Medical Device Clinical Trial Protocol

Reference Number: U0628

Protocol Title:
A prospective, multi-center, single-arm study to evaluate the safety and efficacy of LithoVue ureteroscope system in Chinese patients with urinary disease

Investigational Device:

LithoVue Ureteroscope System (including flexscope catheter and workstation)

Device Model:

LithoVue Flexscope	
• LithoVue Standard	M0067913500
• LithoVue Reverse	M0067913600
LithoVue System Workstation	
• LithoVue System Workstation	M0067911200

Class of device:

Class 3 medical device requiring clinical trials Yes ☐ No☒
Same class device within China Yes ☐ No☒

Protocol version and date: Rev/AB, 2018, Mar 29

Clinical trial sites: Peking University Third Hospital

Principal Investigator: Ma Lulin

Sponsor: BSC International Medical Trading (Shanghai) Co., Ltd, ("BSC China")

Agent: not applicable

A prospective, multi-center, single-arm study to evaluate the safety and efficacy of LithoVue ureteroscope system in Chinese patients with urinary disease

LithoVue China Study

CLINICAL PROTOCOL

BSC Project Number: U0628

Sponsored By

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Investigational Sites	See “LithoVue China Study site list and contact information”

Original Release: Jan 16, 2018

Current Version: Mar 29, 2018

Revision Version	Protocol Date	Template number and version	Protocol Section Modified	Existing Text as Written in Protocol, Version	Revised/New Text as Written in Protocol, Version	Justification for Modification
AA	Jan 16, 2018	90702637 Rev/Ver AI	N/A	N/A	N/A	Initial release
AB	Mar 29,2018	90702637 Rev/Ver AI	17.4	Sponsor Responsibilities , AA	Sponsor Responsibilities , AB	Comments of PI site's EC.

2. Protocol Synopsis

<table>
<tr><th colspan="2">A prospective, multi-center, single-arm study to evaluate the safety and efficacy of LithoVue ureteroscope system in Chinese patients with urinary disease
LithoVue China Study</th></tr>
<tr><td>Objective(s)</td><td>The aim of this study is to evaluate the safety and efficacy of LithoVue ureteroscope system in Chinese population, to support the regulatory approval by CFDA</td></tr>
<tr><td>Planned Indication(s) for Use</td><td>The LithoVue System is intended to be used to visualize organs, cavities and canals in the urinary tract (urethra, bladder, ureter, calyces and renal papillae) via transurethral or percutaneous access routes. It can also be used in conjunction with endoscopic accessories to perform various diagnostic and therapeutic procedures in the urinary tract</td></tr>
<tr><td>Test Device</td><td>LithoVue Ureteroscope System(including flexscope catheter and workstation)

<table><tr><td colspan="2">LithoVue Flexscope</td></tr><tr><td>• LithoVue Standard</td><td>M0067913500</td></tr><tr><td>• LithoVue Reverse</td><td>M0067913600</td></tr><tr><td colspan="2">LithoVue System Workstation</td></tr><tr><td>• LithoVue System Workstation</td><td>M0067911200</td></tr></table></td></tr>
<tr><td>Study Design</td><td>Prospective, multicenter, single-arm, pre-market study</td></tr>
<tr><td>Planned Number of Subjects</td><td>LithoVue China study will enroll 60 patients. The enrolling cap for each participate center is 40 patients.
All procedures in each participate center should be solely performed by experienced urologist who is skilled at therapeutic urology cases.</td></tr>
<tr><td>Planned Number of Centers / Countries</td><td>3 investigational sites in China.</td></tr>
<tr><td>Primary Endpoint</td><td>Procedure success rate of LithoVue ureteroscope system
Procedure success is defined as:
Scope condition is suitable to complete the procedure and not requiring immediate scope substitution; it is also considered as a procedure success if the clinical effect is the same as that from the LithoVue scope per</td></tr>
</table>

A prospective, multi-center, single-arm study to evaluate the safety and efficacy of LithoVue ureteroscope system in Chinese patients with urinary disease LithoVue China Study	
	investigator's judgement in the case of a scope change (non-LithoVue).
Secondary Endpoints	1. Procedure routes: transurethral or percutaneous access 2. Target lesion's size and location 3. Procedure time: defined as the time between LithoVue catheter insertion and removal 4. Hospitalization time: defined as the time between patient admission and discharge 5. Stone clearance rate: clearance is defined as stone free or residual stone's diameter≤4mm on KUB and urinary CT at 4W post procedure. 6. Complication (Clavein-Dindo classification): a) fever(>38.5^{o}) b) urinary tract infection requiring additional antibiotics (routine antibiotics is within 48 hours post procedure) c) Urinary sepsis, defined as infection and qSOFA score ⩾2. (qSOFA score includes • the change of consciousness (Glasgow score < 13) • systolic blood pressure ≤ 100 mmHg • respiratory frequency ⩾22 times / min) d) ureteral injury (moderate, medium and severer) e) bleeding requiring transfusion f) perirenal hematoma g) steinstrasse h) severe abdominal pain (requires additional hospitalization treatment or prolonged hospitalization time) 7. Image quality: Very good, good, fair, poor, bad 8. Maneuverability: Very good, good, fair, poor, bad 9. Surgeon's overall satisfaction: Very good, good, acceptable, poor, bad
Method of	This is a single arm study.

A prospective, multi-center, single-arm study to evaluate the safety and efficacy of LithoVue ureteroscope system in Chinese patients with urinary disease LithoVue China Study	
Assigning Patients to Treatment	
Follow-up Schedule	Follow up points are 48±24 hours post procedure, 4W±7 days post procedure. The visit points are: 1. Baseline 2. Study Procedure 3. 48±24H post procedure 4. 4W ±7 days post procedure
Study Duration	The study is expected to last 9 months after first subject enrollment.
Participant Duration	The study duration for each subject is expected to be approximately 1.5 months.
Inclusion Criteria	1. Willing and able to provide written informed consent to participate in the study. 2. Willing and able to comply with the study procedures. 3. Diagnosed as urinary disease and indicated for flexible ureteroscope procedures 4. For stone cases, the diameter of stones is less than or equal to 2cm in order to avoid staged procedures
Exclusion Criteria	1. Surgeries are contraindicated. 2. Flexible ureterocope procedure is contraindicated 3. Based on doctor's evaluation, the patient's medical condition doesn't fit for this study 4. For stone case, the diameter of stones is greater than 2cm. 5. Women of childbearing potential who are or might be pregnant at the time of this study.
Statistical Methods	

A prospective, multi-center, single-arm study to evaluate the safety and efficacy of LithoVue ureteroscope system in Chinese patients with urinary disease LithoVue China Study	
Primary Statistical Hypothesis	The Procedure success rate of LithoVue ureteroscope system is the primary endpoint. Published literature result regarding this index is 95.6%. Based on previous clinical experience in China, the rate should be more than 85%. So 85% is chosen as the objective performance value. The expected success rate is 95% based on investigator's decision. A hypothesis testing for the primary endpoint will be performed using 85% as the performance goal. For procedure success rate, the 90% exact Clopper-Pearson confidence interval of the proportion will be calculated. The primary objective is met if the lower bound of the confidence interval (LCI) is greater than the PG,
Statistical Test Method	The procedure success rate and other index for LithoVue ureteroscope system will be summarized descriptively. Categorical variables will be tabulated with frequencies, percentages and 95% confidence intervals. Continuous variables will be tabulated with mean, median, standard deviation, minimum, maximum, and 95% confidence interval of the mean.
Sample Size Calculation	The sample size is calculated using according to the text book "Statistic for medical device clinical trials" written by Prof. Li Wei. The formula is : $$n = \left[\frac{z_\alpha\sqrt{P_0(1-P_0)} + z_\beta\sqrt{P_1(1-P_1)}}{P_1 - P_0}\right]^2$$ n is sample size, P_0 is objective performance value, P_1 is expected technique success rate. It is designed P_1 as 0.95, P_0 as 0.85, one-sided α=0.05，β=0.20（power=80%）. As the primary endpoint is captured in ureteroscope procedures, it's not necessary to consider attrition rate. So the final calculated sample size is 60.

