Postmarket Study PS130044
Uphold LITE Study

CLINICAL PROTOCOL

U8090

A Prospective, Non-Randomized, Parallel Cohort, Multi-center Study of Uphold LITE vs. Native Tissue for the Treatment of Women with Anterior/Apical Pelvic Organ Prolapse

Sponsored By

Boston Scientific Corporation

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Revision History

Revision Number	Release Date	Template Number and Version	Section	Change	Reason for Change
01/AA	12 April 2013	90702637 Rev/Ver AC	8. Subject Selection	Updated inclusion/ exclusion criteria	To align with the AUGS PFD Registry
			20. Safety Reporting	Added pelvic floor related events as part of reportable safety events	To align with the AUGS PFD Registry
			4. Device Description	Updated study device information	To reflect newer version of device
			9. Subject Accountability	Updated study timeline	Due to this protocol amendment and the AUGS PFD Registry Database Go-Live projected date
			11. Statistical Considerations	Updated statistical sections	Due to the development of new SAP
02/AB	03 July 2013	90702637 Rev/Ver AC	Various	Updated PS number throughout document	Updated PS number required per FDA

Revision History

Revision Number	Release Date	Template Number and Version	Section	Change	Reason for Change
03/AC	24 October 2014	90702637 Rev/Ver AD	7. Design	Clarify anterior colporrhaphy language	To align with standard of care
			8. Subject Selection	Updated inclusion/ exclusion criteria	To clarify POP-Q score and remove hysterectomy requirement to allow for both vaginal vault suspensions & hysteropexies
			7. Design	Physician training requirement	To allow physicians to verify expertise and training through prior use of Uphold & Uphold LITE devices
			7. Design	Updated number of study sites	To allow for a larger number of participating sites
			8. Subject Selection	Remove English-speaking requirement	To allow enrollment of non-English speaking subjects
			9. Subject Accountability	Updated study timeline	To align with current enrollment cadence
			10. Study Methods	Updated Data Collection Schedules/Tables	To align with content of protocol
			11. Statistical Considerations	Updated ITT definition	To clarify definition
			20. Safety Reporting	Updated Safety Reporting	To align with data collection in the AUGS PFD Registry
04/AD	21 December 2015	90702637 Rev/Ver AF	10. Study Methods	Administrative	To clarify the baseline assessment of urine pregnancy test
			18. Potential Risks and Benefits	Updated Anticipated Adverse Events	To align with the device labeling
05/AF	03 February 2016	90702637 Rev/Ver AF	9. Subject Accountability	Updated study timeline	To reflect new milestone dates
06/AG	25 September 2017*	90702637 Rev/Ver AH	Contact Information	Updated Clinical Contact	To reflect current BSC Clinical Project Manager
			Entire document	Changed reference to the “sponsor” to Boston Scientific	To clarify who the sponsor is

Revision History

Revision Number	Release Date	Template Number and Version	Section	Change	Reason for Change
			2. Protocol Synopsis-Study Duration; 8.1. Scale and Duration; 11.4.7. Months 6, 12, 18, 24, 36 Visits	Deleted "per protocol" from subject description	To clarify the study population
			2. Protocol Synopsis-Planned Number of Subjects; 8.1. Scale and Duration	Deleted reference to mesh subjects	To clarify which subjects will be shared from the PFD Registry
			10.1. Point of Enrollment	Revised study population description	To clarify the Intent-to-Treat and Per Protocol groups
			10.1. Point of Enrollment	Revised study timeline table	To update actual and expected dates for study milestones
			10.2. Withdrawal	Added sections on voluntary and involuntary withdrawal, lost to follow-up, death and documentation	To clarify early withdrawal categories
			11.1. Data Collection; 11.4.5. Follow-Up	Added definition of missed visit and ending 36 Month visit window	To clarify missed visit definition
			12. Statistical Considerations	Various	To align with updated Statistical Analysis Plan
			11.3. Informed Consent; 13.2. Data Retention; 17.1. Statement of Compliance	Replaced reference to ICH-GCP with ISO14155:2011	To clarify which GCP standards were adhered to
			19.2.1. Mesh Exposure and Erosion Event Classification	Replaced physical exam with pelvic exam	To clarify exam type
			20. Informed Consent	Added Boston Scientific or CRO for informed consent review	To clarify informed consent review process
			21. Safety Reporting	Revised section for AE definitions and reporting timelines	To clarify definitions and reporting timelines

Revision History

Revision Number	Release Date	Template Number and Version	Section	Change	Reason for Change
07/AH	05 January 2018*	90702637 Rev/Ver AH	10.2.4. Subject Death; 11.6. Subject Death; 11.1. Data Collection; 21.7. Investigator Reporting Requirements	Revised collection of death information to include all events	To align with FDA Guidance on 522 Post-Market Surveillance
			12.1.1.3. Statistical Methods; 12.2.1. Analysis Sets	Added "per protocol" group to primary safety endpoint evaluation	To clarify evaluation of the primary safety endpoint
			12.3.5.4. Subjects with surgical intervention for recurrence or complications	Added section	To specify the analysis of adverse events by vaginal compartment after re-surgery
08/AI	28 February 2018	90702637 Rev/Ver AH	11.1. Data Collection; 11.4.5. Follow-Up	Increased window for follow-up visits to occur	To reduce number of late visits
			11.4.5. Follow-Up	Provide option for completion of home or phone follow-up visits	To improve collection of follow-up visit data
			12.1.1.3. Statistical Methods	Added tipping point analysis	To clarify the sensitivity analyses to be performed
			12.2.3. Propensity Score Methodology	Added definition of treatment arms	To clarify how logistic regression will be performed
			12.3.8. Interim Analysis	Added details of interim analysis of 12 month outcomes	Requested by FDA

** Not released separately to the study sites*

2. Protocol Synopsis

Postmarket Study PS130044: A Prospective, Non-Randomized, Parallel Cohort, Multi-center Study of Uphold LITE vs. Native Tissue for the Treatment of Women with Anterior/Apical Pelvic Organ Prolapse	
Study Objective(s)	The purpose of this study is to compare transvaginal mesh repair to traditional native tissue repair in women surgically treated for anterior and/or apical pelvic organ prolapse. This study is being conducted in partnership with the American Urogynecologic Society (AUGS) under the Pelvic Floor Disorders Outcome Registry (PFD Registry).
Test Device	Transvaginal mesh (Uphold Lightweight Vaginal Support System)
Control Device	Traditional native repair (sacrospinous ligament fixation or uterosacral ligament suspension and/or colporrhaphy)
Study Design	Non-randomized, parallel cohort, multi-center study. All procedures will be standardized for uniformity. Physicians will have to document a minimum of 10 procedures with either the Uphold device (i.e., Uphold or Uphold LITE) or with native tissue repair prior to participation in order to document competency and experience. Physician training, specialty, and site procedure location (such as private-practice, hospital, academic medical center, etc.) will be recorded. Concomitant procedures including anterior and posterior vaginal wall repair, hysterectomy and sling placement for stress urinary incontinence may be performed, per physician discretion. Sling placement can include a synthetic material; however a concomitant anterior or posterior repair cannot include a mesh implant. An anterior colporrhaphy may be required for cystocele repair, if clinically necessary. All concomitant procedures performed will be recorded**.** Subjects who undergo a medical intervention (surgical or non-surgical) to treat recurrence, persistence of pelvic organ prolapse or a mesh complication will be followed to 36 months from the initial study procedure.
Planned Number of Subjects	Approximately 414 subjects enrolled (207 subjects per arm). Eligible control subjects meeting the study inclusion/exclusion criteria may be shared from the PFD Registry.

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Planned Number of Investigational Sites / Countries	Up to 40 study centers in the United States.
Primary Effectiveness Endpoint(s)	The primary endpoint of the study is to achieve superiority of mesh over native tissue repair at 36 months as compared to baseline. Success will be based on a composite of objective and subjective measures, and subjects will be considered a surgical success if each of the three criteria is met: 1. Objective success is achieved by the subject having an anatomic outcome defined as the leading edge of prolapse at or above the hymen in the operated compartment: • Anterior segment: Leading edge of anterior prolapse is at or above the hymen or POP-Q point Ba ≤ 0. • Apical segment: The vaginal apex does not descend more than one-half into the vaginal canal (i.e. POP-Q point C < -1/2 TVL) for multi-compartment prolapse or POPQ point C ≤ 0 for single compartment apical prolapse. 2. Subjective success is achieved if the patient denies symptoms of vaginal bulging per PFDI-20 question 3, answering "no" or "yes" but "Not at all" bothersome (<2). 3. No retreatment for POP: no additional surgical treatment for POP in the segment(s) of the vagina treated at the index surgery or no pessary use since index surgery (i.e., 'treated segment' refer to the target compartment).
Primary Safety Endpoint(s)	A co-primary endpoint of the study is to achieve non-inferiority of mesh to native tissue repair for safety by comparing rates of serious device or serious procedure-related complications between baseline and the 36 month time point. Serious injury is defined per 21 CFR 803.3, i.e., life threatening, results in permanent impairment of a body function or permanent damage to a body structure, or injury or illness that requires medical or surgical intervention to preclude impairment of a body function or permanent damage to a body structure.

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Secondary Endpoints	1. Incidence of mesh erosion 2. Incidence of mesh exposure 3. Incidence of de novo dyspareunia 4. Improvement in subject specific outcomes at 36 months compared to Baseline (pelvic floor symptoms (PFDI-20), QOL (PFIQ-7), sexual functioning (PISQ-12), TOMUS pain scale 5. Assessment of subject's level of improvement, measured by the Patient Global Impression of Improvement for Prolapse (PGI-I for Prolapse) 6. Absence of re-intervention or re-surgery for recurrence or persistence of POP or mesh exposure/erosion 7. Surgical success based on the following composite outcome: a. Subjective success: patient denies symptoms of vaginal bulging per PFDI-20 question 3, answering "no" or "yes" but "Not at all" bothersome (<2) b. Anatomic success (in the operated compartment): • Anterior Segment: No anterior prolapse at or beyond the hymen or POP-Q point Ba<0 • Apical Segment: The vaginal apex does not descend more than one-half into the vaginal canal (i.e. POP-Q point C < 1/2 TVL) for multi-compartment prolapse or POPQ point C < 0 for single compartment apical prolapse c. No retreatment for POP: No additional surgical treatment for POP in the segment(s) of the vagina treated at the index surgery or no pessary use since index surgery 8. Device or procedure-related incidence of the following: pelvic pain, infection, vaginal shortening, atypical vaginal discharge, neuromuscular problems, vaginal scarring, de novo vaginal bleeding, fistula formation and/or de novo voiding dysfunction

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Method of Assigning Subjects to Treatment	This study is a prospective, non-randomized, parallel cohort, multi-center study. Approximately 414 subjects will be enrolled and will either receive transvaginal mesh (treatment) or a native tissue repair (control) procedure. Study centers will either participate to enroll only mesh subjects or only native tissue subjects to reduce bias; or a combination of mesh and native tissue subjects depending on subject population and per Sponsor discretion.
Follow-up Schedule	Study follow-up duration is for 3 years from primary study procedure: • Screening/Enrollment Visit • Pre-procedure/Baseline Visit • Procedure and Discharge • Month 2 Visit • Month 6 Visit • Month 12 Visit • Month 18 Visit • Month 24 Visit • Month 36 Visit (Primary Endpoint and End of Study)
Study Duration	Approximately 3 years (36 months) from last subject enrolled.
Key Inclusion Criteria	1. Subject is female 2. Subject is ≥18 years of age 3. Subject has pelvic organ prolapse with the leading edge at or beyond the hymen. At or beyond the hymen is defined as POP-Q scores of Ba ≥ 0 (for prolapse of the anterior compartment alone) or C ≥ 0 (for prolapse of the apical compartment alone) or C ≥ -1/2 TVL and Ba ≥ 0 (for a multi-compartment prolapse that includes the anterior and apical compartments) 4. Subject reports of a bothersome bulge they can see or feel per PFDI-20, question 3 response of 2 or higher (i.e. responses of "somewhat", "moderately" or "quite a bit") 5. Subject or subject's legally authorized representative must be willing to provide written informed consent 6. Subject is willing and able to comply with the follow-up regimen

