FDA Presentation: TOPAS™ System for Fecal Incontinence P140006 Statistical Presentation

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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:

$$\mathbf{H_0: } p \leq \mathbf{50\% \text{ vs. } H_a: } p > \mathbf{50\%}$$

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 $p1 < 0.0087$, the study would be stopped with a claim of effectiveness
  - If $p1 \geq 0.0087$, sample size would be re-estimated to have adequate power to achieve $p2 < 0.0087/p1$ (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

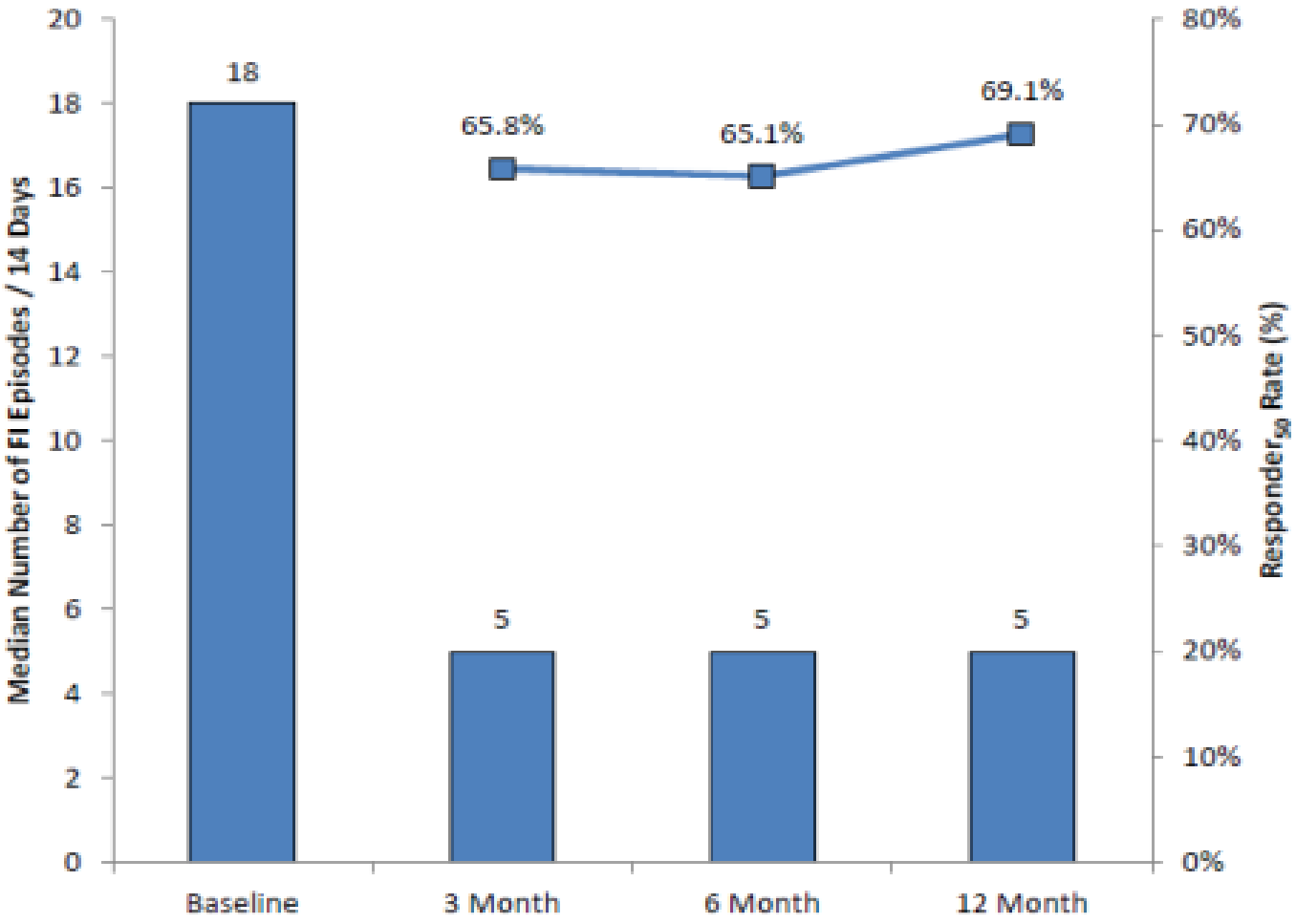
Subject Group	N	Responder50 Rate	95% CI	p-value
Stage I	80	65.0% (52/80)	(53.5%, 75.3%)	0.0048*
Stage II	72	73.6% (53/72)	(61.9%, 83.3%)	<0.0001
All Implanted	152	69.1% (105/152)	(61.1%, 76.3%)#	N/A

