# What Symptoms Drive Global Symptom Improvement with Lubiprostone in Patients with Irritable Bowel Syndrome and Constipation: Data from Two Multicenter, Randomized, Placebo-controlled Trials

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# American Gastroenterological Association Disclosure

- Disclosures have been evaluated for potential commercial bias and, if identified, conflicts of interest have been resolved. These authors have disclosed the following financial or other relationships:
  - William D. Chey
    - Investigator for Sucampo Pharmaceuticals, Inc.
    - Consultant for Takeda Pharmaceuticals North America, Inc.
  - Douglas A. Drossman
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    - Consultant for Takeda Pharmaceuticals North America, Inc.
  - Charles Scott
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  - Raymond Panas
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  - Ryuji Ueno
    - Employee and shareholder of Sucampo Pharmaceuticals, Inc.

Research supported by Sucampo Pharmaceuticals, Inc., and Takeda Pharmaceutical Company, Ltd.

# Background

- Irritable Bowel Syndrome (IBS) is a common condition in which patients experience abdominal pain/discomfort with altered bowel habits
- Lubiprostone is an orally active prostone that locally and selectively activates type-2 chloride channels[1]
  - Enhances intestinal fluid secretion without altering serum electrolyte levels[2]
  - Stimulates recovery of mucosal barrier function in animal models, suggesting a possible mechanism for the clinical improvement observed in patients on this drug as patients with IBS may exhibit abnormal gut permeability and an associated intestinal inflammatory response.[3,4]
  - Phase III randomized, placebo controlled trials reported benefit for global symptoms in patients with IBS-C[5]
  - Lubiprostone, a selective activator of type-2 chloride channels (CIC-2), is approved for the treatment of chronic idiopathic constipation in adults and for the treatment of IBS-C in adult women.


1. Cuppoletti J, et al. *Am J Physiol Cell Physiol.* 2004;287:C1173-C1183.
2. Ueno R, et al. *Gastroenterology.* 2004;126(4 Suppl 2):A-298. Abstract M1109.
3. Moeser AJ, et al. *Am J Physiol.* 2007;292(2):G647-G656.
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5. Drossman D, et al. *Gastroenterology.* 2007;132(7):2586-2587.

# Study Aims

- To understand which individual symptoms drive global response to lubiprostone in patients with IBS-C
- To determine the correlation between individual IBS symptoms in IBS-C patients who respond to lubiprostone

# Responder Analysis--Methodology

- **Responder data from 2 pivotal phase 3 lubiprostone trials in IBS-C was evaluated in a post-hoc analysis:**
  - Protocol SPI/0211SIB-0431, “A 12-Week, Multicenter, Double-Blind, Randomized Efficacy and Safety Study of Lubiprostone for the Treatment of Constipation-Predominant Irritable Bowel Syndrome”
  - Protocol SPI/0211SIB-0432, “A 12-Week, Multicenter, Double-Blind, Randomized Efficacy and Safety Study of Lubiprostone in Subjects with Constipation-Predominant Irritable Bowel Syndrome”

