BOSTON SCIENTIFIC CORPORATION

Uphold LITE Vaginal Support System (P180018) and Xenform Soft Tissue Repair System (P180021)

Prepared for Obstetrics and Gynecology Devices Panel of the Medical Devices Advisory Committee: Transvaginal Mesh for Anterior Prolapse Repair

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SECTION 1: EXECUTIVE SUMMARY

Boston Scientific Corporation (BSC) firmly believes that the totality of clinical evidence supports the positive benefit/risk profile of transvaginal mesh devices to treat pelvic organ prolapse (POP). In particular, as supported by new and compelling data collected through studies designed in conjunction with FDA, as well as reports in the scientific literature, BSC's two transvaginal mesh devices used for repair of POP – the Uphold LITE Vaginal Support System (Uphold LITE) and the Xenform Soft Tissue Repair Matrix (Xenform) – present demonstrable benefits that outweigh their potential and observed risks.

The prospective controlled 522 post market surveillance studies and other controlled studies of Uphold LITE and Xenform available in the published literature have found high rates of both anatomic and subjective success resulting from POP repair with these devices, including better anatomic success over native tissue repair (NTR). This has been supplemented by low rates of POP recurrence signaling a durable treatment effect, based on currently available data.

While mesh presents the potential for certain device-specific risks that are not seen with NTR, the 522 studies demonstrate that at 12 months, there is no greater incidence of serious adverse device-related and/or serious procedure-related risks associated with these products compared to NTR, and further suggest no late term serious adverse device-related risk. With regard to mesh-specific adverse events such as exposure and erosion, these studies have seen zero erosions and low rates of mesh exposure. In conjunction, the rates of non-mesh-specific adverse events seen with Uphold LITE and Xenform are generally comparable to those reported for NTR.

The data from BSC sponsored 522 studies, in conjunction with the literature on BSC's specific devices, demonstrate improved efficacy and fewer complications compared to much of the literature presented during the 2011 FDA panel meeting convened to discuss the risk/benefit profile of transvaginal mesh devices for POP repair. BSCs low density (light weight) mesh products and current clinical practice in terms of patient selection, implantation techniques, and physician training were designed to reduce risks presented by the earlier first-generation mesh products reported on during the 2011 panel meeting. As this document presents in detail, the evidence to-date of the safety and effectiveness of BSC's mesh devices demonstrates a favorable benefit/risk profile for properly chosen patients in the hands of properly trained surgeons.

Medical treatment options are not – and ought not to be – considered one-size-fits-all, and physician selection of the optimal treatment in a particular case must always consider likely benefits and risks in conjunction with the patient's individual characteristics and clinical needs. It is generally desirable that a number of safe and effective treatment options be available so that patients can receive personalized treatment based on their individual clinical characteristics. At the same time, the company has been and remains committed to mitigating the potential for mesh-specific complications through a robust Quality System that identifies complaints and ultimately results in product improvements through the CAPA process. Its offerings include targeted physician and nurse training through its Pelvic Floor Institute that has been vetted with key opinion leaders and aligns with the most contemporary surgical technique training- all with the intent of improving the outcomes of transvaginal mesh surgery for POP repair. As explained further below, these efforts, in conjunction with the totality of recent data support

that Uphold Lite and Xenform merit continued availability as a treatment option for clinicians to consider in caring for their patients.

A. Disease Background

It is estimated that POP impacts approximately 50% of women who have had offspring[1], with women facing an increased risk of prolapse as they age; and over 300,000 surgeries for POP are performed annually in the U.S. POP can have a profound effect on a woman's quality of life and her physical and psychological well-being. Specifically, POP has been associated with a variety of urinary, bowel and sexual symptoms which may significantly compromise patients' comfort and ability to perform daily activities.

Boston Scientific Corporation (BSC) has developed its Uphold LITE and Xenform devices for the treatment of anterior and apical prolapse. Anterior prolapse occurs when the tissues/muscles between the bladder and vagina, which typically hold the bladder up inside the pelvis, weaken and/or stretch. This causes the bladder to fall into the vagina (cystocele), producing a large bulge in the front (anterior) vaginal wall. Apical prolapse is the descent of the uterus, cervix, or vaginal vault which may manifest as uterine prolapse, vaginal vault prolapse, or enterocele.

B. Current Therapies and Clinical Need

Therapeutic interventions available for treatment of POP include both non-surgical and surgical alternatives. The risk and benefit of each treatment approach must be specifically considered for the individual patient based on severity of disease, impact on quality of life, and failure of prior treatments, among other factors.

For asymptomatic or mildly symptomatic POP, regular observation by a clinician along with non-surgical lifestyle modifications may suffice to reduce symptoms. Pelvic floor muscle strengthening exercises can also be helpful to restore support for the impacted organs. Another, non-surgical option is use of a support or space-occupying pessary – a device placed in the vagina to restore the normal anatomic position of prolapsed organs. However, pessaries provide only temporary symptom relief and do not correct the underlying anatomic defect or associated symptoms.

For women with prolapse that is more severe or has not responded to non-surgical alternatives, surgical intervention may be appropriate to restore anatomic position of prolapsed organs and provide support, thereby relieving symptoms and improving or restoring pelvic organ functions and associated quality of life measures. Surgical approaches can be transabdominal or transvaginal, using the patient's own tissue to support the prolapsed organs or reinforcing the repair using surgical mesh. Surgical repair involving plication and suspension of native connective tissues, Native Tissue Repair (NTR), is an effective approach for a large population of women but concerns with this approach include late term recurrent prolapse and/or anatomic failures. Surgical mesh has been considered an alternative to NTR to improve the strength and ultimately the durability of the repair while also relieving symptoms. Implantation of mesh through a transvaginal procedure allows for easier access to prolapsed organs, reduced procedure time, faster recovery, and better

[1] Olsen AL, Smith VJ, Bergstrom JO, Colling JC, Clark AL. Epidemiology of surgically managed pelvic organ prolapse and urinary incontinence. Obstet Gynecol. 1997;89(4):501–6

cosmetic results (i.e., no visible scar) as compared to sacrocolpopexy through open abdominal and minimally-invasive robotic procedures.

C. Boston Scientific's Devices for Transvaginal Repair of Pelvic Organ Prolapse (POP)

BSC makes two distinct mesh products – the Uphold LITE Vaginal Support System ("Uphold LITE") and the Xenform Soft Tissue Repair System ("Xenform") – for use in performing transvaginal repair of anterior and/or apical prolapse. The devices are designed to be implanted to re-create the hammocking support of the bladder and suspension of the vaginal apex that are supposed to be provided by the pubocervical fascia and uterosacral ligament, respectively. It is critical to recognize that Uphold LITE, a second-generation mesh product, improves upon characteristics of first-generation transvaginal mesh products and correspondingly has a more favorable benefit/risk profile, with lower rates of mesh-specific adverse events than discussed at the 2011 panel meeting. Chief among changes that have improved transvaginal mesh outcomes are changes to the physical characteristics of the mesh to use lighter density (light weight) and lower total volume of mesh material, abandonment of the "mesh inlay" surgical technique, and abandonment of the use of trocars to place mesh material.

Each of the devices was originally cleared by FDA through the 510(k) pathway. Following the reclassification of transvaginal mesh devices for POP repair from Class II to class III by FDA, BSC submitted premarket approval applications (PMAs) for both devices: Uphold LITE Vaginal Support System (P180018) and Xenform Soft Tissue Repair Matrix (P180021).

1. Uphold LITE Vaginal Support System with Capio SLIM

The Uphold LITE Vaginal Support System consists of synthetic Surgical Mesh which is supplied with two pre-attached leg assemblies (on each of the lateral sides) designed to facilitate passage of the mesh through bodily tissues for proper placement. It is also supplied with a dedicated FDA-cleared delivery device, the Capio SLIM Suture Capturing Device (K172060), into which the Leg Assemblies are specifically designed to be placed.
The Uphold LITE Surgical Mesh is constructed from knitted, low-density (light weight), polypropylene monofilament fiber, which is dyed blue to improve visibility during the procedure and has an undyed (natural) centerline to facilitate ease of visual orientation during placement. Of note, this lighter density (light weight) synthetic mesh is lower in density compared to older mesh products which are no longer on the U.S. market, a factor understood to reduce associated adverse events. To accommodate physician preferences and patient anatomies, the mesh is offered in a pre-cut configuration that may be further trimmed to fit the patient as needed to achieve the desired repair.

The Uphold LITE mesh is placed transvaginally through an anterior incision in the vaginal wall and secured to provide apical suspension by way of adjustable arms that fixate into the sacrospinous ligament and bladder support by way attaching to the pelvic sidewall. Following implantation, the mesh is incorporated into the surrounding tissue, and collagen deposition and capillary penetration through the mesh result in a tissue/mesh construct that provides long-term support to support the prolapsed organ.

2. Xenform Soft Tissue Repair Matrix

The Xenform Soft Tissue Repair Matrix is a permanent implant comprised of an extracellular collagen material manufactured from bovine skins sourced solely from cattle obtained in compliance with US regulatory requirements. The device is provided in sheet form to be trimmed and sutured by the surgeon to meet individual patient anatomy. Specifically, Xenform is intended to be cut into a trapezoidal shape so that the proximal portion or base is wide enough to suture to the sacrospinous ligaments and long enough to reach the bladder neck, so as to provide both apical suspension and proper bladder/pelvic support.

Trimmed, hydrated Xenform is placed through an anterior incision in the vaginal wall and sutured in the pelvic floor, where it remains in contact with the patient's soft tissue. Following implantation, the Xenform extracellular scaffold serves as a template for regrowth of native tissue for long-term integration; the resulting tissue/mesh construct provides long-term support to the prolapsed organ. The device is only minimally resorbed.[2]

3. Surgical Procedure

The surgical procedure for implantation of both Uphold LITE and Xenform features standardized instructions, including steps to prepare the site for implantation to minimize the risk of mesh extrusion and promote durability of repair, ensure tension-free placement, which may minimize the risks of de novo dyspareunia, promote durability of the repair, and reduce peri-operative complications. Importantly, both products are implanted without trocars, reflecting the evolution to transvaginal mesh surgical techniques which has been attributed to lower rates of adverse events.

4. Labeling

Labeling provided with both the Uphold LITE System and Xenform Soft Tissue Repair Matrix contains information regarding the device, detailed instructions describing the surgical technique for preparation of the surgical site and implantation of the device, and contraindications and warnings to aid in appropriate patient selection. Consistent with the recommendations from the 2011 panel meeting, the labeling also includes a listing of potential adverse events associated with use of transvaginal mesh devices generally, regardless of whether the specific adverse event has been observed with the BSC device. Patient brochures are also available and provide information on treatment options and the benefit/risk profile of the specific device to assist patients in making informed care decisions.

5. Training

BSC has developed a physician training program to help surgeons using Uphold LITE and Xenform devices fully understand the requirements for safe and effective use of these devices. This program complements residency and fellowship training, and emphasizes an understanding

[2] Cornwell K, Zhang , Lineaweaver W, (2016). Bovine fetal collagen reinforcement in a small animal model of hernia with component repair. J. Surgical Research. 201, 416-424.

of patient selection, device mechanisms of action, and proper surgical technique. To achieve these goals, a continuum of product-specific training is employed, including:

- Access to online education covering such topics as disease state, product features, relevant anatomy, surgical technique, and management of complications;
- Proctorship with an experienced surgeon, during which surgical technique tips for use of the specific product are shared and patient outcomes and management of complications are discussed.
- Attendance at a hands-on course that includes a didactic session from a faculty physician as well as training and practice on pelvic and cadaver models
- Preceptorship with an experienced surgeon over a number of cases to increase physician comfort with the relevant surgical technique.

These training efforts are designed to bolster the safety and efficacy of the transvaginal mesh implantation procedure, with focus on critical steps specific to the individual BSC products as well as demonstrated principles in the field.

D. Supporting Clinical Evidence for BSC Devices for POP

The totality of clinical evidence supports the safety and efficacy of the BSC devices for repair of POP. Recent literature specific to Boston Scientific's Uphold LITE and Xenform devices reports low rates of complications that are comparable to those seen with NTR, with positive clinical outcomes reflected by restored anatomical position and subjective/symptomatic clinical benefit. This literature demonstrates a benefit/risk ratio for the BSC transvaginal mesh devices that is comparable to other treatment options available to patients, namely NTR. Importantly, the recent literature shows improved benefits and lower complication rates compared to the data presented by FDA during the previous 2011 panel meeting to discuss transvaginal mesh products. The previously summarized literature addressed in the FDA Executive Summary for the 2011 panel meeting to assess the adverse event rates associated with these devices relied on several systematic meta-analyses which reflected older mesh products. Most notably, retrospective analyses by Abed et al.[3] (incorporating publications from 1950 – 2007) and Diwadkar et al.[4] (incorporating data published from 1985 – 2008) served as primary references to assess complications for transvaginal mesh compared to sacrocolpopexy and NTR. The transvaginal mesh kits represented in these publications include first-generation products that are no longer on the market and share a number of characteristics which have been engineered out of the second-generation mesh kits. These include higher density mesh materials (45-50 gm/m^2), self-fixing arms that must be successfully negotiated across multiple tissue planes and requiring use of a trocar for placement. In contrast, the Uphold LITE mesh is far lighter at 25 gm/m^2, is placed directly via a single incision without trocars, has a smaller surface area and overall mesh footprint, and is directly fixated using the Capio SLIM suturing

[3] Abed et al. Incidence and Management of Graft Erosion, Wound Granulation, and Dyspareunia Following Vaginal Prolapse Repair With Graft Materials: a Systematic Review. Int. Urogynecol J. 2011 22:789-798

[4] Diwadkar GB, et al. Complication and reoperation rates after apical vaginal prolapse surgical repair: a systematic review. Obstet Gynecol. 2009; 113(2 Pt 1): 367-73.

device with adjustable mesh arms that allow for support in both the anterior and apical compartments.

BSC has reviewed and summarized contemporary reports which provide more current assessments of BSC's own devices in treatment of anterior/apical POP (discussed below in **Section 6**). BSC has also conducted prospective clinical studies for each of the Uphold LITE and Xenform devices in response to FDA's 522 orders, as discussed further in the following sections.

1. Published Literature

Uphold LITE

Recent publications indicate success of the Uphold LITE in terms of restoration of anatomical position, improvement to quality of life metrics, and low rates of serious complications and mesh-related events such as extrusion, erosion and exposure. The results as a whole suggest that the benefits from the Uphold LITE System are durable, comparable to (or higher than) NTR, and achieved with low complication rates.

Specifically, numerous studies found anatomical success (defined as achieving POP-Q ≤1) rates that were at least as high, and in some cases notably higher than, those that have been reported with NTR. For instance, Altman, et al. (2011), a study of nearly 400 subjects, reported an 82.3% rate of success in anatomical correction of anterior prolapse using Uphold LITE, as compared to only 47.5% with NTR, and this difference was found to be statistically significant. Success on the study's primary composite endpoint (comprising this anatomic element plus the absence of vaginal bulge symptoms) was 68.0% for the Uphold LITE group as compared to 34.5% for the NTR group, with this difference across groups also found to be statistically significant. Numerous single-arm studies also found high anatomic cure rates for anterior and apical POP with the BSC mesh. Lo, et al. (2018) reported a 97.7% anterior success and 98.9% apical success at 12 months. Moreover, the available long-term data on efficacy outcomes with this specific mesh, albeit somewhat limited, support that the POP repair achieved is durable. Of note, Rahkola-Soisalo et al. (2017), the longest-duration prospective study of Uphold LITE to-date, reported not only a 93.5% apical anatomic success achieved at 1 year, but also no statistically significant decline in anatomic success at 5 years (at which point it was 83.3%).

In terms of subjective success, high rates of symptomatic cure and quality of life improvement as assessed using validated metrics were reported in subjects receiving Uphold LITE. For instance, Altman, et al. (2011) reported 75.4% success on the secondary endpoint for absence of bulge symptoms in the Uphold LITE group as compared to 62.1% in that study's NTR group. Patient satisfaction with the outcomes of transvaginal mesh repair was very high (>90%) in most of the studies evaluating Uphold LITE, and high rates of improvement in quality of life were also reported. For instance, Rahkola-Soisalo et al. reported improved quality of life as assessed per the PFDI-20 in 78.8% of mesh subjects, with a significant decrease of bother that had not changed significantly from the 1-year post-operative visit – again supporting that the mesh achieves durable repair of POP. In addition, this study found that pain levels (VAS scale) decreased after surgery and continued lessening in pain between the one- and five-year follow-up visits. Gutman, et al. found a

95% satisfaction rate (in both mesh and NTR groups) per the PGI-I scale, further confirming that subjective success is comparable with this device and NTR.

These studies highlight that the efficacy profile of Uphold LITE is achieved in conjunction with an acceptable safety profile, and much lower adverse event rates than generally reported in the transvaginal mesh studies reviewed at the 2011 panel meeting. While surgical mesh does pose the risk of certain adverse events which cannot occur with NTR – most notably mesh erosion/exposure/extrusion – the rates for these mesh-specific AEs in the studies assessing Uphold LITE specifically have been low, and the overall AE rates were generally comparable to those observed with native tissue repair. Specifically, rates of mesh erosion or exposure (almost always exposure) were very low, including some studies with zero exposures, and were only 1.4% in the large, long-term Rahkola-Soisalo et al. study. Rates of mesh exposure ranged from 2.6% to 8%, which is still notably lower than the >10% rate reported in Abed, et al. (prior to 2011 and not specific to Uphold LITE). Moreover, all of the studies' reported exposures were primarily of mild or moderate severity, in that the reported rates of re-surgery for exposure/erosion were <5% and some of these cases did not even require a corrective office procedure. These results are much lower than the 7.2% re-surgery rate for mesh specific complications reported in the Diwadkar, et al. assessment referenced in the 2011 panel meeting.

Most of the studies identified as part of our literature search with Uphold LITE also reported relatively low rates of other AEs (non-mesh-specific) that are comparable to those seen with NTR, consistent with the results seen in BSC's 522 studies.

Xenform Soft Tissue Repair Matrix

Limited published literature addresses the use of biologic tissue grafts to treat POP, with only a single publication (Goldstein, et al.[5]) specifically addressing the Xenform device. This study assessed success based on restoration of normal anatomy in any compartment, symptom relief, QoL, and sexual function. The results showed significant improvements in both objective and subjective outcomes at 12 months in subjects who underwent POP repair using Xenform, including an 88% success rate on the primary efficacy endpoint with statistical improvements in both anterior and apical support. In addition, there were no mesh exposures or erosions and minimal other complications, reflecting a positive safety profile.

2. 522 Clinical Studies

BSC conducted prospective clinical studies for each of the Uphold LITE and Xenform devices in response to FDA's 522 orders. The studies were designed with extensive FDA input and the protocols were approved by FDA. The studies enrolled patients who were diagnosed with anterior and/or apical POP and were candidates for surgical repair, and who may or

[5] Goldstein HB, et al. A multicenter prospective trail evaluating fetal bovine dermal graft (Xenform Matrix) for pelvic reconstructive surgery. BMC Urology (2010) 10:21.

may not have required a concomitant procedure (such as hysterectomy or sling placement for stress urinary incontinence).,

A composite endpoint was designed to evaluate the devices, where the endpoints were the same across both studies, as follows:

Primary Efficacy Endpoint

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 Pelvic Organ Prolapse Quantification System (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 POP-Q point C ≤ 0 for single compartment apical prolapse).
2. Subjective success is achieved if the patient denies symptoms of vaginal bulging per Pelvic Floor Distress Inventory (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 anatomic segment(s) treated at the index surgery or no pessary use since index surgery (i.e., ‘treated segment’ refers to the target compartment).

Secondary Efficacy Endpoint

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 Pelvic Organ Prolapse Quantification System (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 POP-Q point C < 0 for single compartment apical prolapse).
2. Subjective success is achieved if the patient denies symptoms of vaginal bulging per Pelvic Floor Distress Inventory (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 anatomic segment(s) treated at the index surgery or no pessary use since index surgery (i.e., ‘treated segment’ refers to the target compartment).

Safety Endpoint

The primary safety endpoint for both studies is a comparison of serious device- and/or serious procedure-related AEs between baseline and the 36-month time point. The

secondary safety endpoints include analysis of overall device- and procedure-related AEs, mesh erosion and exposure, and de novo dyspareunia.

Enrollment and Follow-up schedule

In the Uphold LITE study, a total of 225 patients received the treatment device across 27 centers and 482 underwent native tissue repair. For the Xenform study, a total of 228 patients received the treatment device across 25 centers and 482 underwent native tissue repair. Control group patients were enrolled at dedicated NTR specialty centers or from the AUGS PFD registry.

For both studies, each subject was instructed to return for follow-up visits at 2 and 6 months (± 4 weeks) and at 12, 18, 24 and 36 months (-4/+12 weeks). The primary endpoint was designed for evaluation at 36 months. However, based on FDA's reclassification of surgical mesh devices for POP repair and the timeline for submission of PMA data, FDA and Boston Scientific agreed the PMA applications would present 12-month data, with the presentation of the available longer-term data.

Results

Results from the Uphold LITE and Xenform study, presented below, show that treatment with either device is at least as effective as NTR at 12 months for the composite primary efficacy endpoint addressing objective and subjective surgical success and surgical intervention for POP recurrence, with a comparable safety profile. For the secondary efficacy endpoint, the composite treatment success rate is higher in the Uphold Lite arm compared to the NTR (85.8% vs. 78.4%, p-value = 0.005), while it is comparable between the Xenform and NTR group (85.2% vs. 78.3%, p-value = 0.120). Please note these p-values are not adjusted for multiple comparison. While only limited data is available out to 36 months, the data suggests sustained or increased benefit, without the risk of increased late-term serious adverse events. Additionally, when looking at the individual prongs of the endpoint, objective success is higher with Uphold LITE, driven by the treatment success in the anterior compartment. While the objective success overall and in the anterior compartment for Xenform at 12 months is not statistically significant, it is numerically higher.

Table 1. Summary of Uphold LITE and Xenform Primary Efficacy Results

Variable	Uphold LITE study		Xenform Study	
	Uphold LITE % (count/ sample size)	NTR % (count/ sample size)	Xenform % (count/ sample size)	NTR % (count/ sample size)
12-Month Composite Success	**91.6% (185/202)**	**87.3% (379/434)**	**88.2% (172/195)**	**87.3% (379/434)**
Objective Success	98.0% (198/202)	94.0% (409/435)	96.9% (189/195)	94.0% (409/435)
Anterior Compartment	98.5% (199/202)	93.5% (362/387)	96.9% (189/195)	93.5% (362/387)
Apical Compartment	98.0% (198/202)	98.0% (400/408)	98.4% (190/193)	98.0% (400/408)

Variable	Uphold LITE study		Xenform Study	
	Uphold LITE % (count/ sample size)	NTR % (count/ sample size)	Xenform % (count/ sample size)	NTR % (count/ sample size)
Subjective Success	93.6% (190/203)	92.2% (402/436)	89.8% (176/196)	92.2% (402/436)
No Retreatment for POP	99.6% (224/225)	97.9% (472/482)	99.6% (227/228)	97.9% (472/482)
24-Month Composite Success	**91.7% (88/96)**	**83.7% (221/264)**	**82.4% (140/170)**	**83.7% (221/264)**
Objective Success	96.9% (93/96)	93.5% (244/261)	95.9% (162/169)	93.5% (244/261)
Anterior Compartment	99.0% (95/96)	92.7% (216/233)	95.9% (162/169)	92.7% (216/233)
Apical Compartment	96.9% (93/96)	98.8% (239/242)	97.0% (162/167)	98.8% (239/242)
Subjective Success	93.8% (90/96)	93.9% (246/262)	85.8% (145/169)	93.9% (246/262)
No Retreatment for POP	99.6% (224/225)	96.7% (466/482)	98.2% (224/228)	96.7% (466/482)
36-Month Composite Success	**83.3% (35/42)**	**73.8% (107/145)**	**81.9% (68/83)**	**73.8% (107/145)**
Objective Success	95.2% (40/42)	88.1% (119/135)	95.0% (76/80)	88.1% (119/135)
Anterior Compartment	97.6% (41/42)	87.1% (108/124)	97.5% (78/80)	87.1% (108/124)
Apical Compartment	95.2% (40/42)	97.6% (121/124)	96.3% (77/80)	97.6% (121/124)
Subjective Success	87.5% (35/40)	92.6% (126/136)	88.9% (72/81)	92.6% (126/136)
No Retreatment for POP	99.1% (223/225)	96.3% (464/482)	98.2% (224/228)	96.3% (464/482)

There were measurable improvements in patient-reported outcomes for all study groups in both studies following surgery. Subjects receiving Uphold LITE and Xenform devices showed significant improvement in PFIQ-7 and PFDI-20 scores at 12 months over baseline. Moreover, there was stability in these scores out to 36 months for subjects who have reached this time point. Most subjects in both groups reported they felt “much better” or “very much better” after surgery per responses to PGI-I questionnaire.

Looking at serious device-related and procedure-related adverse events (SADE) for the co-primary safety endpoint, treatment with the Uphold LITE and Xenform demonstrated equivalent SADE rates at 12 months at 2.7% in the respective studies’ intent to treat population. These rates were further equivalent to the 2.7% serious event rate for NTR subjects in both of the studies. Looking at the totality of the data out to 36 months, all SADEs for the Uphold LITE and Xenform devices occurred within the first 6 months following the procedure and all events have been fully resolved. In contrast, 3/17 SADE events for NTR subjects (one infection, one UTI, and one worsening constipation) were late-term complications.

For Uphold LITE, there were no statistically significant differences compared to NTR subjects in the rates of individual AEs emphasized by the FDA at the 2011 Panel meeting: pelvic pain, infection, vaginal shortening, atypical vaginal discharge, neuromuscular problems, vaginal scarring, de novo vaginal bleeding, de novo voiding dysfunction, de novo dyspareunia, and fistula formation. For Xenform, the only event that showed a statistically significant

difference was de novo voiding dysfunction (14.5% vs. 4.4% for NTR). Despite this observation there were no statistically significant differences in UDI6 score between Xenform subjects who did and did not experience de novo voiding dysfunction.

