

LX1032: A Novel Approach For Managing Gastrointestinal Symptoms In Carcinoid Syndrome

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Philip M. Brown, M.D., J.D.
Senior Vice President, Clinical Development
Lexicon Pharmaceuticals, Inc.

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- All authors are full time employees of Lexicon Pharmaceuticals
 - P. Brown, M.D., J.D.
 - C. Pappas, M.D., J.D.
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 - Q. Liu, Ph.D.
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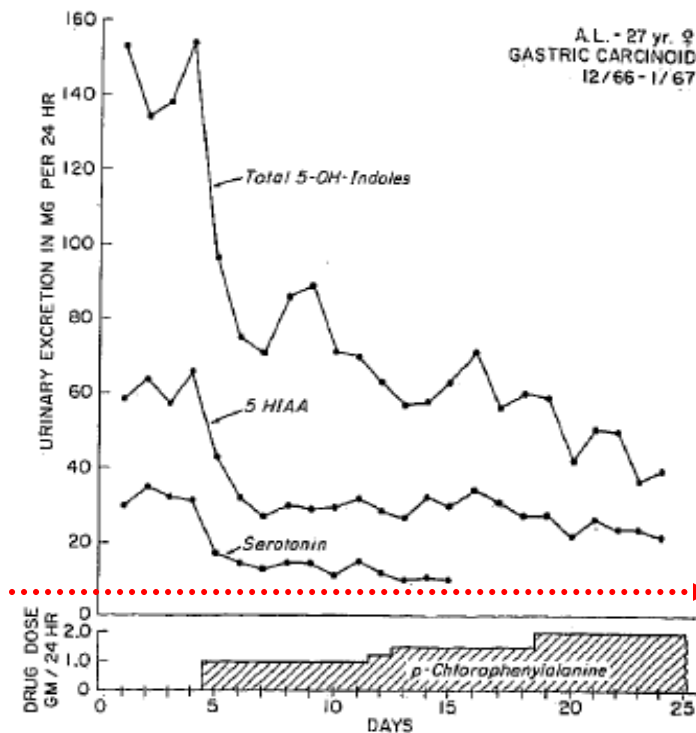
Serotonin is a Key Regulator of Gastrointestinal Physiology

- Serotonin (5-HT) plays a critical role in regulating several physiologic processes of the GI tract, including secretion, sensation, and motility
- Elevated 5-HT is a hallmark of carcinoid tumor
- In advanced tumors, morbidity and mortality relate as much to secretion of 5-HT and peptide hormones as to local and distant spread
- Common morbidity associated with carcinoid syndrome such as diarrhea, abdominal pain, cramping, as well as longer term disease sequelae such as fibrosis may be reduced through reduction in peripheral 5-HT production
- LX1032 is an orally bioavailable small molecule designed to inhibit peripheral 5-HT synthesis



Inhibition of Serotonin Synthesis by Para-chlorophenylalanine in Patients with the Carcinoid Syndrome