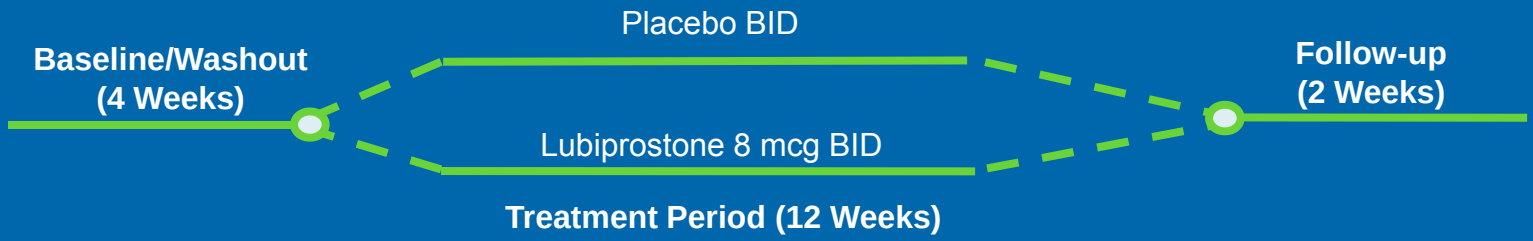
# Phase 3 Study Designs and Objectives

## Study 0431

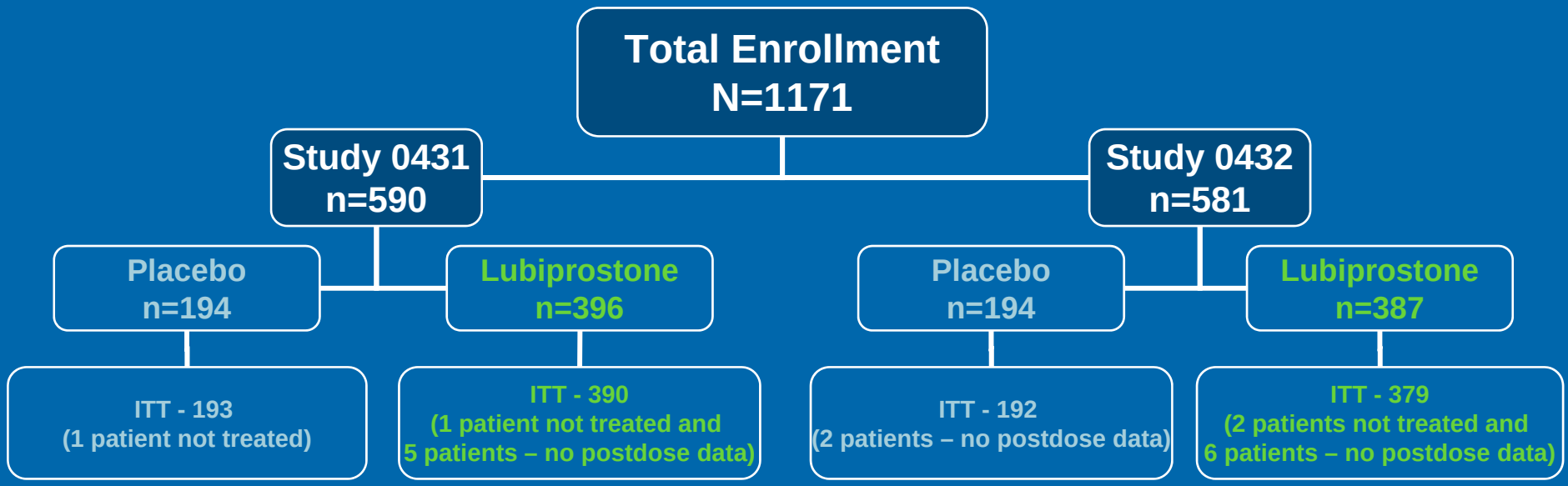
**N=590 Sites=65**


## Study 0432

**N=581 Sites=65**



# Study Populations




- Completion Rate – 73.9%

Discontinuation
n=55/194 (28.4%)
Adverse Event - 4.6%
Lack of Efficacy - 4.1%
Lost to Follow-up - 2.1%
Withdrew Consent - 14.4%
Noncompliance - 1.5%
Other - 1.5%

Discontinuation
n=99/396 (25.0%)
Adverse Event - 5.1%
Lack of Efficacy - 2.5%
Lost to Follow-up - 2.0%
Withdrew Consent - 9.8%
Noncompliance - 3.3%
Other - 2.3%

- Completion Rate – 78.1%

Discontinuation
n=43/194 (22.2%)
Adverse Event - 7.7%
Lack of Efficacy - 4.1%
Lost to Follow-up - 3.1%
Withdrew Consent - 5.2%
Noncompliance - 1.5%
Other - 0.5%

Discontinuation
n=84/387 (21.7%)
Adverse Event - 4.7%
Lack of Efficacy - 4.7%
Lost to Follow-up - 1.6%
Withdrew Consent - 6.5%
Noncompliance - 2.1%
Other - 2.3%

