Artificial Urinary Sphincter Clinical Outcomes

AUSCO

U0669

CLINICAL INVESTIGATION PLAN

National Clinical Trial (NCT) Identified Number: NCT04088331

Sponsored By

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Vendors/External Organizations	A list of vendors/external organizations involved in the trial is maintained by the sponsor.

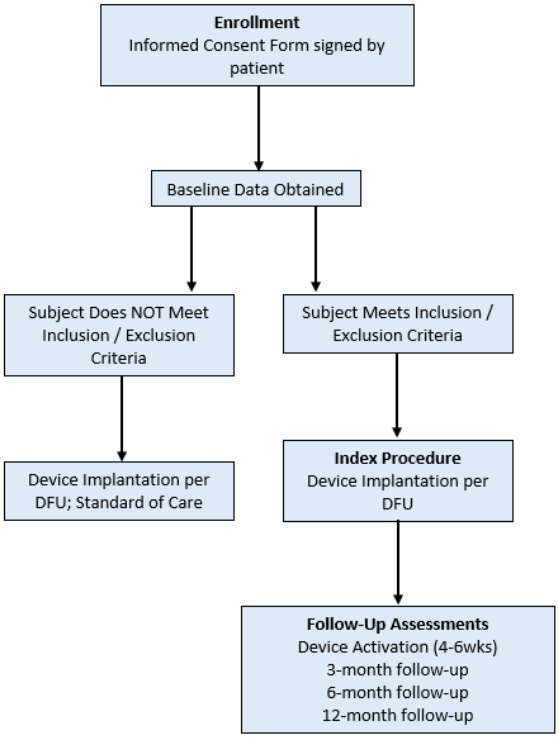
Original Release: July 12, 2019

Current Version: November 10, 2021

Revision Version	Protocol Date	Template number and version	Protocol Section Modified	Summary of Changes	Justification for Modification
Revision A (Initial)	July 12, 2019	92120219 / Ver C	N/A	N/A	Initial Release
Revision B	December 15, 2020	92120219 / Ver F	2. Protocol Synopsis 4.2 Study Rationale 5. Device Description 7. Study Design 8. Subject Selection 10. Study Methods 11.3.1 Other Endpoints 15.2 Investigator Responsibilities 18. Safety Reporting 20. Committees 22. Study Registration	Estimated number of devices used throughout the trial added. Minimum number of procedure subjects specified as 120. Canada was removed throughout the protocol. Adverse Event collection will be limited to device and procedure related events. All Follow-up visits may be completed as remote or in clinic visits. Inclusion Criteria #6 was updated to allow subjects with continuous incontinence to participate. Physical Assessment including height and weight may be self reported if the visit is conducted remotely. Extended visit windows. Removal of requirement for physicians to have previously implanted 10 AMS 800 devices. ISO14155 definitions updated to 2020 revision.	Protocol template updates for Version D, E and F. Number of sites increased due to COVID-19 enrollment challenges. Adverse Event collection reduced as appropriate for a non-mandated post-market study of this nature. Clinical Events Committee reduced to an Independent Medical Reviewer following the adverse event collection changes. Remote visits are allowed for all follow-up visits due to COVID-19 pandemic and the nature of the study does not require in person clinic visits. The requirement for a physician to have implanted 10 AMS800

Revision Version	Protocol Date	Template number and version	Protocol Section Modified	Summary of Changes	Justification for Modification
					devices prior to implanting in the study was removed as this is a post-market study.
Revision C	November 10, 2021		2. Protocol Synopsis	Exclusion criteria updated. Removal of criteria pertaining to radiation, modification of criteria regarding bleeding and modification to criteria concerning genitourinary mechanical prosthesis.	Updated criteria will more accurately reflect real world patient population for the AMS 800
			8.3. Exclusion Criteria	Updated Exclusion criteria. See comment above regarding Synopsis.	See justification above for Synopsis.
			15.2 Investigator Responsibilities	Clarifying language added to reporting of device deficiencies and potential SADE	Align with ISO 14155
			18. Safety Reporting	Revised to align with updated European Regulations	European sites planned in the study

2. Protocol Synopsis

Artificial Urinary Sphincter Clinical Outcomes **AUSCO**	
Study Objective(s)	To evaluate the AMS 800 Artificial Urinary Sphincter™ (AUS) in men with primary stress urinary incontinence as measured by pad weight tests.
Indication(s) for Use	The AMS 800 Artificial Urinary Sphincter is used to treat urinary incontinence due to reduced outlet resistance (intrinsic sphincter deficiency) following prostate surgery.
Device applied as Standard of Care and sizes	The AMS 800 Artificial Urinary Sphincter™ is available with cuff sizes of 3.5cm-11cm, and three (3) pressure regulating balloon ranges of 51-60cm, 61-70cm, and 71-80cm. The device is available both with and without InhibiZone. It is estimated that 120-140 devices will be used for this study.
Study Design	Single-arm, prospective, multi-center study with 12-month follow-up. Note: All follow-up visits may be completed as clinic or remote visits.  **Figure 7.1-1: AUSCO Study Design**

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Planned Number of Subjects	Approximately 175 subjects will be enrolled in total to treat a minimum of 120 procedure subjects.
Planned Number of Sites / Countries	Up to 30 sites will be activated in regions where the AMS 800 is commercially available, including but not limited to the United States, Europe, and Australia.
Primary Endpoint	Treatment success defined as ≥ 50% reduction in 24-hour pad weight test from baseline at 12 months post device activation.
Secondary Endpoints	Incidence of safety parameters at 3 months, 6 months, and 12 months. Safety parameters include device and/or procedure related adverse events, revision rates, and serious adverse events ≥ 50% reduction in urinary incontinence as measured by 24-hour pad weight test at device activation and 6 months post device activation compared to baseline ≥ 75% reduction in urinary incontinence as measured by 24-hour pad weight test at device activation, 6 months, and 12 months post device activation compared to baseline Reduction in # of pads per day at 3 months, 6 months and 12 months post-device activation compared to baseline
Additional Endpoints	Comparison of Pressure Regulating Balloons by subgroup analysis Change in numbers of stress urinary incontinence episodes, fluid intake, urgency urinary incontinence episodes, and frequency of urination based on 3-day electronic diary at 6 months and 12 months post device activation compared to baseline Change in quality of life at 3 months, 6 months, and 12 months post device activation compared to baseline, as measured by the following questionnaires: • IQoL • IIQ-7 • EQ5D (12 Month) • Subject Ease of Use (6 and 12 Month)

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Method of Assigning Patients to Treatment	Patients are considered enrolled once they sign the informed consent form. Subjects will then undergo baseline data collection to confirm eligibility. All eligible subjects are treated with the AMS 800.
Follow-up Schedule	Follow-up visits will occur at 3, 6, and 12 months after device activation. The study will be considered complete after all subjects have completed the 12-month follow-up visit. All follow-up visits may be conducted remotely or in clinic.
Study Duration	Enrollment is expected to be completed in approximately 24 months; therefore, the total study duration is estimated to be approximately 44 months.
Participant Duration	The study duration for each subject is expected to be approximately 12 months from time of device activation. If the subject is seen at the end of their visit window, participant duration would be 13.5 months.
Inclusion Criteria	1. Male 2. ≥ 18 years of age 3. Has undergone either a radical prostatectomy, transurethral resection of the prostate or other invasive prostate surgery 4. Demonstrates primary stress urinary incontinence 5. Positive screening 24-hour pad weight test (≥100 grams) 6. Experiences at least 3 incontinence episodes per day during baseline diary or presents with continuous incontinence 7. Negative urine culture 8. Willing and able to undergo surgical implantation of the AUS device 9. Willing and able to comply with the follow-up requirements 10. Willing and able to forego any other surgical urinary incontinence treatments while participating in the study 11. Willing and able to sign the informed consent
Exclusion Criteria	1. Previously had or currently has a device implanted (AUS/Sling, or otherwise) for treatment of SUI or urge incontinence 2. Primary urgency incontinence 3. Postvoid residual volume greater that 150 ml or a history of difficulty emptying the bladder