K. Engelman, M.D., W. Lovenberg, Ph.D., and A. Sjoerdsma, M.D., Ph.D.

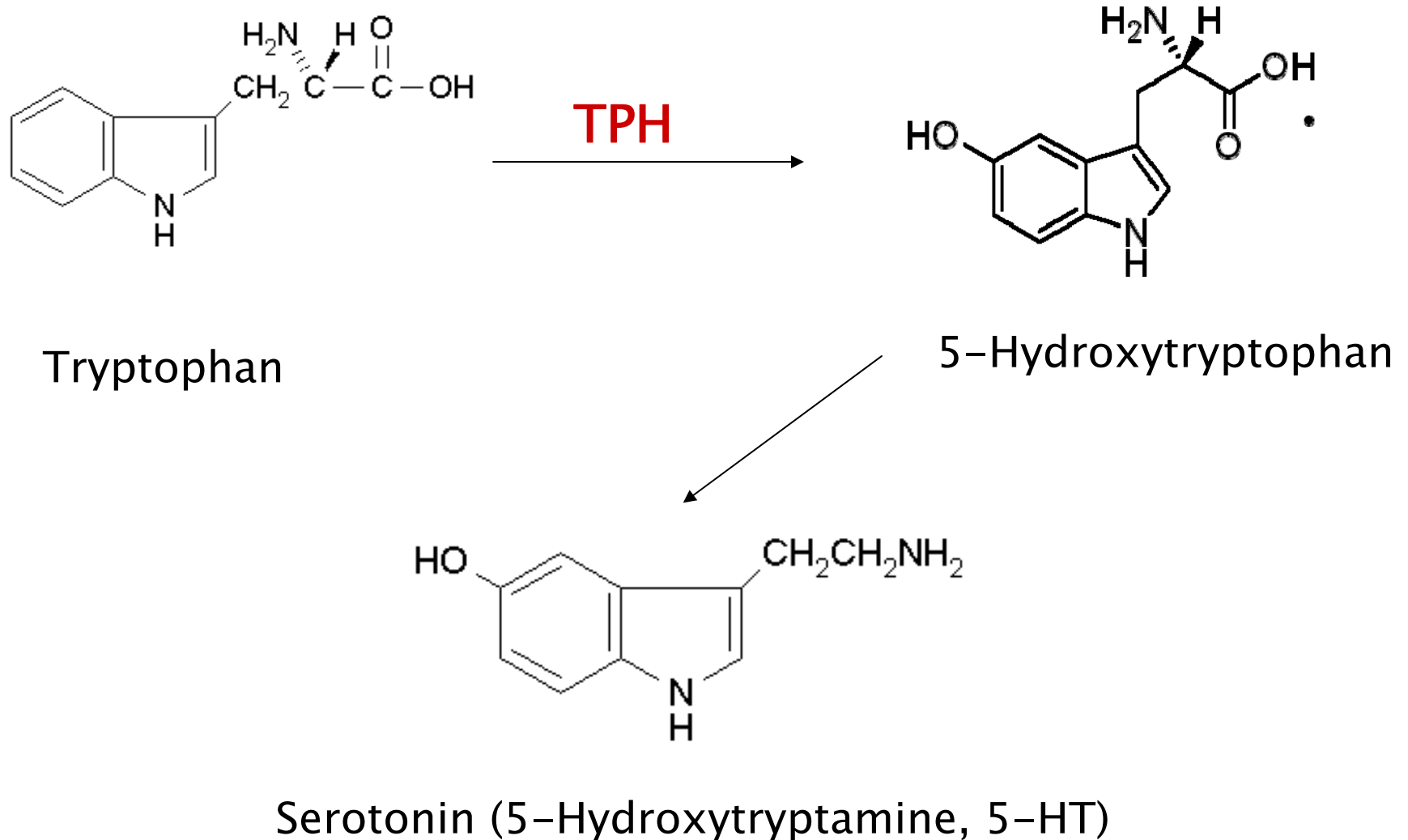


- pCPA controlled diarrhea in 13 out of 16 carcinoid patients
- pCPA treatment also decreased abdominal cramps and pain
- However, pCPA depletes brain 5-HT and causes severe depression
- LX1032 is designed not to affect brain serotonin levels

Normal
5-HIAA

FIGURE 1. Effect of Treatment with PCP on the Urinary Excretion of 5-Hydroxyindole Compounds in a Patient with Metastatic Gastric Carcinoid (Case 1).

Tryptophan Hydroxylase (TPH) Catalyzes the First Step of Serotonin Synthesis



Two Genes Encode Tryptophan Hydroxylase

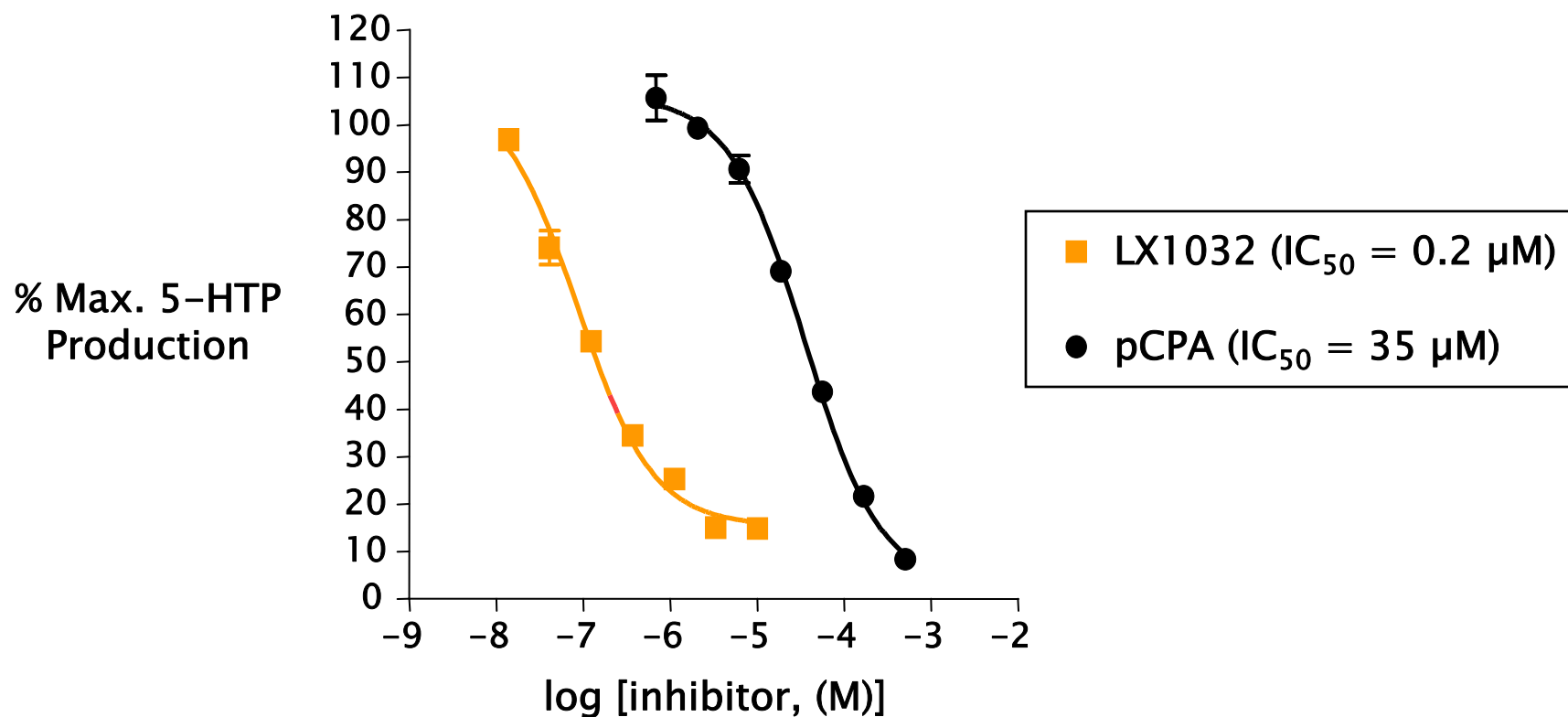
- TPH1:

- Located primarily in enterochromaffin cells of the GI tract
- Responsible for the majority of systemic 5-HT production
- Rate-limiting enzyme in 5-HT synthesis in carcinoid tumors

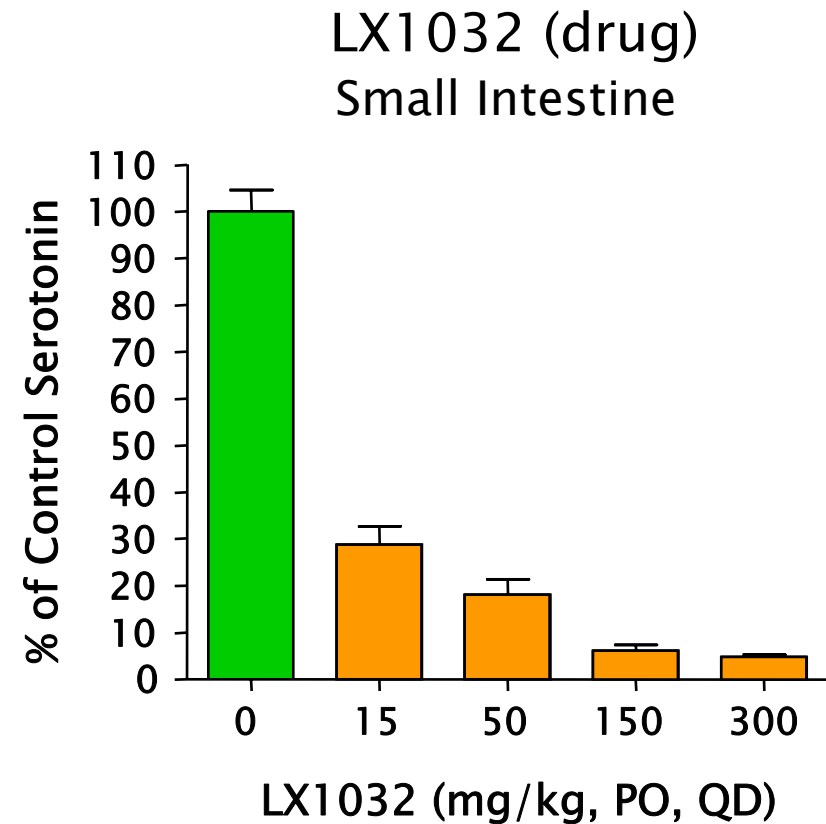
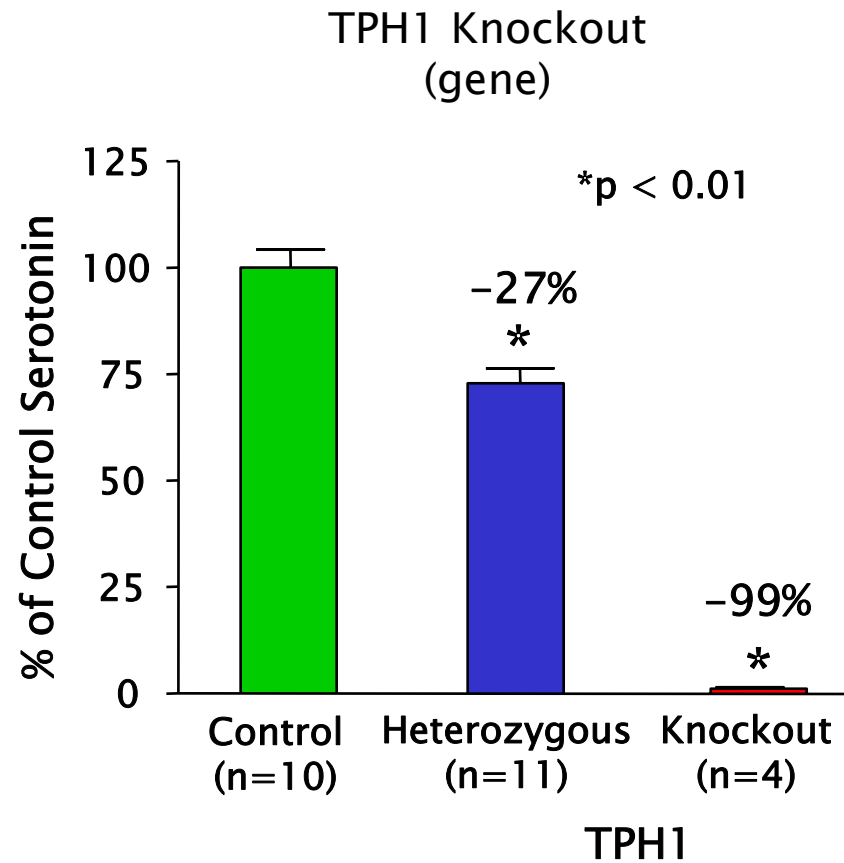
- TPH2:

- Located in central and enteric nervous systems
- Responsible for neuronal 5-HT synthesis

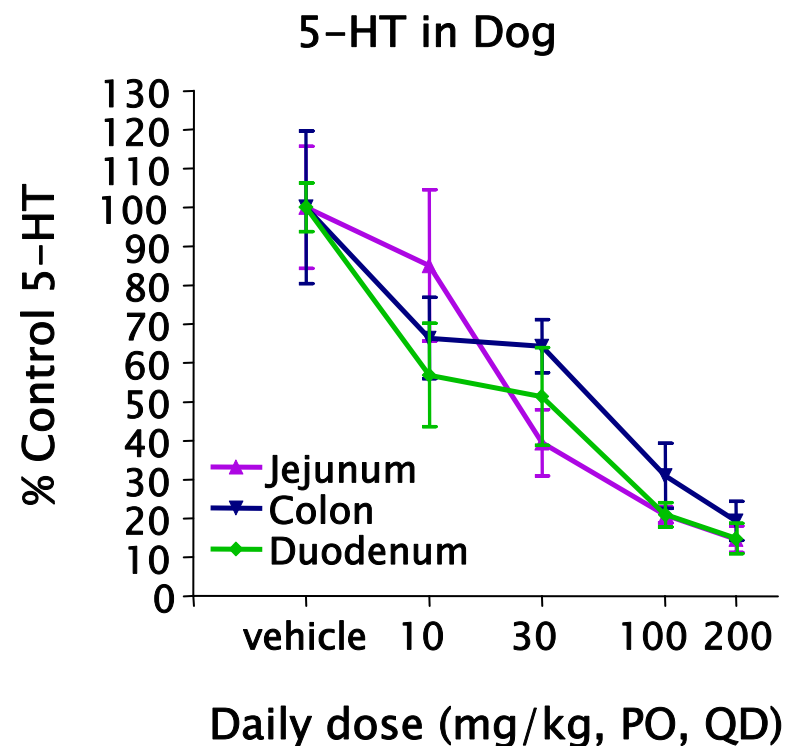
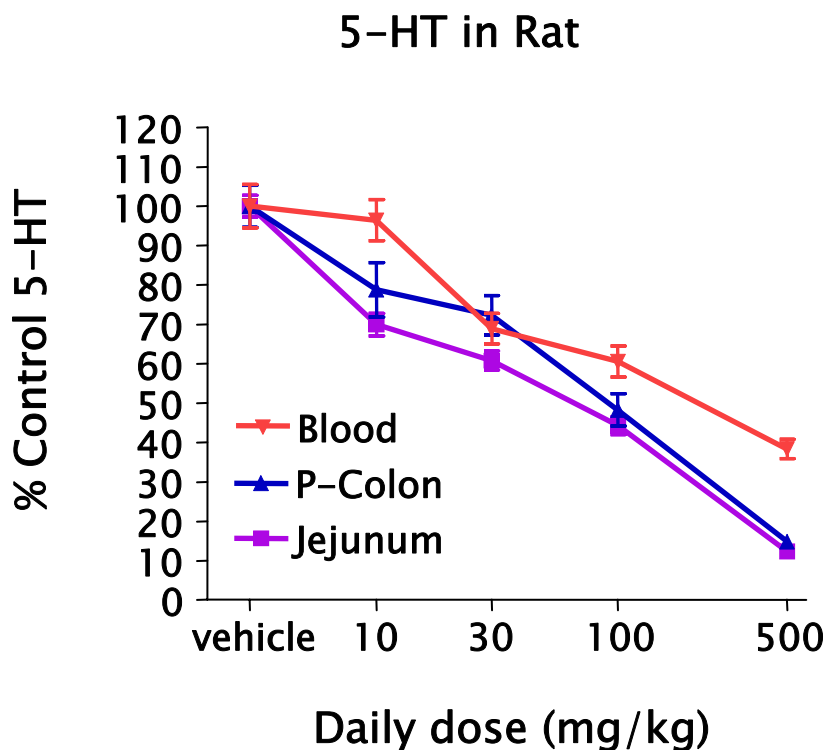
LX1032 is a Potent Inhibitor of Serotonin Production in a Carcinoid Tumor Cell Line