As of March 10, 2018 there were no mesh erosions in either study. A total of 1.8% (4/225) of subjects experienced mesh exposure events in the Uphold LITE study at 12 months, increasing to 3.6% (8/225) by 36 months. The Kaplan Meier estimate for the mesh exposure rate is 6.2% at three years. At 12 months and through 36 months of follow-up, mesh exposure has been documented in 0.9% (2/228) of Xenform subjects. For the majority of these instances, resolution was achieved with either no action taken or office-only procedures, with 4 of the 10 instances requiring surgical intervention.

In summary, the 12-month data demonstrate non-inferiority of Uphold LITE and Xenform to NTR for primary efficacy. In addition, the composite primary and secondary surgical success rates trend in favor of Uphold LITE with numerically higher values at 24 and 36 months based on the limited available data, and objective anatomic success rate is also higher for Uphold LITE at 12 months compared to NTR. Uphold LITE, Xenform, and NTR subjects experienced comparable rates of SADEs at 12 months thus demonstrating that there are not significant additional risks presented by the mesh devices.

Benefit-Risk Analysis and Conclusions

1. Boston Scientific's Devices are Effective in Restoring Anatomical Position and Demonstrating Clinically Meaningful Improvement

   The benefits seen with Boston Scientific's devices are demonstrable and clinically relevant. Based on analysis of the 12-month data from the prospective 522 studies, subjects receiving the Uphold LITE and Xenform devices had comparable or improvedanatomic outcomes compared to subjects undergoing NTR particularly in the anterior compartment. Subjects in each of the BSC device treatment arms further experienced durable effects of treatment, with numerically lower rates of repeat surgical intervention for recurrent prolapse compared to NTR subjects. While subjective success was comparable at 12 months or somewhat lower at later follow up visits in the device groups compared to the NTR groups, these results are somewhat inconsistent, and mesh subjects still experienced clinically meaningful improvements in several validated quality of life measures.

   Looking at these factors in totality, the pre-defined composite efficacy endpoint of the BSC 522 studies demonstrates comparable performance to NTR at 12 months. Moreover, compared to NTR, the available 36-month data for the Uphold LITE appears to show a trend of sustained higher anatomic success compared to NTR. These data are consistent with data reported in the literature in the SUPeR study out to 48 months and Rahkola-Soisalo et al. (2017), the longest-duration prospective study of Uphold LITE to-date, reporting high anatomical success at one year with no statistically significant decline at 5 years (at which time point it was 83.3%) for subjects receiving the Uphold LITE.

2. Boston Scientific's Devices are Safe

   The Uphold LITE and Xenform devices have a demonstrated long-term safety profile established through the prospective 522 studies and reports in the literature.

   The 522 studies demonstrate that at 12 months, there is no greater incidence of serious adverse device-related or serious procedure-related risks associated with the products compared to NTR. Further, the data from these studies do not show an otherwise increased overall risk profile. There was a somewhat higher rate of de novo voiding issues observed with the Xenform device compared to the NTR control. Despite these observed differences there was no statically significant difference in UDI6 between Xenform subjects regardless of whether or not they developed de novo voiding dysfunction. Further, potential risks specific to mesh products such as erosion and exposure saw only limited realization in both studies. The 12 incidents of mesh exposures across the two clinical studies (3.6% Uphold LITE subjects (n=8, two subjects had 2 exposures), 0.9% Xenform (n=2)) required only minimal intervention to achieve resolution, with 2 incidents resolved with outpatient surgical intervention and 2 events requiring surgical intervention and still ongoing. Finally, the available data out to 18, 24, and 36 months show a higher rate of overall device and procedure-related AEs with NTR versus Uphold LITE, and comparable rates for Xenform versus NTR.

   While the literature cited by FDA in the 2011 panel meeting noted higher rates of adverse events for mesh POP repair, BSC's devices are distinguishable compared to the first-generation mesh products that were the subject of many of the studies cited by FDA to establish the complication rate. Notably, the BSC Uphold LITE device uses low density (light weight) mesh, both the Uphold LITE and Xenform are implanted without the use of trocars, and designed for securement to the sacrospinous ligaments to provide hammocking support to the bladder. Accordingly, the adverse event rates reflected in the current literature, the prospective 522 studies are more indicative of the true adverse event rate for these specific devices.

3. The Benefits of the Boston Scientific Transvaginal Mesh Devices Outweigh the Risks

   The Uphold LITE and Xenform devices present demonstrable benefits that outweigh the potential and observed risks specific to these mesh products. The devices serve as a valuable treatment option for patients presenting with anterior and apical prolapse with higher success rate demonstrated at 12 months in the anatomical correction of prolapse and reduction in surgical re-intervention for recurrent prolapse compared to NTR. Subjective success rates and quality of life improvements – an area emphasized by the 2011 Panel in terms of ensuring clinically meaningful outcomes of transvaginal mesh repairs – are also very high with these devices. The rate of serious adverse events is no higher for patients receiving these devices compared to NTR, and the general complication rate is comparable at 12 months and in the available longer-term data. The devices further present longer-term benefits through sustained anatomical correction of the prolapse

without additional safety risks based on the preliminary 522 study data as well as the reports in the literature (e.g., SUPeR study).

The clinical techniques for patient selection, implantation and treatment of patients with transvaginal mesh products in POP repair have shifted in the 8 years since the last advisory committee meeting convened on this topic by FDA. Physicians are currently receiving dedicated and increased training regarding the proper implantation techniques for using such devices, with more training provided by Boston Scientific specific to its Uphold LITE and Xenform devices and credentialing offered by AUGS.

Boston Scientific's Uphold LITE and Xenform transvaginal mesh devices have demonstrated clinical safety and effectiveness, comparable to native tissue repair, based on the prospective 522 clinical studies and the data presented in the literature specific to these devices. These devices therefore present an appropriate and established treatment option for clinicians to consider for their patients in the repair of anterior and apical prolapse. Transvaginal mesh products that demonstrate safety and effectiveness profiles that are comparable or superior to native tissue repair and should continue to be available as a treatment option to serve women experiencing POP.

SECTION 2: PELVIC ORGAN PROLAPSE BACKGROUND AND CLINICAL NEED FOR TREATMENT OPTIONS

A. Pelvic Organ Prolapse (POP)

POP is a condition that occurs in women, where the pelvic organs such as the uterus, bladder, and/or bowel protrude into the vagina due to weakness in the tissues that normally support them. A complex network of muscles, ligaments, and fascia surround and support the vagina and pelvic organs, holding them in place. POP occurs when this support network weakens, allowing one or more of the pelvic organs to descend from its normal anatomic position and push into or up against the wall of the vagina. POP can occur in the anterior, apical, and/or posterior compartments. In the ongoing BSC 522 studies of Uphold LITE Vaginal Support System (Uphold LITE System) and the Xenform Soft Tissue Repair Matrix (Xenform), POP repairs were confined to the anterior and apical compartments; consequently, the remarks herein will be largely confined to anterior/apical POP.

In the United States, over 300,000 surgeries are performed for POP on an annual basis. It is estimated that 50% of parous women will experience POP at some point in their lifetime[1] and up to 11% of women in the United States will undergo a single surgery for POP (including incontinence) by age 80. The most common form of prolapse, anterior prolapse, is two times more common than posterior prolapse and three times more common than apical prolapse.**Error! Bookmark not defined.**

Anterior prolapse occurs when the pubocervical fascia supporting the bladder either tears or loses its lateral and/or apical support attachments, which causes the bladder to fall down into the vagina, producing a cystocele. When the bladder prolapses, it falls towards the vagina and creates a large bulge in the front (anterior) vaginal wall.

Anterior prolapse may be caused by straining the muscles that support the bladder, such as during vaginal childbirth or through chronic activities (e.g., coughing, heavy lifting). Prolapse may be delayed in onset, typically occurring in perimenopausal women when the ovaries gradually begin to make less estrogen, which can affect pelvic region muscle tone.

Anterior prolapse can present in conjunction with other POP, such as apical prolapse which may include uterine prolapse, vaginal vault prolapse, or enterocele. The uterus is held in an anatomically correct location at the vaginal apex by the uterosacral and cardinal ligaments. If the structures become attenuated or rupture, then the uterus will drop down (prolapse) into the vaginal cavity, producing a uterine prolapse. This condition may cause discomfort and difficulty with evacuation of the bowel and/or bladder. Vaginal vault prolapse can occur in women who have previously had a hysterectomy, when the vagina itself falls down even though the uterus is no longer present. This may also be referred to as a post-hysterectomy vaginal prolapse. Lastly, if a fascial defect exists at the apex between the anterior pubocervical fascia and the posterior rectovaginal fascia, then an enterocele can result. This is a herniation of small intestine through the apex into the vagina.

Posterior prolapse can occur due to one or both of the conditions described hereafter. If the rectovaginal fascia either tears and/or loses its lateral or apical attachments, the rectum can bulge into the vagina, producing a rectocele. This condition may cause discomfort, stool

trapping, constipation or fecal incontinence. If the small bowel dissects down into the space between the vaginal fascia and the pararectal fascia (the rectovaginal septum), a posterior protrusion of the posterior wall – referred to as a sliding enterocele – can occur. This may or may not be accompanied by a rectocele.

POP can have a profound effect on a woman's quality of life and her physical and psychological well-being. Specifically, POP has been associated with a variety of urinary, bowel and sexual symptoms which may significantly compromise the quality of life of the patients. Symptoms from the prolapse alone include vaginal lump, effect on daily activities such as walking, dragging discomfort in the lower abdomen, ulceration, and vaginal bleeding. Urinary symptoms include stress urinary incontinence (SUI), urge urinary incontinence, urinary frequency, urinary urgency, incomplete bladder emptying, voiding difficulty, slow stream and intermittent flow. Defecatory/bowel symptoms include straining to defecate, manual reduction to empty bowel, and fecal incontinence. Sexual dysfunctions include lessening of sexual desire, arousal, orgasm, and pain which can affect the relationship between partners. In addition to the above, hysterectomy also carries with it a significantly negative impact on body image and quality of life.[6, 7, 8]

B. Non-Surgical Treatment Options

Physicians have several choices for treatment of POP, including non-surgical and surgical options. Asymptomatic or mildly symptomatic women with POP can be observed at regular intervals without intervention. Non-surgical lifestyle modifications that may reduce prolapse symptoms include weight control, proper nutrition with an appropriate amount of dietary fiber, smoking cessation, and avoidance of strenuous occupational and recreational activities. Pelvic floor muscle strengthening exercises can also be helpful, particularly for milder cases of prolapse to restore support for the impacted organs.

Use of a pessary provides a non-surgical treatment option. A pessary is a device placed in the vagina to restore prolapsed organs to their normal anatomic position. There are two kinds of commonly used pessaries: support pessaries such as a ring pessary, and the space-occupying shelf pessary. Pessaries are used for all stages of POP in women with or without urinary incontinence.[9] However, they may not be suitable for all patients, and several trials may be needed in order to ensure the correct size is selected. Moreover, while pessaries are helpful to provide support to the prolapsed organ and thus provide symptom relief, they do not correct the underlying anatomic defect. As soon as the pessary is removed, the prolapse returns along with the accompanying symptoms. Further, the proper placement of a pessary typically requires insertion in a physician's office, making patients dependent on regular visits to healthcare providers for insertion, removal, and cleaning of the devices.

[6] Jelovsek JE, Barber MD. Women seeking treatment for advanced pelvic organ prolapse have decreased body image and quality of life. Am J Obstet Gynecol. 2006;194(5):1455–1461.
[7] Frick AC, Barber MD, Paraiso Marie Fidela R, Ridgeway B, Jelovsek JE, Walters MD. Attitudes toward hysterectomy in women undergoing evaluation for uterovaginal prolapse. Female Pelvic Med Reconstr Surg. 2013;19:103–9.
[8] Korbly NB, Kassis NC, Good MM, et al. Patient preferences for uterine preservation and hysterectomy in women with pelvic organ prolapse. *Am J Obstet Gynecol* 2013;209:470.e1-6.
[9] Kuncharapu I, Majeroni B, and Johnson D. Pelvic Organ Prolapse. *American Family Physician.* 2010;81(9):1111-1117.

C. Surgical Treatment Options

For patients who have failed to obtain adequate relief with the non-invasive and minimally invasive therapies, surgical intervention may be explored. The general goal of pelvic floor reconstructive surgery is to restore anatomic support and relieve prolapse symptoms, while improving or restoring bladder, bowel, and sexual function. The current gold standard specific to vaginal vault apical prolapse is abdominal sacrocolpopexy. Despite such, no definitive "gold standard" surgical procedure exists for conjunctive prolapse repair of both the apical and anterior compartments, and as the optimal procedure depends on the specific defects present as well as individual patient considerations.

Anterior vaginal wall defects are the predominant cause of pelvic floor dysfunction. Reviewing pelvic floor anatomy provides important insight regarding failure and restoration of anterior vaginal wall support. The anterior vaginal wall resembles a trapezoidal plane. The ventral and more medial attachments are near the pubic symphysis and the dorsal and more lateral attachments are near the ischial spine. The most common surgical management approach for anterior vaginal wall prolapse is anterior colporrhaphy (transvaginal). Additional surgical management procedures include abdominal or vaginal surgical repair, paravaginal repair for treatment of paravaginal cystocele, sacrocolpopexy, vaginal uterosacral ligament suspension, and sacrospinous ligament suspension.[10]

Surgical vaginal repair for POP involving plication and suspension of native connective tissues is an effective approach for a large proportion of women seeking surgery. However, there is a risk of recurrent prolapse following treatment. Key concerns associated with native-tissue plication are that: (1) the use of already weakened tissue may provide a weak repair; and (2) the surgeon may attempt to use stronger lateral tissues for repair and suspension, which can result in undesirable side effects such as constriction or foreshortening of the vagina. This in turn may result in pelvic pain, dyspareunia, and urinary retention.[11] When evaluated in comparison to biologic and polypropylene mesh, recurrent anterior compartment prolapse following native tissue repair (NTR) was predicted to be between 27% - 55% based on 6 and 36 months follow-up data.[12]

Surgical mesh has been used both in sacrocolpopexy and a transvaginal surgical approach for POP repair to bolster and reinforce tissue in order to restore anatomic position and provide support to prolapsed organs, resulting in symptom relief. Mesh is utilized in these procedures to overcome some of the issues experienced with NTR, namely to improve the strength and ultimately the durability of the repair. Historically, sacrocolpopexy was performed in an open abdominal procedure, with significant procedure times, lengthier recovery times and higher risk of infections. Implantation of mesh through a transvaginal procedure allowed for

[10] Brincat C, Larson K, and Fenner D. Anterior Vaginal Wall Prolapse: Assessment and Treatment. *Clinical Obstetrics and Gynecology.* 2010;53(1):51-58.
[11] Jakus S, Shapiro A, and Hall C. Biologic and Synthetic Graft Use in Pelvic Surgery: A Review. *Obstetrical and Gynecological Survey.* 2008;63(4):253-266.
[12] Maher C, Feiner B, Baessler K, Christmann-Schmid C, Haya N, Brown J. Surgery for women with anterior compartment prolapse. Cochrane Database of Systematic Reviews 2016, Issue 11. Pg. 21.

reduction in procedure time, faster recovery, and cosmetic benefits with no visible scar. The increasing use of robotic laparoscopic surgery allows for sacrocolpopexy to be performed in a minimally invasive procedure, though this approach limits access to prolapsed organs and accordingly is commonly used for repair of vaginal vault prolapse (apical), often following hysterectomy. Adverse events for mesh sacrocolpopexy include ileus/small bowel obstruction, dyspareunia, bleeding, mesh/suture complications, infection and urinary tract infection, bowel injury, urinary tract infection.[13]

Literature previously cited in the September 2011 FDA Executive Summary from the Surgical Mesh Obstetrics & Gynecology Advisory Committee Meeting reported significant safety concerns with transvaginal mesh devices, noting a high reoperation rate and generally high rate of adverse events with minimal to no benefit compared to NTR. However, more recent literature (**see discussion in Section 6**), which reflects more modern improved mesh devices and refined surgical techniques, reports lower rates of complications that are more comparable to the rates experienced with NTR, with suggestion of better anatomical outcomes and lower rates of surgical interventions.

SECTION 3: DEVICE DESCRIPTION

BSC is presenting this information to address two distinct mesh products that are indicated for use in the repair of anterior and/or apical prolapse through a transvaginal approach. As explained below, while the two mesh products have the same indications, they are constructed from different materials and are shaped differently. Accordingly, depending on the specific anatomical and clinical considerations for a patient, a physician can choose to use one device over another.

A. Uphold LITE Vaginal Support System with Capio SLIM

The Uphold LITE Vaginal Support System (Uphold LITE System) is a sterile, single use mesh device for transvaginal placement for POP repair. It consists of one Surgical Mesh, which is a permanent implant, and two Leg Assemblies, which are used to place the surgical mesh in the desired location and are then removed and discarded. The surgical mesh is implanted with a dedicated FDA-cleared delivery device, the Capio SLIM Suture Capturing Device (K172060).

Components

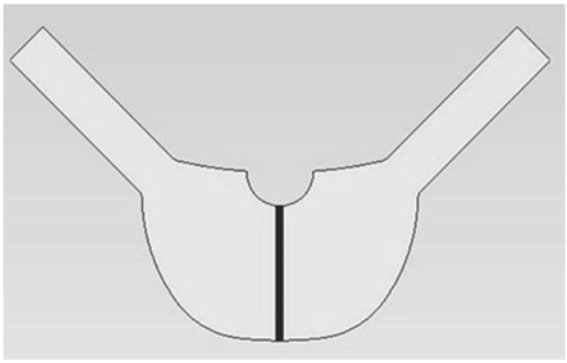
Surgical Mesh

The Surgical Mesh is a knitted, low density (light weight), synthetic mesh that consists of polypropylene monofilament fiber that is dyed blue to improve visibility during the procedure and has an undyed (natural) centerline to facilitate ease of visual orientation during placement. The surgical mesh is offered in a pre-cut configuration as a convenience to physicians. Depending on physician preference for a given procedure,

[13] Nazema Y. SIDDIQUI, MD, MHSc, Cara L. GRIMES, MD, Elizabeth R. Casiano, MD, Husam T. ABED, MD, Peter C. JEPPSON, MD, Cedric K. OLIVERA, MD, Tatiana V. SANSES, MD, Adam C. STEINBERG, DO, Mary M. SOUTH, MD, Ethan M. BALK, MD, MPH, and Vivian W. SUNG, MD, Mesh Sacrocolpopexy Compared With Native Tissue Vaginal Repair: A Systematic Review Group, Obstet Gynecol, 2015 January; 125(1):44-55

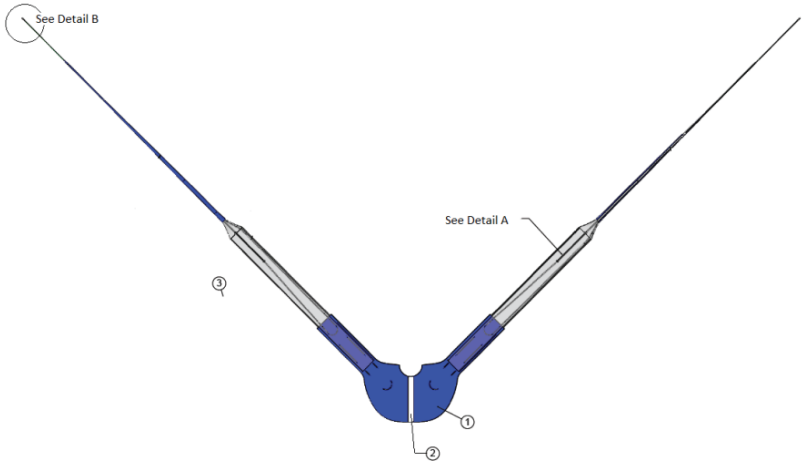
the pre-cut configuration may be modified (i.e., cut) to fit the patient as needed to achieve the desired repair. The pre-cut configuration is shown in **Figure 1**.

Figure 1: Uphold LITE Surgical Mesh Pre-Cut Configuration



The Surgical Mesh is assembled with two integrated Leg Assemblies, as shown in **Figure 2**.

Figure 2: Surgical Mesh with Two Integrated Leg Assemblies



1) Surgical Mesh, 2) Center line, 3) Leg Assembly (See Details A and B in Figures 4 and 5, respectively)

Leg Assembly

Each Leg Assembly, which is pre-attached to the surgical mesh, includes a dart/needle, lead, dilator, two leader loop(s), and a protective sleeve. The dart/needle at the distal end of the Leg Assembly is designed to be placed into the carrier at the distal end of the Capio SLIM delivery device. The Leg Assembly is designed to facilitate the passage and fixation of the Surgical Mesh through the sacrospinous ligament. Each Leg Assembly is used only once, to place the Surgical Mesh on either the left or right side, and is removed and discarded upon placement. The distal and proximal ends of the Leg Assemblies are detailed in **Figure 3** and **Figure 4**, respectively.

Figure 3: Detail A - Distal End of Leg Assembly

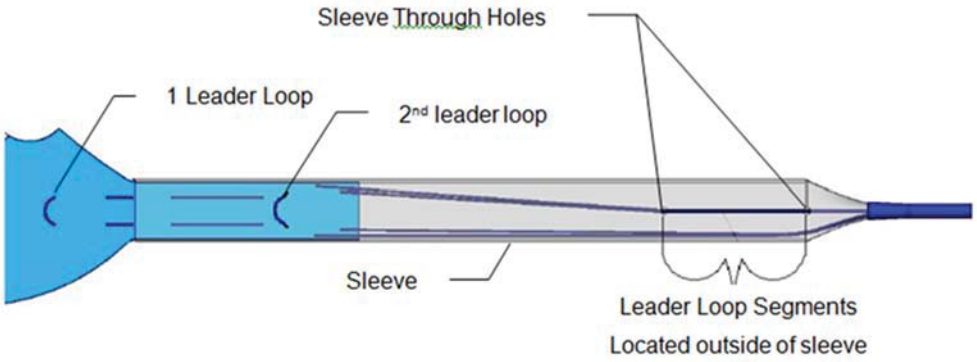
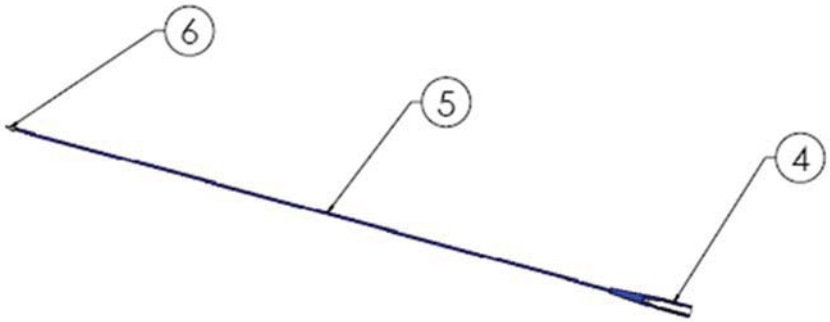


Figure 4: Detail B - Proximal End of Leg Assembly: (4) Dilator, (5) Lead & (6) Dart/Needle



Principles of Operation

The Uphold LITE mesh is intended provide structural support that recreates the hammock effect of the pubocervical fascia anteriorly and suspension of the uterosacral/cardinal ligament complex apically. In doing so, the mesh is designed to provide support of the anterior and apical vaginal compartments.

The Surgical Mesh is placed transvaginally through a single anterior incision in the vaginal wall. The physician utilizes palpation to locate the desired anatomical landmarks and fixation points. Once the desired anatomical landmarks are identified, the surgical

mesh is ready to be placed using the two Leg Assemblies. The physician follows the below steps to implant the mesh:

1. Loads one Leg Assembly onto the Capio SLIM delivery device and, then uses finger palpation to align with the sacrospinous ligament.
2. Depresses the Capio SLIM plunger to pass the dart/needle, lead and dilator portion of the Leg Assembly through the ligament.
3. Removes the Capio SLIM and repeats the process for the second Leg Assembly in the contralateral sacrospinous ligament.
4. Adjusts the Surgical Mesh by pulling outwards on the Leg Assemblies to place the mesh in its final desired location.
5. Removes the Leg Assemblies and discards them per hospital protocol.
6. Closes the vaginal incision to complete the procedure.

Figure 5: Capio SLIM Facilitates Placement

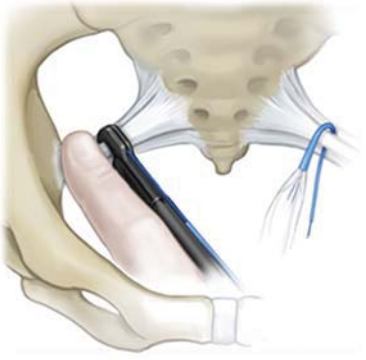
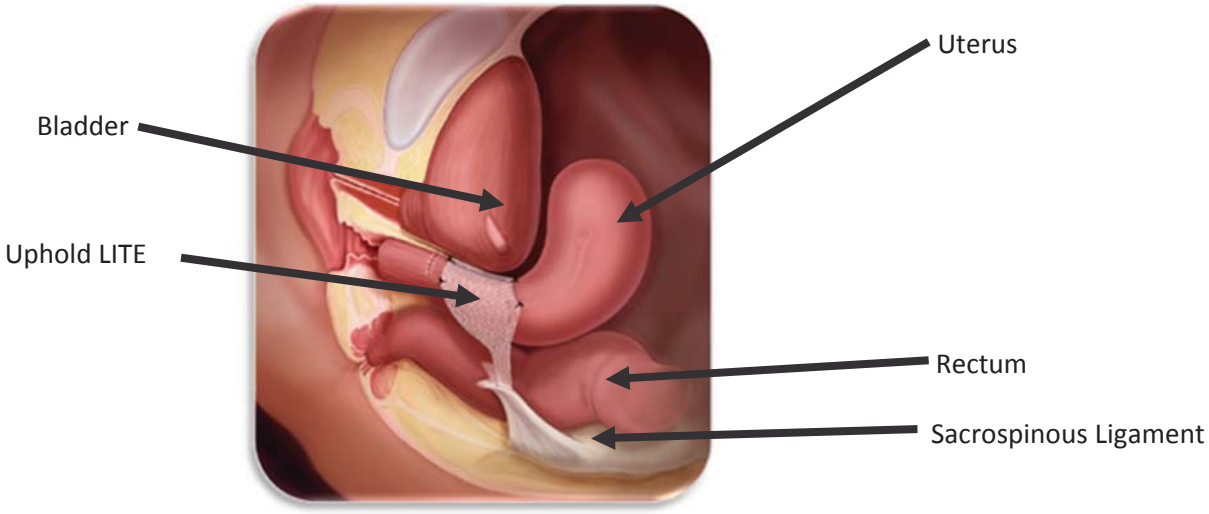


Figure 6: Uphold LITE Surgical Mesh Placement



As with all mesh products, the Uphold LITE implant is incorporated into surrounding tissue following implantation. This process involves collagen deposition and capillary penetration through the mesh construct that, once concluded, signals completion of

scar formation and host inflammatory response to the implant. The resulting tissue/mesh construct provides long term support to the prolapsed organ.

