Guidance for Industry
Irritable Bowel Syndrome — Clinical Evaluation of Drugs for Treatment

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U.S. Department of Health and Human Services
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I.   INTRODUCTION

This guidance is intended to assist the pharmaceutical industry and investigators who are developing drugs[2] for the treatment of irritable bowel syndrome (IBS). IBS diagnosis and assessment of clinical status depend mainly on an evaluation of IBS signs and symptoms that are known to the patient. Capturing all of the clinically important signs and symptoms associated with IBS in a reliable measure of treatment benefit can be challenging. The guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims* (PRO guidance)[3] defines the term *treatment benefit* as "[t]he effect of treatment on how a patient survives, feels, or functions."

This guidance addresses two main topics. Section III discusses the evolution of patient-reported outcome (PRO) measures as primary endpoints for IBS clinical trials; and section IV provides a set of provisional endpoints and trial design recommendations that sponsors may apply to IBS clinical trials as PRO measurements continue to evolve. The guidance also discusses, in section V, the future development of IBS PRO instruments through the FDA qualification process and the FDA's collaboration with the Critical Path Institute. The recommendations provided in this guidance are consistent with good measurement science as reflected in other FDA guidance.

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[1] This guidance has been prepared by the Division of Gastroenterology and Inborn Errors Products and the Study Endpoints and Labeling Development Team in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

[2] For the purposes of this guidance, all references to *drugs* include both human drugs and therapeutic biological products unless otherwise specified.

[3] We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance Web page at
http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

The goal for efficacy endpoints in IBS clinical trials is to assess the treatment effect on the core disease-defining signs and symptoms of IBS in a well-defined and reliable way. Until such endpoints are available, the provisional endpoint assessments suggested in this guidance can be used in the evaluation of treatment benefit in IBS clinical trials.

This guidance applies to the IBS indications for IBS with diarrhea (IBS-D) and IBS with constipation (IBS-C). Sponsors should contact the Division of Gastroenterology and Inborn Errors Products to discuss endpoint assessments and trial design proposals for other IBS populations not discussed in this guidance (i.e., mixed irritable bowel syndrome and unsubtyped irritable bowel syndrome).

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II.   BACKGROUND

IBS is a complex condition that is not well-linked to any readily measured physiological abnormality. Despite advances in our understanding of basic neuroenteric mechanisms and the role of effectors and transmitters in the brain-gut axis, a reliable biologic marker of IBS has yet to be indentified.[4] PRO measures of the signs and symptoms of the condition are the only currently available measures that can adequately define a treatment effect in a clinical trial.

III.   EVOLUTION OF PRO MEASURES IN IBS CLINICAL TRIALS

An adequate measure of treatment benefit should capture the most significant signs and symptoms of IBS. The primary challenge in designing clinical trials to evaluate the efficacy of drugs for this condition has been to define the critical signs and symptoms that are most relevant to patients, and then select or develop adequate assessment tools that measure improvement and decrements in these important signs and symptoms.

In the past, IBS clinical trials commonly used a single-item patient-reported rating of overall change in condition as the primary efficacy endpoint.[5] When the single-item patient-reported rating of change was used as the primary endpoint, specific IBS signs and symptoms were often included as separate secondary endpoints. As detailed in Table 1, examples of single-item patient-reported ratings of change have included questions posed to patients about *adequate relief* or *satisfactory relief* and the single item *Subject Global Assessment of Relief of IBS symptoms*. Usually, the patient-reported ratings of change required patients to average either specific symptoms (e.g., abdominal pain or discomfort) or all signs and symptoms of IBS over a

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[4] See reference numbers 1-8 in the References section at the end of the guidance.

[5] See reference numbers 9-23 in the References section at the end of the guidance.

week's time, and then compare this average to a period in the past, typically before trial entry. Table 1 describes primary endpoints that have been used in several IBS clinical trials. Although these endpoints may well have captured the direction of change (trials were controlled and blinded), they could not provide useful information on the effect of treatment on the severity of a specific sign or symptom.

