Medical Device Clinical Trial Protocol

Protocol Title：A real world study to evaluate the feasibility, preliminary safety and performance of Rezūm system in BPH treatment in China (Rezūm RWS study)

Investigational Device	Rezūm Generator (G2200-0032) Rezūm Delivery Device Kit(M006D2201-0032)
Class of device	Class 3 medical device requiring clinical trials Yes☐ No☒ Same class device within China Yes☐ No☒
Protocol version and date	Rev/Ver B, March 22, 2021
Clinical trial sites	Boao Yiling Life Care Center
Principal Investigator	LIU Ming
Sponsor	BSC International Medical Trading (Shanghai) Co., Ltd, ("BSC China")

A real world study to evaluate the feasibility, preliminary safety and performance of Rezūm system in BPH treatment in China

Rezūm RWS study

U0719

CLINICAL INVESTIGATION PLAN

Sponsored By

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Original Release: Dec 21, 2020

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Revision Version	Protocol Date	Template number and version	Protocol Section Modified	Summary of Changes	Justification for Modification
Rev/Ver A	Dec 21,2020	92120219_Rev/Ver F	NA	NA	First release
Rev/Ver B	Mar 22, 2021	92120219_Rev/Ver F	Synopsis and 6.2.1	Clarify the definition of primary end point: ‘ …… Complications from Rezūm procedure to 3-6M post Rezūm procedure ’	Based on EC comments
Rev/Ver B	Mar 22, 2021	92120219_Rev/Ver F	Synopsis ‘Study Duration’	Added : ‘it will takes about 3 months to complete data collection’	Modified per plan
Rev/Ver B	Mar 22, 2021	92120219_Rev/Ver F	Synopsis and 7	Modified ‘1 invstigation site, Boao Yiling Life Care Center’	Based on EC comments
Rev/Ver B	Mar 22, 2021	92120219_Rev/Ver F	Synopsis and 8.2	1 criteria was added. ‘ The subjects will provide written informed consent form and agree to data collection.’	Based on EC comments
Rev/Ver B	Mar 22, 2021	92120219_Rev/Ver F	Synopsis and 8.3	Delete ‘the subjects who were diagnosed as BPH, ……Hainan medical pilot zone should be enrolled.’	Based on EC comments
Rev/Ver B	Mar 22, 2021	92120219_Rev/Ver F	9.1	Add ‘informed consent ’ in table.	Based on EC comments
Rev/Ver B	Mar 22, 2021	92120219_Rev/Ver F	9.3	Add ‘9.3 informed consent ’, delete waiver of informed consent	Based on EC comments
Rev/Ver B	Mar 22, 2021	92120219_Rev/Ver F	9.6	Modify the wording	Modified per plan

Revision Version	Protocol Date	Template number and version	Protocol Section Modified	Summary of Changes	Justification for Modification
Rev/Ver B	Mar 22, 2021	92120219_Rev/Ver F	13.3	Add the ICF approval by EC/IRB, delete waiver of ICF. Make a minor change in wording.	Based on EC comments
Rev/Ver B	Mar 22, 2021	92120219_Rev/Ver F	13.4	Specify copy the recored of study per regulation	Based on EC comments
Rev/Ver B	Mar 22, 2021	92120219_Rev/Ver F	14	Add ‘signed ICF ’	Based on EC comments
Rev/Ver B	Mar 22, 2021	92120219_Rev/Ver F	15.2	Add private information identifying subject in detail.	Based on EC comments
Rev/Ver B	Mar 22, 2021	92120219_Rev/Ver F	15.3	Risk minimization actions	Based on EC comments
Rev/Ver B	Mar 22, 2021	92120219_Rev/Ver F	17	Add informed consent in detail.	Based on EC comments
Rev/Ver B	Mar 22, 2021	92120219_Rev/Ver F	20.3	Please contact Boston Scientific staff for further information: LinHui, 010-61412942	update
Rev/Ver B	Mar 22, 2021	92120219_Rev/Ver F	Contact Information	Update the adress	update

2. Protocol Synopsis

A real world study to evaluate the feasibility, preliminary safety and performance of Rezūm system in BPH treatment in China（Rezūm RWS study）	
Study Objective(s)	This RWS study is to evaluate the feasibility, preliminary safety and performance of Rezūm system in BPH treatment in China, to generate local real world data from a Chinese BPH population.
Indication(s) for Use	The Rezūm System is intended to relieve symptoms, obstructions, and reduce prostate tissue associated with BPH. It is indicated for men ⩾50 years of age with a prostate volume ⩾ 30cm^3 and ⩽80cm^3. The Rezūm System is also indicated for treatment of prostate with hyperplasia of the central zone and/or a median lobe.
(Commercial) Device/System applied	Rezūm Generator （Model #G2200-0032） Rezūm Delivery Device Kit（Model # M006D2201-0032）
Study Design	Retrospective, single arm, RWS study
Planned Number of Subjects	Up to 30 subjects who were diagnosed as BPH and treated with Rezūm system will be collected to get 22 treated subjects with valid data.
Planned Number of Sites	1 investigation site, Boao Yiling Life Care Center
Primary Endpoint	**Primary Efficacy Endpoint:** IPSS change at 3-6M post Rezūm procedure. **Primary Safety Endpoint:** Device Related Serious Complications from Rezūm procedure to 3-6M post Rezūm procedure. Composite device related serious complications for this endpoint are defined as: 1. Device perforation of the rectum or GI tract; 2. Device related formation of fistula between the rectum and urethra; 3. De novo severe urinary retention lasting more than 21 consecutive days post treatment.