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Key Exclusion Criteria	1. Subject is pregnant or intends to become pregnant during the study 2. Subject has an active or chronic systemic infection including any gynecologic infection, untreated urinary tract infection (UTI) or tissue necrosis 3. Subject has history of pelvic organ cancer (e.g. uterine, ovarian, bladder, colo-rectal or cervical) 4. Subject has had prior or is currently undergoing radiation, laser therapy, or chemotherapy in the pelvic area 5. Subject has taken systemic steroids (within the last month) or immunosuppressive or immunomodulatory treatment (within the last 3 months) 6. Subject has systemic connective tissue disease (e.g. scleroderma, systemic lupus erythematosus (SLE), Marfans syndrome, Ehlers Danlos, collagenosis, polymyositis, polymyalgia rheumatica) 7. Subject has a known neurologic or medical condition affecting bladder function (e.g. multiple sclerosis, spinal cord injury, or stroke with residual neurologic deficit) 8. Subject is seeking obliterative vaginal surgery as treatment for pelvic organ prolapse (colpocleisis) 9. Subject has a previous prolapse repair with mesh in the target compartment 10. Subject is planning to undergo a concomitant repair with use of mesh in the non-target compartment 11. Subject is not able to conform to the modified dorsal lithotomy position 12. Subject has chronic systemic pain that includes the pelvic area or chronic focal pain that includes the pelvis 13. Subject has uncontrolled diabetes mellitus (DM) 14. Subject is currently participating in or plans to participate in another device or drug study during this study 15. Subject has a known hypersensitivity to polypropylene mesh

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Statistical Methods	
Primary Statistical Hypothesis	Transvaginal mesh repair will be superior to traditional native tissue repair in effectiveness and non-inferior in safety. Superiority testing for effectiveness will be performed for the primary hypothesis. Statistical testing will be performed to determine if composite endpoint of anatomic and symptomatic success rate in transvaginal mesh repair (treatment) group will be superior to traditional native tissue repair (control) group. The null hypothesis is that the success rate in treatment group is less than or equal to the success rate in control group: $Ho: \pi_{treatment} - \pi_{control} \leq 0$ The alternative hypothesis is: $Ha: \pi_{treatment} - \pi_{control} > 0$ where $\pi_{treatment}$ and $\pi_{control}$ is the success rate in the treatment group and control group respectively. The rejection of null hypothesis indicates the superiority of the treatment group over the control group. Statistical testing will be performed to determine if the overall complication rate (i.e. serious adverse device effects and serious procedure-related adverse events) of treatment group is non-inferior to that of the control group. The null hypothesis is that the overall complication rate in treatment group is greater than or equal to the rate in control group plus margin: $Ho: \pi_{treatment} - \pi_{control} \geq \Delta$ The alternative hypothesis is: $Ha: \pi_{treatment} - \pi_{control} < \Delta$ where $\pi_{treatment}$ and $\pi_{control}$ are the overall complication rate in treatment group and control group respectively, and $\Delta > 0$ is defined as the non-inferiority margin.
Statistical Test Method	All statistical analyses will be performed by Boston Scientific per the Statistical Analysis Plan. All analyses will be done using SAS (version 8.0 or higher) statistical software. Subject summary tables and data listings will be provided for the data collected.

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Sample Size Parameters	The statistical power calculation is based on a superiority assumption with a binary primary outcome. Success, based on a composite endpoint of anatomic and symptomatic success at 36 month is assumed to be 70.0% for the native tissue arm and 85.0% for transvaginal mesh arm.[17-21] With 2-sided type I error of 0.05 and type II error of 0.1 (power 90%), 316 subjects (158 subjects per arm) are needed to detect 15% difference of transvaginal mesh to native tissue repair. To assess for safety, the overall complication rate (i.e. serious adverse device effects and serious procedure-related adverse events) is anticipated to be approximately 14%.[22] With type I error of 0.05 and type II error of 0.20 (power 80%), 298 subjects (149 subjects per arm) are needed to detect non-inferiority with a margin of 10%. The rate of device or procedure-related AE de novo dyspareunia is anticipated to be approximately 9%.[24] With type I error of 0.05 and type II error of 0.20 (power 80%), 326 subjects (163 subjects per arm) are needed to detect non-inferiority with a margin of 7.9%. The device or procedure-related AE incidence (pelvic pain, infection, vaginal shortening, atypical vaginal discharge, neuromuscular problems, vaginal scarring, de novo vaginal bleeding, fistula formation and/or de novo voiding dysfunction) is anticipated to be approximately 12%.[22] With type I error of 0.05 and type II error of 0.20 (power 80%), 330 subjects (165 subjects per arm) are needed to detect non-inferiority with a margin of 8.9%. To assess for office-based interventions for complications, the rate is anticipated to be approximately 2%.[22] With type I error of 0.025 and type II error of 0.10 (power 90%), 330 subjects (165 subjects per arm) are needed to detect non-inferiority with a margin of 5%. To assess for surgical intervention for complications, the rate is anticipated to be approximately 1%.[22] With type I error of 0.025 and type II error of 0.10 (power 90%), 260 subjects (130 subjects per arm) are needed to detect non-inferiority with a margin of 4%. Non-surgical subjects will be enrolled by the PFD Registry and analyzed with data from this clinical study. Assuming a 20% loss to follow-up rate, a total of 414 subjects (207 per study arm) will be enrolled to achieve the primary endpoint of success at 36 months.

3. Table of Contents

3.1. *Table of Tables*

4. Introduction

Pelvic organ prolapse (POP) of the anterior and posterior vaginal wall, and vaginal apex, are among the most challenging and common aspects of traditional pelvic reconstructive surgery. As life expectancy increases, significantly greater numbers of women will present with POP and stress urinary incontinence (SUI) requiring surgical intervention. Women face an 11% lifetime risk of requiring major surgery for POP.[9]

The main goal of POP surgery is restoration of normal anatomy to achieve proximal vaginal suspension, mid-vaginal lateral attachments and distal vaginal fusion to the urogenital fascia and perineum. Women undergoing pelvic reconstructive surgery for POP hope to achieve relief of symptoms, restoration of normal anatomy, maintenance of vaginal capacity for sexual function and improvement in the quality of life.

The difficulties associated with repair of cystocele were cited by Ahfelt as early as 1909, and reinforced nearly a century later by Weber et al. (2001) who reported recurrence rates as high as 70% in a widely cited randomized controlled study (RCT).[11] Clark et al. estimated that up to 60% of surgical recurrences occur at the same anatomic site as the original repair, highlighting the limitations associated with plicating and/or suspending weakened connective tissues to one another.[1] In recent years, surgical methods such as vaginal mesh repair have become available as an option for treating more advanced and challenging cases.

Vaginal mesh repair, by augmenting native tissues with polypropylene mesh, is the most well established surgical alternative to native tissue plication. Despite a risk of mesh complications (3% - 13%), vaginal mesh repair is quicker and technically easier than trans-abdominal placement using sacral colpopexy.[10,2,6,7,8,4,3]

In an update of surgical treatment of POP, McIntyre et al. (2010) discussed the potential benefits of mesh use. In the treatment of anterior prolapse, studies indicated that potential benefits of mesh include increased durability of repair and improved anatomic outcomes.[5] In one study of 70 subjects using mesh, McIntyre reported three (4.28%) recurrences, mesh extrusion in five subjects (7.1%), and 48 (87.3%) subjects reporting complete subjective satisfaction with their surgery at a follow-up of 18-36 months.

Four recent single-arm studies involving use of a mesh device for treatment of prolapse and one to two year follow-up documented anatomical cure rates ranging from 88.5%-94%.[6,7,2,10] Reported vaginal mesh erosion rates for anterior repair ranged from 3.2%-6.5%, with one study reporting 13% mesh erosion for posterior repair.[6]

According to seven prospective randomized studies possessing at least one year clinical follow up, all but one indicate an exceptional reduction in anatomic recurrences after soft polypropylene mesh when compared to anterior colporrhaphy, with comparable or favorable quality of life and sexual outcomes.[3,13,14,15,16,17,12] Six of seven of these RCT's reported >50% reduction in the cystocele recurrence rate, and four of seven reported $\geq$75% reduction in anatomic failures. Crude recurrence rates were reduced, in these studies, from a range of 28-45% (colporrhaphy) to 7-21% (mesh).

Uphold™ Lightweight Surgical Mesh (Uphold LITE) is an FDA 510(k) cleared mesh implant intended for tissue reinforcement and stabilization of fascial structures of the pelvic floor in vaginal wall prolapse, where surgical treatment is intended, either as mechanical support or bridging material for the fascial defect. Uphold was designed as a VMR that would limit mesh exposures by placement through a horizontal, inverted crescent vaginal incision near the urethrovesical junction. The amount of mesh is approximately 75% less than other kits and apical support is achieved via sacrospinous ligament fixation (SSLF). Use of synthetic mesh grafts in surgical repair of vaginal prolapse has been shown to significantly increase success rates and reduce recurrent prolapse.

5. Device Description

The Uphold LITE Vaginal Support System is a sterile, single use device for transvaginal placement, consisting of one (1) Uphold LITE Synthetic Mesh Assembly and one (1) Capio ™ SLIM Suture Capturing Device. The mesh assembly is a light-weight knitted mesh that consists of undyed and dyed polypropylene and monofilament fiber (phthalocyanine blue, color index number 74160) with two integrated leg assemblies. The leg assemblies include a dart, lead, dilator, two leader loops and protective sleeve. The dart at the distal end of the leg assembly was designed to be placed into the carrier at the distal end of the Capio SLIM Suture Capturing Device. The leg assembly was designed to facilitate the passage of the Uphold LITE Synthetic Mesh Assembly through bodily tissues for placement through sacrospinous ligament. One dilator is striped to differentiate each leg assembly (left/right).

6. Study Objectives

The primary objective is to evaluate clinical effectiveness of transvaginal mesh repair against traditional native tissue repair in women surgically treated for anterior and/or apical pelvic organ prolapse. Secondary objectives are to evaluate mesh-related complications and subject reported outcomes.

7. Study Endpoints

7.1. *Primary Endpoints*

The primary endpoint of the study is to achieve superiority of mesh over native tissue repair at 36 months as compared to baseline.

Success will be based on a composite of objective and subjective measures, and subjects will be considered a surgical success if each of the three criteria is met:

1. Objective success is achieved by the subject having an anatomic outcome defined as the leading edge of prolapse at or above the hymen in the operated compartment:
    - Anterior segment: Leading edge of anterior prolapse is at or above the hymen or POP-Q point Ba ≤ 0.

- Apical segment: The vaginal apex does not descend more than one-half into the vaginal canal (i.e. POP-Q point C < -1/2 TVL) for multi-compartment prolapse or POPQ point C ≤ 0 for single compartment apical prolapse.

2. Subjective success is achieved if the patient denies symptoms of vaginal bulging per PFDI-20 question 3, answering "no" or "yes" but "Not at all" bothersome (<2).
3. No retreatment for POP: no additional surgical treatment for POP in the segment(s) of the vagina treated at the index surgery or no pessary use since index surgery (i.e., 'treated segment' refer to the target compartment).

Additionally, a co-primary endpoint of the study is to achieve non-inferiority of mesh to native tissue repair for safety by comparing rates of serious device or serious procedure complications between baseline and the 36 month time point. Serious injury is defined per 21 CFR 803.3, i.e., life threatening, results in permanent impairment of a body function or permanent damage to a body structure, or injury or illness that requires medical or surgical intervention to preclude impairment of a body function or permanent damage to a body structure.