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4. Introduction

The development of reusable flexible ureteroscopes is a novel innovation to diagnose or treat upper urinary tract. Comparing open surgery, during the past two decades, flexible ureteroscopes provided major diagnostic and treatment advantages concerning most upper urinary tract (UUT) pathologies, with reduction of associated morbidity. Flexible ureteroscopy has allowed for visual inspection of the entire collecting system.[1,2]

The designs of traditional reusable ureteroscopes, however, result in progressive deterioration of scope performance. Sterilization requires dedicated equipment, staff, and time. Decontamination has failed in the past and confers a risk of transmitting infection.[3,4]

As re-usable flexible fiber-optic or digital ureteroscope which has the potential increased risk for scope damage and repair costs compared to single-use scopes, LithoVue system, a single-use, digital, disposable flexible ureteroscope, was introduced to market.

This study aimed to evaluate the safety and efficacy of LithoVue ureteroscope system in Chinese population, to support the regulatory approval by CFDA.

5. Device Description

The LithoVue System is a software-controlled digital flexible ureteroscope system that consists of the LithoVue System Workstation (Touch PC and Cart) and the LithoVue Single-Use Digital Flexible Ureteroscope (sterile, single-use disposable) catheter.

The LithoVue Single-Use Digital Flexible Ureteroscope catheter is a sterile, single-use device comprised of two main components: a handle with articulation controls and accessory access ports, and a flexible shaft portion. The LithoVue Single-Use Digital Flexible Ureteroscope catheter is also referred to as the LithoVue Flexscope or ureteroscope in these instructions. The LithoVue Flexscope catheter is used by physicians to access, visualize, and perform procedures in the urinary tract. The ureteroscope enables delivery and use of accessories such as biopsy forceps, laser fibers, guidewires, graspers and retrieval baskets at a surgical site. The distal tip of the ureteroscope articulates to 270 degrees in two directions, and the distal tip can be rotated a total of 360 degrees by rotating the handle. In addition, the shaft of the ureteroscope features a secondary deflection that is passive.

The LithoVue System Workstation is referred to as the System Workstation, and the

LithoVue Single-Use Digital Flexible Ureteroscope is referred to as the LithoVue Flexscope in these instructions.

The LithoVue Flexscope connects to the System Workstation via the Flexscope Connector Cable Plug Receptacle (hereafter referred to as Workstation Receptacle) on the front of the System Workstation.

The LithoVue System is designed to allow physicians to access, visualize, and perform procedures in the urinary tract, using appropriate accessory devices (e.g., baskets, laser fibers, and forceps).

6. Objectives

The aim of this study is to evaluate the safety and efficacy of LithoVue ureteroscope system in Chinese population, to support the regulatory approval by CFDA.

7. Endpoints

7.1 Primary endpoint:

Procedure success rate of LithoVue ureteroscope system.

Procedure success is defined as:

Scope condition is suitable to complete the procedure and not requiring immediate scope substitution; it is also considered as a procedure success if the clinical effect is the same as that by the LithoVue scope per investigator's judgement in the case of a scope change (non-LithoVue).

7.2 Secondary endpoint:

1. Procedure routes: transurethral or percutaneous access
2. Target lesion's size and location
3. Procedure time: defined as the time between LithoVue catheter insertion and removal
4. Hospitalization time: defined as the time between patient admission and discharge
5. Stone clearance rate: clearance is defined as stone free or residual stone's diameter≤4mm on KUB and urinary CT at 4W post procedure

6. Complication(Clavein-Dindo classification):
    a) fever(>38.5^{o})
    b) urinary tract infection requiring additional antibiotics (routine antibiotics is within 48 hours post procedure)
    c) Urinary sepsis, defined as infection and qSOFA score ⩾2. (qSOFA score includes
        - the change of consciousness (Glasgow score < 13)
        - systolic blood pressure ≤ 100 mmHg
        - respiratory frequency ⩾22 times / min)
    d) ureteral injury (moderate, medium and severer)
    e) bleeding requiring transfusion
    f) perirenal hematoma
    g) steinstrasse
    h) severe abdominal pain (requires additional hospitalization treatment or prolonged hospitalization time)
7. Image quality: Very good, good, fair, poor, bad
8. Maneuverability: Very good, good, fair, poor, bad
9. Surgeon's overall satisfaction: Very good, good, acceptable, poor, bad

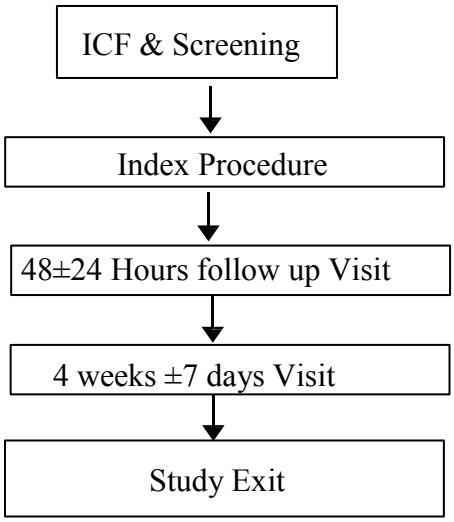
8. Study Design

This study is a prospective, multicenter, single-arm, pre-market study.

8.1 Scale and Duration

This study will be conducted at 3 centers in China. Data will be collected at least 60 patients. All participating patients will sign the informed consent form approved at the participating center per local requirements.

Figure 3.2-1: LithoVue China Study Design



8.2 Treatment Assignment

Subjects in this trial will not be randomized. Eligible subjects will be considered as enrolled into LithoVue China Study at the time of sheath is accessed into the urinary tract or percutaneous route is established.

8.3 Justification for the Study Design

This study is designed to evaluate the safety and efficacy of LithoVue ureteroscope system in Chinese population, to support the regulatory approval by CFDA.

9. Subject Selection

9.1 Study Population and Eligibility

The study population is all patients who need diagnostic or therapeutic flexible ureteroscopy procedures.

9.2 Inclusion Criteria

Subjects who meet all of the following criteria may be given consideration for inclusion in this clinical investigation, provided no exclusion criteria are met (see 9.3).

1. Willing and able to provide written informed consent to participate in the study
2. Willing and able to comply with the study procedures

3. Diagnosed as urinary disease and indicated for flexible ureteroscope procedure
4. For stone cases, the diameter of stones is less than or equal to 2cm in order to avoid staged procedures

9.3 Exclusion Criteria

Subjects who meet any one of the following criteria will be excluded from this clinical study.

1. Surgeries are contraindicated
2. Flexible ureterocope procedure is contraindicated
3. Based on doctor's evaluation, the patient's medical condition doesn't fit for this study
4. For stone cases, the diameter of stones is greater than 2cm
5. Women of childbearing potential who are or might be pregnant at the time of this study

10. Subject Accountability

10.1 Point of Enrollment

The point of enrollment is the time when sheath is accessed into the urinary tract or percutaneous route is established.

10.2 Withdrawal

All subjects enrolled in the clinical study (including those withdrawn from the clinical study or lost to follow-up) shall be accounted for and documented. The Investigator may discontinue a subject from participation in the trial if the Investigator feels that the subject can no longer fully comply with the requirements of the trial or if any of the trial procedures are deemed potentially harmful to the subject. If any subjects withdraw from the study, the replaced subjects shall be enrolled, to meet study designed sample size. If a subject withdraws from the clinical investigation, the reason(s) shall be recorded. If such withdrawal is due to problems related to investigational device safety or performance, the investigator shall ask for the subject's permission to follow his/her status/condition outside of the clinical

study. Data that have already been collected on withdrawn subjects will be retained and used for analysis but no new data will be collected after withdrawal.

