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# The Novel Serotonin Synthesis Inhibitor (SSI), LX1031, Significantly Improves Overall Symptoms in Irritable Bowel Syndrome (IBS)

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# Author Disclosures

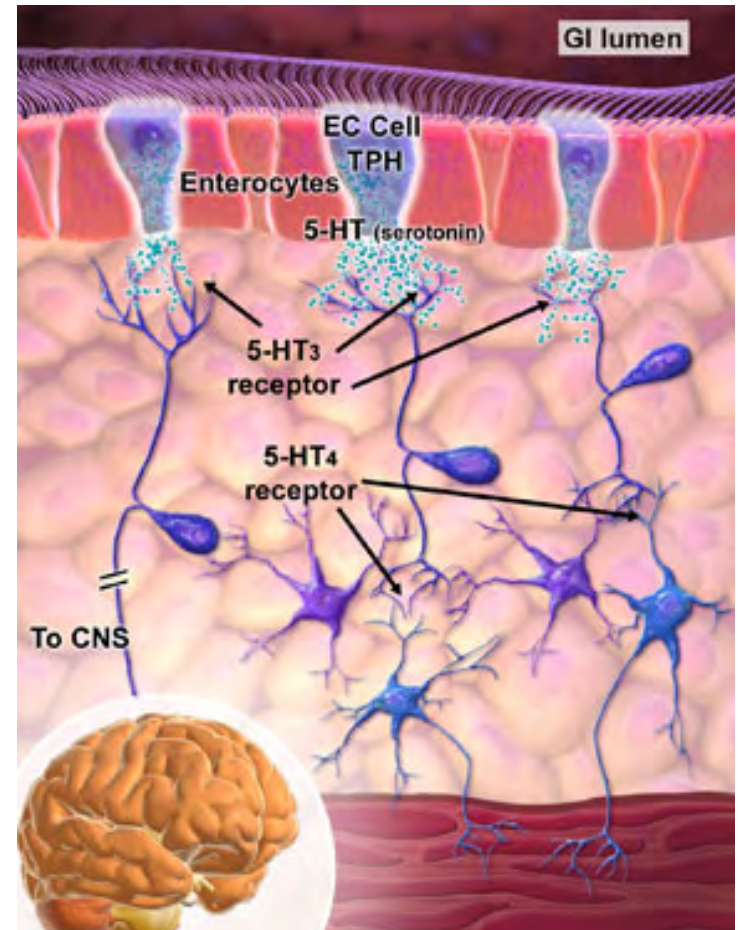
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All authors are employees of and have received stock options and/or other equity compensation from Lexicon Pharmaceuticals, Inc.

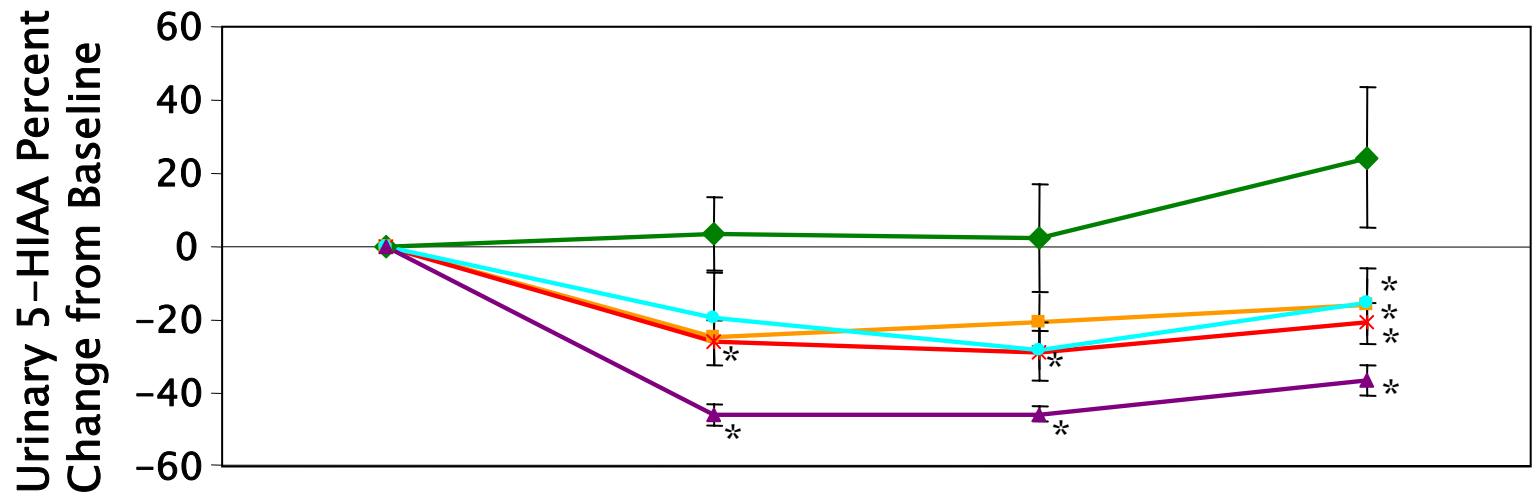
# LX1031: A First-in-Class Oral Serotonin Synthesis Inhibitor (SSI) for IBS

