EVALUATION OF PROLACTIN AS A USEFUL PHARMACODYNAMIC TOOL TO ASSESS ENGAGEMENT OF CENTRAL 5-HT$_{2C}$ RECEPTORS BY LP352, A POTENT AND SELECTIVE 5-HT$_{2C}$ AGONIST

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BACKGROUND

- Modulation of the serotonergic system influences a variety of psychiatric and neurological disorders, including seizure disorders[1,2]
  - Serotonin (5-hydroxytryptamine; 5-HT) agonists can be effective in reducing epileptic seizures, in part by modulating the activity of GABAergic neurons, decreasing excitability of glutaminergic pyramidal cells, and increasing the seizure threshold
- 5-HT plays a stimulatory role in regulating prolactin (PRL) secretion[3-6]
  - Exogenous 5-HT$_{2A}$/5-HT$_{2C}$ receptor agonists can increase serum PRL levels in experimental animals and humans
  - As such, serum PRL levels may represent a useful tool for evaluating effective engagement of central 5-HT receptors in the brain by serotonergic agonists
- LP352 is a potent and selective 5-HT$_{2C}$ superagonist in development for the treatment of seizures associated with developmental and epileptic encephalopathies (DEEs)
  - LP352 demonstrates >200-fold selectivity at 5-HT$_{2C}$ receptors compared with 5-HT$_{2A}$ and 5-HT$_{2B}$ receptors

OBJECTIVES

- Determine the effect of a single dose and repeated multiple doses of LP352 on serum PRL levels

METHODS

- Serum PRL levels were evaluated in two randomized, double-blind, placebo-controlled studies in healthy human volunteers after single and multiple doses of LP352
- Single ascending dose (SAD) study: LP352 or placebo was administered orally as powder in capsule (PIC) to healthy adult females in doses of 1 mg, 3 mg, 6 mg, 12 mg, or 24 mg
  - Study design consisted of a screening period (Days −28 to −2), an assessment period (Days −1 to 5), and a 9-day postdosing follow-up visit (Day 10±1)
  - PRL timepoints: predose, 2 and 24 hours postdose
- Multiple ascending dose (MAD) study: LP352 or placebo was administered orally as PIC to healthy adult participants in doses of 3 mg, 6 mg, 12 mg, or 18 mg three times daily (TID) for 14 days
  - Morning doses on Days 1, 4, 7, 10, and 14 were administered following an overnight fast of at least 10 hours
  - PRL timepoints: Day 1 predose and 2 hours postdose and Day 14 predose and 2 hours postdose
  - An additional group received LP352 titrated from 12 mg to 24 mg; this group has been omitted to facilitate comparison of first/last dose trends
- PRL serum concentrations were summarized by timepoint and dose
  - Predose serum PRL values on Day 1 were considered the baseline values
  - Fold change from baseline was calculated against the maximum PRL level at 2 hours postdose on Day 1 and Day 14

RESULTS

Participants

- Participant demographics (age, sex, ethnicity, race) and baseline characteristics (height, weight, body mass index [BMI]) were similar across cohorts in both studies (**Table 1**)

Table 1. Participant Characteristics

Characteristic	SAD Study N = 40	MAD Study N = 33
Age, mean (SD), years	35.0 (8.01)	34.6 (8.71)
Sex		
Female	40 (100)	22 (66.7)
Male	0	11 (33.3)
Ethnicity		
Hispanic/Latino	3 (7.5)	14 (42.4)
Not Hispanic/Latino	37 (92.5)	19 (57.6)
Race		
Asian	4 (10.0)	2 (6.1)
Black/African American	7 (17.5)	11 (33.3)
White	26 (65.0)	18 (54.5)
Mixed race/Other	3 (7.5)	2 (6.1)
BMI, mean (SD), kg/m^2	23.96 (2.409)	25.83 (2.482)

Data shown are n (%) unless otherwise stated.

Abbreviations **BMI**, body mass index; **MAD**, multiple ascending dose; **PRL**, prolactin; **Rsq**, R squared; **SAD**, single ascending dose; **SD**, standard deviation; **SE**, standard error; **TEAE**, treatment-emergent adverse event; **TID**, three times daily.

References **1.** Akyuz E et al. *Life Sci.* 2021;265:11826. **2.** Di Giovanni G et al. *Pharm Ther.* 2016;157:125-162. **3.** Quattrone A et al. *Br J Clin Pharmacol.* 1983;16:471-475. **4.** Gustafson A et al. *P T.* 2013;38:525-530. **5.** Mallman ES et al. *Neurosci Lett.* 2014;582:71-74. **6.** Chen X et al. *Acta Pharmacologica Sinica.* 2019;40:571-582. **7.** Majumdar A and Mangal NS. *J Hum Reprod Sci.* 2013;6:168-175.

SAD Study

- PRL consistently demonstrated an acute dose-dependent increase at 2 hours following single doses of LP352 1 mg to 24 mg (**Figure 1**)
- Following administration of single doses of LP352, we observed a direct relationship between fold change in PRL and LP352 concentrations (**Figure 2**)
- Increases in PRL were sufficiently large to reflect a difference between placebo and LP352; however, no participants exhibited adverse events associated with hyperprolactinemia even at the highest dose tested

Figure 1. Fold Change in Mean Serum PRL Concentration (±SE) Following Single Doses of LP352

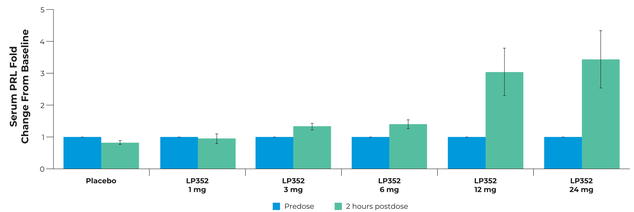
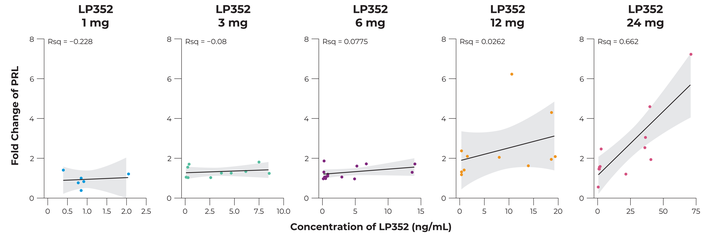


Figure 2. Fold Change in PRL by LP352 Concentration Following Single Doses of LP352



Dots represent individual participants.