7.2. *Secondary Endpoints*

The secondary endpoints of the study include assessments of complications and subject reported outcomes:

1. Incidence of mesh erosion
2. Incidence of mesh exposure
3. Incidence of de novo dyspareunia
4. Improvement in subject-related outcomes at 36 months compared to Baseline ((pelvic floor symptoms (PFDI-20), QOL (PFIQ-7), sexual functioning (PISQ-12) TOMUS pain scale)
5. Assessment of subject's level of improvement, measured by the Patient Global Impression of Improvement for Prolapse (PGI-I for Prolapse)
6. Absence of re-intervention and re-surgery for recurrence of POP, persistence of disease, or mesh exposure/erosion
7. Surgical success based on the following composite outcome:
    a. Subjective success: patient denies symptoms of vaginal bulging per PFDI-20 question 3, answering "no" or "yes" but "Not at all" bothersome (<2)
    b. Anatomic success (in the operated compartment):
        - Anterior Segment: No anterior prolapse at or beyond the hymen or POP-Q point Ba<0
        - Apical Segment: The vaginal apex does not descend more than one-half into the vaginal canal (i.e. POP-Q point C < 1/2 TVL) for multi-

compartment prolapse or POPQ point C < 0 for single compartment apical prolapse.

c. No retreatment for POP: No additional surgical treatment for POP in the segment(s) of the vagina treated at the index surgery or no pessary use since index surgery

8. Incidence of the following device or procedure-related AEs: pelvic pain, infection, vaginal shortening, atypical vaginal discharge, neuromuscular problems, vaginal scarring, de novo vaginal bleeding, fistula formation and/or de novo voiding dysfunction

8. Study Design

This study is a prospective, non-randomized, parallel cohort, multi-center study conducted in partnership with the AUGS PFD Registry.

The primary endpoint will be assessed once all per protocol subjects have completed the 36 month study visit. All per protocol subjects will be followed to month 36, until study completion, or until discontinuation prior to month 36. All study procedures will be standardized for uniformity. Physicians will have to provide documentation of a minimum of 10 procedures (i.e., native tissue repair procedure or Uphold/Uphold LITE procedure) prior to participation in order to document competency and experience. Physician training, specialty, and site procedure location (such as outpatient in private-practice, institutional hospital, etc.) will be recorded.

All efforts will be made to ensure all follow-up anatomic measurements (POP-Q) will be assessed by a healthcare provider to reduce treating surgeon bias on outcomes after the index procedure. In the event the treating surgeon is the only qualified healthcare provider at the site trained in POP-Q assessments, the follow-up anatomic measurements will be performed by the treating surgeon.

All enrolled subjects will have an anterior and/or apical defect. Concomitant procedures to treat a secondary defect can occur (including an anterior repair, posterior repair, hysterectomy, or sling placement for stress urinary incontinence), per physician discretion. Sling placement may include a synthetic material yet a concomitant anterior repair or posterior repair cannot include a mesh implant. An anterior colporrhaphy may be required, if clinically necessary. All concomitant procedures performed will be recorded.

Subjects who undergo a medical intervention (surgical or non-surgical) to treat recurrence, persistence of POP, or a mesh or suture complication will be followed to month 36 from the initial study procedure.

8.1. *Scale and Duration*

The study will be conducted at up to 40 sites at a rate of approximately 1-2 subjects per month. Sites will be encouraged to enroll a minimum of 10 subjects and up to a maximum of 50 subjects.

It is anticipated that approximately 414 subjects will be enrolled in total to achieve 330 subjects (165 subjects per treatment arm) for the co-primary endpoint analysis at 36 months post-surgery to achieve non-inferiority of mesh to native tissue repair for safety by comparing rates of serious procedure-related and device-related complications between baseline and the 36 month time point. Due to the partnership with the PFD Registry, it is anticipated a portion of the control arm subjects will be shared from the Registry.

The enrollment period is expected to be approximately 12 to 18 months after the final study center has been permitted to enroll subjects. A potential 20% "lost to follow-up" rate is anticipated.

Once enrolled into the study, subjects will be followed to 36 months post-surgery to be evaluated for the primary endpoint analysis. The total duration of each subject's participation in the study is 36 months from time of procedure.

Subjects who undergo a medical intervention (surgical or non-surgical) to treat recurrence, persistence of POP, or a mesh or suture complication will be followed to 36 months, post the initial study procedure.

8.2. *Treatment Assignment*

This post-approval study is a prospective, non-randomized, parallel cohort study across multiple centers. Subjects will be screened against the study Inclusion/Exclusion criteria and if eligible, enrolled into the study after providing Informed Consent.

Study centers will be selected by Boston Scientific to perform the study procedure as either a treatment center or a control center, depending on experience to reduce selection bias. Some study centers may be selected to enroll a combination of treatment and control subjects, depending on subject population and per Boston Scientific discretion.

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 three months prior to the study procedure, with confirmation of no evidence of infection prior to the procedure. Due to the allowable window of up to three months between baseline and study procedure, the study staff will confirm that subjects are still electing to undergo the study surgery with confirmation of no evidence of infection.

8.2.1. Treatment and Control

The treatment device in this study is Uphold Lightweight Vaginal Support System with transvaginal mesh (i.e., Uphold LITE). Please refer to the Directions for Use document for device-specific information. The surgical procedure steps will be standardized, including suture type (delayed absorbable or permanent sutures). Physicians will be trained to the standardized procedure steps prior to the first study procedure being performed. Minor modifications to the standardization may be necessary based on a physician's practice and patient care.

The control procedure in this study is traditional native tissue repair, which includes sacrospinous ligament fixation or uterosacral ligament suspension and/or colporrhaphy. The surgical procedure will be standardized, including suture type (delayed absorbable or permanent sutures). Sacrospinous ligament fixation may be performed if the uterosacral ligaments are deemed unusable due to scarring or inability to access.

9. Subject Selection

9.1. *Study Population and Eligibility*

This study will enroll adult, non-pregnant women who have been diagnosed with anterior and/or apical pelvic organ prolapse and will undergo repair surgery, and who may or may not also undergo a concomitant procedure (such as an anterior repair, posterior repair, hysterectomy, or sling placement for stress urinary incontinence). If a concomitant procedure were to occur, the sling placement should be a synthetic material, however the concomitant anterior or posterior repair cannot include a mesh implant. An anterior colporrhaphy may be performed for cystocele repair, if clinically necessary.

To assess for eligibility for this study, inclusion and exclusion criteria are included in Sections 9.2 and 9.3 below.

9.2. *Inclusion Criteria*

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

1. Subject is female
2. Subject is ≥18 years of age
3. Subject has pelvic organ prolapse with the leading edge at or beyond the hymen. At or beyond the hymen is defined as POP-Q scores of Ba≥ 0 (for prolapse of the anterior compartment alone) or C≥ 0 (for prolapse of the Apical compartment alone) or C≥ -1/2 TVL and Ba≥ 0 (for multi-compartment prolapse that includes the anterior and apical compartments)
4. Subject reports of a bothersome bulge they can see or feel per PFDI-20, question 3 response of 2 or higher (i.e. responses of “somewhat”, “moderately”, or “quite a bit)
5. Subject or subject’s legally authorized representative must be willing to provide written informed consent
6. Subject is willing and able to comply with the follow-up regimen

9.3. *Exclusion Criteria*

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

1. Subject is pregnant or intends to become pregnant during the study

2. Subject has an active or chronic systemic infection including any gynecologic infection, untreated urinary tract infection (UTI) or tissue necrosis
3. Subject has history of pelvic organ cancer (e.g. uterine, ovarian, bladder, colo-rectal or cervical)
4. Subject has had prior or is currently undergoing radiation, laser therapy, or chemotherapy in the pelvic area
5. Subject has taken systemic steroids (within the last month), or immunosuppressive or immunomodulatory treatment (within the last 3 weeks)
6. Subject has systemic connective tissue disease (e.g. scleroderma, systemic lupus erythematosus (SLE), Marfans syndrome, Ehlers Danlos, collagenosis, polymyositis, polymyalgia rheumatica)
7. Subject has a known neurologic or medical condition affecting bladder function (e.g. multiple sclerosis, spinal cord injury, or stroke with residual neurologic deficit)
8. Subject is seeking obliterative vaginal surgery as treatment for pelvic organ prolapse (colpoclesis)
9. Subject has a previous prolapse repair with mesh in the target compartment
10. Subject is planning to undergo a concomitant repair with use of mesh in the non-target compartment
11. Subject is not able to conform to the modified dorsal lithotomy position
12. Subject has chronic systemic pain that involves the pelvic area or chronic focal pain that involves the pelvis pelvic pain)
13. Subject has uncontrolled diabetes mellitus (DM)
14. Subject is currently participating in or plans to participate in another device or drug during this study
15. Subject has a known hypersensitivity to polypropylene mesh

10. Subject Accountability

10.1. *Point of Enrollment*

Subjects will be considered enrolled in the study once an incision is made in the vaginal wall. All enrolled subjects will have been consented and assigned to receive either the treatment or control procedure per site assignment. All enrolled subjects with a surgery initiated (i.e. incision in vagina) will be considered part of the Intent-to-Treat (ITT) population for the final study analysis. All ITT subjects who undergo the assigned study procedure and had no major protocol deviations will be considered part of the Per Protocol analysis.

The following study timeline (see Table 10.1-1) is based on milestones completed and the current follow-up visit cadence.

Table 10.1-1: Study Timeline

Milestone	Date
Date of study initiation[1]	August 2013
Date of initiation of subject enrollment	October 2013
Date of enrollment completion	December 2016
Expected date of study follow-up completion	December 2019
Expected date of Final Report submission[2]	June 2020

[1]*Study initiation is defined as the date the first study site is "enrollment ready" (i.e. IRB approved, fully executed contract)*
[2]*Assuming 6 months from last patient visit completion.*

All efforts will be made by site staff to ensure minimal loss to follow-up of patients and will follow a site-specific loss to follow-up plan. These plans will include efforts such as telephone follow-up, Investigator-patient counseling, visit reminder tools, patient stipends if permitted per site budget, and/or other communication methods.

10.2. *Withdrawal*

All subjects enrolled in the clinical study (including those withdrawn from the clinical study or lost to follow-up) will be accounted for and documented. If a subject withdraws from the clinical investigation, the reason(s) will be recorded. Reasons for study withdrawal may include voluntary withdrawal (withdrew consent), involuntary withdrawal, lost to follow-up, subject death or other reasons to be documented on the Case Report Form.

10.2.1. 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.

10.2.2. Involuntary Withdrawal

Subjects may be involuntarily withdrawn from the study if the Investigator determines it is in the subject's best interest.

10.2.3. Lost to Follow-up

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

- Two documented telephone attempts
- One certified letter

If the subject is able to be reached and no longer wishes to participate in the study the Investigator shall document the reason for the withdrawal and complete End of Study Case Report Form. If the subject is not able to be reached after the required attempts to contact the

subject are made and the subject has missed two consecutive follow-up visits within a 12 month calendar period, 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 reason for the withdrawal.

10.2.4. Subject Death

Subjects may be withdrawn from the study in the event of a death. If any serious adverse event results in death (regardless of the relatedness to the study device, procedure, or pelvic floor), the event is to be documented in the source documentation, Case Report Form, and reported to Boston Scientific within the timeframe noted in Table 21.7-1 (Investigator Reporting Requirements). If an autopsy is conducted, a copy of the final autopsy report should be submitted to Boston Scientific or designee. The primary objective of the autopsy is to determine the cause of death, complications and other relevant findings. The investigator will complete an End of Study Case Report Form and an adverse event (if applicable) per Section 11.6.

10.2.5. Documentation of Early Termination

Once a subject withdraws from the study, the Case Report Form will be completed as appropriate up to the point of withdrawal and all Adverse Events shall be closed or documented as appropriate. Withdrawn subjects (who had the study procedure initiated) will be included in the Intent-to-Treat analysis and will not be replaced.

