Zip-Stitch™ for Vaginal Cuff Closure in Laparoscopic Hysterectomy

Safety & Efficacy Study

Protocol Number: QD-PRO-045 Rev 005

Principal Investigator: William Schlaff M.D.

IDE Sponsor: ZSX Medical, LLC

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Summary of Changes from Previous Version:

Primary Affected Section(s)	Summary of Revisions Made	Rationale
3.1	The primary study efficacy endpoint has been modified to evaluate the occurrence of implant passing events against a performance goal of 5% of patients.	FDA requested that the primary efficacy endpoint be implant passing events, without reference to associated safety/healing events.
3.1	The primary safety endpoint has been modified to be evaluated through six weeks	FDA requested that dehiscence be valuated through six weeks for the primary endpoint.
9	Statistical hypotheses have been eliminated. Study sample size rationale has been revised to reflect changes to the primary endpoint and performance goal.	FDA recommendation that comparison to 5% standard can be observational rather than statistical.

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STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with Good Clinical Practices (GCP) and the appropriate national and local regulations of each site. Trial conformance shall include:

United States Food & Drug Administration 21 CFR Part 812: Investigational Device Exemption, 21 CFR Part 50: Protection of Human Subjects, and 21 CFR Part 54: Financial Disclosure by Clinical Investigators.

Additionally, the Principal Investigator will assure that no deviation from, or changes to the protocol or to the Informed Consent form will take place without prior agreement from the sponsor and documented approval from the Institutional Review Board (IRB) and FDA, except where necessary to eliminate an immediate hazard(s) to the trial subjects. All personnel involved in the conduct of this study have completed Human Subjects Protection Training.

I agree to ensure that all staff members involved in the conduct of this study are informed about their obligations in meeting the above commitments.

Principal Investigator: _____

Print/Type Name

Research Site: _____

Print/Type Name

Signed: _____ Date: _____

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	Zip-Stitch™ for Vaginal Cuff Closure in Laparoscopic Hysterectomy - Safety & Efficacy Study
IDE Number:	G190106/A001
Sponsor:	ZSX Medical LLC 3401 Grays Ferry Ave, Bldg. 176 Philadelphia PA, 19146
Study Description:	This is a prospective, blinded, randomized, controlled study to assess the safety and efficacy of the Zip-stitch™ System in maintaining vaginal cuff closure following laparoscopic hysterectomy. Participating subjects will be randomized and evaluated for implant passing, successful cuff closure, healing, adverse events, dyspareunia, and pain. Blinded follow-up will involve in-person visits at one week, six weeks, and six months. There will be an additional unblinded follow-up by telephone at 12 months post operatively.
Objectives:	**Primary Objective:** The primary objective of this study is to evaluate the efficacy and safety of the Zip-stitch™ Vaginal Cuff Closure system. This will be accomplished by determining the frequency of spontaneous implant passing events and frequency of postoperative vaginal cuff dehiscence, respectively. Primary reporting of both endpoints will take place at six weeks postoperative. **Secondary Objectives:** The secondary objective of this study is to demonstrate the safety and efficacy of the Zip-stitch™ System as compared to a reference treatment (VICRYL™). This will be evaluated by assessing cuff closure and healing, adverse events, changes between pre-operative and post-operative pain and dyspareunia, and implant passing.
Endpoints:	**Primary Endpoints:** Efficacy: The primary efficacy endpoint for this study is frequency of implant passing following cuff closure. This will be evaluated through six-weeks post-operative. Safety: The primary safety endpoint in this study is frequency of vaginal cuff dehiscence. This will be evaluated through six-weeks post-operative. **Secondary Endpoints (Exploratory):** (1) Binary assessment of cuff closure one, six weeks, and six months after surgery (test versus reference group) based on surgeon evaluation.

(2) Binary assessment of cuff healing six weeks and six months after surgery (test versus reference group) based on surgeon evaluation.
(3) Comparison of implant passing. Percentage of subjects experiencing implant passing will be compared between test and control groups as of the six-week and six-month visits.
(4) Relationship of implant passing events to adverse events. The frequency of implant passing following cuff closure associated with an Adverse Event will be evaluated through six-weeks post-operative.
(5) Comparison of incidence of adverse events. Adverse events and serious adverse events will be tabulated for both the test and reference groups.
(6) Comparison of change in dyspareunia. Non-increase in reported individual subject dyspareunia from baseline to 6-month follow-up will be compared (test versus reference group) using the relevant sexual discomfort module of the Female Sexual Function Index (FSFI).
(7) Comparison of change in pain. Non-increase in reported individual subject pain from baseline to 6-month follow-up will be compared (test versus reference group) using an 11-point Numerical Rating Scale.

Study Population:

Women above the age of 18 who are undergoing laparoscopic hysterectomy and meet all of the inclusion criteria and none of the exclusion criteria will be eligible for this study.

Sample Size

For the purposes of assessing safety and effectiveness, a target of 59 women will be enrolled in a ratio of 2:1 test to reference (39 test and 20 reference subjects). This is based on a goal of 35 test subjects and an expected 10% of patients lost to follow-up.

Prescreening and informed consent will take place prior to surgery. Enrollment will take place during surgery once it has been confirmed that no intra-operative exclusion criteria are met. Subjects who meet one or more intra-operative exclusion criteria will not be enrolled but will receive standard hysterectomy procedure and follow-up care as they otherwise would.

Inclusion Criteria

1. Provision of signed and dated Informed Consent Form
2. Stated willingness to comply with all study procedures, including participation in follow-up visits and telephonic follow-up
3. Female 18 years or older
4. Indicated for Laparoscopic Hysterectomy (may include TLH, LAVH, robotic assisted vaginal hysterectomy)

Exclusion Criteria

Pre-operative Exclusion Criteria

1. History of HIV
2. History of Hepatitis C

3. History of diabetes, that in the opinion of the investigator may delay healing
4. Current use of systemic corticosteroids
5. Active infection of genitals, vagina, cervix, uterus or urinary tract
6. Active bacteremia, sepsis or other active systemic infection
7. Presence of Sextually Transmitted Infection (STI)
8. Evidence of pelvic inflammatory disease (PID)
9. Known clotting defects or bleeding disorders
10. Hemoglobin < 8 g/dL
11. Metastatic disease
12. On anticoagulant therapy
13. Participation in another interventional trial
14. Pregnancy
15. Abnormal PAP results that have not been fully evaluated, or in the opinion of the investigator may indicate risk of abnormal vaginal cuff healing
16. Co-morbidities that, in the opinion of the investigator, may indicate risk of abnormal vaginal cuff healing

Intra-operative Exclusion Criteria

17. Bowel injury during laparoscopic hysterectomy procedure prior to attempted cuff closure
18. Bladder injury during laparoscopic hysterectomy procedure prior to attempted cuff closure
19. Cases in which surgeon cannot identify adequate tissue along the cuff to apply suture laparoscopically
20. Cases requiring conversion to laparotomy prior to study intervention

Description of Sites/Facilities Enrolling Participants:

The primary sites in this study will be:
Thomas Jefferson University Hospital with locations at 111 South 11th Street, Philadelphia PA, 19107 and 2301 South Broad Street, Philadelphia 19148; and
Hershey Medical Center, Penn State College of Medicine at 500 University Drive Hershey, PA. 17033.

Enrollment may take place at any of these locations.

There may be additional sites within or outside the United States added (but not more than three total institutions), based upon enrollment.

Description of Study Intervention:

The Zip-stitch™ Vaginal Cuff Closure System is a surgical wound closure system consisting of a series of clips and a reusable, re-sterilizable clip applicator. The clips are made of the bio-absorbable polymer poly-p-dioxanone (PDO) and maintain closure of the vaginal cuff during the healing process, then are ultimately absorbed by the body five to eight months after application.

Indication for Use:

The Zip-stitch™ System's indication for use is to close the vaginal cuff following laparoscopic hysterectomy.

Study Duration:

Enrollment is intended to occur over three to five months and follow-up is 12-months long. Consequently, this study is expected to take a total of 15 to 17 months from beginning of enrollment to completion of follow-up. Additionally, study blinding will be removed after the last subject completes their six-week follow-up timepoint, and 6 and 12-month follow-up will be collected unblinded. Data will be submitted for regulatory review following unblinding at six weeks, and again after completion of study follow-up after 6 and 12 months.

Participant Duration:

Intervention will occur at the time of surgery and subjects will complete a 12-month follow-up program, including in-person visits at one week, six weeks, and six months, as well as a telephone follow-up at 12-months.

Statistical Methods:

Analysis Populations:

Intent-to-treat population (ITT): This population will include all subjects enrolled and randomized to test or reference treatment. Subjects will be analyzed according to the treatment to which they were randomized, regardless of the treatment they actually received.

Safety population: This population will include all subjects enrolled and randomized to test or reference treatment. Subjects will be analyzed according to the treatment that they received; patients randomized to the reference arm that receive Zip-stitch™ will be included in the Zip-stitch™ safety population. Similarly, patients randomized to the Zip-stitch™ arm that receive sutures will be included in the reference safety population.

Primary and secondary efficacy endpoint analyses will be performed on the ITT population. All safety analyses will be performed on the Safety population.

Efficacy Analysis:

Unless otherwise stated the analyses of efficacy endpoints will be based on the ITT population as follows.

One-sided endpoint analyses will be performed with 80% statistical power; corresponding *p*-values will be reported, and all two-sided analyses and comparisons between groups will be performed assuming a 0.05 significance level. The corresponding *p*-values and 95% confidence intervals (CIs) will be reported.

<u>Primary Efficacy Endpoint:</u>

Frequency of spontaneous implant passing events will be reported through six weeks. Event frequency will be numerically compared to a performance target of 5%.

Secondary Efficacy Endpoints:

(1) Cuff closure (compared between test and reference groups) will be assessed (yes or no) by an independent surgeon at one and six weeks, as well as at six months. Fisher's Exact Test will be used to assess possible significance of a difference in cuff closure scores between test and reference groups.
(2) Cuff healing (compared between test and reference groups), will be assessed (yes or no) by an independent surgeon at six weeks and six months. Fisher's Exact Test will be used to assess possible significance of a difference in healing scores between test and reference groups.
(3) The percentage of subjects experiencing implant (either clip or suture) passing by six-weeks and by six-months post-operative will be compared between test and control groups using Fisher's Exact Test.
(4) Frequency of implant passing events determined to be associated with an Adverse Event will be reported through six weeks.

Safety Analysis:

The Safety population will be the analysis population for all safety analyses.