B. Xenform Soft Tissue Repair Matrix

The Xenform Soft Tissue Repair Matrix (Xenform) is a device comprised of an extracellular collagen material manufactured from bovine dermis that are sourced solely from cattle obtained in compliance with US regulatory requirements. The device is a permanent implant, with only minimal resorption[2], and is provided in sheet form in a variety of sizes to be trimmed and sutured by the surgeon to meet the individual patient's needs. Each Xenform device is supplied sterile in a single-use, double peel package.

Xenform is cut to size for the desired repair procedure and hydrated in room temperature 0.9% sterile saline. Xenform may be cut prior to hydration or hydrated prior to cutting, per the physician's preference, so long as the device remains immersed in 0.9% sterile saline until ready for use. See **Figure 7** and **Figure 8**.

Trimmed, hydrated Xenform is then surgically placed transvaginally through an anterior incision in the vaginal wall and sutured in the pelvic floor of the patient at the desired location using standard suturing techniques. Xenform is a permanent implant device that remains in contact with the patient's pelvic floor soft tissue once sutured into its desired location by a trained physician. When Xenform is in its final desired location, the physician closes the vaginal incision.

Figure 7: Image of Xenform Being Trimmed

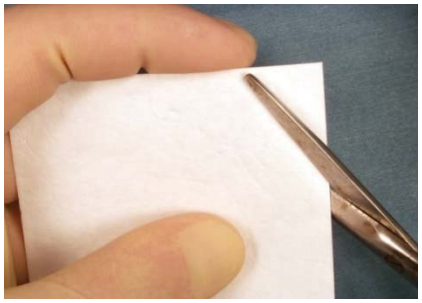


Figure 8: Image of Xenform When Hydrated

Principles of Operation

Xenform is meant for deployment in the anterior and apical vaginal compartments to recreate the hammocking support of the bladder and suspension of the vaginal apex provided anatomically by the pubocervical fascia and uterosacral ligament, respectively. The physician may trim the Xenform sheet into a trapezoidal shaped graft that features a proximal portion or base wide enough to achieve suturing to the sacrospinous ligaments and long enough to reach the bladder neck for apical suspension. The anterior portion lies underneath the bladder and is sutured centrally to the cervix and laterally and distally to the pelvic sidewall and white line for direct support of the bladder.

As with all mesh products, the mesh implant is incorporated into surrounding tissue following implantation. The extracellular scaffold serves as a template for regrowth of native tissue, which is accomplished through the constructive remodeling process that provides for long-term integration into the surrounding native tissues. The resulting tissue/mesh construct provides long term support to support the prolapsed organ.

C. Procedure and Surgical Technique

The surgical procedure for implantation of both Uphold LITE and Xenform mesh features standardized instructions that can be grouped into the following major steps:

- **Graft preparation:** ***This step is specific to the Xenform procedure*** and includes graft hydration, graft cutting into a trapezoidal shape based on the length of the vagina and the anterior vaginal space and the distance between sacrospinous ligaments.
- **Surgical site dissection**
    - Hydrodissection: Saline solution mixed with lidocaine for localized anesthesia and epinephrine for bleeding control is injected into the vaginal wall at full thickness depth, to separate tissues along natural separation lines and create space for the mesh implant to lay.
    - Full thickness incision to reach hydrodissected plane: Full thickness dissection is critical to ensuring maximum separation between the mesh implant and vaginal lumen to minimize risk of extrusions.
    - Expanding dissection plane: this step involves extending dissection in the anterior compartment to the vaginal apex to create adequate space for the mesh to lay, wrinkle- and fold-free, as well as to ensure that the proximal edge of the mesh is at the level of the cervix for durable attachment to the apex, and that maximum vaginal length corresponds to the line of mesh support along the proximal mesh arms.
    - Tunneling to para-rectal space to access and clear sacrospinous ligament: This step is intended to prepare the sacrospinous ligament for fixation. Failure to perform adequate dissection to expose and clear the ligament could lead to poor palpation

of the ligament, resulting in fixation at an unintended site that carries risk of injury to critical structures in the area or poor fixation into the ligament that could compromise durability of overall repair.

- **Mesh/Graft fixation and adjustment**
    - **Uphold LITE:** The Capio SLIM device is used to load and pass the mesh arms through the sacrospinous ligament at 2 cm medial to the ischial spine and to adjust the graft to ensure tension-free placement. Tension-free placement is critical to minimizing potential risk of dyspareunia.
    - **Xenform**: The graft is sutured proximally or at the base of the trapezoid to the sacrospinous ligaments, centrally to the cervix, and laterally and distally to the pelvic sidewall and white line, ensuring there are no folds or bunches in it for implantation.
- **Vaginal incision closure and final exam**: The vaginal incision is closed and cystoscopy and rectal exam are performed to rule out injury to the bladder, ureters, or rectum.

D. Labeling

Labeling provided with the Uphold LITE System and Xenform contains detailed contraindications and warnings to aid in appropriate patient selection. The labeling has also been updated to provide a listing of potential adverse events associated with use of transvaginal mesh devices generally (even if not previously observed with the particular product), consistent with the recommendations from the 2011 panel meeting.

The labeling further provides detailed instructions describing the surgical technique for preparation of the surgical site and implantation of the devices, as described in **Section 3C**. Patient brochures are also available, which provide information on treatment options and the benefit/risk profile of the specific device to assist patients in making informed care decisions.

E. Training

BSC has developed a physician training program that serves as an adjunct to residency and fellowship training with an emphasis on understanding patient selection, each device's mechanism of action, proper surgical technique, and surgical maneuvers. To achieve these goals, BSC's physician training program employs a continuum of product-specific training that includes the following:

Pre-Course Offerings

- Access to online education covering such topics as review of disease state, product features, relevant anatomy, surgical technique, patient selection and management of complications.
- Preceptorship with an experienced surgeon on the observation of product and surgical procedure, during which sharing of specific surgical technique tips and discussion of patient outcomes and management of complications take place.
- Product overview/in-service with a simulation training model on the product features with a Territory Manager.

Hands-On Course

- Hands-on cadaver training course that includes a didactic session from a faculty physician, surgical video overviews and breakdown of procedures, training and practice on a simulation pelvic model allowing the physicians to "implant" the product into the training model, training on a cadaver with a retro-peritoneal dissection to show relevant anatomy, and a hands-on cadaver session for the physician to see and allow full implant of the products, as well as focus on key critical steps to bolster safety and efficacy of the procedure.

Post-Course Offerings

- Proctorship in the trainee's operating room with an experienced surgeon on surgical technique over a number of cases, or until the physician trainee is comfortable with the technique.
- Use of the training model to practice steps and technique.
- Ability to reach out to faculty with questions/comments.

SECTION 4. RELEVANT REGULATORY HISTORY

Uphold LITE and Xenform were initially regulated as Class II medical devices and each received 510(k) clearance prior to marketing. Both devices are commercially available. Over time FDA received adverse event information associated with surgical mesh devices generally used for repair of POP and stress urinary incontinence (SUI), which prompted a public health notification (PHN) and subsequent panel meeting. Ultimately, the FDA mandated that surgical mesh products indicated for transvaginal repair of POP be reclassified from Class II to Class III and subject to Premarket Approval (PMA) requirements, as well as 522 order postmarket studies. BSC has engaged in extensive discussions with the FDA regarding the Uphold LITE System and Xenform Matrix as the regulatory landscape for these products has evolved over the years.

A. Initial 510(k) Clearances

The Uphold LITE System was first cleared per 510(k) K103426 on September 14, 2011. Since K103426, a subsequent 510(k) (K122459) was submitted, and cleared December 13, 2012. No changes were made to the mesh implant itself as part of this submission, but rather minor modifications to the non-implant Leg Assembly.

It's important to note that the Uphold LITE System is a separate and distinct product from the Uphold System. The Uphold System was cleared via K081048 and discontinued on January 31, 2013 [14].

Xenform was originally developed and patented by TEI (Boston, MA, USA), who obtained initial FDA clearance for the device on June 10, 2005 per K051190, and a subsequent clearance, K060984, on May 17, 2006. No changes were made to the device itself, but rather

[14] The Uphold System was a large pore monofilament mesh and had the same shape as Uphold LITE but was denser than Uphold LITE (40 g/m^2).

included changing the product name to Xenform Soft Tissue Repair Matrix and adding a new raw material sourcing geography. At the time of these submissions, TEI was the legal manufacturer of the device and distribution was performed by BSC. In 2014, BSC acquired the design of the device from TEI and has since assumed the requirements as the legal manufacturer, while TEI acts as the contract manufacturer.

The FDA 510(k) Premarket Notification review process did not require that clinical studies be conducted to support clearance of surgical mesh indicated for treatment of POP. The 510(k)s for these devices were instead supported by pre-clinical and bench studies that showed each product was substantially equivalent, in terms of safety and effectiveness, to a legally marketed predicate device.

B. 2008/2011 Public Health Notification

On October 20, 2008, the FDA issued a PHN to inform clinicians and patients about serious complications associated with transvaginal placement of surgical mesh to treat POP and SUI and to provide recommendations for mitigating risks and counseling patients. The Agency monitored adverse events through the MAUDE database and literature, updating the PHN on July 13, 2011 to keep clinicians and patients apprised of the complications related to transvaginal POP repair with mesh and inform them that the FDA no longer considered mesh-related adverse events to be "rare". The update also announced the agency's plan to convene an advisory panel meeting of outside experts to discuss the FDA's findings and the types of clinical studies which may be necessary to better assess the risks and benefits of using transvaginal mesh to treat POP and SUI.

C. 2011 Panel Meeting and Reclassification of Transvaginal Mesh Devices for POP Repair

The FDA convened an Obstetrics & Gynecology Devices Advisory Committee meeting on September 8-9, 2011 to discuss the use of surgical mesh for treatment of POP and SUI (2011 Panel meeting) in light of adverse event information obtained through MAUDE database reports from both the clinical and citizen communities, as well as published literature.

In relation to POP, the Panel was asked to provide input on the risks and benefits of surgical mesh used for repair. The Panel was also asked to weigh in on the FDA's proposed premarket and postmarket regulatory strategies for surgical mesh indicated for POP repair, including the appropriateness of implementing new Class II Special Controls versus re-classifying the device type for this intended use into Class III (PMA), and whether postmarket surveillance (Section 522) studies were required for those devices already on the market.

The Panel consensus was that: *"the safety of surgical mesh for transvaginal POP repair is not well established and that, depending on the compartment, vaginal placement of surgical mesh for POP repair may not be more effective than traditional "native-tissue" repair without mesh. As such, the Panel concluded that the risk/benefit profile of surgical mesh for transvaginal POP repair is not well established. The Panel consensus was that general controls and special controls together would not be sufficient to provide reasonable assurance of the safety and effectiveness of surgical mesh indicated for transvaginal POP*

repair, and that these devices should be reclassified from Class II to Class III."[15] For transvaginal meshes already on the market, the Panel agreed that the FDA should mandate Section 522 postmarket surveillance studies to obtain further clinical data regarding safety and effectiveness. The Panel also recommended that additional work be done to ensure that patient labeling with appropriate benefit-risk information on available treatments for POP, including surgical and nonsurgical options.

Consistent with the Panel's recommendation, FDA reclassified transvaginal mesh devices for POP repair from Class II to Class III. In doing so, the FDA noted that such devices presented perioperative risks, risks of mesh exposure and extrusion that may result in clinical sequelae (e.g., pelvic pain, infection, de novo dyspareunia, fistula formation, corrective surgeries), and occurrence of such sequelae without the presence of mesh exposure or extrusion.

D. 522 Postmarket Study Compliance

The FDA issued Section 522 Orders PS130044 for the Uphold LITE System on July 1, 2013 and PS120081 for Xenform on January 3, 2012. Following these Section 522 study orders, BSC worked in cooperation with the FDA to develop extensive postmarket surveillance studies to compare transvaginal mesh repair for each device to NTR in women undergoing surgical treatment for anterior and/or apical POP. Two separate BSC-sponsored studies were approved by the FDA and are ongoing to evaluate the Uphold LITE and Xenform devices in this context. The study protocols both have co-primary endpoints to evaluate efficacy of each device compared to NTR by a composite of objective and subjective measures, and safety by comparing rates of serious device- and/or serious procedure-related complications, where the composite primary endpoint is defined at 36 months post-surgical procedure. Secondary endpoints include Quality of Life (QOL) measures and additional pelvic-related and mesh-specific adverse events. See further discussion of these studies in **Section 7**.

E. Pre-submission Collaboration with the FDA

As a result of the reclassification of surgical mesh for transvaginal POP repair into Class III, BSC and the FDA have had extensive communications relating to the Uphold LITE System and the Xenform Soft Tissue Repair Matrix. Per direction from the FDA, BSC requested a bundled Pre-Submission Meeting with the FDA to discuss the planned PMA submissions for both the Uphold LITE (Q170382) and Xenform (Q172064) devices. During the meeting, the FDA and Boston Scientific agreed that the PMA submissions would present 12-month data, although the primary endpoint for the studies was defined at 36 months.

F. PMA Submission Summary

The Uphold LITE Vaginal Support System PMA (P180018) was submitted and formally filed by the FDA on June 27, 2018.

[15] https://www.federalregister.gov/documents/2014/05/01/2014-09907/reclassification-of-surgical-mesh-for-transvaginal-pelvic-organ-prolapse-repair-and-surgical

The Xenform Soft Tissue Repair Matrix PMA (P180021) was submitted and formally filed by the FDA on June 28, 2018.

The PMA submissions for both products met the FDA's requirement that PMA applications for transvaginal mesh products on the market be filed by July 5, 2018.

SECTION 5: PRECLINICAL TESTING

The Uphold LITE System and Xenform have undergone extensive pre-clinical testing to support their design. Testing included evaluations to ensure sufficient strength and characteristics of the material, and biocompatibility test results. in accordance with FDA-recognized standards to confirm the devices were biocompatible for their intended use. Both mesh products are implantable devices that are terminally sterilized per ISO 11135 requirements. The devices and their respective packaging each have a validated shelf-life of three years based on testing to ensure continued performance and packaging integrity in accordance with their specifications. Complete information on the preclinical testing was provided in the original 510(k) Premarket Notifications for the devices, as well as in the pending PMA Submissions.

SECTION 6: LITERATURE REVIEW

A. 2011 FDA Panel Literature Review Discussion

In the FDA executive summary for the 2011 Panel meeting, a literature review was included to assess the rate of mesh-specific adverse events. The review relied on a number of systematic meta-analyses that spanned several years, and much of the encompassed literature reflect older synthetic mesh design products and limited literature was incorporated related to biologic mesh devices. The focus of devices subject to the literature review did not fully represent synthetic and biologic mesh products currently on the market.

The retrospective analysis by Abed et al.[3] was used as one of the primary references to establish adverse event rates and included publications from 1950 to 2007. Abed et al. reported exposure rates of 10.3% for non-absorbable synthetic mesh and 10.1% for biologic grafts, where 56% of those experiencing erosion required surgical excision. It is important to note that this retrospective review included literature articles that described off label use of surgical mesh intended for abdominal hernia repair and not necessarily FDA cleared urogynecological mesh intended for POP.

Diwadkar et al.[4], which is based on a review of data published between 1985-2008, also served as a primary reference in the 2011 Panel meeting and was instrumental in what was determined to be complications requiring re-surgery rates for transvaginal mesh compared to sacrocolpopexy and NTR. In this meta-analysis, the re-surgery rates for complications were 7.2% for transvaginal mesh, 4.8% for sacrocolpopexy, and 1.9% for traditional vaginal (presumed native tissue) repair. The transvaginal mesh kits represented included Apogee (American Medical Systems, Inc.), Posterior Gynecare Prolift System and Total Gynecare Prolift System (Ethicon Women's Health and Urology), and Total Vaginal Mesh and Posterior Intravaginal Slingplasty (Tyco Healthcare, United States Surgical).

Other studies also cited in the 2011 Panel meeting were Iglesia et al. (2010)[16], where Ethicon Prolift mesh was evaluated in 32 subjects compared to 33 NTR subjects, and Withagen et al. (2011)[17], evaluating 93 women treated with the Ethicon Prolift mesh delivered through a trocar-guided implantation procedure and 97 NTR subjects. These publications were used to support that there was no evidence that mesh repair of apical prolapse resulted in significant improvement in anatomic outcome.

Many of the procedures performed during the time that the Abed et al. and other publications were written were based on a "mesh inlay technique", which involved fascial plication with placement of mesh on top of it. These procedures represent an early mesh placement technique and do not reflect current standard practice for use of transvaginal mesh in general, or the design of the Uphold LITE device in particular. Attaching mesh to plicated fascia does not offer better results over standard repairs. This can be reasonably explained by the fact that since mesh inlays were only attached to plicated fascia, it can be as susceptible to fail, as either the sutures holding the plicated fascia together or the sutures holding the mesh to the plicated fascia. For patients who suffer from paravaginal failures or separation of pubocervical fascia from pelvic sidewall, attaching mesh to fascia that is already separated and is part of the failure cannot be expected to offer any durability. For mesh to offer durability or provide any structural support, it must be attached laterally to pelvic sidewall to form a hammock similar to the one created anatomically by the pubocervical fascia or to the sacrum to suspend the vaginal apex, as is done with sacrocolpopexy and current techniques for the implantation of transvaginal mesh devices.

In contrast to the synthetic mesh products that were commercially available in the early 2000s, the mesh used in the Uphold LITE Vaginal Support System is far lighter at 25 gm/m^2, it is also placed directly via a single incision without the use of trocars, external incisions, or passes through muscles. In addition, Uphold LITE is directly fixated using the Capio SLIM suturing device, thus avoiding fixation arms across multiple tissue planes. Uphold LITE offers better repair durability than standard repairs given its improved characteristics in terms of lighter density (light weight), lower surface area, and larger pore size. Most importantly, it also offers a fundamentally different structural support and mechanism of repair than mesh inlays and the surgical technique used to implant them. Although Xenform is not a synthetic mesh, as described in **Section 3**, the procedure and surgical technique, including route of placement (transvaginal approach), surgical site dissection, and fixation and adjustment procedural steps are by and large the same as those for Uphold LITE. Both of these devices offer (1) apical suspension that fixate into the sacrospinous ligament and (2) bladder support by way of attaching the mesh to the pelvic sidewall (the vaginal apex), which is considered the cornerstone of pelvic support architecture. Half of the observed variation in anterior compartment support may be explained by apical support and loss of apical support is critical

[16] Iglesia C.B., et al, Vaginal mesh for prolapse: a randomized controlled trial. Obstet Gynecol, 2010. 116(2 Pt 1): p. 293-303.

[17] Withagen M.I., et al, Trocar-guided mesh compared with conventional vaginal repair in recurrent prolapse: a randomized controlled trial. Obstet Gynecol. 2011. 117(2 Pt 1): p. 242-50.

to development of anterior vaginal prolapse.[18] Furthermore, suspension of the vaginal apex is associated with correction of cystoceles in 55% of cases and rectoceles in 30%.[19]

The literature presented herein for Uphold LITE (**Section 6B**) and Xenform (**Section 6C**) offer a significant amount of evidence demonstrating that these devices are effective treatment options achieving both anatomic and subjective success as well as improvements to QOL measures.

B. Uphold LITE Vaginal Support System

Published literature supports the benefit of the Uphold LITE device in terms of repair of prolapse in addition to clinically meaningful measures, and further that these benefits can be achieved with low complication rates. Refer to **Appendix 1** for additional details regarding the literature search strategy.

The five-year prospective study by Rahkola-Soisalo et al.[20] is particularly valuable in that it is relatively large (207 subjects) and represents the longest prospective follow-up of subjects treated with the contemporary Uphold LITE procedure. Strengths of the study include the relatively low loss to follow-up, exclusion of concurrent procedures that may be a cause for misclassification, the standardized surgical method and postoperative protocol, and use of validated instruments for outcome measures. Anatomic success was achieved in 93.5% of subjects at one year and there was not a statistically significant decline at five years ($p = 0.2$). All the domains of the Pelvic Floor Distress Inventory (PFDI-20) improved from the preoperative visit to the five-year follow-up visit, and there were no significant differences in the scores between the one-year and five-year visits. After five years, the total score points exceeded the baseline points in 89.4% of the women, whereas in 78.8% of the women, a minimal clinically important difference (>23 points) was reached.

Between one- and five-year follow-up, a total of 29 (19.7%) of the women had undergone additional pelvic surgery. The majority of additional surgeries performed were not related to recurrent anterior/apical prolapse and not specific to adverse events related to the Uphold LITE device. The most common of these additional surgical procedures were mid-urethral slings, hysterectomy, and posterior colporrhaphy. Seventeen were prolapse-related and included procedures such as posterior colporraphy, hysterectomy, and anterior colporrphia.

Three subjects underwent mesh removal due to pain and the rate of extrusion at five years was 1.4%; all of these subjects were treated with local estrogen and none required surgical intervention. This represents the longest prospectively followed cohort to receive a contemporary Uphold LITE procedure and the results of this study suggest that the benefit seen from the Uphold LITE System can be durable and achieved with modest complication rates, with

[18] DeLancey et al., The Relationship Between Anterior and Apical Compartment Support. American Journal of Obstetrics & Gynecology (2006) 194, 1438-43

[19] Lowder et al., The Role of Apical Vaginal Support in the Appearance of Anterior and Posterior Vaginal Prolapse. Obstetrics & Gynecology 2008; 111 (1): 152-7)

[20] Rahkola-Soisalo et al. Pelvic Organ Prolapse Repair Using the Uphold Vaginal Support System: 5-Year Follow-up. Female Pelvic Medicine and Reconstructive Surgery.

the most common being urinary incontinence (7.2%), prolapse related problems (6.5%), and chronic pain (2.6%).

There have been three recent short and long-term follow-up studies where meaningful numbers of patients were implanted with second-generation mesh that can inform an opinion on whether or not improvements in the physical properties of the transvaginal mesh and use of contemporary surgical techniques for implantation result in improved outcomes and, more importantly, an acceptable risk-benefit ratio. Most recently, the SUPeR study (see discussion in **Section 6.C**) abstract was presented at the 2018 American Urogynecology Society (AUGS) Meeting. Nager et al.[21] was the first long-term, multicenter, prospective, randomized trial comparing Uphold LITE versus hysterectomy and native tissue ureterosacral ligament suspension. Follow-up through 48 months was reported on 175 randomized subjects. The composite primary endpoint was absence of prolapse symptoms, no objective prolapse beyond the hymen, and no retreatment for prolapse. Results demonstrated good efficacy for both the Uphold LITE and NTR. There was no difference in efficacy between the two groups as assessed by the primary endpoint and the mesh exposure rate was 8%.

In 2016, Altman et al.[22] published results from a prospective, multicenter study on 207 patients using the Uphold LITE Vaginal Support System in women with Pelvic Organ Prolapse Quantification (POP-Q) Stage 2 or greater apical POP, with or without concomitant anterior vaginal wall prolapse. After two months of follow-up, 91% (157/172) of subjects achieved the optimal anatomical outcome of POP-Q Stage ≤ 1. After one year of follow-up, the rate of objective success by this metric increased to 94% (154/164 subjects). Assessed separately, both anterior and apical compartments showed significant anatomic improvement ($p < 0.001$). In addition, subjective success was achieved in 91% (165/181) of subjects. With regard to safety, at one-year follow-up, the rate of serious complications was 4.3% (9/207 subjects); this included three surgeries due to mesh exposure (1.4%), two mesh removals because of pain, three bladder perforations, and one case of >1000 mL bleeding.

In 2011, Altman, et al.[23] reported on a multi-center, parallel-group, randomized controlled trial that compared the use of polypropylene mesh repair (Uphold LITE) compared to NTR (colporrhaphy) in women with cystocele. The study enrolled patients with primary or recurrent prolapse of the anterior vaginal wall of POP-Q stage ≥2 and symptoms of vaginal bulge or pelvic heaviness. Two hundred subjects were treated with Uphold LITE and 189 with NTR. The primary outcome was a composite of objective anatomical outcome of stage 0 or 1, as measured by POP-Q, and subjective absence of vaginal bulge symptoms at 12 months.

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[21] Nager CW, Zyczynski H, Rogers RG, Barber MD, Richter HE, Visco AG, Rardin CR, Harvie H, Wallace D, Meikle SF; Pelvic Floor Disorders Network. The Design of a Randomized Trial of Vaginal Surgery for Uterovaginal Prolapse: Vaginal Hysterectomy With Native Tissue Vault Suspension Versus Mesh Hysteropexy Suspension (The Study of Uterine Prolapse Procedures Randomized Trial). Female Pelvic Med Reconstr Surg. 2016 Jul-Aug;22(4):182-9.

[22] Altman D, Mikkola TS, Bek KM, Rahkola-Soisalo P, Gunnarsson J, Engh ME, Falconer C; Nordic TVM Group. Pelvic organ prolapse repair using the Uphold™ Vaginal Support System: a 1-year multicenter study. Int Urogynecol J. 2016 Sep;27(9):1337-45.

[23] Altman D., et al, Anterior Colporrhaphy versus Transvaginal Mesh for Pelvic-Organ Prolapse. N Engl J Med., 2011. 364: p. 1826-36.

