217

Application of Exploratory Factor Analysis to Support the Conceptual Framework of PRO Measures: Results From a Phase 2 Study of Irritable Bowel Syndrome With Constipation

Valerie S.L. Williams, PhD[1], Robyn T. Carson, MPH[2], Lauren M. Nelson, PhD[1], James E. MacDougall, PhD[3], Sheri E. Fehnel, PhD[1], Barbara E. Lewis, PhD, MHA[3], Jeffrey M. Johnston, MD[3]

[1]RTI Health Solutions, Research Triangle Park, NC; [2]Forest Research Institute, Jersey City, NJ; [3]Ironwood Pharmaceuticals, Inc., Cambridge, MA

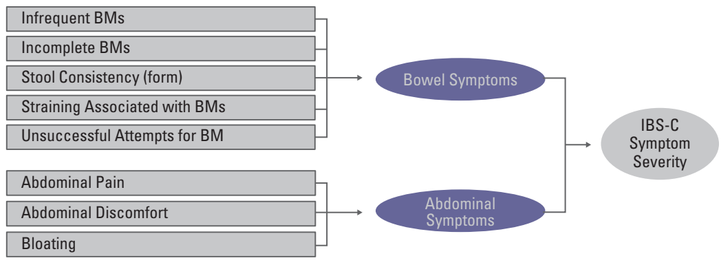
Background

- Irritable bowel syndrome (IBS) is a chronic functional gastrointestinal (GI) disorder characterized by recurrent symptoms of abdominal pain and/or discomfort, accompanied by altered bowel function; IBS is one of the most frequent GI disorders in the United States; data suggest the prevalence of IBS is 11%–14% of the adult population
- IBS is subtyped as IBS with diarrhea (IBS-D) or IBS with constipation (IBS-C) based on Rome II guidelines; subjects who do not fit IBS-C or IBS-D subtypes are classified as mixed/alternating IBS based on guidelines from the ROME Committee
- Currently, only one FDA-approved therapy for the treatment of IBS-C is available; there remains an unmet medical need for additional, well tolerated, and effective therapies for patients with IBS-C that not only increase bowel frequency, but also relieve abdominal symptoms (e.g., abdominal pain, discomfort, bloating, etc.)

Objective

- The objective of this post hoc analysis of a phase 2b clinical trial was to provide support for a draft conceptual framework of IBS-C patient reported outcome (PRO) items, developed based on a synthesis of the relevant literature and patient interviews
  - **Figure 1** shows the conceptual framework depicting the relationships among the symptoms addressed by the individual IBS-C PRO items

Figure 1. Conceptual Framework: Assessment of IBS-C Symptom Severity



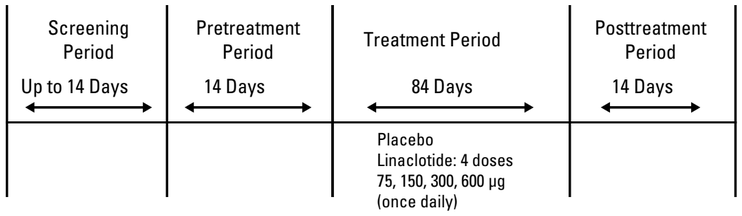
BMs = bowel movements

- A secondary objective of this analysis was to assess the relationship between the daily symptom-specific items addressing each IBS-C symptom and weekly PRO assessments of overall relief or severity, supporting the construct validity of each symptom-specific item

Methods

Clinical Study Design

- This was a phase 2b randomized, double-blind, parallel-group, placebo-controlled, dose-range-finding study



Patient Selection Criteria

- Males and females ≥ 18 years of age
- Modified ROME II criteria for IBS-C
- Meet the following criteria during the 14-day pretreatment period:
  - At least mild abdominal pain or discomfort (≥ 2.0 on a 5-point ordinal scale)
  - < 3 spontaneous bowel movements (SBMs)/week (defined as a bowel movement that occurred in the absence of a laxative/enema/suppository)
  - < 3 complete SBMs (CSBMs)/week (defined as a SBM with a feeling of complete evacuation)
  - No more than 1 SBM with a Bristol Stool Form Scale (BSFS) score of 6 or 7 (mushy or watery stool)

