Flexiva Pulse Laser Fiber Post-Market Patient Registry

Flexiva Pulse Registry

U0703

CLINICAL INVESTIGATION PLAN

Sponsored By

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Revision Version	Protocol Date	Template number and version	Protocol Section Modified	Summary of Changes	Justification for Modification
Revision A (initial)	**20July2021**	**92120219 Rev/Ver G**	**N/A**	**N/A**	**Initial Release**

2. Protocol Synopsis

Flexiva Pulse Laser Fiber Post-Market Patient Registry **Flexiva Pulse Registry**	
Study Objective(s)	To obtain post-market safety and efficacy data for Flexiva™ Pulse High Power Single-Use Laser Fibers during lithotripsy and soft tissue procedure of holmium laser enucleation of the prostate (HoLEP).
Indication(s) for Use	Flexiva Pulse ID and Flexiva Pulse ID TracTip laser fibers are intended to be used as a device that transmits Ho:YAG laser energy from cleared laser consoles to urological anatomy. Flexiva Pulse ID and Flexiva Pulse ID TracTip laser fibers are indicated for urologic applications for which the laser systems are cleared, limited to endoscopic procedures involving vaporization, ablation, hemostasis, coagulation, excision, resection, incision of soft tissue, and lithotripsy of urinary calculi. The fiber is designed for use with a standard SMA-905 connector and has been cleared for surgical use
(Commercial) Device/System applied as Standard of Care and sizes, if applicable	Flexiva Pulse and Flexiva Pulse ID Laser Fibers • Flexiva Pulse High Power Single-Use Fiber • Flexiva Pulse TracTip High Power Single-Use Fiber • Flexiva Pulse ID High Power Single-Use Fiber and • Flexiva Pulse ID TracTip High Power Single-Use Laser Fiber
Study Design	Multi-center, open label, prospective study to document on-going post-market safety and performance of Flexiva Pulse High Power Single-Use Laser Fibers. All subjects meeting the enrollment criteria, signing the consent and undergoing the lithotripsy/HoLEP procedure with the study device(s) will be followed: up to 2 months (60 days) post-discharge from final holmium laser lithotripsy procedure for subjects in the lithotripsy cohort or up to 6 months (180 days + 60 days) post discharge from HoLEP procedure for subjects in the Benign Prostatic Hyperplasia (BPH) cohort.

Flexiva Pulse Laser Fiber Post-Market Patient Registry **Flexiva Pulse Registry**	
Planned Number of Subjects	Approximately 200 subjects will be enrolled and treated for lithotripsy of urinary calculi and BPH indications. • Lithotripsy Cohort – desired number of subjects: 100 • BPH Cohort – desired number of subjects: 100
Planned Number of Sites / Countries	Subjects will be enrolled at approximately 10 sites, starting in the United States. Other geographies that have full regulatory approval may be considered.
Primary Safety Endpoint	The primary safety endpoint is the occurrence of Serious Adverse Device Effects (SADE) related to Flexiva Pulse Laser Fibers during lithotripsy and HoLEP procedures.
Primary Efficacy Endpoints	The primary efficacy endpoints are: • In lithotripsy procedures: Stone clearance assessed by stone free rates (SFR) at the 1 month follow-up. Stone free rates are defined as: Clinically nonsignificant, non-obstructive residual fragments of ≤ 3 mm, asymptomatic and no auxiliary procedures performed between the final Flexiva Pulse holmium laser lithotripsy procedure and the 1 month follow-up. • In HoLEP procedures: Improvement in BPH symptoms from baseline as measured by favorable change in International Prostate Symptom Score (IPSS) at 3 month follow-up.
Secondary Safety Endpoint	Procedure related adverse events and/or adverse device effects related to Flexiva Pulse Laser Fibers, including but not limited to: • Perforation o For Lithotripsy procedures: anywhere in urinary tract o For HoLEP procedures: in prostate capsule, bladder, and/or urethra • Hemorrhage resulting in blood loss of ≥ 500mL • Burn

Flexiva Pulse Laser Fiber Post-Market Patient Registry **Flexiva Pulse Registry**	
Secondary Efficacy Endpoints	For Lithotripsy procedures: • Ability of the laser fiber to deliver energy (successful completion of lithotripsy procedure as indicated) • Compatibility of the laser fiber with endoscope (including successful passage and maneuverability without fracture) For HoLEP procedures: • Improvement in Quality of Life (QoL) from baseline as measured by favorable change in International Prostate Symptom Score (IPSS) at 3-month follow-up • Improvement in uroflowmetry from baseline as measured by change in maximum urinary flow rate (Qmax) at 3-month follow-up • Hemostasis measured by ability to coagulate during HoLEP procedure • Ability of the laser fiber to deliver energy (successful completion of HoLEP procedure as indicated) • Compatibility of the laser fiber with endoscope (including successful passage and maneuverability without fracture)
Additional Endpoint	Fiber tip degradation
Method of Assigning Patients to Treatment	This is an open label, non-randomized study
Follow-up Schedule	For Lithotripsy cohort: • Baseline: Pre-procedure imaging study report within 60 days prior to procedure • Lithotripsy Procedure(s): Laser surgery for stone fragmentation/removal • All follow-up visits within 2 months (60 days) of discharge from final holmium laser lithotripsy procedure per site's Standard of Care (SOC)

Flexiva Pulse Laser Fiber Post-Market Patient Registry **Flexiva Pulse Registry**	
	For BPH cohort: • Baseline • HoLEP Procedure • All follow-up visits within 6 months (180 days + 60 days) of discharge from HoLEP procedure per site's SOC
Study Duration	Enrollment is expected to be completed in approximately 12 months; therefore, the total study duration is estimated to be approximately 20 months.
Participant Duration	The study duration for each subject in the Lithotripsy cohort is expected to be up to 2 months (60 days) post discharge from final holmium laser lithotripsy procedure. The study duration for each subject in the BPH cohort is expected to be up to 6 months (180 days + 60 days) post discharge from HoLEP procedure.
Inclusion Criteria	Enrollment is limited to the following inclusion criteria: For Lithotripsy cohort: 1. Subject is undergoing treatment for urinary calculi 2. Subject is willing and able to return for all follow-up visits For BPH cohort: 1. Subject is ≥ 40 years of age 2. Subject with a diagnosis of benign prostatic hyperplasia (BPH) with lower urinary tract symptoms 3. IPSS (International Prostate Symptom Score) ≥ 12 4. Qmax (Peak Flow Rate) ≤ 15 mL/s 5. Subject is willing and able to return for all follow-up visits
Exclusion Criteria	Subjects are not permitted to enroll if they meet any of the following exclusion criteria: For Lithotripsy cohort: 1. Subject has uncontrolled bleeding disorders and coagulopathy 2. Subject has untreated urinary tract infection (UTI) 3. Subject requires simultaneous HoLEP procedure For BPH cohort:

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	1. Subject has a diagnosis of bladder cancer 2. Subject has a diagnosis of prostate cancer 3. Subject with prostate-specific antigen (PSA) > 10 ng/mL suggestive of prostate cancer is not eligible unless patient has concomitant negative prostate biopsy 4. Subject has acute prostatitis, a prostate abscess, or neurogenic bladder 5. Subject has urethral stricture disorder 6. Subject has uncontrolled bleeding disorders and coagulopathy 7. Subject has untreated urinary tract infection (UTI) 8. Subject requires simultaneous upper urinary calculi lithotripsy procedure (not applicable to bladder calculi)
Statistical Methods	
Primary Statistical Hypothesis	There is no formal hypothesis test.
Statistical Test Method	A two-sided 95% confidence interval will be constructed using exact (Clopper-Pearson) method to estimate the SADE rate for each treatment cohort.
Sample Size Parameters	The sample size justification is based on a confidence interval (CI) approach. As there is limited published literature on the device safety measurement in a clinical study setting, a conservative assumption of 3% SADE rate within 1 month of the procedure for lithotripsy cohort and 5% for BPH cohort within 3 months of the HoLEP procedure was assumed. Ninety (90) subjects are needed for each cohort to construct a 95% two-sided CI with a maximum width of8.4% for lithotripsy cohort and 10.2% for HoLEP cohort. Assuming 10% attrition within 1 month of the procedure for lithotripsy cohort and within 3 months of the HoLEP procedure, it is anticipated that 100 treated subjects will be required for each procedure cohort.

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4. Introduction

4.1. *Background*

The Holmium:yttrium-aluminum-garnet laser (Ho:YAG), is standard for endourological procedures. The Ho:YAG laser is established as the gold standard for endoscopic lithotripsy, used efficiently for any stone composition, and can also be used for other applications including soft-tissue ablation, Holmium laser enucleation of the prostate (HoLEP) for Benign prostatic hyperplasia (BPH), tumor resections, and management of stricture disease[1].

Urolithiasis is the formation of one or more stones in the bladder or urinary tract. Kidney stones are small, hard deposits that can form in the renal pelvis of the kidney. Nonsurgical management and treatment of stone disease involves medical relief of pain, and/or medical expulsive therapy (MET). Observation of small ureteral stones (< 6 mm) with periodic evaluation is feasible in patients who do not develop complications[2]. Another conservative treatment option is MET, which includes the pharmacological use of alpha (α)-blockers, calcium channel blockers, or phosphodiesterase type 5 (PDE5) inhibitors.

Treatment for urolithiasis has evolved from open surgery procedure to now less invasive ureteroscopy. As smaller, more flexible endoscopes became available in the 1990s and were used in conjunction with holmium laser fibers that can fit and bend in these flexible endoscopes, ureteroscopy became a mainstay of urolithiasis treatment[3]. Miniaturized tools are also being used with holmium laser fibers in retrograde intrarenal surgery to treat moderate-to-large stones rather than using extracorporeal shock wave lithotripsy (ESWL)[4]. Holmium laser fibers may also be used as intracorporeal lithotripters in the smallest of tracts during Percutaneous Nephrolithotomy (PCNL) procedures to dust stones of any composition or size[5]. The use of Holmium laser has led to capability of fragmenting all stone types, leading to higher stone-free rates while maintaining a safety profile[7].