10.3 Enrollment Controls

The enrolling cap for each participate center is 40 patients.

10.4 End-of-Study Action Plan

After end of the study, subjects will continue receiving routine clinical practice.

11. Study Methods

11.1 Data Collection

This study will collect data on:

1. Procedure success rate of LithoVue ureteroscope system

   Procedure success is defined as:

   Scope condition is suitable to complete the procedure and not requiring immediate scope substitution; it is also considered as a procedure success if the clinical effect is the same as that by the LithoVue scope per investigator's judgement in the case of a scope change (non-LithoVue).

2. Procedure routes: transurethral or percutaneous access
3. Target lesion's size and location
4. Procedure time: defined as the time between LithoVue catheter insertion and removal
5. Hospitalization time: defined as the time between patient admission and discharge
6. Stone clearance rate: clearance is defined as stone free or residual stone's diameter≤4mm on KUB and urinary CT at 4W post procedure.
7. Complication (Clavein-Dindo classification):
   a) fever(>38.5^{o})
   b) urinary tract infection requiring additional antibiotics (routine antibiotics is within 48 hours post procedure)

c) Urinary sepsis, defined as infection and qSOFA score ⩾2. (qSOFA score includes
   - the change of consciousness (Glasgow score < 13)
   - systolic blood pressure ≤ 100 mmHg
   - respiratory frequency ⩾22 times / min)

d) ureteral injury (moderate, medium and severer)

e) bleeding requiring transfusion

f) perirenal hematoma

g) steinstrasse

h) severe abdominal pain (requires additional hospitalization treatment or prolonged hospitalization time)

8. Image quality: Very good, good, fair, poor, bad

9. Maneuverability: Very good, good, fair, poor, bad

10. Surgeon's overall satisfaction: Very good, good, acceptable, poor, bad

Table 3.2-1: Data Collection Schedule

Procedure/Assessment	Screening (Base Line)	LithoVue Procedure	Follow-up Visits	
			48(±24)hours Visit	4 weeks (± 7 Days) Visit
Informed consent	X	--	--	--
Demographics	X	--	--	--
Physical assessment	X	--	--	--
Pregnancy test(Women of reproductive age)	X	--	--	--
Medical history	X	--	--	--
Procedure information	--	X	--	--
Image quality, maneuverability, Irritation	--	X	--	--
Complication and treatment	--	X	X	X
Hospitalization time	--	--	--	X
Urinary CT and KUB	--	--	--	X
Stone clearance	--	--	--	X
Surgeon's satisfaction	--	--	--	X
Adverse events	--	X	X	X

11.2 Study Candidate Screening

The investigator(s) are to follow local standard of care medical practice to diagnose urinary system disease and determine the eligibility for flexible ureteroscope procedures.
This will be an open-label, single-arm study. All patients who are evaluated and scheduled to have flexible ureteroscope procedures will be approached prior to flexible ureteroscope treatment to see if they are willing to participate in the study.

11.3 Informed Consent

Patients who are interested in participating in the study will sign an Informed Consent prior to undergoing flexible ureteroscope procedures.

11.4 Baseline

1. Age and gender
2. Medical history including diagnosis
3. Physical examination including blood pressure and pulse
4. Pregnancy test(Women of reproductive age)
5. Indication for flexible ureteroscope procedures

11.5 Index procedure

1. Procedure date
2. Side: left, right, bilateral
3. Location: bladder, ureter (proximal, middle, distal), kidney (pelvis, upper calyx, middle calyx, lower calyx)
4. Size of the stone/tumor: single, multiple; diameter(mm)
5. Angle between ureter and stone/tumor(degrees)
6. Procedure routes: transurethral or percutaneous access
7. Procedure time: defined as the time between LithoVue catheter insertion and removal

8. Insertion of the device up to the stone/tumor
9. Image quality vision: Very good, good, fair, poor, bad
10. Maneuverability: Very good, good, fair, poor, bad
11. Irrigation：Very good, good, fair, poor, bad
12. Breakage of scope: if yes, indicate reason
13. Procedure success:

    Procedure success defined as:

    Scope condition is suitable to complete the procedure and not requiring immediate scope substitution; it is also considered as a procedure success if the clinical effect is the same as that by the LithoVue scope per investigator's judgement in the case of a scope change (non-LithoVue).

14. Complications and treatment

    Include immediate bleeding and perforation and the corresponding the treatment(s). If immediate bleeding occurs, the following information needs to be collected: hemoglobin value, the hemostasis method and whether transfusion is used; the amount of the blood transfusion if applicable; and whether it is result in hemorrhagic shock.

15. AE and treatment

11.6 48± 24 hours post procedure

1. Complications and treatment

   Complication (Clavein-Dindo classification):

   a) fever(>38.5^{o})
   b) urinary tract infection requiring additional antibiotics (routine antibiotics is within 48 hours post procedure)
   c) Urinary sepsis, defined as infection and qSOFA score ⩾2. (qSOFA score includes
      - the change of consciousness (Glasgow score < 13)
      - systolic blood pressure ≤ 100 mmHg

- respiratory frequency ⩾22 times / min)

d) ureteral injury (moderate, medium and severer)

e) bleeding requiring transfusion

f) perirenal hematoma

g) steinstrasse

h) severe abdominal pain (requires additional hospitalization treatment or prolonged hospitalization time)

2. AE and treatment

11.7 4 Weeks± 7 days post procedure

1. Complications and treatment

   Complication (Clavein-Dindo classification):

   a) fever(>38.5^{o})

   b) urinary tract infection requiring additional antibiotics (routine antibiotics is within 48 hours post procedure)

   c) Urinary sepsis, defined as infection and qSOFA score ⩾2. (qSOFA score includes

      - the change of consciousness (Glasgow score < 13)
      - systolic blood pressure ≤ 100 mmHg
      - respiratory frequency ⩾22 times / min)

   d) ureteral injury (moderate, medium and severer)

   e) bleeding requiring transfusion

   f) perirenal hematoma

   g) steinstrasse

   h) severe abdominal pain (requires additional hospitalization treatment or prolonged hospitalization time)

2. Stone clearance rate: clearance is defined as stone free or residual stone's diameter≤4mm on KUB and urinary CT at 4W post procedure

3. Hospitalization time: defined as the time between patient admission and discharge

4. Surgeon's overall satisfaction: Very good, good, acceptable, poor, bad

5. AE and treatment

11.8 Study Completion

Data collection for the patient will be completed at the 4 weeks follow up evaluation. The patient will be exited from this study following the successful completion 4 weeks follow-up evaluation.

In the event of a safety concern, the physician may continue follow-up with the participating patient.

11.9 Source Documents

Table 11.9-1 summarizes the source documents required for data collection and verification. Where copies of the original source document as well as printouts of original electronic source documents are retained, these shall be signed and dated by a member of the investigation center team with a statement that it is a true reproduction of the original source document.

Table 3.2-1: Source Documentation Requirements

Requirement	Disposition
Index procedure record	Retain at center
Video data	Retain at center
Urinary CT and KUB	Retain at center
Adverse Event summary: hospitalization records as applicable	Retain at center

12. Statistical Considerations

12.1 Endpoints

12.1.1. Primary Endpoint

Procedure success rate of LithoVue ureteroscope system.