A real world study to evaluate the feasibility, preliminary safety and performance of Rezūm system in BPH treatment in China（Rezūm RWS study）	
Secondary Endpoint	1. Anesthesia method 2. Rezūm procedure time 3. Qmax and Post void residual (PVR） 4. Catheterization time 5. Quality of Life (if available) 6. Ejective function（MSHQ-EjD and IIEF (if available) 7. Surgical retreatment post Rezūm procedure (if available) 8. Medication retreatment post Rezūm procedure (if available) 9. All SAEs
Method of Assigning Patients to Treatment	Not applicable, this is a single-arm study.
Follow-up Schedule	Not applicable, this is a retrospective study with no follow-up visit.
Study Duration	This is a retrospective study, it will takes about 3 months to complete data collection.
Participant Duration	Not applicable, this is a retrospective study.
Inclusion Criteria	• The subjects will provide written informed consent form and agree to data collection. • The subjects who were diagnosed as BPH and treated by Rezūm procedure in Hainan medical pilot zone will be enrolled in this study.
Exclusion Criteria	This is a retrospective study without any formal exclusion criteria.
Statistical Methods	

A real world study to evaluate the feasibility, preliminary safety and performance of Rezūm system in BPH treatment in China（Rezūm RWS study）	
Primary Statistical Hypothesis	The primary endpoint is IPSS change at 3-6M post Rezūm procedure. In Rezūm Pivotal II study, IPSS score represents a 11.2±7.6 point reduction at 3M post Rezūm procedure in treatment arm, while 4.3±6.9 point reduction in sham control. In Pivotal trial, IPSS score in treatment group decreased 25%(5.375) compared to sham control group is recognized as meaningful. As this is a retrospective RWS study, the inclusion/exclusion criteria is not strict, we set up performance goal for score change as 5.5, the expected score change is 10 at 3-6M post Rezūm procedure. A performance goal (PG) testing for the primary endpoint is planned. The decision rule is to calculate the 95% Lower Confidence Interval (LCI) of score change and compare it to the PG, meet PG if LCI is greater than PG.
Statistical Test Method	Study endpoints will be summarized descriptively,when it comes to primary endpoint-IPSS score, last IPSS score during 3-6 moth post procedure of subjects will be used, if they had several IPSS score. Categorical variables will be tabulated with frequencies, percentages and 95% confidence intervals. Continuous variables will be tabulated with mean, median, standard deviation, minimum, maximum, and 95% confidence interval of the mean. This study allows exploratory analysis, eg.the change tendency of IPSS score and variables, sub-group analysis based on IPSS score.
Sample Size Parameters	The sample size is calculated according to below formula: $$n = \frac{(Z_\alpha + Z_\beta)^2 \sigma^2}{\delta^2}$$ n is sample size, we designed 5.5 as performance value, 10 is expected IPSS change, α=0.05，β=0.20（power=80%）Considering the small sample size needs to be iterative distribution, 22 subjects will provide more than 85% power. As this is retrospective study, there are chances of missing data in the study. So the final sample size will be up to 30, to satisfy 22 treated subjects.

3. Table of Contents

3.1. *Table of Tables*

4. Introduction

4.1. *Background*

Benign prostatic hyperplasia (BPH) with associated lower urinary tract symptoms (LUTS) is a common medical condition in the aging male. The incidence has been estimated to increase from 40% among male between the age of 50 and 60 years to 90% among male older than 80 years of age, as cited by Ackerman et al[1]. In 2007, the prevalence of BPH in the U.S. was estimated to be 10.7 million men[2]. In China, the morbidity of BPH in male over 60 years old is more than 50%, and is as high as 83% in male over 80 years[3].

Initially, active surveillance (observing without treatment) is often employed. Treatment initiation usually occurs once symptoms of bladder outlet obstruction and bladder irritability interfere with the subject's quality of life. The American Urological Association Symptom Index (AUASI)/International Prostate Symptom Score (IPSS) is considered the gold standard measurement tool for the assessment of BPH symptoms and response to treatment, both in a clinical practice setting and as an outcome measure in randomized controlled studies[4]. (The AUASI is identical to the seven symptom questions of the IPSS while the IPSS has one more question dealing with how these symptoms affect a patient's quality of life (QoL). Results from the AUASI are referred to as the IPSS; the acronym IPSS is also used as a substitute for AUASI.)

For many men, medications are the most common way to control mild to moderate symptoms of BPH to reduce its major symptoms. However, BPH medications have several systemic side effects, are costly if used for long periods of time, and some subjects have difficulty with complying with medications, particularly in the older population. For severe BPH symptoms, transurethral resection of the prostate (TURP), laser vaporization, or thermal ablation are common treatments of choice.

The Rezūm System is a minimally invasive thermal ablation treatment that may mitigate the symptoms of BPH. The Rezūm System treatment is rapid, preserves the urethra, and subjects may potentially have relief from the symptoms of BPH as soon as 1 week after treatment. The Rezūm System has got CE mark and FDA approval in 2013 and 2015 respectivly, and a series of clinical studies have been conducted worldwide.