ITT – Intent-to-Treat Population

# Demographics

| | Lubiprostone | Placebo | Total* (n=1154) |
|---|---|---|---|
| **Age – Years** *Mean (range)* | **46.1 (19 - 83)** | **47.7 (18 - 85)** | **46.6 (18 - 85)** |
| **Gender** *Female* | **90.8%** | **93.2%** | **91.6%** |
| **Race** *Caucasian* | **77.4%** | **77.4%** | **77.4%** |

*Demographics presented for the intent-to-treat (ITT) population, which includes all patients who took at least one dose of study medication and completed at least one post-baseline efficacy assessment

# Rigorous Responder Definition

- **Responder Question:**

  **"How would you rate your relief of IBS symptoms (abdominal discomfort/pain, bowel habits, and other IBS symptoms) over the past week compared to how you felt before you entered the study?"**

  **7-point balanced scale:**
  **Significantly relieved**
  **Moderately relieved**
  **Somewhat relieved**
  **No change**
  **Somewhat worse**
  **Moderately worse**
  **Significantly worse**

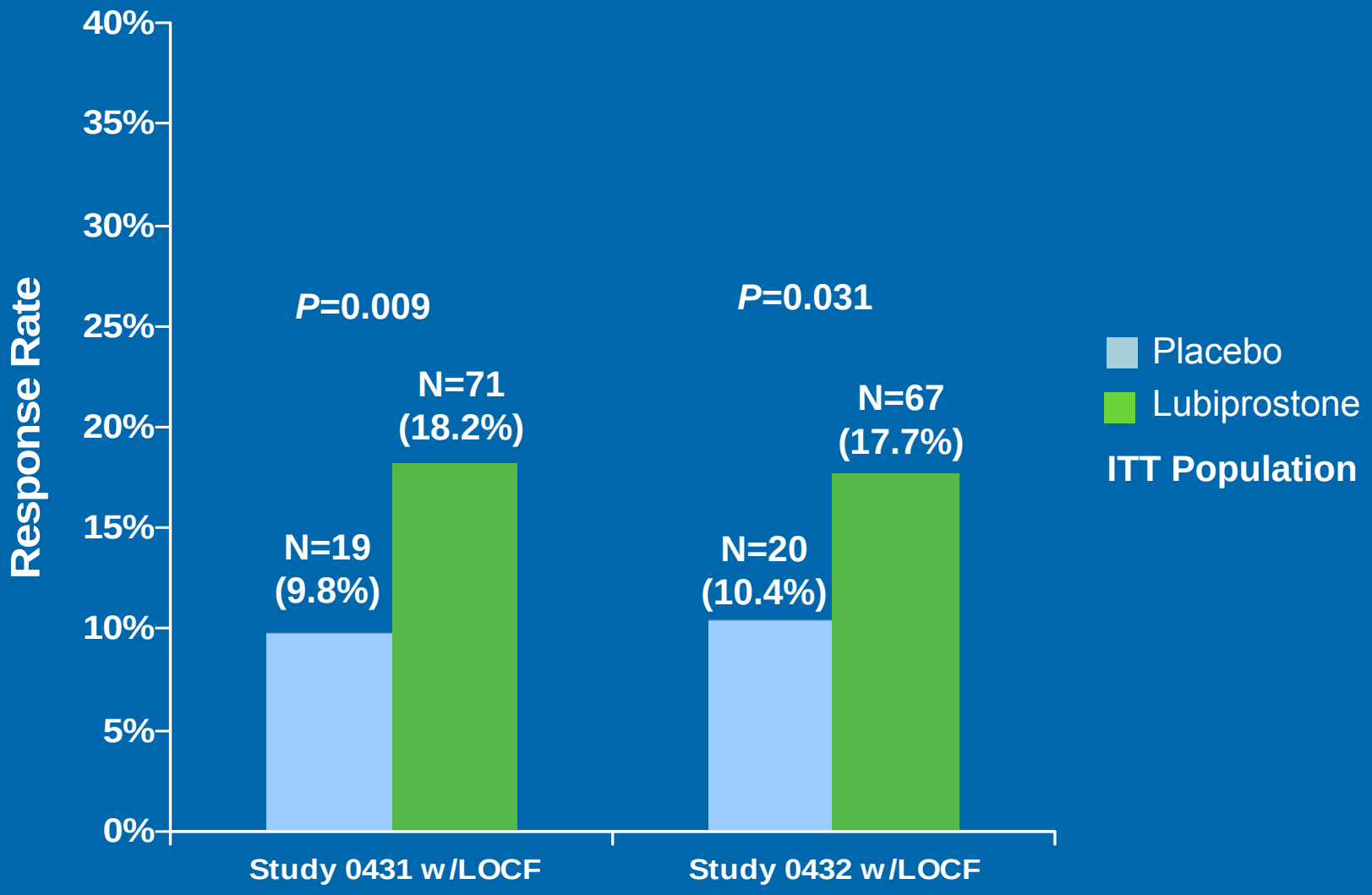
- **Monthly responder:** **A response of "moderately relieved" or better in 4 out of 4 weeks**