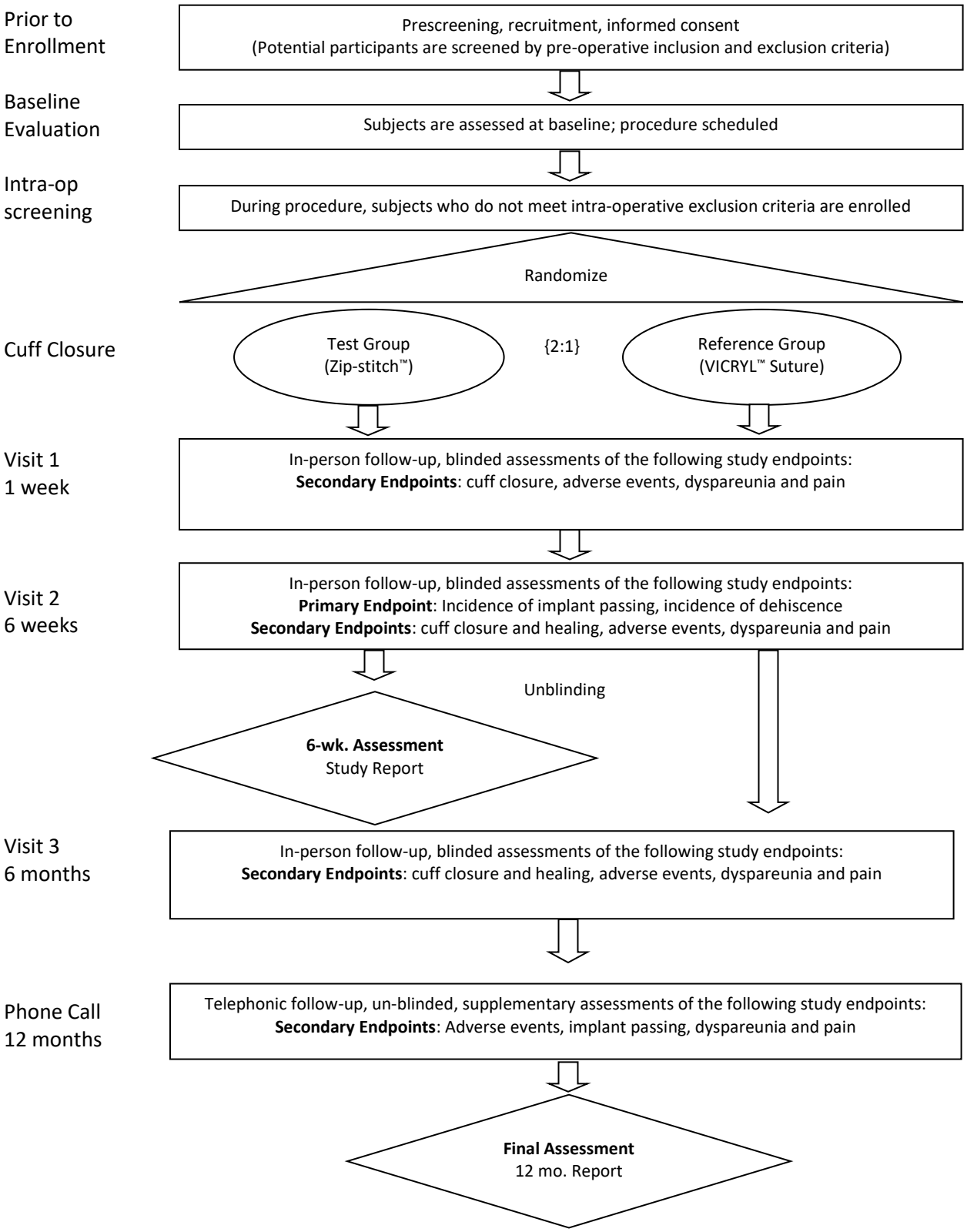
Primary Safety Endpoint:

The primary safety endpoint, frequency of vaginal cuff dehiscence, will be reported through six weeks.

Secondary Safety Endpoints:

(5) The number of adverse events and serious adverse events as well as the proportion of subjects with adverse events, will be summarized by treatment arm, severity, and relatedness to device. Adverse events will be coded using the validated MedDRA system. By-subject listings will be provided for all safety data. Incidence of adverse events will be compared using Fisher's Exact test to assess possible significance of adverse event rate.
(6) Comparison (test to reference group) of non-increase in subject dyspareunia scores from baseline to 6-months post-operative will be assessed using Fisher's Exact Test.
(7) Comparison (test to reference group) of non-increase in subject pain scores from baseline to 6-months post-operative will be assessed using Fisher's Exact Test.

1.2 SCHEMA


Prior to Enrollment
Prescreening, recruitment, informed consent
(Potential participants are screened by pre-operative inclusion and exclusion criteria)
Baseline Evaluation
Subjects are assessed at baseline; procedure scheduled
Intra-op screening
During procedure, subjects who do not meet intra-operative exclusion criteria are enrolled
Randomize
Cuff Closure
Test Group
(Zip-stitch™)
{2:1}
Reference Group
(VICRYL™ Suture)
Visit 1
1 week
In-person follow-up, blinded assessments of the following study endpoints:
Secondary Endpoints: cuff closure, adverse events, dyspareunia and pain
Visit 2
6 weeks
In-person follow-up, blinded assessments of the following study endpoints:
Primary Endpoint: Incidence of implant passing, incidence of dehiscence
Secondary Endpoints: cuff closure and healing, adverse events, dyspareunia and pain
Unblinding
6-wk. Assessment
Study Report
Visit 3
6 months
In-person follow-up, blinded assessments of the following study endpoints:
Secondary Endpoints: cuff closure and healing, adverse events, dyspareunia and pain
Phone Call
12 months
Telephonic follow-up, un-blinded, supplementary assessments of the following study endpoints:
Secondary Endpoints: Adverse events, implant passing, dyspareunia and pain
Final Assessment
12 mo. Report

1.3 SCHEDULE OF ACTIVITIES (SOA)

Assessment	Pre-Visit	Visit 1	Visit 2		Visit 3, 4, & 5	Call 1	Extra
	Site Prep	Screening	Surgery pre-enrollment	Surgery post-enrollment*	Follow-up	Extension Period	Unexpected Visits
Training Logs	X						
Informed Consent Form		X					
Baseline data collection		X					
Inclusion & Exclusion criteria eval		X	X				
Adverse Events review					X	X	X
Closure/Healing assessment					X		X
Dyspareunia/ sexual function assessment		X			X	X	X
Pain assessment		X			X	X	X
Study report form completion(s)		X	X	X	X	X	X
Physical examination		X	X		X		X
Height & weight		X	X		X		X

*Randomization to occur during procedure, after confirmation that intra-operative inclusion and exclusion criteria are both appropriately satisfied.

2 INTRODUCTION

2.1 STUDY RATIONALE

Closing the vaginal cuff is the most technically challenging and time-consuming part of laparoscopic hysterectomy.[1] Traditionally, this is performed through manual laparoscopic suturing, but according to one survey of fellowship directors, 56% of physicians completing general surgery residency cannot suture laparoscopically.[2]

This technical difficulty prevents many low-volume surgeons from adopting minimally-invasive methods and translates to increased surgical time and cost. Additionally, this technical difficulty leads to a long and substantial learning curve that adversely affects patients. One study compared gynecologists who performed a high volume of laparoscopic hysterectomies (more than 30 over the study period) to those who performed few. High volume laparoscopists shaved 45 minutes from their surgical time after their 30th procedure and reduced patients' average hospitalization by 17%. Patients treated by a low-volume surgeon were almost four times as likely to have their laparoscopy fail and have to be converted to an open hysterectomy[3]. Surgical learning curves can result in longer and more invasive procedures, with greater risks of complications and difficult recovery.

In addition to the difficulty associated with traditional laparoscopic vaginal cuff closure, vaginal cuff dehiscence and pelvic adhesive disease are of serious concern. Dehiscence (or rupture) of the vaginal cuff is a major complication of laparoscopic hysterectomy, causes pain and bleeding, and requires

additional surgery. Dehiscence is much more common in laparoscopic hysterectomy than in traditional open hysterectomy[4–6] and has a reported incidence of up to one in twenty (5%) among patients undergoing laparoscopy[5–7] even with robotic assistance.[8]

The Zip-stitch™ system is designed to reduce the time and difficulty of cuff closure during laparoscopic hysterectomy by enabling surgeons to selectively place and clasp biodegradable clips to approximate the two halves of vaginal cuff tissue.

Cuff closure is traditionally performed using suture, and it is difficult to manipulate laparoscopic tools to accurately pierce target tissue with the suture needle, pull the sutures into place, and tie knots to attain even cuff closure. For this reason, laparoscopic surgery takes much longer (~150 minutes versus ~120 minutes)[9–12] than traditional, more invasive, laparotomic approaches. In addition, sutures approximate the vaginal cuff by piercing tissue and compressing wound edges together. The resulting tension can cause high local stress in adjacent tissue and can result in permanent tissue damage. Explicitly, wound closure by sutures has been found to weaken surrounding tissue and lead to local ischemia, tissue necrosis, and delayed hemostasis, all of which hamper wound healing.[13] These affects are also known causes of pelvic adhesive disease.[14]

By closing vaginal cuff tissue with easy to apply, bio-absorbable, non-piercing clips, we expect the Zip-stitch™ system to offer faster, easier, more consistent, and deeper cuff closure, and for the resulting closure to promote comparable or improved cuff healing with potentially fewer complications such as cuff dehiscence and pelvic adhesive disease.

More fully assessing the efficacy and safety profile of the Zip-stitch™ Vaginal Cuff Closure System is necessary to understand the risks and benefits of Zip-stitch™ as compared to suture.

2.2 BACKGROUND

Hysterectomy is the surgical removal of a woman's uterus, and is typically performed as a result of pain, cancer, or abnormal bleeding. Laparoscopic hysterectomy is a minimally invasive approach to this procedure that utilizes an abdominal video camera, endoscopic surgical tools, and one or more small points of entry to operate entirely within the abdomen.

The Zip-stitch™ Vaginal Cuff Closure System, developed by ZSX Medical LLC, can be used for vaginal cuff closure during laparoscopic hysterectomy. The Zip-stitch™ system approximates tissue and maintains tissue closure through healing using a series of bio-absorbable surgical clips deployed with a laparoscopic applicator tool. The Zip-stitch™ system is indicated to close the vaginal cuff following laparoscopic hysterectomy. This is achieved by maintaining tissue approximation without the piercing and high local stresses of suture.

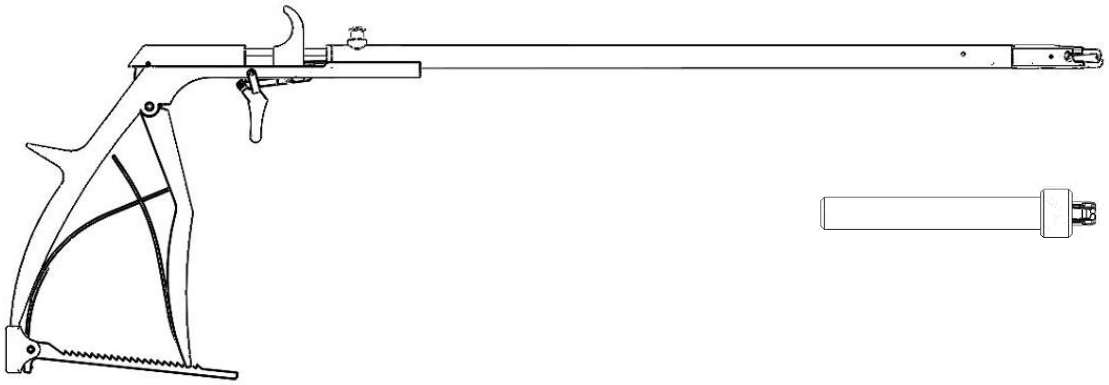


Figure 1 Image of the Zip-stitch™ Reusable Applicator and loading tool with clip

The Zip-stitch™ system is comprised of a handheld applicator and clip loading tool compatible with standard 10mm trocars and laparoscopic surgical equipment as well as a set of bio-absorbable poly-*p*-dioxanone (PDO) clips. This system was developed specifically for closure of the vaginal cuff during laparoscopic hysterectomy as a replacement for traditionally cumbersome laparoscopic suture techniques. The Zip-stitch™ system also includes surgical technique and training to guide the approximation of vaginal cuff tissue and application of the Zip-stitch™ clips using the handheld applicator. The intended use involves the application of four to five clips to the vaginal cuff, resulting in effective and safe closure and healing, followed by subsequent natural breakdown and complete clip degradation.

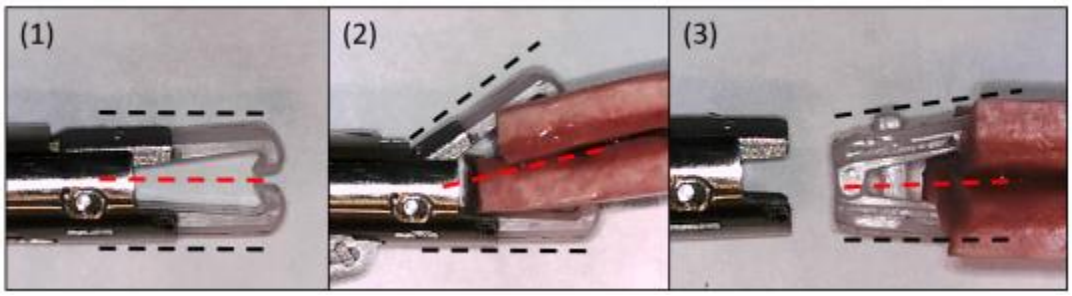


Figure 2 Three distinct configuration states of the Zip-stitch™ clip: (1) stored state, left; (2) open state, middle; (3) closed state, right. Model tissue material used to represent approximated tissue.