The pivotal study of Rezūm System demonstrated its efficacy and safety. 197 males subjects were enrolled in pivotal study, with a prostate size > 30 cm^3 but < 80 cm^3 and IPSS > 13. All eligible subjects were randomized in a 2:1 ratio to receive either the Rezūm vapor ablation treatment , or a control sham procedure. The primary endpiont, the change in IPSS at 3 months post-procedure were 11.2, 4.3 respectively in the Treatment Arm and the Control Arm. The treatment arm's IPSS was 22 at baseline, which improved at 2 weeks after procedure, and the improvement of IPSS were more than 50% at 3, 6, 12 months post- procedure, Qmax at 3 months post-procedure was improved by 6.2ml/s, and remained consistently durable at 12 months post- procedure; There was no de novo ED, with just mild, moderate AE occurred[5]; At 2 years post procedure, convective radiofrequency thermal therapy improved urinary symptoms significantly over controls at 3 months procedure (86.9% (53/61) subjects in the

Control Arm had qualified and elected to cross over to receive the Rezūm treatment following their 3-month postprocedure visit.), and provided a sustained 51% reduction from baseline; This produced a 5- and 8-point or greater score decrease in 84% and 74% of subjects , respectively [6]; There were a more than 50% improvement in the IPSS, quality of life, Qmax, BPH impact index at 3 years post procedure, which were maintained during 3 years after procedure, without late AE, surgical retreatment rate was 4.4% at 3, 4,5 years after water vapor thermal therapy[7,8,9]. As a a minimally invasive medical divice, Rezūm System provides effective early onset, as well as enduring relief of LUTS associated with BPH, with an acceptable side effect profile, and can be performed in an outpatient treatment setting with short procedure time.

4.2. *Study Rationale*

Benign prostatic hyperplasia (BPH) is a disease of aging, whose morbidity increases with age. Progressive prostate enlargement causes bladder outflow obstruction and lower urinary tract symptoms, which have a significant impact on patients' quality of life.In view of the aggravation of the aging process in China and the high incidence rate of male patients over 50 years old , there is a considerable socioeconomic burden to patients and society as it represents the most commonly presenting urological complaint.

BPH medications could relieve LUTS symptoms, but some get unsatisfactory symptom relief, Furthermore, it can be associated with systemic side effects such as postural hypotension, is costly when used for a long time; and some subjects have difficulty complying with the medication regime, particularly among the older population.

Transurethral resection of the prostate (TURP), which is considered the gold standard intervention, have a hgih complication rate, such as TRUS, retrograde ejaculation, erectile dysfunction, urethral stricture; and its surgical retreatment rate was 1–2% per year. Furthermore, it requires the use of general or spinal anaesthesia, which may cause more risks for elderly.

The Rezūm System is a minimally invasive thermal ablation treatment. The treatment with Rezūm System is rapid under local anesthesia and sedation, with the urethra preserved, which may mitigate the symptoms of BPH. The Rezūm System have been on the market for many years with consistently durable efficacy and mild AE. This retrospective study will collect the data of treated subjects in the hospitals in BOAO medical pilot zone, to evaluate it safety and performance in Chinese patients, which will provide real world evidence for extensive use in China.

5. (Commercial) Device Description

5.1. *Commercial Device*

The Rezūm System includes the following major components:
• Rezūm Generator (reusable)/Model # G2200-0032
- ✓ Generator
- ✓ One Power Cord

- ✓ Rezūm Operators Manual

• Rezūm Delivery Device Kit (disposable)/ Model # M006D2201-0032
- ✓ One sterile Delivery Device with cable and tubing
- ✓ One sterile Syringe
- ✓ One sterile Spike Adaptor

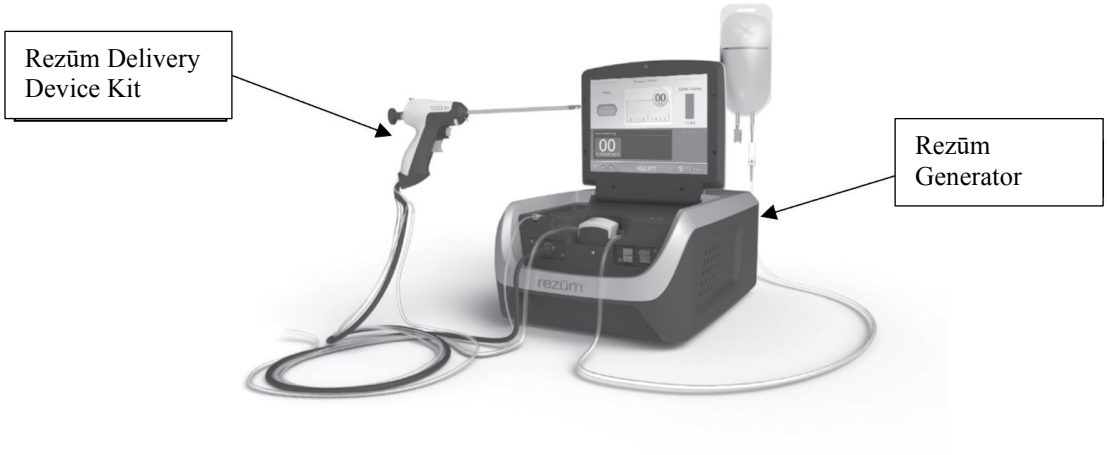

Figure 1 Rezūm System

5.2. *Rationale and principle*

The basic principle of the Rezūm System is to deliver a controlled amount of sterile water vapor directly into the hyperplastic tissue in the transition zone of the prostate using a transurethral approach .The stored thermal energy in the vapor is transferred directly onto the cell membranes as the vapor condenses and releases the heat of condensation, causing cell death. Inaddition, this thermal energy transfer collapses the vasculature within the treatment zone, resulting in a bloodless procedure. During procedure the water vapor is created by a heating element in the Rezūm Delivery Device,Saline flush during vapor delivery protects and preserves the urethra.