Another wide application of holmium:YAG laser in endourology is to ablate prostatic tissue in BPH patients. A common manifestation of prostate disease is lower urinary tract symptoms (LUTS). LUTS can be categorized as storage symptoms (increased frequency, nocturia, urgency) and voiding symptoms (feeling of incomplete emptying, intermittency, straining, and weak stream)[6]. Surgical treatment for these symptoms is required in 25-30% of men 50-80 years of age who suffer from moderate-to-severe LUTS. If left untreated, complications of BPH-related benign prostatic obstruction (BPO) may include renal insufficiency, acute urinary retention, urinary tract infection, bladder stones, bladder decomposition, urinary incontinence, upper urinary tract deterioration and azotemia, and hematuria[6]. The main goal in treating prostatic diseases such as BPO is to alleviate the LUTS. The first step is conservative management. Men who are experiencing nonbothersome LUTS may be assessed and managed with watchful waiting rather than undergoing medical or surgical treatment right away. These patients may also be advised to undergo behavioral (e.g., bladder training, double voiding) and dietary changes (e.g., reduction of fluid intake at specific times, avoidance of caffeine or alcohol).

Pharmacological treatment is a common initial step in managing enlarged prostates and reducing LUTS. When drug treatments for symptomatic BPH have failed or proven to be intolerable due to side effects, surgical options for LUTS are considered. Surgical options ranging from minimally invasive to most invasive include prostatic urethral lift (PUL) with UroLift, laser procedures (vaporization or enucleation with holmium, thulium, greenlight, or diode laser), TUIP (transurethral incision of prostate), TURP (transurethral resection of prostate), Rezūm, and open prostatectomy.

For treatment of BPH, TURP has been considered the gold standard, but the minimally invasive procedure of holmium laser enucleation of the prostate is a viable surgical treatment option with comparable improvements in IPSS and Qmax to TURP with better hemostasis and in turn, a lower risk of blood transfusion. HoLEP is a recommended option by AUA for patients with LUTS attributed to BPH as prostate size-independent option, or those who cannot stop anticoagulation/antiplatelet therapy.

In modern-day urology, surgical treatment options have steered away from open surgery for both urolithiasis and BPH. Holmium laser is among minimally invasive technologies available as alternatives.

Flexiva Pulse and Flexiva Pulse ID Laser Fibers are state of the art devices for delivering holmium laser energy to manage and treat urological pathologies including lithotripsy and ablation and coagulation of tissue in urological applications (e.g., BPH).

4.2. *Study Rationale*

Ureteroscopy became a mainstay of urolithiasis treatment as smaller, more flexible endoscopes became available that are used in conjunction with holmium laser fibers that can fit and bend in these flexible endoscopes[8]. The holmium laser fibers come in varying sizes. In general, larger core fibers (550-1000 µm sizes) are used in a straight configuration with endoscopes used in PCNL procedures; whereas, smaller core fibers (≤ 365 µm) have the greater flexibility required for flexible ureteroscopy (fURS) procedures[9].

Holmium laser enucleation of the prostate (HoLEP) is a minimally invasive surgical procedure for the treatment of BPH. During a HoLEP procedure, a holmium laser fiber (usually 550 µm size[10]) is passed through an endoscope and used to deliver holmium laser energy for enucleation and removal of enlarged prostate tissue away from the prostatic capsule.

Selecting the right fiber size, and its impact on fiber flexibility and flow rates helps in understanding performance of the fiber during clinical use. However, fiber performance and safety data in a clinical setting is limited. The objective of the Flexiva Pulse registry is to collect on-going post-market safety and performance data for the Flexiva Pulse and Flexiva Pulse ID Laser fibers in routine clinical use.

5. Commercial Device Description (part of Standard of Care)

5.1. *Commercial Device Under Study*

Flexiva Pulse and Flexiva Pulse ID Laser Fibers are manufactured in multiple sizes and are available with either a flat tip or a ball-tip (242 µm size only). The universal product numbers (UPNs) for the various models of the subject devices are listed in **Table 5-1.**

Flexiva Pulse and Flexiva Pulse ID Laser Fibers are non-implanted, single-use surgical devices that transiently penetrates inside the body to deliver holmium laser energy. Their intended purpose and indications include urological application for which the laser system is cleared, limited to endoscopic procedures involving vaporization, ablation, coagulation, hemostasis, excision, resection, incision of soft tissue, and lithotripsy of urinary calculi. Flexiva Pulse and Flexiva Pulse ID Laser Fibers are used to treat urinary stones and/or urological soft tissue conditions (e.g., benign prostatic hyperplasia). The intended patient population includes patients who are candidates for the procedures listed in the indications for use. Flexiva Pulse and Flexiva Pulse ID Fibers are contraindicated in patients for whom endoscopic procedures are contraindicated. The intended users of this device are physicians and supporting staff (surgical technicians and nurses) with experience in urological laser surgery.

Table 5-1: Device Universal Part Numbers (UPNs)

Product Description	UPN Product Number	Quantity	Maximum Power	Fiber Length (m)
Flexiva™ Pulse High Power Single-Use Laser Fiber, 242 µm	M006L8405910	1	50W	3.0
	M006L8405911	5		
Flexiva™ Pulse High Power Single-Use Laser Fiber, 365 µm	M006L8405920	1	100W	2.6
	M006L8405921	5		
Flexiva™ Pulse High Power Single-Use Laser Fiber, 550 µm	M006L8405930	1	100W	2.6
	M006L8405931	5		
Flexiva™ Pulse High Power Single-Use Laser Fiber, 910 µm	M006L8405940	1	100W	2.6
	M006L8405941	5		
Flexiva™ Pulse TracTip™ High Power Single-Use Laser Fiber, 242 µm	M006L8405960	1	50W	3.0
	M006L8405961	5		
Flexiva™ Pulse ID High Power Single-Use Laser Fiber, 242 µm	M006L8406910	1	50W	3.0
	M006L8406911	5		
Flexiva™ Pulse ID High Power Single-Use Laser Fiber, 365 µm	M006L8406920	1	100W	2.6
	M006L8406921	5		
Flexiva™ Pulse ID High Power Single-Use Laser Fiber, 550 µm	M006L8406930	1	100W	2.6
	M006L8406931	5		
Flexiva™ Pulse ID High Power Single-Use Laser Fiber, 910 µm	M006L8406940	1	100W	2.6
	M006L8406941	5		
Flexiva™ Pulse ID TracTip™ High Power Single-Use Laser Fiber, 242 µm	M006L8406960	1	50W	3.0
	M006L8406961	5		

Source: Super Fiber Lumenis System Requirements Specification (Windchill 92114496)

A copy of the device labeling and Instructions for Use (IFU) will be provided in local language(s) as required per national regulation. An Investigational Brochure has not been developed and per ISO 14155 is not required for this post-market observational clinical investigation as commercial product information is available and study device(s) are used within the approved indication.

5.2. *Required Medical Equipment*

Equipment for lithotripsy and BPH HoLEP procedures per standard of care will be used including but not limited to a high power holmium laser console.

6. Study Objectives and Endpoints

The objective of this study is to obtain post-market safety and efficacy data for Flexiva Pulse High Power Single-Use Fiber Laser Fiber during Lithotripsy and soft tissue procedure of Holmium Laser Enucleation of the Prostate (HoLEP). An overview of study objectives and endpoints are provided in **Table 6-1.**

Table 6-1: Overview of Objectives and Endpoints

Objectives	Endpoints	Justification for Endpoints
Primary		
The primary objective is to assess the clinical safety and efficacy of Flexiva Pulse Laser Fibers.	**Primary Safety Endpoint:** The occurrence of Serious Adverse Device Effects (SADE), related to Flexiva Pulse Laser Fibers during lithotripsy and HoLEP procedures.	Collect safety events in real-world clinical setting.

Objectives	Endpoints	Justification for Endpoints
	Primary Efficacy Endpoints: • In lithotripsy procedures: Stone clearance assessed by stone free rates (SFR) at 1 month follow-up. Stone free rates defined as: Clinically nonsignificant, non-obstructive residual fragments of ≤ 3 mm, asymptomatic and no auxiliary procedures performed between the final Flexiva Pulse holmium laser lithotripsy procedure and the 1 month follow-up.	Stone free rate is standard clinical outcome measured after a URS with holmium laser lithotripsy procedure.
	• In HoLEP procedures: Improvement in BPH symptoms from Baseline as measured by favorable change in International Prostate Symptom Score (IPSS) at 3 month follow-up.	IPSS is standard clinical measure for HoLEP procedure
Secondary		

	Secondary Safety Endpoint: Procedure related adverse events and/or adverse device effects related to Flexiva Pulse Laser Fibers, including but not limited to:
	
	• Perforation
	  o For Lithotripsy procedures: anywhere in urinary tract
	  o For HoLEP procedures: in prostate capsule, bladder, and/or urethra
	• Hemorrhage resulting in blood loss of ≥ 500mL
	• Burn
		Procedure related AEs and device related ADEs will be collected in a routine clinical setting. The overall performance of the fibers will be collected during the lithotripsy and HoLEP procedure. The IPSS QOL is the standard instrument for the measurement of Lower Urinary Tract Symptoms (LUTS) severity in men with BPH.

Objectives	Endpoints	Justification for Endpoints
	Secondary Efficacy Endpoints: For Lithotripsy procedures: • Ability of the laser fiber to deliver energy (successful completion of lithotripsy procedure as indicated) • Compatibility of the laser fiber with endoscope (including successful passage and maneuverability without fracture) For HoLEP procedures: • Improvement in Quality of life (QoL) from baseline as measured by favorable change in IPSS at 3 month follow-up. • Improvement in uroflowmetry from baseline as measured by change in maximum urinary flow rate (Qmax) at 3 month follow-up • Hemostasis measured by ability to coagulate during HoLEP procedure • Ability of the laser fiber to deliver energy (successful completion of HoLEP procedure as indicated) • Compatibility of the laser fiber with endoscope (including successful passage and maneuverability without fracture)	

Objectives	Endpoints	Justification for Endpoints
Additional		
	Additional Endpoint: • Fiber tip degradation	Fiber tip degradation will be assessed subjectively by the physician after use of the fiber during lithotripsy and/or HoLEP procedure.