Results showed a statistically significant difference in primary success in subjects who were treated with Uphold LITE versus NTR (68.0% vs. 34.5%, p < 0.001). Of further note, mesh repair remained superior to NTR with respect to the primary outcome in a sensitivity analysis that imputed outcomes that were disadvantageous for mesh repair (adjusted odds ratio, 2.1; 95%CI: 1.4-3.3). For secondary outcomes, Uphold LITE was superior to NTR in terms of anterior vaginal wall support restoration to POP-Q stage 0 or 1 (82.3% vs. 47.5%, p < 0.001); superiority of Uphold LITE was also shown for subjective success in patient reporting of symptoms of bulge (75.4% vs. 62.1%, p = 0.008). On quality of life, mean Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire (PISQ-12) scores were modestly improved over baseline and were similar between Uphold LITE and NTR arms. Rates of de novo SUI after surgery were 12.3% for Uphold LITE vs. 6.3% for NTR (p = 0.05), and de novo SUI symptoms were statistically significantly more bothersome in subjects treated with Uphold LITE versus NTR (p = 0.02); however, obstructive symptoms were significantly less bothersome (p = 0.01). Bladder perforation rates were 3.5% for Uphold LITE vs. 0.5% for NTR (p = 0.07). Mesh exposure requiring surgical intervention occurred in 3.2% of Uphold LITE subjects. One subject in the NTR group experienced recurrent prolapse for which a second anterior repair was performed. These results demonstrated that the use of Uphold LITE for primary repair of POP resulted in a higher success rate than NTR based on composite objective and subjective outcomes and a lower risk of prolapse recurrence. While Uphold LITE also demonstrated higher rates of surgical complications and adverse events. The authors concluded the benefits of the higher success rates of Uphold LITE should be balanced against higher complication and AE rates when counseling patients regarding surgical treatment options.

Other noteworthy publications that support both the safety and efficacy of Uphold LITE include Gutman et al.[24] In terms of efficacy, this study reported that laparoscopic sacral hysteropexy (LSHP) and vaginal mesh hysteropexy (VMHP) using Uphold[14] and Uphold LITE had similar cure rates and high satisfaction at one-year post procedure. After adjusting for baseline differences, there was no difference in:

- Composite cure (72% LSHP vs. 74% VMHP; adjusted OR, 0.58; 95% CI, 0.2-1.5; P=0.27);
- Anatomic cure (77% LSHP vs. 80% VMHP; adjusted OR, 0.48; 95% CI, 0.2-1.5; P=0.20);
- Symptomatic cure (90% LSHP vs. 95% VMHP; adjusted OR, 0.4; 95% CI, 0.7-1.8; P=0.22).

The vaginal mesh hysteropexy group had shorter surgical time compared to the laparoscopic group. Both reported similar improvement in pelvic floor symptoms and sexual function. Satisfaction, as measured by the Patient Global Impression of Improvement (PGI-I) questionnaire, was 95% in each group. With respect to safety, overall complication rates were low, with the most commonly reported AE being urinary tract infection. Mesh erosions occurred in 2.7% (2/74) of the LSHP and 6.6% (5/77) of the VMHP groups. Moreover, AE classification using the Clavien-Dindo scale was similar in both groups.

[24] Gutman RE, Rardin CR, Sokol ER, Matthews C, Park AJ, Iglesia CB, Geoffrion R, Sokol AI, Karram M,Cundiff GW, Blomquist JL, Barber MD. Vaginal and laproscopic mesh hysteropexy for uterovaginal prolapse: a parallel cohort study. *Am J Obstet Gynecol.* 2017 Jan; 216(1):38.e1-38.e11.

Lo et al.[25] retrospectively reported on 12-month follow-up of women who underwent correction of anterior – apical prolapse with Uphold LITE between February 2015 and July 2016. Of 89 subjects that met the inclusion criteria, the objective anatomic cure rates were 97.7% anteriorly and 98.9% at the apex. There were no mesh exposures reported and the only SAE reported was a bladder injury.

C. Xenform Soft Tissue Repair Matrix

Published literature supports the benefit of the Xenform device in terms of repair of prolapse in addition to clinically meaningful measures, and further that these benefits can be achieved with low complication rates. Refer to **Appendix 1** for additional details regarding the literature search strategy.

One relevant clinical trial study publication met the inclusion criteria. For this study (Goldstein et al.[5]), restoration of normal anatomy in any compartment, symptom relief, QOL, and sexual function over a one-year period were evaluated. In 43 of 45 patients that completed 12 months of follow-up, the success rate was 88% and there were statistically significant improvements in anterior, posterior, and apical support. Mean PFDI-20 score improvement of 72% indicated significantly improved symptomatic outcomes. PISQ-12 scores also showed significant improvement, indicating no decline in sexual function. Complications were minimal, and there were no graft erosions and no pain lasting more than 30 days. These results demonstrated significant improvement in both objective and subjective outcomes at 12 months in subjects who underwent POP repair using Xenform, reflecting a positive risk/benefit profile for the device.

D. Literature Conclusion

Taken together, the Uphold LITE and Xenform literature demonstrate that these devices are effective treatment options achieving both anatomic and subjective success and improvements to QOL measures. These recent studies further suggest that mesh exposure rates and re-operation rates for mesh exposure for the Uphold LITE System are improved compared to what was reported in the compilation of studies referenced in the in 2011 Panel meeting that largely reported on first generation synthetic mesh kits. It should be noted that the complication rates reported for the Uphold LITE System in the literature are in line with those reported for other second-generation mesh systems. For instance, Su et al.[26] compared the Elevate Anterior & Apical Transvaginal Mesh System in 100 patients to 101 patients who underwent NTR. In the 100 Elevate patients, at one-year follow-up, there was a 3% mesh erosion rate and 1% rate of repeat surgery for mesh erosion. The rates of mesh exposure/erosion reported in the studies discussed above for transvaginal POP repair also compare favorably to the reported rates of mesh-specific complications after sacrocolpopexy.[27]

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[25] Lo et al. Anterior-apical single-incision mesh surgery (uphold): 1-year outcomes on lower urinary tract symptoms, anatomy and ultrasonography. International Urogynecology Journal June 2018.

[26] T.H. Su, H.H. Lau, W.C. Huang, C.H. Hsieh, R.C. Chang, C.H. Su, Single-incision mesh repair versus traditional native tissue repair for pelvic organ prolapse: results of a cohort study, Int Urogynecol J, 25 (2014), pp. 901-908

[27] See, e.g., Nygaard IE, McCreery R, Brubaker L, Connolly A, Cundiff G, Weber AM, Zyczynski H (2004) Abdominal sacrocolpopexy: a comprehensive review. Obstet Gynecol 2004 Oct; 104:805–23 (reporting a 3.4% mesh erosion rate).

These outcomes compare favorably to studies reporting on the efficacy and safety of NTR, as can be seen in the controlled studies discussed above which directly compared an Uphold LITE arm to a control arm, as well as in other studies discussing the outcomes of NTR. The Cochrane review[12] of surgical management of POP, which covered a total of 5,954 women undergoing surgery for POP repair in 56 randomized controlled trials, included assessment of 10 studies comparing NTR with synthetic and biologic mesh for repair of anterior POP. Based on the data from those studies, transvaginal mesh was more effective than NTR both in terms of sustainable anatomic repair and symptomatic improvement. Specifically, NTR was associated with more recurrent anterior prolapse than when supplemented with mesh. Three studies assessing vaginal prolapse in multiple compartments also found a lower prolapse recurrence rate with polypropylene mesh as compared to NTR.

The literature data reported above demonstrates a consistent safety and effectiveness profile for the BSC devices, where effectiveness in both the short and long term is comparable to or better than NTR, and with a comparative rate of serious and non-serious complications.

SECTION 7: CLINICAL EXPERIENCE

This section provides data from the ongoing 522 postmarket studies for the Uphold LITE System and Xenform (**Section 7A**). Note that per the approved protocols, the purpose of the studies is to investigate the long-term safety and effectiveness of the devices out to 36 months. For purposes of the PMA submissions and the re-classification of transvaginal mesh for POP repair, only the complete 12-month data are currently available. Data from additional time points have also been made available for informational purposes only; no conclusions can be drawn based on that data due to the low amount available at the time of database lock and data extraction, and the resulting assessments are likely to evolve as the study progresses.

This section also contains a discussion of all BSC clinical data available for both devices (**Section 7B**), information for one additional clinical study that that has been completed for Uphold LITE (**Section 7C**), and real-world complaint data and analysis for both devices (**Section 7D**).

A Risk Benefit Discussion, which outlines the risk/benefit profile for both devices and justifies, through the data presented in this section, why it is appropriate to continue making these devices available based on the totality of evidence, is provided in **Section 8**.

A. Overview of BSC 522 Postmarket Studies

1. Introduction

BSC is currently conducting two 522 postmarket surveillance studies for POP, one for the Uphold LITE System and one for Xenform. Both studies are prospective, non-randomized, parallel cohort, multi-center clinical investigations designed to compare transvaginal mesh repair (TMR) to NTR in women surgically treated for anterior and/or apical POP. The studies are being conducted in partnership with AUGS under the Pelvic Floor Disorders (PFD) Registry and investigate long-term safety and effectiveness of POP repair out to 36 months.

The studies were developed in collaboration with the FDA and were designed in accordance with recommendations from the 2011 Panel meeting, with extensive communications between BSC and the FDA regarding study design, subject population, statistical analyses, etc. The 522 studies were designed to evaluate two primary endpoints: (1) clinically relevant measures of effectiveness, based on a composite of anatomic and subjective success and absence of retreatment, and (2) assessment of serious device- and procedure-related adverse events (SAEs). The FDA recommended that study subjects should be evaluated at least out to 12 months to support safety and effectiveness of each device prior to submission of a marketing application, with at least an additional two years of postmarket follow-up. During the conduct of the studies, BSC has remained in close contact with the FDA regarding updates to the study protocols, all of which have been fully discussed with and approved by the FDA.

BSC initiated and executed the studies in accordance with the FDA-approved protocols and believes that they include appropriate, clinically relevant subject populations, rigorous study designs, and clinically meaningful efficacy and safety endpoints. BSC believes that these studies satisfy the recommendations set forth by the Panel members during the 2011 Panel meeting, as well as the FDA's recommendations and requirements as included in the

reclassification order, and remain aligned with the FDA's thinking over time on the topic of transvaginal surgical mesh for use in POP repair.

2. Overview of Studies

The Uphold LITE Postmarket Surveillance Study, titled *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*, is registered at ClinicalTrials.gov under number NCT01917968. Subjects enrolled in this study received either transvaginal mesh (Uphold LITE) or NTR (sacrospinous ligament fixation or uterosacral ligament suspension and/or colporrhaphy), with scheduled follow-up visits at 2, 6, 12, 18, 24 and 36 months.

The Xenform Postmarket Surveillance Study, titled *A Prospective, Non-Randomized, Parallel Cohort, Multi-Center Study of Xenform vs. Native Tissue for the Treatment of Women with Anterior/Apical Pelvic Organ Prolapse*, is registered at ClinicalTrials.gov under number NCT01945580. Subjects enrolled in this study received either transvaginal mesh (Xenform) or NTR (sacrospinous ligament fixation or uterosacral ligament suspension and/or colporrhaphy), with scheduled follow-up visits at 2, 6, 12, 18, 24 and 36 months.

The studies utilize co-primary endpoints where the primary efficacy endpoint is a composite of objective, subjective, and retreatment measures and is evaluated in conjunction with the primary safety endpoint. For both studies, the primary efficacy and safety endpoints are scheduled to be evaluated following completion of subject 36-month follow-up visits.

a. Efficacy Endpoints

Both studies evaluate efficacy as a composite of objective, subjective, and retreatment measures to ensure both surgical success and subject satisfaction. The criteria for efficacy were chosen with extensive input from the FDA. The FDA commented in their 2011 Panel meeting presentation that the most used study efficacy endpoint for "ideal pelvic support" was POP-Q stage 0-1, where the most distal prolapse is > 1 cm above the hymen, and the FDA did not believe this was a clinically meaningful outcome measure; the Panel agreed. Thus, the two composite efficacy endpoints were agreed upon to better account for additional relevant considerations in evaluating the treatment's success. The absence of retreatment portion of the primary and secondary efficacy endpoints and inclusion of the assessment of the Trial of Mid-Urethral Slings (TOMUS) pain scale allow the studies to address efficacy in line with concerns expressed by the FDA, specifically for treatment failure and pain.

Both clinical studies utilize the following primary efficacy endpoint:

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 Pelvic Organ Prolapse Quantification System (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 POP-Q 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 anatomic segment(s) treated at the index surgery or no pessary use since index surgery (i.e., 'treated segment' refers to the target compartment).

The secondary efficacy endpoint for both studies also consist of a composite of objective, subjective, and retreatment measures. The secondary efficacy endpoint measures are identical to the primary efficacy endpoint requirements in terms of subjective success and the requirement for there to be no retreatment for POP; however, the anatomic criteria are slightly different. In the secondary endpoint, anatomic success in the operated compartment is defined as follows:

- Anterior segment: No anterior prolapse at or beyond the hymen (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 POP-Q point C ≤ 0 for single compartment apical prolapse).

Patient reported outcomes for various QOL measurements, including pelvic floor symptoms per PFDI-20, QOL per the Pelvic Impact Questionnaire (PFIQ-7), sexual functioning per PISQ-12, pain per the TOMUS pain scale, and subject's level of improvement per PGI-I for Prolapse, are also incorporated as secondary efficacy endpoints.

b. Safety Endpoints

The primary safety endpoint for both studies is a comparison of serious device- and/or serious procedure-related adverse events (AEs) between baseline and the 36-month time point. The secondary safety endpoints include analysis of overall device- and procedure-related AEs, mesh erosion and exposure, and de novo dyspareunia. In order to better understand the potential for pelvic-specific AEs that were discussed during the 2011 Panel meeting, assessments of pelvic pain, infection, vaginal shortening, atypical vaginal discharge, neuromuscular problems, vaginal scarring, de novo vaginal bleeding, de novo voiding dysfunction, and fistula formation were performed. Additionally, in order to address the FDA's concern from the 2011 Panel meeting regarding surgical intervention, BSC analyzed interventions for recurrent prolapse and complications post index procedure as separate secondary endpoints. These endpoints encompass all of the FDA's safety-related concerns associated with the use of transvaginal mesh for POP repair.

3. Study Populations

Both the Uphold LITE and Xenform Postmarket Surveillance Studies enrolled adult, non-pregnant women who had been diagnosed with anterior and/or apical POP (i.e., POP-Q scores of Ba ≥ 0 for anterior prolapse, or C ≥ 0 for apical prolapse, or C ≥ - ½ TVL and Ba ≥ 0 for multi-compartment anterior and apical prolapse; and with subject-reported bothersome bulge they could see or feel), were scheduled to undergo surgical repair, and who may or may not have required a concomitant procedure (such as a posterior repair, hysterectomy, or sling placement for SUI). The enrollment criteria reflected the FDA recommendations from the 2011 Panel meeting including that a population reflect women age 18 years or older with documented POP and who were already scheduled for surgery should be evaluated, with further consideration given to the level of prolapse (i.e., above or below the hymenal ring). Subjects who had a previous prolapse repair with mesh in the target compartment, were planning to undergo a concomitant repair with the use of mesh in the non-target compartment and had chronic systemic or focal pain in the pelvic area were excluded from participation in the study. Following are the specific enrollment (inclusion/exclusion) criteria for each of the studies:

Uphold LITE

Subjects who met all of the following criteria were given consideration for inclusion in the Uphold LITE study (provided no exclusion criterion were met):

- Subject is female
- Subject is ≥ 18 years of age
- 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)
- 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)
- Subject or subject’s legally authorized representative must be willing to provide written informed consent
- Subject is willing and able to comply with the follow-up regimen

Subjects who met any of the following criteria were excluded from the Uphold LITE study:

- Subject is pregnant or intends to become pregnant during the study
- Subject has an active or chronic systemic infection including any gynecologic infection, untreated urinary tract infection (UTI) or tissue necrosis
- Subject has history of pelvic organ cancer (e.g. uterine, ovarian, bladder, colo-rectal or cervical)
- Subject has had prior or is currently undergoing radiation, laser therapy, or chemotherapy in the pelvic area

- Subject has taken systemic steroids (within the last month), or immunosuppressive or immunomodulatory treatment (within the last 3 weeks)
- Subject has systemic connective tissue disease (e.g. scleroderma, systemic lupus erythematosus (SLE), Marfans syndrome, Ehlers Danlos, collagenosis, polymyositis, polymyalgia rheumatica)
- Subject has a known neurologic or medical condition affecting bladder function (e.g. multiple sclerosis, spinal cord injury, or stroke with residual neurologic deficit)
- Subject is seeking obliterative vaginal surgery as treatment for pelvic organ prolapse (colpocleisis)
- Subject has a previous prolapse repair with mesh in the target compartment
- Subject is planning to undergo a concomitant repair with use of mesh in the non-target compartment
- Subject is not able to conform to the modified dorsal lithotomy position
- Subject has chronic systemic pain that involves the pelvic area or chronic focal pain that involves the pelvis pelvic pain)
- Subject has uncontrolled diabetes mellitus (DM)
- Subject is currently participating in or plans to participate in another device or drug during this study
- Subject has a known hypersensitivity to polypropylene mesh

Xenform

Subjects who met all of the following criteria were given consideration for inclusion in the Xenform study (provided no exclusion criterion were met):

- Subject is female
- Subject is ≥ 18 years of age
- 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)
- 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)
- Subject or subject’s legally authorized representative must be willing to provide written informed consent
- Subject is willing and able to comply with the follow-up regimen

Subjects who met any of the following criteria were excluded from the Xenform study:

- Subject is pregnant or intends to become pregnant during the study
- Subject has an active or chronic systemic infection including any gynecologic infection, untreated urinary tract infection (UTI) or tissue necrosis

- Subject has a history of pelvic organ cancer (e.g. uterine, ovarian, bladder, colo-rectal or cervical)
- Subject has had prior or is currently undergoing radiation, laser therapy, or chemotherapy in the pelvic area
- Subject has taken systemic steroids (within the last month), or immunosuppressive or immunomodulatory treatment (within the last 3 months)
- Subject has a systemic connective tissue disease (e.g. scleroderma, systemic lupus erythematosus (SLE), Marfan Syndrome, Ehlers Danlos, collagenosis, polymyositis, polymyalgia rheumatica)
- Subject has chronic systemic pain that includes the pelvic area or chronic focal pain that involves the pelvis
- Subject has uncontrolled diabetes mellitus (DM)
- Subject has a known neurologic or medical condition affecting bladder function (e.g., multiple sclerosis, spinal cord injury or stroke with residual neurologic deficit)
- Subject is seeking obliterative vaginal surgery as treatment for pelvic organ prolapse (colpocleisis)
- Subject is not able to conform to the modified dorsal lithotomy position
- Subject is currently participating in or plans to participate in another device or drug study during this study
- Subject has a known sensitivity to any Xenform component
- Subject has had previous prolapse repair with mesh in the target compartment
- Subject is planning to undergo a concomitant prolapse repair with use of mesh in the non-target compartment

Additionally, the FDA recommended that consideration be given to risk factors such as primary versus recurrent prolapse, menopausal status, estrogen use, age, lifestyle factors, obesity, modification of mesh prior to placement, surgical technique, etc. While these factors did not form the basis of any enrollment criteria, the study protocols specified that demographic information be collected for each subject to understand whether or not these factors were balanced between the treatment and control arms.

In the Uphold LITE and Xenform Postmarket Surveillance Studies, a portion of the NTR control arm subjects were enrolled at the study sites and the remainder of control subjects were shared from the AUGS PFD Registry. This was the result of a collective and joint agreement with the FDA that the AUGS PFD Registry database would be utilized for the study and pooled subjects would be used for the NTR arm for all industry partners. Subjects selected from the AUGS PFD Registry for the NTR arm were required to conform with the inclusion/exclusion criteria for the Uphold LITE and Xenform studies in order to be included in the data analysis.

a. Analysis Populations

Subjects were screened against the study inclusion/exclusion criteria and, if eligible, were asked to provide written Informed Consent. Informed Consent was administered prior to any study procedure; therefore, subjects were considered enrolled into the study once an incision was made in the vaginal wall. All enrolled subjects are considered part of the Intent- to-Treat (ITT) population for analysis. All eligible subjects enrolled who underwent the assigned study procedure and had no inclusion/exclusion criteria violations are considered part of the Per Protocol population. The As Treated population were defined according to study procedures that they actually received.

b. Sample Sizes

For the Uphold LITE Postmarket Surveillance Study, a superiority hypothesis test is specified for the primary efficacy endpoint at 36 months. The co-primary safety endpoint will be assessed as a non-inferiority objective. A sample size of 414 subjects was planned to power the primary efficacy and primary safety objectives at a power level of 80% or above.

For the Xenform Postmarket Surveillance Study, a non-inferiority hypothesis test is specified for the primary efficacy endpoint at 36 months. The co-primary safety endpoint will be assessed as a non-inferiority objective. A sample size of 454 subjects was planned to power the primary efficacy and primary safety objectives at a power level of 80% or above.

4. Follow-up Schedules

For both studies, each subject was instructed to return for follow-up visits at 2 and 6 months (± 4 weeks) and at 12, 18, 24 and 36 months (-4/+12 weeks). The follow-up visit schedule began from the day the subject was discharged post-procedure. All subjects who completed surgery and discharge are being followed out to 36 months. All subjects completing the 36-month follow-up visit will be considered to have completed the studies. Assessments completed at designated follow-up visits include:

- Pelvic exam with vaginal length measurement
- Prolapse Grading (POP-Q Scoring)
- Assessment of pain (TOMUS pain scale) and analgesic intake
- Assessment of pelvic floor symptoms (PFDI-20)
- Assessment of adverse events (device, procedure, or pelvic floor related)
- Assessment of risk factors
- Pelvic Floor Impact Questionnaire (PFIQ-7) (Month 6, 12, 18, 24 and 36 only)
- Pelvic Organ Prolapse/ Urinary Incontinence Sexual Questionnaire (PISQ-12) (Month 6, 12, 18, 24 and 36 only)
- Patient Global Impression of Improvement (PGI-I) for Prolapse (Month 6, 12, 18, 24 and 36 only)

- Surgical Satisfaction Questionnaire (SSQ-8) for surgical satisfaction (Month 6, 12, 24, and 36 only)
- EQ-5D for health status (Month 12, 24, and 36 only)

5. Study Status

Twenty-seven clinical sites actively participated in enrolling subjects into the Uphold LITE Postmarket Surveillance Study and enrollment was completed on December 31, 2016. A total of 289 subjects were enrolled, with 225 subjects in the Uphold LITE treatment group and 64 subjects in the NTR control group. In addition, 418 subjects from the AUGS PFD Registry are included in the NTR population, yielding a total of 482 NTR subjects and 707 subjects overall. The study is currently ongoing and all 12-month follow-up visits have been completed, with an estimated date for completion of all 36-month follow-up visits in December 2019.

Twenty-five clinical sites actively participated in enrolling subjects into the Xenform Postmarket Surveillance Study and enrollment was completed on December 31, 2016. A total of 374 subjects were enrolled, with 228 subjects in the Xenform treatment group and 146 subjects in the NTR control group. In addition, 336 subjects from the AUGS PFD Registry are included in the NTR population, yielding a total of 482 NTR subjects and 710 subjects overall. The study is currently ongoing and all 12-month follow-up visits have been completed, with an estimated date for completion of all 36-month follow-up visits in December 2019.

6. Interim Data Analysis

Although the Uphold LITE and Xenform study designs specific that assessment of the primary endpoints would occur at 36 months, per the request of the FDA BSC conducted interim data analyses at 12 months for both studies. The FDA agreed with non-inferiority hypothesis tests specified for both the primary efficacy and safety objectives at 12 months before BSC started the interim data analyses for the Uphold and Xenform studies.

These analyses consisted of statistical hypothesis testing using a mutually-agreed upon propensity score methodology, which was described in the latest revisions of the FDA-approved study protocols. The Uphold LITE 12-month hypothesis testing results were submitted within PMA Amendment P180018/A001 on June 29, 2018, and the Xenform 12-month hypothesis testing results were submitted within PMA Amendment P180021/A001 on July 2, 2018. The results demonstrate that, at 12 months, both Uphold LITE and Xenform are at least as effective and as safe as NTR for the treatment of anterior and/or apical POP and are further discussed below.

7. Summary of Uphold LITE 12-Month Hypothesis Testing Results (from P180018/A001)

a. Subject Information

As of March 10, 2018, all 707 subjects in the PMA cohort (225 subjects in the Uphold LITE treatment arm and 482 subjects in the NTR control arm) had reached the 12-month

follow up visit, and 179 subjects (42 Uphold LITE and 137 NTR) had reached the 36-month follow-up time point (i.e., study completion) (see **Table 3**). Please note that the PMA submission is still under FDA review; therefore, the data summary presented in this summary section is based on the original and amended PMA submission. **Error! Reference source not found.**

Due to the observational study design, a propensity score methodology was carried out to account for potential differences in baseline characteristics between treatment and control arms. The propensity score analysis was performed after enrollment closure by independent statisticians who were blinded to all clinical outcome data. This analysis included all ITT subjects enrolled into the Uphold LITE and NTR arms of the study, as well as NTR subjects shared from the AUGS PFD Registry.

Factors that may affect the study outcomes were identified based on recommendations of the FDA. These factors included: level of prolapse relative to the hymen (i.e., POP-Q C, POP-Q Ba, and POP-Q Bp measurements), primary or recurrent prolapse, menopausal status, estrogen use, age, smoking, diabetes, body mass index (BMI), prior hysterectomy, concomitant procedure for SUI, and surgeon experience with prolapse repair. In addition, race was included in order to account for possible racial differences.

The baseline characteristics and balance assessment are shown in **Table 1**. The p-values before and after the propensity score adjustment are presented in order to facilitate the assessment of balance between the Uphold LITE treatment arm and the NTR control arm in this study.

Table 1: Uphold LITE Baseline Characteristics and Balance Assessment

	Treatment[a]		p-value	
Variable	**Uphold LITE**	**NTR**	**Before Stratification[b]**	**After Stratification[c]**
Age, yrs	66.6 ± 10.8 (225) (32.5, 67.6, 88.2)	62.5 ± 10.6 (482) (27.1, 64.1, 91.0)	< 0.001	0.79
Race white	93.3% (210/225)	85.0% (407/479)	0.002	0.84
Body Mass Index	28.4 ± 6.1 (225) (15.1, 27.5, 57.8)	28.1 ± 5.4 (482) (17.2, 27.1, 56.5)	0.44	0.97
Smoking, current	8.0% (18/224)	7.9% (38/482)	0.94	0.68
Diabetes	14.2% (32/225)	13.1% (63/482)	0.68	0.91
Post-menopausal	92.9% (209/225)	83.4% (402/482)	< 0.001	0.76
Prolapse repair, prior	17.3% (39/225)	10.4% (50/482)	0.009	0.82
Hysterectomy, prior[28]	64.9% (146/225)	30.1% (145/482)	< 0.001	0.65
Estrogen use at baseline	35.6% (80/225)	32.4% (156/481)	0.41	1.00
POP-Q Apical: C	-1.4 ± 3.7 (225) (-8.0, -3.0, 10.0)	-0.8 ± 3.8 (482) (-9.0, -1.0, 12.0)	0.07	0.94

[28] Hysterectomy requirement was included in initial versions of the protocol and removed in a subsequent version (released on 24OCT2014). 83 Uphold and 60 NTR subjects indicated they had a previous hysterectomy.