Please refer to IFU for more detailed information.

5.3. *Indication*

The Rezūm System is intended to relieve symptoms, obstructions, and reduce prostate tissue associated with BPH. It is indicated for men ≥50 years of age with a prostate volume ≥ 30cm^3 and ≤80cm^3. The Rezūm System is also indicated for treatment of prostate with hyperplasia of the central zone and/or a median lobe.

5.4. *Required Procedures*

A standard 4mm, 30º rigid cystoscopic lens is inserted into the Delivery Device, thereby allowing the Delivery Device to be advanced and positioned under direct visualization within the prostatic urethra.

6. Study Objectives and Endpoints

6.1. *Study objectives*

This retrospective RWS study is to evaluate the safety and efficacy of Rezūm system in BPH treatment, to generate local real world data from a Chinese BPH population for Rezūm System's approval in china.

6.2. *Study endpoints*

6.2.1. Primary endpoints

6.2.1.1. Primary Efficacy Endpoint

Primary efficacy endpoint: IPSS change at 3-6M post Rezūm procedure.

International prostate symptom score (IPSS) is a questionnaire used to indicate the severity of LUTS symptoms, There are 7 questions relating to different symptoms subjects be experiencing and one question relating to overall quality of life.

IPSS at baseline and post procedure will be collected. If several IPSS scores are collectedy, the last IPSS score during 3-6 months post procedure will be used to assess the primary efficacy endpoint.

6.2.1.2. Primary Safety Endpoint

Primary safety endpoint: Device Related Serious Complications from Rezūm procedure to 3-6M post Rezūm procedure.

Composite device related serious complications for this endpoint are defined as:

1. Device perforation of the rectum or GI tract;
2. Device related formation of fistula between the rectum and urethra;
3. De novo severe urinary retention lasting more than 21 consecutive days post treatment.

AEs will be collected and relationship to device will be assessed by investigators, it will be assessed whether meet the pre-specific device related serious complications . It's uncertain that when subject's data of the last follow up get in this retrospective study, so serious complications in up to 6 months post procedure will be used for primary safety endpoint.

6.2.2. Secondery endpoints

1. Anesthesia method

2. Rezūm operation time
3. Qmax and Post Void Residual Urine Volume (PVR）
4. Length of Catheterization
5. Quality of Life (if available)
6. Ejective function（MSHQ-EjD and IIEF (if available)）
7. Surgical retreatment post Rezūm procedure (if available)
8. Medication retreatment post Rezūm procedure (if available)
9. All SAEs

7. Study Design

This is a retrospective, single arm, RWS study, which will be performed in Boao Yiling Life Care Center in Hainan BOAO mecial pilot zone.

7.1. *Scale and Duration*

This RWS study aims to gather no more than 30 BPH subjects datas at basline, procedure and follow-up visits from the medical records, who recerived the thermal ablation treatment via Rezūm System in Boao Yiling Life Care Center in Hainan BOAO mediacl pilot zone, about 22 subjects with valid data will be analysed finally.

This RWS study is based on the medical practices without intervention. All subjects enrolled have been treated by Rezūm System, so participation duration is not applicable, only data generatated in medical practices will be gathered.

7.2. *Treatment Assignment*

Treatment Assignment is not applicable in this retrospective study.

7.3. *Justification for the Study Design*

The Rezūm System has got CE mark and FDA approval in 2013 and 2015 respectivly, and a series of clinical studies have been conducted worldwide, such as FIM, Rezūm I, Rezūm II RCT, and demonstrated its safety and efficacy from histopathology and clinical medicine. Furthermore, It have been on the market for many years with consistently durable effeacy and mild AE. This retrospective study use the data produced in hospitals in BOAO medical pilot zone, to evaluate it safety and performance in Chinese BPH patients, which will provide real world evidence for extensive use in China and approval as well.

8. Subject Selection

8.1. *Study Population and Eligibility*

Target poputions are BPHs who were treated with Rezūm system in hospitals in Hainan medical pilot zone, To be eligible for enrollment in the study, subjects must meet all of the inclusion criteria.

8.2. *Inclusion Criteria*

Subjects who meet all inclusion criteria, and don't meet exclusion criteria will be eligible for enrollment.

- The subjects will provide written informed consent form and agree to data collection.
- The subjects who were diagnosed as BPH and treated by Rezūm procedure in Hainan medical pilot zone with complete procedure recored .

8.3. *Exclusion Criteria*

This is a retrospective study without any formal exclusion criteria.

9. Study Methods

9.1. *Data Collection*

The data collection schedule is shown in Table 9.1-1.