Significant preclinical and clinical study has been performed exploring the safety, functionality, and usability of the Zip-stitch™ Vaginal Cuff Closure System. Prior studies have involved in vitro lab testing including benchtop and 10+ cadaver studies showing that Zip-stitch™ clips can be successfully applied to target vaginal cuff tissue and will adequately maintain cuff closure.

Additionally, in vivo animal testing has been performed in rats, sheep, pigs, and dogs demonstrating safe clip degradation and effective or improved wound healing when compared to sutures. And most recently, ZSX concluded an outside-US (OUS) clinical trial demonstrating surgeon ability to achieve successful cuff closure and long-term healing with Zip-stitch™ in ten out of ten participating subjects. All ten subjects were healed normally after six weeks, and patients were followed through 12 months with no healing difficulties. While the results of this preliminary clinical trial were encouraging, no conclusions could be drawn due to the small sample size. As a result, more clinical data is needed to conclusively assess the safe performance of the Zip-stitch™ system.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS ASSOCIATED WITH LAPAROSCOPIC HYSTERECTOMY

The following list outlines potential expected risks associated with the use of Zip-stitch™, as identified through pre-clinical and clinical research. Many of these known risks are concerns already common to hysterectomy procedures and cuff closure techniques, yet they remain risks nonetheless as the effects of the Zip-stitch™ system on these risks have not yet been proven.

Cuff Dehiscence

Dehiscence (or rupture) of the vaginal cuff is a major complication of laparoscopic hysterectomy, causes pain and bleeding, and must be treated by additional surgery. Cuff dehiscence has not been observed in any pre-clinical or clinical testing with Zip-stitch™. Vaginal cuff dehiscence has a reported incidence of up to one in twenty (5%) among patients undergoing laparoscopy[5–7] even with robotic assistance.[8]

Vaginal Cuff Adhesion

When the vaginal cuff heals after hysterectomy, adhesions can form to other tissues in the abdomen, including the bowel. Pelvic adhesions can lead to complications such as bowel obstruction. Pelvic adhesions have not been observed or associated with Zip-stitch™ in clinical use.

Vaginal Vault Prolapse

Vaginal vault prolapse occurs when the upper part of the vaginal canal inverts after hysterectomy, dropping into the vaginal vault as a result of weakened pelvic and vaginal tissues and muscles. Vaginal vault prolapse has not been observed in clinical or preclinical study with Zip-stitch™.

Bladder Complications

During surgery it is possible that a needle will puncture the bladder, which may lead to additional complications including repeat surgery. Zip-stitch™ eliminates the need for needles, so is expected to reduce the likelihood of bladder puncture.

Granuloma

Vaginal vault granuloma has been observed following clinical use of Zip-stitch™ for vaginal cuff closure. Cuff closure with Zip-stitch™ was associated with a decrease in granuloma as compared to suture in pre-clinical testing.

Infection

Infection is a common complication after hysterectomy. Infection has not been observed following any clinical or pre-clinical testing with Zip-stitch™.

Bleeding

Bleeding is a common complication after hysterectomy. Instances of post-operative vaginal vault bleeding have been reported following clinical use of Zip-stitch™.

Social/Economic Risks

Participation in study may require more hospital/doctor visits than would otherwise be necessary due to trial follow-up schedule, including one week, six-week, and 6-month post-operative visits and a 12-month follow-up phone call. It is not expected that this will present an increased financial burden, but subjects will receive nominal renumeration for their time and travel.

2.3.2 KNOWN POTENTIAL RISKS ASSOCIATED WITH THE USE OF ZIP-STITCH™ IN LAPAROSCOPIC HYSTERECTOMY

Dyspareunia

Dyspareunia is expected to improve following laparoscopic hysterectomy,[15–18] and this has been observed in the clinical study of Zip-stitch™. The presence of Zip-stitch™ has been theorized to contribute to dyspareunia during the post-operative implant degradation period.

Bladder Complications

An improperly placed Zip-stitch™ clip could impinge on the bladder, which may lead to erosion post-operatively.

Clip Passing

Occurrences of Zip-stitch™ clip passing have been observed following clinical use of Zip-stitch™. Events of Zip-stitch™ clip passing have not been related to compromise of vaginal cuff closure or compromise of healing.

Reaction to Clip

As with any foreign body, there is risk of localized reaction to implantation. Extensive biocompatibility testing has been conducted on the Zip-stitch™ clip, and it has been shown to have a good safety profile.

2.3.3 KNOWN POTENTIAL BENEFITS

The following list outlines potential benefits associated with participation in this study, as identified through surgeon assessments, pre-clinical, and clinical research.

Reduced Surgical Time

In a National Science Foundation-sponsored study, the Zip-stitch™ system was used in a surgical training apparatus (box trainer) and was found to reduce cuff closure time from 29 minutes to 4 minutes when compared with suture. Reduced surgical time has been shown to reduce the risk of operative complications, including infections[19,20].

Elimination of Sharps

Elimination of sharps is an advantage in any internal procedure but is particularly valuable in vaginal cuff closure due to the location of the vaginal cuff between the bladder and bowel. There is a danger to the bladder when the needle passes through the cuff during closure with suture.

More Reliable Surgical Closure

In simulated use, surgeons reported that Zip-stitch™ was easier than traditional laparoscopic suturing. In addition, surgeons were able to achieve a more uniform, closure with deeper mucosa-to-mucosa approximations than traditional sutures.

Reduced Surgical Cost

As a consequence of reduced time and difficulty, Zip-stitch™ could reduce surgical costs for both hospitals and patients.

Reduced Risk of Pelvic Adhesive Disease

Preclinical study suggests that Zip-stitch™ decreases damage done to tissue during cuff closure. This could reduce the risk of Pelvic Adhesive Disease.

Reduced Risk of Vaginal Cuff Dehiscence

With more consistent, deeper tissue purchase and reduced time and difficulty, it is possible that the Zip-stitch™ system will reduce the risk of vaginal cuff dehiscence.

Improved Healing

Preclinical study has shown Zip-stitch™ cuff closure to result in comparable or improved wound healing over traditional suturing.

2.3.4 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

A risk analysis of the Zip-stitch™ System has been conducted in compliance with CFR 820/ISO 14971. All potential risks have been mitigated through appropriate System design controls and confirmed by pre-clinical bench and/or laboratory testing. The results of the analysis indicate that all potential device-related hazards have been reduced to an acceptable level. The Zip-stitch™ System materials have been shown to be biocompatible and acceptable for human use.

No major adverse events (AEs) were reported when it was used in a similar population. However, in previous clinical testing reported adverse events include four reported fevers and one case of herpes zoster, all unrelated to Zip-stitch™. Adverse events “possibly related” to the device were one umbilical scar infection, two urinary tract infections, and three cases of post-operative vaginal bleeding. There was also one case of granuloma of the vaginal vault reported at six months. Reported pain continued to decrease over the course of the observed 12-month extension period and was consistent with expectations for this study population. Furthermore, reported dyspareunia was both mild and infrequent, consistent with published literature.

While the benefits of the Zip-stitch™ have not been well characterized (this characterization is part of the purpose of this trial), clinical evaluation reports suggest that the device may be faster and easier to learn and use than the existing standard of care. Additionally, clinical evaluation has noted the added benefit of no sharps hazard.

Risks identified via the device’s risk analysis will be mitigated both at the patient level and at the study/population level. The protocol describes safety related stopping rules in Section 10.1.2.

All of the medical risks identified above are risks typically associated with laparoscopic hysterectomy. Based on existing preclinical and clinical data, there is no reason to believe these concerns will be heightened by use of the Zip-stitch™ system.

Separate from surgery, there is possible social/financial risk associated with study participation, due to the possibility of more travel/visits needed to satisfy follow-up than would otherwise be required. The sponsor will provide nominal renumeration for time and travel consistent with what would normally be required to mitigate this risk.

Finally, the Zip-stitch™ system is a new technology and has not been evaluated to the extent that the comparator (VICRYL™) has been for laparoscopic hysterectomy. However, safety and performance testing has been performed with Zip-stitch™, providing substantial confidence in the ability of the Zip-stitch™ system to safely maintain cuff closure through the healing period, before safely degrading into the body.

Given the possible benefits to patients participating in this trial, as well as possible future accessibility benefits to patients following wider product clearance, the identified risks and product novelty are outweighed.

3 OBJECTIVES AND ENDPOINTS

The primary objectives of this study are to evaluate the efficacy and safety of the Zip-stitch™ Vaginal Cuff Closure System. These will be evaluated by measuring the frequency of implant passing events and frequency of postoperative vaginal cuff dehiscence, respectively.

Additionally, this study aims to further assess and characterize the safety and efficacy of the Zip-stitch™ System as compared to a reference treatment (VICRYL™ suture) through secondary endpoints. These include analysis of cuff closure and healing, adverse events, changes between pre-operative and post-operative pain and dyspareunia, and implant passing.

Data through six months may be used to support market clearance of the device by FDA.

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
The primary objective of this study is to evaluate the efficacy and safety of the Zip-stitch™ Vaginal Cuff Closure System. This will be accomplished by measuring the frequency of implant passing events and frequency of postoperative vaginal cuff dehiscence, respectively.	(Efficacy) The primary efficacy endpoint for this study is frequency of implant passing events (as defined in this protocol), evaluated through six-weeks post-operative. (Safety) The primary safety endpoint in this study is frequency of vaginal cuff dehiscence, evaluated through six-weeks post-operative.	(Efficacy) FDA has expressed interest in determining the frequency of implant passing as a surrogate for Zip-stitch™ function. (Safety) FDA has recognized vaginal cuff dehiscence as an important safety metric for cuff closure.
Secondary		
The secondary objective of this study is to demonstrate the safety and efficacy of the Zip-stitch™	(1) Binary assessment of cuff closure one, six weeks, and six months after surgery (test versus reference group) based on surgeon evaluation.	(1) Comparison of cuff closure up to six months after surgery provides a fundamental evaluation of test and reference device efficacy.