IBS-C PRO Items

- An interactive voice response system (IVRS) was used to collect patient information:
  - Daily study drug administration
  - Daily assessment of abdominal symptoms:
    - Abdominal pain (5-point ordinal scale; 1 = 'none' to 5 = 'very severe')
    - Abdominal discomfort (5-point ordinal scale; 1 = 'none' to 5 = 'very severe')
    - Bloating (5-point ordinal scale; 1 = 'none' to 5 = 'very severe')
  - Daily bowel movement (BM) data:
    - Number of BMs
    - Time of each BM
    - Number of unsuccessful BMs (UBMs)
  - Characteristics of each BM:
    - Stool consistency (7-point BSFS; 1 = 'lumpy hard stools' to 7 = 'entirely liquid')
    - Straining (5-point ordinal scale; 1 = 'not at all' to 5 = 'an extreme amount')
    - Completeness of evacuation (Yes or No)
  - Weekly Assessments:
    - Degree of relief of IBS symptoms (7-point balanced ordinal scale; 1 = 'completely relieved' to 4 = 'unchanged' to 7 = 'as bad as I can imagine')
    - Adequate relief of IBS symptoms (Yes or No)
    - IBS symptom severity (5-point ordinal scale; 1 = 'none' to 5 = 'very severe')
    - Constipation severity (5-point ordinal scale; 1 = 'none' to 5 = 'very severe')

Statistical Analysis Methods

- To explore the correlational structure among the daily IBS-C PRO measures (abdominal pain, abdominal discomfort, bloating, SBM frequency, CSBM frequency, UBM frequency, stool consistency, and straining), the following methods were used:
  - Each of the overall 12-week averages of the PROs were rescaled to a 5-point scale with higher scores corresponding to worsening symptoms
  - Principal components analyses (PCAs) were performed on the PROs to determine the number of underlying dimensions; examination of the eigenvalues and scree plots helped to determine the number of factors for consideration in the exploratory factor analysis (EFA)
  - An EFA was performed to explore the clustering of 7 PROs — abdominal pain, abdominal discomfort, bloating, SBM frequency, CSBM frequency, stool consistency, and straining
  - A separate EFA was performed using all 8 PROs — abdominal pain, abdominal discomfort, bloating, SBM frequency, CSBM frequency, UBM frequency, stool consistency, and straining
  - A minimum factor loading of 0.4 was applied to determine salience for item inclusion into the factor or symptom cluster; an oblique rotation allowed the extracted factors to be correlated
- Multiple regression methods were used to estimate the correlation of the 4 weekly PRO measures — adequate relief, degree of relief, IBS-C severity, and constipation severity — with the daily PRO symptom clusters defined by the EFA

Results

Demographics

Table 1. Baseline Demographics (Intent-to-Treat Population; N = 419)

Demographic Characteristic	Placebo (n = 85)	Linaclotide 75 µg (n = 79)	Linaclotide 150 µg (n = 82)	Linaclotide 300 µg (n = 84)	Linaclotide 600 µg (n = 89)	All (N = 419)
Age, years						
Mean	44.3	42.3	45.6	46.0	43.7	44.4
Range	21 – 65	18 – 69	24 – 70	21 – 72	19 – 69	18 – 72
Gender, n (%)						
Female	78 (91.8)	74 (93.7)	78 (95.1)	77 (91.7)	79 (88.8)	386 (92.1)
Race, n (%)						
Black/African American	16 (18.8)	8 (10.1)	18 (22.0)	12 (14.3)	17 (19.1)	71 (16.9)
White	67 (78.8)	68 (86.1)	62 (75.6)	69 (82.1)	69 (77.5)	335 (80.0)
Other	2 (2.4)	3 (3.8)	2 (2.4)	3 (3.6)	3 (3.3)	13 (3.1)

Correlational Results

- **Table 2** presents the intercorrelations among the overall 12-week averages for the 8 IBS-C PROs (abdominal pain, abdominal discomfort, bloating, SBM frequency, CSBM frequency, UBM frequency, stool consistency, and straining)
- In general, the correlation coefficients are moderate to strong in magnitude, with the exception of small and nonsignificant correlations (r = –0.09) between UBM frequency and stool consistency and between UBM frequency and CSBM frequency

Table 2. Pearson Correlations Among the IBS-C PROs (Overall 12-Week Treatment Average)