Table 9.1-1:The data collection schedule

Procedure/Assessment	Baseline/pre-procedure	Index Procedure	Post procedure/ Prehospital Discharge	follow-up post-precedure #
Informed consent				X&
Demographics	X			
Medical history	X			
Physical examination (height, weight, etc)	X			X
Prostate volume (MRI, DUS)*	X			X
Uroflowmetry(Qmax, Urinary volume)	X			X
PVR	X			X
IPSS	X			X
QoL	X			X
IIEF	X			X
MSHQ-EjD	X			X
Procedure information		X		
Length of catheterization			X	
Surgical retreatment				X
Medication(s) used(LUTS /BPH)	X		X	X
Device Defect (if available)		X		
Adverse events assessment		X	X	X

Note: # All information of subjects available before the defined end of study will be collected in this retrospectively study, data missing will be allowed.

*Prostate volume -data form MRI and DUS are collected, MRI data will be preferred to used for statistic, DUS data will be used ONLY MRI data unavailable.

&Only written informed consent form is provided after initiation , data will be collected.

9.2. *Study Candidate Screening/enrolling*

Subjects with BPH will be screened form the medical recored database in Boao Yiling Life Care Center in BOAO medical pilot zone, and these have been treated with Rezūm system will be enrolled in this study.

9.3. *Informed consent*

Data won't be collected before the informed consent form is signed. Once subjects provide informed consent, he will be enrolled in this study, then medical data will be retrospectively collected.

9.4. *Data collection: Baseline-procedure-discharge*

The pre-procedure examination, procedure and information at discharge of the selected subjects will be collected from the electronic medical record database or paper medical records of hospitals in Hainan Boao Medical Pilot zone.

- Baseline/pre-procedure: Demographics, medical history, physical examination, prostate volume (MRI, DUS), PVR, Uroflowmetry(Qmax, Urinary volume), IPSS and quality of Life questionnaire, sexual function (IIEF and MSHQ-EjD , if available), Medication(s) used(LUTS /BPH).
- Procedure : anesthesia method, Rezūm operation time, key points of operation of Rezūm system, Device Defect (if available),adverse events, etc. Rezūm Operation time is from the time of insertion to the time the Rezūm Delivery Device removed.
- Discharge: Length of catheterization, Medication(s) used(LUTS /BPH), adverse events, etc. Length of Catheterization is form the time of insertion to time the catheter removed.

9.5. *Data collection: visits*

This study is a retrospective study with no formal visit plan. Data post-procedure will be collected form the medical recored database and health examination in Hainan medical pilot zone. All available follow up data before the end of study is suggested to be collected. The pages of follow up visits in CRF will be filled according the time.

Data below will be collected and recored in CRF, if available:

Prostate volume(MRI, DUS), PVR, Uroflowmetry(Qmax, Urinary volume), IPSS score and QoL, sexual function (IIEF and MSHQ-EjD), surguical retreatment and medication for BPH/LUTS, adverse events.

Note: the enrolled subjects must be treated with Rezūm system in hospitals in Hainan Boao Medical Pilot zone, the follow-up visits could be preformed in local hospital. the data can be collected and recorded in CRF, if available.

9.6. *Study Completion*

This study is a retrospective real world study with no formal visit plan, no visit must be performed. The end of study will be scheduled at 4 months post Rezūm procedure of last subject enrolled.

9.7. *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. Statistical Considerations

10.1. *Primary Endpoints*

Primary Efficacy Endpoint: IPSS change at 3-6M post Rezūm procedure.

Primary Safety Endpoint: Device Related Serious Complications from Rezūm procedure to 3-6M post Rezūm procedure.

Composite device related serious complications for this endpoint are defined as:

1. Device perforation of the rectum or GI tract;
2. Device related formation of fistula between the rectum and urethra;
3. De novo severe urinary retention lasting more than 21 consecutive days post treatment.

10.1.1. Hypothsis

The primary endpoint is IPSS change at 3-6M post Rezūm procedure.

In Rezūm Pivotal II study, IPSS score represents a 11.2±7.6 point reduction at 3M post Rezūm procedure in treatment arm, while 4.3±6.9 point reduction in sham control. In Pivotal trial, IPSS score in treatment group decreased 25%(5.375) compared to sham control group is recognized as meaningful.

As this is a retrospective RWS study, the inclusion/exclusion criteria is not strict, we set up performance goal for score change as 5.5, the expected score change is 10 at 3-6M post Rezūm procedure. A performance goal (PG) testing for the primary endpoint is planned. The decision rule is to calculate the Lower Confidence Interval (LCI) of score change and compare it to the PG, meet PG if LCI is greater than PG.

10.1.2. Sample size

The sample size is calculated according to below formula:

$$n = \frac{(Z_\alpha + Z_\beta)^2 \sigma^2}{\delta^2}$$

n is sample size, we designed 5.5 as performance value, 10 is expected IPSS change, α=0.05，β=0.20（power=80%）Considering the small sample size needs to be iterative distribution, 22 subjects will provide more than 85% power. As this is retrospective study, there are chances of missing data in the study. So the final sample size will be up to 30, to satisfy 22 treated subjects.

10.2. *General Statistical Methods*

10.2.1. Analysis Sets

This real world study plans to collect medial data of BPH patients who has been treated with Rezūm system in Hainan BOAO medical pilot zone.