Table 1. Primary Endpoints Used in IBS Clinical Trials

Drug and Indication	Primary Endpoint	Questions (Single-Item) Used to Assess Efficacy	Responses
Alosetron — IBS-D[1]	Adequate relief	*In the past 7 days, have you had adequate relief of your IBS pain or discomfort?*	Binary (Yes/No)
Tegaserod — IBS-C[2]	Satisfactory relief	*Did you have satisfactory relief of your overall IBS symptoms during the last week?*	Binary (Yes/No)
		Did you have satisfactory relief of your abdominal discomfort or pain during the last week?	Binary (Yes/No)
	Subject Global Assessment of Relief (SGA)	*Please consider how you felt during the past treatment period in regard to your IBS, in particular your overall well-being, and symptoms of abdominal pain/discomfort and altered bowel habit. Compared to the way you usually felt before entering the trial, how would you rate your relief of symptoms during the past week?*	5-Point Likert scale
Lubiprostone — IBS-C[3]	Modified version of the SGA	*How would you rate your relief of IBS symptoms (abdominal discomfort/pain, bowel habits, and other IBS symptoms) over the past week compared with how you felt before you entered the trial?*	7-Point Likert scale

[1] See reference numbers 9-14 in the References section at the end of the guidance.
[2] See reference numbers 15-22 in the References section at the end of the guidance.
[3] See reference number 23 in the References section at the end of the guidance.

As noted above, the PRO guidance defines *treatment benefit* as the effect of treatment on how a patient survives, feels, or functions. PRO instruments define and capture the patient's perspective with respect to the disease or condition of interest and can be appropriate for measuring the effect of treatment in a clinical trial, particularly when the desired effect of the treatment is on signs and symptoms known only to the patient. Consistent with FDA regulations for drug approval, the effectiveness of a treatment must be based on substantial evidence including evidence that the method of assessment of subjects' responses are well-defined and reliable (21 CFR 314.126(b)(6)). The PRO guidance sets forth the FDA's review principles for determining whether assessments are well-defined (i.e., valid) and adequately developed (i.e., reliable, sensitive, and interpretable) to measure what they are intended to measure.

As reflected in the PRO guidance, the type of PRO instruments we consider appropriate for data collection to support labeling claims has evolved from what was considered appropriate in the past. For example, we no longer recommend a single general item asking patients to rate change in their overall IBS symptoms as a primary endpoint to support an efficacy claim. A single general item cannot adequately capture whether benefit is achieved in all, or only some, of the important signs and symptoms. For example, a single item that queries a patient about his or her

overall IBS experience will likely not capture a situation where the patient's stool frequency has improved, but abdominal pain has not improved or even worsened.

In recognition of the limitations of using a single-item patient-reported rating of overall change as a primary endpoint and based on the principles explained in the PRO guidance, we now recommend the development of a multi-item PRO instrument. The PRO measure(s) should capture all of the clinically important signs and symptoms of the IBS target population (e.g., IBS-C or IBS-D). Changes from previous scores can then be calculated. If a drug is developed specifically to improve only one of the major signs or symptoms of IBS (e.g., abdominal pain), based on the drug's mechanism of action, it is still important to assess the other important signs and symptoms to document that the drug has not negatively affected those components. Ultimately, the drug's indication should reflect the findings from the clinical trials.

IV. PROVISIONAL ENDPOINTS AND TRIAL DESIGN FOR IBS CLINICAL TRIALS

A well-defined and reliable PRO instrument that measures the clinically important signs and symptoms associated with each IBS subtype would be the ideal primary efficacy assessment tool in clinical trials used to support labeling claims, but at this time such an instrument is not available. We recognize that it will take some time to develop adequate instruments and that in the meantime there is a great need to develop effective therapies for patients with IBS. Therefore, until the appropriate PRO instruments have been developed, sponsors should consider the strategies discussed in the following sections when designing IBS clinical trials. These sections set forth provisional standards with regard to: (1) trial design; (2) trial endpoints; (3) trial populations; (4) efficacy measures; and (5) definition of a responder.