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

Age Group	Responder50 Rate
[32-53] years	68.3% (28/41)
(53-60] years	61.1% (22/36)
(60-66] years	71.1% (27/38)
(66-79] years	75.7% (28/37)

Subgroup Analyses

Responder50 Rates by Specialty

Medical Specialty of Clinical Centers	Responder50 Rate
Colorectal (7)	63.3% (38/60)
Urogynocology (7)	72.8% (67/92)

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

Last Visit Before Alternative Intervention or Exit	Number of Subjects
3 months	1
6 months	2
12 months	9
24 months	5
TOTAL	*17*

Alternative FI Therapies Sought by Subjects After Implantation*

Alternative Therapies	Number of Subjects
Sacral Nerve Stimulator (SNS)	7
Injectable Bulking Agent	3
Sphincteroplasty	1
Other Intervention	1
TOTAL	*12*

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

Secondary Effectiveness Endpoints

Long Term Effectiveness

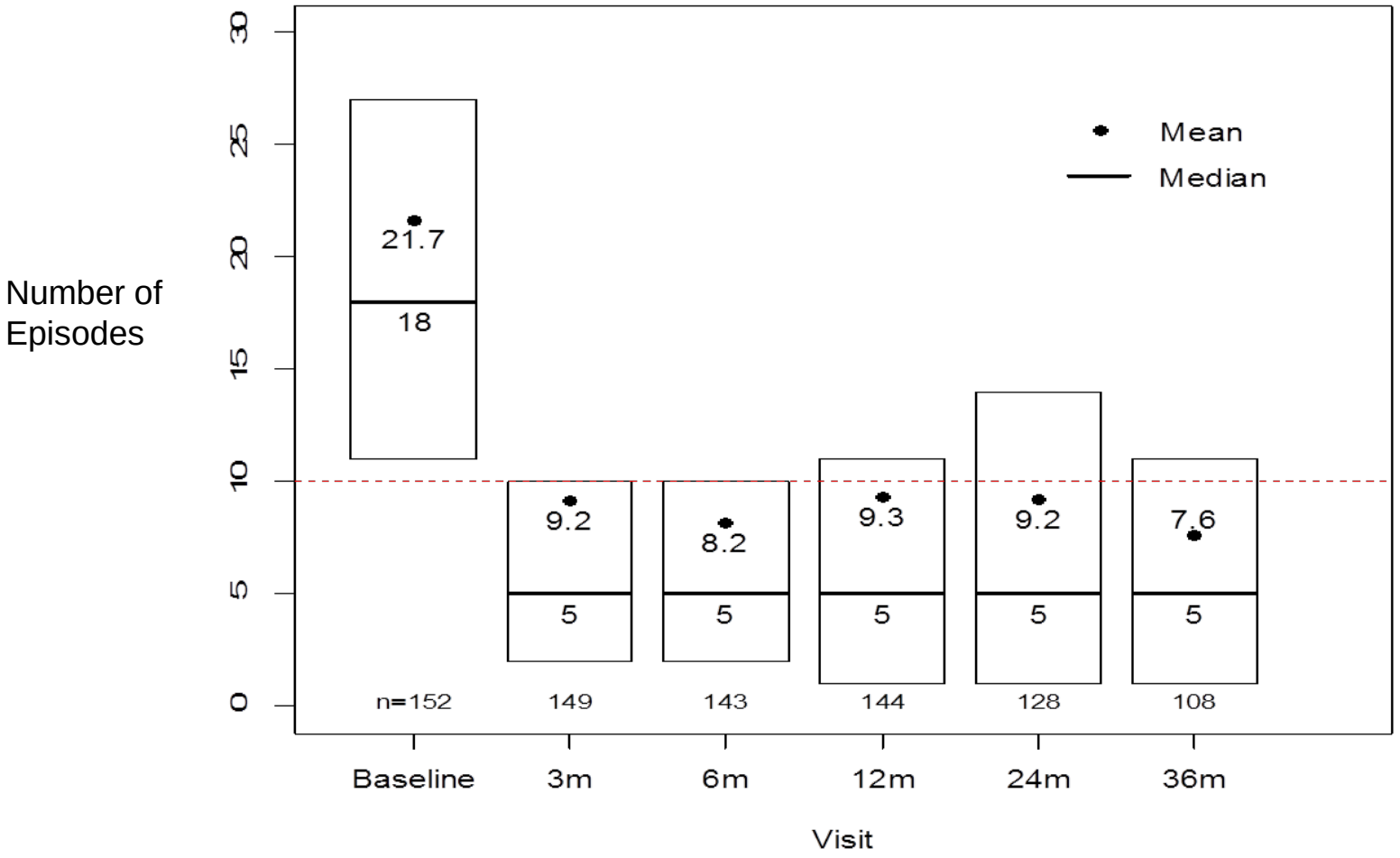
Study Visit	Responder50 Rate# (All Implanted Subjects)	95% Confidence Intervals
12 months	69.1% (105/152)	[61.1%, 76.3%]
24 months	53.3% (81/152)	[45.0%, 61.4%]
36 months	57.8% (78/135*)	[49.0%, 66.2%]