Procedure success is defined as:

Scope condition is suitable to complete the procedure and not requiring immediate scope substitution; it is also considered as a procedure success if the clinical effect is the same as

that by the LithoVue scope per investigator's judgement in the case of a scope change (non-LithoVue).

12.1.1.1. Hypotheses

The Procedure success rate of LithoVue ureteroscope system is the primary endpoint. Published literature result regarding this index is 95.6% [5]. Based on previous clinical experience in China, the rate should be more than 85%. So 85% is chosen as the objective performance value. The expected success rate is 95% based on the investigator's decision.

A hypothesis testing for the primary endpoint will be performed using 85% as the PG. For procedure success rate endpoint, the 90% exact Clopper-Pearson confidence interval of the proportion will be calculated. The primary objective is met if the lower bound of the confidence interval (LCI) is greater than the PG.

12.1.1.2. Sample Size

The sample size is calculated using according to the text book "Statistic for medical device clinical trials" written by Prof. Li Wei. The formula is:

$$n = \left[\frac{z_\alpha\sqrt{p_0(1-p_0)} + z_\beta\sqrt{p_1(1-p_1)}}{p_1 - p_0}\right]^2$$

n is sample size, P_0 is objective performance value, P_1 is expected technique success rate. It is designed P_1 as 0.95, P_0 as 0.85, one-sided α=0.05，β=0.20（power=80%）. As the primary endpoint is captured in ureteroscope procedures, it's not necessary to consider attrition rate. So the final calculated sample size is 60.

12.1.1.3. Statistical Methods

The procedure success rate and other endpoints for LithoVue ureteroscope system will be summarized descriptively. Categorical variables will be tabulated with frequencies, percentages and 95% confidence intervals. Continuous variables will be tabulated with mean, median, standard deviation, minimum, maximum, and 95% confidence interval of the mean.

12.1.2. Secondary Endpoints

1. Procedure routes: transurethral or percutaneous access

2. Target lesion's size and location
3. Procedure time: defined as the time between LithoVue catheter insertion and removal
4. Hospitalization time: defined as the time between patient admission and discharge
5. Stone clearance rate: clearance is defined as stone free or residual stone's diameter≤4mm on KUB and urinary CT at 4W post procedure
6. Complication (Clavein-Dindo classification):
    a) fever(>38.5^{o})
    b) urinary tract infection requiring additional antibiotics (routine antibiotics is within 48 hours post procedure)
    c) Urinary sepsis (defined as infection and qSOFA score ⩾2. (qSOFA score includes
        - the change of consciousness (Glasgow score < 13)
        - systolic blood pressure ≤ 100 mmHg
        - respiratory frequency ⩾22 times / min)
    d) ureteral injury (moderate, medium and severer)
    e) bleeding requiring transfusion
    f) perirenal hematoma
    g) steinstrasse
    h) severe abdominal pain (requires additional hospitalization treatment or prolonged hospitalization time)
7. Image quality: Very good, good, fair, poor, bad
8. Maneuverability: Very good, good, fair, poor, bad
9. Surgeon's overall satisfaction: Very good, good, acceptable, poor, bad

12.2 General Statistical Methods

12.2.1. Analysis Sets

Safety analysis set will be comprised of all subjects that sheath is accessed into the urinary tract or percutaneous route is established.

Efficacy analysis set will be comprised of all subjects that sheath is accessed into the urinary tract or percutaneous route is established.

12.2.2. Number of Subjects per Investigative Site

The enrollment cap for each participating center is 40 patients.

12.3 Data Analyses

1. The following endpoints will be summarized at index procedure:
   (1) Procedure success rate
   (2) Procedure route
   (3) Procedure time
   (4) Target lesion's size and location
   (5) Image quality
   (6) Maneuverability
   (7) Complication
2. The following endpoints will be summarized at 48 hours post procedure:
   (1) Complication
3. The following endpoints will be summarized at 4 weeks post procedure:
   (1) Complication
   (2) Stone clearance
   (3) Hospitalization time
   (4) Surgeon's overall satisfaction

12.3.1. Interim Analyses

No formal interim analyses are planned for this study.

12.3.2. Justification of Pooling

This study will be conducted under a common protocol for each investigational site with the intention of pooling the data for analyses. Every effort will be made to promote consistency in study execution at each investigational site.

12.3.3. Changes to Planned Analyses

Any changes to the planned statistical analyses made prior to performing the analyses will be documented in an amended Statistical Analysis Plan approved prior to performing the analyses. Changes from the planned statistical methods after performing the analyses will be documented in the clinical study report along with a reason for the deviation.

13. Data Management

13.1 Data Collection, Processing, and Review

Subject data will be recorded in a limited access secure electronic data capture (EDC) system.

The clinical database will reside on a production server hosted by EDC. All changes made to the clinical data will be captured in an electronic audit trail and available for review by Boston Scientific Corporation (BSC) or its representative. The associated RAVE software and database have been designed to meet regulatory compliance for deployment as part of a validated system compliant with laws and regulations applicable to the conduct of clinical studies pertaining to the use of electronic records and signatures. Database backups are performed regularly.

The Investigator provides his/her electronic signature on the appropriate electronic case report forms (eCRFs) in compliance with local regulations. A written signature on printouts of the eCRFs must also be provided if required by local regulation. Changes to data previously submitted to the sponsor require a new electronic signature by the Investigator acknowledging and approving the changes.

Visual and/or electronic data review will be performed to identify possible data discrepancies. Manual and/or automatic queries will be created in the EDC system and will be issued to the

site for appropriate response. Site staff will be responsible for resolving all queries in the database.

13.2 Data Retention

The Investigator and site will maintain, at the investigative site, in original format all essential study documents and source documentation that support the data collected on the study subjects in compliance with ISO 14155 or International Conference on Harmonization (ICH)/Good Clinical Practice (GCP) guidelines, China related regulation and guideline. For institute, documents must be retained for at least 10 years after the end of study. For sponsor, documents must be retained until the study device is no longer used in market. last approval of a marketing application or until at least 5 years have elapsed since the formal discontinuation of the clinical investigation of the product. These documents will be retained for a longer period of time by agreement with BSC or in compliance with pertinent individual country laws and regulations.

It is BSC's responsibility to inform the Investigator and site when these documents no longer need to be maintained. The Investigator and site will take measures to ensure that these essential documents are not accidentally damaged or destroyed. If for any reason the Investigator and site withdraw responsibility for maintaining these essential documents, custody must be transferred to an individual who will assume responsibility and BSC must receive written notification of this custodial change.

14. Amendments

If a protocol revision is necessary which affects the rights, safety or welfare of the subject or scientific integrity of the data, an amendment is required. Appropriate approvals (e.g., IRB/EC/FDA/CA) of the revised protocol must be obtained prior to implementation.

15. Deviations

An Investigator must not make any changes or deviate from this protocol, except to protect the life and physical well-being of a subject in an emergency. An investigator shall notify the sponsor and the reviewing IRB/EC of any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency, and those deviations which

affect the scientific integrity of the clinical investigation. Such notice shall be given as soon as possible, but no later than 5 working days after the emergency occurred, or per prevailing local requirements, if sooner than 5 working days.

All deviations from the investigational plan, with the reason for the deviation and the date of occurrence, must be documented and reported to the sponsor using EDC. Sites may also be required to report deviations to the IRB/EC, per local guidelines and government regulations.

Deviations will be reviewed and evaluated on an ongoing basis and, as necessary, appropriate corrective and preventive actions (including notification, site re-training, or site discontinuation/termination) will be put into place by the sponsor.

Deviations will be classified by BSC according to the following definitions:

- Type A - Deviation to protect the life or physical well-being of a patient in an unforeseen emergency.
- Type B - Deviation based on medical judgment.
- Type C - Deviation due to misunderstanding of protocol requirements.
- Type D - Deviation due to a situation that is beyond control.
- Type E - Deviation due to an oversight, error or protocol non-compliance.