  **Or**

  **A response of "significantly relieved" in 2 out of 4 weeks**

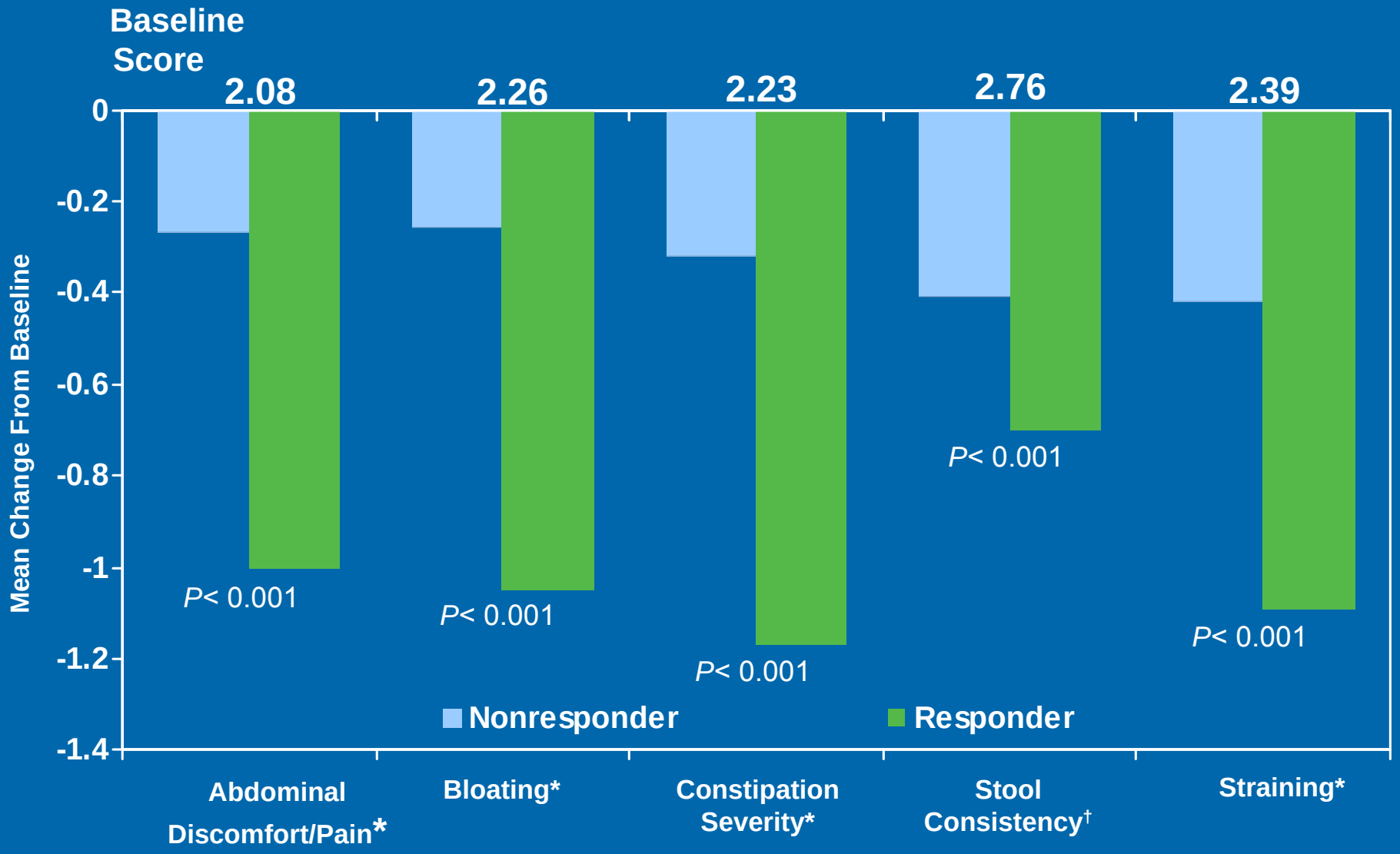
- **Overall responder:** **A monthly responder for at least 2 out of the 3 months of the trial**