Following this discussion is Table 2, which summarizes the provisional standards for IBS-C and IBS-D trial designs, including primary endpoints, patient entry criteria, and responder definitions. Table 2 is intended as a summary of the discussion in this guidance. Sponsors should refer to the text of the guidance for full detail.

1. *Trial Design*

Because the clinical signs and symptoms associated with IBS-C and IBS-D can be significantly different, the two conditions ordinarily should be studied in separate clinical trials.

A randomized, placebo-controlled trial design should include a 1- to 2-week single-blind or open-label screening period. The 1- to 2-week screening period can be used to establish the presence and persistence of trial entry criteria and train patients in the mode of PRO data collection selected for the trial. The screening period can also be used to select patients with specified levels of severity of signs and symptoms. For therapies that will be administered on a chronic and continuous basis, we recommend a treatment period of at least 8 weeks duration, followed by a randomized withdrawal design to address the need for maintenance treatment to prevent sign or symptom recurrence.

For therapies with an intermittent administration schedule, sponsors should provide repeated courses of therapy to demonstrate sustained efficacy over time, and to characterize the safety of intermittent and repeated administration.

2.   *Trial Endpoints*

To support an indication of treatment of IBS, we recommend a primary endpoint that measures the effect of treatment on two major IBS signs and symptoms: abnormal defecation and abdominal pain.[6] The primary efficacy analysis should be a comparison of the response rates between investigational drug and placebo.

For IBS-C, the defecation component of the proposed primary endpoint can be evaluated by assessing stool frequency. Stool frequency, as measured by the number of complete spontaneous bowel movements (CSBMs) per week, is readily defined, has been useful in defining a treatment response in chronic constipation clinical trials, and is clinically relevant for IBS-C patients.

For IBS-D, the defecation component of the proposed primary endpoint can be evaluated by assessing stool consistency.[7] The Bristol Stool Form Scale, which is reproduced in Figure 1, provides a pictorial and verbal description of stool consistency and form and is an appropriate instrument for capturing stool consistency in IBS trials.[8]

Figure 1. Bristol Stool Form Scale

Bristol Stool Chart

Type 1	Separate hard lumps, like nuts (hard to pass)
Type 2	Sausage-shaped but lumpy
Type 3	Like a sausage but with cracks on its surface
Type 4	Like a sausage or snake, smooth and soft
Type 5	Soft blobs with clear-cut edges (passed easily)
Type 6	Fluffy pieces with ragged edges, a mushy stool
Type 7	Watery, no solid pieces. **Entirely Liquid**

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[6] See reference number 24 in the References section at the end of the guidance.

[7] See reference numbers 25 and 26 in the References section at the end of the guidance.

[8] See reference number 27 in the References section at the end of the guidance.

Stool frequency should be evaluated as a key secondary endpoint, using the weekly number of CSBMs. Stool consistency, rather than stool frequency, is the recommended primary endpoint for IBS-D because it is more clinically relevant and better correlated with signs and symptoms of diarrhea. Currently, there are insufficient data to adequately quantify and qualify the concept of urgency based on the patient's perspective and thus to support its use as a component of the primary endpoint definition of treatment response. Until an adequate urgency assessment tool is developed, stool urgency should be assessed as an exploratory endpoint in IBS-D trials.