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	4. Recurrent vesicourethral anastomotic stricture or urethral stricture disease within the past 6 months 5. Known urogenital malignancy other than previously treated prostate cancer 6. Recurrent prostate cancer that is expected to require intervention during the study follow-up period 7. History of recurrent bladder stones within the past 12 months prior to signing the informed consent 8. Neurogenic bladder 9. Need for intermittent catheterization 10. Known history of untreated/uncontrolled bleeding diathesis or coagulopathy 11. Immunosuppressed or on medical therapy which would impact the immune system 12. Uncontrolled diabetes, defined as (HbA1c>10) 13. Has a genitourinary mechanical prosthesis that was implanted within 3 months from the date of consent 14. Had a post-implantation infection associated with the device after genitourinary mechanical prosthesis was implanted 15. Undergone bulking procedure within 6 months of the baseline assessment 16. Poor candidate for surgical procedures and/or anesthesia due to physical or mental conditions 17. Urinary incontinence due to or complicated by an irreversibly obstructed lower urinary tract 18. Irresolvable detrusor hyperreflexia or bladder instability 19. Currently enrolled or plans to enroll in another device or drug clinical trial 20. Currently using an indwelling catheter or condom catheter for treatment of incontinence and is not willing to discontinue use at least 4 weeks prior to baseline assessment 21. Known allergy or sensitivity to rifampin or to minocycline HCl or other tetracyclines *(only applicable when implanting with InhibiZone version of this device)* 22. Systemic lupus erythematosus because minocycline HCl has been reported to aggravate this condition *(only applicable when implanting with InhibiZone version of this device)*

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Statistical Methods	
Primary Statistical Hypothesis	The primary endpoint is treatment success based on the 24-hour pad-weight test on a per-subject basis. A 50% or greater reduction in pad-weight from baseline to 12 months post device activation is considered a treatment success. Hypotheses: H_0: $p \leq 0.65$ H_1: $p > 0.65$ where p = the proportion of subjects who are a treatment success.
Statistical Test Method	The hypotheses will be evaluated using a one-sided exact binomial test. No interim analyses are planned.
Sample Size Parameters	The statistical power calculation is based on an assumption that the treatment success rate is 80%. With a one-sided type I error of 0.025 and a type II error of 0.10 (90% power), a sample size of 96 subjects are needed to demonstrate the proportion of subjects who are a treatment success exceeds 65%. To account for a potential 20% attrition rate, 120 subjects with study procedure are anticipated.

3. Table of Contents

3.1. *Table of Figures*

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4. Introduction

4.1. *Background*

Urinary incontinence (UI) remains a prevalent condition of major impact on a global scale. A major type of UI is stress urinary incontinence (SUI), defined as the complaint of involuntary loss of urine on effort or physical exertion including sporting activities, or on sneezing or coughing. SUI is primarily due to weakness of the components of the urethral sphincter mechanism.

Male SUI is usually iatrogenic in origin, resulting from sphincter insufficiency after surgery or prostatic radiotherapy, referred to as incontinence after prostate treatment (IPT).[1] IPT is not rare following radical prostatectomy, mainly due to damage sustained to the distal urethral sphincter, which results in development of SUI. Post-prostatectomy incontinence (PPI) occurs at rates ranging from 3.0% to 87%, depending on the definition of incontinence applied.[2,3] Moderate to severe SUI constitutes a significant burden to quality of life and carries substantial psychological impact on individuals and their families.[2]

Several treatments are available for male SUI. SUI interventions include observation, behavioral modification (e.g., fluid restriction, limiting caffeine and alcohol, smoking cessation, timed voiding or double voiding, avoiding bladder irritants), pelvic floor training with or without biofeedback, urethral bulking agents, male urethral slings (MUS), adjustable continence balloons, and artificial urinary sphincter (AUS).[4] Of these options, AUS, which includes the AMS 800, remains the gold standard for the treatment of severe IPT due to SUI because of its high success rates, with approximately 80% of patients achieving continence.[4,5,2,6]

Numerous clinical trials have been conducted with the AMS 800 device. Four studies conducted by American Medical Systems (AMS) demonstrated the safety and efficacy of the AMS 800. These studies included 569 patients and include safety and performance data up to 10 years post-implant. Included within the analysis were continence rates, patient satisfaction data, revision rates, and adverse events.

Results from these prospective clinical studies were combined with a Bayesian analysis of data collected from Patient Information Forms (PIFs) to further support the post market application for AMS 800 and included 12,713 patients. This analysis defined the 5-year revision free rate for subjects implanted with the AMS 800 device as equivalent to the 75% predicted by the Bayesian analysis.

In addition, a post market PIF study was completed and reported to the FDA in January 2013 to evaluate the impact of the InhibiZone antibiotic surface treatment on the AMS 800 device. This post market study included 17,063 patients who were followed for up to 5.8 years. This analysis was designed to compare infection rates, mechanical malfunction, and surgical revision rates for InhibiZone treated versus non InhibiZone treated AMS 800s. This study included all patients implanted with the AMS 800 or the AMS 800 with InhibiZone for whom a Patient Information Form (PIF) was collected by AMS from October 2006 to July

2012. The results demonstrated no statistically significant difference in the infection rates between IZ and Non-IZ treated AMS 800 patients.

Overall, the AMS 800 has been studied in over 30,000 patients to support its performance and safety for up to 10 years post-implant. Based on current treatment recommendations, the artificial urinary sphincter, which includes the AMS 800, is the established standard for the treatment of persistent moderate to severe male stress urinary incontinence (SUI).[7,8]

4.2. *Study Rationale*

The AMS 800 has been on the market for several decades. Though the device does predate the Medical Device Amendment to the Food Drug and Cosmetics Act of 1976, the AUS received FDA clearance to market through the 510k process on November 30, 1982 and approval via the PMA process on June 14, 2001. As time has progressed, incremental technological advancements have been implemented to the device, along with the creation of additional tools to assist with the implantation procedure. The study results will provide contemporary data on both the AMS 800 and the AMS tools.

5. Device Description (part of Standard of Care)

5.1. *Commercial Device*

The AMS 800 Artificial Urinary Sphincter (AUS) is an implantable, fluid filled, solid silicone elastomer device used to treat stress urinary incontinence due to reduced urethral/bladder outlet resistance (intrinsic sphincter deficiency). It is designed to restore the natural process of urinary control. The device simulates normal sphincter function by opening and closing the urethra under the control of the patient.

The AUS consists of three interconnected components: a cuff, a pump, and a pressure-regulating balloon (PRB). The three components are connected with kink-resistant tubing. The AMS 800 can be implanted at either the bulbous urethra or the bladder neck. When the cuff is inflated, the urethra is closed, and urine stays in the bladder. When the patient wishes to void, he cycles the device by squeezing and releasing the pump several times, moving the fluid from the cuff to the PRB. The cuff deflates, and urine passes through the open urethra. Pressure from the PRB pushes fluid back into the cuff, occluding the urethra and restoring continence. Figure 5.1-1 depicts the AMS 800 device.

