Topas System Post-Approval Studies (PAS) Considerations

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Reminder

- The discussion of a PAS prior to FDA determination of device approvability should not be interpreted to mean FDA is suggesting that the device is safe and effective.

- The plan to conduct a PAS does not decrease the threshold of evidence required by FDA for device approval.

- The premarket data submitted to the Agency and discussed today must stand on their own in demonstrating a reasonable assurance of safety and effectiveness and an appropriate benefit/risk balance.

Outline

- Postmarket Question
- Extended Follow-Up of Premarket Cohort PAS Proposal
- New Enrollment PAS Proposal
- FDA Assessment of PAS Proposals

Postmarket Question

- What is the long-term safety and effectiveness of the device?

- The applicant is proposing two PASs:

  - Extended follow-up of the TRANSFORM premarket cohort

  - New enrollment post-approval study

Extended Follow-Up of Premarket Cohort

Study Design	Prospective, multi-center, single-arm, open-label cohort study
Study Population	Adult women with FI who have failed more conservative therapies and were participating in the premarket (TRANSFORM) study.
Objectives	Long term efficacy, as measured by a 50% reduction of FI in a 14 day bowel diary at 24, 36, 48 and 60 months. Long term safety, measured as the proportion of patients experiencing at least one device and/or procedure-related SAE lower than 25% at 60 months post-operatively.

Extended Follow-Up of Premarket Cohort (Cont.)

Hypotheses	H_0: $p \geq 25\%$ H_1: $p < 25\%$ where p = proportion of patients with any SAE during the 60 month follow-up.
Sample Size	The 25% performance goal is based on the treatment-related SAEs rate at 60 months in the PMA study of Interstim® for FI. Based on the results of the TRANSFORM study, the 60-month treatment-related SAE rate for Topas System is conservatively assumed to be 12%. Under this assumption, a sample size of 70 patients completing 60-month data will achieve 85% power.

Extended Follow-Up of Premarket Cohort (Cont.)

Statistical Plan	Efficacy: Descriptive statistics will be used to summarize the treatment efficacy at 24, 36, 48 and 60 months. Safety: Hypothesis testing - examining if the upper bound of its one sided 95% CI (log-log scale) for the SAEs at 60 months is lower than 25%.
Follow-up Schedule	Extended follow-up visits are scheduled at 24, 36, 48 and 60 months The Last 60 month study visit is projected to occur in December 2017.

New Enrollment Post-Approval Study

Study Design	Single-arm cohort study
Study Population	Adult women with FI who have failed more conservative therapies.
Primary Safety Objective	To demonstrate that the proportion of patients experiencing at least one SAE is lower than 20% performance goal at 36 months.

New Enrollment PAS (Cont.)

Hypothesis	H_0: p (treatment-related SAE rate) ≥20% H_1: p (treatment-related SAE rate) <20% where p = the proportion of patients experiencing at least one treatment-related SAE at 36 months. The 20% performance goal at 36-month was calculated using a 36-month treatment-related SAE of 13% (Interstim®) plus a 7% margin.

New Enrollment PAS (Cont.)

Sample Size	Assuming SAE rate of 9% at 36 months for patients receiving the TOPAS System, a sample size of 88 patients at 36 months is required to achieve 90% power, with a one-sided 5% type I error rate. A minimum of 114 patients implanted with the TOPAS System are needed based on an annual 8% dropout rate.
Follow-up Schedule	Acute FU: 14-28 days after implant, and then annually through 3 years

New Enrollment PAS (Cont.)

Secondary Objectives	• Demonstrate reduction or improvement from baseline in: o FI and urge FI episodes o Incontinence days o FI symptom severity (Wexner Score) o FI quality of life and Pelvic Floor Distress Inventory • Summarize frequency, severity, and medical intervention of all treatment-related AEs • Characterize treatment-related pelvic area pain severity and location • Quantify patient surgical satisfaction and health resource utilization

New Enrollment PAS (Cont.)

Statistical Plan	• Hypothesis testing will be performed to evaluate if primary safety endpoint is met. • Descriptive statistics and 95% CI will be used to summarize the secondary endpoints. • Repeated measures model or other statistical method will be used to evaluate changes over time in secondary endpoints.

FDA Assessment of Applicant's Proposed PASs

- **Performance Goals**

FDA considers that the following proposed performance goals (PGs) based on a different device are too high:

- 25% for the extended follow-up PAS at 60 months
- 20% for the new enrollment PAS at 36 months

(proposed goals based on Interstim® - SNS that does not modify anatomical structure of pelvic muscles)

- **Panel will be asked to discuss:**

The appropriateness of the proposed safety PGs.

FDA Assessment of New Enrollment PAS

- Data Collection in the Premarket Study was limited:
  - Limited number of patients were evaluated for anal-rectal angle changes
  - No information was systematically collected on fecal obstructive symptoms
  - No validated questionnaire to evaluate pelvic pain was used
  - No clear definition of pelvic organ prolapse
- Evaluation of pelvic floor dysfunction via a POP-Q-like exam are not included in the proposed PAS plan

The Panel will be asked to discuss:

The methods and schedules of diagnostic surveillance proposed by the applicant for following patients in relation to pain, pelvic organ prolapse and other adverse events in the New Enrollment PAS.

Panel will also be asked if there are any additional postmarket concerns that may need to be addressed if the device is approved for market distribution.