TOPAS™ Treatment for Fecal Incontinence

ASTORA Women’s Health

Presentation to the Gastroenterology-Urology Devices Panel

February 25, 2016
TOPAS

Tom Rasmussen
Sr. Director of Clinical & Regulatory Affairs
ASTORA Women’s Health
TOPAS Overview

- New, innovative, minimally invasive approach for women with Fecal Incontinence (FI)
- Uses surgical mesh to safely support a woman’s natural anatomy
  - Reduces episodes of FI
  - Improves patient quality of life
- Not placed transvaginally
A Debilitating Condition

- FI causes shame, embarrassment, depression, poor self-esteem and self-imposed social isolation*

- An inability to control bowel movements
  - Ranges from occasional leakage to complete loss of bowel control
  - Mild, moderate, severe FI undefined
  - Patients may have multiple episodes weekly

* Landefeld et al., 2008; Minor, 2004; Norton, 2004
No One Treatment Works in All Patients

- Successful reduction in FI episodes does not eliminate concomitant treatment
- Some therapies result in additional burdens
  - Complex device management
  - Surgical revisions
  - Device replacement
TOPAS is a New Therapeutic Option

- Different potential MOA and implant location
- Support to the anorectum to compensate for the loss of pelvic floor muscle function
TOPAS Final Placement

- Goal is to place the synthetic mesh inferior to the anorectum and parallel with the puborectalis
- Mesh sits ~2 cm away from the anorectum
Outpatient Procedure Performed in ~30 Minutes With General Anesthesia

This is a brief video of the procedure
Indication for TOPAS

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

- Engaged physicians and statisticians in study design development
  - Single arm, adaptive study design
  - Required ≥ 152 patients
- Pre-market application submitted April 2014
- Not commercially available
TOPAS Meets Criteria for Valid Evidence

- Highest level of evidence are randomized controlled trials
- Valid scientific evidence includes objective trials without matched controls*
- Single arm studies provide valid scientific evidence to determine safety and effectiveness

* 21 CFR 860.7 (c)(2)
TOPAS Exceeded Primary Endpoint

- **Primary Endpoint:** > 50% achieve ≥ 50% reduction in number of FI episodes
  - 69% achieved ≥ 50% reduction in FI episodes versus baseline
  - Reduction was durable over 3-yr follow-up period
- Demonstrated improvements in QoL
TOPAS Demonstrated Favorable Mesh Safety Profile

- Not placed transvaginally
- No organ perforations
- 509 patient-years of follow-up, TOPAS has not seen
  - Erosions into vagina or rectum
  - Extrusions through incision sites
  - Bowel obstructions
<table>
<thead>
<tr>
<th>Agenda</th>
<th>Name</th>
<th>Role</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Unmet Need</strong></td>
<td>Mikio Nihira, MD</td>
<td>Professor of Obstetrics and Gynecology, University of Oklahoma</td>
</tr>
<tr>
<td><strong>Study Design &amp; Efficacy</strong></td>
<td>Dee Fenner, MD</td>
<td>Professor of Obstetrics and Gynecology, University of Michigan</td>
</tr>
<tr>
<td><strong>Safety</strong></td>
<td>Mikio Nihira, MD</td>
<td></td>
</tr>
<tr>
<td><strong>Physician Education &amp; Post-Approval</strong></td>
<td>Paul Below</td>
<td>Principal Clinical Research Specialist, ASTORA Women’s Health</td>
</tr>
<tr>
<td><strong>Clinical Perspective</strong></td>
<td>Dee Fenner, MD</td>
<td></td>
</tr>
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</table>
# Additional Experts

<table>
<thead>
<tr>
<th>Name</th>
<th>Role and Affiliation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Massarat Zutshi, MD</td>
<td>TOPAS Study Investigator, Staff, Colorectal Surgery Department, Cleveland Clinic Foundation, Cleveland, Ohio</td>
</tr>
<tr>
<td>Andy Mugglin, PhD</td>
<td>Statistical Consultant, Paradigm Biostatistics, LLC, Minneapolis, Minnesota</td>
</tr>
<tr>
<td>Charlie Khamis</td>
<td>Director of Medical Science and Surgical Expertise, ASTORA Women’s Health</td>
</tr>
<tr>
<td>Ryan Casey</td>
<td>Senior Manager of Global Physician Training, ASTORA Women’s Health</td>
</tr>
</tbody>
</table>
Unmet Need for Women Living with Fecal Incontinence

Mikio Nihira, MD
Professor of Obstetrics and Gynecology
University of Oklahoma
Presentation Overview

- Pathophysiology
- Undertreated condition that is increasing
- Consequences of FI
- Treatment options
<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Normal Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Innervation</td>
<td>Controlling rectal sensation</td>
</tr>
<tr>
<td>Pelvic Floor and Sphincter Muscles</td>
<td>Working properly</td>
</tr>
<tr>
<td>Stool Consistency</td>
<td>Not too soft to hold</td>
</tr>
<tr>
<td></td>
<td>Not too hard to pass</td>
</tr>
</tbody>
</table>
Multiple Possible Contributing Factors

- Congenital, anatomic, neurologic, functional abnormalities
  - Obstetric trauma
  - Age
  - Diarrheal states
  - Inflammatory Bowel Disease
  - Neurologic conditions: Diabetic neuropathy, Multiple Sclerosis
Poor Correlation Between Diagnostic Tools, Causes and Outcomes

- Several tools to characterize FI
- Diagnostic tools may not be helpful to delineate
  - Pathophysiology
  - Potential treatment responses
Fl in U.S. Women Expected to Increase

- 5-10% of women suffer $\geq 1$ Fl episode/month$^{1,2}$
- In 2010, estimated that 10.6 million US women affected with Fl$^3$
- Increases with age

FI Negatively Affects Quality of Life

- FI limits lifestyle and ability to work
- Embarrassment, increased risk of depression
- Plan life around access to restrooms
- Social isolation

Landefeld et al., 2008; Minor, 2004; Norton, 2004
Treatment Barriers

- Lack of knowledge about available treatment options among patients and providers
- Patients embarrassed to seek medical advice
- < 3 in 10 patients discuss FI with their doctor
- Limited treatment options

Aitola et al, 2010; Harvie et al, 2011
Treatments Range from Non-Surgical to Major Interventions

Conservative Therapy
- Dietary changes
- Medication
- Pelvic floor training

Minimally Invasive Interventions
- Injectable bulking agent
- Sacral neuromodulation

