Functional Dyspepsia Working Group

Presented at the Sixth Annual PRO Consortium Workshop – Silver Spring, MD – April 29-30, 2015

Background

Rationale for Functional Dyspepsia (FD) Working Group (WG)

- PRO Consortium member representatives and FDA advisors identified FD as an area lacking a "well-defined and reliable" measure of treatment benefit

Goal of the FD WG

- To develop a PRO instrument, in accordance with the FDA PRO Guidance, to measure the symptoms of FD for use in clinical trials as a primary endpoint to establish treatment benefit

Targeted Labeling Language

- The PRO measure would support an indication for the treatment of the FD subtype as defined by the Rome III diagnostic criteria:
  1) Postprandial distress syndrome (PDS), which includes symptoms such as postprandial fullness and early satiation;
  2) Epigastric pain syndrome (EPS), which involves symptoms such as epigastric pain and burning; or
  3) Co-existing PDS and EPS subtypes

Milestones

Milestone	Expected Date	Completed Date
Content Validity Stage		
Vendor selection and contracting		September 18, 2012
Complete background research (Literature Review Report and Expert Panel input)		August 30, 2013
Submit Literature Review & Concept Elicitation Protocol to FDA for consultation and advice		October 31, 2013
Received written comments from the FDA		December 20, 2013
Submitted working group's responses to FDA comments		February 7, 2014
Complete initial concept elicitation interviews and generate items (concept elicitation interviews, item generation, expert panel input)		March 2, 2015
Complete translatability and ePRO implementation assessments	April 2015	
Complete cognitive interviews and revise instrument	4Q2015	
Submit Qualitative Research Summary Briefing Document to FDA for review and feedback	1Q2016	
Complete documentation of content validity and cross-sectional evaluation of other measurement properties	TBD	
Submit exploratory endpoint qualification dossier to FDA	TBD	

Content of Interest

Endpoint model for treatment of FD – Postprandial Distress Syndrome (PDS) Subtype

Endpoint Hierarchy	Concept(s)	Endpoint Type
Primary	FD-PDS Subtype • PDS Symptoms Score	PRO instrument under development

Endpoint model for treatment of FD – Epigastric Pain Syndrome (EPS) Subtype

Endpoint Hierarchy	Concept(s)	Endpoint Type
Primary	FD-EPS Subtype • EPS Symptom Score	PRO instrument under development

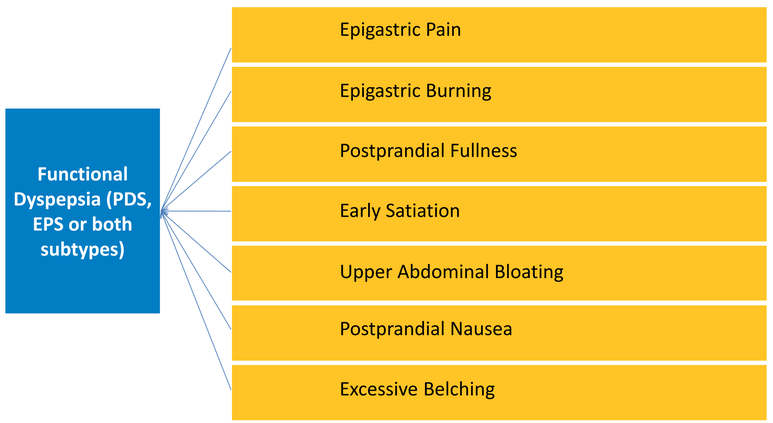
Endpoint model for treatment of FD – Co-existing PDS and EPS symptoms

Endpoint Hierarchy	Concept(s)	Endpoint Type
Primary	FD • PDS and EPS Symptoms Score	PRO instrument under development

Target Population

- U.S. adult patients aged 18 years and older, with a diagnosis of FD (including PDS, EPS, or both) according to the Rome III diagnostic criteria, inclusive of a recent negative endoscopy
- Exclusion criteria include the following conditions: patients with gastroparesis, active irritable bowel syndrome, active chronic constipation, and active GERD (list not exhaustive)

Hypothesized Conceptual Framework



Updates

- Concept elicitation report finalized
- Conceptual framework confirmed by concept elicitation interviews
- Instrument named – *Functional Dyspepsia Symptom Diary (FDSD)*
- Item generation completed – seven items, daily recall, 11-point numeric rating scale (NRS)
- Cognitive interview protocol and interview guide finalized

Working Group Plans

Next Steps

- Complete translatability and electronic implementation assessments
- Complete cognitive interviews by December 2015
- Draft report of cognitive interview findings and update the *FDSD*
- Continue to investigate through quantitative research whether there are two individual subtypes of FD (EPS and PDS)

Information Dissemination Plan

- First manuscript focusing on literature and instrument reviews to be submitted to *Value in Health*
- Second manuscript will focus on the qualitative research

Topics for Discussion

Unique Issues for the Working Group

- Challenges encountered in identifying patients with FD diagnosis that do not have other co-existing GI disorders
  - Very extensive list of exclusion criteria from FDA, further complicated by potential discrepancy between clinician-reported and patient-reported symptoms
  - Compromise reached with the FDA qualification review team (QRT) to allow enrollment of patients with comorbid conditions with future evaluation planned regarding the impact of these comorbid conditions on the patients' FD-symptom experience
- Challenge articulating concepts when developing several key items (i.e., early satiety and burping/belching)
  - Item wording will be tested in cognitive interviews
- Recruitment challenges mitigated by reaching out to 30+ clinical sites, including involvement of the expert panel members

Lessons Learned

- Don't assume an accepted definition of condition exists
- Don't assume that certain terminology is universally understood (e.g., conceptual framework and conceptual model)
- When possible, consult recruiting agencies and clinical sites to assess feasibility of inclusion/exclusion criteria before finalizing
- Despite interest from the FDA for the instrument development sample to be free of confounding conditions (i.e., a "pure-FD" sample), it is critical that the sample represent the real-world population with the disease under study to ensure that future research is feasible and relevant

Working Group Participants

Organization	Name
Actavis, Inc., an affiliate of Forest Research Institute, Inc.	Robyn Carson, MPH (Co-Chair); Steven J. Shiff, MD
Ironwood Pharmaceuticals, Inc.	David Reasner, PhD; Jennifer Hanlon, MPH
Shire Development Inc.	Linda Deal, MS (Co-Chair); Debra G. Silberg, MD, PhD
Expert Panel Members	**Affiliation**
Brian E. Lacy, MD, PhD	Dartmouth-Hitchcock Medical Center
Henry P. Parkman, MD	Temple University
Jan Tack, MD	University of Leuven
Nick Talley, MD, PhD	University of Newcastle
Contract Research Organization	**Research Team**
Adelphi Values	Alan Shields, PhD; Fiona Taylor, MBiochem; Farrah Pompilus, MA; Catherine Foley, MPH, MA; Megan Daggett, BA