Introduction

For the 2009 FDA guidance on patient-reported outcomes (PROs), the development and selection of PRO clinical trial endpoints must be based on:

- Assessment of treatment responses in chronic constipation (CC) clinical trials
- Historically focused on bowel symptoms
- Qualitative evidence from patients to identify all symptoms important to the CC patient population so that they can be assessed in clinical trials

Per the 2009 FDA guidance on patient-reported outcomes (PROs), the development and selection of PRO clinical trial endpoints must be based on:

- Assessment of treatment responses in chronic constipation (CC) clinical trials
- Historically focused on bowel symptoms
- Qualitative evidence from patients to identify all symptoms important to the CC patient population so that they can be assessed in clinical trials

Objectives

- Identify a comprehensive set of symptoms and optimal terminology to assess these symptoms in CC clinical trials

- Ascertain concepts and provide supportive content validity of the corresponding set of endpoints in accordance with the FDA PRO guidance

Methods

- Two iterative sets of interviews were conducted with CC patients in Raleigh, North Carolina (Round 1) and Las Vegas, Nevada (Round 2)

- Participants were referred by local gastroenterologists and not modified from their original criteria for CC

- In accordance with the FDA PRO guidance, recruited patients were similar (clinically and demographically) to participants in ongoing and planned CC clinical trials (Table 1)

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Results

Spontaneous Symptoms Reports

- Participants reported 56 potentially distinct concepts:

  - 12 bowel symptoms and 21 abdominal symptoms (Table 2)

  - 25 additional physical symptoms and mental or emotional issues (Table 3)

  - Participants generally described a similar constellation of bowel and abdominal symptoms, with variability in their choice of descriptors

A list of bowel and abdominal symptom spontaneously reported by multiple participants is provided in Table 2

Additional rating and ranking methods were used to narrow the full list of symptoms to those of greatest importance to the patients for evaluation:

- Participants in both sets of interviews were probed to identify their most bothersome CC symptoms

- Round 1 participants had importance of selected bowel and abdominal symptoms

- Round 2 participants identified the 5 symptoms they would most like to improve

Most bothersome symptoms

- Participants identified certain symptoms (and abdominal symptoms as their most bothersome symptoms) with CC-specific with frequency

- Rectal pain, bloating, abdominal pain, and rectal pain

- Participants reported rectal pain, hemorrhoids, and rectal bleeding simultaneously as I get so big, makes me feel nauseous, hot and why in the world. All the symptoms come at the longer (gap without going)

- “Just that I don’t like feeling bloated. It’s just really, really uncomfortably. Not really sure what do about it, because it gets better. If I do go to the bathroom (bathroom) don’t you know, just I feel like I’ve gone enough”

- “The pain in my lower abdomen and the pressure on my rectum”

- “I would say the straining and not really being able to go, like being able to have one hard stool and then that was it… getting a hemorrhoid from it, that’s really bothersome. Does, I guess the straining and ‘big’ one”

Rating Exercise – Round 1

- When asked to rate the 7 symptoms shown in Table 4, Round 1 participants generally rated both bowel and abdominal symptoms as very important

Table 4. Frequency of Importance Ratings* (Round 1; N = 15)

<table>
<thead>
<tr>
<th>Symptom</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rectal pain</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>93.3%</td>
<td>83.3%</td>
</tr>
<tr>
<td>Bloating</td>
<td>80%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>86.6%</td>
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<tr>
<td>Rectal bleeding</td>
<td>93.3%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>86.6%</td>
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<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>86.6%</td>
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<tr>
<td>Rectal bleeding</td>
<td>73.3%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
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<tr>
<td>Rectal bleeding</td>
<td>66.6%</td>
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<tbody>
<tr>
<td>Abdominal symptoms</td>
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<td>100%</td>
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</tr>
<tr>
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<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>86.6%</td>
</tr>
<tr>
<td>Abdominal discomfort</td>
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<td>100%</td>
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<td>100%</td>
<td>86.6%</td>
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<tr>
<td>Abdominal cramping</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
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<tr>
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<td>100%</td>
<td>100%</td>
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<td>100%</td>
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<tr>
<td>Abdominal discomfort</td>
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<tr>
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Ranking Exercise – Round 2

- Figure 1 summarizes the top 5 symptoms identified by Round 2 participants as those they wished to improve with treatment

- Most of the 13 participants included both bowel and abdominal symptoms in their list

Summary and Conclusions

- This study reports symptoms spontaneously identified by CC patients through open-ended interviews using the methods outlined in the FDA PRO guideline

- Within and across the two separate rounds of interviews, participants consistently reported the importance of bowel symptoms, abdominal symptoms, bloating, abdominal pain, and rectal pain

- A proposed conceptual framework depicting the relationships among the core set of bowel and abdominal symptoms is shown in Figure 2

Reference


Supported by Ironwood Pharmaceuticals, Inc. and Forest Laboratories, Inc.

May 15-19, 2010; Atlanta, GA


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Health Outcomes and Economic Evaluation Research Meeting

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