7. Study Design

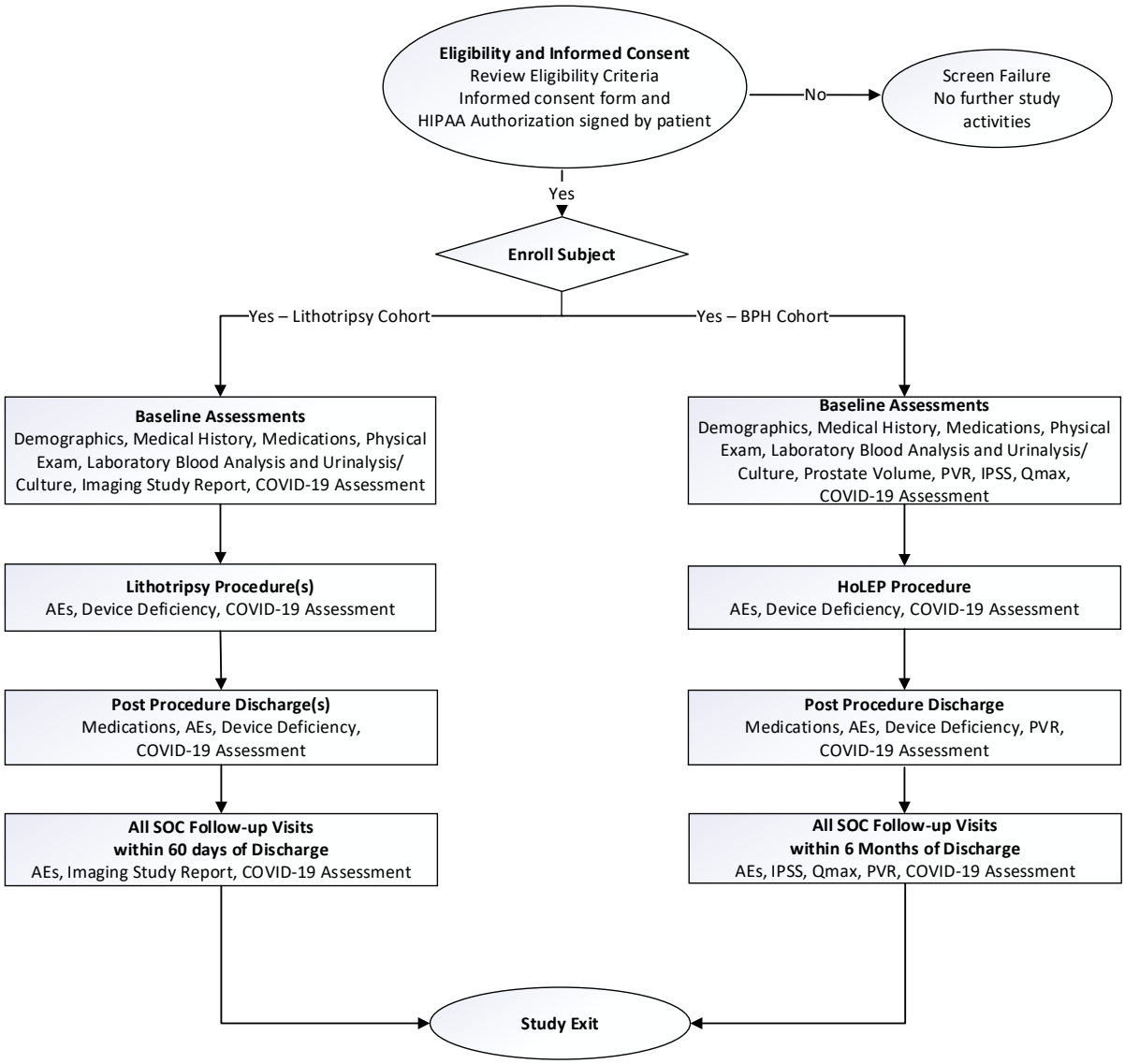
This is a multi-center, open label, prospective study to document the safety and performance of Flexiva Pulse High Power Single-Use Laser Fiber.

7.1. *Scale and Duration*

This study will include:

- Approximately 200 subjects will be enrolled at up to 10 sites starting in the United States. Other geographies that have full regulatory approval may be considered.
- There will be about 100 subjects enrolled in the lithotripsy cohort and 100 subjects enrolled in the BPH cohort.
- The enrollment period will be approximately 12 months.
- This study is expected to take about 20 months from first subject enrollment until the study closeout.
- Each subject will be involved in the study for up to 2 months (60 days) post-discharge from final holmium laser lithotripsy procedure for subjects in the lithotripsy cohort or up to 6 months (180 days + 60 days) post discharge from HoLEP procedure for subjects in the Benign Prostatic Hyperplasia (BPH) cohort. Sites will be encouraged to enroll a minimum of 5 subjects per procedure cohort. A maximum of 25 subjects per procedure cohort may be enrolled at a site, unless the site has received prior approval from the sponsor to enroll additional subjects.

Figure 7.1-1: Flexiva Pulse Laser Fiber Post-Market Registry Study Design



7.2. *Treatment Assignment*

This is a post-market registry study. Any subject who is indicated for lithotripsy or BPH undergoing HoLEP and is willing to provide a written informed consent will be approached and considered for enrollment in the study. The subject is considered enrolled in the study once the subject has signed the informed consent form and the lithotripsy/HoLEP procedure is attempted. Each subject will be assigned a unique subject identifier in the Electronic Data Capture (EDC) system.

7.3. *Justification for the Study Design*

Flexiva Pulse and Flexiva Pulse ID Laser Fibers are commercially available devices that transiently penetrate inside the body to deliver holmium laser energy. With a cohort study design, enrolling subjects undergoing lithotripsy or HoLEP as standard of care procedure will provide real-world safety and performance data.

8. Subject Selection

8.1. *Study Population and Eligibility*

Approximately 200 subjects will be enrolled and treated for lithotripsy of urinary calculi and BPH indications. There will be about 100 subjects enrolled in the lithotripsy cohort and 100 subjects enrolled in the BPH cohort.

Subjects will generally be recruited from physician's practice. Subjects who meet all of the inclusion criteria (see **Table 8.2-1**) and none of the exclusion criteria (see Section 8.3) may be given consideration for inclusion in this clinical investigation.

8.2. *Inclusion Criteria*

Subjects who meet all of the following criteria (see **Table 8.2-1**) may be given consideration for inclusion in this clinical investigation, provided no exclusion criterion (see Section 8.3) is met.

Table 8.2-1: Inclusion Criteria

Inclusion Criteria	For Lithotripsy cohort: 1. Subject is undergoing treatment for urinary calculi 2. Subject is willing and able to return for all follow-up visits For BPH cohort: 1. Subject is ≥ 40 years of age 2. Subject with a diagnosis of benign prostatic hyperplasia with lower urinary tract symptoms 3. IPSS (International Prostate Symptom) Score ≥ 12 4. Qmax (Peak Flow Rate) ≤ 15 mL/s 5. Subject is willing and able to return for all follow-up visits

8.3. *Exclusion Criteria*

Subjects who meet any one of the following criteria (**Table 8.3-1**) cannot be included in this study or will be excluded from this clinical study.

Table 8.3-1: Exclusion Criteria

Exclusion Criteria	For Lithotripsy cohort: 1. Subject has uncontrolled bleeding disorders and coagulopathy 2. Subject has untreated urinary tract infection (UTI) 3. Subject requires simultaneous HoLEP procedure For BPH cohort: 1. Subject has a diagnosis of bladder cancer 2. Subject has a diagnosis of prostate cancer 3. Subject with prostate-specific antigen (PSA) > 10 ng/mL suggestive of prostate cancer is not eligible unless patient has concomitant negative prostate biopsy 4. Subject has acute prostatitis, a prostate abscess, or neurogenic bladder 5. Subject has urethral stricture disorder 6. Subject has uncontrolled bleeding disorders and coagulopathy 7. Subject has untreated urinary tract infection 8. Subject with simultaneous upper urinary calculi lithotripsy and HoLEP procedure (not applicable to bladder calculi)

9. Subject Accountability

9.1. *Point of Enrollment*

A subject will be considered enrolled in the study after the subject signs and dates the informed consent form (ICF) and the lithotripsy/HoLEP procedure is attempted. No study specific (non-standard of care) procedure(s) or assessment(s) can take place until the informed consent is signed.

9.2. *Withdrawal*

All subjects enrolled in the clinical study (including those withdrawn from the clinical study) shall be accounted for and documented. If a subject withdraws from the clinical investigation, the reason(s) shall be reported. If such withdrawal is due to problems related to device safety or performance, the investigator shall ask for the subject's permission to follow the subject's status/condition outside of the clinical study.

Reasons for withdrawal include but are not limited to physician discretion and subject choice to withdraw consent. While study withdrawal is discouraged, subjects may withdraw from the study at any time, with or without reason, and without prejudice to further treatment. All applicable electronic Case Report Forms (eCRFs) up to the point of subject withdrawal and an End of Study eCRF must be completed. Additional data may no longer be collected after the point at which a subject has been withdrawn from the study or the subject withdraws consent.

Data collected up to the point of subject withdrawal may be used for study analysis, unless local regulations apply.

9.2.1. Voluntary Withdrawal

Subjects may withdraw from the study at any time. At the time of withdrawal, the Investigator shall document the reason for the withdrawal. For subjects who withdraw from the study and decide to revoke their authorization to use and disclose their medical information, the information that has already been collected in the study record may continue to be used; however, no new information will be obtained or added.

9.2.2. Involuntary Withdrawal

Subjects may be involuntarily withdrawn from the study if the Investigator determines it is in the subject's best interest. If the subject is withdrawn at the investigator's discretion, the reason for withdrawal must be documented in the subject's medical records.

9.3. *Lost to Follow-Up*

If a subject fails to return to the clinic and/or is unable to be reached for a follow-up visit the site will attempt to contact the subject and reschedule the missed visit and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain if the subject wishes to and/or should continue in the study.

Before the subject may be considered lost to follow-up, the investigator must make the following attempts to contact the subject:

- Three documented telephone attempts
- One certified letter

If the subject can be reached and no longer wishes to participate in the study, the Investigator shall document the reason for the withdrawal and complete the End of Study eCRF.

If the subject is not able to be reached after the required attempts to contact the subject have been made and the subject has missed two consecutive follow-up visits, the subject may be considered lost to follow-up. The Investigator should document in the subject's medical record the attempts to contact the subject and the reason for withdrawal.