Invasive Surgical Interventions
- Sphincter repair surgery
- Colostomy
# FDA Approved FI Devices

<table>
<thead>
<tr>
<th>Device</th>
<th>Type</th>
<th>Ongoing Device Maintenance</th>
<th>MRI Compatible</th>
<th>Commercial Availability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injectable Bulking Agent</td>
<td>Class III (PMA)</td>
<td>Required</td>
<td>Yes</td>
<td>Limited</td>
</tr>
<tr>
<td>Sacral Neuromodulator</td>
<td>Class III (PMA)</td>
<td>Required</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Non-Permanent Vaginal Insert</td>
<td>Class II (510k)</td>
<td>Required</td>
<td>Yes</td>
<td>Limited</td>
</tr>
<tr>
<td>Magnetic Sphincter Augmentation Device</td>
<td>Class III (HDE)</td>
<td>No</td>
<td>No</td>
<td>Limited</td>
</tr>
</tbody>
</table>
Patients Need New, Accessible Treatment Options

- Ideal therapy
  - Efficacious and safe
  - Minimally invasive
  - Low maintenance
  - Improve patients’ lives
Study Design

Dee Fenner, MD
Furlong Professor of Women’s Health
Director of Gynecology
University of Michigan
# Study Design

<table>
<thead>
<tr>
<th>Design</th>
<th>Prospective</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Single Arm</td>
</tr>
<tr>
<td></td>
<td>Open Label</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sites</th>
<th>15 US*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>8 led by colorectal</td>
</tr>
<tr>
<td></td>
<td>surgeons</td>
</tr>
<tr>
<td></td>
<td>7 led by urogynecologists</td>
</tr>
</tbody>
</table>

*One colorectal site closed prior to any patients implanted*
Single Arm Study was Most Appropriate Design

- Study Advisory Committee determined randomization to conservative therapy inappropriate
- No comparable FDA-approved device available
- Benefit did not outweigh risk for sham arm
- Meets FDA standard for valid clinical evidence
50% Reduction in FI Episodes is Standard Outcome = Responders

- Definition of responder
  - ≥ 50% reduction in FI episodes
- Study success criterion
  - > 50% of participants are responders
- Used in recent clinical device trials for FI*

* Wexner et al., 2011; Graf et al., 2011; Richter et al., 2015; Pakravan and Helmes, 2015
Adaptive Design Used

- Two-stage adaptive design
- Planned sample size re-estimation

152 Patients Planned

<table>
<thead>
<tr>
<th>Stage 1</th>
<th>Stage 1</th>
<th>Stage 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>80 patients</td>
<td>12 months follow-up</td>
<td>Ongoing follow-up</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stage 2</th>
<th>Stage 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>At least 72 patients</td>
<td>12 months follow-up</td>
</tr>
</tbody>
</table>
## Regular Follow-up Visits Measured Endpoints

| Physical Exams / AE Assessment | 2 - 4 weeks after surgery  
3 & 6-month follow-up  
Annual thereafter, to 60 months |
|-------------------------------|---------------------------------------------------------------------|
| 14-Day Bowel Diary            | Baseline  
3 & 6-month follow-up  
Annual thereafter, to 60 months |
| Health Questionnaires         |                                                                     |
# Patient Diary Collected Major Outcomes

<table>
<thead>
<tr>
<th>Accident #</th>
<th>Accident Urgency</th>
<th>Accident Consistency</th>
<th>Accident Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1 - Aware</td>
<td>1 - Solid</td>
<td>1 - Small</td>
</tr>
<tr>
<td></td>
<td>2 - Urgent</td>
<td>2 - Mixed</td>
<td>2 - Medium</td>
</tr>
<tr>
<td></td>
<td>3 - Unaware</td>
<td>3 - Liquid</td>
<td>3 - Large</td>
</tr>
</tbody>
</table>

**Accident Urgency**
- Aware – I was aware well before
- Urgent – I was aware suddenly and rushed to the toilet
- Unaware – I was not aware until afterward

**Accident Consistency**
- Solid – Stool has form with definite borders and maintains shape
- Mixed – Stool is watery and contains solid pieces that may be poorly formed
- Liquid – Stool is watery and has no solid pieces with form

**Accident Amount**
- Small – Staining
- Medium – Change pad or undergarments
- Large – Change outer clothing
Primary Efficacy Objective

Demonstrate that more than 50% of study participants could achieve at least a 50% reduction in fecal incontinent episodes from baseline to 12 months.
Handling of Missing Data

- Primary endpoint
  - Missing data as treatment failure
- Long-term follow up
  - Observed cases with missing data excluded
Secondary Objectives to Demonstrate Efficacy Focused on Sustained Results

- Long-term efficacy
- Reduced incontinent days, urge episodes, symptom severity
- Improvement in FI quality of life
- Quantify pelvic floor distress and impact to sexual function
Comprehensive Safety Objective

- Summarize all adverse events
- Quantify pelvic pain
- Known complications of surgical mesh used in pelvic floor reconstruction
Inclusion Criteria

- ≥ 18 years of age
- Tried and failed ≥ 2 conservative therapies
- FI for ≥ 6 months
- ≥ 4 FI episodes in a 14-day period
- Met colon cancer screen guidelines
Exclusion Criteria

- Pregnant or planning future pregnancy
- Diagnosis of inflammatory bowel disease
- Chronic, watery diarrhea
- History of recent gynecologic or gastroenterologic surgical repair procedures
Study Results
Patient Status at 36 Months

All Patients Enrolled
N=207

Patients Implanted
n=152

- Patients Discontinued Prior to 36M
  n=20
  15 = Declined further participation
  2 = Lost to follow-up
  1 = Withdrawn by investigator for SNS implant
  2 = Non-treatment related deaths (Liver Cancer, Non-small cell lung cancer)

- Patients Still Active at 36M
  n=132

Patients Exited Prior to Implant
n=55

- 23 = Declined further participation
- 14 = Did not meet selection criteria
- 5 = Lost to follow-up
- 5 = Withdrawn by investigator
- 4 = Sponsor termination of Site #1011
- 2 = Study implant limit reached
- 1 = AE
- 1 = Subject moved away from site
### Study Population Representative of Women with FI Seeking Treatment