The second component of the primary endpoint in both IBS-C and IBS-D trials is abdominal pain. Although previous IBS clinical trials have used an item that assesses abdominal *pain or discomfort*, it is not clear whether the abdominal pain and abdominal discomfort experienced by patients with IBS are synonymous or two different symptoms. Although adequate qualitative trials have not fully addressed these questions, clinical data provided to and reviewed by the FDA suggest that abdominal pain and discomfort may be different symptoms that should be assessed by different questions. Because frank pain seems to be a symptom that is experienced with more significant intensity than discomfort and because the chronic pain literature suggests that pain intensity may be a more clinically relevant assessment than pain frequency,[9] we recommend abdominal pain intensity as the primary pain assessment in IBS trials. Abdominal discomfort can be evaluated as a secondary endpoint.

We recommend evaluating abdominal pain intensity by using an 11-point (i.e., 0 to 10) numeric rating scale that asks patients daily to rate their *worst abdominal pain over the past 24-hours*.[10]

This type of pain assessment has been used to assess pain in somatic, visceral, and neuropathic chronic pain conditions.[11]

A drug can be specifically developed to treat only one of the major signs or symptoms of IBS, which should be identified as the primary endpoint in the clinical trial. The identification of a single sign or symptom of interest should be based on the mechanism of action of the drug. The other key efficacy endpoints should be assessed in the clinical trial as secondary endpoints. Demonstration of significant and clinically meaningful changes in the targeted single endpoint could serve as a basis for approval, as long as the other important symptoms or signs have not worsened on treatment.

3. Trial Populations

Based upon the evolution of the IBS diagnostic criteria, prospective IBS clinical trials should enroll patients who meet the subtype-specific Rome III IBS diagnostic criteria.[12] In addition, patients who enter the trial should have the clinical manifestations of IBS that will be assessed in

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[9] See reference number 28 in the References section at the end of the guidance.

[10] See reference numbers 28 and 29 in the References section at the end of the guidance.

[11] See reference number 30 in the References section at the end of the guidance.

[12] See reference number 25 in the References section at the end of the guidance.

the trial to define treatment response, and the manifestations should be present with sufficient intensity to make demonstration of a clinically meaningful improvement possible. In light of the components of the primary endpoints for IBS-C and IBS-D previously described, we recommend that trial entry criteria include the following:

IBS-C

- **Abdominal Pain Intensity:** weekly average of *worst daily (in past 24 hours) abdominal pain* score of $\geq$ 3.0 on a 0 to 10 point scale

  and

- **Stool Frequency:** fewer than three CSBMs per week

IBS-D

- **Abdominal Pain Intensity:** weekly average of *worst daily (in past 24 hours) abdominal pain* score of $\geq$ 3.0 on a 0 to 10 point scale

  and

- **Stool Consistency:** at least one stool with a consistency of Type 6 or Type 7 Bristol stool score (BSS) on at least 2 days per week

4. Efficacy Measures

Sponsors should choose a format for daily sign or symptom assessment (e.g., interactive voice response or personal digital assistant) so that patients can evaluate their IBS signs or symptoms on a daily basis throughout the trial. When assessing responses, sponsors should consider two distinct approaches: (1) examining the difference in average score (or average change from baseline score) between the treated and untreated groups; or (2) examining the difference in response rate in the treated and untreated groups, where the response is prospectively defined and represents an effect considered clinically meaningful. In many instances, an effective drug will have an effect on both measures.

5. Definition of a Responder

Definitions of a responder for use in analyses of the primary endpoint should be prospectively described in the protocol and statistical analysis plan. A patient should be categorized as an overall responder if the patient achieved the prespecified improvement in weekly or daily response for at least 50 percent of the weeks or days of treatment (e.g., 6/12 weeks or 42/84 days).

Our recommendations for how to define a weekly or daily response in each IBS setting is as follows:

IBS-C[13]

A patient is categorized as a *weekly responder* if the patient is a weekly responder in **both** pain intensity **and** stool frequency.