Missing data counted as non-responder.

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

Secondary Effectiveness Endpoints

Number of FI Episodes by Visits



Secondary Effectiveness Endpoints

Percent of Subjects With at Least 50% Reduction in Incontinent Days by Visits

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

Missing data counted as failure.

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

Secondary Effectiveness Endpoints

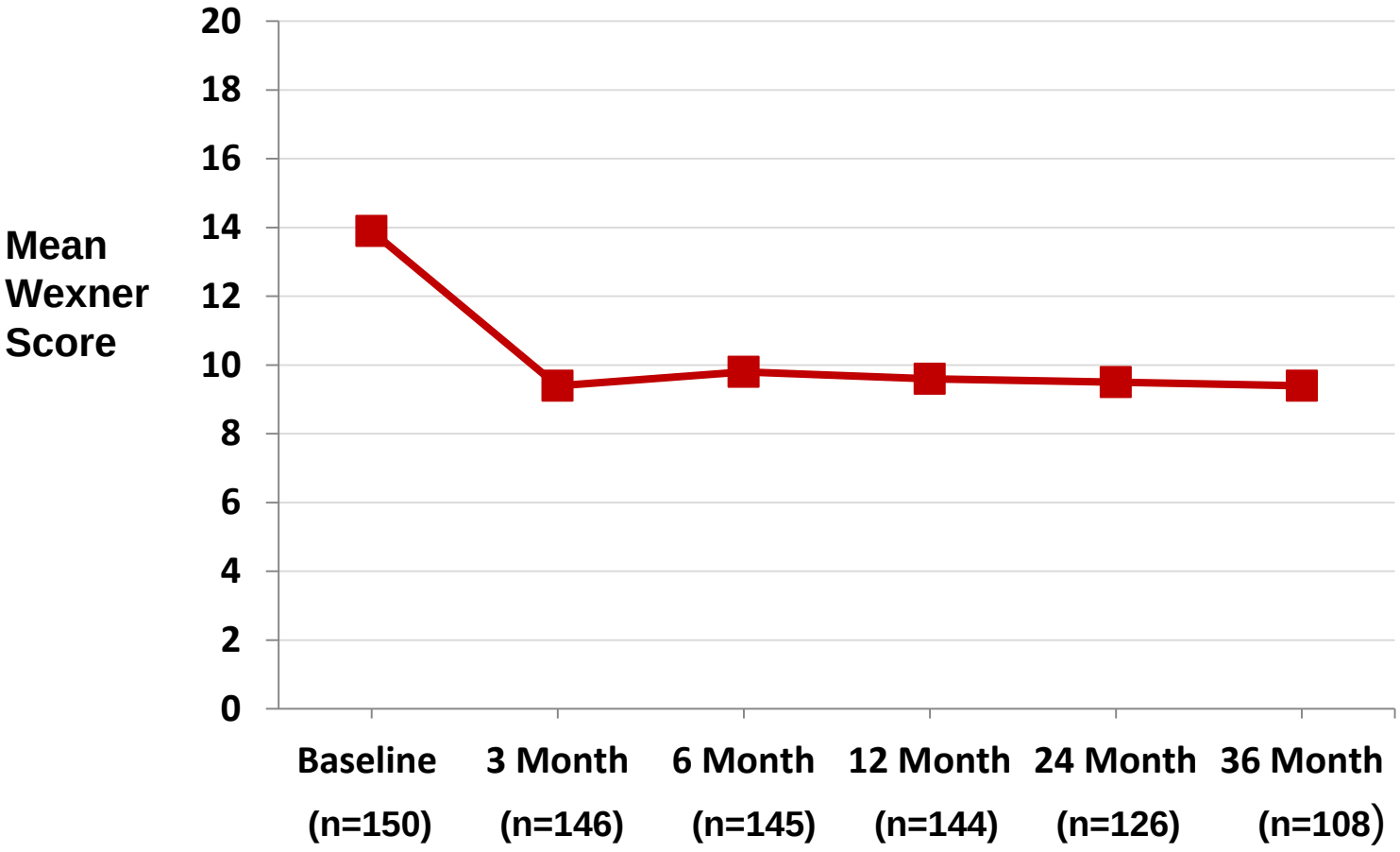
Patient reported questionnaires and QOL

- 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.