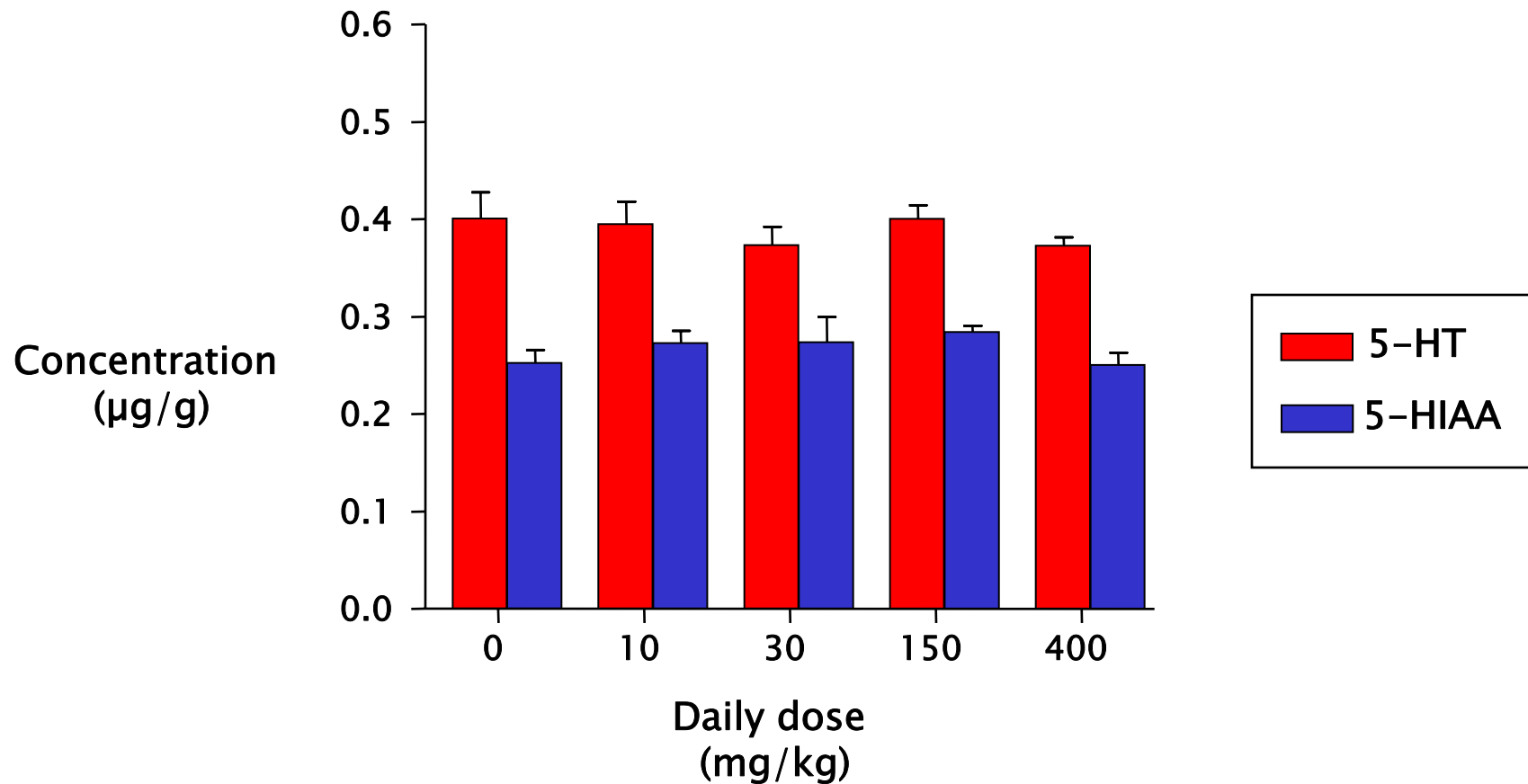
LX1032 Caused Robust, Dose-Dependent 5-HT Reduction in the Mouse Intestine



LX1032 Caused Dose-Dependent 5-HT Reduction in the Rat and Dog



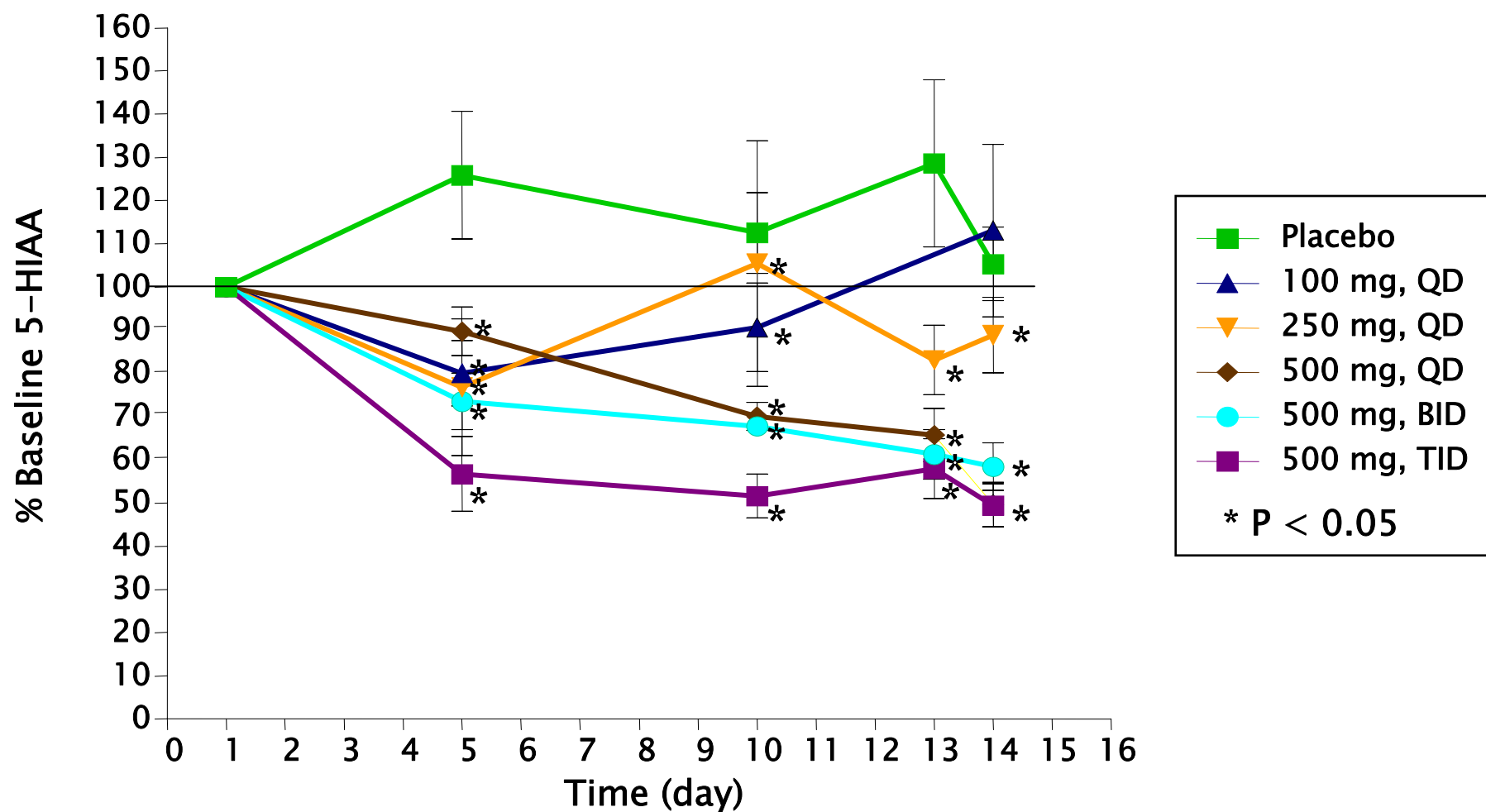
LX1032 Had No Affect on Brain 5-HT and 5-HIAA Levels in Rats