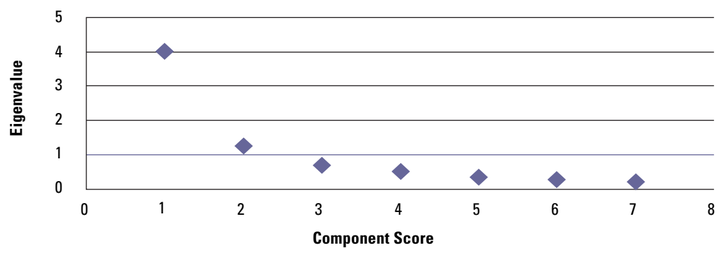
	Abdominal Pain	Abdominal Discomfort	Bloating	CSBM Frequency	SBM Frequency	UBM Frequency	Stool Consistency	Straining
Abdominal Pain	—	0.89*	0.75*	– 0.38*	– 0.25*	0.19*	– 0.24*	0.56*
Abdominal Discomfort		—	0.85*	– 0.42*	– 0.24*	0.24*	– 0.25*	0.61*
Bloating			—	– 0.39*	– 0.21*	0.18*	– 0.23*	0.57*
CSBM Frequency				—	0.62*	– 0.09	0.40*	– 0.50*
SBM Frequency					—	0.15*	0.48*	– 0.37*
UBM Frequency						—	– 0.09	0.26*
Stool Consistency							—	– 0.55*

*$P \leq 0.01$ vs. placebo

PCA Results

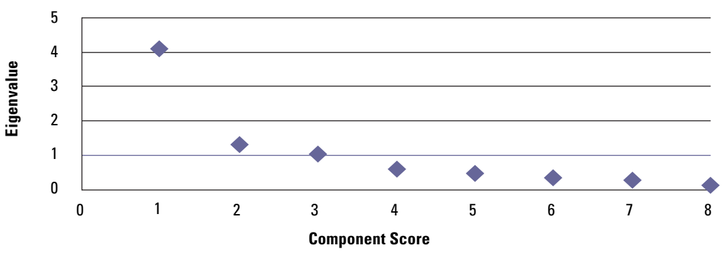
- The PCA of the 7 IBS-C PROs yielded 2 dimensions, which together accounted for 75% of the total variance; the first 3 eigenvalues are 3.99, 1.23, and 0.66
- **Figure 2** is a scree plot of the eigenvalues in order of magnitude; both the scree plot and the eigenvalues-greater-than-one criterion supported the extraction of 2 factors

Figure 2. Scree Plot of Eigenvalues From 7-Item PCA



- The PCA of the 8 IBS-C PROs yielded 3 possible emergent dimensions, which together accounted for more than 79% of the total variance; the first 3 eigenvalues are 4.05, 1.29, and 1.02
- **Figure 3** is a scree plot of the eigenvalues; both 2- and 3-factor solutions were explored

Figure 3. Scree Plot of Eigenvalues From 8-Item PCA



EFA Results

- The factor loadings based on the 2-factor EFAs with an oblique quartimin rotation are presented in **Table 3**; a factor loading ≥ 0.4 was the salience criterion for a daily PRO item to be included in the factor

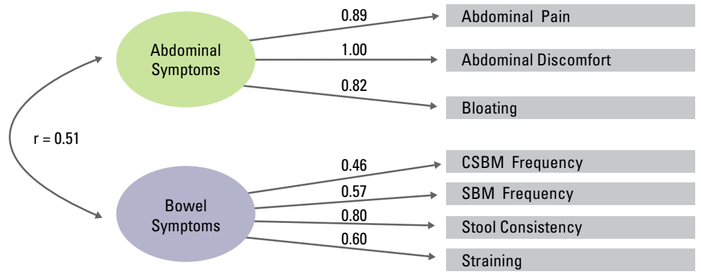
Table 3. Factor Pattern Matrix for 2-Factor Solution of IBS-C PRO Items

	7-Item EFA		8-Item EFA	
IBS-C PRO Item	**Factor 1 Loading**	**Factor 2 Loading**	**Factor 1 Loading**	**Factor 2 Loading**
Abdominal pain	**0.89**	0.00	**0.91**	–0.04
Abdominal discomfort	**1.00**	–0.04	**1.04**	–0.08
Bloating	**0.82**	0.05	**0.84**	0.01
CSBM frequency	0.32	**0.46**	0.34	**0.44**
SBM frequency	0.04	**0.57**	0.06	**0.55**
UBM frequency	—	—	0.21	0.06
Straining	0.32	**0.60**	0.33	**0.60**
Stool consistency	–0.14	**0.80**	–0.13	**0.80**