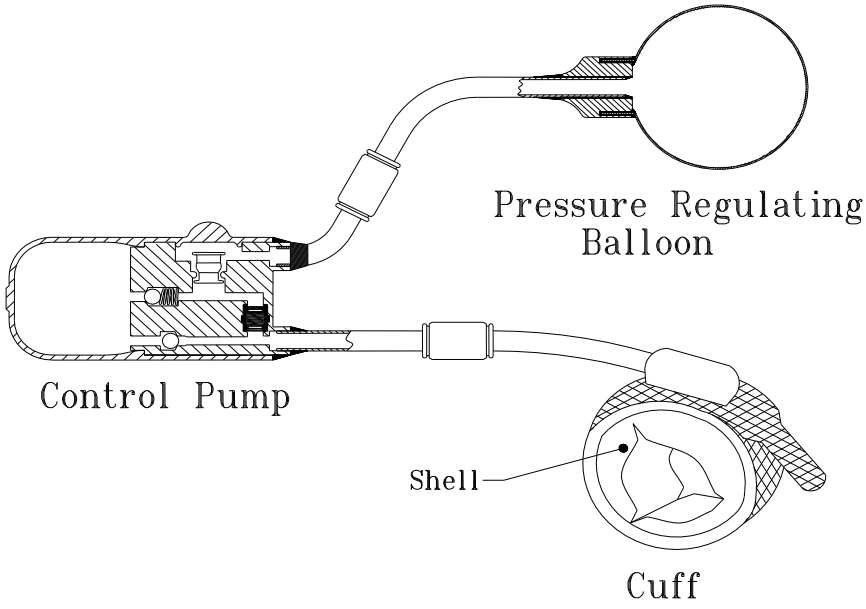

Figure 5.1-1: AMS 800 Artificial Urinary Sphincter

The major components of the device include:

- An occlusive cuff, which is placed around the urethra and applies compression;
- A pressure regulating balloon, which stores filling solution and maintains the system at constant pressure;
- A control pump with a deactivation feature, which is used to fill and empty the cuff;
- Accessory tools, which are used to aid in the implantation of the device;
- Accessory Kit, which contains accessory materials necessary for one implant procedure;
- Insertion Package, which contains two curved tubing passers used to route the tubing of the components through the appropriate tissue planes;
- Deactivation Package, which contains three stainless steel plugs and one suture-tie connector.

Table 5.1-1 provides the product line available for the AMS 800 as of June 19, 2019.

Table 5.1-1: AMS 800 Product line with and without InhibiZone Treatment

Part Number	Description
72400023	BALLOON FGS, 51-60 CM
72400024	BALLOON FGS, 61-70 CM
72400025	BALLOON FGS, 71-80 CM
72400160	BELT CUFF FGS, 4.0 CM
72400161	BELT CUFF FGS, 4.5 CM
72400162	BELT CUFF FGS, 5.0 CM
72400163	BELT CUFF FGS, 5.5 CM
72400164	BELT CUFF FGS, 6.0 CM

72400165	BELT CUFF FGS, 6.5 CM
72400166	BELT CUFF FGS, 7.0 CM
72400167	BELT CUFF FGS, 7.5 CM
72400168	BELT CUFF FGS, 8.0 CM
72400170	BELT CUFF FGS, 9.0 CM
72400172	BELT CUFF FGS, 10.0 CM
72400174	BELT CUFF FGS, 11.0 CM
72404130	BELT CUFF FGS, 4.0 CM, IZ
72404131	BELT CUFF FGS, 4.5 CM, IZ
72404132	BELT CUFF FGS, 5.0 CM, IZ
72404133	BELT CUFF FGS, 5.5 CM, IZ
72404134	BELT CUFF FGS, 6.0 CM, IZ
72404135	BELT CUFF FGS, 6.5 CM, IZ
72404136	BELT CUFF FGS, 7.0 CM, IZ
72404137	BELT CUFF FGS, 7.5 CM, IZ
72404138	BELT CUFF FGS, 8.0 CM, IZ
72404140	BELT CUFF FGS, 9.0 CM, IZ
72404142	BELT CUFF FGS, 10.0 CM, IZ
72404144	BELT CUFF FGS, 11.0 CM, IZ
720133-01	CUFF FGS, 3.5 CM, AUS
720157-01	CUFF FGS, 3.5 CM, INHIBIZONE
72400098	CONTROL PUMP FGS
72404127	CONTROL PUMP FGS, IZ
72100005	INSERTION PACKAGE FG
72400271	CONNECTOR ASSEMBLY TOOL PKG
72400095	DEACTIVATION PKG FGS
72401685	AMS 800 ACCESSORY KIT, OUS

The AMS 800 cuff and pump components are available with and without the InhibiZone treatment, an antibiotic coating of rifampin (also known as rifampicin) and minocycline HCl. The InhibiZone version of AMS 800 is identical to the non-InhibiZone AMS 800 in all technical ways except for the InhibiZone surface treatment. The InhibiZone antibiotic treatment process is intended to elute antibiotics from AMS 800 AUS component surfaces when they are exposed to a warm, moist environment.

A copy of the Instructions for Use (IFU) will be provided in local language(s) as required per national regulations.

Boston Scientific will not conduct investigational study device accountability as required per ISO 14155 as all study devices are commercially available products. The study devices shall be maintained per each institution’s standard practice and are being used within their approved indication.

5.2 Accessory Medical Equipment

Utilization, adverse event, and performance data may be collected on any AMS-/BSC-manufactured tool or accessory used during artificial urinary sphincter surgical procedures. Tools will be assessed once by means of a physician survey (or similar) at the end of enrollment. Examples of tools or accessories may include:

- Connector Assembly Tool (Quick Connect)
- Tubing Passer

6. Study Objectives and Endpoints

The primary objective of the study is to demonstrate that more than 65% of the subjects achieve a clinically meaningful level of dryness, i.e. treatment success. Treatment success is defined as a 50% reduction or greater in baseline urinary incontinence as measured by 24-hour pad weight test at 12 months.[9]

Table 6.1-1 lists the primary endpoint and all secondary and additional endpoints. The objectives and justifications for each endpoint are also provided.

Table 6.1-1: Overview of objectives and endpoints

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
To evaluate the AMS 800 AUS in men with SUI	Treatment success: achieving 50% reduction or greater in baseline urinary incontinence as measured by 24-hour pad weight test at 12 months post device activation	FDA guidance documentation for 50% reduction[9]; 65% based on expected 80% treatment success rate with a 15% margin
Secondary		
To further confirm the safety of the AMS 800 AUS	Incidence of safety parameters at 3 months, 6 months, and 12 months. Safety parameters include device and/or procedure related adverse events, revision rates, and serious adverse events	Common research endpoint
To evaluate the AMS 800 AUS	≥ 50% reduction in urinary incontinence as measured by 24-hour pad weight test at device activation and 6 months post device activation compared to baseline	Assess level of improvement in continence at time points other than primary endpoint
To evaluate the AMS 800 AUS	≥ 75% reduction in urinary incontinence as measured by 24-	Determine level of improvement in

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
	hour pad weight test at device activation, 6 months, and 12 months post device activation compared to baseline	continence with a more stringent measurement than primary endpoint
To evaluate the AMS 800 AUS	Reduction in # of pads per day at 3 months, 6 months and 12 months post-device activation compared to baseline	Objective measurement of number of incontinence episodes per day. Common endpoint to assess urinary incontinence[9,10]
Additional		
To compare the functionality of the offered pressure regulating balloons	Comparison of Pressure Regulating Balloons by subgroup analysis	Compare different pressure regulated balloons
To evaluate the incontinence episodes and changes in voiding function following AMS 800 implantation	Change in numbers of stress urinary incontinence episodes, fluid intake, urgency urinary incontinence episodes, and frequency of urination based on 3-day electronic diary at 6 months and 12 months post device activation compared to baseline	Gather patient reported outcomes on device[9, 10]
To evaluate the quality of life following AMS 800 implantation	Change in quality of life at 3 months, 6 months, and 12 months compared to baseline, as measured by the following questionnaires – IQoL, IIQ-7, EQ5D	Gain information on patient satisfaction and improvement in quality of life using validated questionnaires[10]
To evaluate the quality of life following AMS 800 implantation	Subject Ease of Use questionnaire	Gain information specific to the patient's use of the device

7. Study Design

The study is a single arm, prospective, multi-center study with 12-month follow-up following device activation.