Also, a major PD is a protocol deviation that directly or potentially disrupts the study progress (i.e., the study design, study data and results can be compromised), OR a protocol deviation that compromises the safety and welfare of study participants. A minor PD is a protocol deviation that does not disrupt study progress (i.e., the study design, study data and results will not be compromised), AND does not compromise the safety and welfare of study participants.

16. Device/Equipment Accountability

The investigational devices/equipment shall be securely maintained, controlled, and used only in this clinical study. The current BSC processes will be used to track subjects and device allocations during the study.

The sponsor shall keep records to document the physical location of all investigational devices from shipment of investigational devices to the investigation sites until return or disposal.

Records shall be kept by the principal investigator or an authorized designee to document the physical location and conditions of storage of all investigational devices/equipment.

The principal investigator or an authorized designee shall keep records documenting the receipt, use, return and disposal of the investigational devices/equipment, which shall include the following

- Date of receipt
- Manufacture date of investigational device
- Batch number of investigational device
- Identification of each investigational device/piece of equipment (batch number or unique code)
- Expiry date, as applicable
- Date or dates of use
- Subject identification
- Date on which the investigational device/piece of equipment was returned/explanted from subject, if applicable
- Date of return of unused, expired, or malfunctioning investigational devices/equipment, if applicable.

17. Compliance

17.1 Statement of Compliance

This study will be conducted in accordance with ISO 14155:2011 (2nd Edition; 2011-02-01) Clinical Investigation of Medical Devices for Human Subjects- GCP, or the relevant parts of the ICH Guidelines for GCP, ethical principles that have their origins in the Declaration of

Helsinki, and applicable China's laws and regulations. The study shall not begin until the required approval/favorable opinion from the IRB/EC and/or regulatory authority has been obtained, if appropriate. Also, the study shall not begin prior to issuance of the site Authorization to Enroll, as provided by the sponsor. Any additional requirements imposed by the IRB/EC or regulatory authority shall be followed, if appropriate.

17.2 Investigator Responsibilities

The Principal Investigator of an investigational center is responsible for ensuring that the study is conducted in accordance with the Clinical Study Agreement, the investigational plan/protocol, ISO 14155, ethical principles that have their origins in the Declaration of Helsinki, any conditions of approval imposed by the reviewing IRB/EC, and prevailing local and/or country laws and/or regulations, whichever affords the greater protection to the subject.

The Principal Investigator's responsibilities include, but are not limited to, the following.

- Prior to beginning the study, sign the Clinical Study Agreement and Protocol Signature page documenting his/her agreement to conduct the study in accordance with the protocol.
- Provide his/her qualifications and experience to assume responsibility for the proper conduct of the study and that of key members of the center team through up-to-date curriculum vitae or other relevant documentation and disclose potential conflicts of interest, including financial, that may interfere with the conduct of the clinical study or interpretation of results.
- Make no changes in or deviate from this protocol, except to protect the life and physical well-being of a subject in an emergency; document and explain any deviation from the approved protocol that occurred during the course of the clinical investigation.
- Create and maintain source documents throughout the clinical study and ensure their availability with direct access during monitoring visits or audits; ensure that all clinical-investigation-related records are retained per requirements.
- Ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs and in all required reports.

- Record, report, and assess (seriousness and relationship to the device/procedure) every adverse event and observed device deficiency; and provide analysis report, which includes the causality assessed by both investigator and BSC and decision on study continuance, to IRB/EC per local and/or country requirements.
- Report to sponsor, per the protocol requirements, all SAEs and device deficiencies that could have led to a SAE and potential/USADE or UADE.
- Report to the IRB/EC and regulatory authorities any SAEs and device deficiencies that could have led to a SADE and potential/USADE or UADE, if required by applicable laws or regulations or this protocol or by the IRB/EC, and supply BSC with any additional requested information related to the safety reporting of a particular event; provides all required source documents related to a death event to BSC and the IEC per local requirements.
- Maintain the device accountability records and control of the device, ensuring that the investigational device is used only by authorized/designated users and in accordance with this protocol and instructions/directions for use.
- Allow the sponsor to perform monitoring and auditing activities, and be accessible to the monitor and respond to questions during monitoring visits.
- Allow and support regulatory authorities and the IRB/EC when performing auditing activities.
- Ensure that informed consent is obtained in accordance with applicable laws, this protocol and local IRB/EC requirements.
- Provide adequate medical care to a subject during and after a subject's participation in a clinical study in the case of adverse events, as described in the Informed Consent Form (ICF).
- Inform the subject of the nature and possible cause of any adverse events experienced.
- As applicable, provide the subject with necessary instructions on proper use, handling, storage, and return of the investigational device when it is used/ operated by the subject.

- Inform the subject of any new significant findings occurring during the clinical investigation, including the need for additional medical care that may be required.
- Provide the subject with well-defined procedures for possible emergency situations related to the clinical study, and make the necessary arrangements for emergency treatment, including decoding procedures for blinded/masked clinical investigations, as needed.
- Ensure that clinical medical records are clearly marked to indicate that the subject is enrolled in this clinical study.
- Ensure that, if appropriate, subjects enrolled in the clinical investigation are provided with some means of showing their participation in the clinical investigation, together with identification and compliance information for concomitant treatment measures (contact address and telephone numbers shall be provided).
- Inform, with the subject's approval or when required by national regulations, the subject's personal physician about the subject's participation in the clinical investigation.
- Make all reasonable efforts to ascertain the reason(s) for a subject's premature withdrawal from clinical investigation while fully respecting the subject's rights.
- Ensure that an adequate investigation site team and facilities exist and are maintained and documented during the clinical investigation.
- Ensure that maintenance and calibration of the equipment relevant for the assessment of the clinical investigation is appropriately performed and documented, where applicable.

17.2.1. Delegation of Responsibility

When specific tasks are delegated by an investigator, including but not limited to conducting the informed consent process, the investigator is responsible for providing appropriate training, are competent to perform the tasks they have been delegated and adequate supervision of those to whom tasks are delegated. Where there is a sub-investigator at a site, the sub-investigator should not be delegated the primary supervisory responsibility for the

site. The investigator is accountable for regulatory violations resulting from failure to adequately supervise the conduct of the clinical study.

17.3 Institutional Review Board/ Ethics Committee

Prior to gaining Approval-to-Enroll status, the investigational center will provide to the sponsor documentation verifying that their IRB/EC is registered or that registration has been submitted to the appropriate agency, as applicable according to national/regulatory requirements.

A copy of the written IRB/EC and/or competent authority approval of the protocol (or permission to conduct the study) and Informed Consent Form, must be received by the sponsor before recruitment of subjects into the study and shipment of investigational product/equipment. Prior approval must also be obtained for other materials related to subject recruitment or which will be provided to the subject.

Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the ICF will be IRB approved; a determination will be made regarding whether a new ICF needs to be obtained from participants who provided consent, using a previously approved ICF.

Annual IRB/EC approval and renewals will be obtained throughout the duration of the study as required by local/country or IRB/EC requirements. Copies of the Investigator's reports and the IRB/EC continuance of approval must be provided to the sponsor.

17.4 Sponsor Responsibilities

All information and data sent to BSC concerning subjects or their participation in this study will be considered confidential by BSC. Only authorized BSC personnel or a BSC representative including Contract Research Organization (CRO) will have access to this information. Authorized regulatory personnel have the right to inspect and copy all records pertinent to this study. Study data collected during this study may be only used by BSC for the purposes of this study. All data used in the analysis and reporting of this study will be without identifiable reference to specific subject name.