- An Abdominal Pain Intensity Weekly Responder is defined as a patient who experiences a decrease in the weekly average of worst abdominal pain in the past 24 hours score (measured daily) of at least 30 percent compared with baseline weekly average

- A Stool Frequency Weekly Responder is defined as a patient who experiences an increase of at least one CSBM per week from baseline

IBS-D

A patient is categorized as a *weekly responder* if the patient is a weekly responder in **both** pain intensity **and** stool consistency.

- An Abdominal Pain Intensity Weekly Responder is defined as a patient who experiences a decrease in the weekly average of *worst abdominal pain in the past 24 hours* score of at least 30 percent compared with baseline

- A Stool Consistency Weekly Responder is defined as a patient who experiences a 50 percent or greater reduction in the number of days per week with at least one stool that has a consistency of Type 6 or 7 compared with baseline

A patient is categorized as a *daily responder* if the patient is a responder in **both** pain intensity **and** stool consistency.

- An Abdominal Pain Intensity Daily Responder is defined as a patient who experiences a decrease in *worst abdominal pain in the past 24 hours* score of at least 30 percent compared with baseline

- A Stool Consistency Daily Responder is defined as a patient whose stool consistency (i.e., BSS) is less than 5 for all bowel movements on that day or no bowel movement

For IBS-D, either the weekly responder or daily responder definition may be acceptable. For drugs intended to target only one major IBS sign or symptom, based on their mechanism of action, we recommend the following responder definitions:

Abdominal pain in IBS-C
- An Abdominal Pain Intensity Weekly Responder is defined as a patient who experiences a decrease in the weekly average of worst abdominal pain in the past 24 hours score of at least 30 percent compared with baseline. Stool Frequency (for IBS-C) is unchanged or improved compared with baseline.

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[13] Because IBS-C patients do not have daily bowel movements, even though abdominal pain may occur more frequently, daily response criteria are not relevant to this patient population.

Abdominal pain in IBS-D
- An Abdominal Pain Intensity Weekly Responder is defined as a patient who experiences a decrease in the weekly average of worst abdominal pain in the past 24 hours score of at least 30 percent compared with baseline and the number of days per week with at least one stool with consistency of Type 6 or 7 that is the same as baseline or decreased and the number of stools of Type 6 or 7 on those days remains unchanged or decreased

  or

- An Abdominal Pain Intensity Daily Responder is defined as a patient who experiences a decrease in worst abdominal pain in the past 24 hours score of at least 30 percent compared with baseline and whose stool consistencies during the day are less than 5 for all bowel movements or no bowel movement

Constipation in IBS-C
- A Stool Frequency Responder is defined as a patient who experiences an increase of at least one CSBM per week from baseline, and abdominal pain is unchanged or improved compared with baseline

Diarrhea in IBS-D
- A Stool Consistency Responder is defined as a patient who experiences a 50 percent or greater reduction in the number of days with at least one stool that has a consistency of Type 6 or 7 compared with baseline, and abdominal pain is unchanged or improved in comparison with baseline

Because the responder definitions described in this guidance are not supported by adequate content validation, it is unclear if they represent clinically meaningful changes in abdominal pain and abnormal defecation for patients with IBS. The abdominal pain responder definition of a greater than or equal to 30 percent reduction in abdominal pain intensity compared with baseline is primarily based on published literature concerning other chronic pain conditions.[14] Therefore, we recommend conducting additional responder analyses that evaluate greater reductions in abdominal pain intensity with treatment (i.e., greater than or equal to 40 and/or 50 percent reduction in abdominal pain intensity compared with baseline). In addition, it would be useful to examine the cumulative distribution of several magnitudes of abdominal pain intensity reduction associated with treatment (e.g., 30 percent, 40 percent, 50 percent) as well as particular reductions (e.g., 100 percent pain intensity reduction) as secondary endpoints.