Phase 1 Clinical Study Designs

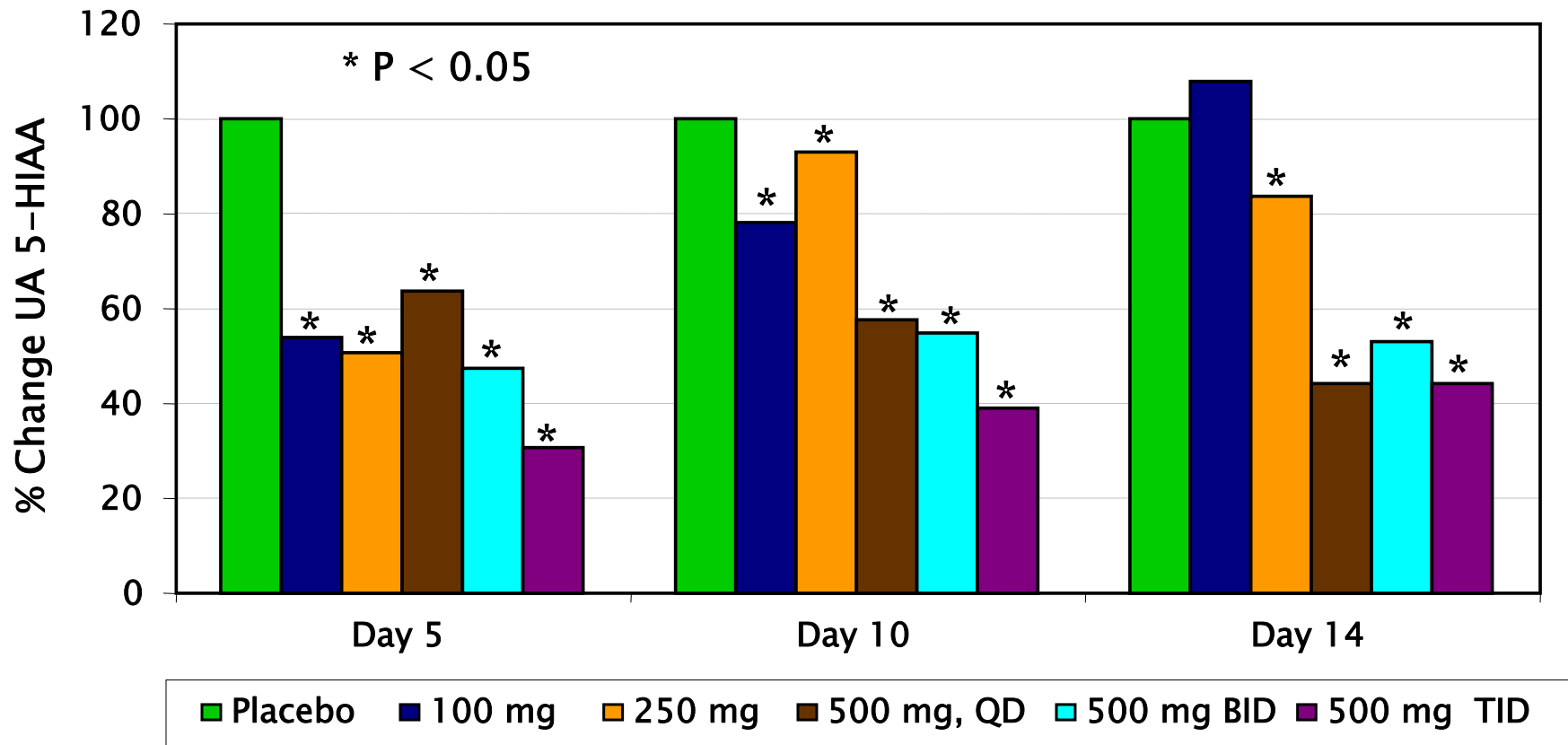
- LX1032 was evaluated in two clinical studies utilizing normal volunteers
 - Subjects were randomized in 3:1 fashion, active:placebo
 - Diet was controlled to minimize foods containing 5-HT
 - Safety, tolerability, pharmacokinetics, and 24-hour urinary 5-HIAA, and blood 5-HT was evaluated
- Single ascending dose tolerance study (n=47)
 - 6 dose levels evaluated: 50 mg to 1,500 mg
- Multiple ascending dose tolerance study (n=40)
 - 5 dose levels evaluated: 100 mg QD, 250 mg QD, 500 mg QD, 500 mg BID, and 500 mg TID, each over 14 days