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
System as compared to a reference treatment (VICRYL™ suture). This will be evaluated by assessing cuff closure and healing, adverse events, changes between pre-operative and post-operative pain and dyspareunia, and implant passing.	(2) Binary assessment of cuff healing six weeks and six months after surgery (test versus reference group) based on surgeon evaluation. (3) Proportion of subjects who experience implant passing will be compared between test and control groups as of the six-week and six-months visits. (4) Frequency of implant passing events associated with an Adverse Event (determination of relationship as defined in this protocol), evaluated through six-weeks post-operative (5) Comparison of incidence of adverse events: adverse events and serious adverse events will be tabulated and compared between the test and reference groups. (6) Comparison of change in dyspareunia: non-increase in reported individual subject dyspareunia from baseline to 6-month follow-up will be compared (test versus reference group) using the relevant sexual discomfort module of the Female Sexual Function Index (FSFI). (7) Comparison of change in pain: non-increase in reported individual subject pain from baseline to 6-month follow-up will be compared (test versus reference group) using an 11-point Numerical Rating Scale	(2) Comparison of cuff healing at six weeks and six months post-operative provides another fundamental evaluation of test and reference device efficacy. (3) Comparing incidence of clip passing to suture passing provides another comparison between the test article and the reference treatment. (4) Relationship of implant passing events to clinically significant outcomes provides context for clip passing as a functional metric of device performance. (5) Comparison of incidence of adverse events directly assesses patient safety during the recovery period. (6) Comparison of change in dyspareunia from pre-operative to six months post-operative measures what effect, if any, the vaginal cuff closure devices have on patient sexual discomfort following laparoscopic hysterectomy. (7) Comparison of change in pain from pre-operative to six months post-operative measures what effect, if any, the vaginal cuff closure devices have on patient pain following laparoscopic hysterectomy.
Additional Exploratory		
Collection of these exploratory endpoints could help characterize the potential benefits of the Zip-stitch™ Vaginal Cuff Closure System.	(1) Comparison of cuff closure time: The time required to close the vaginal cuff will be measured from time of conclusion of uterine excision to time of placement of the final Zip-stitch™	(1) Recorded cuff closure time may illustrate any potential difference the device may play in speed of cuff closure. (2) Recorded surgical times may help illustrate the significance, if any,

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
	clip or completion of final suture. Comparison may be made between the test and reference group. (2) Total surgical time: Total surgical time will be calculated based on procedure start and end times (time from first incision to final port closure). Comparison may be made between the test and reference group. (3) Observation of implants: During visual inspection of the vaginal cuff at each follow-up visit, the surgeon will indicate whether implant material (either clips or suture) can be observed in the vaginal canal.	of the preparation and handling time associated with cuff closure device and techniques. (3) The observation of implant material during visual inspection of the vaginal cuff may provide valuable information regarding implant function, degradation, and impact on subject return to normal life

3.1 PRIMARY ENDPOINT

(Efficacy) Frequency of Implant Passing Events

Frequency of implant passing events will be reported for all subjects. Failure in this endpoint is defined, on a per patient basis, as the presence of one or more spontaneous implant passing events. A single event may be one or more clips or sutures being spontaneously passed by the patient (*i.e.*, not removed by medical staff).

Frequency of implant passing (either clips or sutures) will be explicitly collected at each follow-up visit; however, events may be reported between visits or during unexpected visits. When implant passing is reported, subjects will be asked to collect and provide passed implants, and an in-person evaluation will be performed. This will involve a visual cuff closure and healing assessment.

In the final analysis of this primary efficacy analysis, the rate of implant passage will be reported through six weeks. The primary objective of this endpoint is to observe a study population failure rate of less than 5% and is neither statistically-driven nor comparative.

(Safety) Frequency of Vaginal Cuff Dehiscence

Vaginal cuff dehiscence is defined as rupture of the surgical wound requiring surgical re-intervention. The proportion of subjects who experience vaginal cuff dehiscence up to six weeks after surgery will be evaluated. In the final analysis of this primary safety endpoint, failure will be reported, and test and control groups will be compared using Fisher's exact test to assess for a possible difference between groups.

3.2 SECONDARY ENDPOINTS

(1) Binary assessment of cuff closure

Cuff closure will be assessed by an independent surgeon at one and six weeks, as well as at six months. Surgeon visual assessment will grade vaginal cuffs as closed or not closed, or the surgeon may indicate that it was not possible to determine. As such, subjects who experience a dehiscence and are considered a failure in analysis of the primary study safety endpoint will be a failure in this secondary endpoint (lack of closed cuff at six weeks). However, subjects could fail this secondary endpoint without failing the primary study safety endpoint.

In cases in which a surgeon is unable to assess cuff closure, the most recent successful evaluation of cuff closure (including intra-operative evaluation) will be used; reason for inability to determine will be recorded. Fisher's Exact Test will be used to assess possible significance of a difference in cuff closure scores between test and reference groups.

(2) Binary assessment of cuff healing

Vaginal cuff healing will be visually assessed by an independent surgeon at six weeks and six months. Surgeon visual assessment will grade vaginal cuffs as healed or not healed, or the surgeon may indicate that it was not possible to determine. In cases in which a surgeon is unable to assess cuff healing, the most recent successful evaluation of cuff closure will be used. If no prior evaluation has established cuff healing, the cuff will be assumed to have not healed yet. Reason for inability to determine healing will be recorded. Fisher's Exact Test will be used to assess possible significance of a difference in cuff closure scores between test and reference groups. Additionally, healing will be characterized using a predetermined list of binary assessment questions, these will not be statistically compared, but serve to characterize individual healing scores.

(3) Comparison of implant passing rates

The percentage of subjects experiencing implant (either clip or suture) passing by six-weeks and six-months post-operative will be compared between test and control groups using Fisher's Exact Test.

(4) Frequency of implant passing events associated with an Adverse Event

Frequency of implant passing incidents found to be associated with an Adverse Event will be reported. Failure in this endpoint is defined, on a per patient basis, as the presence of a spontaneous implant passing event (one or more clips being passed) determined by a blinded study investigator to be associated with an Adverse Event (AE), where "Associated" is defined as a device-related AE that is temporally related to the implant passing event. See Section 9.4.2 for a detailed description of investigator determination of Adverse Event relatedness to implant passing events.

Frequency of implant passing (either clips or sutures) will be explicitly collected at each follow-up visit; however, events may be reported between visits or during unexpected visits. When implant passing is reported, subjects will be asked to collect and provide passed implants, and an in-person evaluation will be performed, involving a visual cuff closure and healing assessment.

(5) Comparison of Incidence of adverse events

The number of adverse events and serious adverse events, as well as the proportion of subjects with adverse events, will be summarized by treatment arm, severity, and relatedness to device. Adverse events will be coded using the validated MedDRA system. By-subject listings will be provided for all safety data. Incidence of adverse events will then be compared using Fisher's

Exact test to assess possible significance or relationship of cuff closure device to adverse event rate.

(6) Comparison of change in dyspareunia

Dyspareunia will be pre-operatively baselined and assessed at each follow-up timepoint, including any unexpected visits, using the sexual pain and discomfort domain (four questions) from the validated Female Sexual Function Index (FSFI).[21,22] Individual success is defined as non-increase in dyspareunia from baseline to six months. Fisher's Exact Test will be used to compare this measure between test and reference groups.

(7) Comparison of change in pain

Patient pain will be pre-operatively baselined and assessed at each follow-up timepoint, including any unexpected visits, using a validated 11-point numerical rating scale[23] (no pain: 0 – the most pain: 10). Individual success is defined as non-increase in pain between baseline and six months. Fisher's Exact Test will be used to compare this measure between test and reference groups.

3.3 EXPLORATORY ENDPOINTS

Cuff closure time

The time required to close the vaginal cuff will be measured from time of conclusion of uterine excision to time of placement of the final Zip-stitch™ clip or completion of final suture. Comparison may be made between the test and reference group.

Total surgical time

Total surgical time will be calculated based on procedure start and end times (time from first incision to final port closure). Comparison may be made between the test and reference group.

Visibility of implants in the vaginal canal

During visual inspection of the vaginal cuff at each follow-up visit, the surgeon will indicate whether implant material (either clips or suture) can be observed in the vaginal canal. Any association with adverse events, dyspareunia, or pain will also be noted.

4 STUDY DESIGN

4.1 OVERALL DESIGN

This randomized, controlled, blinded, prospective study will assess the safety and efficacy of the Zip-stitch™ Vaginal Cuff Closure System in achieving vaginal cuff closure following laparoscopic hysterectomy. This pivotal safety and efficacy study will begin at two sites and will be performed by a minimum of three surgeons but may be expanded to additional sites depending on enrollment. Additional sites may be inside or outside the United States.

The purpose of this trial is to evaluate the efficacy and safety of the Zip-stitch™ System. This will be accomplished by measure of the frequency of implant passing events and the frequency of postoperative vaginal cuff dehiscence, respectively. The observed rate of implant passing events will be numerically (not statistically) compared to a performance target of 5%.

A target of 59 women will be enrolled in a ratio of 2:1 test to reference (39 test and 20 reference subjects). This is based on a goal of 35 test subjects and an expected 10% of patients lost to follow-up. (See Section 9 for additional details).

During a pre-operative visit, a co-investigator surgeon may broach participation in this trial with candidate subjects. Potentially interested subjects will then be approached by a study coordinator or co-investigator surgeon other than their primary care provider to discuss study details and informed consent. Once obtained, surgery will be scheduled for interested participants.

Study enrollment will occur during surgery following satisfaction of all intra-operative exclusion criteria. This will take place after successful colpotomy, prior to initiation of vaginal cuff closure. Once enrolled, subjects will be randomized to receive cuff closure with either Zip-stitch™ or with VICRYL™ suture. Sealed randomization envelopes stratified by site and in variable block sizes will be provided in a blinded 2:1 ratio of test to reference cases. After randomization, the investigator surgeon will attempt to approximate and close the vaginal cuff using the assigned device. Integrity of the achieved closure will be visually assessed during each procedure, and laparoscopic video of cuff closure will be saved. Subjects will be blinded to the treatment they receive.

Follow-up will take place in person at one week, six-weeks, and six-months, as well as by telephone at 12-months. Follow-up will be performed by an independent co-investigator who is blinded to the treatment received (investigator who did not complete the procedure and does not have access to the blinded treatment assigned). Data capture will be performed using a validated electronic data capture system (MedNet Solutions, Minnetonka, MN).

Evaluation of the primary study endpoints will be complete after the six-week in-person follow-up visit. Secondary endpoint results will also be collected through the six-month visit and additional data will be collected through 12-months. The primary analysis of the data from this study will be performed when the six-week data are available. Data collected after 6 weeks will be reported in supplemental follow-up reports.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

The primary objective of this study is to evaluate the efficacy and safety of the Zip-stitch™ Vaginal Cuff Closure system. This will be accomplished by measure of the frequency of implant passing events and the frequency of postoperative vaginal cuff dehiscence, respectively.

This study has been sized and designed in response to FDA recommendations regarding primary safety and efficacy concerns. Determination of rate of implant passing and determination of failed vaginal cuff closure are evaluable within the sample size previously proposed by the Agency.

As the primary efficacy endpoints are not comparative to the reference arm, the 2:1 reference group sizing is appropriate for the reference arm of this study. There are limitations to this reference group sizing strategy; primarily, smaller sample sizes provide weaker comparative information for safety and secondary endpoints.

Evaluation of the primary study efficacy endpoint is subject to reporting bias. It is possible that a patient may not realize she has passed an implant, or she may incorrectly report that she has passed an implant. She could, alternatively, pass or report passing multiple degraded part(s) of a single implant. To encourage accurate primary endpoint data collection, patients will be asked to collect and provide to their surgeon(s) any solid objects passed during the post-operative period. If patients do not have a visit schedules within two weeks of reporting an implant passing event, they will come in for an unscheduled

visit as soon as is practical. Events will be recorded as implant passing events only if study personnel can confirm that an implant (or part of an implant) was passed.

Due to the nature of implant passing, the data imputation strategy for the analysis of the primary study efficacy endpoint will exclude from analysis any incomplete follow-up from subjects lost to follow-up prior to their six-week follow-up visit. For example, one-week follow-up data from a subject lost to follow-up between one and six weeks will be included, but the uncompleted six-week data will be excluded, and they will not be included in the efficacy endpoint population totals for uncompleted follow-up timepoints. However, as detailed in the data imputation section of this protocol (Section 9.4.10), sensitivity analysis will be performed on primary endpoint evaluation where all missing data are imputed as successes and separately as failures. Every effort will be made to minimize missing data.

As implant passing is expected to be a spontaneous event with a low occurrence rate (<10%), any method of assumed incidence prior to six weeks is not practical. Instead, exclusion of lost subjects from both the numerator and denominator of implant passing analysis prevents biased subject exclusion and misrepresentative increases in endpoint population size. Furthermore, subjects who experience an implant passing event are more likely to report such an experience than subjects who experience no such event and therefore exclusion of lost subjects from the population total provides the strictest imputation strategy for this endpoint. After completion of six-week follow-up, implant passing data may be imputed for unblinded supplementary reporting based on average existing implant passing data. However, as the primary study endpoints conclude after six weeks, this imputation will be for supplemental analysis only. After six months clips have sufficiently degraded and are therefore unlikely to pass, and even less likely to be identified as having passed by a patient.