	Treatment[a]		p-value	
Variable	Uphold LITE	NTR	Before Stratification[b]	After Stratification[c]
POP-Q Anterior: Ba	2.5 ± 1.4 (225) (-1.5, 2.0, 7.5)	1.9 ± 2.0 (482) (-3.0, 1.5, 12.0)	< 0.001	0.60
POP-Q Posterior: Bp	-0.7 ± 1.6 (225) (-3.0, -1.0, 5.0)	-0.4 ± 2.1 (482 (-3.0, -1.0, 12.0)	0.047	0.88
Concomitant SUI repair	56.4% (127/225)	48.1% (232/482)	0.039	0.97
Surgeon volume > median	48.4% (109/225)	50.8% (245/482)	0.55	0.90

[a] Numbers presented are % (#/n) or mean ± SD, sample size (N), (minimum, median, maximum)

[b] Chi-squared test (categorical variables) or one-way Anova F-test (continuous variables)

[c] Mantel-Haenszel test (categorical variables) or two-way Anova F-test (continuous variables) adjusting for stratum

b. Primary Efficacy Endpoint

At 12 months, the use of Uphold LITE transvaginal mesh (TVM) for the treatment of anterior and/or apical vaginal prolapse was found to be at least as effective as NTR for the composite primary efficacy endpoint, as shown in **Table 2**, with the objective success component defined as the leading edge(s) of the treated segment(s) at or above the hymen. The composite success in the ITT population using multiple imputation to handle missing data is 91.4% (206/225) for Uphold LITE versus 87.1% (420/482) for NTR. The propensity score adjusted treatment difference is 3.8% (90% CI: -1.3%, 9.0%), thus the non-inferiority of Uphold LITE compared to NTR for the composite primary efficacy endpoint at 12 months is established.

Table 2: Uphold LITE Primary Efficacy Endpoint – Composite Anatomic and Symptomatic Success at 12 Months

Missing Data Handling Method and Analysis Population	Uphold LITE % (count/ sample size)	NTR % (count/ sample size)	Unadjusted Treatment Difference (TVM - NTR) Estimate (90% CI)	Propensity Score Adjusted Treatment Difference (TVM - NTR)	
				Estimate (90% CI)	P-value of Superiority Test
Multiple Imputation					
Intent-to-Treat	91.4% (206/225)	87.1% (420/482)	4.3% (0.2%, 8.4%)	3.8% (-1.3%, 9.0%)	0.112
Per Protocol	91.3% (199/218)	87.0% (415/477)	4.2% (-0.0%, 8.5%)	3.4% (-1.9%, 8.8%)	0.147
Available Case Analysis					
Intent-to-Treat	91.6% (185/202)	87.3% (379/434)	4.3% (0.1%, 8.4%)	3.4% (-1.9%, 8.8%)	0.146
Per Protocol	91.3% (179/196)	87.2% (376/431)	4.1% (-0.1%, 8.3%)	3.1% (-2.4%, 8.6%)	0.179

Table 3 presents descriptive statistics for the primary efficacy composite anatomic and symptomatic treatment success rates, as well as the results of the individual

components of the composite endpoint, for the ITT population at the 12, 24 and 36-month follow-up visits. The propensity score adjusted differences between treatment and control arms are only provided for the 12-month follow-up visit, as the numbers of subjects who completed 24 and 36-month follow-up visits are too low for valid statistical analysis.

Table 3: Uphold LITE Primary Efficacy Endpoint - Composite Treatment Success Intent-to-Treat Subjects

Variable	Uphold LITE % (count/ sample size)	NTR % (count/ sample size)	Group Difference (95% CI)	
			No Propensity Score Adjustment	With Propensity Score Adjustment
12-Month Composite Success	**91.6% (185/202)**	**87.3% (379/434)**	**4.3% (-0.7%, 9.2%)**	**3.4% (-3.0%, 9.8%)**
Objective Success	98.0% (198/202)	94.0% (409/435)	4.0% (1.1%, 6.9%)	4.0% (1.1%, 6.9%)
Anterior Compartment	98.5% (199/202)	93.5% (362/387)	5.0% (2.0%, 7.9%)	4.6% (1.6%, 7.6%)
Apical Compartment	98.0% (198/202)	98.0% (400/408)	-0.0% (-2.4%, 2.3%)	0.5% (-1.9%, 3.0%)
Subjective Success	93.6% (190/203)	92.2% (402/436)	1.4% (-2.8%, 5.6%)	1.2% (-4.5%, 6.9%)
No Retreatment for POP	99.6% (224/225)	97.9% (472/482)	1.6% (0.1%, 3.2%)	1.6% (-0.5%, 3.8%)
24-Month Composite Success	**91.7% (88/96)**	**83.7% (221/264)**	**8.0% (0.9%, 15.1%)**	**--**
Objective Success	96.9% (93/96)	93.5% (244/261)	3.4% (-1.2%, 8.0%)	--
Anterior Compartment	99.0% (95/96)	92.7% (216/233)	6.3% (2.3%, 10.2%)	--
Apical Compartment	96.9% (93/96)	98.8% (239/242)	-1.9% (-5.6%, 1.9%)	--
Subjective Success	93.8% (90/96)	93.9% (246/262)	-0.1% (-5.8%, 5.5%)	--
No Retreatment for POP	99.6% (224/225)	96.7% (466/482)	2.9% (1.1%, 4.7%)	--
36-Month Composite Success	**83.3% (35/42)**	**73.8% (107/145)**	**9.5% (-3.8%, 22.9%)**	**--**
Objective Success	95.2% (40/42)	88.1% (119/135)	7.1% (-1.3%, 15.5%)	--
Anterior Compartment	97.6% (41/42)	87.1% (108/124)	10.5% (3.0%, 18.0%)	--
Apical Compartment	95.2% (40/42)	97.6% (121/124)	-2.3% (-9.3%, 4.6%)	--
Subjective Success	87.5% (35/40)	92.6% (126/136)	-5.1% (-16.3%, 6.0%)	--
No Retreatment for POP	99.1% (223/225)	96.3% (464/482)	2.8% (0.8%, 4.9%)	--

The use of both Uphold LITE and NTR for the treatment of anterior and/or apical prolapse produced similar results within the subjective success and free of retreatment for POP components of the primary efficacy endpoint at the 12-month follow-up period. The proportion of subjects with objective success is higher in the Uphold LITE arm, driven by the treatment success in the anterior compartment. Both groups achieved a high rate of initial objective and subjective success evidenced by the low rate of re-treatment at 12 months.

The composite treatment success rates in the Uphold LITE arm were numerically higher than NTR at 24 and 36 months, albeit based on incomplete data. Looking at the anterior compartment specifically, compared to the NTR arm, a higher anatomical success rate in the Uphold LITE arm is shown in the 12-month data, continuing through 36 months. The preliminary 36-month data indicate somewhat lower subjective success for patients in the Uphold LITE arm (assessed by self-reporting of feeling of bulge or whether a bulge is bothersome); however, there were higher rates of re-treatment for POP for NTR subjects. Each of these observations must be carefully considered when one considers the very limited number of subjects that currently have completed follow-up out to these extended time points.

c. Secondary Efficacy Endpoint

The results using the secondary composite efficacy endpoint success rate, with the objective success component defined as the leading edge(s) of the treated segment(s) above the hymen, revealed that the Uphold LITE treatment arm fared better than the NTR control arm (p = 0.005, not adjusted for multiplicity), as shown in **Table 4**. At 12 months, 85.8% (193/225) of subjects in the Uphold LITE treatment arm and 78.4% (378/482) of subjects in the NTR control arm reported treatment success with the multiple imputation method for missing data handling. The propensity score adjusted treatment difference is 9.5% (90% CI; 3.5%, 15.5%).

Table 4: Uphold LITE Secondary Efficacy Endpoint - Composite Anatomic and Subjective Success at 12 Months

Missing Data Handling Method and Analysis Population	Uphold LITE % (count/ sample size)	NTR % (count/ sample size)	Unadjusted Treatment Difference (TVM - NTR) Estimate (90% CI)	Propensity Score Adjusted Treatment Difference (TVM - NTR)	
				Estimate (90% CI)	P-value[a]
Multiple Imputation					
Intent-to-Treat	85.8 (193/225)	78.4 (378/482)	7.6% (2.6%, 12.6%)	9.5% (3.5%, 15.5%)	0.005
Per Protocol	85.3 (186/218)	78.2 (373/477)	7.2% (2.2%, 12.3%)	8.9% (2.8%, 15.0%)	0.008
Available Case Analysis					
Intent-to-Treat	86.1% (174/202)	78.1% (339/434)	8.0% (2.9%, 13.2%)	10.0% (3.9%, 16.1%)	0.004

Missing Data Handling Method and Analysis Population	Uphold LITE % (count/ sample size)	NTR % (count/ sample size)	Unadjusted Treatment Difference (TVM - NTR) Estimate (90% CI)	Propensity Score Adjusted Treatment Difference (TVM - NTR)	
				Estimate (90% CI)	P-value[a]
Per Protocol	85.7% (168/196)	78.0% (336/431)	7.8% (2.5%, 13.0%)	9.6% (3.3%, 15.8%)	0.006

[a] P-values not adjusted for multiple comparisons.

Table 5 presents descriptive statistics for the secondary efficacy composite anatomic and symptomatic treatment success rates, as well as the results of the individual components of the composite endpoint, for the ITT population at the 12, 24 and 36-month follow-up visits. The propensity score adjusted differences between treatment and control arms are only provided for the 12-month follow-up visit, as the numbers of subjects who completed 24 and 36-month follow-up visits are too low for valid statistical analysis.

Table 5: Uphold LITE Secondary Efficacy Endpoint - Composite Surgical Success Intent-to-Treat Subjects

Variable	Uphold LITE % (count/ sample size)	NTR % (count/ sample size)	Group Difference (95% CI)	
			No Propensity Score Adjustment	With Propensity Score Adjustment
12-Month Composite Success	**86.1% (174/202)**	**78.1% (339/434)**	**8.0% (1.9%, 14.2%)**	**10.0% (2.7%, 17.2%)**
Objective Success	91.6% (185/202)	84.1% (366/435)	7.4% (2.3%, 12.6%)	10.1% (4.9%, 15.2%)
Anterior Compartment	92.6% (187/202)	82.7% (320/387)	9.9% (4.7%, 15.1%)	11.6% (6.2%, 17.1%)
Apical Compartment	96.5% (195/202)	97.8% (399/408)	-1.3% (-4.2%, 1.6%)	-0.1% (-2.8%, 2.5%)
Subjective Success	93.6% (190/203)	92.2% (402/436)	1.4% (-2.8%, 5.6%)	1.2% (-4.5%, 6.9%)
No Retreatment for POP	99.6% (224/225)	97.9% (472/482)	1.6% (0.1%, 3.2%)	1.6% (-0.5%, 3.8%)
24-Month Composite Success	**85.4% (82/96)**	**75.0% (198/264)**	**10.4% (1.6%, 19.2%)**	**--**
Objective Success	89.6% (86/96)	83.5% (218/261)	6.1% (-1.5%, 13.6%)	--
Anterior Compartment	91.7% (88/96)	82.0% (191/233)	9.7% (2.3%, 17.1%)	--
Apical Compartment	94.8% (91/96)	98.3% (238/242)	-3.6% (-8.3%, 1.2%)	--
Subjective Success	93.8% (90/96)	93.9% (246/262)	-0.1% (-5.8%, 5.5%)	--

Variable	Uphold LITE % (count/ sample size)	NTR % (count/ sample size)	Group Difference (95% CI)	
			No Propensity Score Adjustment	With Propensity Score Adjustment
No Retreatment for POP	99.6% (224/225)	96.7% (466/482)	2.9% (1.1%, 4.7%)	--
36-Month Composite Success	**81.0% (34/42)**	**67.6% (98/145)**	**13.4% (-0.7%, 27.5%)**	**--**
Objective Success	90.5% (38/42)	81.5% (110/135)	9.0% (-2.0%, 20.0%)	--
Anterior Compartment	92.9% (39/42)	79.8% (99/124)	13.0% (2.5%, 23.5%)	--
Apical Compartment	95.2% (40/42)	97.6% (121/124)	-2.3% (-9.3%, 4.6%)	--
Subjective Success	87.5% (35/40)	92.6% (126/136)	-5.1% (-16.3%, 6.0%)	--
No Retreatment for POP	99.1% (223/225)	96.3% (464/482)	2.8% (0.8%, 4.9%)	--

The composite treatment success rates trend in favor of Uphold LITE with numerically higher values than NTR at 24 and 36 months; however, these observations are limited at these time points due to the limited number of subjects that have completed follow-up out to these extended time points.

d. Quality of Life Results

There were measurable improvements in patient reported outcomes in both Uphold LITE and NTR subjects following surgery. Both Uphold LITE and NTR subjects showed significant improvement per the PFIQ-7 and PFDI-20 scores at 12 months over baseline, and stability in these scores out to 36 months was demonstrated in those subjects who have reached that follow-up. There was modest improvement in sexual function in both groups by the 12-month follow-up per PISQ-12 responses, and that improvement tends to be maintained at 36 months post index procedure. Most subjects in both groups reported they felt “much better” or “very much better” after surgery per responses to the PGI-I questionnaire. Based on TOMUS Pain Scale responses, very few subjects in either group reported pain or analgesic use at baseline, and in those patients for whom longer-term data is available, overall pain levels remained the same or decreased out to 36 months of follow-up. The results of the PFDI-20 are representative of the overall QOL assessments and are presented in **Table 6**. The TOMUS Pain Scale results are presented in **Table 7**.

Table 6: Uphold LITE PFDI-20 Change from Baseline, Intent-to-Treat Subjects

Visit	Uphold LITE			NTR			Group Difference of Change from Baseline with Propensity Score Adjustment
	Score [a]	Change from Baseline [a]	Mean Change 95% CI	Score [a]	Change from Baseline [a]	Mean Change 95% CI	Estimate (95% CI)
Baseline	115.1 ± 57.0 (225) (8.3, 108.3, 268.8)	--	--	109.7 ± 56.1 (482) (4.2, 104.7, 280.2)	--	--	
6 Months	35.7 ± 37.8 (214) (0.0, 25.0, 221.9)	-78.6 ± 57.2 (214) (-268.8, -75.0, 80.2)	-86.3 to -70.9	31.3 ± 36.9 (440) (0.0, 18.8, 249.0)	-77.6 ± 53.3 (440) (-255.2, -71.3, 119.8)	-82.6 to -72.6	0.6 (-10.2, 11.4)
12 Months	36.8 ± 43.7 (203) (0.0, 25.0, 272.9)	-74.6 ± 61.5 (203) (-268.8, -72.9, 131.2)	-83.1 to -66.0	32.0 ± 39.0 (436) (0.0, 16.7, 244.8)	-76.9 ± 54.1 (436) (-256.3, -73.0, 86.5)	-82.0 to -71.8	6.1 (-5.4, 17.6)
18 Months	38.0 ± 47.3 (129) (0.0, 20.8, 241.7)	-74.2 ± 61.3 (129) (-262.5, -70.8, 112.5)	-84.9 to -63.5	32.3 ± 35.9 (329) (0.0, 21.9, 190.6)	-77.7 ± 54.9 (329) (-260.4, -72.9, 65.6)	-83.6 to -71.7	--
24 Months	32.2 ± 38.8 (96) (0.0, 15.6, 168.8)	-81.8 ± 54.6 (96) (-268.8, -78.1, 30.2)	-92.9 to -70.8	33.0 ± 37.9 (263) (0.0, 22.9, 199.0)	-77.6 ± 55.1 (263) (-256.3, -72.9, 75.0)	-84.3 to -70.9	--
36 Months	49.5 ± 53.8 (40) (0.0, 29.2, 190.6)	-72.8 ± 52.6 (40) (-187.5, -62.0, 8.3)	-89.6 to -55.9	33.6 ± 44.1 (136) (0.0, 16.7, 210.4)	-77.9 ± 61.5 (136) (-254.2, -70.8, 110.4)	-88.4 to -67.5	--

[a] Numbers presented are mean ± SD (sample size), (minimum, median, maximum)

Table 7: Uphold LITE TOMUS Pain Score Change from Baseline, Intent-to-Treat Subjects

Visit	Uphold LITE			NTR			Group Difference on Change from Baseline with Propensity Score Adjustment
	Score [a]	Change from Baseline [a]	Mean Change 95% CI	Score [a]	Change from Baseline [a]	Mean Change 95% CI	Estimate (95% CI)
Baseline	8.3 ± 9.3 (225) (0.0, 5.0, 46.0)	--	--	7.7 ± 9.4 (482) (0.0, 4.0, 70.0)	--	--	
6 Months	4.3 ± 6.7 (214) (0.0, 0.0, 44.0)	-3.8 ± 8.1 (214) (-31.0, -2.0, 15.0)	-4.9 to -2.7	4.1 ± 7.0 (440) (0.0, 0.0, 51.0)	-3.3 ± 8.3 (440) (-70.0, -1.0, 32.0)	-4.0 to -2.5	-0.4 (-1.9, 1.1)
12 Months	4.3 ± 7.0 (203) (0.0, 0.0, 34.0)	-3.4 ± 8.3 (203) (-32.0, -1.0, 19.0)	-4.5 to -2.2	3.6 ± 6.2 (436) (0.0, 0.0, 42.0)	-3.8 ± 8.7 (436) (-70.0, -2.0, 26.0)	-4.6 to -3.0	0.6 (-1.1, 2.2)
18 Months	5.6 ± 9.0 (129) (0.0, 1.0, 46.0)	-2.5 ± 11.2 (129) (-32.0, -2.0, 38.0)	-4.5 to -0.6	3.4 ± 6.1 (329) (0.0, 0.0, 46.0)	-4.3 ± 9.1 (329) (-70.0, -2.0, 20.0)	-5.3 to -3.3	--
24 Months	4.8 ± 7.2 (96) (0.0, 0.0, 31.0)	-2.9 ± 9.9 (96) (-31.0, -1.0, 28.0)	-4.9 to -0.9	3.4 ± 5.8 (263) (0.0, 0.0, 30.0)	-4.4 ± 9.3 (263) (-70.0, -1.0, 16.0)	-5.5 to -3.3	--
36 Months	6.3 ± 10.4 (40) (0.0, 0.5, 45.0)	-2.8 ± 11.8 (40) (-31.0, -0.5, 30.0)	-6.6 to 1.0	3.9 ± 6.9 (136) (0.0, 0.0, 42.0)	-3.6 ± 8.3 (136) (-36.0, 0.0, 16.0)	-5.0 to -2.2	--

[a] Numbers presented are mean ± SD (sample size), (minimum, median, maximum)

e. Intervention for Recurrent Prolapse

Recurrent prolapse was reported as 'Prolapse' or 'Sensation of Bulge' (reported by either the patient due to sensation or by the physician during pelvic examination), and was recorded as an adverse event. At 12 months, 4% (9/225) of subjects in the Uphold LITE arm experienced 'Prolapse' and 4% (9/225) experienced 'Sensation of Bulge', while 9.3% (45/482) of subjects experienced 'Prolapse' and 5.4% (26/482) experienced 'Sensation of Bulge' in the NTR arm. **Table 8** shows the results for both office-based and surgical-based interventions for recurrent prolapse following the index procedure in the ITT population within 12 and 36 months. The proportion of subjects who received intervention for recurrent prolapse were similar between the Uphold LITE and NTR arms.

Table 8: Uphold LITE Intervention for Recurrent Prolapse Post Index Procedure

Intervention	Uphold LITE % (count/sample size)	NTR % (count/ sample size)	Adjusted Treatment Difference (TVM - NTR) Estimate (95% CI)
Office-Based Intervention for Recurrence			
Within 12 months	0.4% (1/225)	0.2% (1/482)	0.0% (-0.6%, 0.6%)
Within 36 months	0.4% (1/225)	0.4% (2/482)	-0.2% (-0.9%, 0.5%)
Surgical-Based Intervention for Recurrence			
Within 12 months	0.4% (1/225)	1.5% (7/482)	-0.8% (-2.8%, 1.1%)
Within 36 months	0.9% (2/225)	2.7% (13/482)	-1.9% (-4.3%, 0.5%)

f. Primary Safety Endpoint

Table 9 shows the analysis of device-related or procedure-related serious adverse events (SAEs). At 12 months, 2.7% (6/225) of subjects in the Uphold LITE treatment arm and 2.7% (13/482) of subjects in the NTR control arm reported SAEs. The propensity score adjusted treatment difference is -0.4% (90% CI; -2.6%, 1.8%), thus the non-inferiority of Uphold LITE compared to NTR for the primary safety endpoint is established.

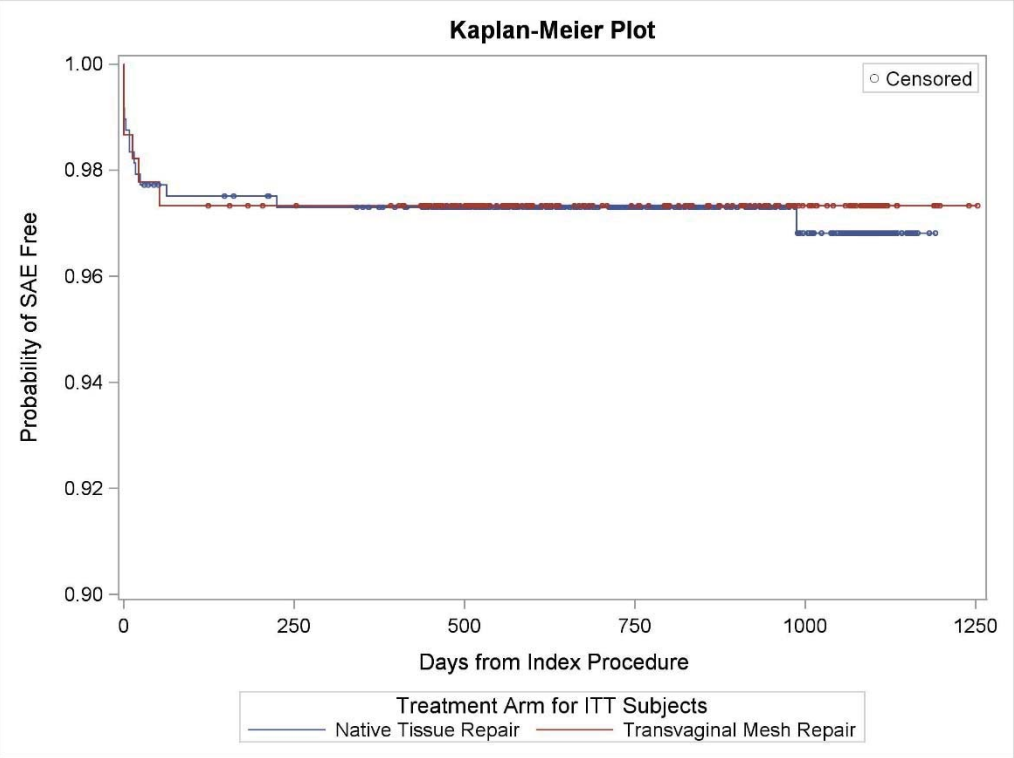
Table 9: Uphold LITE Primary Safety Endpoint – Serious Device- and/or Procedure-Related Adverse Events

Analysis Population[a]	Uphold LITE % (count/ sample size)	NTR % (count/ sample size)	Unadjusted Treatment Difference (TVM – NTR) Estimate (90% CI)	Propensity Score Adjusted Treatment Difference (TVM - NTR) Estimate (90% CI)
Intent-to-Treat	2.7% (6/225)	2.7% (13/482)	-0.0% (-2.2%, 2.1%)	-0.4% (-2.6%, 1.8%)
Per Protocol	2.3% (5/218)	2.7% (13/477)	-0.4% (-2.5%, 1.6%)	-1.2% (-3.1%, 0.6%)
As Treated	2.7% (6/225)	2.7% (13/482)	-0.0% (-2.2%, 2.1%)	-0.4% (-2.6%, 1.8%)

[a] Only events that happened within 12 months of the index procedure and related to the target compartment are included in the analysis.

Kaplan-Meier curves for SAE-free survival exhibit considerable overlap, suggesting that there is no clinically meaningful difference in serious complication rates between the two arms at 12 months (see **Figure 9**Error! Reference source not found.).

Figure 9: Kaplan-Meier Curve of SAE Free Comparing Uphold LITE vs. NTR, Intent-to-Treat Subjects at 12 Months



Looking at the totality of data accounting for patients reaching later study follow-up time points, as of March 10, 2018, there have been a total of 24 serious device- and/or serious procedure-related adverse events that impacted 20 subjects, with seven events in six Uphold LITE subjects and 17 events in 14 NTR subjects. For the Uphold LITE subjects, all events occurred within the first six months following the procedure, and accordingly there were no late-term events. All seven events have been fully resolved. For the NTR subjects, 14 of the 17 events occurred within 180 days post-procedure, whereas three events (one infection, one UTI, and one constipation worsening) were late-term complications. Fifteen of the 17 events have been fully resolved while two (one pelvic infection/abscess and one constipation worsening) remained ongoing as of March 10, 2018. **Table 10**Error! Not a valid bookmark self-reference. provides a summary of the serious device- and/or procedure-related adverse events and their associated interventions in the Uphold LITE treatment arm and the NTR control arm.