Dose-Dependent Reduction in Urinary 5-HIAA Observed Over 14 Days of Dosing

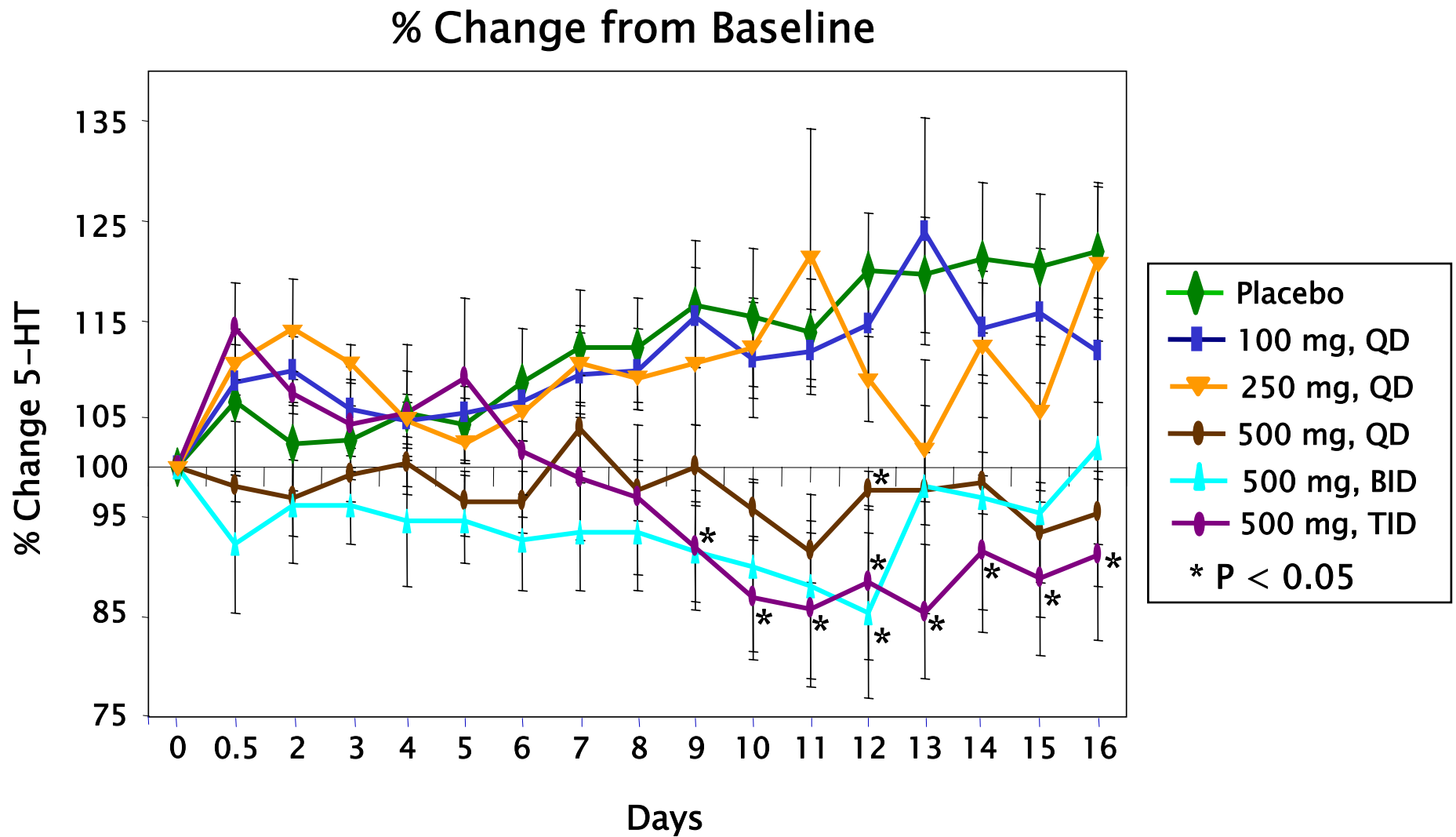


Rapid, Dose-Dependent Reduction in Urinary 5-HIAA Observed

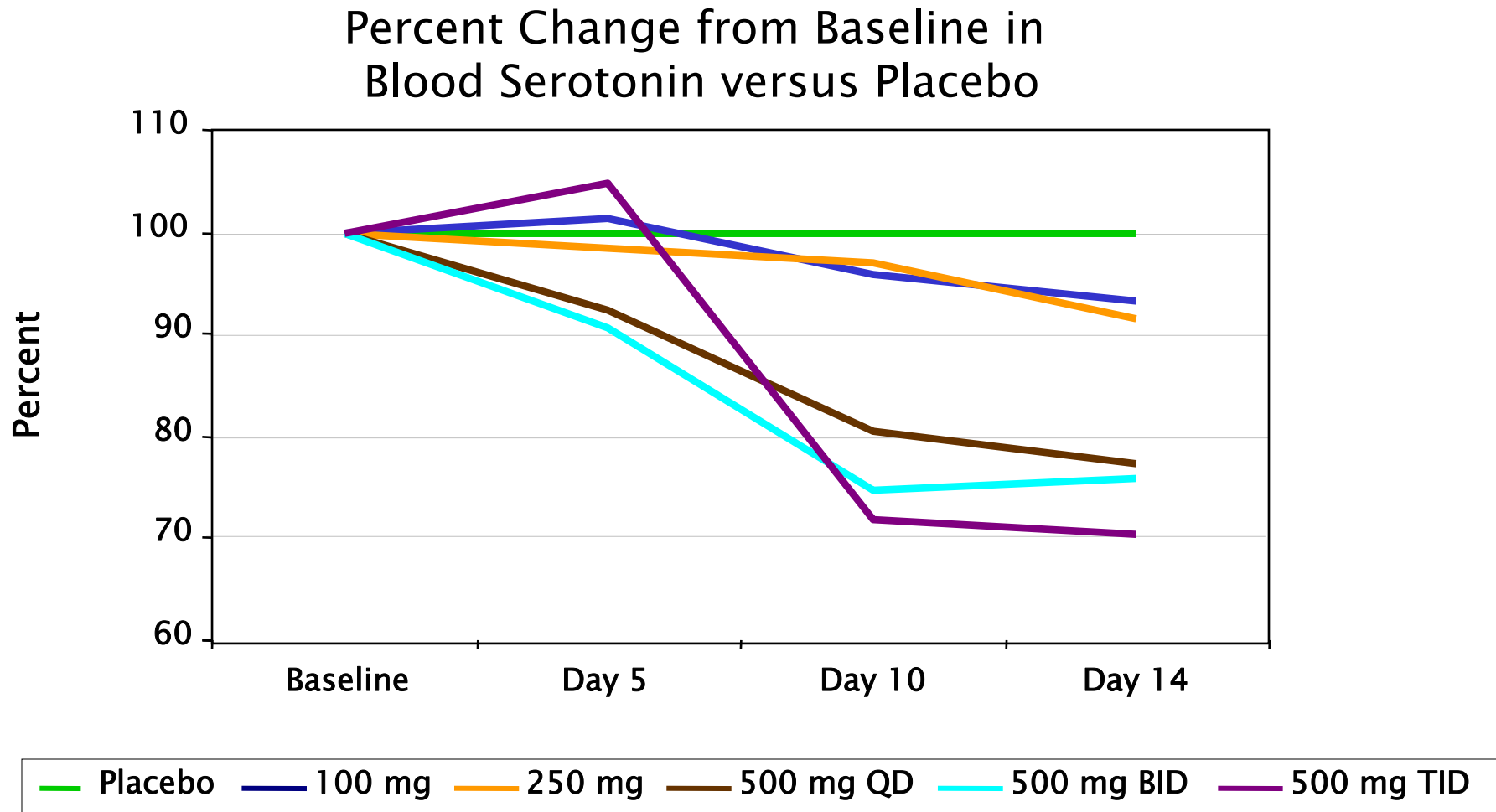
Percent Change from Baseline in Urinary 5-HIAA versus Placebo



Reduction of Whole Blood 5-HT Concentration



LX1032 Demonstrates a Dose-dependent Reduction in Blood Serotonin Over 14 Days of Dosing



LX1032 Adverse Event Summary

- Single doses of LX1032 were well tolerated up to 1,000 mg with mild, self-limited GI events becoming dose limiting at 1,500 mg
- Doses up to 500 mg TID were well tolerated over 14 days
 - Most commonly occurring adverse events were GI disorders: nausea (17%), headache (15%), constipation (10%), diarrhea (10%), and abdominal pain (10%)
 - Dose-dependent, mild increases ($\leq 2 \times$ ULN) in hepatic transaminase levels were observed
 - No clinically significant changes in physical examination, vital signs, or ECG were observed
 - No serious adverse events occurred in either trial

Summary of LX1032 Phase 1 Clinical Results

- Single and multiple dose Phase 1 studies involving 87 subjects demonstrated that LX1032 was tolerated up to the highest dose tested over 14 days (1,500 mg)
- Adverse events were generally mild and evenly distributed throughout all dose groups
- Statistically significant reductions in biomarkers of interest were observed at doses from 500 mg to the maximum dose of 1,500 mg (500 mg TID)
 - 20–30% reduction in blood serotonin
 - 50–60% reduction in 24-hour urinary 5-HIAA

Conclusion

- Reductions in urinary 5-HIAA and whole blood 5-HT confirm preclinical observations and suggest a potent inhibition of peripheral serotonin production
- Reduction in peripheral 5-HT production supports strategy for exploring compound in patients with carcinoid syndrome
- Study in patients with symptomatic carcinoid syndrome despite octreotide therapy being initiated