It is not expected that the primary study safety endpoint will be subject to reporting bias. As a significant clinical event, vaginal cuff dehiscence is unlikely to not be reported or to be subject to recall bias.

Study recruitment is designed to avoid any potential coercion. Potential subjects will have decided with their doctor to undergo minimally invasive hysterectomy prior to discussing possible participation in this trial. Once a potential candidate has been successfully pre-screened, the informed consent process will be conducted by a study investigator or coordinator other than the potential subject's doctor.

Study enrollment takes place during surgery. Intra-operative enrollment criteria are designed to specifically evaluate closure of the vaginal cuff during laparoscopic hysterectomy, the step Zip-stitch™ is designed for. Subjects who may have unforeseen complications during the anesthesia or colpotomy process for example, are not intended for treatment and their procedure should continue according to standard of care.

Study randomization will take place via blinded, variable block size randomization envelopes stratified by site. Subjects will be blinded to the treatment they receive, but as the operating surgeon cannot be blinded to the treatment provided, this study cannot be fully double-blinded. Every effort will be made to minimize opportunities for unblinding during post-operative data collection. In particular data collection will be performed by a different investigator surgeon without access to the blinded to treatment assignment, including through the electronic data capture system.

Data unblinding will take place after completion of six-week follow-up. This enables reporting of the primary study endpoints and most secondary study endpoints. The data collected at the 6 and 12-month follow-up visit and telephone call are limited to dehiscence, pain, dyspareunia, and adverse events. Adverse events are likely to have significant clinical sequelae, and therefore not likely to be forgotten. Pain and dyspareunia are evaluated based on experience in the time frame of the call, and therefore are not affected by recall bias. No statistical comparisons are being made using 12-month data.

Some secondary endpoints evaluate incidence and rate of various events; others compare test and reference groups. Comparisons will be made using two-sided Fisher's Exact Tests. Secondary endpoints are not powered to reach statistical significance but are intended to provide additional information and indicate possible safety and efficacy trends.

The schedule of follow-up has been designed to assess vaginal cuff wound recovery one week after the procedure and six weeks after the procedure, when the vaginal cuff is expected to be significantly if not completely healed. The six-month in person follow-up visit will assess longer term recovery, and the 12-month follow-up phone call is timed to collect additional long-term data about subject recovery and return to normal life. Telephonic follow-up at 12-months is appropriate for this study as a physical exam later than six months is unnecessary and burdensome for subjects. Requiring long-term in-person follow-up risks loss to follow-up, and all data to be collected after six months can be collected over the phone. The FSFI has been validated for telephonic administration,[29,30] as has an 11-point numerical pain scale.[31] Implant passing is not expected beyond six months as clips degrade between 5 and 8 months, and adverse events have clinical sequelae significant enough to avoid recall bias.

Use of the sexual pain and discomfort domain of the validated FSFI is a valuable but limited evaluation of post-operative dyspareunia. The FSFI has been validated only in its entirety, and therefore use of a subset of questions does not allow for conclusions that may otherwise be possible full through use of the full FSFI. However, only the sexual pain and discomfort domain of the FSFI is relevant to the outcomes of this trial, and due to length and content the full FSFI is unnecessary and burdensome.

4.3 END OF STUDY DEFINITION

A subject is considered to have completed the study if she has completed all phases of the study including the last visit shown in the Schedule of Activities (SoA).

Alternatively, a subject may be lost to follow-up or subject to withdrawal or early termination as described in Section 7.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

To be eligible to participate in this study, an individual must meet all of the following criteria:

1. Provision of signed and dated Informed Consent Form
2. Stated willingness to comply with all study procedures, including participation in follow-up visits and telephonic follow-up
3. Female aged 18 years and older
4. Indicated for Laparoscopic Hysterectomy (may include TLH, LAVH, robotic assisted vaginal hysterectomy)

5.2 EXCLUSION CRITERIA

An individual who, as per chart review, meets any of the following criteria prior to the procedure will be excluded from participation in this trial:

1. History of HIV
2. History of Hepatitis C
3. History of diabetes, that in the opinion of the investigator may delay healing
4. Current use of systemic corticosteroids

5. Active infection of genitals, vagina, cervix, uterus or urinary tract
6. Active bacteremia, sepsis or other active systemic infection
7. Presence of Sextually Transmitted Infection (STI)
8. Evidence of pelvic inflammatory disease (PID)
9. Known clotting defects or bleeding disorders
10. Hemoglobin < 8 g/dL
11. Metastatic disease
12. On anticoagulant therapy
13. Participation in another interventional trial
14. Pregnancy
15. Abnormal PAP results that have not been fully evaluated, or in the opinion of the investigator may indicate risk of abnormal vaginal cuff healing
16. Co-morbidities that in the opinion of the investigator may indicate risk of abnormal vaginal cuff healing.

Additionally, an individual who meets any of the following intraoperative criteria during hysterectomy will be excluded from participation in this trial:

17. Bowel injury during laparoscopic hysterectomy procedure prior to attempted cuff closure
18. Bladder injury during laparoscopic hysterectomy procedure prior to attempted cuff closure
19. Cases in which, before study randomization, surgeon cannot identify adequate tissue along the cuff to apply suture laparoscopically
20. Cases requiring conversion to laparotomy prior to study intervention

5.3 LIFESTYLE CONSIDERATIONS

Participation in study may require more hospital/doctor visits than would otherwise be necessary due to trial follow-up schedule, including one week, six weeks, and six months post-operative visits and a 12-month follow-up phone call. It is not expected that this will present an increased financial burden, but subjects will receive nominal renumeration for their time and travel.

As is required with all laparoscopic hysterectomy procedures, participating subjects will be required to abstain from sexual intercourse for a minimum of six weeks after their procedure.

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently randomly assigned to the study intervention or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this trial (screen failures) will not be rescreened.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

This clinical trial will involve one test treatment (and a separate comparative reference treatment) administered at one or more investigative locations. As the treatment is part of laparoscopic hysterectomy procedures, recruitment and retention strategy will concern women above the age of 18 of all races and ethnicities who are intending to undergo laparoscopic hysterectomy. Subject

recruitment will take place in the weeks to months prior to a procedure from the regular patient pool of each investigator. Patients intending to undergo laparoscopic hysterectomy around the time of the study, who are identified as meeting all pre-operative inclusion/exclusion criteria will be approached for participation by the responsible principal investigator. One out of four potential candidates are expected to enroll in this study.

Subjects will be approached for potential participation during a doctor visit as part of their normal medical care. It is not expected that this will present an increased financial burden, but subjects may be nominally remunerated for travel and inconvenience due to participation in this study. All subjects approached but not enrolled will be documented in the study's screening log.

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

The test device being evaluated in this study is the Zip-stitch™ Vaginal Cuff Closure System, as described below.

6.1.2 STUDY AGENT DESCRIPTION

The Zip-stitch™ Vaginal Cuff Closure System is a system for closing the vaginal cuff following hysterectomy. The system includes a series of bioabsorbable clips, a reusable clip applicator, and a reusable clip loading tool. The clips are injection molded from polydioxanone (PDO) and sterilized with ethylene oxide. The applicator and loading tool are reusable surgical instruments made of stainless steel that facilitate delivery of clips to the treatment site.

The clips are inserted into the applicator outside the body using the loading tool, and the system enters the body cavity through a surgical trocar. Through use of the applicator handle, opening lever, and trigger, a clip is applied to interposed leaves of the vaginal cuff. Subsequent clips are applied to the surgical wound until the whole span of the wound has been closed. The clips provide mechanical support to the tissue during the healing process, and clips maintain soft tissue approximation for the critical wound healing period (14 days) while resisting postoperative forces. After this holding period, the clips degrade by hydrolysis and are absorbed by the body after approximately eight months.

All Zip-stitch™ system components will be provided by the study sponsor, ZSX Medical LLC, including Zip-stitch™ system training and methodology. Physical products will be shipped prior to study commencement. The surgical methodology developed for Zip-stitch™ closure of the vaginal cuff during laparoscopic hysterectomy will be provided with this clinical protocol as the device Instructions For Use. Zip-stitch™ system training will be provided by the sponsor ZSX Medical and will take place no longer than two weeks prior to the first procedure performed by each surgeon. Zip-stitch™ System training will involve review of the device Instructions for Use, recommended clinical technique, and an illustrative cuff closure video. Study training will also include discussion of expected technical challenges, such as proper technique for removal and replacement of Zip-stitch™ clips. After training is completed, sponsor representative and recipients of training will sign the training form.

All Zip-stitch™ clips will be provided sterile and will be packaged and labeled appropriately for human use. Each clip will be packaged and labeled individually. Zip-stitch™ clip application systems, including the Zip-stitch™ reusable clip applicator and the Zip-stitch™ reusable clip loading tool, will be provided

packaged and unsterile, with instructions for sterilization prior to use included in the device Instructions for Use contained in packaging.

These Zip-stitch™ products are not available anywhere except through the sponsor, ZSX Medical LLC, but are solely intended for human use as applied in this trial. The Zip-stitch™ system has not yet been cleared by FDA. This study is being conducted under an Investigational Device Exemption. All devices will be labeled, "CAUTION: Investigational Device. Limited by Federal (or United States) law to investigational use."

The study reference device is VICRYL™ suture in a running fashion, used according to product labeling.

Reference device(s) should be used and stored according to their product labeling.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 ACQUISITION AND ACCOUNTABILITY

Test and reference device materials will be delivered to investigational site by the sponsor. Devices are to be handled and stored according to product labeling.

6.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

Each Zip-stitch™ Vaginal Cuff Closure System includes one stainless-steel reusable handheld laparoscopic clip applier and stainless-steel clip loading tool (see Figure 1). These reusable stainless-steel instruments will be provided in disposable labeled white boxes. In addition, Zip-stitch™ clips are provided in cartons each containing five individually pouched and labeled clips. Clip pouches are opened by peeling apart at the indicated chevron and removing the clip from the contained stability mounting card. See instructions for use, contained in both device boxes, for additional information.

The test product, Zip-stitch™, is manufactured and provided by the sponsor:

ZSX Medical LLC
3401 Grays Ferry Ave, Bldg. 176
Philadelphia PA, 19146

The reference product, VICRYL™ suture, is manufactured by Ethicon Inc:

Ethicon Inc,
Somerville, New Jersey

6.2.3 PRODUCT STORAGE AND STABILITY

Test Product:

> Zip-stitch™ clip storage: clips should be stored frozen (-10 to -30°C), as indicated on product labeling, in packaging. clips can be used up to the expiration date indicated on product labeling.
>
> Zip-stitch™ Applicator and loading tool storage: Applicator and loading tool should be stored at room temperature according to normal practices for reusable surgical instruments.

Reference Product:

> VICRYL™ storage: VICRYL™ Sutures should be stored according to device labeling and standard hospital procedures.

Clinical monitoring will regularly ensure both test and reference devices are being stored as indicated.

6.2.4 DEVICE PREPARATION

Zip-stitch™ clips are provided sterile and are ready for use. They should be opened by medical assistant during surgery into the sterile field as indicated in the device Instructions for Use. The Zip-stitch™ reusable applicator and clip loading tools are not provided sterile and must be cleaned and sterilized before each procedure according to the device Instructions for Use provided.

During procedure, clips are to be loaded in the sterile field into applicator jaws using the clip loading tool. Once loaded, the device is ready for use in closing the vaginal cuff.

The reference device, VICRYL™ should be prepared according to device labeling and standard hospital procedures.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Variable block size randomization will be employed to assign a vaginal cuff closure method to each subject. At the time of enrollment and after confirmation of intraoperative eligibility, a subject will be randomly assigned treatment (cuff closure) with the test device (Zip-stitch™) or reference device (VICRYL™). This assignment will be provided via sponsor provided randomization envelopes broken down in 2:1 variable block sizes and stratified by site. Treatment allocation blocks will vary from three to six subjects and will be split 2:1 test to reference assignment. This method helps safeguard against a simple randomization generating a smaller than intended test or reference group.

