoint), Mann-Whitney U test or independent t-tests will be used for comparisons of continuous variables and chi-square or fishers exact test for comparisons of categorical variables.

9.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

To evaluate differences in the incidence of retrograde reflux (Primary endpoint; present, absent) and grading between both arms (Primary endpoint; grades I, II, III, IV, V), chi-square or fishers exact test will be used as appropriate.

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

To analyze USSQ findings between study arms (secondary endpoint), Mann-Whitney U test or independent t-tests will be used for comparisons of continuous variables and chi-square or fishers exact test for comparisons of categorical variables.

9.4.4 SAFETY ANALYSES

Adverse events and serious AEs will be compared between the two cohorts using descriptive and quantitative statistics, and the data will be presented in a table.

9.4.5 BASELINE DESCRIPTIVE STATISTICS

Baseline descriptive statistics will be performed comparing the two cohorts.

9.4.6 PLANNED INTERIM ANALYSES

N/A

9.4.7 SUB-GROUP ANALYSES

Patients will be randomized to receive either the Relief stent or the current standard stent. Patients will be randomized regardless of age, sex, race/ethnicity or other demographic characteristic since stone disease and stent related pain affects patients of all genders.

9.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

Individual participant data will not be listed by measure/time point; rather the data of the entire cohort will be presented I a de-identified way.

9.4.9 EXPLORATORY ANALYSES

N/A

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to investigator, funding agency, the Investigational New Drug (IND) or Investigational Device Exemption (IDE) sponsor and regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and sponsor and will provide the reason(s) for the

termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB and/or Food and Drug Administration (FDA).

10.1.2 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their interventions. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to 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.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), regulatory agencies or pharmaceutical company supplying study product 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. 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 the reviewing IRB, Institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be stored in Redcap. This 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. The study data entry and study management systems will be secured and password protected.

10.1.3 FUTURE USE OF STORED SPECIMENS AND DATA

Data collected for this study will be analyzed and stored at UCSD. After the study is completed, the de-identified, archived data will be stored in RedCap.

10.1.4 KEY ROLES AND STUDY GOVERNANCE

Principal Investigator

Seth Bechis, MD, MS, Associate Professor of Urology
UC San Diego Health
200 W Arbor Dr. San Diego, CA 92103
858-657-7876
sbechis@health.ucsd.edu

10.1.5 SAFETY OVERSIGHT

The group of investigators, including the principal investigator and the research support staff will carry out the Data and Safety Monitoring Plan. Data will be reviewed quarterly to ensure that it is accurate, complete, and that its collection is in compliance with the protocol. There will also be a continual assessment of the risks and benefits.

10.1.6 CLINICAL MONITORING

Clinical site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with International Conference on Harmonisation Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s).

10.1.7 DATA HANDLING AND RECORD KEEPING

10.1.7.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Hardcopies of the study visit worksheets will be provided for use as source document worksheets for recording data for each participant enrolled in the study. Data recorded in the electronic case report form (eCRF) derived from source documents should be consistent with the data recorded on the source documents.

Clinical data (including adverse events (AEs), concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into a Redcap database. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

10.1.7.2 STUDY RECORDS RETENTION

Study documents should be retained for a minimum of 2 years after the last approval of a marketing application in an International Conference on Harmonisation (ICH) region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the

formal discontinuation of clinical development of the study intervention. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

10.1.8 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site investigator to use continuous vigilance to identify and report deviations within 7 working days of identification of the protocol deviation, or within 7 working days of the scheduled protocol-required activity. Protocol deviations must be sent to the reviewing Institutional Review Board (IRB) per their policies. The site investigator is responsible for knowing and adhering to the reviewing IRB requirements. Further details about the handling of protocol deviations will be included in the MOP.

10.2 ADDITIONAL CONSIDERATIONS

N/A

10.3 ABBREVIATIONS

AE	Adverse Event
ANCOVA	Analysis of Covariance
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
COC	Certificate of Confidentiality
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data Safety Monitoring Board
DRE	Disease-Related Event
EC	Ethics Committee
eCRF	Electronic Case Report Forms
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FFR	Federal Financial Report
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
GWAS	Genome-Wide Association Studies
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ISO	International Organization for Standardization
ITT	Intention-To-Treat
LSMEANS	Least-squares Means
MedDRA	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
MSDS	Material Safety Data Sheet
NCT	National Clinical Trial
NIH	National Institutes of Health
NIH IC	NIH Institute or Center
OHRP	Office for Human Research Protections
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SMC	Safety Monitoring Committee
SOA	Schedule of Activities
SOC	System Organ Class
SOP	Standard Operating Procedure

UP	Unanticipated Problem
US	United States

10.4 PROTOCOL AMENDMENT HISTORY

The table below is intended to capture changes of IRB-approved versions of the protocol, including a description of the change and rationale. A Summary of Changes table for the current amendment is located in the Protocol Title Page.

Version	Date	Description of Change	Brief Rationale

11 REFERENCES

1- Chew, B.H., B.E. Knudsen, and J.D. Denstedt, The use of stents in contemporary urology. Current opinion in urology, 2004. 14(2): p. 111-115.
2- Joshi, H., et al., Characterization of urinary symptoms in patients with ureteral stents. Urology, 2002. 59(4): p. 511-516.
3- Chambade, D., et al., Study of the safety of double J ureteric stents. Progres en urologie: journal de l'Association francaise d'urologie et de la Societe francaise d'urologie, 2006. 16(4): p. 445-449.
4- Shao, Y., et al., The influence of ureteral stent on renal pelvic pressure in vivo. Urological research, 2009. 37(4): p. 221-225.
5- Giannarini, G., et al., Predictors of morbidity in patients with indwelling ureteric stents: results of a prospective study using the validated Ureteric Stent Symptoms Questionnaire. BJU international, 2011. 107(4): p. 648-654.
6- Krebs, A., et al., The 'buoy'stent: evaluation of a prototype indwelling ureteric stent in a porcine model. BJU international, 2009. 104(1): p. 88-92.