11. Study Methods

11.1. *Data Collection*

Study data will be collected per the schedule outlined in Table 11.1-1. All study data will be recorded on source documentation and captured within Case Report Forms for the purposes of this study (see Section 13.1, Data Collection, Processing, and Review). 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 11.1-1: Data Collection Schedule

Procedure/Assessment	Screening/ Enrollment Visit[2]	Pre-Operative/ Baseline Visit	Surgery	Discharge	Post-Operative Follow-up Visits[7]					
					Month 2 Visit (± 4 Weeks)	Month 6 Visit (± 4 weeks)	Month 12 Visit (-4/+12 weeks)	Month 18 Visit (-4/+12 weeks)	Month 24 Visit (-4/+12 weeks)	Month 36* Visit (-4/+12 weeks)
Informed Consent	X									
Inclusion/Exclusion Criteria Review	X									
Demographics		X								
Urine Pregnancy Test	X	X								
Physical Examination		X								
Medical History[1]		X								
Pelvic Exam with vaginal length measurement		X			X	X	X	X	X	X
Assessment of Infection (vaginal, bladder)				X	X	X	X	X	X	X
Prolapse Grading (POP-Q Scoring)		X			X	X	X	X	X	X
PFDI-20 (Pelvic Floor Symptoms)		X			X	X	X	X	X	X
PFIQ-7 (Quality of Life)		X				X	X	X	X	X
PISQ-12 (Sexual Functioning)		X				X	X	X	X	X
PGI-I for Prolapse (Patient Improvement)						X	X	X	X	X
TOMUS Pain Scale		X			X	X	X	X	X	X
SSQ-8 for Surgical Satisfaction						X	X		X	X
EQ-5D for Health Status		X					X		X	X
Procedure and Assessments[3]			X							
Post-Operative Assessment[4]				X						
Assessment of Analgesic Intake		X			X	X	X	X	X	X
Assessment of Adverse Events[6]			X	X	X	X	X	X	X	X
Assessment of Risk Factors[5]		X			X	X	X	X	X	X
End of Study										X

*Primary Endpoint

[1]Medical History at baseline includes documented absence of UTI or other vaginal infection (i.e. vaginal culture, etc.).

[2]The Screening/Enrollment Visit and Pre-Operative/Baseline Visit may be combined and occur up to 3 months prior to the study procedure with confirmed absence of infection.

[3]Assessments include cystoscopy (at discretion of surgeon), estimated blood loss (EBL), assessment of concomitant procedures, and assessment of anesthesia type and duration of procedure.

[4]Post-Operative Assessments include assessment of infection (wound, vaginal, bladder), voiding status, and date and time of discharge.

[5]Assessment of Risk Factors includes menopausal status, estrogen use, age, smoking, diabetes status, BMI, hysterectomy status, concomitant procedures, surgeon training and experience.

[6]All serious and non-serious device, procedure, and pelvic floor-related events, any other relevant events pertaining to the pelvic region, and any events resulting in death will be collected.

[7]Every 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 36 visit, the visit is not considered missed until the last day of the visit window.

If a subject requires a re-surgery during the study, please refer to the reduced table below for follow-up assessments. Subjects undergoing re-interventions (non-surgical) continue with the study schedule as noted in Table 11.1-1. Additional data will be collected on subjects requiring a re-surgery, including a second procedure, mesh removal (as applicable), and second hospital discharge. All subjects who are re-operated on will continue with their follow-up schedule until 36 months post their initial study procedure.

Table 11.1-2: Data Collection Schedule for Subjects Requiring a Re-Surgery

Procedure/Assessment	Screening/ Enrollment Visit	Pre-Operative/ Baseline Visit	Surgery	Discharge	Post-Operative Follow-up Visits (± 4 Weeks)				
					Month 2 Visit (± 4 Weeks)	Re-Surgery	Discharge	Next Scheduled Follow-up Visit (-4/+12 weeks)	Month 36 Visit** (-4/+12 weeks)
Informed Consent	X							After a re-surgery, subjects will return to the clinic on the date of their next regular study visit per the Schedule of Events table above. Subjects will continue to return for all scheduled Follow-up Visits until 36 months post their initial study procedure.	
Inclusion/Exclusion Criteria Review	X								
Demographics		X							
Urine Pregnancy Test	X	X							
Physical Examination		X							
Medical History[1]		X							
Pelvic Exam with vaginal length measurement		X			X				X
Assessment of infection (vaginal, bladder)				X	X		X		X
Prolapse Grading (POP-Q Scoring)		X			X				X
PFDI-20 (Pelvic Floor Symptoms)		X			X				X
PFIQ-7 (Quality of Life)		X							X
PISQ-12 (Sexual Functioning)		X							X
PGI-I for Prolapse (Patient Improvement)									X
TOMUS Pain Scale		X			X				X
SSQ-8 for Surgical Satisfaction									X
EQ-5D for Health Status		X							X
Procedure and Assessments[3]			X			X			
Post-Operative Assessment[4]				X					
Assessment of Analgesic Intake		X			X				X
Assessment of Adverse Events[6]			X	X	X	X	X		X
Assessment of Risk Factors[5]		X			X				X
End of Study									X

11.2. *Study Candidate Screening*

Potential subjects will be identified by qualified staff at each selected study center as per their individual processes that will be documented at either the Site Qualification Visit and/or the Site Initiation Visit.

Subjects will be screened against the inclusion and exclusion criteria and, if confirmed to meet all requirements will be eligible to be consented for enrollment into the study.

Subjects who do not meet the inclusion and exclusion criteria and/or are not enrolled into the study are considered screening failures. Information on screen failure subjects will be captured in the source documentation and screening logs and will include reason(s) for screen failure.

11.3. *Informed Consent*

Prior to any study-related assessments, each subject must sign an IRB-approved informed consent document to participate in the study as described in the Declaration of Helsinki and ISO 14155:2011 (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 the IRB) will be given ample opportunity to inquire about details of the study to decide whether or not 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 11.1-1 (Data Collection Schedule).

11.4. *Study Visit Schedule*

The schedule of assessments is detailed in Table 11.1-1 (Data Collection Schedule).

11.4.1. Screening/Enrollment Visit

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

- Informed consent
- Review of inclusion/exclusion criteria

11.4.2. Pre-Operative/Baseline Visit

The Pre-operative/Baseline Visit will occur prior to the subject having surgery. The assessments below must be completed prior to study surgery. This visit may be combined

with the Screening/Enrollment Visit and occur up to 3 months prior to surgery with confirmed absence of infection.

- Urine pregnancy test (for women of child-bearing potential only)
- Medical history and physical examination: assessment of urinary tract infection (UTI) or other vaginal infection
- Pelvic examination, vaginal length measurement
- Prolapse grading (POP-Q scoring)
- Assess baseline quality of life (PFIQ-7), sexual functioning (PISQ-12), pelvic floor symptoms (PFDI-20)
- Assess baseline level of pain (TOMUS pain scale) and analgesic use
- Assess baseline health status (EQ-5D)
- Assessment of risk factors (includes menopausal status, estrogen use, age, smoking, diabetes status, body mass index, hysterectomy status, concomitant procedures, surgeon training and expertise)

11.4.3. Surgery (≤ 3 months from Baseline Visit)

All procedures are to be performed with either Uphold LITE or native tissue repair, depending on which group to which the subject has been assigned. Concomitant procedures including anterior or posterior repair or sling placement for stress urinary incontinence can occur, per physician discretion. All concomitant procedures will be documented.

- Study procedure
- Cystoscopy, if clinically necessary
- Estimated blood loss
- Documentation of concomitant procedures
- Document anesthesia type
- Document duration of procedure
- Assessment of adverse events (device, procedure, or pelvic floor related)

11.4.4. Discharge

The subject may be discharged from the hospital and/or treatment facility per standard of care and/or at the Investigator's discretion. Before the subject is discharged, the following assessments must be completed.

- Assessment of infection (wound, vaginal, bladder)
- Assessment of voiding status at discharge (i.e., subject discharged with indwelling catheter or performing self-catheterization to empty bladder or date/time of first void)

- Date and time of discharge
- Assessment of adverse events (device, procedure, or pelvic floor related)

11.4.5. Follow-Up

Subjects will be scheduled for follow-up visits as outlined in Table 11.1-1 (Data Collection Schedule). The follow-up visit schedule begins from the day the subject is discharged (e.g. leaves hospital/clinic) post-procedure and includes visit windows (counted in calendar days).Every 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 36 visit, the visit is not considered missed until the last day of the visit window.

Every effort should be made to conduct the follow-up visit at the study site location. However, if the subject cannot physically return to the site for any reason, the follow-up visit may be conducted at the subject's home with their consent and if allowed by local institutional policy and the IRB/EC. If a home visit is not possible, every effort should be made to conduct as much of the visit as possible by phone (i.e., assess adverse events, risk factors, and analgesic intake) and to send the subject questionnaires by mail for completion.

11.4.6. Month 2 Visit (±4 Weeks)

- Pelvic exam with vaginal length measurement
- Assessment of infection (vaginal, bladder)
- Prolapse grading (POP-Q Scoring)
- Assess pelvic floor symptoms (PFDI-20)
- Assessment of pain (TOMUS pain scale) and analgesic intake
- Assessment of adverse events (device, procedure, or pelvic floor related)
- Assessment of risk factors

11.4.7. Months 6, 12, 18, 24, 36 Visits (-4/+12 weeks)

- Pelvic exam with vaginal length measurement
- Assessment of infection (vaginal, bladder)
- Prolapse grading (POP-Q Scoring)
- Assessment of pain (TOMUS pain scale) and analgesic intake
- PFDI-20
- PFIQ-7
- PISQ-12

- PGI-I for Prolapse
- SSQ-8 for surgical satisfaction (Months 6, 12, 24, 36 only)
- EQ-5D for health status (Months 12, 24, 36 only)
- Assessment of adverse events (device, procedure, or pelvic floor related)
- Assessment of risk factors
- Study completion (Month 36 only)

All subjects who have completed the study surgery and discharge will proceed to be followed through the above-outlined study visits to Month 36 where the primary endpoint analysis will be achieved when the last subject completes this visit. All subjects completing the Month 36 visit will be considered to have completed the study.

11.5. *Re-Intervention/Re-Surgery*

It is the intention of this study to demonstrate an improvement in anterior/apical pelvic organ prolapse through clinical effectiveness of a transvaginal prolapse repair kit. However, it is recognized that during the course of the study, there is a possibility subjects may require a medical re-intervention for events including but not limited to failed prolapse repair, persistence of prolapse symptoms, or a mesh or procedure-related complication. A re-intervention may include surgical or non-surgical treatments and can occur for a medical complication or for prolapse recurrence. For the purpose of this study surgical interventions shall be classified as "re-surgery" and non-surgical interventions shall be classified as "re-interventions". Analyses will be performed to compare the rate of office-based interventions and of surgical interventions for medical complications and for prolapse recurrence in both treatment groups.

Non-surgical interventions (re-interventions) are defined as office-based procedures and do not involve an operating room procedure. Examples of non-surgical interventions may include but are not limited to an office visit to trim exposed mesh or suture in the vagina, a pessary, or physical therapy to treat procedural complications or persistent prolapse symptoms. Data on non-surgical interventions will be captured in the CRFs. Subjects will continue to be followed per the regular study visit schedule.

Surgical interventions (re-surgery) are surgical operations performed to correct recurring prolapse symptoms, a procedural complication, or a mesh-related complication. These surgical events typically may occur on an outpatient basis yet can require admission to a hospital. The decision to perform a re-surgery for failed prolapse repair or persistence of prolapse symptoms will be per physician and subject discretion and all re-surgery data will be captured in the Case Report Forms. All subjects defined as having a prolapse recurrence will be those who have anatomic and symptomatic failure of their prolapse surgery (prolapse beyond the hymen and symptoms of vaginal bulge).

Subjects undergoing a re-surgery will be followed to 36 months post their initial study procedure as indicated in Table 10.1-2. The subject should return to the clinic for the next regular study visit as per her original schedule. If the subject elects to not undergo re-

surgery, then the subject will be followed to the Month 36 visit unless the subject chooses to withdraw consent from the study. No subject will be followed for more than 36 months beyond their initial study procedure.

11.6. *Subject Death*

If any serious adverse event results in death (regardless of the relatedness to the study device, procedure, or pelvic floor), the event is to be documented in the source documentation, Case Report Form, and reported to the Sponsor within the timeframe noted in Table 21.7-1 (Investigator Reporting Requirements). If an autopsy is conducted, a copy of the final autopsy report should be submitted to the Sponsor or designee. The primary objective of the autopsy is to determine the cause of death, complications and other relevant findings.

12. Statistical Considerations

12.1. *Endpoints*

12.1.1. Primary Endpoint

The primary endpoint is an assessment of improvement in pelvic organ prolapse severity at 36 months as compared to Baseline.

12.1.1.1. Hypotheses

Superiority testing for effectiveness will be performed for the primary hypothesis.