The primary endpoint will be evaluated once all Intent-To-Treat (ITT) subjects have completed the 12-month study visit. All subjects will be followed to month 12, until study completion, or until discontinuation prior to month 12. All study procedures will be standardized for uniformity.

Physician specialty and site procedure location (such as private-practice, hospital, academic medical center, etc.) will be recorded in the site selection questionnaire.

7.1. *Scale and Duration*

The study will be conducted at up to 30sites. Study sites will be considered in regions where the AMS 800 device is commercially available, including but not limited to the United States, Europe, and Australia. Sites will be encouraged to enroll a minimum of 5 subjects and up to a maximum of 25 subjects. The enrollment period is expected to be approximately 24 months after the final study center has been activated to enroll subjects.

It is anticipated that approximately 175 subjects will be enrolled in total to treat approximately 120 procedure subjects. The number of enrolled subjects allows for subjects to screen fail after signing the informed consent based on collected baseline data.

Figure 7.1-1 below depicts a high-level flow diagram, which visualizes the study design, enrollment process, and follow-up schedule. Note: All follow-up visits may be completed either remote or in clinic.

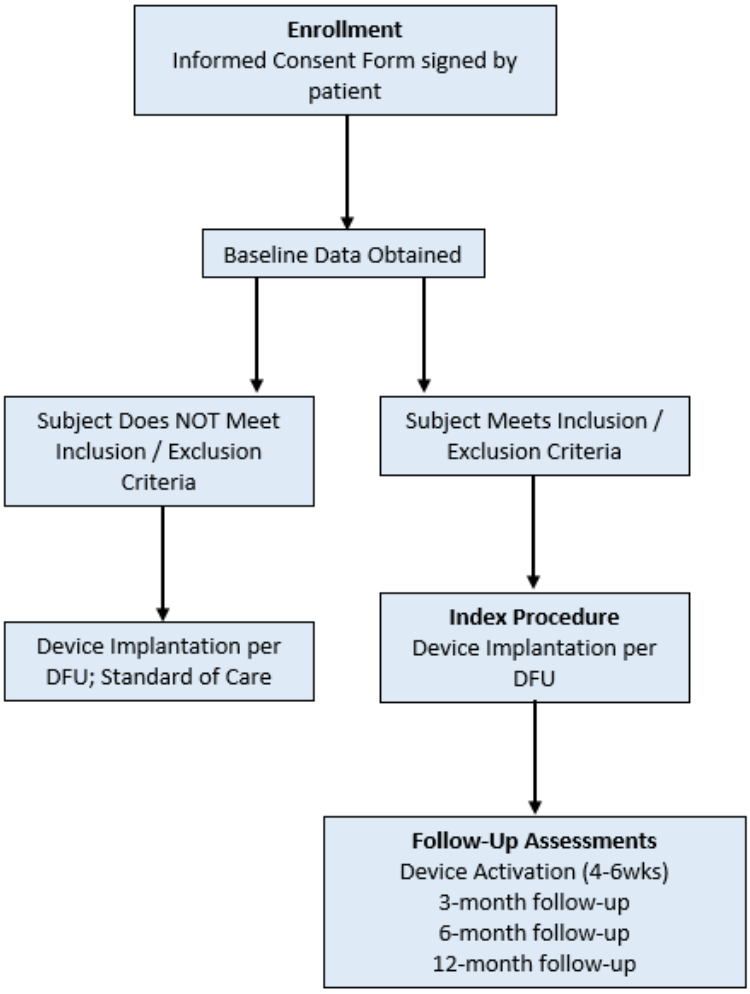

Figure 7.1-1: AUSCO Study Design

7.2. *Treatment Assignment*

This study is a single-arm trial for a post market device. Subjects will serve as their own controls; follow-up assessments will be compared to values obtained at baseline. Subjects will be enrolled into the study after providing informed consent.

Treatment will occur after all baseline procedures have been completed and the subject has been deemed eligible for the study. Baseline procedures may be combined with the screening visit and may occur within 90 days prior to the study procedure. Due to the allowable window of up to 90 days between baseline and study procedure, the study staff will confirm that subjects are still electing to undergo the study surgery prior to implantation and note the subject's approval in their medical records and on the procedure CRF.

7.3. *Justification for the Study Design*

Artificial urinary sphincters are considered the gold standard for the treatment of moderate to severe post-prostatectomy SUI.[4,5,2,6] With a single arm study design, all subjects receive the standard of care procedure.

8. Subject Selection

8.1. *Study Population and Eligibility*

This study will enroll adult males with moderate to severe primary stress urinary incontinence (as assessed by a baseline pad weight test) due to ISD who meet the indications for surgical correction of urinary incontinence.

To assess for eligibility for this study, inclusion and exclusion criteria are included in Sections 8.2 and 8.3 below.

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.

The inclusion criteria below are based on clinical standards for AUS surgery and the Instructions for Use.

Table 8.2-1: Inclusion Criteria

Inclusion Criteria	1. Male 2. ≥ 18 years of age 3. Has undergone either a radical prostatectomy, transurethral resection of the prostate or other invasive prostate surgery 4. Demonstrates primary stress urinary incontinence 5. Positive screening 24-hour pad weight test (≥100 grams) 6. Experiences at least 3 incontinence episodes per day during baseline diary or presents with continuous incontinence 7. Negative urine culture 8. Willing and able to undergo surgical implantation of the AUS device 9. Willing and able to comply with the follow-up requirements 10. Willing and able to forego any other surgical urinary incontinence treatments while participating in the study 11. Willing and able to sign the informed consent

8.3. *Exclusion Criteria*

Subjects who meet any one of the following criteria (**Error! Reference source not found.**) cannot be included in this study and will be excluded from this clinical study.

Table 8.3-1: Exclusion Criteria

Exclusion Criteria	1. Previously had or currently has a device implanted (AUS/Sling, or otherwise) for treatment of SUI or urge incontinence 2. Primary urgency incontinence 3. Postvoid residual volume greater that 150 ml or a history of difficulty emptying the bladder 4. Recurrent vesicourethral anastomotic stricture or urethral stricture disease within the past 6 months 5. Known urogenital malignancy other than previously treated prostate cancer 6. Recurrent prostate cancer that is expected to require intervention during the study follow-up period 7. History of recurrent bladder stones within the past 12 months prior to signing the informed consent 8. Neurogenic bladder 9. Need for intermittent catheterization 10. Known history of untreated/uncontrolled bleeding diathesis or coagulopathy 11. Immunosuppressed or on medical therapy which would impact the immune system 12. Uncontrolled diabetes, defined as (HbA1c>10) 13. Has a genitourinary mechanical prosthesis that was implanted within 3 months from the date of consent 14. Had a post-implantation infection associated with the device after genitourinary mechanical prosthesis was implanted 15. Undergone bulking procedure within 6 months of the baseline assessment 16. Poor candidate for surgical procedures and/or anesthesia due to physical or mental conditions 17. Urinary incontinence due to or complicated by an irreversibly obstructed lower urinary tract 18. Irresolvable detrusor hyperreflexia or bladder instability 19. Currently enrolled or plans to enroll in another device or drug clinical trial 20. Currently using an indwelling catheter or condom catheter for treatment of incontinence and is not willing to discontinue use at least 4 weeks prior to baseline assessment 21. Known allergy or sensitivity to rifampin or to minocycline HCl or other tetracyclines *(only applicable when implanting with InhibiZone version of this device)* 22. Systemic lupus erythematosus because minocycline HCl has been reported to aggravate this condition *(only applicable when implanting with InhibiZone version of this device)*

9. Subject Accountability

9.1. *Point of Enrollment*

Subjects will be considered enrolled in the study once they sign the informed consent. All enrolled subjects will have been consented prior to the procedure. All enrolled subjects with a surgery initiated (i.e. first incision) will be considered part of the Intent-to-Treat (ITT) population.