# Overall Responder Rate




- "Monthly Responder" for ≥ 2/3 months during treatment

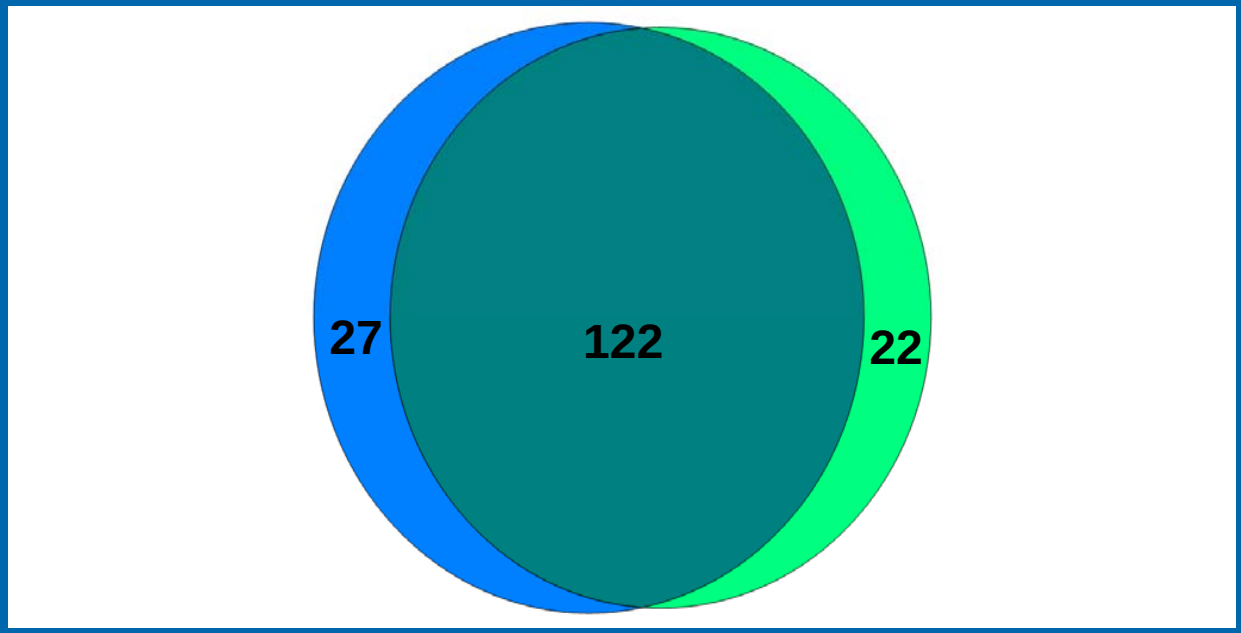
# Lubiprostone Symptom Change: Responder vs Nonresponder




*0 (absent), 1 (mild), 2 (moderate), 3 (severe), 4 (very severe)

