Irritable Bowel Syndrome Working Group

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PRO CONSORTIUM CRITICAL PATH INSTITUTE

Background

Rationale for Irritable Bowel Syndrome (IBS) Working Group (WG)

- IBS is one of the most common gastrointestinal (GI) disorders
- As of 2009, IBS lacked a standard "fit-for-purpose" PRO measure for assessing important patient-experienced signs and symptoms of IBS
- PRO Consortium member firm representatives and FDA advisors identified IBS as a priority area for the development of a PRO measure

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 to support primary and secondary endpoints to establish clinical benefit

Concept of Interest

- IBS sign and symptom severity

Targeted Labeling Language

- [*Drug 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)]
- [*Drug X*] improved abdominal symptoms and bowel movement (BM)-related signs and symptoms

Milestones

Milestone	Expected Date	Completed Date
Briefing package submission to FDA (final Cognitive Interview Report and updated Briefing Document)		AUG 2014
Received FDA response and approval to conduct quantitative pilot study		DEC 2014
Quantitative pilot study protocol and quantitative analysis plan (QAP) submission to FDA		DEC 2015
Full Qualification Package submission for *DIBSS-C* to FDA		DEC 2018
Responded to Information Request 1 received from FDA on 02/14/19		MAR 2019
Responded to Information Request 2 received from FDA on 06/06/19		DEC 2019
Responded to Information Request 3 received from FDA on 03/14/20		MAR 2020
Received FDA qualification for *DIBSS-C* on December 18, 2020		DEC 2020
Qualification Plan submission for *DIBSS-D* to FDA		DEC 2022
Full Qualification Package submission for *DIBSS-D* to FDA	TBD	
Qualification Plan submission for *DIBSS-M* to FDA	TBD	
Full Qualification Package submission for *DIBSS-M* to FDA	TBD	

Highlights

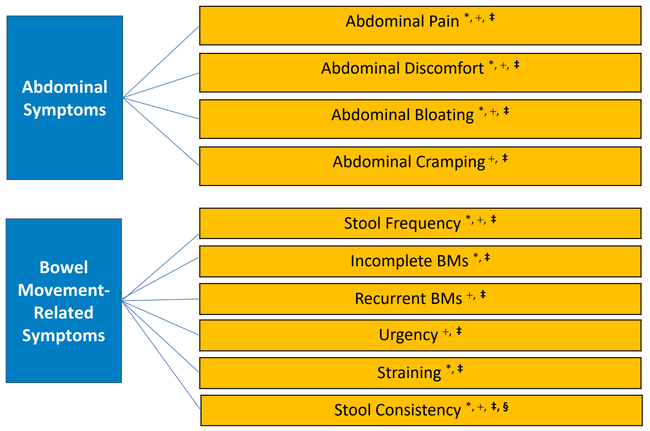
Example Endpoint Model for Treatment of IBS-C

Endpoint Hierarchy	Endpoint Concept(s)	Endpoint Type
Primary	Overall response indicating improvement in IBS-C symptom severity • Improvement in abdominal symptoms (abdominal pain, discomfort, and bloating) • Improvement in complete spontaneous BM frequency	PRO (*DIBSS-C*)
Secondary	Improvement in straining during BM	PRO (*DIBSS-C*)

Target Population

- Adult patients (18 years and older; males and non-pregnant females)
- Diagnosis of one of the three main IBS subtypes: IBS-C, IBS-D, or IBS-M
- 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 motility, constipation, or other IBS symptoms

Conceptual Framework



Abdominal and Bowel movement-related symptoms pertain to the following subtypes: * IBS-C; + IBS-D; ‡ IBS-M
§ The stool consistency item was not supported in FDA's Qualification Statement for deriving an efficacy endpoint. Sponsors seeking to use the stool consistency item to support a label claim should discuss the approach with the appropriate CDER review division.

Measures– *Diary for Irritable Bowel Syndrome Symptoms (C, D, M)*

Measures developed for each subtype:
***Diary for Irritable Bowel Syndrome Symptoms–C (DIBSS-C)* for constipation predominant**
***Diary for Irritable Bowel Syndrome Symptoms–D (DIBSS-D)* for diarrhea predominant**
***Diary for Irritable Bowel Syndrome Symptoms–M (DIBSS-M)* for mixed symptoms**

Core Items: Abdominal symptoms and bowel movement-related signs/symptoms
Recall Period: Event-driven and 24-hour (end of day)
Response Options: Verbal rating scales, bivariate response, 11-point numeric rating scales
Data Collection Mode: Smartphone device used for quantitative pilot study

Working Group Activities

Information Dissemination (Selected)

- Fehnel, S. et al. Development of the Diary for Irritable Bowel Syndrome Symptoms (DIBSS) to assess treatment benefit in clinical trials: Foundational qualitative research. *Value in Health* 2017;20(4):618-626
- Coon, C. et al. Psychometric Analysis of the Abdominal Score From the Diary for Irritable Bowel Syndrome Symptoms-Constipation Using Phase IIb Clinical Trial Data. *Value in Health* 2020;23(3):362-369

Substantive FDA Interaction (Selected)

- Following completion of the quantitative pilot study, C-Path and RTI-HS held a full-day, face-to-face meeting on July 12, 2018, with the IBS WG, FDA's Qualification Review Team (QRT), a patient representative, and the project's expert panel. This meeting was key to obtain patient, expert, and regulatory input regarding finalization of the *DIBSS-C/D/M* content, to identify the most appropriate endpoints for IBS-C in clinical trials and discuss plans for further evaluation of the *DIBSS-D* and *DIBSS-M* in the context of clinical trials.
- A meeting was held with FDA's QRT on December 2, 2021, following submission by the WG of a dossier supporting urgency as the BM-related component of the co-primary endpoint for IBS-D trials. After discussion, FDA's position was that it was premature to replace stool consistency with urgency as the BM-related component. FDA indicated it was open to considering urgency-related secondary endpoints.

Lessons Learned

- Ensure there is clarity about what is being qualified (i.e., measure versus endpoint)
- Submission of patient-level interventional trial data and the related statistical programs is required by FDA to support qualification of a primary or secondary endpoint measure.
- Close collaboration is vital between the eCOA provider and measure development team to ensure successful implementation.

Next Steps

- Acceptance and publication of the manuscript based on the *DIBSS-C* quantitative study data
- Upon approval by FDA of the *DIBSS-D* Qualification Plan, prepare and submit the Full Qualification Package; FDA issued the Reviewability Memorandum deeming the QP reviewable on March 7, 2023

Working Group Participants

Company/Organization	Representatives
AbbVie	Robyn T. Carson, MPH (Co-Chair); Julia Vishnevetsky, MPH; Yanqing Xu, PhD
Ironwood Pharmaceuticals, Inc.	Douglas Taylor, MBA (Co-Chair)
Takeda Pharmaceuticals International	Note: Takeda provided funding for the IBS WG but is no longer an active participant.
Other Participant	**Affiliation**
Ceciel T. Rooker	International Foundation for Gastrointestinal Disorders
Expert Panel Members	**Affiliation**
Lin Chang, MD	University of California, Los Angeles
William D. Chey, MD	University of Michigan
Douglas A. Drossman, MD	Drossman Gastroenterology, PLLC
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Research Partner	**Research Team**
RTI Health Solutions	Sheri Fehnel, PhD; Claire Ervin, MPH; Lori McLeod, PhD; Diana Goss