Subjects will be blinded to the cuff closure method they receive during surgery. Because operating surgeons cannot be blinded to the treatment they are providing, this trial cannot be completely double-blinded. Every effort will be made to minimize bias in post-operative data collection. Data collection will be performed by an investigator without access to the blinded to treatment assignment. Treatment assignment will be recorded at the time of procedure in the electronic data capture system. After this point, the investigator collecting follow-up data will be blinded to medical records and treatment group. The operative surgeon cannot be blinded as the performed treatment. They will be available during follow-up as needed but will not participate in data collection for patients that they provided treatment.

Database lock and data un-blinding will take place after completion of the last six-week follow-up visit. Subjects will still participate in the 6 and 12-month visit and extension period call, but data will be unblinded. The data collected at the 12-month telephone visit are limited to pain, dyspareunia, and adverse events. Adverse events are likely to have significant clinical sequelae, and therefore not likely to be forgotten. Pain and dyspareunia are evaluated based on experience in the time frame of the call, and therefore are not affected by recall bias.

6.4 STUDY INTERVENTION COMPLIANCE

Protocol adherence is the responsibility of all investigator and will be regularly monitored by a study monitor in accordance with Sponsor clinical monitoring standard operating procedures. Any deviation from study protocol will cause a protocol deviation to be logged in the protocol deviation form on the electronic data capture system. All protocol deviations will be reported to the study sponsor and to required regulatory bodies in accordance with GCP.

6.5 CONCOMITANT THERAPY

For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications to be reported in the Case Report Form (CRF) are concomitant prescription medications, over-the-counter medications and supplements.

6.5.1 RESCUE TREATMENT

In the event that a subject is enrolled, and a random treatment is assigned, but the surgeon is unable to achieve cuff closure with the assigned cuff closure method, the surgeon may close the cuff using an alternate method. This event would be considered a protocol deviation and these subjects will be included in analysis of the primary efficacy outcome. These subjects will also be included in secondary endpoint ITT and safety populations, and subject safety data will be included in study analysis.

7 PARTICIPANT DISCONTINUATION, WITHDRAWAL, AND LOSS TO FOLLOWUP

7.1 DISCONTINUATION OF STUDY INTERVENTION

As this study involves a single surgical treatment, discontinuation from study test intervention occurs in the circumstance of an additional procedure required to address failed cuff closure, or dehiscence. In this case, cuff closure with the test or reference article will have failed and will be reflected in cuff closure failure rate reported the secondary study endpoint analysis. If a subject receives an additional procedure to address vaginal cuff dehiscence, they will re-start study follow-up, including one week, six week, and six month in-person visits and a 12-month phone call. All secondary endpoint data collection will be re-performed according to the new follow-up schedule and will be included in secondary endpoint analysis.

In any circumstance in which an investigator determines it necessary to discontinue subject participation for reasons other than vaginal cuff dehiscence, that subject will be discontinued from the study and may not be included in study analysis. The reason(s) for discontinuation will be documented on the End of Study CRF.

Overall study discontinuation and closure is further discussed in section 10.1.2.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request.
An investigator may discontinue or withdraw a participant from the study for the following reasons:

- Reported sexual activity prior to six-week follow-up;
- If any clinical adverse event (AE), abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant; or
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation.

Follow-up will continue for any subjects who are withdrawn from the study by an investigator for any of the above reasons. These subjects will remain part of the ITT population for the evaluation of the primary endpoint and will be included in the study safety population.

The reason for participant discontinuation or withdrawal from the study will be recorded on the End of Study Case Report Form (CRF). Subjects who sign the informed consent form and are randomized but do not receive the study intervention may be replaced. Subjects who sign the informed consent form, and

are randomized and receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study, will not be replaced.

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if she fails to return for any follow-up visit and is unable to be contacted by the study site staff. If a subject participates in all follow-up requirements through six months but does not participate in 12-month follow-up and is unable to be contacted by study site staff, their data will be reported through six months in the initial study reporting and may be imputed based on existing data as part of the 12-month supplementary report.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed as soon as possible, will counsel the participant on the importance of maintaining the assigned visit schedule, and will ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record, study file, and ultimately on the end of study CRF.
- Should the participant continue to be unreachable, she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 ENDPOINT ASSESSMENTS

The following will take place during the study, as outlined in the Schedule of Activities (SoA).

Prescreening

- Prescreening will take place prior to the approach of a potential subject.
- Each PI or a co-investigator surgeon will pre-screen potential subjects for conformance to inclusion and exclusion criteria after determining that a laparoscopic hysterectomy procedure is clinically appropriate and consistent with standard care.

Recruitment

- Recruitment will take place following prescreening and in parallel with hysterectomy scheduling.
- A potential subject's surgeon will inform potential subject of the existence of the trial once a potential subject has met all inclusion and exclusion criteria regarding study participation.

Screening

- Following initial study recruitment and displayed patient interest/willingness an investigator will screen subjects using patient medical history for conformance to all pre-operative study inclusion and exclusion criteria.
- An investigator will then complete the Pre-Enrollment screening form confirming subject conformance to all study inclusion and exclusion criteria.

Informed Consent

- Once a potential subject has been identified as satisfying the necessary pre-operative inclusion/exclusion criteria, an investigator will explain to the subject that they qualify for participation in this investigation. To avoid the potential for coercive influence by the study surgeon, the informed consent process will be performed by study personnel other than the investigator. Informed consent will be obtained using an IRB approved Informed Consent Form.
- Once a subject has provided Informed Consent, the site will schedule the procedure.

Baseline Data Collection

- Following completion of ICF, an investigator will complete baseline data collection according to the Baseline Data Collection form.
- Hemoglobin and pregnancy tests are to be performed prior to surgery as part of standard pre-operative care for hysterectomy procedures. If not part of standard hospital care, pregnancy and hemoglobin tests are to be performed.

Intra-Operative Screening

- Results of hemoglobin and pregnancy test are to be re-confirmed as part of intra-operative screening.
- Enrollment (or exclusion) will occur during the laparoscopic hysterectomy procedure, following uterine excision, just before cuff closure. Reasons for mid-operative exclusion may include transition to laparotomy, surgeon's decision to close the cuff using suture with or without robotic assistance, realized subject satisfaction of exclusion criteria, or other complications.
- Investigator or coordinator will complete the Intra-Operative Screening Form during the procedure to confirm subject enrollment or exclusion.
- Once a subject has been enrolled, the subject will be assigned to a study group according to study randomization strategy.

Surgery – Cuff Closure

- Following intra-operative study enrollment, surgeon will close the cuff according to the subject's assigned study group.
- Surgeon will visually confirm the integrity of achieved vaginal cuff closure.
- The laparoscopic surgical video will be collected for reference.
- An investigator or coordinator will complete the Intra-Operative Report form and ensure surgeon evaluates cuff closure integrity and that laparoscopic video is saved.

One Week In-Person Follow-Up Visit

- This in-person follow-up visit should take place 7 ± 3 days of the study procedure and will include a vaginal examination for visual assessment of cuff closure.
- The subject will be assessed for study endpoints including implant passing, cuff closure evaluation, adverse events, pain, and dyspareunia.
- An investigator or coordinator other than that which provided cuff closure treatment will collect information for completion of case report forms by site coordinators as indicated in the SoA.

Six Week In-Person Follow-up Visit

- This in-person follow-up visit should take place within six weeks ± five days of the study procedure and will include a vaginal examination for visual assessment of cuff closure and healing.

- The subject will be assessed for study endpoints including implant passing, cuff closure and healing evaluation, adverse events, pain, and dyspareunia.
- An investigator or coordinator other than that which provided cuff closure treatment will collect information for completion of case report forms by site coordinators as indicated in the SoA.

Six Month In-Person Follow-up Visit

- This in-person follow-up visit should take place within six months ± one week of the study procedure.
- The subject will be assessed for study endpoints including implant passing, cuff closure and healing evaluation, adverse events, pain, and dyspareunia.
- There will be a visual inspection of the vaginal cuff at this visit. An investigator or coordinator other than that which provided cuff closure treatment will collect information for completion of case report forms by site coordinators as indicated in the SoA.
- Data will be unblinded following completion of all six month follow-up visits.

12-Month Extension Period Call

- This assessment can take place in person or over the phone and should take place within 12 months ± four weeks of the study procedure.
- The subject will be assessed for study endpoints including implant passing, pain, dyspareunia, and adverse events.
- An investigator or coordinator other than that which provided cuff closure treatment will collect information for completion of case report forms by site coordinators as indicated in the SoA.

8.2 EVALUATION OF SPONTANEOUS EVENTS

Since implant passing and adverse events are spontaneous, such events may not align with study data collection. As such data collection is prepared for unscheduled follow-up visits; reporting and evaluation of implant passing and adverse events will be explicitly requested at all follow-up timepoints.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS (AE)

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

Adverse Event details will be classified and reported by a study investigator and confirmed by the study PI. Classifications of adverse events are described below. Clip passing, by itself, is *not* an adverse event.

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of

the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

Adverse events will be coded using a validated medical dictionary (MedDRA - Medical Dictionary for Regulatory Activities, (McLean, VA)).

SEVERITY OF EVENT

The following guidelines will be used to describe the severity of an adverse event.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

RELATIONSHIP TO STUDY INTERVENTION

The clinician's assessment of an AE's relationship to study intervention (Zip-stitch™ system or VICRYL™) is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt whether a clinical observation is an AE, the event should be reported. All AEs must have their relationship to study agent assessed. For all collected AEs, the clinician who examines and evaluates subjects will determine the AE's likely causality based on temporal relationship and his/her clinical judgment. The causality will be graded using the categories below:

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study intervention administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study intervention should be clinically plausible.
- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal.
- **Potentially Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.
- **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the

study intervention) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- **Not Related** – The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

OUTCOME OF EVENT

The following guidelines will be used to categorize and describe the outcome of an adverse event:

- **Fatal** - Event has caused patient death.
- **Ongoing, not improving** - Subject has not recovered and is *not* improving since initial reporting of event.
- **Ongoing, improving** - Subject has not recovered, but is improving since initial reporting of event.
- **Recovered w/ sequelae** - Subject has recovered from event, but with complications.
- **Resolved** - Subject has completely recovered from event, with no complications.

TREATMENT OF EVENT

The following guidelines will be used to categorize and describe the treatment of an adverse event:

- **None** - Subject was administered no treatment for the event.
- **Medication(s)** - Subject was prescribed medication to treat the event. Medication, including dosing, should be recorded in the Concomitant Medications/Therapies portion of Adverse event log.
- **Non-medication** - Subject was administered some treatment or therapy other than medication in effort to address the event. This includes outpatient treatment only.
- **Hospitalization** - Subject was admitted to the hospital for treatment of this event.
- **Other** - Another type of treatment was administered, to be described in the Adverse Event Log.

EXPECTEDNESS

An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study agent in Section 2. In other words, expectedness is binary and will be recorded as Yes or No in an Adverse Event Log as determined by the PI according to identified risks.

8.3.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

Any medical condition that is present at the time that the subject is screened, but does not exclude said subject, will be considered as baseline and not reported as an AE. However, if the study subject's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized by surgeon to be intermittent, or having distinct episodes, require documentation of onset and duration of each episode.

An investigator will record all reportable events with start dates occurring any time after informed consent is obtained until the last day of study participation, AEs occurring before, but not resolving by, the last day of study participation will be followed for an additional 7 (for non-serious AEs) or 30 days

(for SAEs) after. If such an SAE is determined to be probably or definitely related to the investigational device, then it may be followed for longer.

At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization. All AEs will be followed to adequate resolution.

8.3.5 ADVERSE EVENT REPORTING

The PI or Site Coordinator shall complete an Adverse Event Form via the electronic data capture system for each adverse event.