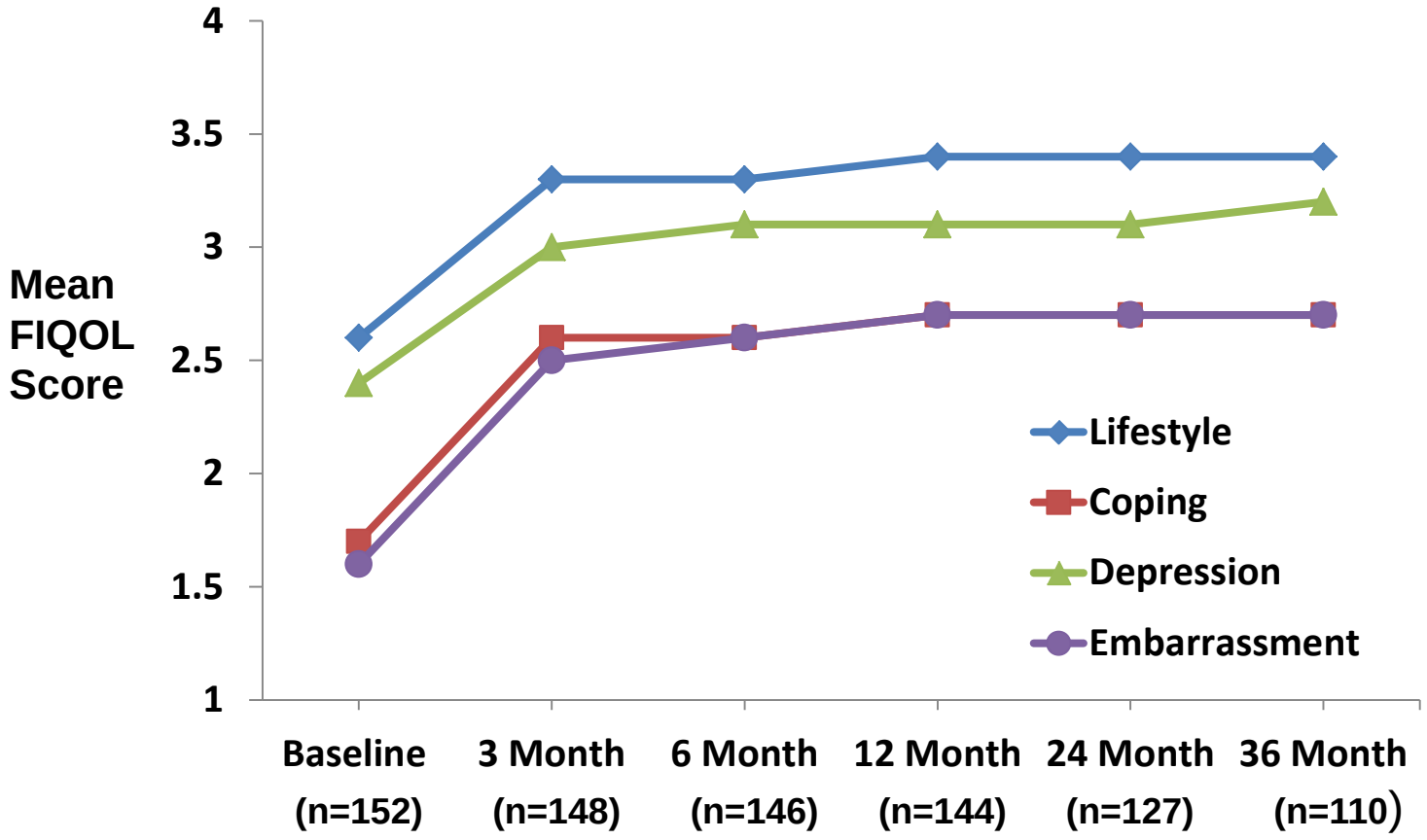
Secondary Effectiveness Endpoints

Wexner Symptom Severity Score