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 his/her 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 withdraws his/her consent. Data collected up to the point of subject withdrawal may be used for study analysis, unless local regulations specify differently.

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 participant fails to contact the clinic for a required study visit, the site will attempt to contact the participant and reschedule the missed visit prior to the next visit window, and are encouraged to remind the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.

Before 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 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 within the 12-month follow-up schedule, or the subject has missed the final 12-month follow-up visit, 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*

Subjects are enrolled once they complete the informed consent process. However, some subjects may not meet all inclusion/exclusion criteria and subsequently are not counted toward the enrollment ceiling. The following definitions are intended to classify subjects based on their study eligibility:

- Consent Ineligible: A subject who has signed the ICF but is found to not meet eligibility criteria. The subjects will be exited and will not undergo any study related procedures once their ineligibility has been determined. These subjects do not count toward enrollment.
- Exited Prior to Procedure: A subject who signs the informed consent, meets eligibility criteria, but then does not have the study procedure initiated (first incision). The original ICF and screening documentation for these patients should be maintained in the site's files. There are no follow-up requirements and any data collected prior to procedure is not included in statistical analyses.
- Intent to Treat: A subject who signs the informed consent, and for whom the index procedure is initiated (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 and count toward enrollment.

9.5. *End-of-Study Definition*

The clinical trial is considered completed when participants are no longer being examined or the last participant's last study visit has occurred.

A participant is considered to have completed the study if he has completed the Month 12 visit as shown in the Data Collection Schedule (see Section 10 for details).

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. All study data will be recorded on source documentation and captured within Case Report Forms (CRFs) 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

Procedure/Assessment	Screening / Enrollment Visit[2]	Pre-Operative / Baseline Visit (≤90 calendar days before index procedure)	Index Procedure (≤90 calendar days from screening visit)	Device Activation (30-45 calendar days post index procedure)	Follow-up Visits[4]		
					3 Month Visit[5] (±6 Weeks)	6 Month Visit[5] (± 3 Months)	12 Month Visit[5] (± 3 Months)
Informed consent process, including informed consent signature and date	X						
Inclusion/Exclusion Criteria Review	X	X					
Demographics		X					
Physical assessment, including weight and height		X				X[6]	X[6]
Medical history[1]	X	X					
3-day eDiary		X				X	X
24-hour Pad Weight Test		X		X		X	X
# Pads per Day		X			X	X	X
IQoL (Urinary Incontinence Quality of Life)		X			X	X	X
IIQ-7 (Incontinence Impact Questionnaire)		X			X	X	X
EQ-5D (Health Status)		X					X
Patient Ease of Use Questionnaire						X	X
Index Procedure			X				
Assessment of Adverse Events and Device Deficiencies[3]			X	X	X	X	X
End of Study							X

1Medical History at baseline includes documented absence of urine culture.
2The Screening/Enrollment Visit and Pre-Operative/Baseline Visit may be combined and occur up to 90 calendar days prior to the study procedure with confirmed absence of infection.
3Reportable events include (procedure related) AEs, SAEs, SADEs, ADEs and device deficiencies. Adverse events that are not related to the device and not related to the procedure will not be collected; however, these assessments should be noted in the subject's medical records.
4Every effort should be made to do the follow-up visit within the window; however, if this is not possible, the site should attempt to complete the visit as soon as possible, but before the next visit window opens. Follow-up visits will be considered missed once the visit window for the next follow-up visit opens. For the Month 12 visit, the visit is not considered missed until the last day of the visit window. All follow-up visit windows start from the day of device activation.
5Visits may be conducted in clinic or remote.
6Optional assessment. Height and weight may be patient reported.

10.2. *Study Candidate Screening*

Subjects will be screened against the inclusion/exclusion criteria and if confirmed to meet all the requirements attainable per standard of care, will be eligible to be consented for enrollment into the study. Any non-standard of care assessments that must be conducted in order to complete the inclusion/exclusion criteria review will be completed after the subject has completed the informed consent process.

Subjects who do not meet the inclusion/exclusion criteria and were not enrolled into the study are considered screen failures. Information on screen failures will be captured in the source documentation and screening logs and should include reasons for screen failure. These screen failures will not count toward the enrollment ceiling.

If the subject has completed the informed consent process and met all inclusion/exclusion criteria, the subject will progress to the index procedure and follow-up phases of the study.

10.2.1. Strategies for Recruitment and Retention

Subjects will be recruited from clinician practice.

Subjects will be compensated for visit related expenses. The compensation will be modest in nature and approved by the reviewing IRB/EC.

10.3. *Informed Consent*

Prior to any study-related assessments, each subject must complete the informed consent process and sign an IRB/EC-approved informed consent document to participate in the study as described in the Declaration of Helsinki and ISO 14155:2020 (Clinical Investigation of Medical Devices for Human Subjects- Good Clinical Practice) and will be in accordance with all applicable laws and regulations. The informed consent form will describe the planned and permitted uses, transfers and disclosures of the subject's personal health information.

The subject or legally authorized representative (if approved by IRB/EC) will be given ample opportunity to inquire about details of the study to decide whether to participate in the study. Copies of the informed consent form will be provided to the subject and original documents filed at each study center as per regulatory requirements.

Once the subject voluntarily agrees to participate in the study, then the Study Visit Schedule will be followed per below and as outlined in Table 10.1-1.

10.4. *Screening/Enrollment Visit*

The Screening/Enrollment may occur prior to the Pre-Operative/Baseline Visit. At this visit, the assessments below must be completed:

- Informed Consent Process, including informed consent signature
- Review of Inclusion/Exclusion Criteria

- Medical History

10.5. *Pre-Operative/Baseline Visit [≤90 calendar days before Index Procedure]*

The Pre-operative/Baseline Visit will occur prior to the subject having surgery. The assessments below must be completed prior to index procedure. This visit may be combined with the Screening/Enrollment Visit and may occur up to 90 calendar days prior to surgery.

- Demographics and physical examination
- Medical History
- 3-day eDiary
- 24-hour pad weight test
- Number of pads per day
- IQoL
- IIQ-7
- EQ-5D

10.6. *Index Procedure [≤90 calendar days from Baseline]*

All procedures are to be performed with the AMS 800 Artificial Urinary Sphincter. Concomitant procedures are not allowed. Physicians should follow the IFU during the procedure. The following data must be collected during the index procedure:

- Study device component information
- Estimated blood loss
- Anesthesia type
- Duration of procedure, defined as time of first incision to time of closure
- Assessment of adverse events and device deficiencies

Once enrollment is complete, each study site investigator will be sent one AMS tools questionnaire to complete based on the AMS tools used during the index procedures.

10.7. *Device Activation [Approximately 30-45 days post index procedure] and Follow-up Procedures*

Subjects will be scheduled for follow-up visits as outlined in Table 10.1-1 (Data Collection Study Schedule).

Every effort should be made to complete the follow-up visit within the window; however, if this is not possible, the site should attempt to complete the visit as soon as possible but before the next visit window opens. Follow-up visits will be considered missed once the visit window for the next follow-up visit opens. For the Month 12 visit, the visit is not considered missed until the last day of the visit window.

Subjects will be scheduled for device activation approximately 4-6 weeks following the index procedure per standard of care. The following assessments will be attained 24 to 48 hours after the device activation:

- 24-hour pad weight test
- Adverse event and device deficiency collection

10.8. *Month 3 Follow-up Visit [± 6 weeks post device activation]*

The 3-month follow-up visit occurs 90 calendar days after the day of device activation, ± 6 weeks.

Subjects can be contacted via a remote visit for their 3-month follow-up visit. A clinic visit is also allowed, though not required. Remote contacts must be documented in the subject's medical records.

Questionnaires cannot be completed over the phone. The site must mail the questionnaires to the subjects and the subjects should return the questionnaires to the site as soon as possible.