Statistical testing will be performed to determine if composite endpoint of anatomic and symptomatic success rate in transvaginal mesh repair (treatment) group will be superior to traditional native tissue repair (control) group. The null hypothesis is that the success rate in treatment group is less than or equal to the success rate in control group:

$$Ho: \pi_{treatment} - \pi_{control} \leq 0$$

The alternative hypothesis is:

$$Ha: \pi_{treatment} - \pi_{control} > 0$$

where $\pi_{treatment}$ and $\pi_{control}$ is the probability of success in treatment group and control group respectively. The rejection of null hypothesis indicates the superiority of the treatment group over the control group.

Statistical testing will be performed to determine if the overall complication rate (i.e. serious adverse device effects and serious procedure-related adverse events) of treatment group is non-inferior to the control group. The null hypothesis is that the complication rate in treatment group is greater than or equal to the rate in control group plus margin:

$$Ho: \pi_{treatment} - \pi_{control} \geq \Delta$$

The alternative hypothesis is:

$$Ha: \pi_{treatment} - \pi_{control} < \Delta$$

where $\pi_{treatment}$ and $\pi_{control}$ are the overall complication rate in treatment group and control group respectively, and $\Delta > 0$ is defined as the non-inferiority margin.

12.1.1.2. Sample Size

The statistical power calculation is based on a superiority assumption with a binary primary outcome. Success, based on a composite endpoint of anatomic and symptomatic success at 36 month is assumed to be 70.0% for the native tissue arm and 85.0% for transvaginal mesh arm.[17-21] With 2-sided type I error of 0.05 and type II error of 0.1 (power 90%), 316 subjects (158 subjects per arm) are needed to detect 15% difference of transvaginal mesh to native tissue repair. In addition to a superiority assumption, statistical testing will be performed for non-inferiority using a margin of -12%.

To assess for safety, the overall complication rate (i.e. serious adverse device effects and serious procedure-related adverse events) is anticipated to be approximately 14%.[22] With type I error of 0.05 and type II error of 0.20 (power 80%), 298 subjects (149 subjects per arm) are needed to detect non-inferiority with a margin of 10%.

To assess for office-based interventions for complications, the rate is anticipated to be approximately 2%.[22] With type I error of 0.025 and type II error of 0.10 (power 90%), 330 subjects (165 subjects per arm) are needed to detect non-inferiority with a margin of 5%.

To assess for of surgical intervention for complications, the rate is anticipated to be approximately 1%.[22] With type I error of 0.025 and type II error of 0.10 (power 90%), 260 subjects (130 subjects per arm) are needed to detect non-inferiority with a margin of 4%.

Non-surgical subjects will be enrolled by the PFD Registry and analyzed in this clinical study. Non-surgical subjects will not be enrolled into this clinical study. Using the above calculations and assuming a 20% loss to follow-up rate, a total of 414 subjects (207 per study arm) will be enrolled to achieve the primary endpoint of success at 36 months.

12.1.1.3. Statistical Methods

For the primary efficacy endpoint, the comparisons of mesh repair to native tissue repair will be based on a two-sided 95% confidence interval for the treatment difference (mesh minus native tissue repair). If the entire confidence interval is above zero, superiority of mesh repair to native tissue repair will be demonstrated. The confidence interval will be calculated based on the pooling of treatment differences across propensity score strata for a binary endpoint, as described in Section 12.2.3 (Propensity Score Methodology).

If any data on the primary efficacy endpoint is missing, multiple imputation will be performed in which the missing values will be imputed five times under a logistic distribution model, using a fully conditional specification that includes the treatment arm and the assessments of the treatment success endpoint at each of 2, 6, 12, 18, and 24 months. As a sensitivity analysis, the comparison of treatments will also be performed using the following methods:

- Tipping point analysis
- Available cases only (i.e., only the subjects for whom the endpoint was assessed)

For the primary safety endpoint, the proportions will be calculated using for the numerator the number of subjects with an endpoint event and for the denominator the number of subjects in the analysis population (ITT and per protocol group). Non-inferiority will be evaluated using a two-sided 90% confidence interval for the treatment difference (mesh minus native tissue repair). If the entire confidence interval is below the margin (10%), non-inferiority will be demonstrated. The confidence interval will be calculated based on the pooling of treatment differences across propensity score strata for a binary endpoint, as described in Section 12.2.3 (Propensity Score Methodology).

12.1.2. Secondary Endpoints

Secondary endpoints will be to evaluate mesh-related complications and subject reported outcomes as safety endpoints between baseline and 36 months:

1. Incidence of mesh erosion
2. Incidence of mesh exposure
3. Incidence of de novo dyspareunia
4. Improvement in subject specific outcomes at 36 months compared to Baseline (pelvic floor symptoms (PFDI-20), QOL (PFIQ-7), sexual functioning (PISQ-12), TOMUS pain scale)
5. Assessment of subject's level of improvement, measured by the Patient Global Impression of Improvement for Prolapse (PGI-I for Prolapse)
6. Absence of re-intervention or re-surgery for recurrence or persistence of POP or mesh exposure/erosion
7. Surgical success based on the following composite outcome:
    a. Subjective success: patient denies symptoms of vaginal bulging per PFDI-20 question 3, answering "no" or "yes" but "Not at all" bothersome (<2)
    b. Anatomic success (in the operated compartment):
        - Anterior Segment: No anterior prolapse at or beyond the hymen or POP-Q point Ba<0
        - Apical Segment: The vaginal apex does not descend more than one-half into the vaginal canal (i.e. POP-Q point C < 1/2 TVL) for multi-compartment prolapse or POPQ point C < 0 for single compartment apical prolapse.
    c. No retreatment for POP: No additional surgical treatment for POP in the segment(s) of the vagina treated at the index surgery or no pessary use since index surgery
8. Device or procedure-related incidence of the following: pelvic pain, infection, vaginal shortening, atypical vaginal discharge, neuromuscular problems, vaginal scarring, de novo vaginal bleeding, fistula formation and/or de novo voiding dysfunction

Definitions for the above listed adverse events are included in Section 21.2 (Definitions and Classifications). Rates of incidence for the adverse events will be stratified by primary or recurrent prolapse in both treatment groups.

12.1.2.1. Hypotheses

Statistical testing will be performed to determine if the de novo dyspareunia rate of treatment group is non-inferior to the control group. The null hypothesis is that the de novo dyspareunia rate in treatment group is greater than or equal to the rate in control group plus margin:

$$Ho: \pi_{treatment} - \pi_{control} \geq \Delta$$

The alternative hypothesis is:

$$Ha: \pi_{treatment} - \pi_{control} < \Delta$$

where $\pi_{treatment}$ and $\pi_{control}$ are the de novo dyspareunia rate in treatment group and control group respectively, and $\Delta > 0$ is defined as the non-inferiority margin.

Statistical testing will be performed to determine if the AE incidences (pelvic pain, infection, vaginal shortening, atypical vaginal discharge, neuromuscular problems, vaginal scarring, de novo vaginal bleeding, fistula formation and/or de novo voiding dysfunction) rate of treatment group is non-inferior to the control group. The null hypothesis is that the AE incidences rate in treatment group is greater than or equal to the rate in control group plus margin:

$$Ho: \pi_{treatment} - \pi_{control} \geq \Delta$$

The alternative hypothesis is:

$$Ha: \pi_{treatment} - \pi_{control} < \Delta$$

where $\pi_{treatment}$ and $\pi_{control}$ are the AE incidence rates in treatment group and control group respectively, and $\Delta > 0$ is defined as the non-inferiority margin.

The propensity score adjusted confidence intervals described in Section 12.2.3. (Propensity Score Methodology) will be used to summarize the mean score improvement of Quality of Life (PFIQ, PFDI, PISQ, TOMUS pain scale) of the mesh (treatment) group compared to that of the native repair (control) group.

12.1.2.2. Sample Size

The rate of de novo dyspareunia is anticipated to be approximately 9%.[24] With type I error of 0.05 and type II error of 0.20 (power 80%), 326 subjects (163 subjects per arm) are needed to detect non-inferiority with a margin of 7.9%.

The rate of AE incidence (pelvic pain, infection, vaginal shortening, atypical vaginal discharge, neuromuscular problems, vaginal scarring, de novo vaginal bleeding, fistula formation and/or de novo voiding dysfunction) is anticipated to be approximately 12%.[22] With type I error of 0.05 and type II error of 0.20 (power 80%), 330 subjects (165 subjects per arm) are needed to detect non-inferiority with a margin of 8.9%.

12.1.2.3. Statistical Methods

A comparison of data for all subjects will be included per the following statistical analyses to measure for secondary endpoints:

- Rate of adverse device or procedural-related effects within 6, 12, 18, 24 and 36 months
- Overall rate of adverse device or procedural-related effects within 6, 12, 18, 24, 36 months
- Comparison of adverse device or procedural-related effects between treatment groups
- Rate and severity of mesh exposure and erosion within 6, 12, 18, 24, 36 months
- Assessment of rate of adverse device or procedural-related effects in subjects with reoperation for failed prolapse repair
- Assessment of rates of/times to reoperation
- Comparison of rate of adverse device or procedural-related events in subjects with re-surgery in both treatment groups
- Assessment and comparison between groups of analgesic intake and pain scoring at post-operative 6 weeks, 12, 18, 24, 36 months. Pain score improvement will be analyzed with a paired t-test for each group on all patients and with the propensity score adjusted confidence intervals for the pain score differences between groups. Change in analgesic intake from baseline will be analyzed by McNemar's test for each group on all patients.
- Assessment of severe blood loss during surgical procedure
- Duration of surgery from operative report
- Assessment of re-treatment interventions (i.e. surgery, office-procedure, etc.)
- Assessment of days to discharge and return to normal activity
- Assessment of risk factors, including menopausal status, estrogen use, age smoking, diagnosis of diabetes, body mass index, concomitant procedures, surgeon training and experience

A comparison of data between baseline and 36 months for all subjects will be included per the following statistical analyses to measure for secondary endpoints:

- Quality of Life Assessments (PFIQ, PFDI, PISQ, TOMUS) at 6, 12, 18, 24, 36 months as compared to baseline: paired t-test will be used to compare mean QOL score improvement from baseline to 6, 12, 18, 24 and 36 months for each group.
- Comparison of Quality of Life Assessments improvements between treatment groups
- Assessment of Quality of Life in subjects with re-surgery after re-surgery
- Assessment of subject satisfaction at 6, 12, 18, 24, 36 months (PGI-I for Prolapse)

Propensity score adjusted confidence intervals described in Section 12.2.3 (Propensity Score Methodology) will be used to evaluate continuous variables including QOL score improvements between two groups.

12.2. *General Statistical Methods*

12.2.1. Analysis Sets

The Intent-to-Treat (ITT) subject population includes all subjects who provide written informed consent to be enrolled into the study and have a surgery initiated (i.e. incision in vagina) regardless of their adherence with the entry criteria, regardless of treatment and withdrawal/protocol deviations.

The treated population includes all subjects who undergo a study surgical procedure. The subject is defined to have successfully completed the surgical procedure (i.e. prolapse repair successful) and discharged.

The Per Protocol (PP) population includes all subjects in the ITT Population who received the assigned treatment and had no major protocol deviations.

All primary and secondary endpoints will be analyzed on the ITT Population. The primary safety and non-safety endpoints will also be analyzed on the per-protocol population.

12.2.2. Control of Systematic Error/Bias

To reduce selection bias in this non-randomized study, each study center will be permitted to enroll subjects in only one of the treatment groups. Physicians will be selected based on device and clinical research experience and the decision as to which device to implant in subjects prior to study initiation at each center. Some study centers may be permitted per Boston Scientific to enroll subjects in both treatment and control groups. All decisions will be documented prior to subject enrollment. All subjects meeting the eligibility criteria at the study center will be screened and enrolled as applicable.

Propensity score stratification will be utilized to address the potential imbalance in risk factors between groups, described in Section 12.2.3 (Propensity Score Methodology). This analysis will be performed blind to all clinical outcome data and prior to performing any analysis of endpoints.

12.2.3. Propensity Score Methodology

Analyses comparing the treatment groups will be adjusted for the propensity score. The propensity score is the probability that the subject enrolled in the mesh arm rather than the native tissue (control) arm, given the characteristics of the subject and center. The characteristics identified are as follows: age, race, body mass index, smoking, diabetes, post-menopausal, prior prolapse repair, prior hysterectomy, estrogen use, POP-Q C measurement, POP-Q Ba measurement, POP-Q Bp measurement, concomitant repair for stress urinary incontinence, and surgeon case volume. Logistic regression of both treatment arms (i.e., (transvaginal mesh repair vs. native tissue repair) on these characteristics will be used to estimate the propensity score. The subjects will then be partitioned into five strata

corresponding to quintiles of the propensity score. If the balance between treatment arms within the strata is deemed adequate, the treatment difference adjusted for propensity score stratum will be estimated as described in the following.