Table 10: Safety Summary of Serious Device- and/or Procedure-Related Adverse Events, Intent-to-Treat Subjects

	Uphold LITE (N = 225)		Intervention			NTR Arm (N= 482)		Intervention		
Description	**Events**	**Proportion of Subjects with ≥1 Event[a]**	**Non-Surgical**	**Surgical[b]**	**Hospital-ization**	**Events**	**Proportion of Subjects with ≥1 Event[a]**	**Non-Surgical**	**Surgical[b]**	**Hospital-ization**
Infection - Other, specify type	2	0.4%(1/225)	2	0	2	3	0.6% (3/482)	3	0	3
Ureteral Kink / Injury	1	0.4%(1/225)	0	1	0	2	0.4% (2/482)	1	2	1
Mesh Exposure in Vagina	1	0.4%(1/225)	0	1	0	N/A	-	-	-	-
Bleeding	1	0.4%(1/225)	1	0	1	0	-	-	-	-
Bleeding Requiring Blood Transfusion	1	0.4%(1/225)	1	0	0	0	-	-	-	-
Fever	1	0.4%(1/225)	1	0	1	0	-	-	-	-
Ileus / Bowel Obstruction	0	-	-	-	-	2	0.4% (2/482)	1	2	2
Pelvic Infection / Abscess	0	-	-	-	-	2	0.4% (2/482)	1	0	2
Urinary Tract Infection (UTI), Lower	0	-	-	-	-	2	0.4% (2/482)	2	0	2
Cardiac Event - NEW	0	-	-	-	-	1	0.2% (1/482)	1	0	1
Constipation - Worsening	0	-	-	-	-	1	0.2% (1/482)	1	0	0
Hematoma - Retropubic	0	-	-	-	-	1	0.2% (1/482)	1	0	1
Diarrhea	0	-	-	-	-	1	0.2% (1/482)	0	0	1
Pulmonary Event, Specify - Worsening	0	-	-	-	-	1	0.2% (1/482)	1	0	0
Thrombotic Event	0	-	-	-	-	1	0.2% (1/482)	1	0	1
Total	7	2.7%(6/225)	5	2	4	17	2.9% (14/482)	13	4	14

[a] Numbers are percentage (count/sample size)

[b] Inpatient or outpatient surgical intervention

g. Secondary Safety Endpoint

The secondary safety endpoint included analysis of overall device-related and procedure-related AEs. Additionally, in order to better understand the potential for pelvic-specific AEs that were discussed during the 2011 panel meeting, BSC evaluated a group of specific AEs that included pelvic pain, infection, vaginal shortening, atypical vaginal discharge, neuromuscular problems, vaginal scarring, de novo vaginal bleeding, de novo voiding dysfunction, de novo dyspareunia, and fistula formation. Mesh erosion and mesh exposures were also separately evaluated.

Table 11 summarizes the overall device- and/or procedure-related AEs in the ITT population at 6, 12, 18, 24 and 36 months. Overall AEs are very similar between the Uphold LITE and NTR arms within 12 months, with a rate of 28.9% (65/225) for Uphold LITE subjects and 34.9% (168/482) for NTR subjects (-7.2% difference with propensity score adjustment; 95% CI: -15.8, 1.4%). By the 36-month time point, the difference in overall AEs between the two groups (32.0% for Uphold LITE subjects vs. 40.0% for NTR subjects) had increased to -10.7% (with propensity score adjustment; 95%CI: -19.5%, -2.0%).

Table 11: Uphold LITE Secondary Safety Endpoint – Overall Device- and/or Procedure-Related Adverse Events, Intent-to-Treat Subjects

	Uphold LITE % (count/ sample size)	NTR % (count/ sample size)	Group Difference (95% CI)	
			No Propensity Score Adjustment	With Propensity Score Adjustment
Overall Adverse Events[a]				
Occurred within 6 months	24.9% (56/225)	29.0% (140/482)	-4.2% (-11.1%, 2.8%)	-6.5% (-14.6%, 1.6%)
Occurred within 12 months	28.9% (65/225)	34.9% (168/482)	-6.0% (-13.3%, 1.3%)	-7.2% (-15.8%, 1.4%)
Occurred within 18 months	30.2% (68/225)	37.6% (181/482)	-7.3% (-14.7%, 0.1%)	-8.9% (-17.6%, -0.2%)
Occurred within 24 months	31.1% (70/225)	38.6% (186/482)	-7.5% (-14.9%, -0.0%)	-9.4% (-18.1%, -0.7%)
Occurred within 36 months	32.0% (72/225)	40.0% (193/482)	-8.0% (-15.5%, -0.5%)	-10.7% (-19.5%, -2.0%)

[a] Only device- and/or procedure-related adverse events related to the target compartment are included in the analysis.

Table 12 Error! Reference source not found.presents analysis of device and/or procedure-related AEs reported as of March 10, 2018 for the ITT population.

Table 12: Summary of Device- and/or Procedure-Related Adverse Events, Intent-to-Treat Subjects

	Uphold LITE (N=225)			NTR (N=482)		
	Events	Proportion of Subjects with ≥1 Event[a]	KM Estimate at 3 Years[b]	Events	Proportion of Subjects with ≥1 Event[a]	KM Estimate at 3 Years[b]
Atypical vaginal discharge	2	0.9% (2/225)	0.9%	3	0.6% (3/482)	0.6%
De novo dyspareunia	2	0.9% (2/225)	1.5%	7	1.5% (7/482)	1.5%
De novo vaginal bleeding	0	0.0% (0/225)	0.0%	7	1.5% (7/482)	1.5%
De novo voiding dysfunction (including de novo incontinence)	12	4.9% (11/225)	4.9%	24	4.4% (21/482)	4.8%
Difficulty Emptying Bladder - NEW	5	2.2% (5/225)	2.2%	16	3.3% (16/482)	3.4%
Stress Incontinence – NEW	4	1.8% (4/225)	1.8%	4	0.8% (4/482)	1.1%
Urge Incontinence – NEW	3	1.3% (3/225)	1.3%	4	0.8% (4/482)	1.1%
Fistula formation	0	0.0% (0/225)	0.0%	0	0.0% (0/482)	0.0%
Infection	31	9.8% (22/225)	10.4%	98	13.5% (65/482)	14.9%
Infection / Inflammation of Bone	0	0.0% (0/225)	0.0%	0	0.0% (0/482)	0.0%
Infection - Other, specify type	5	0.9% (2/225)	0.9%	6	1.0% (5/482)	1.1%
Pelvic Infection / Abscess	1	0.4% (1/225)	0.4%	4	0.8% (4/482)	0.9%
Sinus Tract	0	0.0% (0/225)	0.0%	0	0.0% (0/482)	0.0%
Urinary Tract Infection (UTI), Lower	23	8.0% (18/225)	8.6%	84	11.8% (57/482)	13.2%
Vaginal Infection	2	0.9% (2/225)	0.9%	4	0.8% (4/482)	1.2%
Mesh Exposure in Vagina	10	3.6% (8/225)	6.2%	0	0.0% (0/482)	0.0%
Mesh Erosion	0	0% (0/225)	0%	0	0.0% (0/482)	0.0%
Neuromuscular problems (including groin and leg pain)	9	4.0% (9/225)	4.0%	13	2.7% (13/482)	3.4%
Pelvic Pain	12	5.3% (12/225)	5.7%	27	5.6% (27/482)	6.8%
Pelvic Pain - NEW	12	5.3% (12/225)	5.7%	26	5.4% (26/482)	6.6%
Pelvic Pain - Worsening	0	0.0% (0/225)	0.0%	1	0.2% (1/482)	0.3%
Vaginal scarring	0	0.0% (0/225)	0.0%	1	0.2% (1/482)	0.2%
Vaginal shortening	1	0.4% (1/225)	0.5%	0	0.0% (0/482)	0.0%

[a] Numbers are percentage (count/sample size)

[b] Estimated event rate at 3 years using Kaplan Meier (KM) method

For the ITT population similar event rates were observed between the Uphold LITE and NTR arms for pelvic pain, infection, vaginal shortening, atypical vaginal discharge,

neuromuscular problems, vaginal scarring, de novo vaginal bleeding, de novo voiding dysfunction, de novo dyspareunia, and fistula formation.

As of March 10, 2018, there have been no reported mesh erosions in the Uphold LITE study population. Eight subjects had experienced a mesh exposure, with two subjects each reporting two mesh exposure events, yielding a total of 10 events. The Kaplan Meier estimate for the mesh exposure rate is 6.2% at three years. None of the mesh exposures have been severe[29]; two events were of moderate severity and the remainder of mild severity. Six mesh exposures have been fully resolved with either no action taken (two events), office only procedures (two events), or surgical intervention (two events). One event was recovering with office intervention and medication. Three events were not yet resolved at the time of data review, among which two received outpatient surgical intervention and one received no intervention.

8. Summary of Xenform 12-Month Hypothesis Testing Results (from P180021/A001)

a. Subject Information

As of March 10, 2018, all 710 subjects in the PMA cohort (228 subjects in the Xenform treatment arm and 482 subjects in the NTR control arm) had reached the 12-month post-procedure visit, and 218 subjects (81 in the Xenform group and 137 in the NTR group) had reached the 36-month follow-up time point (i.e., study completion). (see **Table 18**). Please note that the PMA submission is still under FDA interactive review; therefore, the data summary presented in this summary section is based on the original and subsequent amendments to PMA submission. **Error! Reference source not found.**

Due to the observational study design, a propensity score methodology was carried out to account for differences in baseline characteristics between treatment and control arms and to assess the balance between Xenform and NTR subjects on relevant baseline characteristics. The propensity score analysis was performed after enrollment closure by independent statisticians who were blinded to all clinical outcome data. This analysis included all ITT subjects enrolled into the Xenform and NTR arms of the study, as well as NTR subjects extracted from the AUGS PFD Registry.

Factors that may affect the study outcomes were identified based on FDA recommendations and included: level of prolapse relative to the hymen (i.e., POP-Q C, POP-Q Ba, and POP-Q Bp measurements), primary or recurrent prolapse, menopausal status, estrogen use, age, smoking, diabetes, BMI, prior hysterectomy, concomitant procedure for SUI, and surgeon experience with prolapse repair. In addition, race was included in order to account for possible racial differences.

[29] Severity of events was classified as follows: Mild - Awareness of signs or symptoms, but easily tolerated and are of minor irritant type causing no loss of time from normal activities. Symptoms do not require therapy or a medical evaluation; signs and symptoms are transient; Moderate - Events introduce a low level of inconvenience or concern to the participant and may interfere with daily activities, but are usually improved by simple therapeutic measures; moderate experiences may cause some interference with functioning; Severe - Events interrupt the participant's normal daily activities and generally require systemic drug therapy or other treatment; they are usually incapacitating

The baseline characteristics and balance assessment are shown in **Table 13**. The p-values before and after the propensity score adjustment are presented in order to facilitate the assessment of balance between the Xenform treatment arm and the NTR control arm.

Table 13: Xenform Baseline Characteristics and Balance Assessment

	Treatment[a]		p-value	
Variable	**Xenform**	**NTR**	**Before Stratification[b]**	**After Stratification[c]**
Age, yrs.	58.7 ± 12.7 (228)	62.5 ± 10.6 (482)	< 0.001	0.58
	(29.2, 60.4, 83.1)	(27.1, 64.1, 91.0)		
Race white	88.8% (198/223)	85.0% (407/479)	0.17	0.80
BMI	28.5 ± 5.5 (228)	28.1 ± 5.4 (482)	0.30	0.91
	(17.6, 28.2, 47.7)	(17.2, 27.1, 56.5)		
Smoking, current	9.3% (21/226)	7.9% (38/482)	0.53	0.97
Diabetes	9.6% (22/228)	13.1% (63/482)	0.19	0.88
Post-menopausal	74.1% (169/228)	83.4% (402/482)	0.004	0.67
Prolapse repair, prior	11.0% (25/228)	10.4% (50/482)	0.81	0.95
Hysterectomy, prior	34.6% (79/228)	30.1% (145/482)	0.22	0.95
Estrogen use at baseline	34.2% (78/228)	32.4% (156/481)	0.64	0.88
POP-Q Apical: C	-2.9 ± 3.5 (228)	-0.8 ± 3.8 (482)	< 0.001	0.59
	(-10.0, -4.0, 10.0)	(-9.0, -1.0, 12.0)		
POP-Q Anterior: Ba	1.4 ± 1.6 (228)	1.9 ± 2.0 (482)	0.001	0.90
	(-2.0, 1.0, 10.0)	(-3.0, 1.5, 12.0)		
POP-Q Posterior: Bp	-0.5 ± 2.2 (228)	-0.4 ± 2.1 (482)	0.49	0.98
	(-3.0, -1.0, 10.0)	(-3.0, -1.0, 12.0)		
Concomitant SUI repair	61.0% (139/228)	48.1% (232/482)	0.001	0.68
Surgeon volume > 126	58.8% (134/228)	39.6% (191/482)	< 0.001	0.67

[a] Numbers presented are % (#/n) or mean ± SD, sample size (N), (minimum, median, maximum)

[b] Chi-squared test (categorical variables) or one-way ANOVA F-test (continuous variables)

[c] Mantel-Haenszel test (categorical variables) or two-way ANOVA F-test (continuous variables) adjusting for stratum

b. Primary Efficacy Endpoint

At 12 months, the use of Xenform TVM for the treatment of anterior and/or apical vaginal prolapse was found to be non-inferior to NTR for the composite primary efficacy endpoint, as shown in **Table 14**, with the objective success component defined as the leading edge(s) of the treated segment(s) at or above the hymen. The composite success in the ITT population using multiple imputation to handle missing data is 88.9% (203/228) for Xenform versus 87.0% (419/482) for NTR. The propensity score adjusted treatment difference is 0.6% (90% CI: -4.5%, 5.6%); thus the non-inferiority of Xenform compared to NTR for the composite primary efficacy endpoint is established.

Table 14: Xenform Primary Efficacy Endpoint – Composite Anatomic and Symptomatic Success at 12 Months

Missing Data Handling Method and Analysis Population	Xenform	NTR	Unadjusted Treatment Difference (TVM - NTR) Estimate (90% CI)	Propensity Adjusted Treatment Difference (TVM - NTR)	
				Estimate (90% CI)	P-value of Superiority Test
Multiple Imputation					
Intent-to-Treat	88.9% (203/228)	87.0% (419/482)	1.9% (-2.7%, 6.6%)	0.6% (-4.5%, 5.6%)	0.427
Per Protocol	88.0% (187/213)	87.0% (415/477)	1.0% (-3.5%, 5.6%)	-0.1% (-5.1%, 4.9%)	0.515
Available Case Analysis					
Intent-to-Treat[a]	88.2% (172/195)	87.3% (379/434)	0.9% (-3.7%, 5.5%)	-0.5% (-5.5%, 4.5%)	0.565
Per Protocol	87.4% (160/183)	87.2% (376/431)	0.2% (-4.6%, 5.0%)	-0.9% (-6.1%, 4.3%)	0.613

Table 15 presents descriptive statistics for the primary efficacy composite anatomic and symptomatic treatment success rates, as well as the results of the individual components of the composite endpoint, for the ITT population at the 12, 24, and 36-month follow-up visits. The propensity score adjusted differences between the treatment and control arms are only provided for the 12-month follow-up visit, as the numbers of subjects who completed 24 and 36-month follow-up visits were too low for valid statistical analysis.

Table 15: Xenform Primary Efficacy Endpoint - Composite Treatment Success, Intent-to-Treat Subjects

Variable	Xenform	NTR	Group Difference (95% CI)	
			No Propensity Score Adjustment	With Propensity Score Adjustment
12-Month Composite Success	**88.2% (172/195)**	**87.3% (379/434)**	**0.9% (-4.6%, 6.4%)**	**-0.5% (-6.4%, 5.4%)**
Objective Success	96.9% (189/195)	94.0% (409/435)	2.9% (-0.4%, 6.2%)	1.8% (-1.7%, 5.3%)
Anterior Compartment	96.9% (189/195)	93.5% (362/387)	3.4% (-0.1%, 6.8%)	2.3% (-1.2%, 5.8%)
Apical Compartment	98.4% (190/193)	98.0% (400/408)	0.4% (-1.8%, 2.6%)	-0.2% (-2.7%, 2.3%)
Subjective Success	89.8% (176/196)	92.2% (402/436)	-2.4% (-7.3%, 2.5%)	-2.4% (-7.3%, 2.6%)
No Retreatment for POP	99.6% (227/228)	97.9% (472/482)	1.6% (0.1%, 3.2%)	0.9% (-1.6%, 3.4%)

Variable	Xenform	NTR	Group Difference (95% CI)	
			No Propensity Score Adjustment	With Propensity Score Adjustment
24-Month Composite Success	**82.4% (140/170)**	**83.7% (221/264)**	**-1.4% (-8.6%, 5.9%)**	**--**
Objective Success	95.9% (162/169)	93.5% (244/261)	2.4% (-1.9%, 6.6%)	--
Anterior Compartment	95.9% (162/169)	92.7% (216/233)	3.2% (-1.3%, 7.6%)	--
Apical Compartment	97.0% (162/167)	98.8% (239/242)	-1.8% (-4.7%, 1.2%)	--
Subjective Success	85.8% (145/169)	93.9% (246/262)	-8.1% (-14.1%, -2.1%)	--
No Retreatment for POP	98.2% (224/228)	96.7% (466/482)	1.6% (-0.8%, 3.9%)	--
36-Month Composite Success	**81.9% (68/83)**	**73.8% (107/145)**	**8.1% (-2.8%, 19.1%)**	**--**
Objective Success	95.0% (76/80)	88.1% (119/135)	6.9% (-0.4%, 14.1%)	--
Anterior Compartment	97.5% (78/80)	87.1% (108/124)	10.4% (3.6%, 17.2%)	--
Apical Compartment	96.3% (77/80)	97.6% (121/124)	-1.3% (-6.3%, 3.6%)	--
Subjective Success	88.9% (72/81)	92.6% (126/136)	-3.8% (-11.9%, 4.4%)	--
No Retreatment for POP	98.2% (224/228)	96.3% (464/482)	2.0% (-0.4%, 4.4%)	--

At 12 months, the use of both Xenform and NTR for the treatment of anterior and/or apical prolapse produced similar results within each component of the primary efficacy endpoint . Both Xenform and NTR achieved a high rate of objective and subjective success and had a durable prolapse repair evidenced by the low rate of re-treatment at 12 months. The composite treatment success rate at 24 months was slightly lower for Xenform as compared to NTR, and at 36 months the rate was numerically higher than NTR, based on incomplete data.

c. Secondary Efficacy Endpoint

The results using the secondary composite efficacy endpoint success rate, with the objective success component defined as the leading edge(s) of the treated segment(s) at or beyond the hymen, demonstrated similar results for Xenform and NTR for the composite secondary efficacy endpoint (p = 0.120, not adjusted for multiplicity), as shown in **Table 16**. At 12 months, 85.2% (194/228) of subjects in the Xenform treatment arm and 78.3% (377/482) of subjects in the NTR control arm reported treatment success. The propensity score adjusted treatment difference is 4.3% (90% CI; -1.7%, 10.3%).

Table 16: Secondary Efficacy Endpoint – Composite Anatomic and Symptomatic Success in Intent-to-Treat Subjects at 12 Months

Missing Data Handling Method and Analysis Population	Xenform	NTR	Unadjusted Treatment Difference (TVM - NTR) Estimate (90% CI)	Propensity Score Adjusted Treatment Difference (TVM - NTR)	
				Estimate (90% CI)	P-value*
Multiple Imputation					
Intent-to-Treat	85.2% (194/228)	78.3% (377/482)	6.9% (1.5%, 12.4%)	4.3% (-1.7%, 10.3%)	0.120
Per Protocol	83.8% (179/213)	77.9% (372/477)	5.9% (0.6%, 11.3%)	3.8% (-2.0%, 9.6%)	0.138
Available Case Analysis					
Intent-to-Treat	84.1% (164/195)	78.1% (339/434)	6.0% (0.6%, 11.4%)	3.3% (-2.6%, 9.2%)	0.178
Per Protocol	83.1% (152/183)	78.0% (336/431)	5.1% (-0.5%, 10.7%)	2.8% (-3.3%, 9.0%)	0.223

*P-values not adjusted for multiple comparisons

Table 17 presents descriptive statistics for the secondary efficacy composite anatomic and symptomatic treatment success rates, as well as the results of the individual components of the composite endpoint, for the ITT population at the 12, 24 and 36-month follow-up visits. The propensity score adjusted differences between treatment arms are only provided for the 12-month follow-up visit, as the numbers of subjects who completed 24 and 36-month follow-up visits are too low for valid statistical analysis.

Table 17: Xenform Secondary Efficacy Endpoint - Composite Surgical Success, Intent-to-Treat Subjects

Variable	Xenform	NTR	Group Difference (95% CI)	
			No Propensity Score Adjustment	With Propensity Score Adjustment
12-Month Composite Success	**84.1% (164/195)**	**78.1% (339/434)**	**6.0% (-0.4%, 12.4%)**	**3.3% (-3.7%, 10.4%)**
Objective Success	91.8% (179/195)	84.1% (366/435)	7.7% (2.5%, 12.8%)	5.6% (-0.1%, 11.2%)
Anterior Compartment	92.3% (180/195)	82.7% (320/387)	9.6% (4.3%, 14.9%)	8.2% (3.0%, 13.4%)
Apical Compartment	97.9% (189/193)	97.8% (399/408)	0.1% (-2.3%, 2.6%)	-1.3% (-4.9%, 2.2%)
Subjective Success	89.8% (176/196)	92.2% (402/436)	-2.4% (-7.3%, 2.5%)	-2.4% (-7.3%, 2.6%)
No Retreatment for POP	99.6% (227/228)	97.9% (472/482)	1.6% (0.1%, 3.2%)	0.9% (-1.6%, 3.4%)

Variable	Xenform	NTR	Group Difference (95% CI)	
			No Propensity Score Adjustment	With Propensity Score Adjustment
24-Month Composite Success	**77.1% (131/170)**	**75.0% (198/264)**	**2.1% (-6.1%, 10.3%)**	**--**
Objective Success	87.0% (147/169)	83.5% (218/261)	3.5% (-3.3%, 10.2%)	--
Anterior Compartment	87.6% (148/169)	82.0% (191/233)	5.6% (-1.4%, 12.6%)	--
Apical Compartment	95.2% (159/167)	98.3% (238/242)	-3.1% (-6.8%, 0.5%)	--
Subjective Success	85.8% (145/169)	93.9% (246/262)	-8.1% (-14.1%, -2.1%)	--
No Retreatment for POP	98.2% (224/228)	96.7% (466/482)	1.6% (-0.8%, 3.9%)	--
36-Month Composite Success	**74.7% (62/83)**	**67.6% (98/145)**	**7.1% (-5.0%, 19.2%)**	**--**
Objective Success	86.3% (69/80)	81.5% (110/135)	4.8% (-5.2%, 14.8%)	--
Anterior Compartment	88.8% (71/80)	79.8% (99/124)	8.9% (-1.0%, 18.8%)	--
Apical Compartment	93.8% (75/80)	97.6% (121/124)	-3.8% (-9.8%, 2.1%)	--
Subjective Success	88.9% (72/81)	92.6% (126/136)	-3.8% (-11.9%, 4.4%)	--
No Retreatment for POP	98.2% (224/228)	96.3% (464/482)	2.0% (-0.4%, 4.4%)	--

The use of Xenform for the treatment of anterior and/or apical prolapse produced a similar composite treatment success rate compared to NTR. These results are consistent at 24 and 36 months; however, these observations are limited at these time points due to the limited number of subjects that have completed follow-up out to these extended time points.

d. Quality of Life Results

There were measurable improvements in patient reported outcomes in both Xenform and NTR subjects following surgery. Both Xenform and NTR subjects showed significant improvement, per the PFIQ-7 and PFDI-20 scores at 12 months over baseline, and stability in these scores out to 36 months for subjects who have reached this time point. There was modest improvement in sexual function in both groups by the 12-month follow-up, per the PISQ-12 scores, and that improvement was maintained at 36 months post index procedure. Most subjects in both groups reported they felt “much better” or “very much better” after surgery per responses to the PGI-I questionnaires. Based on TOMUS Pain Scale responses, very few subjects in either group reported pain or

analgesic use at baseline and, in those subjects for whom longer-term data are available, overall pain levels remained the same or decreased out to 36 months of follow-up. The results of the PFDI-20 are representative of the overall QOL assessments and are presented in **Table 18**. The TOMUS Pain Scale results are presented in **Table 19**.