The following data will be collected at the 3-month visit:

- Number of pads per day
- IQoL
- IIQ-7
- Assessment of adverse events and device deficiencies

10.9. *Months 6 [± 3 Months] and 12 Visit [± 3 Months]*

The 6-month follow-up visit occurs 180 calendar days after the day of device activation, ± 3 months. The 12-month follow-up visit occurs 365 calendar days after the day of device activation, ± 3 months. These visits may occur either remotely or in clinic.

Questionnaires cannot be completed over the phone. The site must mail the questionnaires to the subjects and the subjects should return the questionnaires to the site as soon as possible. Pads can be mailed to subjects and returned per the pad weight protocol or dropped off by the subject.

The following data will be collected at the 6-month and 12-month visits:

- Physical examination including height and weight (Note: If a remote visit is completed, the subject may self report his height and weight.)
- 3-day eDiary
- 24-hour pad weight test
- Number of pads per day
- IQoL
- IIQ-7

- EQ-5D (Month 12 only)
- Patient Ease of Use
- Assessment of adverse events and device deficiencies
- Study completion (12-month follow-up only)

10.10. *Study Completion*

All subjects completing the 12-month follow-up visit will be considered to have completed the study.

Upon completion of the study, all adverse events indicated as "ongoing" should be changed to one of the following outcomes:

- Not Recovered/Not Resolved
- Resolved
- Resolved with sequelae
- Unknown

The outcome of "unknown" should only be used for subjects who are lost to follow-up. Whenever possible, sites should enter a reason for each ongoing/unresolved adverse event at time of study exit.

10.11. *Revision Surgery*

It is recognized that during the course of the study, there is a possibility subjects may require a medical revision of the implant for events including but not limited to infection, erosion, and mechanical malfunction.

A medical revision is defined as a secondary surgery to modify or replace the initially implanted device. A replacement is a subset of medical revision, defined as removal of one or more components of the AMS 800 and/or implantation of a new component. Components include the cuff, pump, and PRB.

Any subject who receives a medical revision should return to the clinic for the next regular study visit as per his original schedule.

10.12. *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.

11. Statistical Considerations

11.1. *Endpoints*

11.1.1. Primary Endpoint

The primary endpoint is defined as treatment success based on the 24-hour pad-weight test. A 50% or greater reduction in pad-weight from baseline to 12 months post-device activation is considered a treatment success.

11.1.1.1. Hypotheses

The study will evaluate whether the proportion of subjects experiencing a treatment success exceeds 65% at 12 months. The null and alternative hypotheses for this evaluation are

H_0: $p \leq 65\%$

H_1: $p > 65\%$

where p is the proportion of subjects who are a treatment success at 12 months.

11.1.1.2. Sample Size

The sample size calculation is based on an assumption that the treatment success rate is 80%[4]. With a one-sided type I error of 0.025 and a type II error of 0.10 (90% power), a sample size of 96 subjects are needed to demonstrate the proportion of subjects who are a treatment success exceeds 65%. Assuming a 20% attrition rate, at least 120 subjects with AMS 800 AUS procedure are required.

11.1.1.3. Statistical Methods

The hypotheses will be evaluated using a one-sided exact binomial test. In addition, a two-sided 95% exact (Clopper-Pearson) confidence interval will be presented. Sensitivity analysis to missing data will be performed using tipping-point analysis. If a medical revision is performed due to efficacy reasons at or prior to the 12 month visit, then the subject is considered as experiencing a treatment failure.

11.1.2. Secondary Endpoints

The secondary endpoints are explanatory in nature; descriptive statistics including 95% confidence intervals will be used to summarize all these endpoints unless specified otherwise.

11.1.2.1. Secondary Endpoint 1 –Serious Adverse Events

The endpoint is a serious adverse event.

11.1.2.1.1 Statistical Methods

Serious adverse events will be summarized using descriptive statistics (event counts, proportion of subjects with a serious adverse event), and by relatedness to procedure and/or

device. The serious adverse event rates will be summarized by the Kaplan-Meier estimate at 3 months (90 days), 6 months (180 days) and 12 months (365 days) post device activation.

11.1.2.2. Secondary Endpoint 2 - Revision

The endpoint is a medical revision of the implant for events including but not limited to infection, erosion, and mechanical malfunction.

11.1.2.2.1 Statistical Methods

The proportion of subjects with a revision will be summarized by the Kaplan-Meier estimate at 3 months (90 days), 6 months (180 days) and 12 months (365 days) post device activation. The revision rate will be summarized by a revision reason, e.g. infection, erosion, and mechanical malfunction if applicable.

11.1.2.3. Secondary Endpoint 3 – 50% Reduction in pad weight

The endpoint is the proportion of subjects with at least 50% reduction from baseline in urinary incontinence as measured by 24-hour pad weight test at device activation, and 6 months post device activation.

11.1.2.3.1 Statistical Methods

Descriptive statistics including 95% two-sided confidence intervals will be used to summarize the percentage of subjects with at least 50% reduction from baseline in 24-hour pad weight at device activation, and 6 months post device activation.

11.1.2.4. Secondary Endpoint 4 – 75% Reduction in pad weight

The endpoint is the proportion of subjects with at least 75% reduction from baseline in urinary incontinence as measured by 24-hour pad weight test at device activation, 6 months and 12 months post device activation.

11.1.2.4.1 Statistical Methods

Descriptive statistics including 95% two-sided confidence intervals will be used to summarize the percentage of subjects with at least 75% reduction from baseline in 24-hour pad weight at device activation, 6 months and 12 months post device activation.

11.1.2.5. Secondary Endpoint 5 – number of pads per day

The endpoint is change in number of pads per day at 3 months, 6 months and 12 months post device activation compared to baseline.

11.1.2.5.1 Statistical Methods

Descriptive statistics (N, mean, standard deviation, minimum, Q1, median, Q3 and maximum) will be used to summarize the number of pads per day at Baseline, 3 months, 6 months and 12 months post device activation along with change and percent change from baseline when applicable.

11.2. *General Statistical Methods*

The Intent-to-Treat (ITT) subject population includes all subjects who provide written informed consent to be enrolled into the study, and have a surgery initiated (defined as the first incision).

The As Treated (AT) Population includes all subjects for whom implantation of the device is successful.

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

The endpoint analyses will be performed for the ITT population. The AT and PP populations will be evaluated as sensitivity analyses for the primary endpoint, and the safety outcomes will also be assessed using AT population.

11.2.1. Control of Systematic Error/Bias

All subjects will be treated according to the directions in the Operating Manual and Instructions for Use.

The primary endpoint analysis based on the exact binomial test is specified to be conservative in order to avoid bias toward demonstrating the primary hypothesis (i.e., achieving the performance goal) of the study. Furthermore, the potential of bias from missing data for the primary endpoint will be assessed through tipping point analysis.

11.2.2. Number of Subjects per Investigative Site

The study will be conducted at up to 30 sites. Sites will be encouraged to enroll a minimum of 5 subjects; a maximum of 25 subjects 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 only the available cases 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. Other Endpoints/Measurements

11.3.1.1. Additional Endpoint 1 – stress urinary incontinence episodes per day

The endpoint is change in number of stress urinary incontinence episodes per day at 6 months and 12 months post device activation compared to baseline. The stress urinary incontinence episodes are collected in the three day electronic diary.

11.3.1.1.1 Statistical Methods

For those patients without the continuous leakage at baseline, descriptive statistics (N, mean, standard deviation, minimum, Q1, median, Q3 and maximum) will be used to summarize the stress urinary incontinence episodes per day at baseline, 6 months and 12 months post device activation along with change and percent change from baseline when applicable.

For those patients with the continuous leakage at baseline, descriptive statistics (N, mean, standard deviation, minimum, Q1, median, Q3 and maximum) will be used to summarize the stress urinary incontinence episodes per day at 6 months and 12 months post device activation. If a subject experiences continuous leakage at a follow up visit, the number of stress urinary incontinence episodes will not be imputed.