- Serotonin regulates GI function
  - IBS therapies target 5-HT receptors
- Tryptophan hydroxylase (TPH)–rate limiting enzyme in serotonin production
- LX1031:
  - Orally active
  - Local inhibitor of GI TPH
  - Does not cross the blood–brain barrier



# Significant Reductions in 24-hour urinary 5-HIAA Observed in Phase 1b Multiple-Dose Study

## LX1031 14-Day Study in 40 Normal Volunteers



	Baseline	Day 5	Day 10	Day 14
◆ Placebo	0	3.45	2.35	24.21
■ 250 mg QID	0	-24.84*	-20.66	-15.86*
✱ 500 mg QID	0	-26.17*	-28.64*	-20.69*
● 750 mg QID	0	-19.68	-28.30*	-15.00*
▲ 1000 mg QID	0	-45.64*	-45.63*	-36.59*

\*  $P < 0.050$

# LX1031 Phase 2 Study Hypothesis

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Inhibition of GI TPH by LX1031 is predicted to:

- Reduce serotonin production
  - Measured as metabolite—urinary 5-HIAA
- Benefit patients with IBS
- Correlate with urinary 5-HIAA reduction

# LX1031 in Non-Constipating IBS Patients

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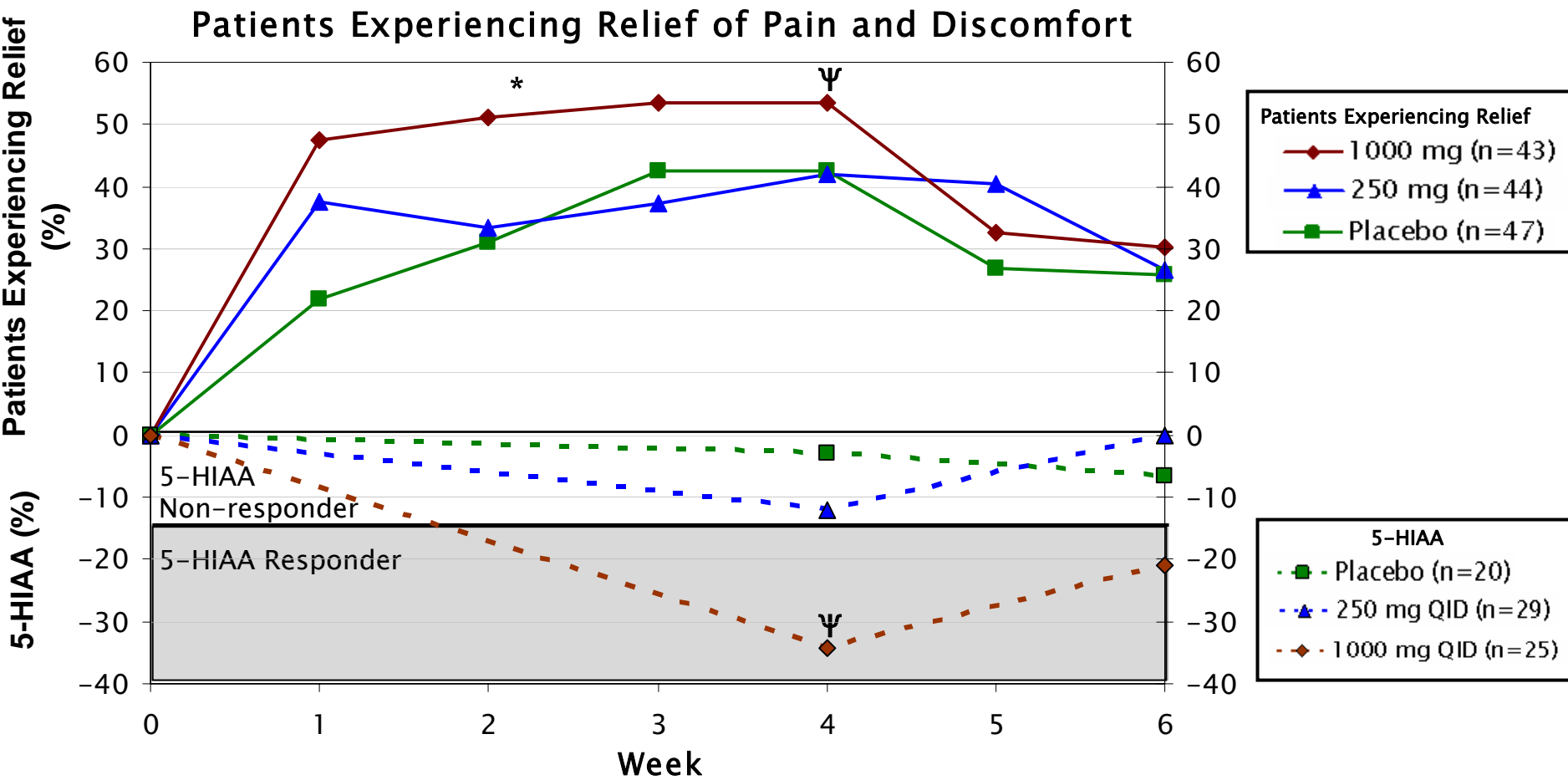
- Randomized, double-blind, placebo-controlled trial
  - Three arms 28 day treatment period:
    - Placebo (n=47)
    - LX1031 250 mg QID (n=44)
    - LX1031 1000 mg QID (n=43)
  - 2 week run-in period
  - 2 week follow-up period
- Patients
  - Average age: 48.1 years (range 21–68 years)
  - 16% Males, 84% Females
  - 23.9% IBS-Mixed
  - 76.1% IBS-Diarrhea
- 24-hour urinary 5-HIAA (n=74)
  - Baseline
  - Week 4
  - 2 week follow up

# LX1031 Well Tolerated With Favorable Safety Profile; No Dose-Dependent Toxicities Observed

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- Adverse Events (AEs)
  - Mild, self-limited and equally distributed overall
  - More frequent than placebo:
    - Nausea, diarrhea, dyspepsia, vomiting and headache
  - One serious adverse event unrelated to study drug
- 13 discontinuations
  - 7 due to AEs
    - Placebo (n=1), low dose (n=4), high dose (n=2)

