CO55

Psychometric Evaluation of the Measurement Properties of a Pediatric Clinical Outcome Assessment for Functional Constipation: Data from a Phase 3 Clinical Trial

Douglas CA Taylor,[1] Yanqing Xu,[2] Julia Vishnevetsky,[3] Jessica L Abel,[3] Xiaolan Ye,[2] Cheryl D Coon[4,*]

[1]Former employee of Ironwood Pharmaceuticals, Inc., Boston, Massachusetts, USA; [2]AbbVie, Inc., North Chicago, Illinois, USA; [3]AbbVie, Inc., Madison, New Jersey, USA; [4]Outcometrix, Salida, Colorado, USA

**Employer is now Critical Path Institute*

OBJECTIVE

To evaluate the psychometric properties of scores on the Pediatric Functional Constipation Symptom Diary (PFCSD) administered twice daily to measure bowel movement characteristics (stool frequency, stool consistency, complete evacuation, straining) associated with functional constipation in a pediatric population

CONCLUSION

This confirmatory psychometric evaluation provides sufficient evidence for reliability, validity, and responsiveness of the spontaneous bowel movement and stool consistency scores based on the PFCSD, and provides guidance for interpreting within-patient meaningful change on these scores

For additional information or to obtain a PDF of this poster

Scan QR code or use the following link to download an electronic version of this presentation and other AbbVie ISPOR 2023 scientific presentations:

https://abbvie1.outsystemsenterprise.com/GMAEventPublications/Assets.aspx?ConferenceId=674

QR Code expiration: April 14, 2024

To submit a medical question, please visit www.abbviemedinfo.com

Presented at the International Society for Pharmacoeconomics and Outcomes Research (ISPOR), Boston, MA, USA, May 7–10, 2023

BACKGROUND

- Functional constipation (FC), often described as difficult or infrequent bowel movements (BM) associated with painful defecation and straining, is prevalent among children and adolescents and can significantly impact quality of life[1,2]
- Currently, there are no prescription therapies approved by the FDA for the treatment of FC in pediatric patients[3,4]
- Linaclotide, a guanylate cyclase-C agonist, is FDA-approved for the treatment of irritable bowel syndrome with constipation and chronic idiopathic constipation in adults[5] and is currently being developed for the treatment of FC in children and adolescents aged 6 to 17 years
- Since there are no clinical or biological measures to assess key symptoms of FC, reports on symptom severity must come directly from the patients; thus, treatment effects are measured exclusively through patient-reported outcomes
- A novel patient-reported electronic diary (eDiary), the Pediatric Functional Constipation Symptom Diary (PFCSD), was developed to assess BM characteristics and abdominal symptoms associated with FC
- The PFCSD was implemented in Phase 2 and Phase 3 trials in pediatric patients aged 6 to 17 years with FC to assess the efficacy and safety of linaclotide vs placebo
- Psychometric analyses were conducted utilizing data from the Phase 3 trial to confirm the measurement properties of the PFCSD previously established using the Phase 2 data

METHODS

Clinical Trial Description

- Data were collected from a Phase 3, multicenter, randomized, double-blind, placebo-controlled study (LIN-MD-64) of linaclotide 72 µg in 6–17-year-olds (n = 328) meeting modified Rome III criteria for child/adolescent FC (**Figure 1**)
- Participants who met entry criteria entered the 12-week intervention period utilizing the PFCSD
- The primary endpoint was the 12-week change from baseline (CFB) in weekly spontaneous BM (SBM) frequency
  - A SBM was defined as a BM that occurred in the absence of additional laxative, enema, or suppository use on the calendar day of, or the calendar day before, the BM
- The secondary endpoint was the CFB in stool consistency

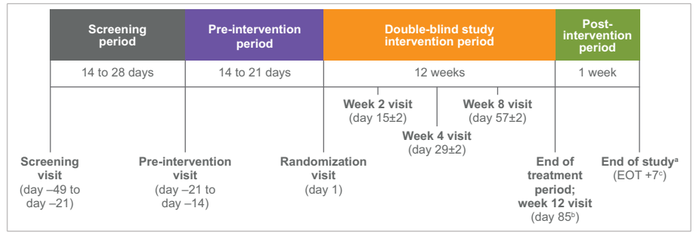
eDiary Assessments

- Patients completed daily and weekly assessments in an eDiary throughout the 12-week intervention period
- Items completed in the PFCSD evaluated SBM frequency, stool consistency, completeness of evacuation, and straining
  - Stool consistency was measured by the pediatric Bristol Stool Form Scale (p-BSFS), with responses ranging from type 1 = small hard lumps or balls to type 7 = watery, looks like a milkshake
  - Straining was measured by a 5-point scale (0, not hard at all; 4, pushed very hard)
- Patient global impression of severity (PGIS) item assessed pooping problems every 7 days