9.4. *Subject Status and Classification*

A subject will be considered enrolled after a signed informed consent form is obtained and the lithotripsy/HoLEP procedure is attempted. A subject's participation ends when he or she has completed all phases of the study including the last visit as shown in the Data Collection Schedule (see **Table 10.1-1** and **Table 10.1-2**).

9.5. *End-of-Study Definition*

The study is considered completed when participants are no longer being examined or the last participant's last study visit has occurred, and study closeout activities are completed.

A subject is considered to have completed the study after the subject has completed all phases of the study including the last visit shown in the Data Collection Schedule (see **Table 10.1-1** and **Table 10.1-2**).

The end of the study is defined as completion of the final Clinical Study Report.

10. Study Methods

10.1. *Data Collection*

The data collection schedule is shown in **Table 10.1-1** and **Table 10.1-2**. Assessments will be completed based on standard of care practices at the site. For Lithotripsy Cohort, data from all SOC follow-up visits within 60 days of discharge from final Flexiva Pulse holmium laser Lithotripsy procedure will be collected. For BPH Cohort, data from all SOC follow-up visits within 6 months (180 days + 60 days) of discharge from HoLEP procedure will be collected. All study data will be recorded on source documentation and captured within electronic Case Report Forms (eCRFs) for the purposes of this study. Study data will be monitored by Boston Scientific or representatives and as applicable on a regular basis as outlined in the study Monitoring Plan.

Table 10.1-1: Data Collection Schedule - Lithotripsy Cohort

Procedure/ Assessment	Screening	Baseline[3]	Lithotripsy Procedure[2]	Post Procedure Discharge[2]	Post final Flexiva Pulse holmium laser Lithotripsy Procedure Follow-up (FU) Visits	Unscheduled Visit
					All SOC FU visits within 2 months (60 days) of discharge	
Eligibility criteria	X					
Informed consent process, including informed consent signature date	X					
Demographics		X				
Medical history		X				
Physical examination, including weight and height		X				
Imaging Study Report		X			X[4]	
Medications		X		X		
Laboratory Blood Analysis for Lithotripsy Cohort: CBC, coagulation testing (PT, PTT, INR), serum creatinine, uric acid, CRP, BMP		X[1]				
Laboratory Urinalysis/Culture: Pregnancy Test and UTI		X				
Adverse Events assessment			X	X	X	X
Device Deficiency assessment			X	X		
COVID-19 Assessment		X[1]	X[1]	X[1]	X[1]	X[1]

X = required

[1] = If available

[2] = If additional Flexiva Fiber holmium laser lithotripsy procedure is performed, complete additional procedure and discharge CRF

[3] = Pregnancy test and urinalysis/culture must be completed within 30 days of procedure, and all other baseline data may be within 60 days

[4] = At least one imaging study report required within 60 days of discharge for stone free rate assessment

Table 10.1-2: Data Collection Schedule - BPH Cohort

Procedure/ Assessment	Screening	Baseline[3]	HoLEP Procedure	Post Procedure Discharge	Post HoLEP Procedure Follow-up (FU) Visits	Unscheduled Visit
					All SOC FU visits within 6 months (180 days + 60 days) of discharge	
Eligibility criteria	X					
Informed consent process, including informed consent signature date	X					
Demographics		X				
Medical history		X				
Physical examination, including weight and height		X				
Prostate Volume		X				
Medications		X		X		
Laboratory Blood Analysis for BPH Cohort: CBC, coagulation testing (PT, PTT, INR), PSA		X[1]				
Laboratory Urinalysis/Culture: UTI		X				
Post Void Residual		X[1,2]		X[1,2]	X[1,2]	
IPSS		X[2]			X[2]	
Maximum urinary flow rate (Qmax)		X[1,2]			X[1,2]	
Adverse Events assessment			X	X	X	X
Device Deficiency assessment			X	X		
COVID-19 Assessment		X[1]	X[1]	X[1]	X[1]	X[1]

X = required

[1] = If available

[2] = If subject does not have a catheter

[3] = Urinalysis/culture must be completed within 30 days of procedure, and all other baseline data may be within 60 days

10.2. *Study Candidate Screening*

All interested subjects will undergo screening during which their eligibility for the study will be determined. Sites are expected to follow standard of care testing to diagnose and screen subjects for inclusion in the study.

Subjects who do not meet the inclusion/exclusion criteria are considered screen failures.

If the subject has completed the informed consent process and met all inclusion and none of the exclusion criteria, the subject will progress to the Lithotripsy/HoLEP procedure and follow-up phase of the study.

10.2.1. Strategies for Recruitment and Retention

Subjects will be recruited from clinician practice who are receiving device as standard of care.

10.3. *Informed Consent*

Written informed consent must be obtained from all potential study candidates before any study specific, non-standard of care screening tests or procedures are performed. Only current Institutional Review Board (IRB), Ethics Committee (EC) or Research Ethics Board (REB) approved study specific ICF must be used. Study personnel should explain that even if a subject agrees to participate in the study and signs an ICF, certain screening procedures might demonstrate that the subject is not eligible to continue participation. Written informed consent must be recorded appropriately by means of the subject's dated signature.

10.4. *Screening Assessments/Procedures*

The Screening and Baseline visits may occur on the same day or on different days. The following must be completed prior to collecting baseline data described in section 10.5:

- Review of Eligibility Criteria
- Informed Consent Process, including informed consent signature

10.5. *Baseline Visit*

The Baseline Visit and assessments will occur prior to the subject having Lithotripsy/HoLEP procedure. Pregnancy test and urinalysis/culture must be completed within 30 days of procedure, and all other baseline data may be completed within 60 days of procedure.

The baseline assessments below can be completed on the same day as Screening.

<u>Baseline Assessments for both cohorts</u>

- Demographics: Age, Gender, Race and Ethnicityy

- Medical History: Only current medical conditions in the past 12 months prior to Baseline assessment and lifetime history of stones and/or BPH (including all surgical and medical treatments).
- Physical Examination
- Medications: only active medications at Baseline and lifetime history of medications for treatment of stones and/or BPH.
- Urinalysis/culture
- Urinary Tract Infection status
- COVID-19 assessment: prior diagnosis, test result, vaccination status (if available)

Baseline Assessments for Lithotripsy cohort only

- Imaging Study Report: Computed Tomography (CT) or x-ray or ultrasound of kidneys, ureters, and bladder (KUB) – Lithotripsy cohort only
- Laboratory Blood Tests (if available): Complete Blood Count (CBC), coagulation testing (Prothrombin Time, Partial Thromboplastin Time, International Normalized Ratio), serum creatinine, uric acid, C-Reactive Protein, Basic Metabolic Panel
- Pregnancy test for women of child-bearing potential

Baseline Assessments for BPH cohort only

- Prostate Volume – BPH cohort only
- Laboratory Blood Tests (if available): Complete Blood Count, coagulation testing (Prothrombin Time, Partial Thromboplastin Time, International Normalized Ratio), Prostate Specific Antigen
- International Prostate Symptom Score (IPSS) – except if patient is catheterized and IPSS cannot be done.
- Maximum urinary flow rate (Qmax) – except if patient is catheterized and uroflow test cannot be done (if available)
- Post Void Residual (PVR), except if patient is catheterized and PVR cannot be done (if available)

10.6. *Lithotripsy/HoLEP Procedure Visit*

Lithotripsy/HoLEP procedure is defined as the start time of sedation and/or anesthesia and includes the entirety of the holmium laser Lithotripsy or HoLEP procedure. The procedure will be performed by a trained physician and per the Flexiva Pulse Laser Fiber IFU.

It is recommended that surgeons perform a second evaluation at the time of the lithotripsy procedure to ensure all stones have been removed.

If multi-staged lithotripsy procedures are performed using the Flexiva Pulse Laser Fibers, then data will also be collected on the additional procedures. **If the additional lithotripsy procedure performed does not use the Flexiva Pulse Laser Fibers, then subject should be exited from the study at the time of the additional procedure**.

If subject is undergoing HoLEP and simultaneous holmium laser lithotripsy using Flexiva Pulse Laser Fibers to remove bladder calculi, data will also be collected on the lithotripsy procedure.

Baseline visit information may be collected on same day, prior to the Lithotripsy/HoLEP procedure.

After the Lithotripsy/HoLEP procedure, the following data will be collected:

- Procedure information and evaluation of applicable BSC devices used. It is recommended that User Feedback Evaluations are **completed within 1 week of procedure.**
- Fiber Information – type, size, number of fibers used, model of scope, number of passes per fiber, fiber fracture, fiber deflection, if fiber was stripped/cleaved
- Fiber Performance – fiber tip degradation
- Assessment of adverse events and device deficiencies
- COVID-19 assessment: prior diagnosis, test result, vaccination status (if available)

10.7. *Post-Procedure Discharge*

At the time of post-procedure discharge, the following information will be collected:

Lithotripsy Cohort

- Medications
- Assessment of adverse events and device deficiencies
- COVID-19 assessment: prior diagnosis, test result, vaccination status (if available)

Note: If multi-staged procedures are performed using the Flexiva Pulse fibers, then discharge data will also be collected on the additional procedures.

BPH Cohort

- Medications
- Post Void Residual (PVR) if subject is discharged to home without a catheter (if available)
- Assessment of adverse events and device deficiencies
- COVID-19 assessment: prior diagnosis, test result, vaccination status (if available)

10.8. *Post Lithotripsy/HoLEP Procedure Follow-up Visits*

10.8.1. All SOC Follow-up Visits within 60 days post discharge from final Flexiva Pulse holmium laser Lithotripsy procedure

For any follow-up visit(s) that occurs within 60 days post discharge from final Flexiva Pulse holmium laser lithotripsy procedure per site's standard of care, the following assessments will be performed and data points collected if available:

- Imaging Study Report: Computed Tomography (CT) or x-ray or ultrasound of kidneys, ureters, and bladder (KUB). **At least one imaging study report is required within 60 days of discharge for stone free rate assessment.**
- Assessment of adverse events
- COVID-19 assessment: prior diagnosis, test result, vaccination status
- Study Exit at last follow-up visit within 60 days post discharge

10.8.2. All SOC Follow-up Visits within 6 months (180 days + 60 days) post discharge from HoLEP procedure

For any follow-up visit(s) that occur within 6 months (180 days + 60 days) post discharge from HoLEP procedure per site's standard of care, the following assessments will be performed and data points collected:

- Post Void Residual (if available)
- International Prostate Symptom Score (IPSS)
- Maximum urinary flow rate (if available)
- Assessment of adverse events
- COVID-19 assessment: prior diagnosis, test result, vaccination status (if available)
- Study Exit at last follow-up visit within 6 months (180 days + 60 days) post discharge

10.9. *Unscheduled Visit*

Subjects may have additional visits (other than the study visits specified above), that are unplanned visits and are considered as unscheduled visits. Some examples of these visits may include a visit for a change in symptoms or to check on a medical event that could not be resolved during one of the scheduled study visits.