<table>
<thead>
<tr>
<th></th>
<th>N=152</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Mean ± SD)</td>
<td>59.6 ± 9.7</td>
</tr>
<tr>
<td>Duration of FI (Years) (Mean ± SD)</td>
<td>9.2 ± 9.5</td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>90%</td>
</tr>
<tr>
<td>African American</td>
<td>7%</td>
</tr>
<tr>
<td>Other</td>
<td>3%</td>
</tr>
<tr>
<td>BMI (kg/m²) (Mean ± SD)</td>
<td>27.8 ± 5.4</td>
</tr>
<tr>
<td>FI Episodes (14-day period)</td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>21.7 ± 15.4</td>
</tr>
<tr>
<td>Median</td>
<td>18</td>
</tr>
<tr>
<td>Etiology of FI</td>
<td></td>
</tr>
<tr>
<td>Obstetric Trauma</td>
<td>57%</td>
</tr>
<tr>
<td>Idiopathic</td>
<td>41%</td>
</tr>
<tr>
<td>Other</td>
<td>7%</td>
</tr>
</tbody>
</table>

*Melville et al., 2005; Menees et al., 2013*
## Baseline Medical Characteristics

<table>
<thead>
<tr>
<th>Medical History</th>
<th>N=152</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior Hysterectomy and/or Oophorectomy</td>
<td>49%</td>
</tr>
<tr>
<td>Previous Prolapse and/or UI Repair</td>
<td>46%</td>
</tr>
<tr>
<td>Urinary Incontinence</td>
<td>26%</td>
</tr>
<tr>
<td>Previous Anal Sphincter Repair</td>
<td>20%</td>
</tr>
<tr>
<td>Vaginal Prolapse</td>
<td>5%</td>
</tr>
<tr>
<td>Rectal Prolapse</td>
<td>4%</td>
</tr>
<tr>
<td>Failed Conservative Treatment</td>
<td></td>
</tr>
<tr>
<td>At Least Two</td>
<td>100%</td>
</tr>
<tr>
<td>All Three</td>
<td>40%</td>
</tr>
</tbody>
</table>
Study Met its Primary Endpoint of Reducing FI Episodes at 12 Months

<table>
<thead>
<tr>
<th>Subject Group</th>
<th>N</th>
<th>Treatment Success Rate % (95% CI)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>80</td>
<td>65% (54, 75)</td>
<td>0.0048</td>
</tr>
<tr>
<td>Stage II</td>
<td>72</td>
<td>74% (62, 83)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>All Implanted</td>
<td>152</td>
<td>69% (61, 76)</td>
<td>NA</td>
</tr>
</tbody>
</table>

Missing = treatment failure
Reduction in Median FI Episodes

Median Number of FI Episodes in 14 Days

- Baseline (n=152): 18
- 3 Month (n=149): 5
- 6 Month (n=143): 5
- 12 Month (n=144): 5
- 24 Month (n=128): 5
- 36 Month (n=108): 5

Error bars = 25th and 75th percentile

72% reduction

Study Visit
Responder Rate is Stable Over Time

Resonder Rate (± 95% CI)

- 12 Month: 72% (n=144)
- 24 Month: 61% (n=128)
- 36 Month: 68% (n=108)

Completed Visits

Missing = Treatment Failure
# Improvement Categories at 12 Months

<table>
<thead>
<tr>
<th>Change in FI Episodes From Baseline</th>
<th>Rate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increase in Episodes</td>
<td>12% (7, 18)</td>
</tr>
<tr>
<td>No Change in Episodes</td>
<td>7% (4, 13)</td>
</tr>
<tr>
<td>Improvement in Episodes</td>
<td></td>
</tr>
<tr>
<td>&gt; 0% Improvement</td>
<td>81% (74, 87)</td>
</tr>
<tr>
<td>≥ 25% Improvement</td>
<td>77% (70, 83)</td>
</tr>
<tr>
<td>≥ 50% Improvement</td>
<td>69% (61, 76)</td>
</tr>
<tr>
<td>≥ 75% Improvement</td>
<td>42% (34, 50)</td>
</tr>
<tr>
<td>Complete Continence</td>
<td>19% (13, 26)</td>
</tr>
</tbody>
</table>

*Missing = treatment failure*
No Factors Found to Predict Results

<table>
<thead>
<tr>
<th>Age</th>
<th>Treatment Response Rate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>32-53 (n=41)</td>
<td></td>
</tr>
<tr>
<td>&gt;53-60 (n=36)</td>
<td></td>
</tr>
<tr>
<td>&gt;60-66 (n=38)</td>
<td></td>
</tr>
<tr>
<td>&gt;66-79 (n=37)</td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td></td>
</tr>
<tr>
<td>&lt; 30 (n=107)</td>
<td></td>
</tr>
<tr>
<td>≥ 30 (n=45)</td>
<td></td>
</tr>
<tr>
<td>External Sphincter Defect</td>
<td></td>
</tr>
<tr>
<td>No (n=73)</td>
<td></td>
</tr>
<tr>
<td>Yes (degree ≤ 90) (n=41)</td>
<td></td>
</tr>
<tr>
<td>Yes (degree ≥ 90) (n=38)</td>
<td></td>
</tr>
<tr>
<td>FI Severity (# of Episodes)</td>
<td></td>
</tr>
<tr>
<td>4-10 (n=36)</td>
<td></td>
</tr>
<tr>
<td>11-17 (n=38)</td>
<td></td>
</tr>
<tr>
<td>18-26 (n=39)</td>
<td></td>
</tr>
<tr>
<td>≥ 27 (n=39)</td>
<td></td>
</tr>
</tbody>
</table>

Missing = treatment failure
Median Number of Incontinent Days Decreased From Baseline

Error bars = 25th and 75th percentile

<table>
<thead>
<tr>
<th>Study Visit</th>
<th>Median (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>10</td>
</tr>
<tr>
<td>3 Month</td>
<td>4</td>
</tr>
<tr>
<td>6 Month</td>
<td>4</td>
</tr>
<tr>
<td>12 Month</td>
<td>4</td>
</tr>
<tr>
<td>24 Month</td>
<td>4</td>
</tr>
<tr>
<td>36 Month</td>
<td>4</td>
</tr>
</tbody>
</table>
Number of Urge Episodes Decreased From Baseline

Accident Urgency
“I was aware suddenly and rushed to the toilet”