MAD Study

- On Day 1 of TID dosing, PRL demonstrated an acute dose-dependent increase at 2 hours following administration of LP352 3 mg to 18 mg (**Figure 3A**)
- Following 14 days of TID LP352, no persistent systematic differences were observed between LP352 and placebo in PRL concentrations, suggesting that LP352-dependent increases in PRL are not sustained during continuous repeated dosing (**Figure 3B**)
- Following administration of single doses of LP352, we observed a direct relationship between fold change in PRL and LP352 concentrations (**Figure 4**)

Figure 3. Fold Change in Mean Serum PRL Concentration (±SE) Following Administration of LP352

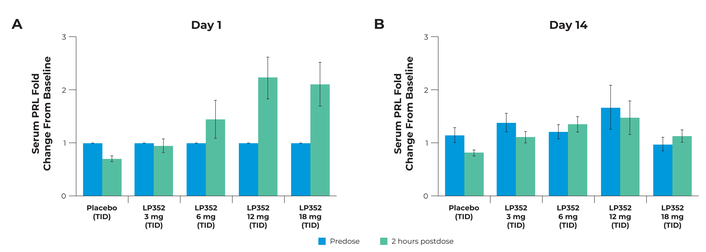
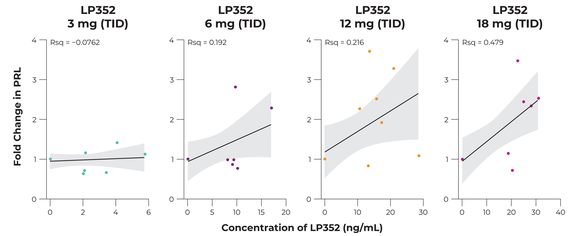


Figure 4. Fold Change in PRL by LP352 Concentration Following Single Doses of LP352



Dots represent individual participants.

Participant Safety

- Multiple doses of LP352 were generally well tolerated (**Table 2**)
- Most treatment-emergent adverse events (TEAEs) occurred within 24 hours of dosing and resolved by study completion
- No participant reported any TEAE that could be attributed to hyperprolactinemia (eg, galactorrhea, gynecomastia)[7]

Table 2. MAD Study: Treatment-Emergent Adverse Events

	Multiple Ascending Dose					
Event, n (%)	LP352 3 mg TID (n = 6)	LP352 6 mg TID (n = 6)	LP352 12 mg TID (n = 7)	LP352 18 mg TID (n = 6)	Pooled Placebo (n = 8)	Pooled LP352 (n = 25)
Participants with ≥1 TEAE[a]	5 (83.3)	6 (100)	6 (85.7)	6 (100)	4 (50.0)	23 (92.0)
Headache	2 (33.3)	2 (33.3)	2 (28.6)	4 (66.7)	1 (12.5)	10 (40.0)
Somnolence	1 (16.7)	1 (16.7)	4 (57.1)	3 (50.0)	0	9 (36.0)
Dizziness	0	3 (50.0)	2 (28.6)	2 (33.3)	0	7 (28.0)
Micturition urgency	1 (16.7)	0	1 (14.3)	5 (83.3)	0	7 (28.0)
Dizziness – postural	0	0	1 (14.3)	5 (83.3)	0	6 (24.0)
Diarrhea	1 (16.7)	4 (66.7)	1 (14.3)	0	0	6 (24.0)
Orthostatic hypotension	0	0	2 (28.6)	4 (66.7)	0	6 (24.0)
Constipation	1 (16.7)	1 (16.7)	2 (28.6)	1 (16.7)	1 (12.5)	6 (24.0)
Nausea	1 (16.7)	0	1 (14.3)	2 (33.3)	1 (12.5)	4 (16.0)
Paresthesia	0	1 (16.7)	2 (28.6)	1 (16.7)	0	4 (16.0)
Chills	0	0	1 (14.3)	3 (50.0)	0	4 (16.0)
Anxiety	0	2 (33.3)	0	2 (33.3)	0	4 (16.0)
Orthostatic heart rate response increased	0	0	0	3 (50.0)	1 (12.5)	3 (12.0)
Dysmenorrhea	1 (16.7)	0	0	2 (33.3)	1 (12.5)	3 (12.0)
Fatigue	0	2 (33.3)	0	0	0	2 (8.0)
Vessel puncture site bruise	0	0	0	2 (33.3)	0	2 (8.0)
Hypotension	0	2 (33.3)	0	0	0	2 (8.0)

[a]Refers to individual participants, not individual events.

CONCLUSIONS

- **In combination, these data suggest that:**
  - **LP352 effectively engages central 5-HT$_{2C}$ receptors at physiologically relevant concentrations**
  - **PRL, due to its acute nature of response, may be a suitable neuroendocrine biomarker of 5-HT$_{2C}$ agonism in the early period of dosing**
  - **LP352-dependent increases in PRL are transient, are not maintained following repeated continuous dosing, and are not associated with hyperprolactinemia-associated adverse events**