If an unscheduled visit occurs, the following information will be collected:

- Assessment of adverse events
- COVID-19 assessment: prior diagnosis, test result, vaccination status (if available)

10.10. *Study Completion*

Each subject in the Lithotripsy cohort will be followed up to 60 days post discharge from final Flexiva Pulse holmium laser Lithotripsy procedure per site's SOC. Each subject in the BPH cohort will be followed up to 6 months (180 days + 60 days) post discharge from HoLEP procedure per site's SOC. All subjects completing the last follow-up visit per site's SOC and their respective cohorts, will be considered to have completed the study. Subjects with any ongoing Adverse Events at the end of the study should be followed per institutions' standard of care.

If subject in the Lithotripsy cohort is undergoing a multi-staged lithotripsy procedure that does not use the Flexiva Pulse Laser Fibers, then subject should be exited from the study at the time of the additional procedure.

10.11. *Source Documents*

It is preferable that original source documents are maintained, when available. In lieu of original source documents, certified copies are required to be maintained. A certified copy is a copy (irrespective of the type of media used) of the original record that has been verified (i.e., by a dated signature or by generation through a validated process) to have the same information, including data that describe the context, content, and structure, as the original.

10.12. *Local Laboratory documentation*

The laboratory (blood and urine) analysis, collected in the study will be completed at the local centers per standard of care. Appropriate laboratory certifications and documentation records are required to be maintained at the site.

11. Statistical Considerations

11.1. *Endpoints*

11.1.1. Primary Safety Endpoint

The primary safety endpoint is the occurrence of any Serious Adverse Device Effects (SADE) (including burn, perforation, and hemorrhage) during Lithotripsy and BPH procedures.

11.1.1.1. Hypotheses

There is no formal hypothesis test. The study is designed to evaluate primary safety endpoints with desired precision.

11.1.1.2. Sample Size

The sample size justification is based on a confidence interval (CI) approach. As there is limited published literature on the device safety measurement in a clinical study setting, a conservative assumption of 3% SADE rate within 1 month of the procedure for lithotripsy cohort and 5% for BPH cohort within 3 months of the HoLEP procedure was assumed. Ninety

(90) subjects are needed for each cohort to construct a 95% two-sided CI with a maximum width of 8.4% for lithotripsy cohort and 10.2% for HoLEP cohort. Assuming 10% attrition within 1 month of the procedure for lithotripsy cohort and within 3 months of the HoLEP procedure, it is anticipated that 100 treated subjects will be required for each procedure cohort.

11.1.1.3. Statistical Methods

A two-sided 95% confidence interval will be constructed using exact (Clopper-Pearson) method to estimate the SADE rate at 30 days post procedure for lithotripsy cohort and the SADE rate at 3-month post procedure for BPH cohort.

11.1.2. Primary Efficacy Endpoints

Lithotripsy procedure cohort: Stone clearance assessed by stone free rates (SFR) at 1 month follow-up. SFR is defined as clinically nonsignificant, non-obstructive residual fragments of ≤ 3 mm, asymptomatic and no auxiliary procedures performed between the final Flexiva Pulse holmium laser lithotripsy procedure and the 1 month follow-up.

BPH procedure cohort: Improvement in BPH symptoms from Baseline as measured by favorable change in International Prostate Symptom Score (IPSS) at 3-month follow-up.

11.1.2.1. Hypotheses

There is no pre-specified hypothesis. All the endpoints are descriptive in nature.

11.1.2.2. Statistical Methods

Lithotripsy procedure cohort: The proportion of subjects who achieved stone clearance at 1 month follow-up post lithotripsy procedure will be calculated.

BPH procedure cohort: The change of IPSS total score at 3-month and 6-month post BPH procedure from baseline will be summarized using descriptive statistics. The same analysis will be performed for subjects with and without catheter at baseline if applicable.

11.2. *General Statistical Methods*

11.2.1. Analysis Sets

The Intent-to-Treat (ITT) subject population includes all subjects who provide written informed consent to be enrolled into the study, and have the Lithotripsy or BPH procedure attempted.

The As Treated (AT) subject population includes all the ITT subjects who had the Lithotripsy or BPH procedure completed.

The Per Protocol (PP) subject population includes all the AT subjects who also meet all eligibility criteria and have no major protocol deviations.

The primary analysis of all the endpoints will be performed for the ITT population. Efficacy endpoints will be evaluated for the PP population as a sensitivity analysis and safety endpoints will be evaluated for the AS population as a sensitivity analysis.

11.2.2. Control of Systematic Error/Bias

Registry is open to subjects planning to undergo a procedure with the Flexiva Pulse and Flexiva Pulse ID Laser Fibers for any indication per the IFU and at multiple centers. All subjects will be treated according to the directions in the Operating Manual and IFU/DFU. The primary safety endpoint analysis which is based on the exact Clopper-Pearson confidence interval is specified to be conservative in nature.

11.2.3. Number of Subjects per Investigative Site

The study will be conducted at up to 10 sites. Sites will be encouraged to enroll a minimum of 5 subjects per procedure cohort. A maximum of 25 subjects per procedure cohort may be enrolled at a site, unless the site has received prior approval from the sponsor to enroll additional subjects.

11.3. *Data Analyses*

The analyses will include the available cases only unless specified otherwise. Presentation of summary statistics for continuous variables will include N, mean, median, standard deviation, minimum, and maximum values. For categorical variables, the number and percentage under each category will be presented

11.3.1. Secondary Endpoints

11.3.1.1. Secondary Safety Endpoint – Procedure related adverse events and/or adverse device effects

This endpoint applies to both procedure cohorts. Procedure related adverse events and/or adverse device effects related to Flexiva Pulse Laser Fibers including but not limited to:

- Perforation
  - For HoLEP procedures: in prostate capsule, bladder, and/or urethra
  - For Lithotripsy procedures: anywhere in urinary tract
- Hemorrhage resulting in blood loss of ≥ 500mL
- Burn

11.3.1.1.1 Statistical Methods

For each procedure cohort, summary statistics will be calculated for overall device and/or procedure related AEs, and for the device and/or procedure related perforation, hemorrhage and burn effects, respectively. The summary statistics includes but not limited to event count, event rate by seriousness procedure relatedness, and device relatedness.

11.3.1.2. Secondary Efficacy Endpoint 1 – Ability of the laser fiber to deliver energy

This endpoint applies to both procedure cohorts. This endpoint is measured by whether or not the index procedure was successfully completed as indicated.

11.3.1.2.1 Statistical Methods

For each procedure cohort, the proportion of subjects who had successful completion of the index procedure will be estimated.

11.3.1.3. Secondary Efficacy Endpoint 2 – Compatibility of the laser fiber with endoscope

This endpoint applies to both procedure cohorts. It is measured by whether of not the laser fiber is compatible with the endoscope used in the index procedure, including successful passage and maneuverability without fracture.

11.3.1.3.1 Statistical Methods

The proportion of fibers which are compatible with the endoscope among all the fiber used in the index procedure will be estimated.

11.3.1.4. Secondary Efficacy Endpoint 3 – Improvement in Quality of life (QoL) from baseline

This endpoint applies to HoLEP procedure cohort only. The QoL improvement is measured by favorable change in IPSS total score and IPSS QoL score at 3-month follow up from baseline.

11.3.1.4.1 Statistical Methods

The change of IPSS total and QoL scores at 3-month post HoLEP procedure from baseline will be summarized using descriptive statistics.

11.3.1.5. Secondary Efficacy Endpoint 4 – Improvement in uroflow

This endpoint applies to HoLEP procedure cohort only. Improvement in uroflow is measured by the change of maximum urinary flow rate (Qmax) at 3-month follow up from baseline.

11.3.1.5.1 Statistical Methods

The change of Qmax at 3-month post HoLEP procedure from baseline will be summarized using descriptive statistics.

11.3.1.6. Secondary Efficacy Endpoint 5 – Hemostasis during HoLEP procedure

This endpoint applies to HoLEP procedure cohort only. Hemostasis is measured by ability to coagulate during HoLEP procedure.

11.3.1.6.1 Statistical Methods

The proportion of subjects in whom the hemostasis has been achieved as intended during the index HoLEP procedurewill be estimated.

11.3.2. Additional Endpoint

The additional endpoint apply to both lithotripsy procedure and HoLEP procedure cohorts.

11.3.2.1. Additional Endpoint – Fiber tip degradation

Fiber tip degradation is measured with a three-level scale of 'Outperformed', 'Equivalent' and 'Underperformed' compared to physician's current fiber.

11.3.2.1.1 Statistical Methods

Proportion of fibers that are used in the Lithotripsy/HoLEP procedure with tip degradation will be calculated by each response scale for each procedure groups.

11.3.3. Interim Analyses

No formal interim analyses are planned for the purpose of stopping the study early for declaring effectiveness or for futility.

11.3.4. Subgroup Analyses

Primary safety and efficacy endpoints will be evaluated for subjects in the subgroups listed below if applicable:

* With and without staged procedure in the Lithotripsy procedure cohort.
* Unilateral and bilateral procedures in the Lithotripsy procedure cohort.
* With and without previous BPH surgery in the HoLEP procedure cohort.

11.3.5. Justification of Pooling

Fisher's exact test will be applied to evaluate the homogeneity of the primary safety endpoint across study sites for each procedure cohorts respectively. Sites with less than 5 ITT subjects will be pooled together.

11.3.6. Multivariable Analyses

There are no planned multivariable analyses.

11.3.7. 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.

12. Data Management

12.1. *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 Medidata EDC System. All changes made to the clinical data will be captured in an electronic audit trail and available for review by the sponsor 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 their 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 Medidata EDC system and will be issued to the site for appropriate response. Site staff will be responsible for resolving all queries in the database.