<table>
<thead>
<tr>
<th>Study Visit</th>
<th>Median Number of Urge Episodes in 14 Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline (n=152)</td>
<td>4</td>
</tr>
<tr>
<td>3 Month (n=149)</td>
<td>0</td>
</tr>
<tr>
<td>6 Month (n=143)</td>
<td>0</td>
</tr>
<tr>
<td>12 Month (n=144)</td>
<td>0</td>
</tr>
<tr>
<td>24 Month (n=128)</td>
<td>0</td>
</tr>
<tr>
<td>36 Month (n=108)</td>
<td>0</td>
</tr>
</tbody>
</table>

Error bars = 25th and 75th percentile
## Improvements in Patient Reported Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wexner Symptom Severity Score</td>
<td>✓</td>
</tr>
<tr>
<td>Fecal Incontinence Quality of Life</td>
<td>✓</td>
</tr>
<tr>
<td>Pelvic Floor Distress Inventory</td>
<td>✓</td>
</tr>
<tr>
<td>CRADI Subscale</td>
<td>✓</td>
</tr>
<tr>
<td>Pelvic Floor Impact Questionnaire</td>
<td>✓</td>
</tr>
<tr>
<td>CRAIQ Subscale</td>
<td>✓</td>
</tr>
<tr>
<td>Sexual Function Questionnaire</td>
<td>No impact</td>
</tr>
</tbody>
</table>
Wexner Symptom Severity Score

<table>
<thead>
<tr>
<th></th>
<th>Never</th>
<th>Rarely</th>
<th>Sometimes</th>
<th>Often</th>
<th>Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solid</td>
<td>□ 0</td>
<td>□ 1</td>
<td>☒ 2</td>
<td>☒ 3</td>
<td>□ 4</td>
</tr>
<tr>
<td>Liquid</td>
<td>□ 0</td>
<td>□ 1</td>
<td>☒ 2</td>
<td>□ 3</td>
<td>□ 4</td>
</tr>
<tr>
<td>Gas</td>
<td>□ 0</td>
<td>□ 1</td>
<td>□ 2</td>
<td>☒ 3</td>
<td>□ 4</td>
</tr>
<tr>
<td>Wears pad</td>
<td>□ 0</td>
<td>□ 1</td>
<td>☒ 2</td>
<td>□ 3</td>
<td>☒ 4</td>
</tr>
<tr>
<td>Lifestyle alteration</td>
<td>☒ 0</td>
<td>□ 1</td>
<td>□ 2</td>
<td>☒ 3</td>
<td>□ 4</td>
</tr>
</tbody>
</table>

Total=9       Total=15

Rarely = less than once per month
Sometimes = between once per week and once per month
Often = between once per day and once per week
Always = at least once per day
Meaningful Change in Wexner Score

Mean Wexner Symptom Severity Score
0-20 (± 95% CI)

Reduction = Improvement in FI symptoms

Study Visit

Baseline (n=150) 3 Month (n=146) 6 Month (n=145) 12 Month (n=144) 24 Month (n=126) 36 Month (n=108)
Improvement in Fecal Incontinence Quality of Life Score (FIQoL)

- **Lifestyle**
- **Depression**
- **Coping**
- **Embarrassment**

Higher scores = Better QoL

<table>
<thead>
<tr>
<th>Study Visit</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>
</table>
Positive Correlation Between Treatment Response and QoL

FIQOL Score Change at 12 Months

Embarrassment

FI Episodes Improvement Category (%)

0-25

25-50

50-75

75-100

100

QoL Improvement
## Colo-Rectal-Anal Distress Inventory (CRADI) and Impact Questionnaire (CRAIQ)

<table>
<thead>
<tr>
<th>CRADI</th>
<th>CRAIQ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Do you usually lose stool beyond your control if your stool is loose or liquid?</td>
<td>Does your FI usually affect your ability to do household chores?</td>
</tr>
<tr>
<td>Do you experience a strong sense of urgency and have to rush to the bathroom to have a bowel movement?</td>
<td>Does your FI usually affect your ability to participate in social activities outside your home?</td>
</tr>
</tbody>
</table>

- Scores range from 0 - 100; lower scores = less distress or patient impact
- Established MCID values
Improved CRADI Score Exceeded MCID

Mean Score (± 95% CI)

Study Visit

Baseline (n=151) 3 Month (n=147) 6 Month (n=145) 12 Month (n=143) 24 Month (n=127) 36 Month (n=108)

MCID = Δ 5*

*Jelovsek et al., 2014
Improved CRAIQ Score Exceeded MCID

Mean Score (± 95% CI)

Baseline (n=149) 3 Month (n=147) 6 Month (n=141) 12 Month (n=143) 24 Month (n=126) 36 Month (n=110)

MCID = Δ 8*

*Jelovsek et al., 2014
Improvements in Other Tangible Measures

- Results when patients were asked, during the last year, aside from study procedure and study visit:

<table>
<thead>
<tr>
<th>Question</th>
<th>Baseline (N=152)</th>
<th>36 Month (N=108)</th>
<th>% Change</th>
</tr>
</thead>
<tbody>
<tr>
<td># of pads per day taken for FI</td>
<td>2.4 ± 2.1</td>
<td>1.2 ± 1.6</td>
<td>-50%</td>
</tr>
<tr>
<td>Total # of health care provider visits due to FI</td>
<td>5.0 ± 7.6</td>
<td>0.3 ± 1.1</td>
<td>-94%</td>
</tr>
<tr>
<td>Total # of days taken off work due to FI</td>
<td>6.4 ± 34.0</td>
<td>0.9 ± 9.5</td>
<td>-86%</td>
</tr>
</tbody>
</table>

Data are mean ± SD
### Positive Response to Surgical Satisfaction Questionnaire

Survey was offered on a one-time basis to all active patients between 3 and 36 months post-operatively (mean 26.7 +/- 8.8 months)

<table>
<thead>
<tr>
<th>Question</th>
<th>All Patients (n=86)</th>
<th>Responders (n=63)</th>
<th>Non-Responders (n=23)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Looking back, if “had to do it all over again” would you have the surgery again?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Satisfied or Very Satisfied</td>
<td>80.2%</td>
<td>84.1%</td>
<td>69.6%</td>
</tr>
<tr>
<td>Neutral</td>
<td>10.5%</td>
<td>12.7%</td>
<td>4.3%</td>
</tr>
<tr>
<td>Unsatisfied or Very Unsatisfied</td>
<td>9.3%</td>
<td>3.2%</td>
<td>26.1%</td>
</tr>
<tr>
<td>Would you recommend this surgery to someone else?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>80.2%</td>
<td>82.5%</td>
<td>73.9%</td>
</tr>
<tr>
<td>Neutral</td>
<td>14.0%</td>
<td>14.3%</td>
<td>13.0%</td>
</tr>
<tr>
<td>Negative</td>
<td>5.8%</td>
<td>3.2%</td>
<td>13.0%</td>
</tr>
</tbody>
</table>
Primary Efficacy Conclusions