# Reduction in Urinary 5-HIAA Correlates with Adequate Relief of Pain and Discomfort



**Median Percent Change from Baseline in Urinary 5-HIAA**

\* AUC analysis 1000 mg QID vs. Placebo p = 0.046

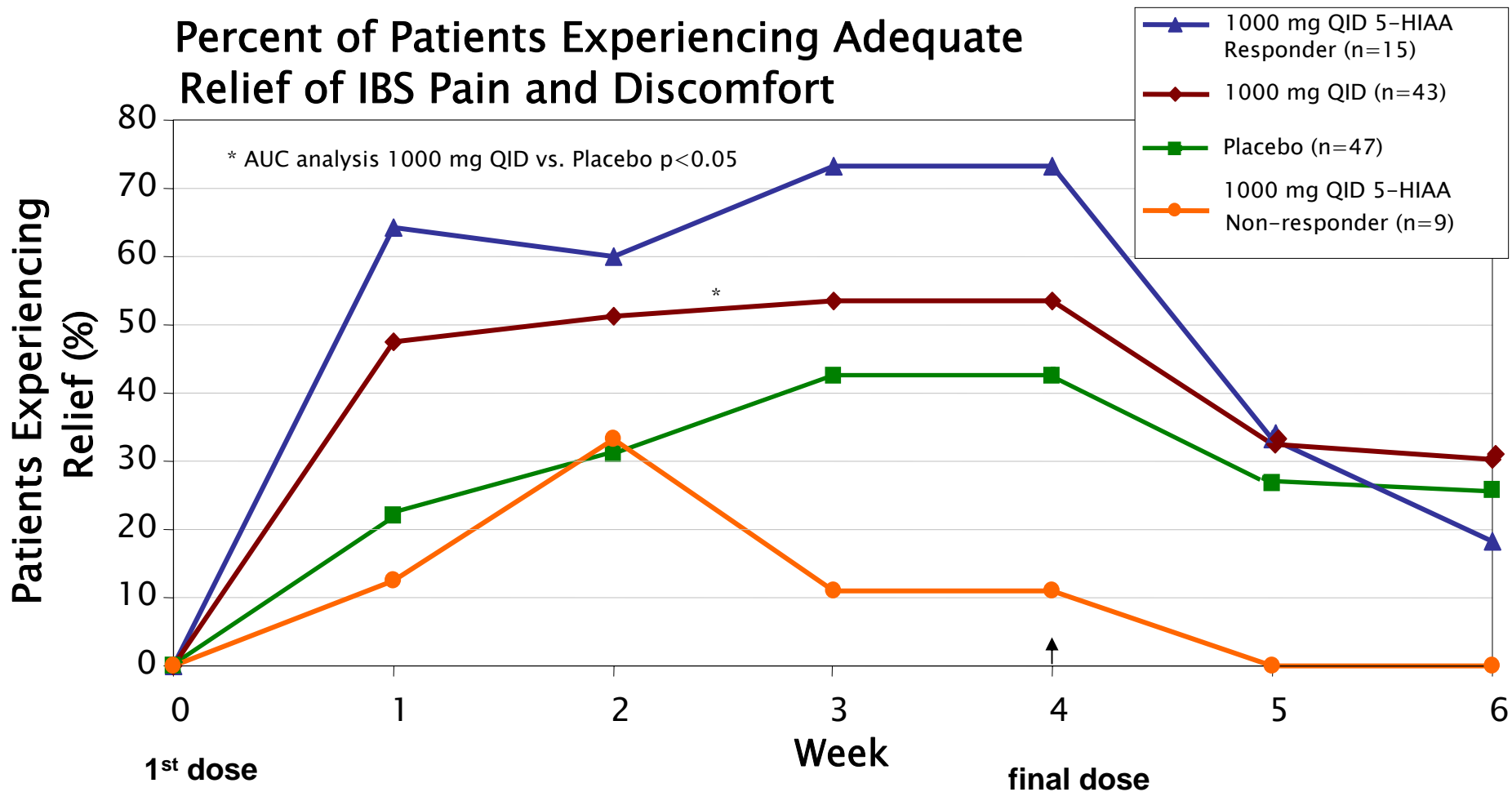
$\Psi$  correlation p = 0.027

# Clinical Response and Biomarker Response: 5-HIAA Reduction At Week 4

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- Two groups of patients defined by biomarker response
  - 5-HIAA biomarker responder
    - $\geq 15\%$  reduction in 5-HIAA
  - 5-HIAA biomarker non-responder
    - $< 15\%$  reduction in 5-HIAA