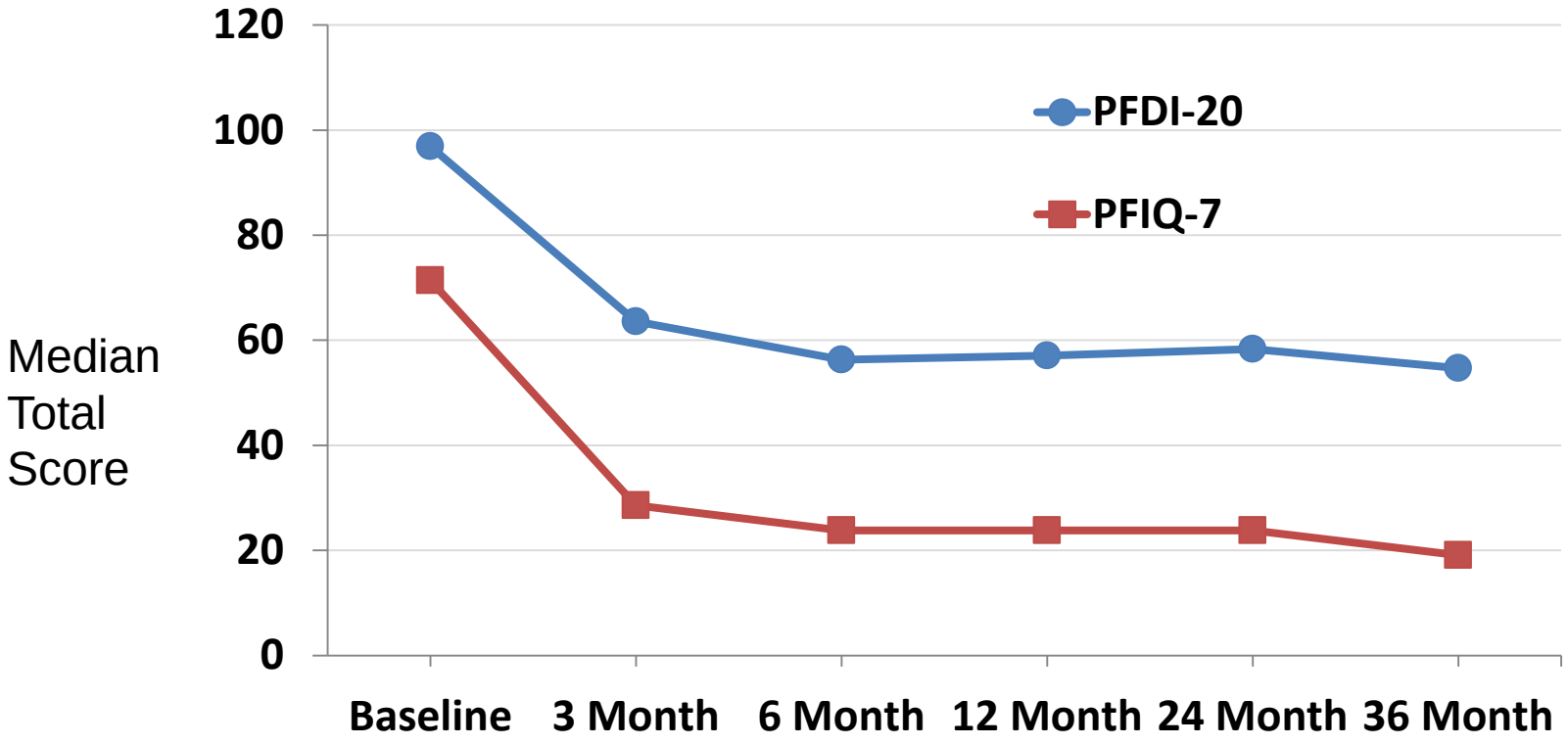
Secondary Effectiveness Endpoints

FI Quality of Life (FIQOL)