- Primary endpoint met
- 69% experienced at least a 50% reduction in fecal incontinent episodes
Secondary Efficacy Conclusions

- Secondary efficacy objective support TOPAS benefit
  - Sustained decrease in FI episodes
  - Decrease in FI urge episodes and incontinent days
  - Improvement in patient reported outcomes
- TOPAS treatment effect is immediate, consistent, durable, positive life changes
Safety

Mikio Nihira, MD, MPH
Professor of Obstetrics and Gynecology
Division of Female Pelvic Medicine and Reconstructive Surgery, University of Oklahoma
Safety Overview

- Implant review
- Study safety objectives
- Data collection
- Treatment-related adverse events, serious adverse events, adverse events of special interest
TOPAS Has Unique Mesh Safety Profile

- Placed lateral to levator ani muscle and below anal sphincter
- ~2 cm tissue buffer between mesh and anus
- No transvaginal incisions
TOPAS Demonstrates Favorable Safety Profile in 509 Patient-Years

To date, TOPAS study has not seen

- Erosions
- Extrusions
- Organ perforations
- Bowel obstructions
- Device revisions
- Unanticipated adverse device effects (UADEs)
Safety Objective: Fully Characterize Safety Profile, Mesh-Related AEs

- Systematically collected all adverse events
- Mesh-related adverse events
  - Specified in protocol
  - Addressed in mandatory training
- Specified assessing patient for erosion, extrusion, infection, pelvic pain, leg pain and dyspareunia.
Adverse Events Assessed Throughout the Study

- Required at every follow-up visit
  - Physical exam
  - Patient questioning
- AEs assessed at all unscheduled visits
  - Patient-reported issues
- Standard of care assessments
All Adverse Events Reviewed by an Independent Expert Committee

- **Adverse Event Adjudication Committee (AEAC)**
  - Urogynecologist: Rebecca Rogers, MD
    - University of New Mexico
  - Gastroenterologist: Satish Rao, MD
    - University of Georgia
  - Colorectal Surgeon: Anthony Senagore, MD
    - Parma Medical Center, Ohio

- **Data Monitoring Committee (DMC)**
  - AEAC Members
  - Statistician: William Thomas, PhD
    - University of Minnesota
  - Patient Advocate: Nancy Norton
    - Founder, International Foundation for Functional GI Disorders
Treatment-Related AEs

As of August 2015

Patients (N=152)
677 events

Treatment-related
115 events

Non-serious
107 events

UADEs
0 events

Serious
8 events

Deaths
0 events

Non Treatment-related
562 events

Serious
70 events

Deaths
2 events
## Majority of Treatment-Related Events Were Not Serious and Resolved

<table>
<thead>
<tr>
<th>Treatment Related AE Type</th>
<th>All Events (Patients)</th>
<th>Non-SEAs Events</th>
<th>SAEs Events</th>
<th>Resolved Non-SEAs</th>
<th>Resolved SAEs</th>
</tr>
</thead>
<tbody>
<tr>
<td>TOTAL</td>
<td>115 (72)</td>
<td>107</td>
<td>8</td>
<td>80%</td>
<td>88%</td>
</tr>
<tr>
<td>Pelvic Area Pain</td>
<td>50 (43)</td>
<td>49</td>
<td>1</td>
<td>82%</td>
<td>100%</td>
</tr>
<tr>
<td>Infection</td>
<td>25 (22)</td>
<td>24</td>
<td>1</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Urinary Problems</td>
<td>8 (8)</td>
<td>8</td>
<td>0</td>
<td>63%</td>
<td>NA</td>
</tr>
<tr>
<td>Pelvic Organ Prolapse</td>
<td>13 (9)</td>
<td>10</td>
<td>3</td>
<td>30%</td>
<td>100%</td>
</tr>
<tr>
<td>Defecatory Disorder</td>
<td>4 (4)</td>
<td>4</td>
<td>0</td>
<td>50%</td>
<td>NA</td>
</tr>
<tr>
<td>Bleeding</td>
<td>1 (1)</td>
<td>1</td>
<td>0</td>
<td>100%</td>
<td>NA</td>
</tr>
<tr>
<td>Other</td>
<td>14 (14)</td>
<td>11</td>
<td>3</td>
<td>100%</td>
<td>67%</td>
</tr>
</tbody>
</table>
Majority of Treatment-Related Events Were Short in Duration

- 54% lasted \( \leq 30 \) days
- Median duration of 25 days
- 81% resolved
- Unresolved events
  - Pelvic area pain \((n=9)\)
  - Pelvic organ prolapse \((n=7)\)
  - Urinary problems \((n=3)\)
  - Other \((n=3)\)
Status of Adverse Events

- Resolved events
  - Patient reported / physician assessment
  - Duration calculated from onset to resolution

- Ongoing events
  - Active participants
  - Patients who have exited study
  - Accumulated until resolution
92% Treatment-Related AEs Managed w/o Therapy or Received Non-Surgical Treatment

- Interventions included medication and physical therapy
- 8% required surgery (9 events)
  - 6 related to pre-existing conditions
    - 4 cases worsening pelvic organ prolapse
    - 1 case worsening sciatica
    - 1 case worsening urge incontinence
  - 3 cases de novo pelvic organ prolapse
8 Treatment-Related SAEs; None Life-Threatening

- 4 SAEs related to pre-existing conditions
  - 1 PTSD case 1 week before surgery
  - 1 case COPD exacerbation
  - 1 case worsening sciatica
  - 1 case worsening pelvic organ prolapse
- 4 other SAEs
  - 1 case deep vein thrombosis
  - 1 case MRSA infection on left hand
  - 2 cases de novo pelvic organ prolapse
- All but PTSD resolved without reported sequela
82% Pelvic Area Pain Events Resolved