All access to the clinical database will be changed to "Read only" after all data is either "Hard Locked" or "Entry Locked". Once acceptance of the final report or finalization of publications (as applicable) is received, final database storage and archiving activities can begin. Once all closeout activities are completed, a request to IT is submitted to have the "Database Locked" or Decommissioned and all database access revoked.

12.2. *Data Retention*

The Principal Investigator or designee or Investigational site will maintain all essential study documents and source documentation that support the data collected on the study subjects in compliance with applicable regulatory requirements.

The Principal Investigator or designee will take measures to prevent accidental or premature destruction of these documents. If for any reason the Principal Investigator or designee withdraws 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. Sites are required to inform BSC in writing where paper or electronic files are maintained in case files are stored off site and are not readily available.

13. 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/REB, and the regulatory authority if applicable 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 by completing the Protocol Deviation eCRF in Rave EDC. Sites may also be required to report deviations to the IRB/EC/REB, and the regulatory authority, per local guidelines and national/government regulations.

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

The sponsor will not approve protocol waivers.

14. Compliance

14.1. *Statement of Compliance*

This clinical investigation is financed by the study sponsor. Before the investigational site can be "Authorized to Enroll," the investigational site must enter into a Clinical Study Agreement with the sponsor that details the financing of the study as well as the rights and obligations of the investigational site and the investigator. This study will be conducted in accordance with applicable FDA regulations (21 CFR 50, 54, 56), ISO 14155: Clinical Investigation of Medical Devices for Human Subjects, ICH Good Clinical Practice, ethical principles that have their origins in the Declaration of Helsinki, and applicable individual country laws and regulations.

Applicability of the above principles have been reviewed for this post-market observational clinical investigation and justifications for ISO 14155 exemptions are noted in the appropriate sections.

The study shall not begin until the required approval/favorable opinion from the IRB/EC/REB 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/REB or regulatory authority shall be followed, if appropriate.

14.2. *Investigator Responsibilities*

The Principal Investigator of an investigational site is responsible for ensuring that the study is conducted in accordance with the Clinical Study Agreement, the clinical investigation plan, the spirit of ISO 14155, ethical principles that have their origins in the Declaration of Helsinki, any conditions of approval imposed by the reviewing IRB/EC/REB, 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 comply with the Investigator responsibilities as described in such Agreement.
- Provide personal qualifications and experience to assume responsibility for the proper conduct of the study and that of key members of the site 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 as applicable per the protocol and observed device deficiency.
- Report to sponsor, per the protocol requirements, all reportable events.
- Report to the IRB/EC/REB 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/REB, and supply BSC with any additional requested information related to the safety reporting of a particular event.
- Allow the sponsor to perform monitoring and auditing activities, and be accessible to the clinical research monitor or auditor and respond to questions during monitoring visits or audit(s).
- Allow and support regulatory authorities and the IRB/EC/REB when performing auditing activities.
- Ensure that informed consent is obtained in accordance with applicable laws, this protocol and local IRB/EC/REB 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 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.
- Discuss or review questionnaire responses with subjects and subsequently report adverse event(s) if warranted.

All investigators will provide their qualifications and experience to assume responsibility for their delegated tasks 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.

14.2.1. Delegation of Responsibility

When specific tasks are delegated by an investigator, including but not limited to conducting the informed consent process, the Principal Investigator is responsible for ensuring competency of those to whom tasks are delegated as well as providing appropriate training to them, and adequate supervision of those to whom tasks are delegated. The Principal Investigator will provide both the training documents and a signed training log to BSC. 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.

14.3. *Institutional Review Board/ Ethics Committee*

The investigational site will obtain the written and dated approval/favorable opinion of the IRB/EC/REB for the clinical investigation before recruiting subjects and implementing all subsequent amendments, if required.

A copy of the written IRB/EC/REB and/or competent authority (CA) approval of the protocol (or permission to conduct the study) and ICF, must be received by the sponsor before recruitment of subjects into the study. 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/EC/REB before the changes are implemented to the study. All changes to the ICF will be IRB/EC/REB 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/REB approval and renewals will be obtained throughout the duration of the study as required by applicable local/country laws or regulations or IRB/EC/REB requirements. Copies of the study reports and the IRB/EC/REB continuance of approval must be provided to the sponsor.

14.4. *Sponsor Responsibilities*

All information and data sent to BSC concerning subjects or their participation in this study will be considered confidential by BSC and will be kept confidential in accordance with all applicable laws and regulations. Only authorized BSC personnel and/or a BSC representative including, but not limited to 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 used by BSC for the purposes of this study, publication, and to support future research and/or other business purposes, such as overseeing and improving the performance of its device, new medical research and proposals for developing new medical products and procedures. All data used in the analysis and reporting of this study or shared with a third-party researcher will be without identifiable reference to specific subjects.

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.

14.5. *General Data Protection Regulations (GDPR)*

Data collected from clinical trial data subjects are considered “personal data” (including sensitive personal data in some cases). The protection of clinical trial subject personal data and compliance with privacy, data protection laws and regulations are of critical importance to BSC. Data collection has been carefully considered for this study and has been restricted to the strict essentials with a clear, specific and detailed purpose to mitigate the risk and the impact of data breach and to comply with data privacy laws (including but not limited to HIPAA and GDPR). Section 10 of the protocol defines the data that need to be collected to fulfill the objectives of the clinical study.

Personal data collected by BSC includes, but is not limited to:

- Geographic data (site name)
- Important Dates
    - Informed consent date
    - Age at the time of study enrollment
    - Procedure date
    - Adverse event start/end date
    - Hospitalization admission/discharge date
    - Subject visit dates

The purposes of the personal data processing will be carefully defined within the informed consent form. Personal data will not be used for a purpose other than the one stated in the informed consent provided to the subjects. Personal data shall not be disclosed, made available,

or otherwise used, processed, transferred, or stored for purposes other than those specified in the informed consent form, except:

- with the consent of the data subject; or
- processing is necessary for compliance with a legal obligation.

14.5.1. Transparency

BSC must only collect personal data by fair and lawful means. BSC must be transparent and open with individuals about how BSC collects and uses personal data, with whom BSC shares it, and where it may be processed.

For this transparency principle, BSC must provide information to our health care providers and their study subjects about the purpose for collecting their personal data; who will have access to the data and to whom it may be shared, if it will be accessed or transferred to another country; and who to contact with questions or requests.

14.5.2. Rights to Data Subjects

In GDPR, a data subject is any living individual to whom the personal data relates. A data subject includes study subjects. Data subjects shall have the right to:

- obtain from BSC confirmation of whether BSC has data relating to the individual;
- have data relating to them communicated:
    - within a reasonable time (within 30 days from receipt of request, extendable if complicated or unclear request);
    - at a charge, if any, that is not excessive;
    - in a reasonable manner; and
    - in a form that is readily intelligible to the individual;
- be given reasons if a request made under subparagraphs (a) and (b) is denied, and to be able to challenge such denial;
- challenge data relating to the individual and, if the challenge is successful, to have the data erased, rectified, completed, or amended. During the period of such challenge, the individual can require that access to the data be restricted;
- "opt out"/oppose that their personal data are used for marketing purposes; and,
- when requested, BSC must also communicate any rectification or erasure of personal data or restriction of processing to each recipient to whom the personal data have been disclosed, unless this proves impossible or involves disproportionate effort.

These rights will also be listed in the subject informed consent form.

14.6. *Insurance*

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

15. Monitoring

Monitoring will be performed during the study to assess continued compliance with the protocol and applicable regulations. In addition, the clinical research monitor verifies that study records are adequately maintained, that data are reported in a satisfactory manner with respect to timeliness, adequacy, and accuracy, and that the Principal Investigator continues to have sufficient staff and facilities to conduct the study safely and effectively. The Principal Investigator/institution guarantees direct access to original source documents by BSC personnel, their designees, and appropriate regulatory authorities.

The sponsor will put a plan in place to document the specific monitoring requirements.

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 Principal Investigator and relevant study personnel are available during on-site monitoring visits or audits and that sufficient time is devoted to the process.

16. Potential Risks and Benefits

16.1. *Instructions for Use*

Please refer to the Instructions for Use for an overview of anticipated adverse (device) effects, and risks associated to the commercial device(s).

16.2. *Risks associated with Participation in the Clinical Study*

The Flexiva Pulse and Flexiva Pulse ID Laser Fibers are commercially available devices. None of the procedures associated with this study fall outside of a standard of care procedure. Therefore, there are no foreseen additional risks associated with the procedure, testing, or withdrawal from the study.

16.3. *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.

16.4. *Anticipated Benefits*

There are no guaranteed benefits from participation in this study. Potential benefits include stone clearance, improved urodynamics, and improved quality of life. The Flexiva Pulse and Flexiva Pulse ID Laser Fibers are commercially available devices and can be utilized with or without enrollment in this study. However, information gained from the conduct of this study may be of benefit to others with the same medical conditions.

Refer to the Instructions for Use for further information.

17. Safety Reporting

17.1. *Reportable Events by investigational site to BSC*

It is the responsibility of the investigator to assess and report to BSC any event which occurs in any of following categories, from the time of Lithotripsy/HoLEP procedure to the end of the study:

- Serious Adverse Device Effects (SADEs)
- Procedure Related Serious Adverse Events (SAEs)
- Fatal Serious Adverse Events (SAEs)
- Adverse Device Effects (ADEs)
- Procedure Related Adverse Events (AEs)
- Device Deficiencies (including BSC devices used during the procedure)

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 reportable event must be recorded in the eCRF.

The Investigator or designee is responsible for updating the eCRF with new and/or updated information in relation to the already reported event as soon as he/she becomes aware.

Underlying diseases and chronic conditions 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 17.2-**1 for AE definitions).

Refer to Instructions for Use for the known risks associated with the commercial device(s).

17.2. *Definitions and Classification*

Safety definitions are provided in **Table 17.2-1**. Administrative edits were made on the safety definitions from applicable regulations and guidance including (but not limited to) 21 CFR Part 812, ISO 14155 and EU MDR 2017/745/ MDCG 2020-10/1 Guidance on Safety Reporting in Clinical Investigations for clarification purposes.