Note: Bold font indicates salient loadings ≥ 0.4

- **Figure 4** illustrates the results of the 7-variable 2-factor EFA with an oblique quartimin rotation; one factor consists of abdominal symptoms (abdominal pain, abdominal discomfort, and bloating) and the second factor consists of bowel symptoms (SBM frequency, CSBM frequency, stool consistency, and straining); these 2 factors were strongly correlated (r = 0.51)

Figure 4. Illustration of the 2-Factor EFA Model



- Using the full set of 8 IBS-C PROs, 3 factors were extracted and rotated; in this solution, abdominal pain, abdominal discomfort, and bloating loaded together, as did SBM frequency, stool consistency, and straining; CSBM frequency was divided between factor 1 and factor 2; factor 3 comprised SBM frequency and, to a lesser degree, UBM frequency; the factor loadings based on the 3-factor EFA of the 8 IBS-C PRO items are presented in **Table 4**

Table 4. Factor Pattern Matrix for 3-Factor Solution of 8 IBS-C PRO Items

IBS-C PRO Item	Factor 1 Loading	Factor 2 Loading	Factor 3 Loading
Abdominal pain	**0.91**	–0.04	0.01
Abdominal discomfort	**1.04**	–0.08	–0.01
Bloating	**0.83**	0.02	–0.05
CSBM frequency	0.39	0.36	0.17
SBM frequency	0.19	**0.45**	**0.80**
UBM frequency	0.11	0.18	–0.34
Straining	0.16	**0.86**	–0.24
Stool consistency	–0.07	**0.66**	0.07

Note: Bold font indicates salient loadings ≥ 0.4

Regression Results

- **Table 5** displays the correlation coefficients based on a multiple regression of each of the 4 weekly PROs with the 3 sets of items — abdominal symptoms (abdominal pain, abdominal discomfort, and bloating) and bowel symptoms (SBM frequency, CSBM frequency, UBM frequency, stool consistency, and straining) both with and without UBM frequency
  - Each of the 4 weekly PROs (adequate relief, degree of relief, IBS-C symptom severity, and constipation severity) was strongly correlated with the abdominal symptoms score (r = 0.61 to 0.84)
  - With respect to the bowel symptoms items, the correlations were slightly higher with the inclusion of UBM frequency, as would be expected with the inclusion of an additional variable in the multiple regression equation

Table 5. Correlations Between the Weekly PROs and the Abdominal Symptoms Items and Bowel Symptoms Items

Global IBS-C PROs	Abdominal Symptoms	Bowel Symptoms (4 IBS-C Items[a])	Bowel Symptoms (5 IBS-C Items[b])
Constipation severity	0.79	0.73	0.73
IBS symptom severity	0.84	0.65	0.66
Adequate relief	0.61	0.58	0.60
Degree of relief	0.68	0.62	0.62

[a]SBM frequency, CSBM frequency, stool consistency, and straining
[b]SBM frequency, CSBM frequency, UBM frequency, stool consistency, and straining

Conclusions

- The EFA results for the set of 8 IBS-C PROs are somewhat ambiguous; although there is some support for 2 underlying domains (abdominal symptoms and bowel symptoms), the factors are not as clear-cut as those from the 7-variable EFA
- From **Table 2**, it can be seen that UBM frequency did not correlate strongly with the other IBS-C PRO items; these correlations ranged from |0.09| to |0.26|; correlations between the 4 other bowel symptoms (SBM frequency, CSBM frequency, stool consistency, and straining) ranged from |0.37| to |0.62|; correlations between the 7 IBS-C PRO items (not including UBM frequency), which loaded on 2 separate factors (see **Table 3**), ranged from |0.21| to |0.89|
  - As expected, the inclusion of UBM frequency in the EFAs complicated the factor analysis results
  - The number of unsuccessful BM attempts is not a pure symptom in that it is directly influenced by the number of times one decides to try to pass stool; it does not simply measure a symptom, but also individual behaviors and therefore has a high potential for measurement error
- The factor-analytic and correlational results for the set of 7 IBS-C PROs are empirical, quantitative evidence in support of previous qualitative research indicating that symptoms elicited from patient interviews belong to 1 of 2 underlying domains — abdominal symptoms and bowel symptoms
  - The IBS-C conceptual framework was ultimately supported by these analyses, with the possible exception of the inclusion of UBM frequency
- The weekly PRO items measuring overall relief or severity are strongly correlated with both abdominal and bowel symptom measures

Supported by Ironwood Pharmaceuticals, Inc. and Forest Laboratories, Inc.
Presented at the International Society for Quality of Life Research 2010 Annual Meeting