Psychometric Analyses of the PFCSD

- Psychometric analyses were conducted to evaluate the measurement properties of the PFCSD
- Test-retest reliability was assessed through intraclass correlation coefficients (ICC), construct validity using convergent and discriminant validity correlations, and known-groups methods (**Table 1**)
- The pooping problems item was used as the anchor for estimating within-patient meaningful change thresholds (MCTs)
- Responsiveness was assessed through Guyatt's responsiveness statistic (GRS)
- All analyses were performed using SAS version 9.4 on pooled data without regard to treatment assignment

Figure 1. Study Design



[a]Patients who rolled over to the long-term safety study, LIN-MD-66, before the end-of-study visit were not required to have this visit; [b]Week 12 visit at the end of the treatment period occurred within +3 days of day 85; [c]The end of study visit, defined as EOT +7 days, occurred within +7 days of this date

EOT, end of treatment

Table 1. Psychometric Analyses Measure Descriptions

Measure	Description
Test-retest reliability	Scores are similar across repeated administrations when the condition being measured is stable (eg, based on the same responses to global severity at both times)
Construct validity	
Convergent validity	A score is related to scores on other instruments that measure similar concepts (eg, among BM-related scores)
Discriminant validity	A score is less related to scores on other instruments that measure dissimilar concepts (eg, between BM-related scores and abdominal scores)
Known-groups method	A score shows differences between groups that are known to differ (eg, high and low global severity)
Responsiveness	Ability to detect changes in the concept it is measuring when true changes exist
Individual change thresholds	The amount of change on a score that is considered meaningful for an individual patient (ie, used to define treatment responders)

BM, bowel movement

RESULTS

Patient Population

- Among the 328 patients, the majority were aged 6–11 years (55%) and female (55%); 45% were of Hispanic or Latino ethnicity (**Table 2**)
- Descriptive statistics for outcomes captured in the PFCSD are shown in **Table 3**

Table 2. Patient Demographics

Variable	Frequency (%)
Age	328 (100)
6–11 years	181 (55.2)
12–17 years	147 (44.8)
Sex	
Female	181 (55.2)
Male	147 (44.8)
Race	
White	229 (69.8)
Black or African American	86 (26.2)
Asian	5 (1.5)
Native, Hawaiian or Other Pacific Islander	4 (1.2)
Multiple	3 (0.9)
American Indian or Alaska Native	1 (0.3)
Ethnicity	
Not Hispanic or Latino	180 (54.9)
Hispanic or Latino	148 (45.1)

Psychometric Analyses

- ICC for SBMs showed good test-retest reliability (ICC = 0.91); ICC for stool consistency showed moderate test-retest reliability (ICC = 0.56) at weeks 11 to 12

Table 3. Descriptive Statistics for the Pediatric FC Symptom Diary at Selected Timepoints

eDiary Score	Study Period	N	Mean (SD)
SBM frequency rate	Baseline	328	1.22 (0.85)
	Intervention[a]	328	2.85 (2.47)
Stool consistency	Baseline	276	2.36 (0.93)
	Intervention[a]	318	3.37 (1.02)
CSBM frequency rate	Baseline	328	0.57 (0.74)
	Intervention[a]	328	1.95 (2.21)
Straining	Baseline	280	2.50 (1.07)
	Intervention[a]	320	1.53 (1.00)

[a]Defined as the average across the 12-week period
CSBM, complete spontaneous bowel movement; FC, functional constipation; SBM, spontaneous bowel movement; SD, standard deviation

- Construct validity correlations during the intervention were generally consistent with hypotheses (**Table 4**)
  - SBMs were strongly correlated with complete SBMs (CSBMs; $r = 0.82$) and moderately correlated with straining ($r = –0.32$)
  - Stool consistency was moderately correlated with straining ($r = –0.49$), but less correlated with SBMs ($r = 0.22$) and CSBMs ($r = 0.21$)
- Construct validity using known-groups methods found significant differences for SBM frequency rate and stool consistency by participant PGIS scores at week 12 ($P<0.001$), with medium effect sizes (**Table 5**)

Table 4. Inter-item Correlations at Baseline and Intervention[a]

eDiary Score	SBM Frequency Rate	Stool Consistency	CSBM Frequency Rate	Straining
SBM frequency rate	–	0.09	0.65	0.22
Stool consistency	0.22	–	0.15	–0.44
CSBM frequency rate	0.82	0.21	–	–0.40
Straining	–0.32	–0.49	–0.44	–