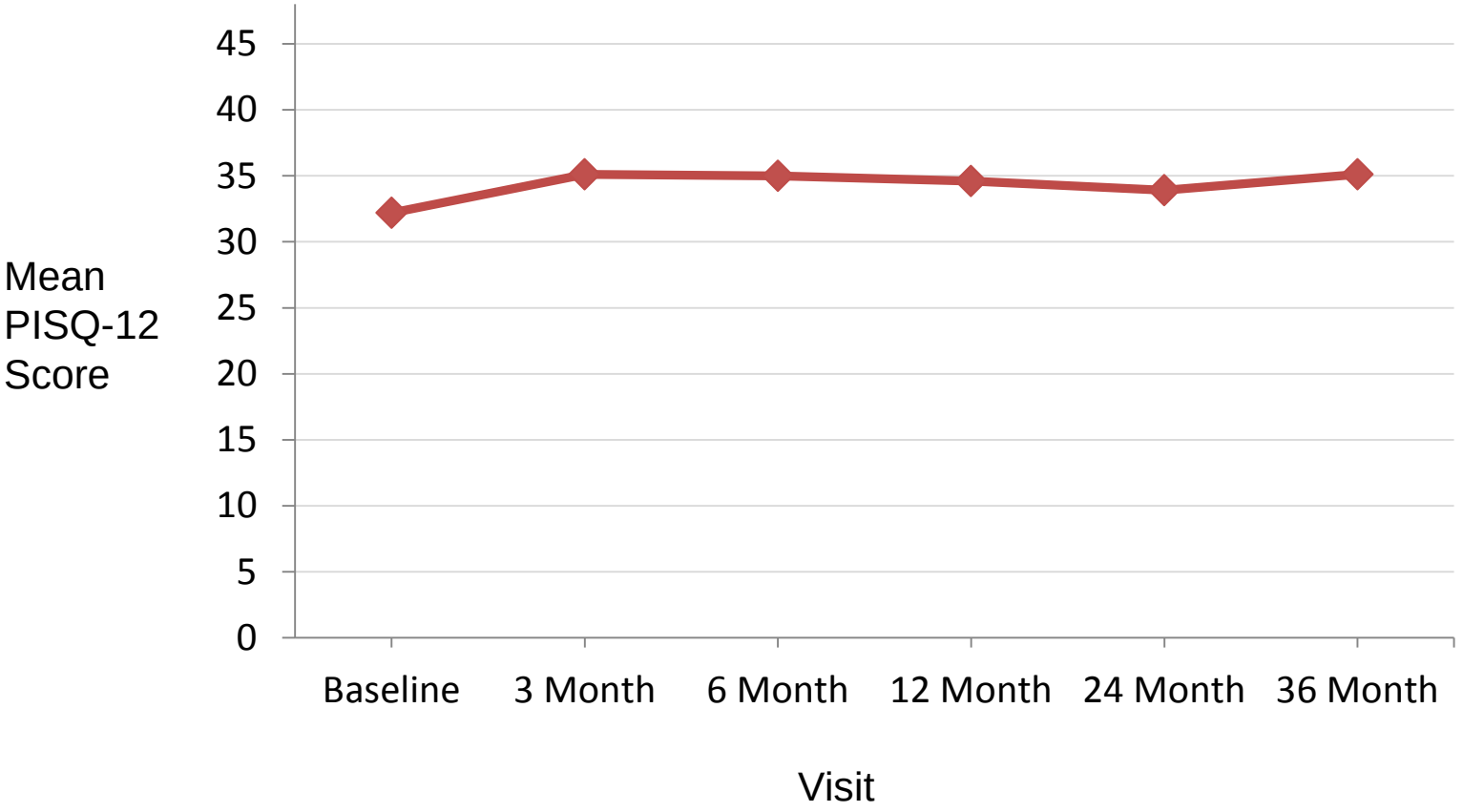
Secondary Effectiveness Endpoints

PFDI-20 and PFIQ-7



Secondary Effectiveness Endpoints

Pelvic Organ Prolapse/Urinary Incontinence /Sexual Function Questionnaire (PISQ-12)



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