Panel Questions: P140006 ASTORA Women's Health, LLC
TOPAS Treatment for Fecal Incontinence
February 25th, 2016

Discussion Questions

Effectiveness

1. The primary effectiveness endpoint of the TRANSFORM study was based on subjects having a ≥ 50% reduction in the number of fecal incontinence (FI) episodes documented by a 14 day bowel diary at 12 months compared to baseline ($Responder_{50}$ rate). The primary endpoint of the study was met based on the results of the first interim analysis of 80 subjects (52/80=65%, p=0.0048). Among all 152 subjects implanted with the TOPAS System, 105 experienced treatment success, corresponding to a $Responder_{50}$ rate of 69.1% with a 95% confidence interval of [61.0%, 76.3%].

   Please discuss whether these results support the effectiveness of the TOPAS device.

2. The TRANSFORM study also had several descriptive secondary effectiveness endpoints (Section 9.2 of Executive Summary), including the long term effectiveness of the TOPAS Sling System, a reduction in incontinent days, a reduction in urge FI episodes, a reduction in symptom severity (Wexner score), and other quality of life assessment tools.

   Please discuss whether the results for these endpoints support the effectiveness of the TOPAS device.

Safety

3. The primary evidence provided in support of safety showed that there were 115 treatment related (device and /or procedure) adverse events reported in 72 (47.4%) subjects. These adverse events included pain (43.5%), infection (21.7%), de novo and worsening pelvic organ prolapse (11.3%), and urinary incontinence (6.9%).

   a. Please discuss whether the pain, which was the most frequently reported complication, has been adequately characterized and evaluated, and possible reasons for the pain.

   b. Please discuss the rate of pelvic organ prolapse, which frequently required surgical intervention or was ongoing, and its potential association with this procedure.

   c. Is the safety profile of this device for the intended population adequately described?

d. Please discuss whether the results demonstrate device safety for the intended population.

Labeling

4. The applicant has proposed the following Indications for Use for the TOPAS System:

> "The TOPAS Treatment for Fecal Incontinence is intended to treat women with fecal incontinence (also referred to accidental bowel leakage) who have failed more conservative therapies."

The inclusion and exclusion criteria for the study required that subjects be 18 years old and over, not pregnant, and not planning a future pregnancy, and that subjects have failed two modalities of conservative therapies such as dietary modification, pharmacologic intervention, or pelvic floor muscle training.

a. Should the labeling exclude patients who are pregnant or may become pregnant?

b. Should the labeling include any age restrictions?

c. Should the labeling specify other interventions that should be used prior to the use of this device?

5. In the clinical study, urogynecologists and colorectal surgeons implanted this device. There was no statistical difference shown for the primary effectiveness endpoint; however, regarding safety, there was a trend toward fewer AEs (e.g., pelvic pain reports, pain duration, pain resolution) following implantation by urogynecologists.. Please discuss the following:

a. the clinical training or experience that should be required for physicians implanting this device

b. other measures that could be taken to ensure patient success.

Post Approval Study

Note: The inclusion of a Post-Approval Study (PAS) section in this summary should not be interpreted to mean that FDA has made a decision or is making a recommendation on the approvability of this PMA device. The presence of a post-approval study plan or commitment does not in any way alter the requirements for premarket approval and a recommendation from the Panel on whether the risks outweigh the benefits. The premarket data must reach the threshold for providing reasonable assurance of safety and effectiveness before the device can be

found approvable and any post-approval study could be considered. The issues noted below are FDA's comments regarding potential post-approval studies, for the Panel to include in the deliberations, should FDA find the device approvable based upon the clinical premarket data.

The applicant is proposing to conduct two PASs. The first proposal, the Extended Follow-up of the Premarket Cohort, is a continuation of the premarket study cohort; the second proposal is a New Enrollment PAS that will enroll patients in the US and Europe. The overall goal of these PASs is to evaluate the long-term safety of the TOPAS system in the postmarket setting in women with FI who have failed more conservative therapies.

6. For the two proposed PAS, the primary safety objective is to demonstrate that the proportion of subjects experiencing at least one device- and/or procedure-related serious adverse event (SAE) meets a performance goal.
    - For the Extended Follow-up of the Premarket Cohort, the proposed performance goal is 25% at 60 months.
    - For the New Enrollment PAS, the proposed performance goal is 20% at 36 months.

    These performance goals are based on the performance of a different device that does not modify the anatomical structure of the pelvic muscles (Interstim® sacral nerve stimulation (SNS) therapy). FDA is concerned that these performance goals are too high. The FDA recommends the applicant take into consideration the nature of the implanted device, the risk/benefit ratio, and the results from the TOPAS premarket study when developing the performance goal for the post-approval study.

    Please discuss the appropriateness of the 25% and 20% performance goals listed above.

7. Regarding the New Enrollment PAS:

    a. Does the panel have any recommendations about the method or schedule of diagnostic surveillance for following subjects in relation to pain?

    b. Does the panel have any recommendations about the method or schedule of diagnostic surveillance for following subjects in relation to pelvic organ prolapse?

    c. Does the panel have any recommendations about the method or schedule of diagnostic surveillance for following subjects in relation to other adverse events?

    d. Are there any other concerns which the panel recommends the PAS address?

Voting Questions

Following the panel discussion, CDRH will ask panel members to vote by ballot on the following questions:

The TOPAS System is a permanently implanted mesh device to be placed around the base of the puborectalis muscle intended to treat women 18 years and over, with fecal incontinence (also referred to accidental bowel leakage) who have failed more conservative therapies.

The applicant has proposed the following Indications for Use for the TOPAS System:

> The TOPAS Treatment for Fecal Incontinence is intended to treat women with fecal incontinence (also referred to accidental bowel leakage) who have failed more conservative therapies.

The following questions related to the approvability of the TOPAS System. Please answer them based on your expertise, the information you reviewed in preparation for this meeting, and the information presented today:

- Voting Question 1: Is there reasonable assurance that the TOPAS System is safe for the proposed indication for use (e.g. the device will not expose patients to an unreasonable or significant risk of illness or injury)?

- Voting Question 2: Is there reasonable assurance that the TOPAS System is effective for the proposed indications for use?

- Voting Question 3: Do the benefits of the TOPAS System for the proposed indications for use outweigh the risks of the TOPAS in patients who meet the criteria specified in the proposed indication?

Panel members will be asked to state how they answered each question and to explain their answers. If the panel member answered "no" to any question, he or she will be asked whether changes to labeling, restrictions on use, longer term follow-up, or other controls, would change his or her response

If the evidence provided is insufficient to allow for any of the determinations, the panel member should state this as the reason for answering "no." A description of any remedial studies or actions should be given.