Table 17.2-1: Safety Definitions

Term	Definition
Adverse Event (AE) *Ref: ISO 14155* *Ref: MDCG 2020-10/1*	Any untoward medical occurrence, unintended disease or injury, or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons, in the context of a clinical investigation, whether or not related to the study medical device and whether anticipated or unanticipated. **NOTE 1**: This includes events related to the study medical device or comparator. **NOTE 2**: This definition includes events related to the procedures involved. **NOTE 3**: For users or other persons, this definition is restricted to events related to the study medical device.
Adverse Device Effect (ADE) *Ref: ISO 14155* *Ref: MDCG 2020-10/1*	Adverse event related to the use of the study medical device **NOTE 1**: This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the study medical device. **NOTE 2**: This definition includes any event resulting from use error or from intentional misuse of the study medical device. **NOTE 3**: This includes 'comparator' if the comparator is a medical device.
Serious Adverse Event (SAE) *Ref: ISO 14155* *Ref: MDCG 2020-10/1*	Adverse event that led to any of the following: a) death, b) serious deterioration in the health of the subject, users or other persons as defined by either: 1) a life-threatening illness or injury, or 2) a permanent impairment of a body structure or a body function, including chronic diseases, or 3) in-patient hospitalization or prolongation 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) fetal distress, fetal death, or a congenital abnormality or birth defect including physical or mental impairment. **NOTE 1:** Planned hospitalization for a pre-existing condition, or a procedure required by the clinical investigational plan, without a serious deterioration in health, is not considered a serious adverse event.
Serious Adverse Device Effect (SADE) *Ref: ISO 14155* *Ref: MDCG 2020-10/1*	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.
Unanticipated Adverse Device Effect (UADE)	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

Table 17.2-1: Safety Definitions

Term	Definition
Ref: 21 CFR Part 812	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: MDCG 2020-10/1*	Serious adverse device effect which by its nature, incidence, severity, or outcome has not been identified in the current risk assessment. **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 assessment.
Serious Health Threat *Ref: ISO 14155*	Signal from any adverse event or device deficiency that indicates an imminent risk of death or a serious deterioration in the health in subjects, users or other persons, and that requires prompt remedial action for other subjects, users or other persons. **NOTE 1**: This would include events that are of significant and unexpected nature such that they become alarming as a potential serious health hazard or possibility of multiple deaths occurring at short intervals.
Device Deficiency *Ref: ISO 14155* *Ref: MDCG 2020-10/1*	An inadequacy of a medical device related to its identity, quality, durability, reliability, usability, safety or performance. **NOTE 1**: Device deficiencies include malfunctions, use errors, and inadequacy in the information supplied by the manufacturer including labelling. **NOTE 2**: This definition includes device deficiencies related to the device under study or the comparator.
The following definitions will be used for defining hospitalization or prolongation of hospitalization for SAE classification purposes:	
Hospitalizations	Hospitalization does not include: • emergency room visit that does not result in in-patient admission Note: although an emergency room visit does not itself meet the definition for hospitalization, it may meet other serious criteria (e.g. medical or surgical intervention to prevent permanent impairment or damage) • elective and pre-planned treatment/surgery for a pre-existing condition that is documented in the subject's record at the time of consent/enrollment • admission for social reasons and/or respite care in the absence of any deterioration in the subject's general condition (e.g. subject is homeless, caregiver relief) • pre-planned, protocol-specified admission related to the clinical study (e.g. procedure required by protocol)
Prolongation of hospitalization	In-patient admission to the hospital that is prolonged beyond the expected standard duration for the condition under treatment. Note: new adverse events occurring during the hospitalization are evaluated to determine if they prolonged hospitalization or meet another SAE criteria.

17.3. *Relationship to Study Device(s) (Device Under Study and Comparator Device, if applicable) and/or Study Procedure*

The Investigator must assess the relationship of the reportable AE to the study device(s), and/or study procedure. See criteria in **Table 17.3-1**:

Table 17.3-1: Criteria for Assessing Relationship of Study Device(s) (Device Under Study and Comparator Device, if applicable) or Procedure to Adverse Event

Classification	Description
Not Related *Ref: MDCG 2020-10/1*	Relationship to the device, comparator or procedures can be excluded when: - the event has no temporal relationship with the use of the study device or the procedures related to the use of the study device; - 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 that cannot 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 study device used for diagnosis, when applicable; - 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.
Possibly Related *Ref: MDCG 2020-10/1*	The relationship with the use of the study device or comparator, or the relationship with procedures 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 where relatedness cannot be assessed or no information has been obtained should also be classified as possible.
Probably Related *Ref: MDCG 2020-10/1*	The relationship with the use of the study device or, comparator, or the relationship with procedures seems relevant and/or the event cannot be reasonably explained by another cause.

Table 17.3-1: Criteria for Assessing Relationship of Study Device(s) (Device Under Study and Comparator Device, if applicable) or Procedure to Adverse Event

Classification	Description
Causal Relationship *Ref: MDCG 2020-10/1*	The serious event is associated with the study device, comparator or with procedures beyond reasonable doubt when: - 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 the study device use/application or procedures; - the event involves a body-site or organ that -the study device or procedures are applied to; -the study 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 study 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.

17.4. *Investigator Reporting Requirements*

The communication requirements for reportable events to BSC are as shown below.

Table 17.4-1: Investigator Requirements for Reporting

Event Classification	Communication Method	Communication Timeline post-market studies (*EU MDR 2017/745, MDCG 2020-10/1*MEDDEV 2.12/1: Guidelines on a Medical Device Vigilance System)
Unanticipated Adverse Device Effect / Unanticipated Serious Adverse Device Effect	Complete AE eCRF page with all available new and updated information.	• Within 1 business day of first becoming aware of the event. • Terminating at the end of the study.
	Provide all relevant source documentation (de-identified/ pseudonymized) for reported event.	• Upon request of sponsor.

Event Classification	**Communication Method**	**Communication Timeline post-market studies** (*EU MDR 2017/745, MDCG 2020-10/1*MEDDEV 2.12/1: Guidelines on a Medical Device Vigilance System)
Serious Adverse Event	Complete AE eCRF page with all available new and updated information.	• Within 10 calendar days after becoming aware of the event or as per local/regional regulations. • Reporting required through the end of the study
	Provide all relevant source documentation (de-identified/ pseudonymized) for reported event.	• When documentation is available • Upon request of sponsor
Serious Adverse Device Effects	Complete AE eCRF page with all available new and updated information.	• Within 3 calendar days of first becoming aware of the event or as per local/regional regulations. • Reporting required through the end of the study
	Provide all relevant source documentation (de-identified/ pseudonymized) for reported event.	• When documentation is available • Upon request of sponsor
Device Deficiencies (including but not limited to malfunctions, use errors, and inadequacy in information supplied by the manufacturer, including labelling) Note: Any Device Deficiency that might have led to a serious adverse event if appropriate action had not been taken, intervention had not occurred, circumstances had been less fortunate is considered a reportable event.	Complete Device Deficiency eCRF with all available new and updated information.	• Within 3 calendar days of first becoming aware of the event. Reporting required through the end of the study
	Provide all relevant source documentation (de-identified/ pseudonymized) for reported event.	• Upon request of sponsor
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.	• Adverse Device Effects (or other key events of interest, e.g., Heart Failure): In a timely manner but not later than 30 business days after becoming aware of the information • Adverse Events: In a timely manner but recommend within 30 business days after becoming aware of the information • Reporting required through the end of the study • Upon request of sponsor
	Provide all relevant source documentation (de-identified/ pseudonymized) for reported event.	

17.5. *BSC Device Deficiencies*

Device deficiencies will be collected for BSC devices only and will be documented and reported to BSC. If possible, the device(s) should be returned to BSC for analysis. Instructions for returning the device(s) will be provided by the Clinical Project Manager. Device deficiencies should also be documented in the subject's source records.

Device deficiencies are not adverse events. However, an adverse event that results from a device deficiency, would be recorded as an adverse event on the appropriate eCRF.

17.6. *Reporting to Regulatory Authorities / IRBs / ECs / REBs/ Investigators*

BSC is responsible for reporting adverse event information to all participating Principal Investigators, IRBs/ECs/REBs and regulatory authorities, as applicable.

The Principal Investigator is responsible for informing the IRB/EC/REB, and regulatory authorities of UADEs and SAEs as required by local/regional regulations.

17.7. *Subject Death Reporting*

A subject death during the study should be reported to BSC as soon as possible and, in any event, within three (3) calendar days of site notification. The site's IRB/EC/REB must be notified of any deaths in accordance with that site's IRB/EC/REB policies and procedures.

Notification of death must include a detailed narrative (death letter) that provides detailed information describing the circumstances surrounding the death. A death narrative in the local language is acceptable, if accompanied by a translation in English. The details listed below should be addressed in the death narrative, in order for BSC to understand the circumstance surrounding the death:

- Date of death
- Immediate cause of death
- Whether the death was related to the device or to the procedure
- Any other circumstances surrounding the death
- Investigator or sub-investigator signature and date

Also submit the following documentation:

- If the patient expired in the hospital:
    - A copy of the medical records for that admission (e.g., History and Physical, consults, test results, operative reports, and/or progress notes from the hospital chart)
    - Death certificate (if available)
    - Autopsy report (if applicable and available)
- If the patient expired outside of the hospital (e.g., home):
    - A copy of the most recent clinic visit (if not already submitted to BSC)

- Death certificate (if available)

The Clinical Events Committee (CEC) will review information regarding subject deaths.

18. Informed Consent

Subject participation in this clinical study is voluntary. Informed Consent is required from each subject or subject's legally authorized representative. The Investigator is responsible for ensuring that Informed Consent is obtained prior to the use of any study 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, as applicable. The ICF must be accepted by BSC or its delegate (e.g. CRO), and approved by the site's IRB/EC/REB, or central IRB, if applicable.

BSC 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 site's IRB/EC/REB. Any modification requires acceptance 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 site in obtaining a written consent translation. Translated consent forms must also have IRB/EC/REB 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 subject's 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 subject's medical condition allows. The original signed

ICF will be retained by the site 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 must be reported to BSC. Any violations of the informed consent process must be reported as deviations to the sponsor and local regulatory authorities (e.g. IRB/EC/REB), 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/REB. The new version of the ICF must be approved by the IRB/EC/REB. Acceptance by BSC is required if changes to the revised ICF are requested by the site's IRB/EC/REB. The IRB/EC/REB will determine the subject population to be re-consented.