Boston Scientific will keep subjects' health information confidential in accordance with all applicable laws and regulations. Information received during the study will not be used to market to subjects; subject names will not be placed on any mailing lists or sold to anyone for marketing purposes.

17.4.1. Role of Boston Scientific Representatives

Boston Scientific personnel can provide technical support to the investigator and other health care personnel (collectively HCP) as needed during implant, testing required by the protocol, and follow-ups. Support may include HCP training, addressing HCP questions, or providing clarifications to HCPs concerning the operation of BSC equipment/devices (including programmers, analyzers, and other support equipment).

Typical tasks may include the following.

- Interrogating the device or programming device parameters to investigator-requested settings as well as operating investigational equipment
- Performing lead diagnostic testing using a Pacing System Analyzer or programmer to obtain pacing and sensing thresholds and impedance measurements
- Clarifying device behavior, operation or diagnostic output as requested by the investigator or other health care personnel
- Assisting with the collection of study data from Pacing System Analyzers, programmers, and other equipment

In addition, BSC personnel may perform certain activities to ensure study quality. These activities may include the following.

- Observing testing or medical procedures to provide information relevant to protocol compliance
- Reviewing collected data and study documentation for completeness and accuracy

Boston Scientific personnel will not do the following.

- Practice medicine

- Provide medical diagnosis or treatment to subjects
- Discuss a subject's condition or treatment with a subject without the approval and presence of the HCP
- Independently collect critical study data (defined as primary or secondary endpoint data)
- Enter data in electronic data capture systems or on paper case report forms

17.5 Insurance

Where required by local/country regulation, proof and type of insurance coverage, by BSC for subjects in the study will be obtained.

18. Monitoring

Monitoring will be performed during the study, according to the study Monitoring Plan, to assess continued compliance with the current, approved protocol/amendment(s) and applicable regulations. In addition, the monitor verifies that informed consent is obtained from all enrolled study subjects, study records are adequately maintained, that data are reported in a satisfactory manner with respect to timeliness, adequacy, and accuracy, and that the Investigator continues to have sufficient staff and facilities to conduct the study safely and effectively. Pre-defined thresholds for protocol deviation and compliance once met or exceeded, can also trigger increased monitoring frequency and/or the implementation of corrective action plans at clinical sites. For the LithoVue China trial, source documents include, at a minimum but not limited to, the ICF; patient medical records, including nursing records and laboratory records; treatment records; reports of SAEs; and device accountability logs. Data documented in the eCRF relevant to device deficiencies, relationship of AE to study device(s), procedure, and anticipatedness assessment of ADEs, may be considered source data for the study.

The Investigator/institution guarantees direct access to original source documents (electronic or paper) by BSC personnel, their designees, and appropriate regulatory authorities. In the event that the original medical records cannot be obtained for a subject that is seen by a non-study physician at a non-study institution, photocopies of the original source documents must be made available for review. Photocopies of original source documents related to SAEs

(from either the study site or a non-study institution, if applicable) must also be made available for submission to the BSC Safety Office as described in Section 20.

The study may also be subject to a quality assurance audit by BSC or its designees, as well as inspection by appropriate regulatory authorities. It is important that the Investigator and relevant study personnel are available during on-site monitoring visits or audits and that sufficient time is devoted to the process.

19. Potential Risks and Benefits

19.1 Anticipated Adverse Events

The following anticipated adverse events (AE) have been identified for this study, including but not limited to:

- Bleeding
- Fever
- Avulsion
- Sepsis
- Stenosis / Stricture
- Renal failure
- Inflammation
- Perforation (ureter, renal pelvis or bladder)
- Laceration
- Hematuria
- Pain
- Ureteral Reflux
- Discomfort
- Hematoma
- Urinoma
- Urothelial damage
- Infection

19.2 Anticipated Adverse Device Effects

From the Anticipated Adverse Events listed above, the following anticipated adverse device effects (ADE) have been identified for this study, but not limited to:

- Bleeding
- Fever
- Avulsion
- Sepsis
- Stenosis / Stricture
- Renal failure
- Inflammation
- Perforation (ureter, renal pelvis or bladder)
- Laceration
- Hematuria
- Pain
- Ureteral Reflux
- Discomfort
- Hematoma
- Urinoma
- Urothelial damage
- Infection

19.3 Risks Associated with the Study Device(s)

No incremental risks that are associated with the study device and are above those of market available products.

19.4 Risks associated with Participation in the Clinical Study

Subjects participating in this study will be exposed to similar risks shared by all subjects who undergo flexible ureteroscope procedure with similar device but are not in this study.

19.5 Possible Interactions with Concomitant Medical Treatments

No additional medical treatments are prescribed for participation in the study. Patients are undergoing flexible ureteroscope procedure that is prescribed by their surgeon.

19.6 Risk Minimization Actions

Additional risks may exist. Risks can be minimized through compliance with this protocol, performing procedures in the appropriate hospital environment, adherence to subject selection criteria, close monitoring of the subject's physiologic status during research procedures and/or follow-ups and by promptly supplying BSC with all pertinent information required by this protocol.

19.7 Anticipated Benefits

The participation of subject contributes to expand the knowledge base with respect to LithoVue ureteroscope system in Chinese population, which may assist Investigators in their device choice of treating any future patients with urinary disease in flexible ureteroscope procedure.

19.8 Risk to Benefit Rationale

The therapeutic effectiveness of LithoVue ureteroscope system is proven using the evaluated literature.

The use of LithoVue ureteroscope system does not involve any incalculable risks for the experienced user. The risk/benefit assessment is positive.

20. Safety Reporting

20.1 Reportable Events by investigational site to Boston Scientific

It is the responsibility of the investigator to assess and report to BSC any event which occurs in any of following categories:

- All Adverse Events
- All Serious Adverse Events
- All Investigational Device Deficiencies

- Unanticipated Adverse Device Effects/Unanticipated Serious Adverse Device Effects
- New findings/updates in relation to already reported events

When possible, the medical diagnosis should be reported as the Event Term instead of individual symptoms.

If it is unclear whether or not an event fits one of the above categories, or if the event cannot be isolated from the device or procedure, it should be submitted as an adverse event and/or device deficiency.

Any AE event required by the protocol, experienced by the study subject after informed consent and once considered enrolled in the study (as defined in study subject classification section), whether during or subsequent to the procedure, must be recorded in the eCRF.

Underlying diseases are not reported as AEs unless there is an increase in severity or frequency during the course of the investigation. Death should not be recorded as an AE, but should only be reflected as an outcome of one (1) specific SAE (see Table 3.2-1 for AE definitions).

Refer to Section 19 for the known risks associated with the study device(s).

20.2 Definitions and Classification

Adverse event definitions are provided in Table 3.2-1. Administrative edits were made on the safety definitions from ISO 14155 and MEDDEV 2.7/3for clarification purposes.