[a]Defined as the average across the 12-week period
Baseline correlations are above the diagonal in purple and intervention correlations are below the diagonal in orange
CSBM, complete spontaneous bowel movement; SBM, spontaneous bowel movement

Table 5. Construct Validity Using Known-groups Methods

eDiary Score	Time	Groups	N	Mean	SD	Effect Size	*P*-value
SBM frequency rate	Week –1	High severity	143	1.41	1.08	0.00	0.894
		Low severity	82	1.43	1.25	–	–
	Week 12	High severity	28	1.50	1.75	0.09	<0.001
		Low severity	89	3.61	3.12	–	–
Stool consistency	Week –1	High severity	111	2.31	1.18	0.02	0.073
		Low severity	57	2.64	1.01	–	–
	Week 12	High severity	17	2.65	1.42	0.12	<0.001
		Low severity	77	3.78	1.13	–	–

SBM, spontaneous bowel movement; SD, standard deviation

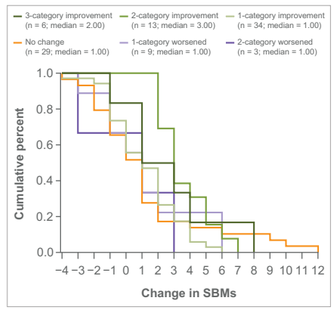
- For the PGIS item, GRS was small for SBM frequency rate and large for stool consistency (**Table 6**)
- MCTs were estimated to be a CFB of ⩾2 SBMs and 0.8–1.7 for p-BSFS based on triangulation across empirical cumulative distribution function (**Figures 2** and **3**, respectively), as well as classification statistics

Table 6. Responsiveness

eDiary Score	Group	N	Mean	SD	GRS for Improved vs Stable	GRS for Improved vs Worsened
SBM frequency rate	Improved	53	1.94	2.42	0.20	0.32
	Stable	29	1.21	3.77	–	–
	Worsened	12	1.00	2.95	–	–
Stool consistency	Improved	35	1.20	1.41	1.12	1.70
	Stable	13	0.19	0.90	–	–
	Worsened	4	0.19	0.59	–	–

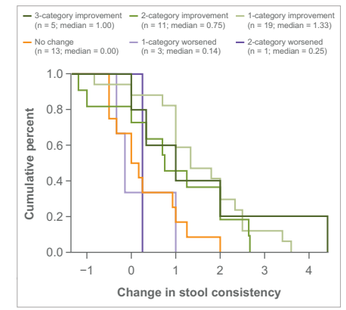
GRS, Guyatt's responsiveness statistic; SBM, spontaneous bowel movement; SD, standard deviation

Figure 2. eCDF of eDiary SBMs Change from Week -1 to Week 12



eCDF, empirical cumulative distribution function; SBM, spontaneous bowel movement

Figure 3. eCDF of eDiary Stool Consistency Change from Week –1 to Week 12



eCDF, empirical cumulative distribution function

Disclosures

Financial arrangements of the authors with companies whose products may be related to the present report are listed below, as declared by the authors.

Douglas CA Taylor is a former employee of Ironwood Pharmaceuticals, Inc. and may own stock or stock options. Yanqing Xu, Julia Vishnevetsky, Jessica L Abel, and Xiaolan Ye are employees of AbbVie Inc. and may own stock or stock options. Cheryl D Coon was an employee of Outcometrix and received funding for this psychometric analysis from AbbVie Inc. and Ironwood Pharmaceuticals, Inc.

Acknowledgments

All authors had access to relevant data and participated in the drafting, review, and approval of this poster. No honoraria or payments were made for authorship. Medical writing, editorial assistance, and poster production support were provided by Complete Healthvizion, IPG Health Medical Communications, funded by AbbVie Inc. and Ironwood Pharmaceuticals, Inc.

References

1. Vernon-Roberts A, et al. *J Clin Med.* 2021;10:5087.
2. Flemming, G. (2018). Chronic Functional Constipation in Infants and Children. In Koss, W., Schwab, M., van den Anker, J. (eds) Pediatric Pharmacotherapy - Handbook of Experimental Pharmacology, vol 261. Springer, Cham.
3. van Mill MJ, et al. *Curr Gastroenterol Rep.* 2019;21(6):23.
4. de Geus A, et al. Pediatr Drugs. 2023; online ahead of publication. doi: 10.1007/s40272-023-00563-5
5. Allergan and Ironwood Pharmaceuticals. Linzess® (linaclotide). Highlights of prescribing information. 2021. https://www.rxabbvie.com/pdf/linzess_pi.pdf

abbvie Ironwood