<table>
<thead>
<tr>
<th>Pelvic Area Pain</th>
<th>50 Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>28% (43/152)</td>
</tr>
<tr>
<td>Duration</td>
<td></td>
</tr>
<tr>
<td>Median days (range)</td>
<td>88 (0-1536)</td>
</tr>
<tr>
<td>≤ 30 days</td>
<td>21</td>
</tr>
<tr>
<td>31-120 days</td>
<td>8</td>
</tr>
<tr>
<td>&gt; 121 days</td>
<td>21</td>
</tr>
<tr>
<td>Resolved</td>
<td>82% (41/50)</td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
</tr>
<tr>
<td>Surgical</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>None</td>
<td>17 (34%)</td>
</tr>
<tr>
<td>Non-surgical</td>
<td>32 (64%)</td>
</tr>
<tr>
<td>Treatment Responders</td>
<td>67% (29/43)</td>
</tr>
</tbody>
</table>
Majority of Pelvic Area Pain Events Were Mild
Patients with Prolonged Pain had Average Pain Score in Mild Range

- 21 prolonged pain events in 18 patients

0.8
2.1

0 1 2 3 4 5 6 7 8 9 10

No Pain Mild Moderate Severe
Prolonged Pain After 12 Months

- Question #20 of PFDI assessed pain
  - 67% (12/18) reported they did not usually experience pain
- 9 out of 18 patients resolved
  - 368 mean days to resolution
- 9 with ongoing pain
  - 5 exited the study, pain status unknown
  - 4 active patients continue to have ongoing pain as of August 2015
All Infections Resolved Without Reported Sequela

- 25 infection AEs
  - 9 incision site
    - Infection criteria quite liberal
  - 2 abscesses
  - 14 others (e.g. fungal, UTI, MRSA)
- All treated non-surgically
- Average duration < 30 days
Urinary Problems Were Infrequent

- Urinary problems (8 events)
  - 3 cases of urinary retention
  - 3 cases of worsening urinary incontinence
  - 1 case of new onset urinary incontinence
  - 1 case of dysuria
# Rectal and Vaginal Prolapse

<table>
<thead>
<tr>
<th></th>
<th>Events (n=13)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Recurrent</td>
</tr>
<tr>
<td>Rectal (n=5)</td>
<td>3</td>
</tr>
<tr>
<td>Full</td>
<td>3</td>
</tr>
<tr>
<td>Mucosal</td>
<td>0</td>
</tr>
<tr>
<td>Vaginal (n=8)</td>
<td>2</td>
</tr>
<tr>
<td>Cystocele</td>
<td>1</td>
</tr>
<tr>
<td>Rectocele</td>
<td>1</td>
</tr>
<tr>
<td>Multi Compartment</td>
<td>0</td>
</tr>
</tbody>
</table>

- No adverse events of increased fecal retention or straining
## Treatment-Related AEs Did Not Preclude Patients From Experiencing Benefits

<table>
<thead>
<tr>
<th>Fecal Incontinence Quality of Life Scores</th>
<th>Reported Improvements at 12 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients (n=72) with Treatment-Related AEs</td>
</tr>
<tr>
<td>Lifestyle</td>
<td>82%</td>
</tr>
<tr>
<td>Embarrassment</td>
<td>82%</td>
</tr>
<tr>
<td>Coping</td>
<td>80%</td>
</tr>
<tr>
<td>Depression</td>
<td>80%</td>
</tr>
<tr>
<td>Responder Rate</td>
<td>65%</td>
</tr>
</tbody>
</table>
No Observed Erosions, Extrusions, Perforations, Obstructions

TOPAS has not seen

- Erosions into vagina or rectum
- Extrusions through incision sites
- Perforations into vagina, bowel or bladder
- Bowel obstructions
AEAC Confirmed No Mesh Erosion or Obstructions

- FDA questions regarding possible events
  - Mesh erosion
  - Obstruction/straining
- Sponsor obtained all available medical records and interviewed treating surgeons
  - Repeated vaginal, rectal examinations performed
- AEAC concluded no mesh erosions or obstructions
Safety Conclusion

- TOPAS is well-tolerated and offers a safe treatment option
- Observed treatment-related adverse events were manageable
  - Majority were short in duration, mild, and resolved without reported sequelae
  - 8 SAEs
  - 92% were managed without therapy or received non-surgical treatment
Physician Education Program

Paul Below
Principal Clinical Research Specialist
ASTORA Women’s Health
Comprehensive Education Program for Best Possible Patient Outcomes

- Modeled after successful TOPAS study training curriculum and input from Physician Advisory Committee
- Addresses disease state, relevant anatomy, patient selection, and procedural requirements
Education Program Open to Highly Qualified Physicians

- 3 requirements
  - Board certified in Female Pelvic Medicine and Reconstructive Surgery or Colon and Rectal Surgery;
  - Currently treating FI patients; and
  - Surgical experience implanting other FI devices or mesh in the pelvic floor.
3-Phase Physician Training Program

Phase One
E-Learning Introductory Course

Phase Two
Classroom Course with Hands-on Component

Phase Three
Surgical Experience Overseen by Qualified Proctor
Phase One: Framework for Treating FI

- **E-Learning Curriculum**
  - Module 1: FI Overview, Epidemiology
  - Module 2: Anatomy & Physiology
  - Module 3: FI Therapies & TOPAS
  - Module 4: Clinical Evidence
  - Module 5: Patient Preparation
  - Module 6: TOPAS Procedure
  - Module 7: Managing Complications

- Demonstrate understanding of material before advancing to next phase
Phase Two: Hands On With Device

- Classroom Curriculum:
  - Review of e-learning topics
  - Case studies on patient selection and managing complications
- Hands-on experience implanting TOPAS in a pelvic model and cadavers
Phase Three: Proctored Surgical Experience

- Perform the procedure with oversight of physician proctor
- Demonstrate ability to perform all steps of the procedure
- 2 proctored cases required
- Receive record of training completion from ASTORA
Refresher course available for all TOPAS-trained physicians

- Repeat e-learning modules and pelvic model hands-on training
- Option of additional cadaver training and proctoring
- Required for those who have not completed ≥ 8 cases annually
ASTORA to Provide Ongoing Physician Support

- Physician Advisory Committee to advise on managing complication cases
- Ongoing collaboration with physician advisors and FDA on program development
- Proper training is key to successful outcomes and improving quality of life for patients with FI
Post-Approval
Comprehensive, Proactive, Long-Term Surveillance Program for TOPAS

Two-Part Plan

- Extension of TOPAS Study to 5 Years
- New Post-Approval Study
Ongoing Evaluation of Long-Term Safety and Performance