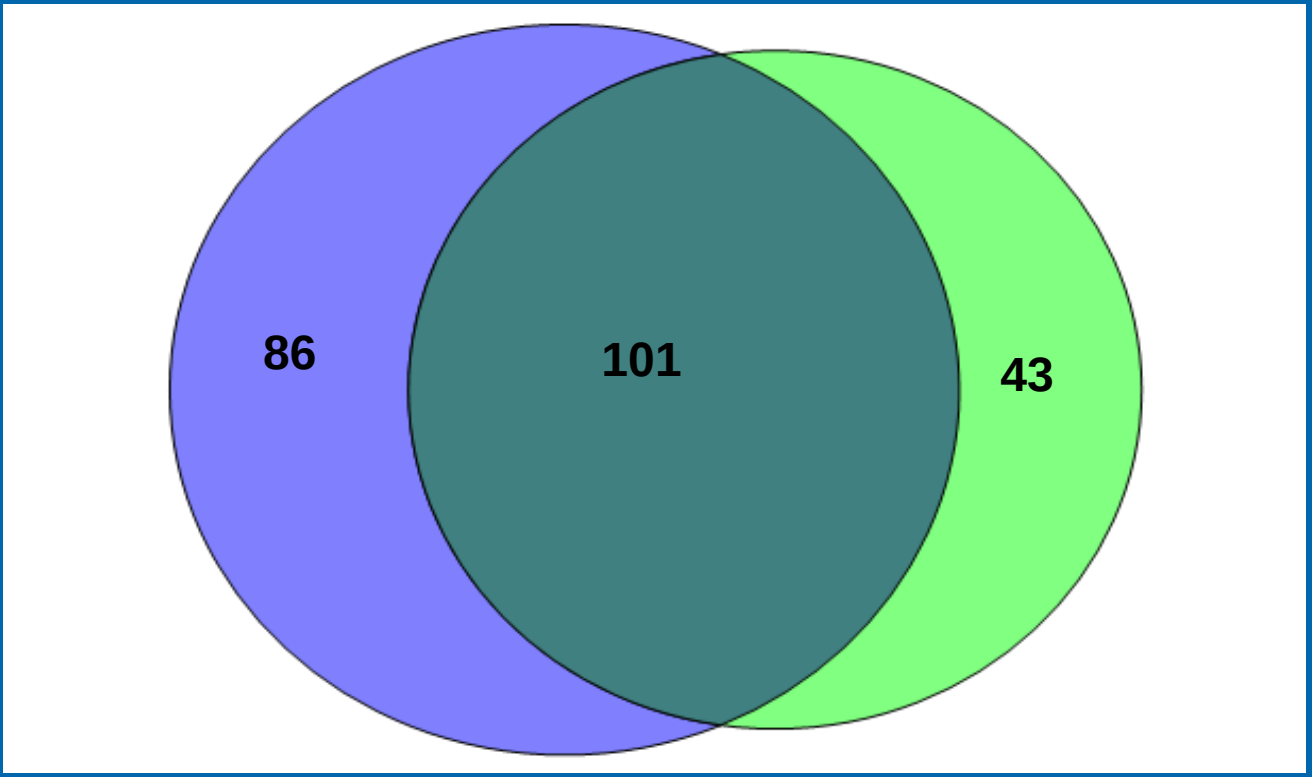
†0 (very loose [watery]), 1 (loose), **2 (normal),** 3 (hard), 4 (very hard [little balls])

# Correlation Between ≥1 Point Improvement in Pain (Green) and ≥1 Point Improvement in Bloating (Blue) at Week 12 with Lubiprostone




- 122/149 (82%) with an improvement in bloating reported an improvement in pain
- 122/144 (85%) with an improvement in pain reported an improvement in bloating

# Correlation Between Improvements in Pain (Green) and Straining (Purple) at Week 12 with Lubiprostone




- 101/187 (54%) with an improvement in straining reported an improvement in pain
- 101/144 (70%) with an improvement in pain reported an improvement in straining

# Conclusions

- Lubiprostone led to a nearly two-fold increase in the likelihood of achieving improvement in global IBS symptoms
- Patients who met the global responder criteria experienced improvements in multiple IBS symptoms
  - No single symptom drove global IBS response
- Improvements in pain and bloating were highly correlated by week 12
- Improvements in pain and straining were less likely to be correlated