Number and percentage of patients with continuous leakage will be reported separately at baseline, 6 months and 12 months post device activation.

Similar analyses will be performed for the other parameters collected in the three day electronic diary (urgency urinary incontinence episodes, fluid intake, and frequency of urination) when applicable.

11.3.1.2. Additional Endpoint 2 - IQoL

To evaluate the change in quality of life as measured by Incontinence Quality of Life (IQoL) at 3 months, 6 months and 12 months post device activation compared to baseline.

The endpoints are the IQoL total score and each of the three subscales of the IQoL, a 22 items tool quantifying the quality of life. The three subscales are the Avoidance & Limiting Behaviors (ALB), Psychosocial Impact (PS) and the Social Embarrassment (SE).

11.3.1.2.1 Statistical Methods

Descriptive statistics including 95% confidence intervals will be used to summarize the IQoL total scores and the three subscale scores at baseline, 3 months, 6 months and 12 months post device activation along with change from baseline.

11.3.1.3. Additional Endpoint 3 – IIQ-7

To evaluate the life impact of UI as measured by Incontinence Impact Questionnaire (IIQ-7) at 3 months, 6 months and 12 months post device activation compared to baseline.

The endpoint is the IIQ-7 score.

11.3.1.3.1 Statistical Methods

Descriptive statistics including 95% confidence intervals will be used to summarize the IIQ-7 score at baseline, 3 months, 6 months and 12 months post device activation along with change from baseline.

11.3.1.4. Additional Endpoint 4 – EQ-5D

To quantify the health states as measured by Health Status (EQ-5D) at 12 months post device activation compared to baseline.

The endpoints are EQ-5D descriptive system and EQ VAS, and it may be converted into a single index value.

11.3.1.4.1 Statistical Methods

For a categorical variable, the frequency or the proportion of a category will be calculated at baseline and 12 months post device implantation. For a continuous variable, descriptive statistics including 95% confidence intervals will be used to summarize the value at baseline, and 12 months post device activation.

11.3.1.5. Additional Endpoint 5 – Patient Ease of Use

To evaluate the patient use of device as measured by Patient Ease of Use Questionnaire at 6 months and 12 months post device activation.

The endpoint is the patient ease of use of the device.

11.3.1.5.1 Statistical Methods

The frequency and the proportion of a category will be calculated at 6 months and 12 months post device activation.

11.3.2. Interim Analyses

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

11.3.3. Subgroup Analyses

Treatment success rates will be calculated by three Pressure Regulating Balloon subgroups (Balloon FGS 51-60 cm, 61-70 cm, 71-80 cm), and Fisher's Exact test or Chi-squared test will be applied to evaluate if there is a correlation between treatment success and Pressure Regulating Balloons.

11.3.4. Justification of Pooling

Fisher's Exact test or Chi-squared test will be applied to evaluate the homogeneity of the treatment success rates across the study centers.

11.3.5. Multivariable Analyses

There are no planned multivariable analyses.

11.3.6. 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. Health Economics Outcomes

A formal health economics analysis may be conducted after the trial is completed, given meaningful clinical results are obtained. In addition to the primary clinical endpoints, the EQ-5D-5L questionnaire, a standardized instrument, will be collected prospectively in all subjects at baseline and 12-month follow up as a measure of non-disease-specific health-related quality of life and used to obtain health utility scores. The health economics analysis may take into consideration any differences in clinical endpoints, complication rates, quality of life, and resource utilization.

13. Data Management

13.1. *Data Collection, Processing, and Review*

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

The clinical database will reside on a production server hosted by 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.

13.1.1. Subject Diaries

This study will capture subject diary data electronically via a secure application (Medidata Rave Patient Cloud) directly integrated with the 21 CFR Part 11-compliant Rave EDC system or on a paper version of the diary. The subject can utilize their own device (i.e. smartphone or tablet) to access the application, or the subject will be provided with an off-the shelf, commercially available device. The subject will use the Patient Cloud Application to respond to diary questions and/or questionnaires. Data will be automatically uploaded into the EDC system via the Internet or cellular signal. Entries on the paper version of the diary will be manually entered by site staff.

13.1.2. Questionnaires

Paper questionnaires that are completed by the subject are transcribed into the EDC database by the site staff. The Patient Ease of Use questionnaire will be provided in electronic form directly within the subject diaries' secure application or on a paper version. Data will be uploaded automatically into the EDC system via the Internet (Wi-Fi) or cellular signal. Completed paper versions of the Patient Ease of Use questionnaire will be manually entered by site staff.

13.2. *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.

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 Boston Scientific 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.

14. 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/REB/Regulatory Authority/, site re-training, or site discontinuation/termination) will be put into place by the sponsor.

The sponsor will not approve protocol waivers.

15. Compliance

15.1. *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), European Medical Device Regulation, the spirit of EN 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.

15.2. *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 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.
- 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 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 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.

15.2.1. 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 for providing appropriate training to, and adequate supervision of them. 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.

15.3. *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 trial. 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.

15.4. *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.

15.5. *General Data Protection Regulations*

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 is 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 Boston Scientific includes, but is not limited to:

- Geographic data (site name)
- Important Dates
    - Informed consent date
    - Date of birth
    - 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.

15.5.1. 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.

15.5.2. 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.

Physicians are also data subjects in this study. As data subjects, they have the same rights as study subjects, listed above. For the purposes of this study, data collected on physicians includes but is not limited to:

- Documentation such as:
    - Curriculum Vitaes
    - Medical Licenses

- Identifying information such as:
    - Medical license number
    - Place of work
    - Telephone numbers
    - Email addresses

15.6. *Insurance*

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

16. 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.

17. Potential Risks and Benefits

17.1. *Instructions for Use*

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

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

The AMS 800 AUS is a commercially available device. None of the procedures associated with this study fall outside of standard of care procedure. Therefore, there are no foreseen additional risks associated with the study follow-up schedules, study procedures, testing, or withdrawal from the study.

17.3. *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.

17.4. *Anticipated Benefits*

There are no guaranteed benefits from participation in this study. The AMS 800 AUS is a commercially available device, and can be implanted 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 on benefists and risks associated with the use of the AMS 800.

18. Safety Reporting

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

It is the responsibility of the investigator to assess and report the following events to BSC if they occurred from the time of index procedure through the end of the subject's participation in the study:

- Serious Adverse Events
- Serious Adverse Device Effects
- Adverse Device Effects
- Procedure Related Adverse Events
- Device Deficiencies

Events to be reported include both anticipated and expected post procedural events, in addition to any other unanticipated and unexpected 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.

Reportable events must be recorded in the eCRF. The Investigator or designee is responsible for updating the eCRF with new 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 18.2-1 for Safety definitions).

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

18.2. *Definitions and Classification*

Safety definitions are provided in Table 18.2-1. 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 18.2-1: 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 misuseof 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, user 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 impairement. **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)	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

Table 18.2-1: Safety Definitions

Term	Definition
Ref: ISO 14155 *Ref: MDCG 2020-10/1*	
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.
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.

18.3. *Relationship to Study Deviceand/or Study Procedure*

The Investigator must assess the relationship of the reportable event to the study device and/or study procedure. See criteria in Table 18.3-1: .

Table 18.3-1: Criteria for Assessing Relationship of Study Device or Procedure to Adverse Event

Classification	Description
Not Related *Ref: MDCG 2020-10/1*	Relationship to the device 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 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 the relationship with procedures seems relevant and/or the event cannot be reasonably explained by another cause.

Table 18.3-1: Criteria for Assessing Relationship of Study Device or Procedure to Adverse Event

Classification	Description
Causal Relationship *Ref: MDCG 2020-10/1*	The serious event is associated with the study device 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.