The efficacy analysis set includes subjects with IPSS scores at baseline and at 3-6 months post-procedure.

The safety analysis set includes all subjects who has been treated with Rezūm system in hospitals in Hainan BOAO medical pilot zone.

10.2.2. Control of Systematic Error/Bias

All subjects treated with treated with Rezūm system in Hainan BOAO medical pilot zone will be enrolled to reduce select bias duing given time. The data will be collected completely and accurately, stratified analysis or Multivariate analysis may be used to find and control the bias.

10.2.3. The method of handling missing, incorrect data(including subjects withdrawal and lost to follow-up) and unreasonable data

Missing data will be excluded for primary analysis in this small sample size study. Imputation with mean or median where applicable for continuous variable, and tipping point analysis for categorical variable might be conducted for sensitivity analysis. Incorrect and unreasonable data will be clarified before database lock.

10.2.4. Data Analyses

Study endpoints will be summarized descriptively, when it comes to primary endpoint-IPSS score, last IPSS socre during 3-6 moth post procedure of subjects will be used, if they had several IPSS questionares. Continuous variables will be tabulated with mean, median, standard deviation, minimum, maximum, and 95% confidence interval of the mean. Categorical variables will be tabulated with frequencies, percentages and 95% confidence intervals.

This study may allow explorative statistics based on collected data, which may include, but is not limited to, the change tendency of IPSS score and variables, sub-group analysis based on IPSS score. All the analysis details will be added in statistical analysis plan.

11. Data Management

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

Visual and/or electronic data review will be performed to identify possible data discrepancies. Manual and/or automatic queries will be created in the 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 of the closeout activities are completed a request to IT is submitted to have the “Database Locked” or Decommissioned and all database access revoked.

11.2. *Data Retention*

The Principal Investigator or his/her 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. Documents must be retained for 10 years after the formal discontinuation of the clinical investigation of the product. These documents will be retained by BSC until the product/device is no longer in use in compliance with local regulations.

The Principal Investigator or his/her designee will take measures to prevent accidental or premature destruction of these documents. If for any reason the Principal Investigator or his/her 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 Boston Scientific in writing where paper or electronic files are maintained in case files are stored off site and are not readily available.

12. Amendment

The investigator should adhere to the approved protocol.Any modification to the protocol (management information or alterations of the study , etc.) during the study implementation shall be submitted to the EC for approval or recored by the investigator upon approved by the sponsor. Appropriate approvals (e.g., EC) of the revised protocol must be obtained prior to implementation.

13. Compliance

13.1. *Statement of Compliance*

This real world study 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 ISO14155、ICH-GCP, ethical principles that have their origins in the Declaration of Helsinki, and applicable Chinese laws and regulations. The study shall not begin until the required approval/favorable opinion from the IRB/EC and/or regulatory authority has been obtained, if appropriate. Also, the study shall not begin prior to issuance of the site Authorization to Enroll, as provided by the sponsor. Any additional requirements imposed by the IRB/EC or regulatory authority shall be followed, if appropriate.

13.2. *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, 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.
- Prior to beginning the study, sign the IB（if available）and protocol, and comply with study schedule in protocol.
- Provide his/her 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.
- 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 and regulatory authorities any SAEs and device deficiencies that could have led to a SADE and potential/USADE or UADE, if required by applicable laws or regulations or this protocol or by the IRB/EC, and supply BSC with any additional requested information related to the safety reporting of a particular event.
- 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 when performing auditing activities.
- Ensure that an adequate investigation site team and facilities exist and are maintained and documented during the clinical investigation.

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.

Delegation of Responsibility
When specific tasks are delegated by an investigator, including but not limited to conducting data collection process, the Principal Investigator is responsible for providing appropriate training, are competent to perform the tasks they have been delegated and adequate supervision of those to whom tasks are delegated. Where there is a sub investigator at a site, the sub investigator should not be delegated the primary supervisory responsibility for the site. The investigator is accountable for regulatory violations resulting from failure to adequately supervise the conduct of the clinical study.

13.3. *Institutional Review Board/ Ethics Committee*

The investigational site will obtain the written and dated approval/favorable opinion of the IRB/EC for the clinical investigation and ICF before recruiting subjects.

A copy of the written IRB/EC 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.

Any amendment to the protocol will require review and approval by the IRB/EC before the changes are implemented to the study. Any amendment to ICF will require review and approval by IRB/EC.Annual IRB/EC approval and renewals will be obtained throughout the

duration of the study as required by applicable local/country laws or regulations or IRB/EC requirements. Copies of the study reports and the IRB/EC continuance of approval must be provided to the sponsor.

13.4. *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 per guidelines issued by NMPA. Study data collected during this study may be used by BSC for the purposes of this study and publication, 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.

BSC adhere to all applicable regulations and laws. 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.

Role of Boston Scientific Representatives
BSC personnel may perform certain activities to ensure study quality. These activities may include the following.

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

Boston Scientific personnel will not do the following.

- Practice medicine
- Provide medical diagnosis or treatment to subjects
- Discuss a subject's condition or treatment with a subject
- Independently collect critical study data (defined as primary or secondary endpoint data)
- Enter data in electronic data capture systems or on paper case report forms

14. 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 source documents include but not limit to signed ICF, mdical recoredsy, image(if any), lab tests (if

any) and SAE. The Device deficiencies, relationships of AE and medical device/ procedure recored in the CRF will be considered as souce documents in this study. The sponsor will put a plan in place to document the specific monitoring requirements.

