Irritable Bowel Syndrome Working Group
Presented at the Sixth Annual PRO Consortium Workshop – Silver Spring, MD – April 29-30, 2015

Background

Rationale for Irritable Bowel Syndrome (IBS) Working Group (WG)
- IBS is one of the most commonly diagnosed GI disorders
- IBS lacks a standard and fit for purpose PRO instrument for measuring important patient-experienced signs and symptoms of IBS
- PRO Consortium member representatives and FDA advisors identified IBS as a priority area for the development of a PRO instrument

Goal of the IBS WG
- To develop three PRO measures for patient-reported symptoms in IBS with constipation (IBS-C), IBS with diarrhea (IBS-D), and IBS with mixed symptoms (IBS-M) for use in clinical trials as a primary endpoint to establish treatment benefit

Targeted Labeling Language
- Product X is indicated in adults for the treatment of symptoms associated with irritable bowel syndrome [with constipation (IBS-C), with diarrhea (IBS-D), or mixed (IBS-M)]
- Product X improved abdominal symptoms (as measured by the abdominal symptom severity subscale) and bowel movement-related symptoms (as measured by an appropriate BM-related symptom subscale).

Note: This indication would be supported by an improvement in both abdominal symptoms and bowel movement-related symptoms

Milestones

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<tr>
<th>Milestone</th>
<th>Expected Date</th>
<th>Completed Date</th>
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<tbody>
<tr>
<td>Content Validity Stage</td>
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<tr>
<td>Vendor selection and contracting</td>
<td>10/29/2010</td>
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<tr>
<td>Complete background research (literature review and Expert Panel Meeting)</td>
<td>01/12/2011</td>
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<tr>
<td>Draft Instrument: Complete initial qualitative research and generate items (concept elicitation interviews, item generation, expert panel input, and two rounds of cognitive interviews)</td>
<td>09/09/2011</td>
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<td>Submit Qualitative Research Summary Interim Briefing Document to FDA for review and feedback</td>
<td>09/26/2011</td>
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<td>Received comments from FDA</td>
<td>12/6/2013</td>
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<td>Teleconference</td>
<td>12/11/2013</td>
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<tr>
<td>Define initial instrument (final cognitive interviews on demo ePRO device)</td>
<td>2/21/2014</td>
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<tr>
<td>Complete qualitative research phase; submit briefing package to FDA (Final Cognitive Interview Report and Updated Briefing Document)</td>
<td>8/15/2014</td>
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<tr>
<td>Complete documentation of content validity via quantitative evaluation of item functioning</td>
<td>Q42016</td>
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<tr>
<td>Submit exploratory endpoint qualification briefing document to FDA</td>
<td>1Q2017</td>
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Content of Interest

Endpoint Model for Treatment of IBS (Example provided for IBS-M)

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<tr>
<th>Endpoint</th>
<th>Endpoint Concept(s)</th>
<th>Endpoint Type</th>
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<tr>
<td>Primary</td>
<td>Overall response (TBD) indicating improvement in IBS-M symptom severity</td>
<td>PRO</td>
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<td>Improvement in abdominal symptoms (abdominal pain, discomfort, bloating, cramping)</td>
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<td></td>
<td>Improvement in selected BM-related symptoms (stool consistency, stool frequency, incomplete BMs, straining, recurrent BMs, urgency)</td>
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Target Population
- US-based adult patients (18 years and older; males and non-pregnant females)
- Diagnosis of IBS of three main subtypes based on Rome III criteria (i.e., IBS-C, IBS-M, and IBS-D)
- Patients without known or suspected organic disorder (e.g., Crohn’s disease) that would better explain symptoms
- Patients not concomitantly using medications known to affect GI mobility, constipation, or other IBS symptoms

Hypothesized Conceptual Framework

- Abdominal Symptoms
- Bowel Movement-Related Symptoms

IBS lacks a standard and fit for purpose PRO instrument for measuring important patient-experienced signs and symptoms of IBS.

Updates
- Conceptual framework confirmed by qualitative research
- Final Qualitative Research Summary Briefing Document for three PRO instruments (IBS-C, IBS-D, and IBS-M) submitted to FDA on August 15, 2014
- Received FDA agreement to advance instruments to quantitative evaluation on December 4, 2014
- Quantitative pilot study proposal finalized and contracts executed

Working Group Plans

Next Steps
- Develop preliminary scoring algorithm and protocol for quantitative evaluation of scale and item functioning
- Quantitative pilot study protocol to be submitted to FDA for review – 3Q2015

Dissemination Plan
- Qualitative research phase manuscript under development for submission to Value in Health

Topics for Discussion

Unique Issues for the Working Group and Their Resolution
- Continued evaluation during upcoming quantitative pilot study needed to consider potential item reduction around abdominal pain and discomfort
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- Ensure representation of patients who are 18 to 21 years of age in quantitative pilot study
- Evaluate whether there are different symptom experiences by gender, age and race

Lessons learned
- Important to consider and develop hypothesized preliminary scoring algorithm prior to quantitative phase

Working Group Participants

Company/Organization | Name | Affiliation
----------------------|------|------------------|
Artaxis, Inc., an affiliate of Forest Research Institute, Inc. | Robin T. Carson, MPH (Co-Chair); Steven J. Shif, MD; Jessica Bunno | |
Ironwood Pharmaceuticals, Inc. | Gianna Rigoni, PharmD (Co-Chair); Maria Claudia Perez; Charles Baum, MD | |
Takeda Pharmaceuticals International | | |
Nonmember Participants | Affiliation
Nancy Norton, BS | International Foundation for Functional Gastrointestinal Disorders (IFFGD)

Expert Panel Members | Affiliation
Lin Chang, MD | University of California, Los Angeles
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Brennan M.R. Spiegel, MD, MSHS | University of California, Los Angeles

Contract Research Organization | Research Team
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