Although we do not recommend a patient rating of change as a primary endpoint, because a single general item cannot adequately capture the treatment effect on all of the clinically important signs and symptoms of IBS, it can be useful in defining a clinically meaningful change in another measure through an anchor-based approach (relating changes in scores to a measure that is different from the specific measure itself). Therefore, we recommend including patient ratings of change anchors as exploratory endpoints in conjunction with the endpoints included in this guidance. The global assessment should ask patients to evaluate only their current IBS

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[14] See reference number 31 in the References section at the end of the guidance.

status and not compare their current IBS signs and symptoms to another point in time, such as baseline status. Examples of such assessments include the following questions, which could be asked of patients on a weekly basis:

- "How would you rate your abdominal pain overall over the past 7 days?"

- "How would you rate your constipation (for IBS-C) or diarrhea (for IBS-D) overall over the past 7 days?"

- "How would you rate your IBS signs or symptoms overall over the past 7 days?"

Sponsors can consider Likert scale response options, such as: **2** = Significantly Relieved, **1** = Moderately Relieved, **0** = Unchanged, -**1** = Moderately Worse, and **-2** = Significantly Worse.

Table 2. Summary of Recommended Provisional Primary Endpoints,* Entry Criteria, and Responder Definition

Indication	Primary Endpoints	Entry Criteria	Responder Definition
IBS-C	Abdominal Pain Intensity AND Stool Frequency	**Abdominal Pain Intensity** Weekly average of *worst abdominal pain in past 24 hours* score of $\geq$ 3.0 on a 0 to 10 point scale AND **Stool Frequency** < 3 CSBMs per week	**Abdominal Pain Intensity** Decrease in weekly average of *worst abdominal pain in the past 24 hours* score of at least 30% compared with baseline AND **Stool Frequency** Increase of 1 or more CSBM per week compared with baseline
IBS-D	Abdominal Pain Intensity AND Stool Consistency	**Abdominal Pain Intensity** Weekly average of *worst abdominal pain in past 24 hours* score of $\geq$ 3.0 on a 0 to 10 point scale AND **Stool Consistency** At least 2 days per week with at least one stool that has a consistency of Type 6 or Type 7 BSS (see Figure 1 for details)	**Abdominal Pain Intensity** Weekly responder defined as: decrease in weekly average of *worst abdominal pain in past 24 hours* score of at least 30% compared with baseline Daily responder defined as: decrease in *worst abdominal pain in the past 24 hours* score of at least 30% compared with baseline AND **Stool Consistency** Weekly responder defined as: decrease at least 50% in the number of days per week with at least one stool that has a consistency of Type 6 or 7 compared with baseline Daily responder defined as: a patient whose stool consistency is less than 5 for all bowel movements on that day or no bowel movement

* Drugs may be designed to improve only one of the major signs or symptoms of IBS. For further detail, please refer to the discussion in Section IV of this guidance.

V. FUTURE DEVELOPMENT OF IBS PRO INSTRUMENTS

In October 2010, we published the draft guidance for industry *Qualification Process for Drug Development Tools*.[15] Drug development tools (DDTs) intended for potential use, over time, in multiple drug development programs include, but are not limited to, biomarkers and clinical outcome assessments including PRO instruments. FDA qualification is a conclusion that within the stated context of use, the results of assessment with a DDT can be relied upon to have a specific interpretation and application in drug development and regulatory decision-making.

The qualification process provides an efficient means for DDT development. Because qualification requires significant work, the formation of collaborative groups may lessen the resource burden upon any individual or company. One such collaborative group, the PRO Consortium, formed in 2008 at the Critical Path Institute, is a public-private partnership. The PRO Consortium is charged with the task of efficiently and collaboratively developing reliable, interpretable instruments that will be available in the public domain for all sponsors to use in medical product clinical trials. The collaboration includes members from the FDA, industry, academia, professional organizations, patient advocacy groups, and other governmental agencies. Additional information about the PRO Consortium can be found at http://www.c-path.org.

