FDA Presentation: TOPAS™ System for Fecal Incontinence
P140006
Statistical Presentation
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Division of Biostatistics
Office of Surveillance and Biostatistics

GU Advisory Panel Meeting
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Outline

• Study Design

• Effectiveness Results

• Summary of Effectiveness
Study Design

• Multicenter, single-arm study with one interim analysis
  – Primary and secondary endpoints are subjective

• One interim analysis
  – Possible early stopping for effectiveness
  – Option for sample size adjustment

• Potential issues with single-arm study designs
  – Regression to the mean could account for some of the observed improvement
  – Lack of blinding
  – Lack of control arm making device effectiveness and safety difficult to evaluate
Primary Endpoint and Study Hypothesis

• The primary effectiveness endpoint:
  – Responder50: ≥ 50% reduction in the number of FI episodes in a 14 day bowel diary at 12 months compared to baseline.

• The study hypotheses:
  \[ H_0: p \leq 50\% \quad \text{vs.} \quad H_a: p > 50\% \]
  \( p \) is probability of Responder50, 50\% is the pre-specified performance goal (PG).

• One-sided exact binomial test at 5\% significance level.
Analysis of Primary Endpoint

• Interim Analysis of Primary Effectiveness Endpoint

When 80 subjects have finished 12 months of follow-up (Stage I)
– If $p_1 < 0.0087$, the study would be stopped with a claim of effectiveness
– If $p_1 \geq 0.0087$, sample size would be re-estimated to have adequate power to achieve $p_2 < 0.0087/p_1$ (Stage II)

Per the Bauer and Kohne reference, Stage I and Stage II tests were to be performed separately, and data not to be pooled for inference.

• Analysis of the Primary Effectiveness Endpoint:
– Based on all implanted subjects (ITT)
– Missing 12 month data were treated as failure (non-responder)
Sample Size

Planned sample size was 152 implanted subjects with a possibility to increase.

• One interim analysis for effectiveness and sample size adjustment when 80 subjects finished 12 months of follow-up

• Assuming 61% response rate and 5% level, N=152 would provide approximately 81% power

Final sample size was 152 subjects:
• Stage I: 80 subjects
• Stage II: 72 subjects
Primary Effectiveness Endpoint

<table>
<thead>
<tr>
<th>Subject Group</th>
<th>N</th>
<th>Responder50 Rate</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>80</td>
<td>65.0% (52/80)</td>
<td>(53.5%, 75.3%)</td>
<td>0.0048*</td>
</tr>
<tr>
<td>Stage II</td>
<td>72</td>
<td>73.6% (53/72)</td>
<td>(61.9%, 83.3%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>All Implanted</td>
<td>152</td>
<td>69.1% (105/152)</td>
<td>(61.1%, 76.3%)#</td>
<td>N/A</td>
</tr>
</tbody>
</table>

# Based on fixed sample

* Primary effectiveness endpoint was met.
Median Number of All FI Episodes and Responder50 Rates

through 12 months for all implanted subjects
Subgroup Analyses

- Effectiveness endpoint was analyzed by various baseline variables

- Subgroup analyses were not pre-specified and should be viewed as exploratory

- Effectiveness results by:
  - Age
  - Specialty of Clinical Center
Subgroup Analyses
Responder50 Rates by Age

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Responder50 Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>[32-53] years</td>
<td>68.3% (28/41)</td>
</tr>
<tr>
<td>(53-60] years</td>
<td>61.1% (22/36)</td>
</tr>
<tr>
<td>(60-66] years</td>
<td>71.1% (27/38)</td>
</tr>
<tr>
<td>(66-79] years</td>
<td>75.7% (28/37)</td>
</tr>
</tbody>
</table>
### Subgroup Analyses

#### Responder50 Rates by Specialty

<table>
<thead>
<tr>
<th>Medical Specialty of Clinical Centers</th>
<th>Responder50 Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colorectal (7)</td>
<td>63.3% (38/60)</td>
</tr>
<tr>
<td>Urogynocology (7)</td>
<td>72.8% (67/92)</td>
</tr>
</tbody>
</table>
Subgroup Analyses

Other Factors

• FI medication
• BMI
• Smoking
• Baseline FI episode
• Vaginal deliveries
• FI etiology
• Internal and external sphincter defects
• Medical history

None of these factors seemed to have substantial impact on the Responder50 rate.
Alternative Interventions and/or Withdrawals for Treatment Failures

• 17 patients either received other interventions for FI after TOPAS implant or withdrew for reasons related to treatment failure.

• Analyses based on ITT population (152 implanted subjects):
  – 17 were counted as “non-responders.”

• Astora Women’s Health’s analyses based on “completed visits only” (Responder50 at 12-36m, Wexner and other QoL Questionnaires):
  – 17 were excluded from the analysis.
Patients Receiving Alternative FI Therapies and/or Withdrawals Relating to Treatment Failure

<table>
<thead>
<tr>
<th>Last Visit Before Alternative Intervention or Exit</th>
<th>Number of Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 months</td>
<td>1</td>
</tr>
<tr>
<td>6 months</td>
<td>2</td>
</tr>
<tr>
<td>12 months</td>
<td>9</td>
</tr>
<tr>
<td>24 months</td>
<td>5</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>17</strong></td>
</tr>
</tbody>
</table>
### Alternative FI Therapies Sought by Subjects After Implantation*