19. Committees

19.1. *Safety Monitoring Process*

The BSC personnel from the Medical Safety and Safety Trial Operations group review safety data as it is reported by the sites throughout the duration of the study. During scheduled monitoring activities, clinical research monitors further support this review through their review of source documents and other data information. The BSC Medical Safety and Safety Trial Operations team include health care providers with the necessary therapeutic and subject matter expertise to evaluate and classify the events into the categories outlined above.

19.2. *Clinical Events Committee*

Adjudication of clinical events will be performed by an independent physician or group of physicians with pertinent expertise. Independent physician(s) will review and adjudicate important endpoints and relevant adverse events reported by study investigators. Independent physician(s) will review a safety event dossier, which may include copies of subject source documents provided by study sites.

Membership will include practitioner(s) of urology with the necessary therapeutic and subject matter expertise to adjudicate important endpoints and relevant adverse events reported by study investigators. Adjudication responsibilities, qualifications, membership, and adjudication procedures are outlined in the adjudication charter. The adjudication charter will also specify the stage at which adjudication activities will cease and events will be reviewed internally by BSC.

20. Suspension or Termination

20.1 Premature Termination of the Study

BSC 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/REBs, and regulatory authorities, as applicable, will be notified in writing in the event of study termination.

20.1.1 Criteria for Premature Termination of the Study

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

- Suspicion of an unacceptable risk, including serious health threat. In this case, the sponsor shall suspend the clinical investigation while the risk is assessed. The sponsor shall terminate the clinical investigation if an unacceptable risk which cannot be controlled is confirmed.
- Instructions by the IRB/EC/REB or regulatory authorities to suspend or terminate the clinical investigation.
- An enrollment rate far below expectation that prejudices the conclusion of the study.
- A decision on the part of BSC to suspend or discontinue development/marketing of the device.

20.2 Termination of Study Participation by the Investigator or Withdrawal of IRB/ EC/REB Approval

Any investigator, or associated IRB/EC/REB or regulatory authority may discontinue participation in the study or withdraw approval of the study, respectively, with suitable written notice to BSC. Investigators, associated IRBs/ECs/REBs, and regulatory authorities, as applicable, will be notified in writing in the event of these occurrences.

20.3 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 sites by BSC. The IRB/EC/REB 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/EC/REB terminates participation in the study, participating investigators, associated IRBs/ECs/REBs, and regulatory authorities, as applicable, will be notified in writing. Detailed information on how enrolled subjects will be managed thereafter will be provided by BSC.

In the event a Principal Investigator terminates participation in the study, study responsibility will be transferred to another investigator, if possible. In the event there are no opportunities

to transfer Principal Investigator responsibility; detailed information on how enrolled subjects will be managed thereafter will be provided by BSC.

The Principal Investigator or designee must return all study-related documents and devices, if supplied by BSC, unless this action would jeopardize the rights, safety, or welfare of the subjects.

20.4 Criteria for Suspending/Terminating a Study Site

BSC 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 6 months after site initiation, or if the site has multiple or severe protocol violations/noncompliance without justification and/or fails to follow remedial actions.

In the event of termination of site participation, all 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 IRB/EC/REB and regulatory authorities, as applicable, will be notified. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

21. Study Registration and Results

21.1. *Study Registration*

To comply with applicable laws and regulations, the study will be registered on a publicly accessible database.

21.2. *Clinical Investigation Report*

Study results will be made available in accordance with the legal requirements and the recognized ethical principles, in accordance with the BSC Policy. A Clinical Investigation Report will be made available to all investigators, IRB/EC/REB and regulatory authorities, as applicable in accordance with the BSC Policy and local requirements. As applicable an abbreviated Clinical Investigation Report will be made available on a publicly accessible database.

21.3. *Publication Policy*

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. BSC may submit study results for publication (regardless of study outcome) following the conclusion or termination of the study. BSC 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.

The data, analytic methods, and study materials for this clinical trial may be made available to other researchers in accordance with the BSC Data Sharing Policy (https://www.bostonscientific.com/).

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23. Abbreviations and Definitions

23.1. *Abbreviations*

Abbreviations are shown in **Table 23.1-1**

Table 23.1-1: Abbreviations

Abbreviation/Acronym	Term
ADE	Adverse Device Effect
AE	Adverse Event
AT	As Treated
BPH	Benign Prostatic Hyperplasia
BPO	Benign Prostatic Obstruction
BSC	Boston Scientific Corporation
CA	Competent Authority
CBC	Complete Blood Count
CEC	Clinical Events Committee
CFR	Code of Federal Regulations
CI	Confidence Interval
CRF	Case Report Form
CRO	Contract Research Organization
CT	Computed Tomography
EAU	European Association of Urology
EC	Ethics Committee
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
ESWL	Extracorporeal Shock Wave Lithotripsy
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GDPR	Global Data Protection
H & P	History and Physical
HIPAA	Health Information Portability and Accountability Act
HoLEP	Holmium Laser Enucleation of the Prostate
Ho: YAG	Holmium: yttrium-aluminum-garnet Laser
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ICMJE	International Committee of Medical Journal Editors
IFU	Instructions For Use
INR	International Normalized Ratio
IPSS	International Prostate Symptom Score
IRB	Institutional Review Board
ISO	International Organization for Standardization
ITT	Intent To Treat
LUTS	Lower Urinary Tract Symptoms

Table 23.1-1: Abbreviations

Abbreviation/Acronym	Term
MET	Medical Expulsive Therapy
NIH	National Institutes of Health
OHRP	Office for Human Research Protections
PCNL	Percutaneous Nephrolithotomy Procedures
PP	Per Protocol
PSA	Prostate-Specific Antigen
PT	Prothrombin Time
PTT	Patrial Thromboplastin Time
PUL	Prostatic Urethral Lift
PVR	Post Void Residual
QOL	Quality of Life
REB	Research Ethics Board
SAE	Serious Adverse Event
SADE	Serious Adverse Device Effect
SFR	Stone Free Rate
SOC	Standard of Care
TUIP	Transurethral Incision of Prostate
TURP	Transurethral Resection of Prostate
UADE	Unanticipated Adverse Device Effects
UPN	Universal Product Number
USADE	Unanticipated Serious Adverse Device Effects
UTI	Urinary Tract Infection

23.2. *Definitions*

Terms are defined in **Table 23.2-1**.

Table 23.2-1: Definitions

Term	Definition
Adverse Device Effect (ADE)	See Table 17.2-1: Safety Definitions
Adverse Event (ADE)	See Table 17.2-1: Safety Definitions
As Treated	All subjects for whom treatment is attempted.
Clinical Events Committee	An independent or group of physicians with trial relevant therapeutic expertise whose purpose is to review and adjudicate important endpoints and/or specific adverse events.
Data Subject	In GDPR: Any living individual to whom the personal data relates. Examples of data subjects in this study are physicians and subjects.

Term	Definition
Deviation (Clinical Protocol)	A departure from the requirements established in the clinical trial protocol (e.g., inclusion/exclusion criteria; visit windows, required procedures, and any specified consenting process requirements).
Device Deficiency	See Table 17.2-1: Safety Definitions
General Data Protection Regulation (GDPR)	The General Data Protection Regulation (GDPR) is a European law that will govern how companies (whether EU-based or not) use personal data.
Hospitalization	See Table 17.2-1: Safety Definitions
Intent-To-Treat	A subject who signs the informed consent, meets eligibility criteria, and for whom the Lithotripsy/HoLEP procedure is initiated but not completed (first incision). The original ICF and screening documentation for intent to treat patients should be maintained in the site's files. These patients are followed in accordance with the study follow up schedule for safety and count toward enrollment.
Monitoring	EN ISO 14155:2020-3.29 - Act of overseeing the progress of a clinical investigation to ensure that it is conducted, recorded, and reported in accordance with the CIP, written procedures, this document, and the applicable regulatory requirements. ICH E6 1.38 - The act of overseeing the progress of a clinical study and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, Standard Operating Procedures (SOPs), GCP, and the applicable regulatory requirement(s). FDA Guidance - Generally refers to the methods used by sponsors of investigational studies, or CROs delegated responsibilities for the conduct of such studies, to oversee the conduct of and reporting of data from clinical investigations, including appropriate investigator supervision of study site staff and third-party contractors.
Multi-center study	A clinical trial conducted according to a single protocol but at more than one site, and therefore carried out by more than one investigator.
Per Protocol	All subjects in the As Treated Population who have no major protocol deviations.
Personal Data	GDPR defines "Personal data" to be any information relating to an identified or identifiable natural person ('data subject'); an identifiable natural person is one who can be identified, directly or indirectly, in particular by reference to an identifier such as a name, an identification number, location data, an online identifier or to one or more factors specific to the physical, physiological, genetic, mental, economic, cultural or social identity of that natural person.
Point of Enrollment	Time at which, following recruitment, a subject signs and dates the informed consent form
Processing	Any use of personal data by BSC (or a third party on behalf of BSC), including data collection, data sharing, anonymization, and data storage (note the mere storage of data is considered as processing).

Term	Definition
RAVE	Proprietary electronic data capture system for capturing, managing and reporting clinical study data.
Recruitment	Active efforts to identify subjects who may be suitable for enrollment in the clinical investigation.
Sensitive Personal Data	GDPR defines "Sensitive personal" data as a subset of Personal Data, which, due to their nature have been classified as deserving additional privacy and security protections because their processing may create a risk for an individual's fundamental right and freedom.
Serious Adverse Device Effect (SADE)	See Table 17.2-1: Safety Definitions
Serious Adverse Event (SAE)	See Table 17.2-1: Safety Definitions
Site Noncompliance	A departure from the regulations established by the relevant regulatory authorities. Includes all clinical site noncompliance that does not represent a direct deviation from the clinical trial protocol, e.g. IRB/IEC and sponsor reporting, device storage and accountability, staff qualifications and training, facilities, and equipment required to conduct the clinical trial, collection and documentation of data in source documents and CRFs, investigator oversight, etc.
Source Document	Original or certified copy of printed, optical or electronic document containing source data *(Ref. ISO 14155-2020)*