Table 18: Xenform PFDI-20 Change from Baseline, Intent-to-Treat Subjects

Visit	Xenform			NTR			Group Difference on Change from Baseline with Propensity Score Adjustment
	Score	Change from Baseline	Mean Change 95% CI	Score	Change from Baseline	Mean Change 95% CI	Estimate (95% CI)
Baseline	115.4 ± 61.0(228) (8.3,103.6,284.4)	--	--	109.7 ± 56.1(482) (4.2,104.7,280.2)	--	--	--
6 Months	34.3 ± 35.2(209) (0.0,25.0,158.3)	-79.7 ± 56.8(209) (-240.6,-77.1,104.2)	-87.4 to -72.0	31.3 ± 36.9(440) (0.0,18.8,249.0)	-77.6 ± 53.3(440) (-255.2,-71.3,119.8)	-82.6 to -72.6	4.4 (-5.6, 14.4)
12 Months	33.8 ± 34.6(196) (0.0,24.5,211.5)	-77.5 ± 54.7(196) (-240.6,-75.0,82.3)	-85.2 to -69.7	32.0 ± 39.0(436) (0.0,16.7,244.8)	-76.9 ± 54.1(436) (-256.3,-73.0,86.5)	-82.0 to -71.8	6.3 (-2.7, 15.2)
18 Months	32.1 ± 33.5(176) (0.0,23.4,209.4)	-80.1 ± 59.6(176) (-262.5,-76.0,40.2)	-89.0 to -71.2	32.3 ± 35.9(329) (0.0,21.9,190.6)	-77.7 ± 54.9(329) (-260.4,-72.9,65.6)	-83.6 to -71.7	--
24 Months	30.1 ± 32.8(169) (0.0,21.9,205.2)	-83.5 ± 56.0(169) (-238.5,-81.3,39.6)	-92.0 to -75.0	33.0 ± 37.9(263) (0.0,22.9,199.0)	-77.6 ± 55.1(263) (-256.3,-72.9,75.0)	-84.3 to -70.9	--
36 Months	27.3 ± 29.5(81) (0.0,18.8,143.8)	-84.2 ± 51.8(81) (-240.6,-83.3,12.5)	-95.7 to -72.8	33.6 ± 44.1(136) (0.0,16.7,210.4)	-77.9 ± 61.5(136) (-254.2,-70.8,110.4)	-88.4 to -67.5	--

[a] Numbers presented are mean ± SD (sample size), (minimum, median, maximum)

Table 19: Xenform TOMUS Pain Score Change from Baseline, Intent-to-Treat Subjects

Visit	Xenform			NTR			Group Difference on Change from Baseline with Propensity Score Adjustment
	Score	Change from Baseline	Mean Change 95% CI	Score	Change from Baseline	Mean Change 95% CI	Estimate (95% CI)
Baseline	8.9 ± 11.4(228) (0.0,5.0,70.0)	--	--	7.7 ± 9.4(482) (0.0,4.0,70.0)	--	--	--
6 Months	4.3 ± 6.8(208) (0.0,0.0,37.0)	-4.4 ± 10.2(208) (-70.0,-2.0,28.0)	-5.8 to -3.0	4.1 ± 7.0(440) (0.0,0.0,51.0)	-3.3 ± 8.3(440) (-70.0,-1.0,32.0)	-4.0 to -2.5	-0.8 (-2.4, 0.9)
12 Months	3.4 ± 6.2(196) (0.0,0.0,50.0)	-4.6 ± 9.4(196) (-70.0,-2.0,18.0)	-5.9 to -3.3	3.6 ± 6.2(436) (0.0,0.0,42.0)	-3.8 ± 8.7(436) (-70.0,-2.0,26.0)	-4.6 to -3.0	-0.1 (-1.6, 1.5)
18 Months	3.1 ± 5.7(176) (0.0,0.0,34.0)	-5.0 ± 9.7(176) (-70.0,-2.0,24.0)	-6.4 to -3.5	3.4 ± 6.1(329) (0.0,0.0,46.0)	-4.3 ± 9.1(329) (-70.0,-2.0,20.0)	-5.3 to -3.3	--
24 Months	3.3 ± 7.1(169) (0.0,0.0,63.0)	-4.4 ± 9.5(169) (-70.0,-2.0,36.0)	-5.9 to -3.0	3.4 ± 5.8(263) (0.0,0.0,30.0)	-4.4 ± 9.3(263) (-70.0,-1.0,16.0)	-5.5 to -3.3	--
36 Months	2.6 ± 4.5(81) (0.0,0.0,23.0)	-4.6 ± 9.6(81) (-70.0,-3.0,9.0)	-6.7 to -2.5	3.9 ± 6.9(136) (0.0,0.0,42.0)	-3.6 ± 8.3(136) (-36.0,0.0,16.0)	-5.0 to -2.2	--

[a] Numbers presented are mean ± SD (sample size), (minimum, median, maximum)

e. Intervention for Recurrent Prolapse

Recurrent prolapse was reported as 'Prolapse' or 'Sensation of Bulge' (reported by either the patient due to sensation or by the physician during pelvic examination), and was recorded as an adverse event. At 12 months, 6.6% (15/228) of subjects in the Xenform arm experienced 'Prolapse' and 9.6% (22/228) experienced 'Sensation of Bulge', while 9.3% (45/482) of subjects experienced 'Prolapse' and 5.4% (26/482) experienced 'Sensation of Bulge' in the NTR arm. **Table 20** shows the results for both office-based and surgical-based intervention for recurrent prolapse following the index procedure in the ITT population within 12 and 36 months. The proportion of subjects who received intervention for recurrent prolapse were similar between the Xenform and NTR arms.

Table 20: Xenform Intervention for Recurrent Prolapse Post Index Procedure

Time Period	Xenform	NTR	Adjusted Treatment Difference (TVM - NTR) Estimate (95% CI)
Office-based Intervention for Recurrence			
Within 12 months	0.4% (1/228)	0.2% (1/482)	0.4% (-0.8%, 1.7%)
Within 36 months	0.4% (1/228)	0.4% (2/482)	0.3% (-1.0%, 1.6%)
Surgical-based Intervention for Recurrence			
Within 12 months	0.9% (2/228)	1.5% (7/482)	0.3% (-2.3%, 3.0%)
Within 36 months	1.8% (4/228)	2.7% (13/482)	-0.2% (-3.4%, 2.9%)

f. Primary Safety Endpoint

Table 21 shows the analysis of device-related or procedure-related SAEs. At 12 months, 2.6% (6/228) of subjects in the Xenform treatment arm and 2.7% (13/482) of subjects in the NTR control arm reported SAEs. The propensity score adjusted treatment difference is 0.1% (90% CI; -2.3%, 2.6%), thus the non-inferiority of Xenform compared to NTR for the primary safety endpoint is established.

Table 21: Xenform Primary Safety Endpoint – Serious Device- and/or Procedure-Related Adverse Events at 12 Months

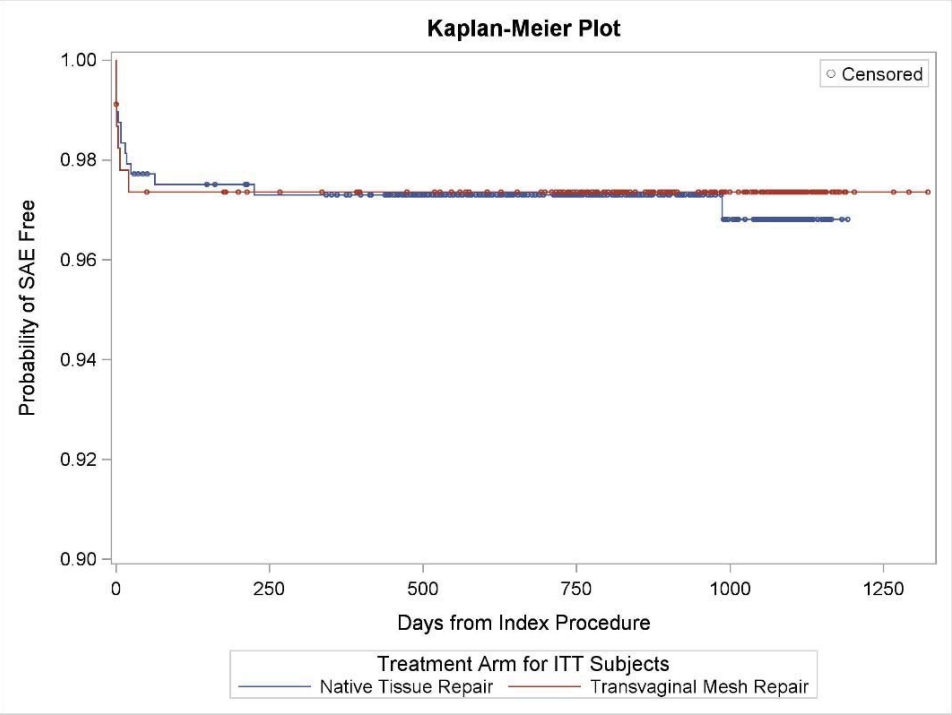
Analysis Population[a]	Xenform	NTR	Unadjusted Treatment Difference (TVM - NTR) Estimate (90% CI)	Propensity Score Adjusted Treatment Difference (TVM - NTR) Estimate (90% CI)
Intent-to-Treat	2.6% (6/228)	2.7% (13/482)	-0.1% (-2.2%, 2.1%)	0.1% (-2.3%, 2.6%)

Analysis Population[a]	Xenform	NTR	Unadjusted Treatment Difference (TVM - NTR) Estimate (90% CI)	Propensity Score Adjusted Treatment Difference (TVM - NTR) Estimate (90% CI)
Per Protocol	2.3% (5/213)	2.7% (13/477)	-0.4% (-2.5%, 1.7%)	-0.1% (-2.6%, 2.5%)
As Treated	2.7% (6/226)	2.7% (13/484)	-0.0% (-2.2%, 2.1%)	0.2% (-2.3%, 2.6%)

[a] Only events that happened within 12 months of the index procedure and related to the target compartment are included in the analysis.

Kaplan-Meier curves for SAE-free survival exhibit considerable overlap, suggesting that there is no clinically meaningful difference in serious complication rates between the two arms (see Error! Reference source not found.).

Figure 10: Kaplan-Meier Curve of SAE Free Comparing Xenform vs. NTR, Intent-to-Treat Subjects



Looking at the totality of data accounting for patients reaching later study follow-up time points, as of March 10, 2018, there were 23 serious device- and/or serious procedure-related adverse events that impacted 20 subjects, with six events in six Xenform subjects and 17 events in 14 NTR subjects. For Xenform subjects, all six events occurred within 180 days of the index procedure, with no late-term complications. Two events (one infection and one cardiac event, worsening) remained ongoing as of March 10, 2018. For the NTR subjects, 14 of the 17 events occurred within 180 days post-procedure, whereas three events (one infection, one UTI, and one constipation worsening) were late-term complications. Fifteen of the 17 events have been fully resolved while two (one pelvic infection/abscess and one

constipation worsening) remained ongoing as of March 10, 2018. **Table 22** provides a summary of the serious device- and/or procedure-related adverse events and their associated interventions in the Uphold LITE treatment arm and the NTR control arm.

provides a summary of the serious device- and/or procedure-related adverse events and their associated interventions in the Xenform treatment arm and NTR control arm.

Table 22: Safety Summary of Serious Device- and/or Procedure-Related Adverse, Intent-to-Treat Subjects

	Xenform (N = 228)		Intervention			NTR Arm (N= 482)		Intervention		
	Events	Proportion of Subjects with ≥1 Event[a]	Non-Surgical	Surgical[b]	Hospital-ization	Events	Proportion of Subjects with ≥1 Event[a]	Non-Surgical	Surgical[b]	Hospital-ization
Infection - Other, specify type	2	0.9% (2/228)	1	0	2	3	0.6% (3/482)	3	0	3
Ureteral Kink / Injury	0	-	-	-	-	2	0.4% (2/482)	1	2	1
Cardiac Events - Worsening	1	0.4%(1/228)	1	0	1	N/A	-	-	-	-
Difficulty Emptying Bladder- new	1	0.4%(1/228)	0	1	0	0	-	-	-	-
Bleeding Requiring Blood Transfusion	1	0.4%(1/228)	1	0	0	0	-	-	-	-
Visceral Organ Injury	1	0.4%(1/228)	1	0	1	0	-	-	-	-
Ileus / Bowel Obstruction	0	-	-	-	-	2	0.4% (2/482)	1	2	2
Pelvic Infection / Abscess	0	-	-	-	-	2	0.4% (2/482)	1	0	2
Urinary Tract Infection (UTI), Lower	0	-	-	-	-	2	0.4% (2/482)	2	0	2
Cardiac Event - NEW	0	-	-	-	-	1	0.2% (1/482)	1	0	1
Constipation - Worsening	0	-	-	-	-	1	0.2% (1/482)	1	0	0
Hematoma - Retropubic	0	-	-	-	-	1	0.2% (1/482)	1	0	1
Diarrhea	0	-	-	-	-	1	0.2% (1/482)	0	0	1
Pulmonary Event, Specify - Worsening	0	-	-	-	-	1	0.2% (1/482)	1	0	0
Thrombotic Event	0	-	-	-	-	1	0.2% (1/482)	1	0	1
Total	6	2.6%(6/228)	4	1	4	17	2.9% (14/482)	13	4	14

[a] Numbers are percentage (count/sample size)

[b] Inpatient or outpatient surgical intervention

g. Secondary Safety Endpoint

The secondary safety endpoint included analysis of overall device-related and procedure-related AEs. Additionally, in order to better understand the potential for pelvic-specific AEs that were discussed during the 2011 Panel meeting, BSC evaluated a group of specific AEs that included pelvic pain, infection, vaginal shortening, atypical vaginal discharge, neuromuscular problems, vaginal scarring, de novo vaginal bleeding, de novo voiding dysfunction, de novo dyspareunia, and fistula formation. Mesh erosion and mesh exposures were also evaluated.

Table 23 summarizes the overall device- and/or procedure-related AEs in the ITT population at 6, 12, 18, 24 and 36 months. Overall device- and/or procedure-related AEs are very similar between Xenform and NTR arms within 12 months, with a rate of 38.6% (88/228) for Xenform subjects and 34.9% (168/482) for NTR subjects (7.7% difference with propensity score adjustment; 95% CI: -0.8, 16.1%). By the 36-month time point, the difference in overall AEs between the two groups (42.5% for Xenform subjects vs. 40.0% for NTR subjects) had decreased to 5.9% (with propensity score adjustment; 95%CI: -2.7%, 14.4%). The overall AE rates are comparable between the two study arms.

Table 23: Xenform Secondary Safety Endpoint – Overall Device- and Procedure-Related Adverse Events, Intent-to-Treat Subjects

	Xenform % (count/ sample size)	NTR % (count/ sample size)	Group Difference (95% CI)	
			No Propensity Score Adjustment	With Propensity Score Adjustment
Overall Adverse Events[a]				
Occurred within 6 months	33.3% (76/228)	29.0% (140/482)	4.3% (-3.1%, 11.6%)	8.2% (-0.0%, 16.4%)
Occurred within 12 months	38.6% (88/228)	34.9% (168/482)	3.7% (-3.9%, 11.4%)	7.7% (-0.8%, 16.1%)
Occurred within 18 months	39.9% (91/228)	37.6% (181/482)	2.4% (-5.3%, 10.0%)	6.1% (-2.4%, 14.6%)
Occurred within 24 months	40.4% (92/228)	38.6% (186/482)	1.8% (-5.9%, 9.5%)	5.1% (-3.4%, 13.6%)
Occurred within 36 months	42.5% (97/228)	40.0% (193/482)	2.5% (-5.3%, 10.3%)	5.9% (-2.7%, 14.4%)

[a] Only device- and/or procedure-related adverse events related to the target compartment are included in the analysis.

Table 24 presents analysis of device- and/or procedure-related AEs reported as of March 10, 2018 for the ITT population.

Table 24: Summary of Device- and/or Procedure-Related Adverse Events, Intent-to-Treat Subjects

	Xenform (N=228)			NTR (N=482)		
	Events	Proportion of Subjects with ≥1 Event[a]	KM Estimate at 3 Years[b]	Events	Proportion of Subjects with ≥1 Event[a]	KM Estimate at 3 Years[b]
Atypical vaginal discharge	1	0.4% (1/228)	0.4%	3	0.6% (3/482)	0.6%
De novo dyspareunia	3	1.3% (3/228)	0.9%	7	1.5% (7/482)	1.5%
De novo vaginal bleeding	4	1.8% (4/228)	1.8%	7	1.5% (7/482)	1.5%
De novo voiding dysfunction	41	14.5% (33/228)	14.8%	24	4.4% (21/482)	4.8%
Difficulty Emptying Bladder - NEW	26	11.0% (25/228)	11.1%	16	3.3% (16/482)	3.4%
Stress Incontinence - NEW	7	3.1% (7/228)	3.2%	4	0.8% (4/482)	1.1%
Urge Incontinence - NEW	8	3.5% (8/228)	3.8%	4	0.8% (4/482)	1.1%
Fistula formation	0	0.0% (0/228)	0.0%	0	0.0% (0/482)	0.0%
Infection	33	9.6% (22/228)	9.9%	98	13.5% (65/482)	14.9%
Infection / Inflammation of Bone	0	0.0% (0/228)	0.0%	0	0.0% (0/482)	0.0%
Infection - Other, specify type	4	1.8% (4/228)	1.8%	6	1.0% (5/482)	1.1%
Pelvic Infection / Abscess	0	0.0% (0/228)	0.0%	4	0.8% (4/482)	0.9%
Sinus Tract	0	0.0% (0/228)	0.0%	0	0.0% (0/482)	0.0%
Urinary Tract Infection (UTI), Lower	23	6.1% (14/228)	6.3%	84	11.8% (57/482)	13.2%
Vaginal Infection	6	2.6% (6/228)	2.7%	4	0.8% (4/482)	1.2%
Mesh Exposure in Vagina	2	0.9% (2/228)	0.9%	0	0.0% (0/482)	0.0%
Mesh Erosion	0	0.0% (0/228)	0.0%	0	0.0% (0/482)	0.0%
Neuromuscular problems (including groin and leg pain)	2	0.9% (2/228)	0.9%	13	2.7% (13/482)	3.4%
Pelvic Pain	15	6.6% (15/228)	6.8%	27	5.6% (27/482)	6.8%
Pelvic Pain - NEW	14	6.1% (14/228)	6.3%	26	5.4% (26/482)	6.6%
Pelvic Pain - Worsening	1	0.4% (1/228)	0.5%	1	0.2% (1/482)	0.3%
Vaginal scarring	3	1.3% (3/228)	1.3%	1	0.2% (1/482)	0.2%
Vaginal shortening	0	0.0% (0/228)	0.0%	0	0.0% (0/482)	0.0%

[a] Numbers are percentage (count/sample size)

[b] Estimated event rate at 3 years using Kaplan Meier (KM) method

For the ITT population, similar event rates were observed between the Xenform and NTR arms for pelvic pain, infection, vaginal shortening, atypical vaginal discharge, neuromuscular problems, vaginal scarring, de novo vaginal bleeding, fistula formation, and de novo dyspareunia.

Subjects in the Xenform arm experienced a higher rate of de novo voiding dysfunction: 14.5% (33/228) compared with 4.4% (21/482) in the NTR arm. De novo voiding dysfunction is a composite of difficulty emptying the bladder, stress, and urge urinary incontinence. For each of these categories, the percentage of affected subjects is greater in the Xenform treatment group than the NTR control group. Specifically, 11.0% (25/228) of Xenform subjects versus 3.3% (16/482) of NTR subjects experienced de novo difficulty emptying of the bladder. 3.1% (7/228) of Xenform subjects experienced stress incontinence while 3.5% (8/228) experienced urge incontinence; the corresponding numbers of NTR subjects were 0.8% (4/482) and 0.8% (4/482) for stress and urge incontinence, respectively. While the observed rate of de novo voiding dysfunction in the Xenform group is higher than that observed in the NTR group, only three events required surgical intervention or hospitalization. De novo voiding dysfunction did not appear to affect QOL since there was not an appreciable difference in UDI-6 score between Xenform subjects who did and did not experience de novo voiding dysfunction (see **Table 25**).

Table 25. UDI-6 Score for Subjects with Device- and/or Procedure-Related De Novo Voiding Dysfunction in the Xenform Arm

	Subjects with De Novo Voiding Dysfunction?		
Variables	**No[a] (N=195)**	**Yes[a] (N=33)**	**P Value[b]**
UDI-6 at Baseline	46.5 ± 28.9 (n=195, 41.7, 20.8 - 66.7)	44.2 ± 26.2 (n=33, 45.8, 25.0 - 66.7)	0.769
UDI-6 at 6 Months	15.2 ± 18.6 (n=178, 8.3, 0.0 - 25.0)	15.2 ± 15.2 (n=31, 12.5, 0.0 - 16.7)	0.455
UDI-6 at 12 Months	14.5 ± 17.8 (n=166, 8.3, 0.0 - 25.0)	15.7 ± 16.8 (n=30, 8.3, 4.2 - 20.8)	0.395
UDI-6 at 18 Months	13.1 ± 17.4 (n=150, 8.3, 0.0 - 20.8)	13.0 ± 15.2 (n=26, 8.3, 0.0 - 20.8)	0.786
UDI-6 at 24 Months	12.2 ± 16.9 (n=145, 8.3, 0.0 - 16.7)	12.0 ± 15.5 (n=24, 8.3, 0.0 - 16.7)	0.664
UDI-6 at 36 Months	10.4 ± 14.1 (n=70, 2.1, 0.0 - 16.7)	16.7 ± 18.6 (n=11, 8.3, 0.0 - 37.5)	0.298

[a] Data presented as Mean ± SD (n=, Median, Q1-Q3).

[b] Wilcoxcon Rank Sum test

As of March 10, 2018, there have been no reported mesh erosions in the Xenform study population. At 12 months and through 36 months of follow-up, mesh exposure has been documented in 0.9% (2/228) of Xenform subjects. These two mesh exposures were both mild in severity, did not require any surgical intervention, and have fully resolved.

B. Discussion of Clinical Data Analysis

1. Clinical Efficacy Outcomes

The data from the Uphold LITE and Xenform BSC Postmarket Surveillance Studies show similar results with respect to clinical efficacy of transvaginal mesh compared to NTR. Analyses of the primary efficacy endpoint, a composite of objective and subjective surgical success, demonstrate that both Uphold LITE and Xenform are at least as effective as NTR at 12 months.

a. Uphold LITE Postmarket Surveillance Study

The use of Uphold LITE and NTR for the treatment of anterior and/or apical prolapse produced similar results that are non-inferior for the composite primary efficacy endpoint at the 12-month follow-up point. Both POP treatment approaches achieve a high rate of objective and subjective success and have durable prolapse repair, evidenced by low rates of re-treatment at 12 months. Looking at the individual prongs of the primary composite endpoint, the proportion of subjects with objective success is higher in the Uphold LITE arm, driven by the treatment success in the anterior compartment. A higher anatomic success rate is shown in the Uphold LITE arm in the anterior compartment continuing through 36 months, albeit based on limited available data.

When the objective success component of the composite primary endpoint is defined as the leading edge of anterior prolapse at or above the hymen, Uphold LITE is found to be similar to NTR, as noted above. When the objective success component of the composite secondary efficacy endpoint is defined as no anterior prolapse at or beyond the hymen, Uphold LITE is found to be greater than NTR. Subjective success of Uphold LITE is comparable to that of NTR, as demonstrated by the patient reported outcomes on the various administered QOL questionnaires, including the PFDI-20, PFIQ-7, PISQ-12, TOMUS pain scale, and PGI-I. The rates of office-based and surgical-based interventions for recurrent prolapse and complications are comparable whether a subject received an Uphold LITE mesh repair or NTR.

In summary, the 12-month data demonstrate non-inferiority of Uphold LITE to NTR for primary efficacy, and the treatment success rate is higher in the Uphold LITE arm compared to the NTR arm for secondary efficacy. In addition, the composite primary and secondary surgical success rates trend in favor of Uphold LITE with numerically higher values at 24 and 36 months; however, these observations are based on a limited subset of data.

b. Xenform Postmarket Surveillance Study

The use of Xenform and NTR for the treatment of anterior and/or apical prolapse produced similar results that are non-inferior for the composite primary efficacy endpoint at the 12-month follow-up point. Both POP treatment approaches achieve a high rate of objective and subjective success and have durable prolapse repair, evidenced by low rates of re-treatment at 12 months.

When the objective success component of the composite efficacy endpoint is defined as the leading edge of anterior prolapse at or above the hymen (primary anatomic success criterion), or no anterior prolapse at or beyond the hymen (secondary anatomic success criterion), Xenform is comparable to NTR. The subjective success of Xenform is also comparable to that of NTR. The impact on the patients' quality of life is comparable between the treatment arms, as demonstrated by the patient reported outcomes on the various administered QOL questionnaires, including the PFDI-20, PFIQ-7, PISQ-12, TOMUS pain scale, and PGI-I. The rates of office-based and surgical-based interventions for recurrent prolapse and complications are generally not different between the groups.

In summary, the 12-month data demonstrate non-inferiority of Xenform to NTR for the primary effectiveness endpoint. The secondary endpoint outcomes were similar between the Xenform and NTR at 12 months. Similar results were shown for the composite primary and secondary success rates at 24 and 36 months; however, these observations are based on a limited subset of data.

2. Clinical Safety Outcomes

The data from the Uphold LITE and Xenform Postmarket Surveillance Studies show similar results with respect to the safety of transvaginal mesh for anterior and/or apical POP repair. Analyses of the co-primary safety endpoint, serious device-related or serious procedure-related AEs, demonstrate that POP repairs using Uphold LITE or Xenform are non-inferior to NTR at 12 months. The compilation of data demonstrates that patients opting for either of these two surgical approaches to POP repair can expect similar safety profiles.

a. Uphold LITE Postmarket Surveillance Study

Uphold LITE and NTR subjects experienced the same rate of SAEs, 2.7%, at 12 months and the non-inferiority of Uphold LITE compared to NTR for safety is established. Kaplan Meier curves for SAE-free survival exhibit considerable overlap, suggesting that there is no clinically meaningful difference in serious complication rates between the two arms. No late-term SAEs were observed in the Uphold LITE arm, whereas three late-term events (post 180 days) were observed in the NTR arm.

Analysis of the secondary safety endpoints show similar results for rates of overall device- and/or procedure-related AEs (28.9% for Uphold LITE versus 34.9% for NTR) at 12 months. There were no differences in the rates of individual AEs that were of concern to the FDA at the 2011 Panel meeting: pelvic pain, infection, vaginal shortening, atypical vaginal discharge, neuromuscular problems, vaginal scarring, de novo vaginal bleeding, de novo voiding dysfunction, de novo dyspareunia, and fistula formation.

There have been no reports of mesh erosion in the Uphold LITE Postmarket Surveillance Study. Eight subjects reported a total of 10 mesh exposures: six subjects reported a single mesh exposure and two subjects each reported two mesh exposures. None of the events were severe: eight were classified as mild and two were classified as moderate in

severity. One event was classified as serious by the study investigator and resolved with outpatient surgical intervention.

b. Xenform Postmarket Surveillance Study

Xenform subjects and NTR subjects experienced nearly identical rates of SAEs at 12 months, 2.6% and 2.7%, respectively, and the non-inferiority of Xenform compared to NTR for primary safety endpoint is established. Kaplan Meier curves for SAE-free survival exhibit considerable overlap, suggesting that there is no clinically meaningful difference in serious AE rates between the two arms at 12 months. No late term SAEs were observed in the Xenform arm, whereas three late term events (post 180 days) were observed in the NTR arm.

Analysis of the secondary safety endpoints at 12 months shows similar results for rates of overall device- and/or procedure-related AEs (38.6% for Xenform versus 34.9% for NTR). The only AE that was different for Xenform compared to NTR was de novo voiding dysfunction (14.5% for Xenform versus 4.4% for NTR). and only three events required surgical intervention or hospitalization, and this did not impact QOL scores on patient-reported measures. Despite this observation there were no appreciable differences in UDI-6 scores between Xenform subjects who did and did not experience de novo voiding dysfunction.

There have been no reports of mesh erosion in the Xenform Postmarket Surveillance Study. Two subjects each reported a single mesh exposure, where both events were mild in severity and neither event required surgical intervention. Both events were classified as non-serious by the study investigators.