The propensity adjusted treatment difference will be based on averaging the treatment differences of the propensity score strata. For a binary outcome, the within-stratum treatment difference is $D_j = p_{T_j} - p_{C_j}$, where p_{T_j} and p_{C_j} is the proportion of treatment and control subjects, respectively, in stratum *j*. The variance of D_j is approximately

$$V_j = \frac{p_{T_j}(1 - p_{T_j})}{n_{T_j}} + \frac{p_{C_j}(1 - p_{C_j})}{n_{C_j}}$$

Denoting the number of subjects in stratum *j* by $n_j = n_{T_j} + n_{C_j}$, the treatment difference will be estimated by the (weighted) mean of the within-stratum treatment differences

$$D = \sum_j \frac{n_j}{n} D_j$$

where $n = \sum_j n_j$ is the total sample size across all strata and study arms. *D* is approximately normally distributed with variance

$$V = \sum_j \left(\frac{n_j}{n}\right)^2 V_j$$

from which a confidence interval for the true treatment difference will be constructed. For each continuous outcome, the confidence interval will be constructed similarly, with *D* and *V* obtained as above with the treatment difference within each stratum replaced by $D_j = \bar{X}_{T_j} - \bar{X}_{C_j}$, where $\bar{X}_{T_j}$ and $\bar{X}_{C_j}$, respectively, is the mean of the treatment and control subjects, and

$$V_j = \frac{S^2_{T_j}}{n_{T_j}} + \frac{S^2_{C_j}}{n_{C_j}}$$

where $S^2_{T_j}$ and $S^2_{C_j}$ are the variances of the treatment and control subjects in stratum *j*.

12.3. *Data Analyses*

Presentation of summary statistics for continuous variables will include N, mean, median, standard deviation, minimum, and maximum values for non-missing data. For categorical variables, the number and percentage under each category for non-missing data will be presented.

Additionally, subjects meeting this study's eligibility criteria under the PFD Registry may be included in the analyses plan. The intention is to utilize a shared control arm from the PFD Registry.

12.3.1. Rate of Office-Based Intervention for Recurrence

Statistical testing will be performed to determine if the rate of office-based intervention for recurrence in the treatment group will be superior to the control group. The null hypothesis is that the rate of office-based intervention for recurrence in treatment group is greater than or equal to the rate in control group:

$$Ho: \pi_{treatment} - \pi_{control} \geq 0$$

The alternative hypothesis is:

$$Ha: \pi_{treatment} - \pi_{control} < 0$$

where $\pi_{treatment}$ and $\pi_{control}$ are the office-based intervention rates for recurrence in treatment group and control group respectively. The rejection of null hypothesis indicates the superiority of the treatment group over the control group.

12.3.2. Rate of Surgical Intervention for Recurrence

Statistical testing will be performed to determine if the rate of surgical intervention for recurrence in treatment group will be superior to the control group. The null hypothesis is that the rate of surgical intervention for recurrence in treatment group is greater than or equal to the rate in control group:

$$Ho: \pi_{treatment} - \pi_{control} \geq 0$$

The alternative hypothesis is:

$$Ha: \pi_{treatment} - \pi_{control} < 0$$

where $\pi_{treatment}$ and $\pi_{control}$ are the surgical intervention rates for recurrence in treatment group and control group respectively. The rejection of null hypothesis indicates the superiority of the treatment group over the control group.

The propensity score adjusted analysis described in Section 12.2.3 (Propensity Score Methodology) will be used for testing the null hypothesis and computing the confidence intervals for rate of office-based intervention for recurrence and surgical intervention for recurrence between treatment group and control group.

12.3.3. Rate of Office-Based Intervention for Complications

Statistical testing will be performed to determine if the rate of office-based intervention for complications in the mesh (treatment) group is non-inferior to the native tissue repair (control) group. The null hypothesis is that the rate of office-based intervention for complications in treatment group is greater than or equal to the rate in control group plus margin:

$$Ho: \pi_{treatment} - \pi_{control} \geq \Delta$$

The alternative hypothesis is:

$$Ha: \pi_{treatment} - \pi_{control} < \Delta$$

where $\pi_{treatment}$ and $\pi_{control}$ are the office-based intervention rates for complication in treatment group and control group respectively, and Δ >0 is defined as the non-inferiority margin.

The rate of office-based intervention for complication is anticipated to be approximately 2%. With type I error of 0.025 and type II error of 0.10 (power 90%), 330 subjects (165 subjects per arm) are needed to detect non-inferiority with a margin of 5%.

12.3.4. Rate of Surgical Intervention for Complications

Statistical testing will be performed to determine if the rate of surgical intervention for complications of the mesh (treatment) group is non-inferior to the native tissue repair (control) group. The null hypothesis is that the rate of surgical intervention for complications in treatment group is greater than or equal to the rate in control group plus margin:

$$Ho: \pi_{treatment} - \pi_{control} \geq \Delta$$

The alternative hypothesis is:

$$Ha: \pi_{treatment} - \pi_{control} < \Delta$$

where $\pi_{treatment}$ and $\pi_{control}$ are the probabilities of having surgical intervention for complication in treatment group and control group respectively, and Δ >0 is defined as the non-inferiority margin.

The rate of surgical intervention complication is anticipated to be approximately 1%. With type I error of 0.025 and type II error of 0.10 (power 90%), 260 subjects (130 subjects per arm) are needed to detect non-inferiority with a margin of 4%.

The propensity score adjusted analysis described in Section 12.2.3 (Propensity Score Methodology) will be used for testing the null hypothesis and computing the confidence intervals for rate office-based intervention for complication and surgical intervention for complication between treatment group and control group.

For each group, logistic regression will be performed, to include office-based intervention for recurrence as a covariate for analyzing the primary endpoint (success rate of improvement in pelvic organ prolapse at 36 months) data.

For each group, Cox regression will be performed, to include surgical intervention for recurrent prolapse as a covariate for analyzing adverse events (pelvic pain, infection, vaginal shortening, vaginal scarring, de novo vaginal bleeding, fistula formation and/or de novo voiding dysfunction) data.

Descriptive statistics for the baseline characteristics and QOL outcome for the non-surgery (i.e. pessary) group will be summarized from the AUGS PFD Registry Level 1/2 database.

12.3.5. Sub-Analysis for Sling Repair and Interventions for Recurrence

12.3.5.1. Subjects with only POP repair and those with sling and prolapse repair

A two sample t-test will be performed in pain score change from baseline to each follow-up visit within mesh or native tissue repair group, to compare groups with and without SUI

surgery. Using this method of analysis will make it less difficult to assess causality for adverse events, including pain.

12.3.5.2. Subjects with office-based intervention for recurrence

Adverse procedural/device event rates and QOL information will be collected for 36 months, regardless of whether or not the subject has office-based intervention for recurrence.

Event rate for each of device-related or procedure-related adverse events of specified AE type (mesh erosion, mesh exposure, dyspareunia) during the period after the intervention will be summarized by treatment group. Treatment groups will be compared using Cox regression for the event-free survival time (starting at the time of first office based intervention) with treatment arm.

For each QOL instrument, a comparison using a t-test will be performed between native tissue repair and mesh group on the basis of QOL score at the first scheduled follow-up after office-based intervention for recurrence.

A two sample t-test will be used to compare groups with office-based intervention for recurrence and without intervention within each treatment group. QOL score change will be reported from the last follow-up visit before office-based intervention for recurrence, to the next scheduled follow-up visit after office-based intervention for recurrence within each treatment group. For those subjects without recurrence, we will use baseline as the "before" time point in analysis, and the QOL data at 6 month follow-up visit as the "after" time point.

Similarly, event rate for each adverse device and procedure-related event type specified (mesh erosion, mesh exposure, dyspareunia) will be compared between subjects with office-based intervention for recurrence and those without. This will be done using a Cox regression of time to the first onset of each adverse event after the starting time to compare groups with office-based intervention for recurrence and within each treatment group. The starting time will be baseline for those subjects without intervention, and time of office-based intervention for recurrence for those with intervention.

12.3.5.3. Subjects with surgical intervention for recurrence

The above mentioned analyses for the subgroup with office based intervention for recurrence will be repeated for subjects with surgical intervention for recurrence.

12.3.5.4. Subjects with surgical intervention for recurrence or complications

Each of device-related or procedure-related adverse events during the period after the re-surgery will be summarized by the vaginal compartment(s) (i.e. apical only, anterior only, apical and anterior) treated in the index procedure within each treatment group.

12.3.6. Additional Data Analyses

- Assessment of EQ-5D score for health status at 12, 24 and 36 month as compared to baseline
- Assessment of SSQ-8 score for surgical satisfaction at 6, 12, 24 and 36 month

Propensity score adjusted confidence intervals described in Section 12.2.3 (Propensity Score Methodology) will be used to summarize EQ-5D and SSQ-8 score improvements between two groups.

12.3.7. Sub-Analysis for Interventions for Complications

The above sub-analyses in Section 12.3.5 will be repeated for re-surgery for complications or recurrence.

12.3.8. Interim Analysis

An interim analysis will be performed at 12 months from the last subject enrolled in the study; all subjects will be followed to 36 months for the primary endpoint and final analysis. This analysis will consist of the primary and some or all of the secondary endpoints and demographics if deemed necessary.

Descriptive statistics by treatment arm along with 95% confidence interval for the treatment difference will be reported after adjusting for propensity scores. The descriptive statistics includes mean, standard deviation, n, minimum, and maximum for continuous variables and frequency statistics for discrete variables[1].

12.3.8.1. Hypotheses[2]

The interim analysis hypothesis is that transvaginal mesh repair (treatment) is non-inferior to traditional native tissue repair (control) in both effectiveness and safety at 12 months.

Statistical testing will be performed to evaluate whether transvaginal mesh repair (treatment) is non-inferior to native tissue repair with respect to the composite treatment success endpoint. The null hypothesis is that the success rate for Uphold LITE is inferior to that of the control at a non-inferiority margin of 12%:

$$Ho: \pi_{treatment} - \pi_{control} \leq -12\%$$

where $\pi_{treatment}$ and $\pi_{control}$ is the success rate in the treatment and control group, respectively. The alternative hypothesis is:

$$Ha: \pi_{treatment} - \pi_{control} > -12\%$$

The rejection of null hypothesis indicates the non-inferiority of transvaginal mesh repair.

If non-inferiority is demonstrated, then the superiority of transvaginal mesh repair at 12 months will be evaluated, for which the hypotheses are:

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[1] To support United States Premarket Approval Activities, as agreed to on the Presubmission call held on May 24, 2017 (Q170382), Boston Scientific will submit descriptive statistics for the submission of the PMA, which per reclassification document number 2015-33165, is required to be accepted and filed on or before July 5, 2018.

[2] To support the continued review of the Premarket Approval Application for the United States, Boston Scientific will submit hypothesis testing as an Amendment to the initial PMA following acceptance and filing.

$Ho: \pi_{treatment} \leq \pi_{control}$

$Ha: \pi_{treatment} > \pi_{control}$

The rejection of null hypothesis indicates the superiority of transvaginal mesh repair.

Statistical testing will be performed to determine if the serious complication rate (i.e. serious adverse device effects and serious procedure-related adverse events) of the treatment group is non-inferior to the control group at 12 months. The null hypothesis is that the serious complication rate in treatment group is greater than or equal to the rate in control group plus margin of 10%:

$Ho: \pi_{treatment} - \pi_{control} \geq 10\%$

where $\pi_{treatment}$ and $\pi_{control}$ is the serious complication rate in the treatment group and control group, respectively. The alternative hypothesis is:

$Ha: \pi_{treatment} - \pi_{control} < 10\%$

12.3.8.2. Statistical Methods

The comparisons of mesh repair to native tissue repair will be based on a two-sided 90% confidence interval for the treatment difference. The confidence interval will be calculated based on the pooling of treatment differences across propensity score strata for a binary endpoint, as described in Section 12.2.3 (Propensity Score Methodology).