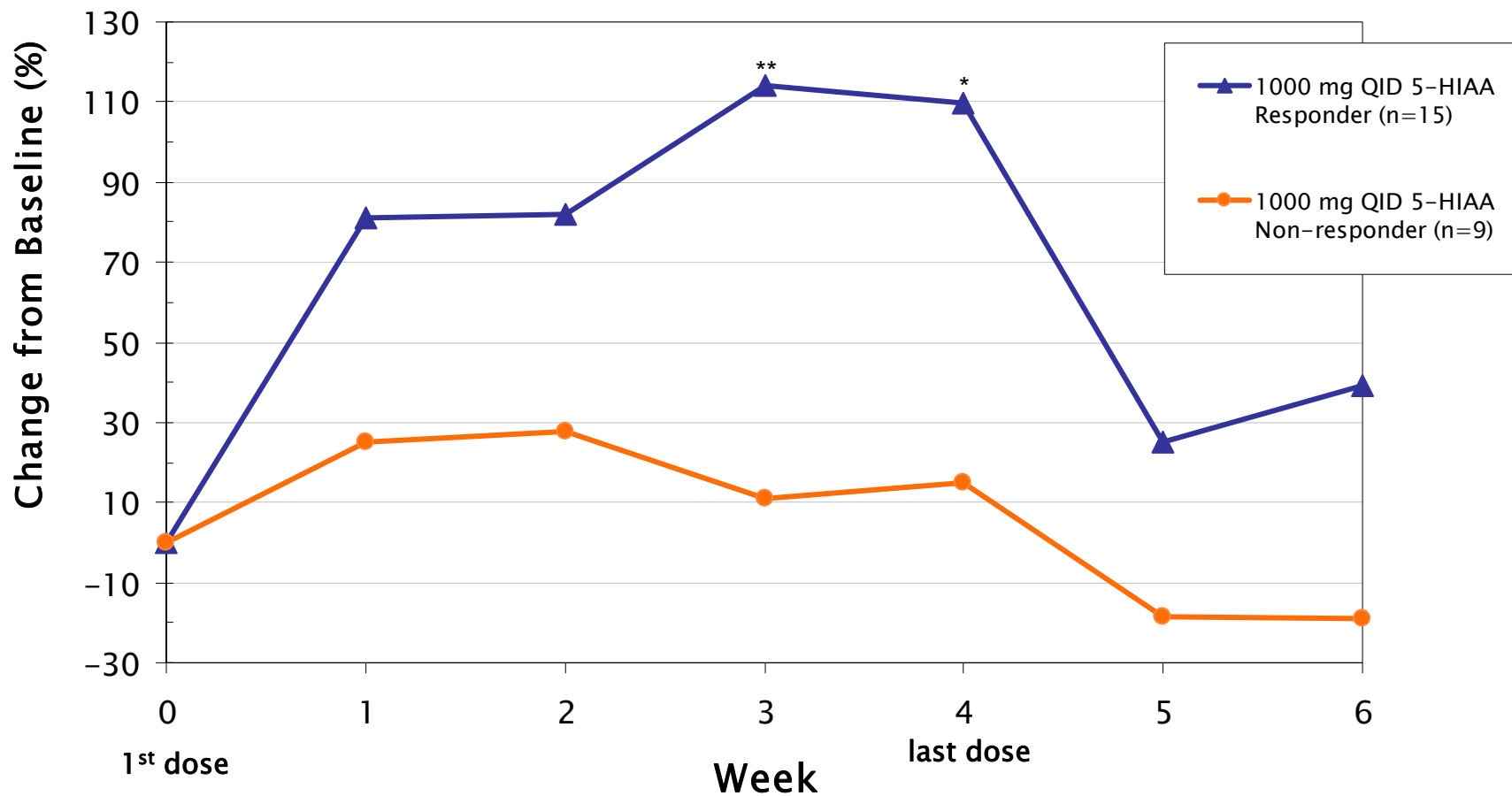
# High Dose 5-HIAA Biomarker Responders Show Enhanced Improvement in Global Outcome