The study Sponsor contact information is provided in Section 10.1.4, Key Roles. The study Sponsor is responsible for conducting an evaluation of an unanticipated adverse device effect and shall report the results of such evaluation to FDA as appropriate and to all reviewing IRBs and participating investigators within 10 working days after the sponsor first receives notice of the effect. Thereafter the sponsor shall submit such additional reports concerning the effect as requested by regulatory authorities.

8.3.6 SERIOUS ADVERSE EVENT REPORTING

Serious Adverse Events require completion of a Serious Adverse Event Report Form an investigator. Reported SAEs regardless of classification must be reviewed by study PI and reported as soon as possible, but in no event later than 10 working days after an investigator first learns of the event (§ 812.150(a)(1)).

The study investigator is also responsible for completing an Unanticipated Adverse Device Effect Form and submit to the study sponsor and to the reviewing Institutional Review Board (IRB) as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect. The study sponsor is responsible for conducting an evaluation of an unanticipated adverse device effect and shall report the results of such evaluation to the Food and Drug Administration (FDA) and to all reviewing IRBs and participating investigators within 10 working days after the sponsor first receives notice of the effect. Thereafter, the sponsor shall submit such additional reports concerning the effect as FDA requests. See Section 10.1.4 for contact information.

All SAEs will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the outcome to be stable. Other supporting documentation of the event may be requested by the FDA or study sponsor and should be provided as soon as possible. The study sponsor will be responsible for notifying FDA of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible but in no case later than seven calendar days after the sponsor's initial receipt of the information.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

This study will evaluate the hypothesis that more than 5% patients with Zip-stitch™ clips applied to their vaginal cuffs will pass implants. The implant passage rate will be calculated upon conclusion of six-week post-operative follow-up.

The implant passing rate will simply be numerically compared to the established 5% performance target. No formal statistical test will be used to evaluate this hypothesis.

9.2 SAMPLE SIZE DETERMINATION

The study size was based on FDA's recommendation of the sufficient sample size to support a future 510(k) notification.

A minimum of 30 and a maximum of 40 subjects in the test group have been requested for this study. Assuming a 10% loss to follow-up, a goal of 39 (maximum of 44) subjects are expected to be enrolled in the test group, and a goal of 20 (maximum of 22) are expected to be enrolled in the reference group, for a total goal of 59 (maximum of 66).

No statistical assessment of the rate of successful cuff closure is required for analysis of the primary study endpoints. The rate of implant passing events on a per-patient basis will be numerically compared to the 5% performance target. Nonetheless, the 95% confidence interval will be reported for this endpoint.

This study is also not powered to address secondary endpoints. It is not expected that statistical analyses will yield conclusive results on exploratory endpoints.

9.3 POPULATIONS FOR ANALYSES

Intent-to-treat population (ITT): This population will include all subjects enrolled and randomized to test or reference treatment. Subjects will be analyzed according to the treatment to which they were randomized, regardless of the treatment they actually received.

Safety Population: This population will include all subjects enrolled and randomized to test or reference treatment. Subjects will be analyzed according to the treatment that they received; patients randomized to the reference arm that receive Zip-stitch™ will be included in the Zip-stitch™ safety population. Similarly, patients randomized to the Zip-stitch™ arm that receive sutures will be included in the reference safety population.

Primary and secondary efficacy analyses will be performed on the ITT population. All safety analyses will be performed on the Safety population.

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

In general, continuous variables will be summarized by providing the number of subjects with available data (n), the mean, median, standard deviation, minimum, and maximum values. For categorical variables, the number and percentage of subjects that are in each category will be provided. Unless otherwise specified (such as for the primary endpoint), the denominator for percentages will be all relevant subjects in a particular analysis, excluding those for whom data are not available prior to the relevant endpoint timepoint. For subjects lost to follow-up prior to evaluation of an endpoint, their data will be subject to the data imputation plan detailed in Section 9.4.10.

The ITT population will be the analysis population for all efficacy analyses.

Statistical analyses will be performed using SAS v9.4 or later (SAS Institute Inc., Cary, NC, USA).

9.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT

The primary efficacy endpoint in this study is frequency of implant passing incidents evaluated through six weeks post-operative. Subjects who report an implant passing event up to six weeks after surgery

will be asked to collect and return the passed implant, and to come in for a follow-up visit within two weeks. If there is no planned visit within that window, the subject should have an unscheduled visit as soon as they are able. The surgeon will first confirm that it was an implant that was passed, then during the visit, a visual surgeon assessment of cuff closure, healing, and assess any possible relationship of implant passing to adverse events (secondary efficacy endpoint 4).

The final analysis of the primary efficacy endpoint will be implant passing rate, which will be numerically compared to the established 5% performance target.

9.4.3 ANALYSIS OF THE PRIMARY SAFETY ENDPOINT

The primary safety endpoint in this study is the rate of vaginal cuff dehiscence through six months. Vaginal cuff dehiscence is defined as rupture of the surgical wound requiring surgical re-intervention. Subjects who experience vaginal cuff dehiscence up to six months after surgery will also be considered a cuff closure failure.

The number and proportion of subjects with vaginal cuff dehiscence at 6 weeks will be presented. The 95% confidence interval of the proportion will also be reported.

9.4.4 ANALYSIS OF SECONDARY EFFICACY ENDPOINTS

Secondary Endpoint (1) Cuff closure (compared between test and reference groups) will be assessed (yes or no) by an independent surgeon at one and six weeks, as well as at six months.

> **Data collection:** Surgeon will visually assess vaginal cuff closure, indicating whether the vaginal mucosa is intact. If the vaginal cuff closure is determined not to be intact, then failure of this study endpoint will be indicated and the subject will be included in the ITT population for remaining study endpoints. If additional surgical intervention is necessary to address lack of cuff closure, follow-up will restart following the new procedure date. In this circumstance the new follow-up schedule will be included in the evaluation of remaining efficacy endpoints in the ITT population and will be included in the safety population.
>
> **Acceptance Criteria:** Endpoint success at each timepoint is defined as test group cuff closure failure rate less than or equal to that of the reference group.
>
> **Statistical Analysis Method:** A two-sided Fisher's Exact Test will compare (test versus reference) rate of dehiscence at each timepoint. Assessment of this endpoint is independent of primary study endpoint results.

Secondary Endpoint (2) Cuff healing (compared between test and reference groups), will be assessed (yes or no) by an independent surgeon at six weeks and six months.

> **Data collection:** Surgeon visual assessment of cuff healing is limited to a single binary assessment ("healed" or "not healed"). Additional descriptive observations are included during data collection but are not used in comparative analysis. If the vaginal cuff is determined not to be healed, then failure of this study endpoint will be indicated. If additional surgical intervention is necessary, follow-up will restart following the new procedure date. In this circumstance the new follow-up schedule will be included in the evaluation of remaining efficacy endpoints in the ITT population and will be included in the safety population.

Acceptance Criteria: Endpoint success is defined as a test group cuff healing failure rate less than or equal to that of the reference group**.**

Statistical Analysis Method: A two-sided Fisher's Exact Test will compare (test versus reference) rate of visually assessed, failed cuff healing at each post-operative timepoint. Assessment of this endpoint is independent of the primary safety endpoint.

Secondary Endpoint (3) Comparison of implant passing rates.

Data collection: Implant passing rates will be calculated and the percentage of subjects experiencing one or more implant passing events will be compared between the test and control groups at six weeks and at six months.

Acceptance Criteria: Endpoint success is defined as a percentage of subjects experiencing implant passing in the test group less than or equal to that of the reference group.

Statistical Analysis Method: A two-sided Fisher's Exact Test will compare (test versus reference) percentage of subjects experiencing implant passing events between test and reference groups. Assessment of this is independent of the primary study endpoints.

Secondary Endpoint (4) Relationship of Implant passing to Adverse Events.

Data collection: Frequency of implant passing events associated with an Adverse Event will be evaluated through six-weeks post-operative. Associating implant passing to an Adverse Event will include consideration of temporal and possible causal relationship. The AE relatedness terms described in Section 8.3.3 will be utilized in determination of implant passing to a given Adverse Event, where "relatedness to study intervention" is replaced with "relatedness to implant passage." This will not replace determination of relatedness to the study device, which will be performed separately according to study safety reporting details. Adverse Events determined to be 'probably' or 'definitely' related to an implant passing event will be considered a per patient failure of the primary efficacy endpoint. Relationship of implant passing events to AEs will be reported independently and compared between test and control groups.

Acceptance Criteria: Endpoint success is defined as a percentage of subjects experiencing implant passing event related to an AE in the test group less than or equal to that of the reference group.

Statistical Analysis Method: A two-sided Fisher's Exact Test will compare (test versus reference) percentage of subjects experiencing implant passing event associated with an AE between test and reference groups. Assessment of this is independent of the primary study endpoints.

9.4.5 ANALYSIS OF SECONDARY SAFETY ENDPOINTS

The Safety population will be the analysis population for all safety analyses.

Secondary Endpoint (5) Comparison of incidence of adverse events.

Data collection: Adverse Events will be tabulated for both the test and reference groups. All AEs and SAEs will be MedDRA-coded and summarized by treatment arm. In addition, the number and proportion of AEs and SAEs will be calculated for each group. For each MedDRA-coded medical term, the proportion of subjects who experience at least one of the following will be reported and compared.

- Adverse event

- Adverse event related to treatment
- Serious adverse event
- Serious adverse event related to treatment
- Adverse event leading to study discontinuation
- Serious adverse event leading to study discontinuation

Classification of AEs will also be presented and compared. Events will be reported by MedDRA system organ class and preferred term. Adverse Events will be compared by severity and device relatedness between the test and reference groups.

Acceptance Criteria: There is no defined endpoint acceptance criteria for the comparison of adverse events.

Statistical Analysis Method: A two-sided Fisher's Exact Test will compare (test versus reference) rate of incidence of adverse events by six months post-operative. Assessment of this is independent of the primary study endpoints.

Secondary Endpoint (6) Comparison (test to reference group) of non-increase in subject dyspareunia scores from baseline to 6-months post-operative.

Data collection: Individual subject dyspareunia will be assessed using the relevant sexual discomfort module of the validated Female Sexual Function Index (FSFI).[21,22] Higher scores indicate good sexual function with little or no sexual discomfort, and lower scores indicate poor sexual function with higher levels of sexual discomfort. Scores of zero indicate no sexual activity and will not be included in comparison of non-increase in dyspareunia.

Acceptance Criteria: A subject level failure is defined as a decrease in sexual function score (signifying an increase in dyspareunia). Endpoint success is defined as the same or lower rate of FSFI score decrease in the test group at six months when compared to the reference group at six months.

Statistical Analysis Method: Comparison (test versus reference group) of failure rates from baseline to six-month follow-up will be made using a two-sided Fisher's Exact Test. Assessment of this is independent of the primary study endpoints.

Secondary Endpoint (7) Comparison (test to reference group) of non-increase in subject pain scores from baseline to 6-months post-operative.

Data collection: Individual subject pain will assed using a validated 11-point numerical pain rating scale, where "0" corresponds to no pain and "10" corresponds to the most pain possible. Pain score will be collected at all study timepoints and unexpected visits; however, statistical assessment will be performed between baseline and six-month score.

Acceptance Criteria: A subject level failure is defined as an increase in reported subject pain score. Endpoint success is defined as the same or lower rate of increase in reported pain in the test group at six months when compared to the reference group at six months.

Statistical Analysis Method: Comparison (test versus reference group) of failure rates from baseline to six-month follow-up will be made using a two-sided Fisher's Exact Test. Assessment of this is independent of the primary study endpoints.

9.4.6 BASELINE DESCRIPTIVE STATISTICS

Demographic characteristics (age, ethnicity), height and weight, and disease characteristics will be summarized using descriptive statistics. Subjects in the ITT and Safety populations will be summarized within each treatment group and overall.