18.4. *Investigator Reporting Requirements*

The communication requirements for reporting to BSC are as shown in Table 18.4-1.

Table 18.4-1: Reporting Timelines

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.

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)
	Provide all relevant source documentation (de-identified/ pseudonymized) for reported event.	• When documentation is available (recommend within 60 calendar days) • 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 (recommend within 30 calendar days) • 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 if circumstances had been less fortunate is considered a reportable event.	Complete Device Event CRF 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.
Procedure-Related Adverse Events and 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: In a timely manner but not later than 30 business days after becoming aware of the information. • Procedure-Related 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.
	Provide all relevant source documentation (de-identified/ pseudonymized) for reported event as required.	

18.5. *Device Deficiencies*

Device deficiencies (including but not limited to failures, malfunctions, use errors, product nonconformities, and inadequacy in the information supplied by the manufacturer) for BSC

devices will be documented and reported to BSC. If possible, the device(s) under study should be returned to BSC for analysis. Instructions for returning the device(s) will be provided by the Clinical Project Manager and will be filed in the investigator site file. If it is not possible to return the device, the investigator should document why the device was not returned and the final disposition of the device. Device 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.

18.6. *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 SAEs as required by local/regional regulations.

18.7. *Subject Death Reporting*

A subject death that occurs during the study should be reported to Boston Scientific 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 should include a narrative that provides detailed information describing the circumstances surrounding the death. 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 study device or 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., H & P, consults, test results, operative reports, and/or progress notes from the hospital chart)
    - Death certificate (if available)
    - Autopsy report (if applicable)
- If the patient expired outside of the hospital (e.g., home):
    - A copy of the most recent clinic visit (if not already submitted to Boston Scientific)

- Death certificate (if available)

19. 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 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.

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/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 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 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 Boston Scientific 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.

A Screening/Enrollment Log will be maintained to document select information about candidates who fail to meet the general or "other specific" entry criteria.

20. Committees

20.1. *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 document 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.

20.2. *Independent Medical Reviewer*

An Independent Medical Reviewer (IMR) is an independent practitioner with trial relevant therapeutic expertise that reviews and adjudicates important endpoints and relevant adverse events reported by study investigators. The IMR will review a safety event dossier, which may include copies of subject source documents provided by study sites, for all reportable events, excluding device deficiencies. IMR responsibilities, qualifications, membership, and procedures are outlined in the IMR Charter.

21. Suspension or Termination

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

21.1.1 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 Boston Scientific to suspend or discontinue development/marketing of the device.

21.2 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 Boston Scientific. Investigators, associated IRBs/ECs/REBs, and regulatory authorities, as applicable, will be notified in writing in the event of these occurrences.

21.3 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/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 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 devices, if supplied by Boston Scientific, unless this action would jeopardize the rights, safety, or welfare of the subjects.

21.4 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.

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.

22. Study Registration and Results

22.1. *Study Registration*

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

22.2. *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/REB 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.

23. 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 (https://www.bostonscientific.com/).

24. Reimbursement and Compensation for Subjects

24.1. *Subject Reimbursement*

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

24.2. *Compensation for Subject's Health Injury*

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

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26. Abbreviations and Definitions

26.1. *Abbreviations*

Abbreviations are shown in Table 26.1-1-1.

Table 26.1-1: Abbreviations

Abbreviation/Acronym	Term
AE	Adverse Event
AT	As Treated
AMS	American Medical Systems
AUS	Artificial Urinary Sphincter
BSC	Boston Scientific Corporation
CA	Competent Authority
CCGs	Case Report Form Completion Guidelines
CRO	Contract Research Organization
EC	Ethics Committee
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
GDPR	Global Data Protection
HIPAA	Health Information Portability and Accountability Act
ICF	Informed Consent Form
IFU	Instructions for Use
IMR	Independent Medical Reviewer
IPT	Incontinence after Prostate Treatment
IRB	Institutional Review Board
ISD	Intrinsic Sphincteric Deficiency
ITT	Intent to Treat
IZ	InhibiZone
MUS	Male Urethral Sling
PIF	Patient Information Forms
PP	Per Protocol
PPI	Post Prostatectomy Incontinence
PRB	Pressure Regulating Balloon
REB	Research Ethics Board
SAE	Serious Adverse Event
SUI	Stress Urinary Incontinence
UI	Urinary Incontinence

26.2. *Definitions*

Terms are defined in Table 26.2-1-1.

Table 26.2-1: Definitions

Term	Definition
Adverse Device Effect	See Table 18.2-1, Safety Definitions
Adverse Event	See Table 18.2-1, Safety Definitions
As Treated	All subjects for whom implantation of the device is attempted.
Consent Ineligible	A subject who has signed the ICF but is found to not meet eligibility criteria. These subjects can still receive the AMS 800 per standard of care treatment, but do not count toward enrollment. The subjects will be exited and will not undergo any study related procedures once their ineligibility has been determined. These subjects do not count toward enrollment.
Data Controller	In GDPR: The entity which determines the purposes (why the entity needs to process data) and means (database managed through a software, hard copy files, centralized database) of personal information processing.
Data Processor	In GDPR: The person or entity processing the data on behalf and according to the instructions of the data controller. An entity which uses an external data processor must ensure that, in the contract, its data processor offers adequate guarantees to ensure the security and confidentiality of the data communicated.
Data Subject	In GDPR: Any living individual to whom the personal data relates. Examples of data subjects in this study are physicians and subjects.
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).
Exited Prior to Procedure	A subject who signs the informed consent, meets eligibility criteria but then does not undergo having the index study procedure initiated (first incision) or receive the study device. The original ICF and screening documentation for these patients should be maintained in the site's files. There are no follow-up requirements and these subjects do not count toward enrollment. Any data collected prior to procedure is not included in statistical analyses. These subjects do not count toward enrollment.
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 18.2-1 Safety Definitions
Identifiers	"Identifiers" are personal data that can be used alone or in combination with other identifiers to identify an individual.
Independent Medical Reviewer	An independent practitioner with trial relevant therapeutic expertise that reviews and adjudicates important endpoints and relevant adverse events reported by study investigators.
Index Procedure	The primary procedure for treatment with the study device (test and/or control device).
Intent-To-Treat	A subject who signs the informed consent, meets eligibility criteria, and for whom the index procedure is initiated but not completed (first incision). The original ICF and screening documentation for intent to treat patients should be

Table 26.2-1: Definitions

Term	Definition
	maintained in the site's files. These patients are followed in accordance with the study follow up schedule for safety and count toward enrollment.
Intrinsic Sphincter Deficiency	Stress incontinence caused by weakness of the urinary sphincter.
Medical Revision	A medical revision is defined as a secondary surgery to modify or replace the initially implanted device. See section 10.11.
Minimal Risk	The probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.
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.
Patient-Reported Outcome (PRO)	A measurement based on a report that comes directly from the patient (i.e., study subject) about the status of a patient's health condition without amendment or interpretation of the patient's response by a clinician or anyone else. A PRO can be measured by self-report or by interview provided that the interviewer records only the patient's response.
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).

Table 26.2-1: Definitions

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.
Replacement	Removal of one or more components of the AMS 800 and implantation of a new component. See section 10.11.
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 18.2-1, Safety Definitions
Serious Adverse Event (SAE)	See Table 18.2-1, 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 Data	All information in original records, certified copies of original records of clinical findings, observations, or other activities in a clinical investigation, necessary for the reconstruction and evaluation of the clinical investigation *(Ref. ISO 14155-2020)*
Source Document	Original or certified copy of printed, optical or electronic document containing source data *(Ref. ISO 14155-2020)*
Stress Urinary Incontinence	Urinary incontinence is the unintentional loss of urine. Stress incontinence is defined as the complaint of involuntary loss of urine on effort or physical exertion including sporting activities, or on sneezing or coughing.