# High-Dose Biomarker Responder Shows Effect in IBS-GAI Scale Assessment of Symptom Response

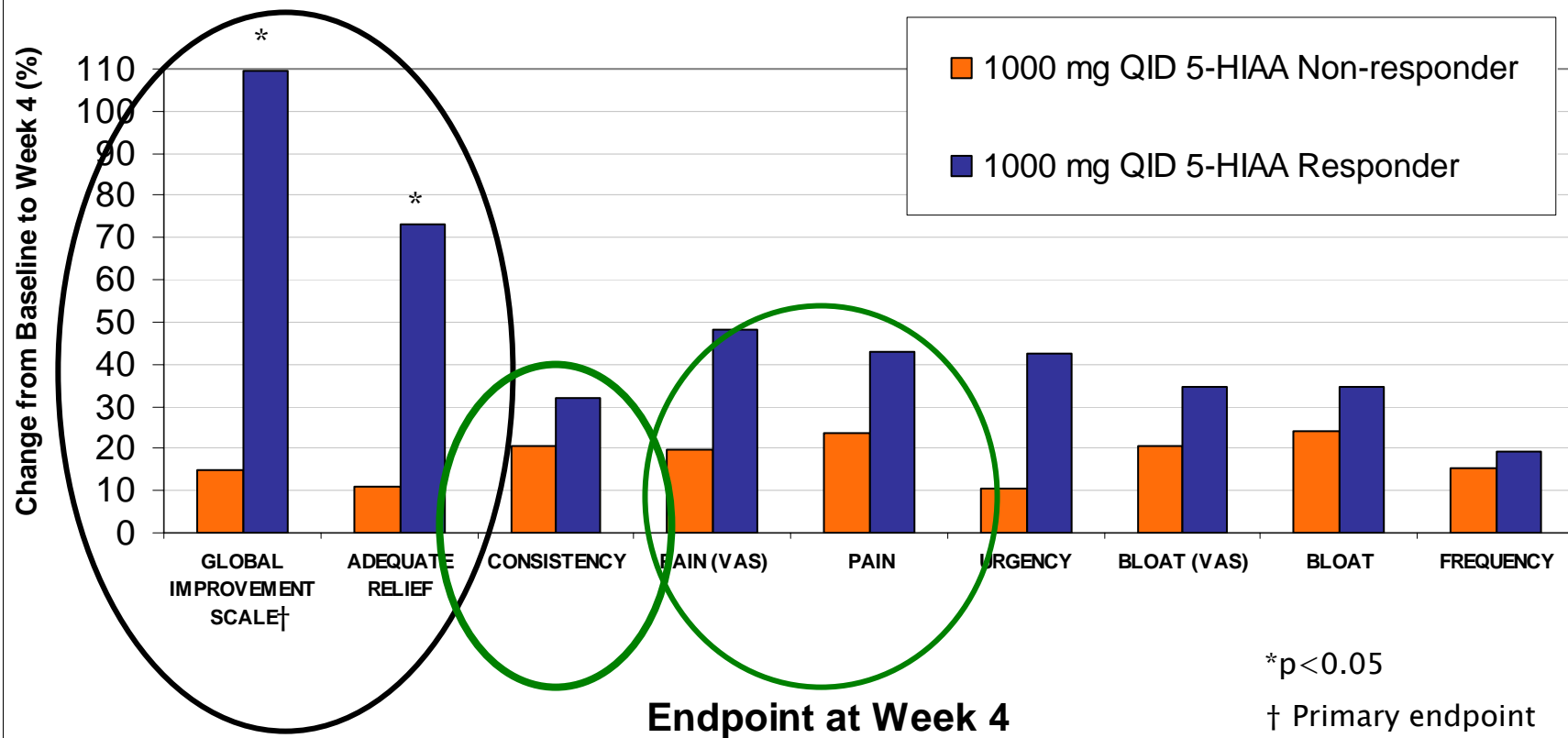
Percent Change from Baseline in Global Improvement Scale (IBS-GAI)



\* P<0.05 Responder vs. Non-responder at Week 4  
\*\*P<0.01 Responder vs. Non-responder at Week 3

# High-Dose 5-HIAA Biomarker Response Corresponds With Clinical Benefit in Multiple Parameters

Percent Improvement from Baseline to Week 4 in Efficacy Endpoints  
1000 mg Sub-study Group



# LX1031, a Novel SSI, Demonstrates Clinical Benefit in Patients with Non-Constipating IBS

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- LX1031 was well tolerated
- Benefits in high dose LX1031 arm:
  - Rapid, durable improvement in global assessment
  - Improved stool consistency
- 5-HIAA biomarker: a potential guide to IBS therapy
  - 5-HIAA reduction correlates to improvements in global assessment
  - High dose 5-HIAA biomarker responders exhibit enhanced clinical benefits across multiple endpoints