Extension of TOPAS Study to 5 Years

- 5 years follow-up in clinical trial
  - Annual safety and efficacy updates to FDA
  - Updates include:
    - Monitoring all AEs
    - 60 month safety endpoint of <25% SAEs
    - Digital rectal exam at 48 and 60 month follow-up visits
    - Continue patient bowel diaries, QoL surveys
Post-Approval Study to Enroll New Cohort of Patients to Monitor Safety

New Post-Approval Study

- New cohort of patients
- Draft study protocol detailed in FDA’s Executive Summary
- Primary objective will focus on safety
- ASTORA will continue working with agency on study design
Additional Safety Assessments in the Post-Approval Study

- Collection of additional bowel habit information in the patient diary
- Assessment of pelvic organ prolapse at baseline and post-operatively
- Detailed assessment of pelvic pain
- Additional imaging techniques to study anorectal changes
Comprehensive Safety and Performance Monitoring Plan

- Long-term surveillance plan
  1. Extension of TOPAS Study to 5 Years
  2. New Post-Approval Study

- Limited launch to previous TOPAS study implanters and investigators in new post-approval study
- Physician education + post-approval study monitoring will mitigate risk, prepare doctors
Clinical Perspective

Dee Fenner, MD
Furlong Professor of Women’s Health
Director of Gynecology
University of Michigan
Demonstrates Favorable Benefit-Risk Profile for Women Living with FI

- Unique anatomical placement
- Offers important new treatment option to patients
New FI Treatment Options Needed

- No single treatment works for all FI patients
- Even with new therapies, significant unmet need persists
- TOPAS is first device providing anatomical support to the anorectum
- Need treatments not requiring multiple therapeutic adjustments
Study Limitations

- Single arm study
- Caucasian population > 30 years of age
- Not powered for predictors of efficacy
- No restrictions on medications and diet changes
- Mechanism of action not fully understood
Study Strengths

- Both colorectal and urogynecology surgeons
- > 500 patient-years of follow-up
- Objective and subjective endpoints
- Validated disease-specific questionnaires
TOPAS Study Met Primary Endpoint and Demonstrated QoL Improvements

- 69% of patients experienced ≥ 50% reduction in number of FI episodes
- Secondary efficacy objectives demonstrated improvements in FI symptom severity and quality of life
- Reduced healthcare resource utilization
Safe, Manageable Treatment Option

- Observed pain events generally mild
- Prolapse cases manageable
- Infections were treatable and resolved
- 8 treatment-related SAEs
  - 4 due to pre-existing conditions
  - 7 resolved without reported sequelae
- No mesh erosions, extrusions, perforations, dyspareunia, foreign body reaction, or surgical revisions
TOPAS Benefits Outweigh Risks

- Almost 70% achieved ≥ 50% reduction in FI episodes
- Patients experiencing any decrease in FI episodes reported improved QoL
- TOPAS is well tolerated
- Offers safe treatment option
Favorable Benefit-Risk Profile

- Study results demonstrate that TOPAS is a viable, safe, effective option for patients
- TOPAS should be an option for patients
TOPAS™ Treatment for Fecal Incontinence

ASTORA Women’s Health

Presentation to the Gastroenterology-Urology Devices Panel

February 25, 2016
ONSCREEN BACK-UP SLIDES
Rationale for One-Sided Test

- For a single-arm trial, there is no clinical meaning attached to the concept that the treatment may be significantly worse than a pre-specified performance goal or objective performance criterion.
- Efficacy is only proven if it can be established that the treatment is better than the performance goal.
- Given that this is the only meaningful tail of the null distribution, a 1-sided test appropriate for this study.
No Learning Effect on Efficacy Response

Responder Rate

<table>
<thead>
<tr>
<th>Implant Sequence</th>
<th>1-2 (n=43)</th>
<th>3-4 (n=30)</th>
<th>5-6 (n=25)</th>
<th>7-9 (n=21)</th>
<th>10+ (n=33)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>65%</td>
<td>67%</td>
<td>72%</td>
<td>71%</td>
<td>73%</td>
</tr>
</tbody>
</table>
# Defecography Data

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline Mean ± SD (n, median, range)</th>
<th>6 Month Mean ± SD (n, median, range)</th>
<th>Δ from Baseline* Mean [95% CI], n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anorectal Angle at Rest (degrees)</td>
<td>133.5 ± 17.7 (n=26, 132, 107-172)</td>
<td>132.4 ± 16.6 (n=26, 132, 99-165)</td>
<td>-3.7 [-7.8, 0.5] n=20</td>
</tr>
<tr>
<td>Anorectal Angle at Evacuation (degrees)</td>
<td>141.0 ± 20.1 (n=21, 144, 98-174)</td>
<td>143.2 ± 16.4 (n=22, 143, 98-168)</td>
<td>1.4 [-5.7, 8.5] n=15</td>
</tr>
<tr>
<td>Length of Anal Canal (cm)</td>
<td>2.5 ± 0.6 (n=14, 2.4, 1.7- 4)</td>
<td>3.1 ± 0.9 (n=15, 2.8, 2.2-5.1)</td>
<td>0.5 [-0.1, 1.0] n=8</td>
</tr>
</tbody>
</table>

* Change from baseline was calculated on a subject level using matched pairs of data
Pelvic Area Pain Risk Factors – Medical Specialty

Pelvic Area Pain Rates by Specialty

- Colorectal: 45.0% (27/60 subjects)
- Urogynecology: 17.4% (16/92 subjects)
No Predictive Patient Factors for Pelvic Area Pain

Univariate logistic regression model for the following covariates

- Age, BMI, parity
- Medical Hx (including systemic & pelvic pain)
- QoL scores
- Responder rates at 12 months
- Medical specialty*

* Medical specialty originally showed up as significant due to a center difference (sites 1008 & 1010).
Buttock Incisions
Instructions for Optimal Mesh Tensioning

- The implanter is instructed to conduct rectal palpation during tensioning so that a slight ridge or bump can be felt.
- Should not cause significant deformity or compression of the anal canal.
Standardized Tensioning Training

1. [Image of a medical training model with a string protruding from a hole.]
2. [Image of the same model showing the internal structure.]
3. [Image of a hand pulling a string through the model.]