Table 3.2-1: Safety Definitions

Term	Definition
Adverse Event (AE) *Ref: ISO 14155* *Ref: MEDDEV 2.7/3*	Any untoward medical occurrence, unintended disease or injury, or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons, whether or not related to the investigational medical device. NOTE 1: This includes events related to the investigational medical device or comparator. NOTE 2: This definition includes events related to the procedures involved (any procedure in the clinical investigation plan). NOTE 3: For users or other persons, this definition is restricted to events related to the investigational medical device.
Adverse Device Effect (ADE) *Ref: ISO 14155*	Adverse event related to the use of an investigational medical device NOTE 1: This definition includes any adverse event resulting from

Table 3.2-1: Safety Definitions

Term	Definition
Ref: MEDDEV 2.7/3	insufficient or inadequate instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device. NOTE 2: This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.
Serious Adverse Event (SAE) *Ref: ISO 14155* *Ref: MEDDEV 2.7/3*	Adverse event that: a) Led to death, b) Led to serious deterioration in the health of the subject, that either resulted in: 1) a life-threatening illness or injury, or 2) a permanent impairment of a body structure or a body function, or 3) in-patient or prolonged hospitalization of existing hospitalization, or 4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function c) Led to fetal distress, fetal death, or a congenital abnormality or birth defect. **NOTE 1**: Planned hospitalization for a pre-existing condition, or a procedure required by the clinical investigational plan, without serious deterioration in health, is not considered a serious adverse event.
Serious Adverse Device Effect (SADE) *Ref: ISO 14155* *Ref: MEDDEV 2.7/3*	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.
Unanticipated Adverse Device Effect (UADE) *Ref: 21 CFR Part 812*	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.
Unanticipated Serious Adverse Device Effect (USADE) *Ref: ISO 14155* *Ref: MEDDEV 2.7/3*	Serious adverse device effect which by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis report. **NOTE 1**: Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report.
Device Deficiency *Ref: ISO 14155*	A device deficiency is any inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. **NOTE 1**: Device deficiencies include malfunctions, misuse or use errors,

Table 3.2-1: Safety Definitions

Term	Definition
Ref: MEDDEV 2.7/3	and inadequate labeling.

Device deficiencies and other device issues should not be reported as AEs. Instead, they should be reported on the appropriate eCRF per the study CRF Completion Guidelines. If an AE results from a device deficiency or other device issue, the AE should be reported on the appropriate eCRF.

In-patient hospitalization is defined as the subjects being admitted to the hospital, with the following exceptions.

- A hospitalization that is uncomplicated and elective/planned (i.e., planned prior to enrollment) does not have to be reported as an SAE.
- If complications or AEs occur during an elective/planned (i.e., planned prior to enrollment) hospitalization after enrollment, the complications and AEs must be reported as AEs or SAEs if they meet the protocol-specified definitions. However, the original elective/planned hospitalization(s) itself should not be reported as an SAE.

20.3 Relationship to Study Devices

The Investigator must assess the relationship of the reportable AE to the study device or procedure. See criteria in **Error! Reference source not found.**:

Table 3.2-1: Criteria for Assessing Relationship of Study Device/Procedure to Adverse Event

Classification	Description
Not Related	Relationship to the device or procedures can be excluded when: - the event is not a known side effect of the product category the device belongs to or of similar devices and procedures; - the event has no temporal relationship with the use of the investigational device or the procedures; - the serious event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible; - the discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible – and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious event; - the event involves a body-site or an organ not expected to be affected by the device or procedure; the serious event can be attributed to another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors); - the event does not depend on a false result given by the investigational device used for diagnosis, when applicable; harms to the subject are not clearly due to use error; - In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.
Unlikely Related	The relationship with the use of the device seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.
Possibly Related	The relationship with the use of the investigational device is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases were relatedness cannot be assessed or no information has been obtained should also be classified as possible.
Probably Related	The relationship with the use of the investigational device seems relevant and/or the event cannot reasonably explained by another cause, but additional information may be obtained.
Causal Relationship	The serious event is associated with the investigational device or with procedures beyond reasonable doubt when:

Table 3.2-1: Criteria for Assessing Relationship of Study Device/Procedure to Adverse Event

Classification	Description
	- the event is a known side effect of the product category the device belongs to or of similar devices and procedures; - the event has a temporal relationship with investigational device use/application or procedures; - the event involves a body-site or organ that o the investigational device or procedures are applied to; o the investigational device or procedures have an effect on; - the serious event follows a known response pattern to the medical device (if the response pattern is previously known); - the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the serious event (when clinically feasible); - other possible causes (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out; - harm to the subject is due to error in use; - the event depends on a false result given by the investigational device used for diagnosis, when applicable; - In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

20.4 Investigator Reporting Requirements

The communication requirements for reporting to BSC are as shown in Table 3.2-1.

The study will collect all adverse events for participating subjects and analyze procedure/device related adverse events for participating subjects.

Table 3.2-1: Investigator Reporting Requirements

Event Classification	Communication Method	Communication Timeline
Unanticipated Adverse Device Effect / Unanticipated Serious Adverse Device Effect	Complete AE eCRF page with all available new and updated information.	• Within 24 hours of first becoming aware of the event
Serious Adverse Event	Complete AE eCRF page	• Within 24 hours of first

Table 3.2-1: Investigator Reporting Requirements

Event Classification	Communication Method	Communication Timeline
	with all available new and updated information.	becoming aware of the event
	Provide all relevant source documentation of the reported event	d) When documentation is available
Serious Adverse Device Effects	Complete AE eCRF page with all available new and updated information.	• Within 24 hours of first becoming aware of the event
	Provide all relevant source documentation of the reported event	e) When documentation is available
Device Deficiencies (including but not limited to failures, malfunctions, and product nonconformities) Note: Any Investigational Device Deficiency that might have led to a serious adverse event if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate is considered a reportable event.	Complete AE eCRF page with all available new and updated information.	f) Within 24 hours of first becoming aware of the event
Adverse Event including Adverse Device Effects	Complete AE eCRF page, which contains such information as date of AE, treatment of AE resolution, assessment of seriousness and relationship to the device.	Within 10 business days after becoming aware of the information

20.5 Boston Scientific Device Deficiencies

All device deficiencies (including but not limited to failures, malfunctions, use errors, product nonconformities, and labeling errors) will be documented and reported to BSC. If possible, the device(s) should be returned to BSC for analysis. Instructions for returning the investigational device(s) will be provided. If it is not possible to return the device, the

investigator should document why the device was not returned and the final disposition of the device. Device failures and malfunctions should also be documented in the subject's medical record.

Device deficiencies (including but not limited to failures, malfunctions, and product nonconformities) are not to be reported as adverse events. However, if there is an adverse event that results from a device failure or malfunction, that specific event would be recorded on the appropriate eCRF.

And, any Investigational Device Deficiency that might have led to a serious adverse event if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate is considered a reportable event, and should be reported according to Table 3.2-1.

20.6 Reporting to Regulatory Authorities / ECs / Investigators

Boston Scientific Corporation will notify all participating study centers if UADE/USADE/SAEs/SADEs or device deficiency occur which imply a possible increase in the anticipated risk of the procedure or use of the device or if the occurrence of certain SAEs/SADEs demands changes to the protocol or the conduct of the study in order to further minimize the unanticipated risks.

Boston Scientific Corporation is responsible for reporting AE and device deficiencies information to all participating investigators, IRBs/IECs, and regulatory authorities as applicable according to China local reporting requirements.

According to China local reporting requirements, Boston Scientific Corporation will report all SAEs and device deficiencies that could lead to SAEs to the local regulatory authorities within 5 business days of BSC first becoming aware of the event, and notify all participating investigators/sites and IRBs/ECs in a timely manner.

21. Informed Consent

Subject participation in this clinical study is voluntary. Informed Consent is required from all subjects or their legally authorized representative. The Investigator is responsible for

ensuring that Informed Consent is obtained prior to the use of any investigational devices, study-required procedures and/or testing, or data collection.

The obtaining and documentation of Informed Consent must be in accordance with the principles of the Declaration of Helsinki, ISO 14155, any applicable national regulations, and local Ethics Committee and/or Regulatory authority body, as applicable. The ICF must be approved by BSC or its delegate (e.g. CRO), the center's IRB/EC, or central IRB, if applicable.

Boston Scientific will provide a study-specific template of the ICF to investigators participating in this study. The ICF template may be modified to meet the requirements of the investigative center's IRB/EC. Any modification requires approval from BSC prior to use of the form. The ICF must be in a language understandable to the subject and if needed, BSC will assist the center in obtaining a written consent translation. Translated consent forms must also have IRB/EC approval prior to their use. Privacy language shall be included in the body of the form or as a separate form as applicable.

