Solyx Statistical Analysis Plan (U9915)

Cover Page

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A prospective, Non-randomized, Parallel Cohort, Multi-Center Study of the Solyx™ Single Incision Sling System Vs. The Obtryx II™ Sling System for the Treatment of Women with Stress Urinary Incontinence

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Statistical Analysis Plan

A PROSPECTIVE, NON-RANDOMIZED, PARALLEL COHORT, MULTI-CENTER STUDY OF THE SOLYX™ SINGLE INCISION SLING SYSTEM VS. THE OBTRYX™ II SLING SYSTEM FOR THE TREATMENT OF WOMEN WITH STRESS URINARY INCONTINENCE

Solyx™ Study

Postmarket Study PS120093

[redacted]

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APPROVALS (Check/Complete one below):

☒ Approvals are captured electronically

☐ An electronic system for capturing approvals is not being used for this study; wet signatures are captured below:

[redacted]

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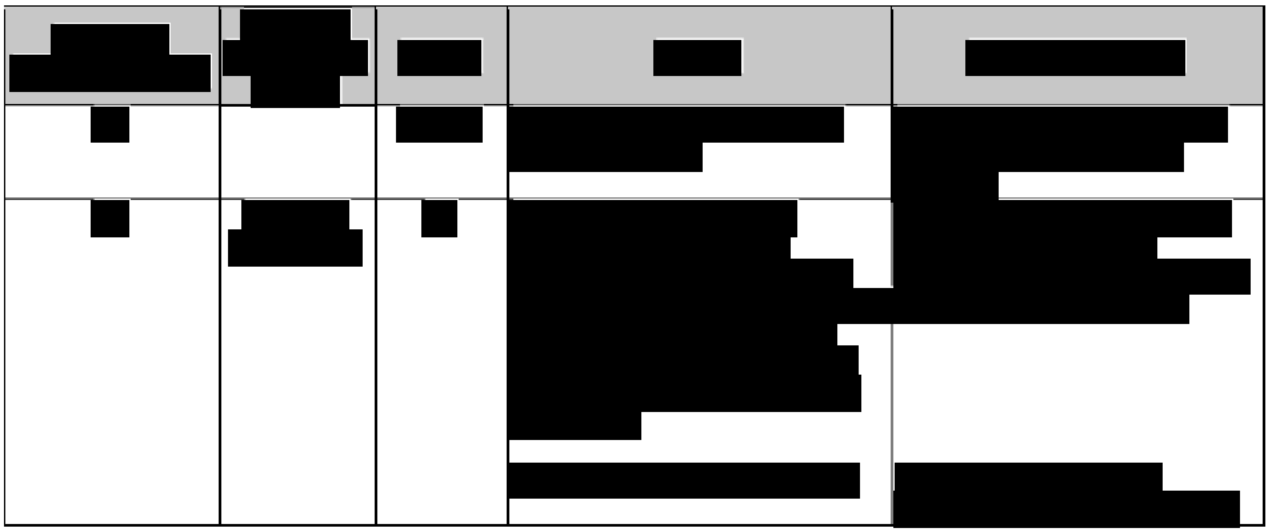

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1 PROTOCOL SUMMARY

Objective	The purpose of this study is to compare a single incision midurethral sling to a standard outside-in transobturator sling for the treatment of female stress urinary incontinence.
Test Device	Solyx™ Single Incision Sling System
Control Device	Obtryx™ II Sling System (outside-in transobturator sling)
Study Design	Prospective, non-randomized, parallel cohort, multi-center study
Planned Number of Subjects	Approximately 280 subjects (140 in each study arm) are planned
Planned Number of Centers	Up to 30 study centers
Primary Endpoint	Treatment success at 36 months defined as negative cough stress test with protocol required bladder fill procedure and subject self-reported improvement in their condition as compared to baseline on the Patient Global Impression of Improvement (PGI-I).
[redacted]	[redacted]
Method of Assigning Subjects to Treatment	Physicians and study centers will be selected based on their device experience and will be device-specific centers (i.e. Solyx™ or Obtryx II™ subjects only).
Follow-up Schedule	Study follow-up duration is for 3 years from primary study procedure: • Screening/Enrollment Visit • Pre-operative/Baseline Visit

	• Surgery and Discharge • Week 2 Visit • Week 6 Visit • Month 6 Visit • Month 12 Visit • Month 18 Visit • Month 24 Visit • Month 36 Visit (End of study)
Key Inclusion Criteria	1. Female ≥ 18 years of age 2. Willing and able to comply with the study procedures and provide written informed consent to participate in the study (subject or legal representative) 3. Diagnosed with predominant SUI confirmed by positive cough stress test during the protocol required bladder fill procedure (see manual of operations) 4. Confirmed SUI is greater than urge incontinence with MESA 5. Cystometric capacity ≥ 300 cc 6. Post-void residual (PVR) of ≤ 150 cc 7. Medically approved for general, regional or monitored anesthesia