Missing 12 month data for the composite efficacy endpoint will be handled by multiple imputation under a logistic regression model using a fully conditional specification. The imputation model will include treatment group and primary efficacy outcome at 2 and 6 month. A total of 5 imputed data sets will be generated.

The following methods will also be used as sensitivity analyses:

- Observed data only
- Tipping point analysis

12.3.9. Justification of Pooling

The analyses will be presented using pooled data across institutions. For each group, an analysis of the poolability will be made using logistic regression for binary outcomes, or analysis of variance for continuous outcomes, to assess differences between study institutions and to justify pooling data across institutions. Centers with less than 5 ITT patients may be combined.

12.3.10. Multivariable Analyses

For each treatment group, univariate and multivariate analyses will be performed to assess possible predictors of the improvement in pelvic organ prolapse at 36 month, mesh-related complications and subject reported outcomes. Possible predictors may include, but not limited to, demographic/baseline data and risk factors data. Factors from the univariate model with $p \leq 0.20$ will also be put into multivariate model using a stepwise procedure in a

logistic regression model. The significance thresholds for entry and exit into the model will be set to $p<0.10$. Analysis of Covariance (ANCOVA) will be performed for subject reported outcome with appropriate predictors.

13. Data Management

13.1. *Data Collection, Processing, and Review*

Good Clinical Practice Guidelines require that investigators maintain information (i.e., Source Data) in the subject's medical records, laboratory reports, clinic charts, etc. (i.e., Source Documents) that corresponds to data recorded on the Case Report Forms. In order to comply with these requirements, the following information should be maintained as source documentation, including but not limited to:

- Medical history/physical condition of the subject before enrollment
- Protocol entry criteria
- Dated and signed notes for specific results of procedures and exams
- Laboratory reports
- Information related to adverse device effects
- Surgical notes, including subject condition and re-surgery if applicable
- Quality of life assessments and TOMUS pain scales
- Discharge Summaries/Procedure reports
- Autopsy reports

Subject data will be recorded on Case Report Forms which will be provided by Boston Scientific or designated vendor. The Source Data reported on the Case Report Forms shall be derived from source documentation and shall be consistent with these source documents. Any discrepancies shall be explained and documented. Any change or correction made to the clinical data will be dated, initialed, and explained, if necessary, and shall not obscure the original entry. An audit trail shall be maintained which will be made available for review by Boston Scientific or its representative. Any queries to the data will be addressed by the study center staff in a timely manner.

13.2. *Data Retention*

The investigator will maintain, at the investigative site, in original format all essential study documents and source documentation that support the data collected on study subjects in compliance with ISO 14155:2011 (Clinical investigation of medical devices for human subjects - Good clinical practice). Documents must be retained for at least 2 years after the last approval of a marketing application or until at least 2 years have elapsed since the formal discontinuation of the clinical investigation of the product. These documents will be retained for a longer period of time by agreement with Boston Scientific or in compliance with other local regulations. It is Boston Scientific's responsibility to inform the investigator when

these documents no longer need to be maintained. The investigator will take measures to ensure that these essential documents are not accidentally damaged or destroyed. If for any reason the investigator 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.

14. Amendments

If a protocol revision is necessary for reasons including but not limited to, the rights, safety or welfare of the subject, or scientific integrity of the data, an amendment is required. Appropriate approvals (e.g., IRB/EC/FDA/CA) of the revised protocol must be obtained prior to implementation.

15. Deviations

An Investigator must not make any changes or deviate from this protocol, except to protect the life and physical well-being of a subject in an emergency. An investigator shall notify Boston Scientific and the reviewing IRB/EC of any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency, and those deviations which affect the scientific integrity of the clinical investigation. Such notice shall be given as soon as possible, but no later than 5 working days after the emergency occurred, or per prevailing local requirements, if sooner than 5 working days.

All deviations from the investigational plan, with the reason for the deviation and the date of occurrence, must be documented and reported to Boston Scientific. Study centers may also be required to report deviations to their IRB/EC, per local guidelines and government regulations.

Deviations will be reviewed and evaluated on an ongoing basis and, as necessary, appropriate corrective and preventive actions (including notification, center re-training, or discontinuation) will be put into place by Boston Scientific.

16. Device/Equipment Accountability

This is a post-market study and therefore no investigational devices are being used. All commercial and institutional policies regarding but not limited to device use, purchase and/or storage will be followed.

17. Compliance

17.1. *Statement of Compliance*

This study will be conducted in accordance with ISO 14155:2011 (Clinical investigation of medical devices for human subjects - Good clinical practice), ethical principles that have their origins in the Declaration of Helsinki, and pertinent individual country laws and regulations. The study shall not begin until the required approval/favorable opinion from the

IRB/EC and/or regulatory authority has been obtained, as appropriate. Any additional requirements imposed by the IRB/EC or regulatory authority shall be followed, if appropriate.

17.2. *Investigator Responsibilities*

The Principal Investigator of an investigational center is responsible for ensuring that the study is conducted in accordance with the Clinical Study Agreement, the investigational plan/protocol, ISO 14155:2011 (Clinical investigation of medical devices for human subjects - Good clinical practice), ethical principles that have their origins in the Declaration of Helsinki, any conditions of approval imposed by the reviewing IRB/EC, and prevailing local and/or country laws and/or regulations, whichever affords the greater protection to the subject.

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

- Prior to beginning the study, sign the Investigator Agreement and Protocol Signature page documenting his/her agreement to conduct the study in accordance with the protocol.
- Provide his/her qualifications and experience to assume responsibility for the proper conduct of the study and that of key members of the center team through up-to-date curriculum vitae or other relevant documentation and disclose potential conflicts of interest, including financial, that may interfere with the conduct of the clinical study or interpretation of results.
- Make no changes in or deviate from this protocol, except to protect the life and physical well-being of a subject in an emergency; document and explain any deviation from the approved protocol that occurred during the course of the clinical investigation.
- Create and maintain source documents throughout the clinical study and ensure their availability with direct access during monitoring visits or audits; ensure that all clinical-investigation-related records are retained per requirements.
- Ensure the accuracy, completeness, legibility, and timeliness of the data reported to Boston Scientific in the CRFs and in all required reports.
- Record, report, and assess (seriousness and relationship to the device/procedure) every adverse event and observed device deficiency.
- Report to Boston Scientific, per the protocol requirements, all SAEs and device deficiencies that could have led to a SADE.
- Report to the IRB/EC and regulatory authorities any SAEs and device deficiencies that could have led to a SADE, if required by the national regulations or this protocol or by the IRB/EC, and supply Boston Scientific with any additional requested information related to the safety reporting of a particular event.
- Allow Boston Scientific or its designee to perform monitoring and auditing activities, and be accessible to the monitor and respond to questions during monitoring visits.

- Allow and support regulatory authorities and the IRB/EC when performing auditing activities.
- Ensure that informed consent is obtained in accordance with this protocol and local IRB/EC requirements.
- Provide adequate medical care to a subject during and after a subject's participation in a clinical study in the case of adverse events, as described in the Informed Consent Form (ICF).
- Inform the subject of the nature and possible cause of any adverse events experienced.
- Inform the subject of any new significant findings occurring during the clinical investigation, including the need for additional medical care that may be required.
- Ensure that clinical medical records are clearly marked to indicate that the subject is enrolled in this clinical study.
- Ensure that, if appropriate, subjects enrolled in the clinical investigation are provided with some means of showing their participation in the clinical investigation, together with identification and compliance information for concomitant treatment measures (contact address and telephone numbers shall be provided).
- Inform, with the subject's approval or when required by national regulations, the subject's personal physician about the subject's participation in the clinical investigation.
- Make all reasonable efforts to ascertain the reason(s) for a subject's premature withdrawal from clinical investigation while fully respecting the subject's rights.
- Ensure that an adequate investigation site team and facilities exist and are maintained and documented during the clinical investigation.
- Ensure that maintenance and calibration of the equipment relevant for the assessment of the clinical investigation is appropriately performed and documented, where applicable.

17.2.1. Delegation of Responsibility

When specific tasks are delegated by an investigator, included but not limited to conducting the informed consent process, the investigator is responsible for providing appropriate training and adequate supervision of those to whom tasks are delegated. The investigator is accountable for regulatory violations resulting from failure to adequately supervise the conduct of the clinical study.

17.3. *Institutional Review Board/ Ethics Committee*

Prior to gaining Approval-to-Enroll status, the investigational center will provide to the sponsor documentation verifying that their IRB/EC is registered or that registration has been

submitted to the appropriate agency, as applicable according to national/regulatory requirements.

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

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

17.4. *Sponsor Responsibilities*

All information and data sent to Boston Scientific concerning subjects or their participation in this study will be considered confidential by Boston Scientific. Only authorized Boston Scientific personnel or a Boston Scientific representative will have access to these confidential records. 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 Boston Scientific for the purposes of this study, publication, and to support future research and/or other business purposes. All data used in the analysis and reporting of this study will be without identifiable reference to specific subject name.

Boston Scientific will keep subjects' health information confidential in accordance with all applicable laws and regulations. Boston Scientific may use subjects' health information to conduct this research, as well as for additional purposes, such as overseeing and improving the performance of its device, new medical research and proposals for developing new medical products or procedures, and other business purposes. Information received during the study will not be used to market to subjects; subject names will not be placed on any mailing lists or sold to anyone for marketing purposes.

17.5. *Insurance*

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

18. Monitoring

Monitoring will be performed during the study to assess continued compliance with the protocol and applicable regulations. In addition, the 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 investigator continues to have sufficient staff and facilities to conduct the study safely and effectively. The investigator/institution guarantees direct access to original source documents by Boston Scientific personnel, their designees, and appropriate regulatory authorities.

The study may also be subject to a quality assurance audit by Boston Scientific or its designees, as well as inspection by appropriate regulatory authorities. It is important that the

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

19. Potential Risks and Benefits

19.1. *General*

The risks and benefits of performing a transvaginal procedure to treat pelvic organ prolapse in the following subjects should be carefully considered due to additional risks associated with their conditions:

- Women planning future pregnancies
- Overweight women (weight parameters to be determined by the physician)
- Subjects with blood coagulation disorder
- Subjects with a compromised immune system or any other condition that would compromise healing
- Subjects with renal insufficiency or upper urinary tract obstruction

19.2. *Anticipated Adverse Events*

The following anticipated adverse events (AE) have been reported due to transvaginal prolapse kit placement, but are not limited to:

- Abscess
- Adhesion formation
- Allergic reaction, hypersensitivity or other immune reaction
- Bleeding
- Bruising/Hematoma
- Constipation/defecatory dysfunction
- Dehiscence of vaginal incision (Wound Dehiscence/Surgical Site Wound Irritation)
- Dehiscence and/or Necrosis
- Detrusor Instability
- De Novo Dyspareunia
- Edema/Erythema
- Exposure
- Erosion
- Extrusion
- Fistula

- Granulation tissue formation
- Hemorrhage
- Incontinence (Urinary)
- Infection/Sepsis potentiation
- Inflammation
- Irritation/Discomfort
- Migration of device from desired location
- Neuromuscular Events (including groin and leg pain)
- Organ perforation
- Overactive bladder
- Pain
- Recurrence
- Re-surgery
- Retained foreign body (foreign body reaction)
- Ureteric Injury
- Urinary Retention
- Urinary Tract Obstruction (Ureter Obstruction)
- Vessel/Nerve Injury/Perforation
- Vaginal Discharge (e.g. atypical)
- Vaginal shortening or stenosis, mesh and/or tissue contracture
- Sexual Dysfunction

19.2.1. Mesh Exposure and Erosion Event Classification

Assessment of mesh exposure and/or erosion will occur at all follow-up visits with pelvic examinations performed at 2, 6, 12, 18, 24, and 36 Months post-procedure. Identification of mesh exposure and/or erosion will occur by the medical staff member performing the pelvic exam and will be documented as an adverse event on the Case Report Forms.

19.3. *Risks Associated with Participation in the Clinical Study*

There are no additional risks with participation in this clinical study outside of the anticipated risks (see Section 19.2) for pelvic organ prolapse as conducted according to standard of care procedures.