The process of obtaining Informed Consent shall at a minimum include the following steps, as well as any other steps required by applicable laws, rules, regulations and guidelines:

- be conducted by the Principal Investigator or designee authorized to conduct the process,
- include a description of all aspects of the clinical study that are relevant to the subject's decision to participate throughout the clinical study,
- avoid any coercion of or undue influence of subjects to participate,
- not waive or appear to waive subject's legal rights,
- use native language that is non-technical and understandable to the subject or his/her legal representative,
- provide ample time for the subject to consider participation and ask questions if necessary,
- ensure important new information is provided to new and existing subjects throughout the clinical study.

The ICF shall always be signed and personally dated by the subject or legal representative competent to sign the ICF under the applicable laws, rules, regulations and guidelines and by the investigator and/or an authorized designee responsible for conducting the informed consent process. If a legal representative signs, the subject shall be asked to provide informed consent for continued participation as soon as his/her medical condition allows. The original signed ICF will be retained by the center and a copy of the signed and dated document and any other written information must be given to the person signing the form.

Failure to obtain subject consent will be reported by BSC to the applicable regulatory body according to their requirements (e.g., FDA requirement is within 5 working days of learning of such an event). Any violations of the informed consent process must be reported as deviations to the sponsor and local regulatory authorities (e.g. IRB/EC), as appropriate.

If new information becomes available that can significantly affect a subject's future health and medical care, that information shall be provided to the affected subject(s) in written form via a revised ICF or, in some situations, enrolled subjects may be requested to sign and date an addendum to the ICF. In addition to new significant information during the course of a study, other situations may necessitate revision of the ICF, such as if there are amendments to the applicable laws, protocol, a change in Principal Investigator, administrative changes, or following annual review by the IRB/EC. The new version of the ICF must be approved by the IRB/EC. Boston Scientific approval is required if changes to the revised ICF are requested by the center's IRB/EC. The IRB/EC will determine the subject population to be re-consented.

22. Committees

22.1 Safety Monitoring Process

To promote early detection of safety issues, BSC safety team and its delegated CRO Safety team will provide review, process, monitor and evaluations of safety events as defined in the study-specific safety plan. Success of this program requires dynamic collection of unmonitored data as soon as the event is reported.

During regularly scheduled monitoring visits, clinical research monitors will support the dynamic reporting process through their review of source document information and other data information. The BSC Medical Safety group includes physicians with expertise in urinary surgery and with the necessary therapeutic and subject matter expertise to evaluate and classify the events into the categories outlined above.

23. Suspension or Termination

23.1 Premature Termination of the Study

Boston Scientific Corporation reserves the right to terminate the study at any stage but intends to exercise this right only for valid scientific or business reasons and reasons related to protection of subjects. Investigators, associated IRBs/ECs, and regulatory authorities, as applicable, will be notified in writing in the event of study termination.

23.1.1. Criteria for Premature Termination of the Study

Possible reasons for premature study termination include, but are not limited to, the following.

- Important information that impacts the progression of the study (e.g. safety or production performance).
- Regulatory authorities decide to terminate the study.
- A decision on the part of Boston Scientific to suspend or discontinue development of the device.
- An enrollment rate far below expectation that prejudices the conclusion of the study.

Note: According to requirements in section20, even if the LithoVue China study is terminated, subjects with study device(s) shall be followed up for AE, SAE, SADE and device deficiency, which are to be assessed and reported.

23.2 Termination of Study Participation by the Investigator or Withdrawal of EC Approval

Any investigator, or IRB/ EC/ REB in the LithoVue China study may discontinue participation in the study or withdrawal approval of the study, respectively, with suitable written notice to Boston Scientific. Investigators, associated ECs, and regulatory authorities, as applicable, will be notified in writing in the event of these occurrences.

23.3 Requirements for Documentation and Subject Follow-up

In the event of premature study termination a written statement as to why the premature termination has occurred will be provided to all participating centers by Boston Scientific. The IRB/EC and regulatory authorities, as applicable, will be notified. Detailed information on how enrolled subjects will be managed thereafter will be provided.

In the event an IRB or EC terminates participation in the study, participating investigators, associated IRBs/ECs, and regulatory authorities, as applicable, will be notified in writing. Detailed information on how enrolled subjects will be managed thereafter will be provided by Boston Scientific.

In the event an investigator terminates participation in the study, study responsibility will be transferred to a co-investigator, if possible. In the event there are no opportunities to transfer investigator responsibility; detailed information on how enrolled subjects will be managed thereafter will be provided by Boston Scientific.

The investigator must return all documents and investigational product to Boston Scientific, unless this action would jeopardize the rights, safety, or welfare of the subjects.

23.4 Criteria for Suspending/Terminating a Study Center

Boston Scientific Corporation reserves the right to stop the inclusion of subjects at a study site at any time after the study initiation visit if no subjects have been enrolled for a period beyond 3 months after site initiation, or if the site has multiple or severe protocol deviations/noncompliance without justification and/or fails to follow remedial actions.

In the event of termination of site participation, all study devices and testing equipment, as applicable, will be returned to BSC unless this action would jeopardize the rights, safety or well-being of the subjects. The EC and regulatory authorities, as applicable, will be notified. All subjects enrolled in the study at the site will continue to be followed till end of the study. The Principal Investigator at the site must make provision for these follow-up visits unless BSC notifies the investigational site otherwise.

According to section20, all subjects with study device(s) shall be followed up for AEs, which are to be assessed and reported. The Principal Investigator at the site must make provision for these follow-up visits unless BSC notifies the investigational site otherwise.

24. Publication Policy

In accordance with the Corporate Policy on the Conduct of Human Subject Research, BSC requires disclosure of its involvement as a sponsor or financial supporter in any publication or presentation relating to a BSC study or its results. In accordance with the Corporate Policy for the Conduct of Human Subject Research, BSC will submit study results for publication (regardless of study outcome) following the conclusion or termination of the study. Boston Scientific Corporation adheres to the Contributorship Criteria set forth in the Uniform Requirements of the International Committee of Medical Journal Editors (ICMJE; http://www.icmje.org). In order to ensure the public disclosure of study results in a timely manner, while maintaining an unbiased presentation of study outcomes, BSC personnel may assist authors and investigators in publication preparation provided the following guidelines are followed.

- All authorship and contributorship requirements as described above must be followed.
- BSC involvement in the publication preparation and the BSC Publication Policy should be discussed with the Coordinating Principal Investigator(s) and/or Executive/Steering Committee at the onset of the project.
- The First and Senior authors are the primary drivers of decisions regarding publication content, review, approval, and submission.

25. Reimbursement and Compensation for Subjects

25.1 Subject Reimbursement

Travel and other expenses incurred by subjects as a result of participation in the study will be reimbursed in accordance with pertinent country laws and regulations and per the study site's regulations.

25.2 Compensation for Subject's Health Injury

Boston Scientific Corporation will purchase an insurance policy to cover the cost of potential health injury for study subjects, if required by applicable law.

26. Bibliography

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27. Abbreviations and Definitions

Abbreviations are shown in Table 3.2-1.

Table 3.2-1: Abbreviations

Abbreviation/Acronym	Term
ADE	Adverse Device Effect
AE	Adverse Event
BSC	Boston Scientific
CFDA	China Food and Drug Administration
CRF	Case Report Form
EC	Ethics Committee
eCRF	Electronic Case Report Form
EDC	Electronic data capture
FDA	Food and Drug Administration
GCP	Good Clinical Practice
ICF	Informed Consent Form
KUB	Kidney, Ureter, Bladder X-ray
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
UADE	Unanticipated Adverse Device Effect
USADE	Unanticipated Serious Adverse Device Effect