The Principal Investigator/institution guarantees direct access to original or electronical source documents by BSC personnel, their designees, and appropriate regulatory authorities. If the souce docment can't be acquired for subjects went to non-investigation hospital, the certified copies should be got and maintained. Source document related to SAE should be copied (if applicable) and sent to BSC safety.

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.

15. Potential Risks and Benefits

15.1. *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).

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

This study is retrocpective real world study, that the medical data generated in the previous clinical practice will be used, no new or additional intervention will be imposed on the subjects without additional risks, and there was no impacts on the health and right of the subjects. During the data collection in the study, no private information that can identify the subject will be collected, such as, name, ID number, hospital number, telephone number, address etc.

15.3. *Risk minimization actions*

There may be other unkonown risk. Risk related the data collection will be minimized via protecting subject privacy, abiding by the protocol and regulations of clinical study.

15.4. *Anticipated Benefits*

There is No anticipated benefits for subjects enrolled in this estrospective study.

16. Safety Reporting

16.1. *Reportable Events by investigational site to Boston Scientific*

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

- All adverse events
- All Serious Adverse Events

- All device related adverse events
- All device related Serious Adverse Events
- All procedure related adverse events
- All procedure related Serious Adverse Events
- All Device Deficiencies
- Unanticipated Adverse Device Effects/Unanticipated Serious Adverse Device Effects
- New findings/updates in relation to already reported events

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

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

Any reportable event, whether prior to, during or subsequent to the procedure, must be recorded in the CRF.

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 16.2-1 for AE definitions).

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

16.2. *Definitions and Classification*

Adverse event definitions are provided in Table 16.2-1. Administrative edits were made on the safety definitions from ISO 14155 and EU 2017/745 for clarification purposes.

Table 16.2-1: Safety Definitions

Term	Definition
Adverse Event (AE) *Ref: ISO 14155* *Ref: MEDDEV 2.7/3*	Any untoward medical occurrence, unintended disease or injury, or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons, 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*	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

Table 16.2-1: Safety Definitions

Term	Definition
Ref: MEDDEV 2.7/3	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: MEDDEV 2.7/3*	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) foetal distress, foetal 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: MEDDEV 2.7/3*	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.
Unanticipated Adverse Device Effect (UADE) *Ref: 21 CFR Part 812*	Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.
Unanticipated Serious Adverse Device Effect (USADE) *Ref: ISO 14155* *Ref: MEDDEV 2.7/3*	Serious adverse device effect which by its nature, incidence, severity, or outcome has not been identified in the current 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.

Table 16.2-1: Safety Definitions

Term	Definition
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 to entry: 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: MEDDEV 2.7/3*	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 investigational medical device 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.

16.3. *Relationship to Device(s) and/or Study Procedure*

The Investigator must assess the relationship of the reportable AE to the device, and/or study procedure. See criteria in Table 16.3-1.Table 16.3-1:

Table 16.3-1: Criteria for Assessing Relationship of Study Device or Procedure to Adverse Event

Classification	Description
Not Related *Ref: MEDDEV 2.7/3*	Relationship to the device, comparator or procedures can be excluded when: - the event is not a known side effect of the product category the device belongs to or of similar devices and procedures; - the event has no temporal relationship with the use of the study device or the procedures; - the serious event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible; - the discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible – and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious event; - the event involves a body-site or an organ not expected to be affected by the device or procedure; - the serious event can be attributed to another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors); - the event does not depend on a false result given by the study device used for diagnosis, when applicable; harms to the subject are not clearly due to use error; - In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.
Possibly Related *Ref: MEDDEV 2.7/3*	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 were relatedness cannot be assessed or no information has been obtained should also be classified as possible.
Probably Related *Ref: MEDDEV 2.7/3*	The relationship with the use of the study device, comparator, or the relationship with procedures seems relevant and/or the event cannot be reasonably explained by another cause, but additional information may be obtained.

Table 16.3-1: Criteria for Assessing Relationship of Study Device or Procedure to Adverse Event

Classification	Description
Causal Relationship *Ref: MEDDEV 2.7/3*	The serious event is associated with the study device or 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.

16.4. *Investigator Reporting Requirements*

The communication requirements for reporting to BSC are as shown in Table 16.4-1.

NOTE: Considering that this is a retrospective study base on licensed device used in BOAO pilot medical zone , the Requirements for reporting is not provided in current regulations. The enents will be reported as below, which is defined according to retrospective study and operation.

Table 16.4-1:Requirements for reporting

Event Classification	Communication Method	Communication Timeline post-market studies* (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.	• In period of data collection，within 5 business day of the event identified for applicable study*. • Terminating at the end of the study.