C. Additional Clinical Studies

The Uphold LITE System is also being evaluated in a postmarket study sponsored by the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), and subject follow-up is currently ongoing. There are no additional clinical studies for the Xenform Soft Tissue Repair Matrix.

The *Study of Uterine Prolapse Procedures Randomized Trial (SUPeR)* (hereinafter "SUPeR Study") is a randomized, multi-center, superiority trial that compares long-term safety and effectiveness of two transvaginal apical suspension surgeries for uterovaginal prolapse. An abstract containing the results of this study was presented at the 2018 American Urogynecology Society Meeting. This abstract is also described in **Section 6A**.[21] Nine clinical sites participated in the study and 175 women were randomly assigned and masked to receive either vaginal hysterectomy with native tissue uterosacral ligament suspension (hysterectomy) (n=87) or Uphold LITE mesh hysteropexy (hysteropexy) (n=88).

The composite primary outcome of success was defined as no prolapse symptoms, no objective prolapse beyond the hymen, and no retreatment for prolapse. This primary outcome was evaluated a minimum of 36 months post-surgery with survival models using a piece-wise proportional hazard model. Secondary outcomes were measured at baseline and every 6

months post-surgery. These outcomes included AEs, condition-specific QOL assessments, body image, and sexual function measures. The secondary outcomes were evaluated with longitudinal models or chi-square tests, as appropriate.

There was no difference in primary outcome in women undergoing hysterectomy versus hysteropexy (aHR 0.63, 95% CI: 0.39, 1.03). Operative time was significantly less in the hysteropexy group (111.5 ± 4.2 min) versus the hysterectomy group (156.7 ± 4.7 min). Post-operative anterior wall support, POP-Q point Ba (mean, SD) was borderline statistically significantly different between the hysteropexy group (-1.2, 1.4) and the hysterectomy group (-0.7, 1.5) at 36 months ($p = 0.050$). Hysteropexy mesh exposure rate was reported to be 8%, with one single patient required surgical intervention. At the time of the abstract publication, no additional information regarding the severity, complications, or resolution of these events was made available. After 12 weeks, granulation tissue and permanent suture exposure was more common in the hysterectomy group (11% vs 1%, $p < 0.01$ and 20% vs 3%, $p<0.001$, respectively). There was no difference in patient reported outcomes including pain, sexual pain, and sexual function.

Similar to the Uphold LITE Postmarket Surveillance Study, the SUPeR Study evaluated surgical success based on composite primary outcomes of anatomic, symptomatic, and retreatment measures, as well as overall AEs and secondary QOL patient reported outcomes and pelvic-specific safety measures. While superiority of hysteropexy over hysterectomy was not established at 36 months based on the composite endpoint, the study has been extended to follow subjects out to 60 months. The adverse event profile observed in the SUPeR Study is closely aligned with that seen in the Uphold LITE Postmarket Surveillance Study. Results from both studies included instances of mesh exposures that resolved without medical intervention and accordingly were not considered serious events.

The data from the SUPeR Study indicate that surgical success, QOL, and safety were similar between the hysteropexy and hysterectomy groups at 36 months. Accordingly, women undergoing vaginal surgery for apical anterior prolapse can anticipate equal efficacy and safety outcomes regardless of which of these two surgical techniques is chosen. These results are consistent with those seen in the Uphold LITE 522 Postmarket Surveillance Study through 12 months of follow-up.

D. MAUDE Data Considerations

In the Executive Summary from the 2011 Panel meeting, a listing of adverse events was presented showing the number of MDRs and rates for each as reported in the MAUDE database. BSC believes that there are limitations in considering the MAUDE data alone and believes our internal complaint system provides an accurate representation of adverse event rates based on sales. While the MAUDE data provides adverse event data on medical devices and is an excellent source of data for manufacturers to use, research, and assist in understanding potential adverse events throughout a product's lifecycle, there are limitations in that the data may not be comprehensive, may contain redundant information, and no denominator data is available in order to assess these complaints in proper context. Thus, BSC is uncertain that the MAUDE data alone provides anything other than a signal that bears investigation and did not perform a comprehensive review of the content within the MAUDE data.

SECTION 8. BENEFIT/RISK DISCUSSION

In addressing the potential for clinical benefit, several therapeutic elements must be considered by physicians on an individual per-patient basis to ensure that the benefits of any intervention will outweigh the potential risks. Such elements include:

- the degree to which the disease is life threatening,
- whether or not there are alternative therapies that present more or less risk than the therapy in question,
- specific clinical criteria that render other therapies ineffective or inappropriate compared to the therapy in question for certain patients, and
- quality of life aspects that favor the therapy in question in comparison to competing therapies.

Based on the totality of the evidence from the prospective 522 postmarket studies and a review of the more recent literature, there are demonstrable benefits for use of Uphold LITE and Xenform transvaginal mesh products for the repair of POP in the anterior and apical compartments. Further, it is BSC's position that these benefits outweigh the risks presented by the devices, which are generally comparable to the level of risk experienced by alternative invasive treatment options, including NTR. The risks of transvaginal mesh products have been mitigated, as compared to the use of previous generation POP surgical mesh devices. This has been achieved through improvements in device design, refined surgical technique, and the availability of structured education via fellowship, society-sponsored courses, and industry-sponsored product-specific education, all of which contribute to significant mitigation of the risks associated with contemporary transvaginal mesh products. For these reasons, BSC believes that it is important, in terms of women's health, for transvaginal mesh to remain a treatment option that appropriately trained physicians may select where surgery is deemed appropriate for POP repair.

A. There are Significant Benefits Realized by POP Repair with TVM

There are significant and proven benefits for use of Uphold LITE and Xenform transvaginal mesh products for the repair of POP in the anterior and apical compartments.

Looking at composite success rates that encompass objective success, subjective success, and re-operation rates for recurrence, the results from the Uphold LITE and Xenform Postmarket Surveillance Studies demonstrate that, at 12 months, both Uphold LITE and Xenform are at least as effective as NTR for the treatment of anterior and/or apical POP. High rates of primary objective success (defined as the leading edge of prolapse at or above the hymen in the operative compartment) were achieved at 12 months for both Uphold LITE (91.6%) and Xenform devices (88.2%), with good durability shown in the available 36-month data. Moreover, Uphold LITE subjects demonstrated benefit compared to NTR in improvement of anatomic outcome for apical prolapse repair, which persists through 36-month follow-up based on the limited data available beyond 12 months. Uphold LITE also showed improvement over NTR for the secondary composite efficacy endpoint at 12 months, and Xenform was found to be at least as effective as NTR for composite secondary efficacy.

The Uphold LITE and Xenform Postmarket Surveillance Studies' results regarding anatomic outcomes of transvaginal mesh POP repair are further validated by the literature addressing the commercially available Uphold LITE device, such as Altman et al. (2016) reporting 94% anatomic success (POP-Q ≤1) and Rahkola-Soisalo et al. reporting 93.5% anatomic success in the apical compartment at one year; where Rahkola-Soisalo demonstrated sustained improvement with no statistically significant decline in anatomic success at five years. These recent studies directly address performance with Uphold LITE and are more representative of contemporary surgical procedures and the second-generation mesh products when compared to the contrasting literature reports cited at the 2011 panel meeting, where trocar-guided implantation procedures for the Ethicon Prolift mesh evaluated by Iglesia et al. (2010) and Withagen et al. (2011) concluded that there was no evidence that mesh repair of apical prolapse resulted in significant improvement in anatomic outcome.

Further, these anatomic benefits experienced by patients are also clinically significant. Sustained improvements in anatomical success were shown in the Uphold LITE and Xenform Postmarket Surveillance Studies to result in numerically lower re-operation rates for POP recurrence when compared to the NTR control arm. Patients treated with Uphold LITE and Xenform also experienced clinically significant improvements in quality of life measures as reflected in patient-reported outcome measures and pain metrics. The quality of life benefits are comparable to NTR at 12 months, with a potential increased benefit in the long term, based on the limited data currently available out to 36 months. These benefits are consistently reflected across the published literature for the BSC devices. For example, with Rahkola-Soisalo et al. reporting 89.4% of subjects having an improvement at five years in PFDI-20 scores, with 78.8% achieving minimal clinically important difference and Gutman et al. reporting 95% patient satisfaction for treatment of anterior POP ≥ 2.

B. The Risks Presented by the TVM Devices are Comparable to Other Invasive Therapies for POP Repair

Given that there are substantial numbers of women for whom mesh may represent the best opportunity for both cure and maintenance of body image/QOL, it is important to assess the relative safety of transvaginal mesh compared to other treatment modalities.

In BSC's 522 studies, both Uphold LITE and Xenform demonstrated non-inferiority for the primary safety endpoint, device-related/procedure-related serious adverse events (SAE) rates, compared to NTR. At 12 months in the respective ITT study populations, the rates were 2.7% for the Uphold LITE subjects and 2.6% for the Xenform subjects, which did not differ from the 2.7% serious event rate for NTR subjects in both studies. Further, no late term SAEs were experienced with the Uphold LITE and Xenform devices. whereas three subjects experienced late term SAEs in the NTR control arm. Surgical intervention and hospitalization was required a higher percentage of the time to address SAEs in the NTR arm compared to events experienced with the Uphold LITE or Xenform devices.

The total device-related and procedure-related AE rates were 28.9% for Uphold LITE subjects and 38.6% for Xenform versus 34.9% for NTR subjects. In both studies, there were no large differences in overall AE rates between the two study arms at each follow-up time point. For Uphold LITE, there were no large differences in the rates of individual AEs emphasized by the FDA at the 2011 Panel meeting: pelvic pain, infection, vaginal shortening, atypical vaginal discharge, neuromuscular problems, vaginal scarring, de novo vaginal bleeding, de novo voiding dysfunction, de novo dyspareunia, and fistula formation. For Xenform, the only one of these AEs where a difference was seen is de novo voiding dysfunction (14.5% vs. 4.4% for NTR), and the majority of cases were transient and resolved with minimal or no medical intervention and did not impact QOL scores on patient-reported measures. Despite this observation there were no large differences in UDI-6- scores between Xenform subjects who did and did not experience de novo voiding dysfunction.

Regarding mesh erosion and exposure, the FDA and the 2011 Panel raised concerns regarding these adverse events and their clinical sequelae, given their potential to introduce risks to patients that would not occur if undergoing NTR. In the 2011 Panel meeting, the FDA indicated that events of mesh erosion were reported throughout the follow-up period of six months to three years and ranged from 7.7% to 19%. Importantly, these cited mesh erosion rates are not specific to Uphold LITE or Xenform devices but are reported from a variety of mesh devices that are no longer marketed, many of them previous generation devices and techniques that have since been improved upon. These previously reported data are inconsistent with the specific data for Uphold LITE and Xenform devices, where there have been no mesh erosions reported in either the Uphold LITE or XenformPostmarket Surveillance Studies, and mesh exposure rates were reported at 3.6% for Uphold LITE subjects and 0.9% for Xenform subjects. An evaluation of the symptoms present accompanying the exposure and the medical intervention necessary to achieve resolution led to the conclusion that only one of these exposures warranted classification as serious. Most of these events were resolved with no or minimal treatment/surgical intervention and did not result in any negative impact to the subject's bodily function/structure, physical activities, or quality of life.

The rates for mesh erosion and exposure in these recent studies where the BSC Uphold LITE or Xenform devices were used for POP repair are generally consistent with the data reported in the literature, and present lower rates than those previously published in the literature presented by the FDA in the 2011 Panel meeting, which reported on heavier weight and higher density mesh implanted with more invasive techniques using trocars. Specifically, in the more recent

studies specific to BSC's devices presenting a minimum of 12 months of follow-up, with many studies showing long-term follow-up results of 30 months or greater, the rate of mesh erosion ranges from 1.4% to 6.6% and the rate of mesh exposure ranges from 2.6% to 8%. Further, occurrences of erosion and exposure did not necessarily result in surgical interventions.

The risks presented by the Uphold LITE and Xenform devices are in line with the risks presented by other surgical repair options for NTR, with comparable SAE and general complication rates equivalent to those presented by NTR. The potential mesh-related complications do not present additional significant risks to patients, as these rates are captured in the SAE rates and overall AE rates, which, as per the prospective controlled 522 studies, are comparable between the BSC devices and NTR. In a meta-analysis, the mesh exposure rate for sacrocolpopexy ranged between 1.4% and 10% with a mean of 4.2%. These rates are similar to those observed in the BSC 522 studies. Finally, BSC believes the available data out to 18, 24, and 36 months show a higher rate of overall device and procedure-related AEs with NTR versus Uphold LITE, and comparable rates for Xenform versus NTR.

C. The Benefits of TVM Outweigh the Risks

In summary, BSC believes that the improvements in mesh products and surgical technique and corresponding reductions in complication rates, the established benefits and generally comparable risks versus NTR based on BSC's 522 study data to-date, and the recent literature support that the benefits of these treatments outweigh the risks. Further, there are not additional risks presented by the use of these devices compared to other surgical options such as NTR. The broad study population treated in the 522 studies experienced comparable, if not increased, benefits compared to NTR, without increased serious or other risks presented by use of the mesh devices. The baseline characteristics for the patients evaluated in these studies reflect the general population seeking surgical repair. Accordingly, the availability of these TVM devices appears to provide a viable treatment option for women who choose to pursue surgical repair of POP and longer-term benefits through sustained anatomical correction of the prolapse without additional safety risks. This is based on the preliminary 522 study data as well as the reports in the literature (e.g., SUPeR study)

Further, there are defined populations for whom transvaginal mesh may be the best treatment option available for their POP repair. In establishing the benefit-risk ratio for transvaginal mesh for POP repair, it is also relevant to examine any specific populations of women who might benefit from mesh compared to NTR and thus be accepting of any incremental risk. There are several subpopulations of women suffering from POP, where the benefit/risk profile of TVM is potentially more favorable. Specifically, these include (at a minimum): (1) women who seek uterine preservation; (2) women who have previously failed NTR; (3) women with high-stage POP; and (4) women with connective tissue disorders. Therefore, in the face of similar safety profiles and where clinically indicated, it is critical for transvaginal mesh to remain an option for clinicians and patients to consider in electing a surgical repair for anterior and/or apical POP.

Multiple recent studies have shown that, given the option, 36% -60% of women would choose uterine preservation at the time of prolapse repair.[30] Moreover, preservation of the uterus is associated with reduced rates of mesh exposure.[31] Therefore, there is considerable interest in hysteropexy with uterine preservation as a treatment for anterior and apical prolapse. The use of Uphold LITE in conjunction with uterine preservation was specifically assessed in the prospective randomized SUPeR Study, which evaluated the effectiveness and safety of mesh augmented hysteropexy using the Uphold LITE System compared to vaginal hysterectomy and uterosacral ligament suspension (USLS). Importantly, there was no difference in primary outcome and failure risk between treatment arms for the composite primary efficacy outcome at 48 months. The estimated composite endpoint treatment success rate from the survival model trends higher for Uphold LITE at 36 months. The success rate was 74% for Uphold LITE compared to 63% for Hysterectomy & USLS. In terms of safety, this study had an 8% mesh exposure rate in the Uphold LITE arm and a 20% suture exposure rate in the hysterectomy arm. Importantly, women in the Uphold LITE arm were not only able to preserve their uterus, but also suffered less vaginal shortening, had shorter operating time, less blood loss, and required fewer blood transfusions. In the face of similar safety profiles and where clinically indicated women often prefer uterine preservation when electing surgical repair for POP, transvaginal mesh hysteropexy would be a potential and clinically beneficial treatment option.

Women who have failed NTR represent another population that could benefit from transvaginal mesh over repeated NTR. There are several risk factors that predict failure of NTR including levator ani avulsion, stage of POP (3/4), parity and BMI. NTR has been associated with a failure rate of 27% up to as much as 55%. Many of these women will require re-operation to correct their prolapse and will not have organic tissue integrity that supports a successful repair. Recognizing that this population would be served by an alternative surgical approach, certain guidelines, such as those recently proposed by the UK National Institute for Health and Care Excellence (NICE), recommend that transvaginal mesh be considered in women who have failed previous NTR. In the 522 studies, treatment success on the primary composite efficacy endpoint in the Uphold LITE arm at 12 months for women with previous failed NTR repair is 88.9% (32/36) and in the NTR arm is 83.7% (36/43), whereas Xenform subjects achieved composite success in 82.3% of cases.

Relatedly, women with high-stage (3/4) POP – which is one of the key risk factors for failure of NTR – present another subpopulation for whom the benefit-risk profile of TVM may be favorable. In the 522 studies, treatment success on the primary composite efficacy endpoint in the Uphold LITE arm at 12 months for women with anterior/apical prolapse graded as stage 3 and 4 subjects is 91.4% (159/174) and in the NTR arm is 87.8% (224/255), whereas Xenform subjects achieved composite success in 86.7% (78/90) of cases.

Finally, women with connective tissue disorders (*e.g.,* Marfan Syndrome, Ehlers-Danlos syndrome, or a forme fruste of either), may be genetically predisposed to developing POP and may not have the tissue integrity necessary for a successful NTR. Thus, women with Marfan's or

[30] Frick et al. FPM & Recon Surg 19(2) pp.103-109 March/April 2013 and Korbly et al. Am J Obst & Gyn 2013;209:470.e1-6. *See also* Jelovsek and Barber, Am J Obstet Gynecol. 2006 May; 194(5):1455-61 (finding that hysterectomy has a significantly negative impact on body image and quality of life).

[31] Meriwether et al. Am J Obstet Gynecol. 2018 Aug;219(2):129-146.e2

Ehlers-Danlos syndromes or a forme fruste of either, who choose surgical repair of POP, could benefit from the opportunity to be treated with transvaginal mesh.

D. Additional Controls Support the Positive Benefit/Risk Ratio

To ensure that physicians understand the BSC devices, the appropriate patient population, and implantation techniques, the labeling for the devices has been updated to provide further guidance, as described in **Section 3E**. BSC has also developed patient-specific labeling, as recommended by the 2011 Panel, to provide information regarding the benefits and risks of TVM to help patients make informed healthcare decisions in conjunction with their physician.

BSC is further committed to physician education as a tool for mitigating patient risks associated with product use. BSC provides detailed physician education comprising a continuum of training aimed at advancing physician familiarity with the product and procedure and maximizing patient outcomes. Training available and provided includes access to online educational information and hands-on experience through directed training courses, surgical models, proctorships, preceptorships.

Benefit/Risk Conclusions

In summary, BSC believes that the benefits outweigh the risks for both Uphold LITE and Xenform for the following reasons:

- The benefits of repair with mesh are clearly demonstrated with studies evaluating the BSC devices showing efficacy in restoring anatomy and clinically significant improvement in patient symptoms at 12 months.
- Objective success rates were numerically higher for the Uphold LITE device compared to NTR at 12 months overall and in the apical compartment, which appears to persist and increase out to the 36-month endpoint based on the available data.
- Re-operation rates for POP recurrence were comparable or lower compared to NTR.
- Improvements in the physical characteristics of polypropylene mesh and in surgical technique for implanting it have contributed to declining adverse event rates.
- Adverse events associated with transvaginal repair of POP with BSC's devices have generally been minor and temporary. The rate of serious adverse events observed in the 522 studies was comparable for both the Uphold LITE and Xenform subjects to the corresponding rates for NTR subjects.
- BSC has an extensive physician education and training program in place to provide support for physicians who desire supplemental education on surgical technique, patient selection, and management of complications.
- The prospective controlled data and literature concerning transvaginal mesh POP repair support that (1) mesh should be considered as an alternative to NTR generally, and (2) certain subpopulations who many not be appropriate candidates for NTR could benefit from TVM procedures.

SECTION 9: CONCLUSION

In summary, the existing data presented in the literature and the prospective controlled studies evaluating the Uphold LITE and Xenform devices demonstrates that there is sufficient information to support the safety and efficacy of surgical mesh for transvaginal POP repair. The available data provide conclusive evidence that the transvaginal placement of surgical mesh for POP repair provides at least comparable results as NTR, without presentation of significant additional and unwarranted risks. The reported incidence of mesh exposure and erosion and subsequent required surgical intervention presented during the 2011 Panel meeting is not reflective of current mesh devices used in transvaginal mesh repair of POP, or of the implantation techniques now used for the devices. More recent literature demonstrates a shift in the adverse event rate, with a comparable risk/benefit profile to NTR. Further, longer term data suggest there may be increased benefits in at least a subset of women suffering from POP.

Preclinical and clinical information demonstrate a reasonable assurance of safety and efficacy for TVM in treating anterior/apical POP, and these devices should remain on the market as a therapeutic option for indicated patients. The continued availability of these products, including the Uphold LITE and Xenform devices, would ensure improved patient treatment allowing safety and effective options available to physicians for making the appropriate clinical care decision in an individual case. The industry-wide training programs already in place, coupled with the detailed surgical instructions for use and available training information and surgical implantation technique, will further ensure that TVM procedures result in minimal complications, consistent with the more recent literature and the data in BSC's prospective 522 studies, thus further improving the benefit/risk ratio of the devices.

Boston Scientific Corporation firmly believes that the totality of clinical evidence supports the positive benefit/risk profile of its Uphold LITE and Xenform transvaginal mesh devices to treat pelvic organ prolapse (POP).

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APPENDIX 1

Literature Search Strategy

Uphold LITE Vaginal Support System

Numerous literature searches have been conducted, both nationally and internationally, to fully assess and support the clinical and safety profile of Uphold LITE Vaginal Support System. The searches were conducted in the online database Medline, EMBASE, and Articles of Interest. The search strategy is determined by the Search Criteria and employed within research databases using Boolean logic for information retrieval. Each search "set" progresses the overall search results from general to specific findings. The search strategy is captured to illustrate the precise search approach taken to yield search results.

Literature Search #1: BSC periodically conducts literature search to support BSC's internal clinical documentation for currently marketed devices. Search criteria listed below were included in the initial search for the time period of April 1, 2014 through September 30, 2016.

Literature Search Inclusion Criteria

- **Topic:** Surgical mesh or grafts used for pelvic floor prolapse. Devices of particular interest include: BSC's Uphold and Pinnacle, Astora Women's Health(Endo Intl, formerly AMS, American Medical Systems)' Elevate Prolapse Repair System and Perigee Transobturator Anterior, Apogee Vault Prolapse Repair Systems or Gynecare's (Ethicon/J&J)'s Prolift Pelvic Floor Repair system;
- **Document Types:** clinical studies, review articles
- **Language:** English language full-text
- **Time Period:** April 1, 2014 through September 30, 2016

Literature Search #2: To further support Uphold LITE's Post Market Approval application, currently under review, an additional search was conducted with the previous search criteria for an extended time period.

Literature Search Inclusion Criteria

- **Topic:** any mention of BSC's Uphold or Uphold LITE
- **Document Types:** Clinical Studies (including meta-analysis), review articles.
- **Language:** English language full-text
- **Time Period:** Publication year 2012 to May 2018

Literature Search #3: Additionally, BSC conducted a third search, specific to available conference meeting abstracts for the time period of 2000 to March 2018.

Literature Search Inclusion Criteria

- **Topic:** Uphold LITE. The following conferences were of particular interest: AAGL, ACOG, AUA, AUGS, ICS, IUGA, SGS, SUFU.
- **Document Types:** meeting abstracts.
- **Language:** English language full text.
- **Time Period:** publication year 2000 to March 2018.

Conference Abstracts not available through a commercial database (CD), where available (through subscription or open access), journal abstract supplements were checked for the following conferences and years:

1) **AAGL(American Association of Gynecologic Laparoscopists):** CD included 2010-2017 (2018 not yet published); checked journal supplements (J Minimally Invas Gynecol) for 2005 to 2009. Nothing available for 2000-2004.
2) **ACOG (American College of Obstretricians and Gynecologists)**: CD included 2014-2017 (2018 not yet available). Journal supplements checked (Obstet Gyn) for 2000-2013.
3) **AUA (American Urological Association):** CD included 2009-2017 (2018 not yet available). Journal supplements checked (J Urol) 2000-2008.
4) **AUGS (American Urogynecologic Society)**: CD included 2011-2017 (2018 not yet available). Journal supplements checked (Female Pelvic Med Reconstr. 2010; J Pelvic Med Surg 2002-2005, 2007-2009). Abstracts were not found for 2000-2001 or 2006.
5) **ICS (International Continence Society):** CD included 2009-2017 (2018 not yet available). Journal supplements checked from the Library's article collection, previously purchased content, because the journal is not an active subscription (Neurourol Urodyn 2004, 2007, 2008). Unable to access full abstracts for 2000-2003, 2005-2006.
6) **IUGA(International Urogynecological Association):** CD included 2010-2008. Journal supplements checked from the Library's article collection, previously purchased content, because the journal is not an active subscription (Int Urogynecol J 2004 and 2007). Unable to access the full abstracts for 2000-2003, 2005-2006.
7) **SGS (Society of Gynecologic Surgeons)**: CD included 2009-2013, 2015-2018. Journal supplements checked (J Minnimally Invas Gyn 2014, J Pelvic Med Surg 2004-2006, 2008). Accessed the SGS website to retrieve the abstract program for 2007. Unable to access full abstracts for 2000-2003.
8) **SUFU(Society for Urodynamics and Female Urology):** CD included 2014-2018. Journal supplements checked from the Library's article collection, previously purchased content, because the journal is not an active subscription (Neurourol Urodyn 2007-2013). Unable to access the full abstracts for 2000-2006.

Articles were excluded if they were:

- specific to products other than Uphold LITE
- Interim reports/duplicate references
- In vitro studies and animal studies
- Reports and articles available only in foreign language
- Nonsystematic reviews, editorials, letters
- Unsubstantiated opinions
- Unrelated to search topic

These were supplemented with an additional manual search for published literature specific to Uphold LITE which included a full review of relevant articles referenced in the September 2011 FDA Executive Summary from the Surgical Mesh Obstetrics & Gynecology Advisory Committee

Meeting, suggested articles by Key Opinion Leaders, as well as articles found through reference mining.

Xenform Soft Tissue Repair Matrix

BSC performed a literature search of the MEDLINE, Embase and Google Scholar databases to identify publications specific to Xenform for use in POP. The following search and inclusion criteria were used:

Document types:	Clinical studies (including meta-analyses), review articles.
Language:	English Language full-text
Time period:	April 26, 2008 April 26, 2018
Search Terms:	Xenform