We are actively participating with the PRO Consortium and others in the consultation and advice stage of qualification for the development of PRO measures of the signs and symptoms of IBS-C and IBS-D. Once qualified, these IBS subtype-specific PRO measures will replace the provisional endpoints described in this guidance as the FDA's recommended measures of treatment benefit for use in IBS-C and IBS-D clinical trials.

VI. CONCLUSION

The provisional endpoints and trial design recommendations in this guidance are currently acceptable for use in the evaluation of drugs for the treatment of IBS-D and IBS-C. These recommendations will assist drug developers in developing treatments to address the needs of patients with IBS while the important work of developing well-defined and reliable PRO instruments for FDA qualification continues.

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[15] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA Drugs guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

REFERENCES

1. Mayer, EA, S Bradesi, L Chang et al., 2008, Functional GI Disorders: From Animal Models to Drug Development, Gut, 57:384-404.

2. Camilleri, M and NJ Talley, 2004, Pathophysiology as a Basis for Understanding Symptom Complexes and Therapeutic Targets, Neurogastroenterol Motil, 16:135-142.

3. Andresen, V, VM Montori, J Keller et al., 2008, Effects of 5-Hydroxytryptamine (Serotonin) Type 3 Antagonists on Symptom Relief and Constipation in Nonconstipated Irritable Bowel Syndrome: A Systematic Review and Meta-Analysis of Randomized Controlled Trials, Clin Gastroenterol Hepatol, 6:545-555.

4. Heaton, KW, J Radvan, H Cripps et al., 1992, Defecation Frequency and Timing, and Stool Form in the General Population: A Prospective Study, Gut, 33:818-824.

5. Horikawa, Y, H Mieno, M Inoue et al., 1999, Gastrointestinal Motility in Patients With Irritable Bowel Syndrome Studied by Using Radiopaque Markers, Scand J Gastroenterol, 34:1190-1195.

6. Sadik, R, PO Stotzer, M Simrén et al., 2008, Gastrointestinal Transit Abnormalities Are Frequently Detected in Patients With Unexplained GI Symptoms at a Tertiary Centre, Neurogastroenterol Motil, 20:197-205.

7. Gorard, DA, GW Libby, MJ Farthing, 1995, Effect of a Tricyclic Antidepressant on Small Intestinal Motility in Health and Diarrhea Predominant Irritable Bowel Syndrome, Dig Dis Sci, 40:86-95.

8. Camilleri, M and L Chang, 2008, Challenges to the Therapeutic Pipeline for Irritable Bowel Syndrome: End Points and Regulatory Hurdles, Gastroenterology, 135:1877-1891.

9. Jones, RH, G Holtmann, L Rodrigo et al., 1999, Alosetron Relieves Pain and Improves Bowel Function Compared With Mebeverine in Female Non-Constipated IBS Patients, Aliment Pharmacol Ther, 13:1419-1427.

10. Camilleri, M, EA Mayer, DA Drossman et al.,1999, Improvement in Pain and Bowel Function in Female IBS With Alosetron, A 5-HT3 Receptor Antagonist, Aliment Pharmacol Ther, 13:1149-1159.

11. Camilleri, M, AR Northcutt, S Kong et al., 2000, Efficacy and Safety of Alosetron in Women With IBS: A Randomised, Placebo-Controlled Trial, Lancet, 355:1035-1040.

12. Camilleri, M, WY Chey, EA Mayer et al., 2001, A Randomized Controlled Clinical Trial of Serotonin Type 3 Receptor Antagonist Alosetron in Women With Diarrhea-Predominant IBS, Arch Intern Med, 161:1733-1740.

13. Chey, WD, WY Chey, AT Heath et al., 2004, Long-Term Safety and Efficacy of Alosetron in Women With Severe Diarrhea-Predominant IBS, Am J Gastroenterol, 99:2195-2203.

14. Chang, L, VZ Ameen, GE Dukes et al., 2005, A Dose-Ranging, Phase II Study of the Efficacy and Safety of Alosetron in Men With Diarrhea Predominant IBS, Am J Gastroenterol, 100:115-123.