Event Classification	**Communication Method**	**Communication Timeline post-market studies*** (MEDDEV 2.12/1: GUIDELINES ON A MEDICAL DEVICE VIGILANCE SYSTEM)
		*Applicable study= post market interventional study non-standard of care
	Provide all relevant source documentation (de-identified/ pseudonymized) for reported event.	• Upon request of sponsor.
Serious Adverse Event,include Serious Adverse Device Effect	Complete AE eCRF page with all available new and updated information.	• In period of data collection， within 5 business day of the event identified or as per local/regional regulations. • Reporting required through the end of 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 failures, malfunctions, and product nonconformities) Note: Any Device Deficiency that might have led to a serious adverse event if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate is considered a reportable event.	Complete eCRFwith all available new and updated information.	• In period of data collection，within 5 business day of the event identified. 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.	• In period of data collection，within 10 business day of the event identified • Reporting required through the end of study • Upon request of sponsor
	Provide all relevant source documentation (de-identified/ pseudonymized) for reported event.	

16.5. *Boston Scientific Device Deficiencies*

Device deficiencies (including but not limit to malfunction, faulty production, etc) will be documented and reported to BSC. If possible, the device(s) should be returned to BSC for analysis.

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.

16.6. *Reporting to Regulatory Authorities / IRBs / ECs / Investigators*

BSC is responsible for reporting all adverse event and device deficiency information to IRB/EC, as applicable.

The Principal Investigator is responsible for informing the IRB/EC, and regulatory authorities of U(S)ADEs and SAEs as required by China regulations.

BSC will report all serious adverce events and device deficiencies which may lead to SAE to regulatory authorities in Hainan and Shanghai Within 10 business day of first becoming aware of the even duing data collection, and notify IRB/IEC in a timely manner.

17. Informed Consent

Subject participation in this clinical study is voluntary. Informed Consent is required from each subject or his/her legally authorized representative. The Investigator is responsible for ensuring that Informed Consent is obtained prior to data collection.

The obtaining and documentation of Informed Consent must be in accordance with the principles of the Declaration of Helsinki, ISO 14155, and china NMPA regulations, 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, or central IRB, if applicable.

Boston Scientific will provide a study-specific template of the ICF to investigators participating in this study. The ICF template may be modified to meet the requirements of the investigative site's IRB/EC. 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 approval prior to their use.

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

- be conducted by the Principal Investigator or designee authorized to conduct the process,
- include a description of all aspects of the clinical study that are relevant to the subject's decision to participate throughout the clinical study,
- avoid any coercion of or undue influence of subjects to participate,
- not waive or appear to waive subject's legal rights,

- use native language that is non-technical and understandable to the subject or his/her legal representative,
- provide ample time for the subject to consider participation and ask questions if necessary,
- ensure important new information is provided to new and existing subjects throughout the clinical study.

The ICF shall always be signed and personally dated by the subject or legal representative competent to sign the ICF under the applicable laws, rules, regulations and guidelines and by the investigator and/or an authorized designee responsible for conducting the informed consent process. If a legal representative signs, the subject shall be asked to provide informed consent for continued participation as soon as his/her medical condition allows. The original signed ICF will be retained by the 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 will be reported by BSC to the applicable regulatory authority according to their requirements (e.g., FDA requirement is within 5 working days of learning of such an event). Any violations of the informed consent process must be reported as deviations to the sponsor and local regulatory authorities (e.g. IRB/EC), as appropriate.

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

18. Committees

18.1. *Safety Monitoring Process*

The BSC personnel from the Medical Safety and Safety Trial Operation 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 expertise in urology and with the necessary therapeutic and subject matter expertise to evaluate and classify the events into the categories outlined above.
No committee will be included in this study ,such as clinical event committee, data monitoring committee, independent reviewer, etc.

19. Suspension or Termination

19.1 Premature Termination of the Study

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

19.1.1 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 or regulatory authorities to suspend or terminate the clinical investigation.
- An enrollment rate far below expectation that prejudices the conclusion of the study.

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

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

19.3 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 Boston Scientific. The IRB/EC and regulatory authorities, as applicable, will be notified.

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

In the event 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 Boston Scientific.

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

19.4 Criteria for Suspending/Terminating a Study Site

Boston Scientific 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.

The IRB/EC and regulatory authorities, as applicable, will be notified.

20. Study Registration and Results

20.1. *Study Registration*

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

20.2. *Clinical Investigation Report*

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

20.3. *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. Boston Scientific 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 Boston Scientific Data Sharing Policy (Please contact Boston Scientific staff for further information: Lin Hui，010-61412942).

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22. Abbreviations and Definitions

22.1. *Abbreviations*

Abbreviations are shown in Table22.1-1.

Table 22.1-1: Abbreviations

Abbreviation/Acronym	Term
AE	Adverse event
AUASI	The American Urological Association Symptom Index
BPH	Benign prostatic hyperplasia
CRF	case report form
DUS	Doppler ultrasound
eCRF	Electronical case report form
FDA	Food and drug administration
GCP	Good clinical practice
ICH	International Conference on Harmonization
IIEF	The International Index of Erectile Function
IPSS	International Prostate Symptom Score
IRB	Institutional Review Board
LCI	Lower confidence interval
LUTS	lower urinary tract symptoms
MSHQ-EjD	Male Sexual Health Questionnaire Short Form- Ejaculation dysfunction
MRI	Magnetic Resonance Imaging
PVR	Post Void Residual Urine Volume
Qmax	Peak Flow Rate
QoL	quality of life
SADE	serious adverse device effect
SAE	serious adverse event
TURP	transurethral resection of the prostate
UADE	unanticipated adverse device effect
USADE	unanticipated serious adverse device effect