19.4. *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 Boston Scientific with all pertinent information required by this protocol.

19.5. *Anticipated Benefits*

Theoretical benefits of transvaginally placed mesh for the treatment of pelvic organ prolapse may include reduction in POP symptoms.

19.6. *Risk to Benefit Rationale*

The use of transvaginally placed mesh has been shown to reduce recurrent prolapse following pelvic floor repair. There have been many randomized controlled trials comparing outcomes for pelvic floor repair procedures using mesh grafts to non-mesh repair. Of those studies, a reduced incidence of recurrent prolapse in the mesh-procedure group has been reported as compared to non-mesh groups.

However, the risk of mesh-related complications has been reported and can be linked to risk factors including body mass index (BMI), concomitant hysterectomy, and physician experience. There is no new literature to indicate there would be an unsatisfactory risk benefit profile for the use of transvaginally placed mesh for the treatment of POP.

20. Informed Consent

Subject participation in this clinical study is voluntary. Informed Consent is required from all subjects or their legally authorized representative. The Investigator is responsible for ensuring that Informed Consent is obtained prior to performing any 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 14155:2011 (Clinical investigation of medical devices for human subjects - Good clinical practice), any applicable national regulations, and local Ethics Committee and/or Regulatory authority body, as applicable. The ICF must be accepted by Boston Scientific or its designee (e.g., CRO), and approved by the center's IRB/EC, or central IRB, if applicable.

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

The process of obtaining Informed Consent shall:

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

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

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

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

21. Safety Reporting

21.1. *Reportable Events by Investigational Site to Boston Scientific*

Any device-related, procedure-related, or pelvic floor-related adverse event experienced by the study subject after informed consent and once considered enrolled in the study, whether during or subsequent to the procedure, must be recorded in the CRF.

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

Definitions of the adverse events included in the secondary endpoint will match the definitions created for the AUGS PFD Registry. All event definitions will be provided to the sites as part of a dictionary in the Manual of Operations.

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.

Underlying diseases are not reported as AEs unless there is an increase in severity or frequency during the course of the investigation. Death should not be recorded as an AE, but should only be reflected as an outcome of a specific SAE (see Section 21.2 for AE definitions).

21.2. *Definitions and Classification*

Adverse event definitions are provided in Table 21.2-1. Administrative edits were made to combine definitions from ISO 14155:2011 (Clinical investigation of medical devices for human subjects - Good clinical practice) and MEDDEV 2.7/3 12/2010.

Table 21.2-1: Adverse Event Definitions

Term	Definition
Adverse Event (AE) *Ref: ISO 14155:2011* *Ref: MEDDEV 2.7/3 12/2010*	Any untoward medical occurrence, unintended disease or injury, or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons, whether or not related to the investigational medical device. NOTE 1: This includes events related to the investigational medical device or comparator. NOTE 2: This definition includes events related to the procedures involved (any procedure in the clinical investigation plan). NOTE 3: For users or other persons, this definition is restricted to events related to the investigational medical device.

Table 21.2-1: Adverse Event Definitions

Term	Definition
Serious Adverse Event (SAE) *Ref: ISO 14155:2011* *Ref: MEDDEV 2.7/3 12/2010*	Adverse event that: • Led to death, • Led to serious deterioration in the health of the subject, that either resulted in: – a life-threatening illness or injury, or – a permanent impairment of a body structure or a body function, or – in-patient or prolonged hospitalization of existing hospitalization, or – medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function • Led to fetal distress, fetal death, or a congenital abnormality or birth defect. NOTE**:** Planned hospitalization for a pre-existing condition, or a procedure required by the clinical investigational plan, without serious deterioration in health, is not considered a serious adverse event.
Device Deficiency *Ref: ISO 14155:2011* *Ref: MEDDEV 2.7/3 12/2010*	A device deficiency is any inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. NOTE**:** Device deficiencies include malfunctions, misuse or use errors, and inadequate labeling.

Abbreviations: EC=Ethics Committee; IRB=Institutional Review Board

21.3. *Relationship to Study Device (Mesh Cohort Only)*

The investigator must assess the relationship of the AE to the study device as related or unrelated. See criteria in Table 21.3-1:

Table 21.3-1: Criteria for Assessing Relationship of Study Device to Adverse Event

Classification	Description
Unrelated (Not Related)	• The adverse event is determined to be due to a concurrent illness or effect of another device/drug and is not related to the investigational product.
Related (Possible, Probable or Definite)	• The adverse event is determined to be potentially related to the investigational product, and an alternative etiology is equally or less likely compared to the potential relationship to investigational product, or • There is a strong relationship to investigational product, or recurs on re-challenge, and another etiology is unlikely, or • There is no other reasonable medical explanation for the event.

21.4. *Relationship to Study Delivery Device (Mesh Cohort Only)*

The investigator must assess the relationship of the AE to the study delivery device as related or unrelated. See criteria in Table 21.4-1:

Table 21.4-1: Criteria for Assessing Relationship of Study Delivery Device to Adverse Event

Classification	Description
Unrelated (Not Related)	• The adverse event is determined to be due to a concurrent illness or effect of another device/drug and is not related to the investigational product.
Related (Possible, Probable or Definite)	• The adverse event is determined to be potentially related to the investigational product, and an alternative etiology is equally or less likely compared to the potential relationship to investigational product, or • There is a strong relationship to investigational product, or recurs on re-challenge, and another etiology is unlikely, or • There is no other reasonable medical explanation for the event.

21.5. *Relationship to Study Procedure*

The investigator must assess the relationship of the AE to the study procedure as unrelated, possibly related, probably related, or definitely related. See criteria in Table 21.5-1.

Table 21.5-1: Criteria for Assessing Relationship to Study Procedure

Classification	Description
Unrelated (Not Related)	• No evidence that the timing of the adverse event has a relationship to the study procedure performed.
Possibly Related	• The adverse event has a timely relationship to the study procedure performed. However, a potential alternative etiology may be responsible for the adverse event.
Probably Related	• The adverse event has a timely relationship to the study procedure performed and the causative relationship can be clearly established. No potential alternative etiology is apparent.
Definitely Related	• The adverse event has a timely relationship to the study procedure performed and the causative relationship can be clearly established. No potential alternative etiology is apparent. • There is no other reasonable medical explanation for the event.

21.6. *Relationship to Pelvic Floor*

The investigator must assess the relationship of the AE to the pelvic floor as unrelated or related. See criteria in Table 21.6-1.

Table 21.6-1: Criteria for Assessing Relationship to Pelvic Floor

Classification	Description
Unrelated	• No evidence that the adverse event has a relationship to the pelvic floor and supporting tissues.
Related	• The adverse event is determined to be potentially related to the pelvic floor and supporting tissues including but not limited to lacerations, avulsions, tears, pelvic organ prolapse (cystocele, rectocele, enterocele, uterine, rectal), urinary incontinence (stress, urge), urinary voiding dysfunction (retention, obstructed voiding, incomplete emptying), fecal incontinence (urgency, irritable bowel syndrome), defecatory dysfunction (constipation, obstipation, stool trapping, IBS), pain (dyspareunia, pelvic, perineal), and infection (bladder, urinary tract, vaginal). • There is a strong relationship to the pelvic floor and supporting tissues, and another etiology is unlikely, or • There is no other reasonable medical explanation for the event.

21.7. *Investigator Reporting Requirements*

The communication requirements for reporting to BSC are as shown in Table 21.7-1.

Table 21.7-1: Investigator Reporting Requirements

Event Classification	Communication Method	Communication Timeline
Serious Adverse Events related to the study device, procedure and/or pelvic floor or events resulting in death regardless of relationship to the device, procedure or pelvic floor.	Complete AE CRF page with all available new and updated information.	• Within 2 business days of first becoming aware of the event or as per local/regional regulations. • Reporting required through the end of the study.
	If requested by Sponsor, provide all relevant source documentation (unidentified) for the reported event.	• When documentation is available

Table 21.7-1: Investigator Reporting Requirements

Event Classification	Communication Method	Communication Timeline
Adverse Events related to the study device and/or procedure. Events assessed for reporting shall include but are not limited to: • Pelvic pain • Infection (by type) • De novo dyspareunia • Vaginal shortening • Vaginal scarring • De novo vaginal bleeding • Atypical vaginal discharge • Fistula formation • De novo voiding dysfunction (including de novo incontinence) • Neuromuscular problems (including groin and leg pain) • Revision/re-surgery • Recurrent prolapse • Mesh exposure • Mesh erosion	Complete the AE CRF page, which contains such information as onset date of the AE, treatment provided if any, resolution, assessment of seriousness, and relationship to study device.	• In a timely manner (e.g., recommended within 10 business days of first becoming aware of the event). • Reporting required through end of subject participation.
Adverse Events related to the pelvic floor. Events assessed for reporting shall include but are not limited to: • Urinary tract infections • Pelvic organ prolapse • Urinary incontinence • Fecal incontinence • Pelvic Pain	Complete the AE CRF page, which contains such information as onset date of the AE, treatment provided if any, resolution, assessment of seriousness, and relationship to study device.	• In a timely manner (e.g., recommended within 10 business days of first becoming aware of the event). • Reporting required through end of subject participation.
Device Deficiencies (including but not limited to failures, malfunctions, and product nonconformities) NOTE: Any Investigational Device Deficiency that might have led to a serious adverse event if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate is considered a reportable event.	Complete CRF with all available new and updated information.	• Within 1 business day of first becoming aware of the event. • Reporting required through the end of the study.

Abbreviations: AE=adverse event; CRF=case report form

21.8. *Boston Scientific Device Deficiencies*

All device deficiencies (including but not limited to complications, malfunctions, use errors, product nonconformities, and labeling errors) will be documented and reported to Boston Scientific. If possible, the device(s) should be returned to BSC for analysis. Instructions for returning the device(s) will be provided. If it is not possible to return the device, the investigator should document why the device was not returned and the final disposition of the device. Device failures and malfunctions should also be documented in the subject's medical record.

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

Any Device Deficiency that might have led to a serious adverse event if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate is considered a reportable event.

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

Boston Scientific is responsible for reporting adverse event information to all participating investigators and regulatory authorities, as applicable.

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

22. Committees

22.1. *Safety Monitoring Process*

To promote early detection of safety issues, an internal Safety Monitoring Team will provide evaluations of safety events. Success of this program requires dynamic collection of unmonitored data as soon as the event is reported. This is expedited through Boston Scientific's Safety Office, which is responsible for coordinating the collection of information for the subject dossier from the centers. During regularly scheduled monitoring visits, clinical research monitors will support the dynamic reporting process through their review of source document information.

23. Suspension or Termination

23.1. *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 administrative reasons and reasons related to protection of subjects. Investigators, associated IRBs/ECs, and regulatory authorities, as applicable, will be notified in writing in the event of study termination.

23.1.1. Criteria for Premature Termination of the Study

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

- The occurrence of safety events that present a significant or unreasonable risk to subjects enrolled in the study.
- 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 of the device.

23.2. *Termination of Study Participation by the Investigator or Withdrawal of IRB/ EC Approval*

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

23.3. *Requirements for Documentation and Subject Follow-up*

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

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

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

23.4. *Criteria for Suspending/Terminating a Study Center*

Boston Scientific reserves the right to stop the inclusion of subjects at a study center at any time after the study initiation visit if no subjects have been enrolled for a period beyond 12 months after center initiation, or if the center has multiple or severe protocol violations/noncompliance without justification and/or fails to follow remedial actions.

In the event of termination of investigator participation, all testing equipment, as applicable, will be returned to Boston Scientific unless this action would jeopardize the rights, safety or well-being of the subjects. The IRB/EC and regulatory authorities, as applicable, should be notified. All subjects enrolled in the study at the center will continue to be followed per

protocol requirements. The Principal Investigator at the center must make provision for these follow-up visits unless BSC notifies the investigational center otherwise.

24. Publication Policy

In accordance with the Corporate Policy on the Conduct of Human Subject Research, BSC requires disclosure of its involvement as a sponsor or financial supporter in any publication or presentation relating to a Boston Scientific study or its results. In accordance with the Corporate Policy for the Conduct of Human Subject Research, Boston Scientific will 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.
- Boston Scientific involvement in the publication preparation and the Boston Scientific 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.

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