[Images depict the process of tensioning in a medical training setup.]
Diversity in Patient Population

- No reason to believe there are racial differences from an anatomical position.
- Centers were intentionally selected in diverse geographic locations; including regions with high percentages of minorities.
- Patient sub-groups were not stratified to ensure patient diversity. Study sites were dependent on patients who sought participation in the trial.
- Didn’t advertise for patients.
Majority of Pelvic Area Pain Patients Reported No to Mild Pain at Last Visit

% of Patients (n=32*)

<table>
<thead>
<tr>
<th>Pain Score</th>
<th>% of Patients (n=43)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>78.1</td>
</tr>
<tr>
<td>Mild (1-3)</td>
<td>18.8</td>
</tr>
<tr>
<td>Moderate (4-6)</td>
<td>3.1</td>
</tr>
<tr>
<td>Severe (7-10)</td>
<td>1.3</td>
</tr>
</tbody>
</table>

Mean NPPS = 0.5

NPPS Pain Score

<table>
<thead>
<tr>
<th>Pain Score</th>
<th>Mean NPPS</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.5</td>
</tr>
<tr>
<td>Mild (1-3)</td>
<td>18.6</td>
</tr>
<tr>
<td>Moderate (4-6)</td>
<td>7</td>
</tr>
<tr>
<td>Severe (7-10)</td>
<td>4.7</td>
</tr>
</tbody>
</table>

Mean NPPS = 1

*11 patients had no pain score at baseline
## Similar Efficacy Results for Both Medical Specialties

<table>
<thead>
<tr>
<th>Medical Specialty</th>
<th>Treatment Success Rate %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colorectal</td>
<td>63.3% (36/60)</td>
</tr>
<tr>
<td>Urogynecology</td>
<td>72.8% (67/92)</td>
</tr>
</tbody>
</table>

*p-value*  
0.216

*Missing = treatment failure
*Chi-squared test*
Coronal View of TOPAS System
# Treatment Related Pelvic Area Pain Events (n=43)

<table>
<thead>
<tr>
<th>Age</th>
<th>Treatment Related Pelvic Pain Rate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>32-53 (n=9/41)</td>
<td></td>
</tr>
<tr>
<td>&gt;53-60 (n=10/36)</td>
<td></td>
</tr>
<tr>
<td>&gt;60-66 (n=14/38)</td>
<td></td>
</tr>
<tr>
<td>&gt;66-79 (n=10/37)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>BMI</th>
<th>Treatment Related Pelvic Pain Rate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 30 (n=30/107)</td>
<td></td>
</tr>
<tr>
<td>≥ 30 (n=13/45)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>External Sphincter Defect</th>
<th>Treatment Related Pelvic Pain Rate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No (n=24/73)</td>
<td></td>
</tr>
<tr>
<td>Yes (degree ≤ 90) (n=9/41)</td>
<td></td>
</tr>
<tr>
<td>Yes (degree ≥ 90) (n=10/38)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>FI Severity (# of Episodes)</th>
<th>Treatment Related Pelvic Pain Rate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-10 (n=9/36)</td>
<td></td>
</tr>
<tr>
<td>11-17 (n=9/38)</td>
<td></td>
</tr>
<tr>
<td>18-26 (n=8/39)</td>
<td></td>
</tr>
<tr>
<td>≥ 27 (n=17/39)</td>
<td></td>
</tr>
</tbody>
</table>

Missing = treatment failure
Pelvic Area Pain Risk Factors – Medical Specialty

Pelvic Pain by Site and Specialty

Site within Specialty

<table>
<thead>
<tr>
<th>Site</th>
<th>Urogyn</th>
<th>Colorectal</th>
</tr>
</thead>
<tbody>
<tr>
<td>1008</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1010</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1016</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1056</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1013</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1015</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1014</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1009</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1020</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1023</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1019</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Pelvic Area Pain Risk Factors – Medical Specialty

Pelvic Pain by Site and Specialty

Subjects

Urogyn
1008 1010 1016 1056 1013 1015 1014

Colorectal
1009 Combo 1020 1023 1019

Site within Specialty

No
Yes
Treatment Related Pelvic Area Pain: Implant Sequence

- 1-2 (n=14): 33%
- 3-4 (n=10): 33%
- 5-6 (n=7): 28%
- 7-9 (n=7): 33%
- 10+ (n=5): 15%

Treatment Related Pelvic Pain (95% CI)
## Rectal Prolapse Events

<table>
<thead>
<tr>
<th>Event ID</th>
<th>De Novo / Recurrent</th>
<th>Symptoms</th>
<th>Diagnosis</th>
<th>Treatment</th>
<th>Days to onset</th>
<th>Resolution Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>1008-025-AE02</td>
<td>Recurrent</td>
<td>rectal prolapse/bulge outside of her rectum when straining</td>
<td>Rectal Exam: Full Thickness Rectal</td>
<td>robotic assisted laparoscopic rectopexy</td>
<td>122</td>
<td>Resolved 55 days</td>
</tr>
<tr>
<td>1008-025-AE03</td>
<td>Recurrent</td>
<td>c/o feeling something protruding from the rectum c/o rectal bleeding and mucous discharge</td>
<td>Rectal Exam: Prolapsed Lip</td>
<td>2 doses of sclerotherapy</td>
<td>261</td>
<td>Ongoing 1075 days</td>
</tr>
<tr>
<td>1008-035-AE01</td>
<td>Recurrent</td>
<td>rectal prolapse felt when bearing down</td>
<td>Rectal Exam: Full Thickness Rectal</td>
<td>anterior rectopexy</td>
<td>76</td>
<td>Ongoing 1029 days</td>
</tr>
<tr>
<td>1020-011-AE06</td>
<td>De Novo</td>
<td>No Signs / Symptoms Reported</td>
<td>Defecography: Internal Rectal prolapse</td>
<td>None</td>
<td>159</td>
<td>Ongoing 1104 days</td>
</tr>
<tr>
<td>1022-003-AE08</td>
<td>De Novo</td>
<td>Participants falls like a grape size skin coming out of the anus after shower</td>
<td>Rectal Exam</td>
<td>Delorme procedure excision rectal procedencia with anastomosis</td>
<td>128</td>
<td>Resolved 579 days</td>
</tr>
</tbody>
</table>
Baseline and Follow-Up

Cohen Kappa = 0.01

<table>
<thead>
<tr>
<th>Baseline</th>
<th>Last Available Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>Yes</td>
<td>24</td>
</tr>
<tr>
<td>No</td>
<td>19</td>
</tr>
</tbody>
</table>