9.4.7 PLANNED INTERIM ANALYSES

There is no interim analysis planned. Primary endpoint analysis and reporting will take place after completion of all six-week follow-up. This report will be considered the final study report and will completely assess the primary study endpoint. There will be additional supplementary reports with follow-up endpoint analysis at 6 and 12-months. See study design rationale for additional details.

9.4.8 SUB-GROUP ANALYSES

There are no subgroup-analyses planned.

9.4.9 TABULATION OF INDIVIDUAL PARTICIPANT DATA

Individual participant data will be listed by measure and time point.

9.4.10 MISSING DATA & DATA IMPUTATION

Because implant passing is expected to be spontaneous, missing data will not be imputed for analysis of the primary study endpoint. Instead, if a subject is lost to follow-up prior to their six-week in-person visit, they will be included in the ITT population, but any incomplete data collection will be excluded from the total population evaluated for the primary study endpoint. For example, completed one-week follow-up data from a subject lost to follow-up between their one and six week visits will be included, but the uncompleted six-week data will be excluded, and they will not be included in the efficacy endpoint population totals for uncompleted follow-up timepoints. Data may be imputed based on existing data averages for subjects lost to follow-up after their six-week visit as part of additional study analysis, such as the 12-month unblinded follow-up reporting.

Sensitivity analysis will be performed on ITT population evaluation of the primary endpoint where all missing data are imputed as successes and separately as failures. Results of these analyses will be presented alongside primary endpoint evaluation. Every effort will be made to minimize missing data.

Additionally, any cases of vaginal cuff closure performed with a rescue method in accordance with protocol Section 6.5.1 will have their primary endpoint value set to missing. Their values will be imputed using multiple imputation. Additional information will be provided in the statistical analysis plan (SAP). These cases will also be included in sensitivity analysis determining possible effect of exclusion of these subjects from primary endpoint analysis.

Data imputation may be performed for appropriate secondary endpoints. Imputation will only be performed for secondary endpoints evaluating, or based on evaluation of, a status (as opposed to an incidence) and if a subject is lost to follow-up *after* their six-week visit. Data for subjects lost to follow-up before their six-week visit will not be imputed. Secondary endpoints that may allow for data imputation include (1) status of cuff closure, (2) status of cuff healing, (6) change in dyspareunia, and (7) change in pain.

9.4.11 EXPLORATORY ANALYSES

Additional exploratory endpoints will be collected. These include cuff closure time (the time required to close the vaginal cuff as measured from time of conclusion of uterine excision to time of placement of the final Zip-stitch™ clip or completion of final suture), total surgical time (calculated based on procedure start and end times (time from first incision to final port closure)), and whether implant material can be observed in the vaginal canal during visual cuff inspection.

Cuff closure time and total surgical time will be summarized by providing the number of subjects with available data (n), the mean, median, standard deviation, minimum, and maximum values. Observation of implant material will be reported and compared between test and reference groups.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in full relevant detail the Zip-stitch™ study procedures and components, as well as risks, are given to the subjects. This Informed Consent Form will be approved by an IRB prior to enrollment.

Written documentation of informed consent is required prior to enrollment.

CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process initiated prior to an individual's agreeing to participate in this study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of participation will be provided to the subjects and their families. Consent forms will be IRB-approved, and the subject will be asked to read and review the document. The investigator will explain the research study to the subject and answer any questions that may arise. All subjects will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research subjects. Subjects will have the opportunity to carefully review the written consent form and ask questions prior to signing. Subjects should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. Study participation will be discussed in a manner which will avoid any potential or perceived coercive influence by the patient's surgeon. Should subjects elect to participate they will sign the informed consent document prior to any procedures being done specifically for the study. The subjects may withdraw consent at any time throughout the course of the study. A copy of the informed consent document will be given to the subjects for their records. The rights and welfare of the subjects will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient cause. Written notification, documenting the reason for study suspension or termination, will be provided by the

suspending or terminating party to the principal investigator, the sponsor: ZSX Medical LLC, and regulatory authorities including appropriate IRBs and FDA.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination of futility

Study may resume once the concern leading to study suspension is addressed sufficiently to satisfy the sponsor, IRBs and FDA.

The primary study stopping rule is defined in terms of subject safety. The study will be paused and an unblinded analysis will be performed by the independent safety monitor if at least three cuff dehiscences and a failure rate of at least 5% of the enrolled study population has been realized. Upon unblinded review, the study will continue unless vaginal cuff closure failures with study test device (Zip-stitch™ clips) are found to be at least 3 cases and a rate of greater than 5% of the enrolled study population. Study stoppage rules apply only to the test device and not to the standard-of-care reference device (VICRYL™).

10.1.3 CONFIDENTIALITY AND PRIVACY

Subject confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor and their agents. The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or study data will be released to any unauthorized third party without prior written approval of the sponsor.

The study monitor, other authorized representatives of the sponsor, or representatives of the IRB may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and any pharmacy records for the subjects in this study. The clinical study site will permit access to such records.

The study subject's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and institutional regulations.

10.1.4 KEY ROLES AND STUDY GOVERNANCE

Sponsor
ZSX Medical LLC
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Principal Investigator
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Medical Monitor

Greg Fossum, M.D.
Baptist Health
gregory.fossum@comcast.net
ph. 215-429-8358

Monitoring & Statistics

The Sponsor will manage monitoring and statistics through third party consultants.

10.1.5 SAFETY OVERSIGHT

Greg Fossum, M.D. is the medical monitor for this study. Dr. Fossum is an independent physician not affiliated with this clinical trial in any other way. Dr. Fossum will be contacted in the event of any serious or unexpected adverse events to determine whether the SAE or AE is test article related. He will also provide independent safety review of any analysis related to study stoppage (See section 10.1.2 for study stoppage rules), as well as independent adjudication of all study safety events.

10.1.6 CLINICAL MONITORING

Clinical site monitoring is to be performed in compliance with ZSX Medical's Clinical Monitoring Standard Operating Procedure. Clinical monitoring is performed to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of this trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with all applicable regulatory requirement(s). The clinical trial monitor will also be responsible for assisting the study sponsor in any resolving data queries that may result from site reporting.

Clinical monitoring will be performed by one or more Clinical Research Associates for as long as patients are in trial schedule. This includes, but is not limited to, patient involvement from recruitment to completion of follow-up and extension period phone calls, as outlined follow-up schedule in Section 1.3.

Monitoring will involve site facilities review, study trainings and query resolution, regular review and maintenance of essential trial documents for completeness and correctness, confirmation of accurate reporting of participant informed consent, safety data and study endpoints, and maintenance of records of monitoring communication.

Visits will include Site Initiation, regular Interim Visits dependent on enrollment progress and study safety and conformance, and a Closeout Visit. For-cause visits may also take place as appropriate and can be mandated by the Sponsor, the study IRB, FDA, or can be requested by the site. Monitoring reports will be produced following each visit, and all monitoring communication will be maintained.

10.1.7 QUALITY ASSURANCE AND QUALITY CONTROL

Each clinical site will perform internal quality management of study conduct, data collection, documentation and completion. An individualized quality management plan will be developed to describe a site's quality management.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted and data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

10.1.8 DATA HANDLING AND RECORD KEEPING

DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

All study data will be collected and maintained using a validated eData capture system provided by MedNet Solutions (Minnetonka, MN). The system will be accessible only through unique role-based login/password requirements.

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site PI. The PI is responsible for the accuracy, completeness, legibility, and timeliness of the data reported. Any physically completed source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Black ink is required to ensure clarity of reproduced copies. When making changes or corrections, cross out the original entry with a single line, and initial and date the change. Do not erase, overwrite, or use correction fluid or tape on original reports.

STUDY RECORDS RETENTION

Study documents will be retained for a minimum of 2 years after final study termination date and until there are no pending or contemplated marketing applications in an International Council for Harmonization (ICH) region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

No biological samples handled in this study will be stored, transported or used for any reason as part of this study.

10.1.9 PROTOCOL DEVIATIONS

It is the responsibility of the Principal Investigator to use continuous vigilance to identify and report deviations within five working days of identification of the protocol deviation, or within 5 working days of the scheduled protocol-required activity. All deviations must be addressed according to study source documents and reported to sponsor and relevant regulatory/review boards per their guidelines. This includes completion of the Protocol Deviation Tracking Log.

10.1.10 PUBLICATION AND DATA SHARING POLICY

The Sponsor shall own and have the right to use the Data in accordance with the signed informed consent and authorization form, applicable laws, and the terms of this Agreement. Notwithstanding any licenses or other rights granted to Sponsor herein, but in accordance with the confidentiality and publication sections herein, Institution shall retain the right to use the Data and results for its publication, IRB, regulatory, legal, clinical, educational, and internal research purposes.

10.1.11 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the medical device industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the trial.

10.2 ABBREVIATIONS AND DEFINITIONS

Adverse Events (AE)

> For the purpose of this clinical investigation plan, an adverse event (AE) is any untoward medical occurrence, unintended disease or injury or any untoward clinical signs in subjects whether or not related to the Investigational Product and includes events related to the procedures involved (any procedure in the clinical investigation plan). All Adverse Events (including serious Adverse Events) will be classified by outcome, severity, treatment taken, and attribution to study intervention. See Section 8.3 for more details.

Associated Adverse Event

> Defined as an AE that is both device-related (to either clip or reference device in accordance with Section 8.3.3) and that is temporally related to the implant passing event.

Body Mass Index (BMI)

Code of Federal Regulations (CFR)

Vaginal Cuff Dehiscence

> Vaginal cuff dehiscence has a reported incidence of up to one in twenty (5%) among patients undergoing laparoscopy[5–7] even with robotic assistance.[8] Vaginal cuff dehiscence has been defined in this study as a rupture of the surgical wound requiring surgical re-intervention. Small openings in approximated vaginal mucosa that resolve without intervention will be recorded as part of cuff closure and healing characterization endpoints, but will not be deemed as failures, since intervention was not required to bring about recovery

Food & Drug Administration (FDA)

Good Clinical Practice (GCP)

Informed Consent Form (ICF)

Institutional Review Board (IRB)

Instructions For Use (IFU)

Investigational Device Exemption (IDE)

Laparoscopic Assisted Vaginal Hysterectomy (LAVH)

LAVH is the surgical excision of a women's uterus using a combination of vaginal and laparoscopic approaches LAVH typically includes laparoscopically detaching the uterine body from the surrounding upper supporting structures. The vaginal apex is entered using a vaginal approach, and the cervix and uterus are detached from the remaining supporting structures. The uterus is then removed through the vagina.

Poly-*p*-dioxanone (PDO)

A biologically inert, bio-absorbable polymer that degrades naturally by hydrolysis. Both traditional suture and Zip-stitch™ clips are composed of this material.

Principal Investigator (PI)

Serious Adverse Events (SAE)

Serious AEs are a subset of AEs. An SAE is one that:

- Results in death
- Results in life-threatening illness or injury
- Results in a permanent impairment of a body structure or function
- Requires inpatient hospitalization or prolongation of an existing hospitalization
- Results in a medical or surgical intervention to prevent a permanent impairment to a body structure or function
- Results in fetal distress, fetal death, or a congenital abnormality or birth defect.

A planned inpatient hospitalization, without a serious deterioration in health, is not considered to be a serious adverse event. Reports relating to the subject's subsequent medical course must be submitted to the sponsor or sponsor's designee and the reviewing IRB until the event has subsided or, in the case of permanent impairment, until the event has stabilized and the overall clinical outcome has been ascertained.

Total Laparoscopic Hysterectomy (TLH)

TLH is the surgical excision of a women's uterus using laparoscopic ports. Typically, the surgeon laparoscopically detached the entire uterine cervix and body from the surrounding supporting structures. The uterus can be removed through the vagina or abdomen. The vaginal cuff is closed at the end of the procedure.

11 REFERENCES

11.1 ADDITIONAL STUDY DOCUMENTS

QD-PRO-005 Rev 002 – Investigators Brochure

QD-PRO-046 Rev 005 – Informed Consent Form

11.2 LITERATURE REFERENCES

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