Key Exclusion Criteria	1. Subjects who are pregnant, lactating, or planning future pregnancies 2. Subjects with a chief complaint of overactive bladder 3. Subjects with a pattern of recurrent urinary tract infections, defined as ≥ 2 culture-proven urinary tract infections during a 6-month period prior to surgery or ≥ 3 in a 12-month period 4. Subjects with previous surgical procedures for SUI including bulking, urethral sling, bone anchor, Burch procedure, pubo-vaginal sling, and MMK procedure. Previous surgical procedures for SUI does not include Kelly plication, Botox, anterior repair, or Inter-Stim. 5. Subjects with prior pelvic organ prolapse surgery who experienced mesh complications 6. Subjects with previous radiation therapy to the pelvis 7. Subjects with known or suspected hypersensitivity to polypropylene mesh 8. Subjects with any of the following confounding conditions: a. Neurogenic bladder b. Urethral stricture and bladder neck contracture c. Bladder stones or tumors d. Urinary tract fistula or diverticula e. Pathology which would compromise implant placement including subjects currently taking anticoagulation therapy f. Pathology that would limit blood supply or infections that would compromise healing including chemotherapy, systemic steroids and systemic immunosuppressants 9. Subjects with diabetes and an A1c ≥ 7% 10. Non-English speaking subjects 11. Subjects who have participated in an investigational study (medical device or drug) within 30 days of study entry that may impact analysis of this device or have previously participated in the current study
Primary Statistical Hypothesis	The efficacy of the single incision sling treatment is non-inferior to that of the standard outside-in transobturator sling treatment.

2 INTRODUCTION

This is a post-market surveillance study required by the Food and Drug Administration per Section 522 of the Federal Food, Drug, and Cosmetic Act. [redacted]

[redacted]

3 ENDPOINT ANALYSIS

3.1 Primary Endpoint

The primary endpoint of the study is treatment success at 36 months defined as a negative cough stress test and a subject-reported improvement in their condition through the Patient Global Impression of Improvement (PGI-I). Improvement per the PGI-I is defined as a response of "A little better", "Much better", or "Very much better". A negative cough stress test is defined as an answer of "No" to the item "Direct observation of urine loss with cough provocation".

3.1.1 Hypotheses

The study will evaluate whether the single-incision sling treatment (Solyx) is non-inferior to the outside-in transobturator (Obtryx) treatment. The null and alternative hypotheses for this evaluation are

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

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

where $\pi_{treatment}$ and $\pi_{control}$ are the proportions of subjects with treatment success in the treatment and control groups, respectively, and Δ is the non-inferiority margin.

[redacted]

3.1.3 Statistical Methods

Non-inferiority will be evaluated using a two-sided 90% confidence interval for the treatment difference (single-incision minus transobturator). If the entire confidence interval is above -15%, non-inferiority will be demonstrated. The confidence interval will be calculated based on the pooling of treatment differences across propensity score strata for a binary endpoint, as described in Section 4.3.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

4 GENERAL STATISTICAL METHODS

4.1 Analysis Sets

The Intent-to-Treat (ITT) subject population includes all subjects who provide written informed consent to be enrolled into the study, met all eligibility criteria, and have a surgery initiated (i.e. anesthesia administered).

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

All primary [redacted] endpoint analyses will be performed on both the ITT and PP populations, with ITT considered the main analysis and PP as a sensitivity analysis; [redacted]

4.2 Control of Systematic Error/Bias

To reduce selection bias in this non-randomized study, each study center will be permitted to enroll subjects in only one of the treatment groups. Physicians will be selected based on device and clinical research experience and will decide which device to implant in subjects prior to study initiation at their center. This decision will be documented. All subjects meeting the eligibility criteria at the study center will be screened and enrolled, as applicable.

Imbalance between the treatment arms at baseline is a potential source of bias. To facilitate an unbiased treatment comparison, the analyses of outcomes will be based on stratification on the propensity score, as described in Section 4.3. The propensity score will be calculated from only baseline data prior to performing any analysis of endpoints, in order to avoid introducing bias from knowledge of outcome data.

4.3 Propensity Score Analysis

Analyses comparing the treatment groups will be adjusted for the propensity score. [redacted]

[redacted]

[redacted]

4.4 Summary Statistics

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

[redacted]

4.6 Methods for Handling Missing Data

The analyses will include only the available cases, unless specified otherwise.

Censoring times for time-to-event analyses will be at the earliest of the subject's end of study participation, death, and the time point of the analysis (e.g., for the Kaplan-Meier estimate through 12 months, the time point for the analysis is 365 days).

[redacted]

- [redacted]

[redacted]

[redacted]

5 ADDITIONAL DATA ANALYSES

5.1 Interim Analyses

No formal interim analysis is planned. [redacted]

5.2 Justification of Pooling

In this study, the treatment difference will be estimated by pooling across propensity score strata. An analysis of the poolability will be made using logistic regression for the primary endpoint with fixed effects for treatment arm, propensity score stratum, and their interaction. The interaction will be evaluated to assess the extent of heterogeneity in the treatment difference across strata, and hence whether pooling the within-stratum treatment differences is justified. In addition, within each treatment arm, a chi-squared test will be applied to assess whether the distribution of the primary endpoint varies across the study centers. The above methods will be used in lieu of performing the protocol-specified logistic regression with effects for treatment arm and study center, since the treatment arm and center are confounded.

[redacted]

[redacted]

[redacted]

5.5 Changes to Planned Analyses

Any changes to the planned statistical analyses made prior to performing the analyses will be documented in an amended Statistical Analysis Plan. Changes from the planned statistical methods after performing the analyses will be documented in the clinical study report along with a reason for the deviation.

[redacted]

[redacted]

[redacted]