<table>
<thead>
<tr>
<th>Alternative Therapies</th>
<th>Number of Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sacral Nerve Stimulator (SNS)</td>
<td>7</td>
</tr>
<tr>
<td>Injectable Bulking Agent</td>
<td>3</td>
</tr>
<tr>
<td>Sphincteroplasty</td>
<td>1</td>
</tr>
<tr>
<td>Other Intervention</td>
<td>1</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>12</strong></td>
</tr>
</tbody>
</table>

*5 subjects withdrew because of dissatisfaction with the TOPAS treatment. It is unknown if they sought additional therapies.
## Secondary Effectiveness Endpoints

### Long Term Effectiveness

<table>
<thead>
<tr>
<th>Study Visit</th>
<th>Responder50 Rate# (All Implanted Subjects)</th>
<th>95% Confidence Intervals</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 months</td>
<td>69.1% (105/152)</td>
<td>[61.1%, 76.3%]</td>
</tr>
<tr>
<td>24 months</td>
<td>53.3% (81/152)</td>
<td>[45.0%, 61.4%]</td>
</tr>
<tr>
<td>36 months</td>
<td>57.8% (78/135*)</td>
<td>[49.0%, 66.2%]</td>
</tr>
</tbody>
</table>

# Missing data counted as non-responder.

* 17 patients had not yet completed the 36m visits.
Secondary Effectiveness Endpoints

Number of FI Episodes by Visits

- **Mean**
- **Median**

Number of Episodes

Visit:
- Baseline
- 3m
- 6m
- 12m
- 24m
- 36m

- Baseline: 18 episodes, 21.7 mean
- 3m: 9.2 episodes, 5 mean
- 6m: 8.2 episodes, 5 mean
- 12m: 9.3 episodes, 5 mean
- 24m: 9.2 episodes, 5 mean
- 36m: 7.6 episodes, 5 mean

Combined: 152 episodes, 149 at 3m, 143 at 6m, 144 at 12m, 128 at 24m, 108 at 36m
## Secondary Effectiveness Endpoints
### Percent of Subjects With at Least 50% Reduction in Incontinent Days by Visits

<table>
<thead>
<tr>
<th>Subject Group</th>
<th>At Least 50% Reduction in Incontinent Days# (All implanted subjects)</th>
<th>95% Confidence Intervals</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 months</td>
<td>54.6% (83/152)</td>
<td>[46.3%, 62.7%]</td>
</tr>
<tr>
<td>24 months</td>
<td>46.1% (70/152)</td>
<td>[37.9%, 54.3%]</td>
</tr>
<tr>
<td>36 months</td>
<td>47.4% (64/135*)</td>
<td>[38.8%, 56.2%]</td>
</tr>
</tbody>
</table>

# Missing data counted as failure.

*17 subjects had not yet completed the 36m visit.*
Secondary Effectiveness Endpoints

Patient reported questionnaires and QOL

• Five instruments, evaluating severity of FI, impact on quality of life, degree of bother and distress on pelvic floor, and sexual function.

• Based on available data except that patients received alternative intervention prior to the study visit were excluded.
Secondary Effectiveness Endpoints

Wexner Symptom Severity Score

<table>
<thead>
<tr>
<th>Time</th>
<th>Mean Wexner Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>14</td>
</tr>
<tr>
<td>3 Month</td>
<td>10</td>
</tr>
<tr>
<td>6 Month</td>
<td>9</td>
</tr>
<tr>
<td>12 Month</td>
<td>8</td>
</tr>
<tr>
<td>24 Month</td>
<td>8</td>
</tr>
<tr>
<td>36 Month</td>
<td>8</td>
</tr>
</tbody>
</table>

(n=150)  (n=146)  (n=145)  (n=144)  (n=126)  (n=108)
# Secondary Effectiveness Endpoints

## FI Quality of Life (FIQOL)

<table>
<thead>
<tr>
<th>Mean FIQOL Score</th>
<th>Baseline (n=152)</th>
<th>3 Month (n=148)</th>
<th>6 Month (n=146)</th>
<th>12 Month (n=144)</th>
<th>24 Month (n=127)</th>
<th>36 Month (n=110)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lifestyle</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coping</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Embarrassment</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

- **Baseline:**
  - Lifestyle: Mean score
  - Coping: Mean score
  - Depression: Mean score
  - Embarrassment: Mean score

- **3 Month:**
  - Lifestyle: Mean score
  - Coping: Mean score
  - Depression: Mean score
  - Embarrassment: Mean score

- **6 Month:**
  - Lifestyle: Mean score
  - Coping: Mean score
  - Depression: Mean score
  - Embarrassment: Mean score

- **12 Month:**
  - Lifestyle: Mean score
  - Coping: Mean score
  - Depression: Mean score
  - Embarrassment: Mean score

- **24 Month:**
  - Lifestyle: Mean score
  - Coping: Mean score
  - Depression: Mean score
  - Embarrassment: Mean score

- **36 Month:**
  - Lifestyle: Mean score
  - Coping: Mean score
  - Depression: Mean score
  - Embarrassment: Mean score
Secondary Effectiveness Endpoints

PFDI-20 and PFIQ-7

Median Total Score

Baseline 3 Month 6 Month 12 Month 24 Month 36 Month

PFDI-20

PFIQ-7
Summary of Effectiveness

• The primary effectiveness endpoint was met based on the interim analysis of 80 subjects

• For the full cohort of 152 subjects, 69% (105) of subjects experienced at least a 50% reduction in the number of FI episodes from baseline, with the 95% CI [61%, 76%]

• Long term effectiveness data and patient reported questionnaire data indicate that the TOPAS System may provide treatment benefit