15. Kellow, J, OY Lee, FY Change et al., 2003, An Asia-Pacific, Double-Blind, Placebo-Controlled, Randomized Study to Evaluate the Efficacy, Safety, and Tolerability of Tegaserod in Patients With IBS, Gut, 52:671-676.

16. Nyhlin, H, C Bang, J Elsborg et al., 2004, A Double-Blind, Placebo Controlled, Randomized Study to Evaluate the Efficacy, Safety and Tolerability of Tegaserod in Patients With IBS, Scand J Gastroenterol, 39:119-126.

17. Muller-Lissner, S, G Holtmann, P Rueegg et al., 2005, Tegaserod Is Effective in the Initial and Re-Treatment of IBS With Constipation, Aliment Pharmacol Ther, 21:11-20.

18. Tack, J, S Muller-Lissner, P Bytzer et al., 2005, A Randomized Controlled Trial Assessing the Efficacy and Safety of Repeated Tegaserod Therapy in Women With Irritable Bowel Syndrome With Constipation, Gut, 54:1707-1713.

19. Fried, M, C Beglinger, N Gilgen Bobalj et al., 2005, Tegaserod Is Safe, Well-Tolerated and Effective in the Treatment of Patients With Non-Diarrhea IBS, Eur J Gastroenterol Hepatol, 17:421-427.

20. Novick, J, P Miner, R Krause et al., 2002, A Randomized, Double-Blind, Placebo-Controlled Trial of Tegaserod in Female Patients Suffering From IBS-C, Aliment Pharmacol Ther, 16:1877-1888.

21. Muller-Lissner, SA, I Fumagalli, KD Bardhan et al., 2001, Tegaserod, A 5-HT4 Receptor Partial Agonist, Relieves Symptoms in IBS Patients With Abdominal Pain, Bloating, and Constipation, Aliment Pharmacol Ther, 15:1655-1666.

22. Muller-Lissner, S, G Koch, NJ Talley et al., 2004, Subject's Global Assessment of Relief: An Appropriate Method to Assess the Impact of Treatment on IBS-Related Symptoms in Clinical Trials, J Clin Epidemiol, 56:310-316.

23. Drossman, DA, W Chey, R Panas et al., 2007, Lubiprostone Significantly Improves Symptom Relief Rates in Adults With IBS, Gastroenterology, 132:2586-2587.

24. Longstreth, GF, WG Thompson, WD Chey, LA Houghton, F Mearin, RC Spiller, 2006, Functional Bowel Disorders, Gastroenterology, Apr;130(5):1480-91.

25. Rome Endpoints and Outcomes Conference 2009: http://www.romecriteria.org/meetings_events/endout_conf_program.cfm#

26. Talley, NJ, 2009, Green Light From the FDA for New Drug Development in Irritable Bowel Syndrome and Functional Dyspepsia, Am J Gastroenterol, 104:1339-1341.

27. Lewis, SJ and KW Heaton, 1997, Stool Form Scale as a Useful Guide to Intestinal Transit Time, Scand. J. Gastroenterol, 32(9):920-4.

28. Turk, DC, RH Dworkin et al., 2003, Core Outcome Domains for Chronic Pain Clinical Trials: IMMPACT Recommendations, Pain, 106:337-345.

29. Cleeland, CS and KM Ryan, 1994, Pain Assessment: Global Use of the Brief Pain Inventory, Ann Academic Medicine, 23(2):129-138.

30. Dworkin, RH et al., 2005, Core Outcome Measures for Chronic Pain Clinical Trials: IMMPACT Recommendations, Pain, 113:9-19.

31. Dworkin, RH et al., 2008, Interpreting the Clinical Importance of Treatment Outcomes in Chronic Pain Clinical Trials: IMMPACT Recommendations, Pain, 9(2):105-121.