746

# A PHASE 1 CLINICAL STUDY SHOWS ROBUST LP352 CSF EXPOSURES SUPPORTING DOSE OPTIMIZATION FOR 5-HT$_{2C}$ RECEPTOR ENGAGEMENT

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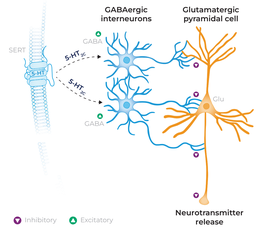
## BACKGROUND

- Developmental and epileptic encephalopathies (DEEs) are rare neurodevelopmental disorders characterized by early-onset seizures that are often difficult to control, accompanied by abnormal electroencephalogram activity and developmental delay or regression[1-3]
- LP352 is a potent and selective 5-hydroxytryptamine (5-HT)$_{2C}$ agonist designed for the treatment of patients with DEEs (**Figure 1**)
  - LP352 demonstrates increased selectivity for the 5-HT$_{2C}$ receptor compared with serotonergic agonists such as fenfluramine and lorcaserin, which may reduce the potential for adverse effects associated with 5-HT$_{2A}$ (eg, hallucinogenic activity)[4] and 5-HT$_{2B}$ agonism (eg, cardiotoxicity)[5,6]

## OBJECTIVE

- To evaluate the cerebrospinal fluid (CSF) pharmacokinetics (PK) relative to the in vitro 5-HT$_{2C}$ binding constant (Ki) of LP352 in healthy volunteers compared with published lorcaserin data

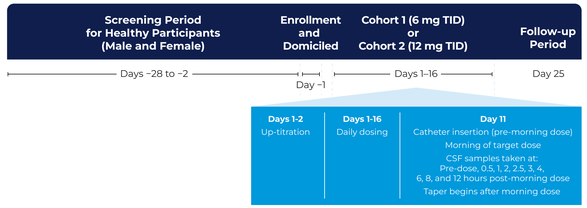
### Figure 1. LP352 Proposed Mechanism of Action




## METHODS

- This was an open-label, multiple-dose, phase 1 study in healthy adults (**Figure 2**)
- Eligible patients were included if:
  - They were determined to be healthy by medical history, physical examination, 12-lead electrocardiogram, and laboratory tests
  - At screening, they were 18 to 55 years old (inclusive) and had a body mass index (BMI) between 18.5 and 30.0 kg/m$^2$ and a weight of at least 50 kg
- Participants were excluded from the study if they had any evidence of renal impairment according to the Chronic Kidney Disease Epidemiology Collaboration, as indicated by an estimated glomerular filtration rate of <80 mL/min/1.73m$^2$ at screening

### Figure 2. LP352 Study Design




- Participants received liquid oral doses of LP352 6 mg or 12 mg 3 times daily (TID)
  - All dose regimens included up-titration (days 1 and 2) followed by target dosing to the morning of day 11; taper-down phase began on day 11 after the morning dose
- Serial CSF samples were taken at steady state on day 11
  - Pre-morning dose (within 1 h prior), 0.5, 1, 2, 2.5, 3, 4, 6, 8, and 12 h after the first pre-morning dose of that day
  - A lumbar catheter was inserted (within 1 h) before dosing and removed after the 12-h CSF sample
  - CSF samples of approximately 30 mL were collected from each participant
- Published lorcaserin 10 mg BID CSF PK data[7] and Ki value (2.5 ng/mL)[8] are presented in **Figure 4** and **Table 2** for comparison

## RESULTS

### Participants

- 20 healthy adult volunteers were included, and their demographic characteristics can be found in **Table 1**

### Table 1. Participant Characteristics

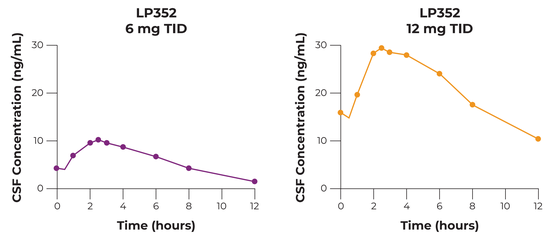
| Characteristic | LP352 6 mg TID n = 10 | LP352 12 mg TID n = 10 |
|---|---|---|
| Age, mean (SD), years[a] | 40.7 (7.48) | 34.9 (6.98) |
| Sex, n (%) | | |
| Male | 6 (60.0) | 7 (70.0) |
| Female | 4 (40.0) | 3 (30.0) |
| Race/Ethnicity, n (%) | | |
| Asian | 1 (10.0) | 2 (20.0) |
| Black or African American | 3 (30.0) | 0 |
| White | 6 (60.0) | 8 (80.0) |
| Native Hawaiian or Other Pacific Islander | 0 | 0 |
| Other | 0 | 0 |
| Hispanic or Latino | 4 (40.0) | 0 |
| Not Hispanic or Latino | 6 (60.0) | 10 (100.0) |
| BMI, mean (SD) | 25.6 (3.822) | 24.89 (2.512) |

[a]Age was derived from date of birth to the date of informed consent.

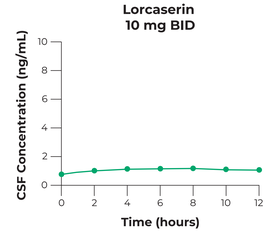
### Pharmacokinetics

- Regardless of the dose levels, LP352 CSF levels increased after dosing, with an attainment of peak concentrations within 2-3 h of day 11 dosing and were measurable up to 12 h after dose (**Figure 3**)
- LP352 exhibited consistent and dose-linear PK, with both doses resulting in robust CSF concentrations (**Figure 3, Table 2**)

### Figure 3. CSF Concentrations With LP352 6 mg and 12 mg TID Dosing

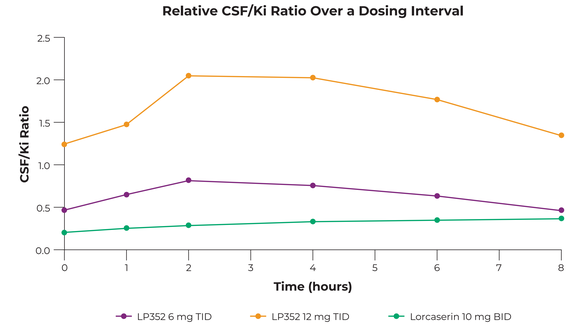



### Figure 4. Published Lorcaserin 10 mg BID CSF PK Data[7]




- Using CSF/Ki ratio as a surrogate for 5-HT$_{2C}$ target engagement, both doses of LP352 demonstrated a potential for greater engagement of 5-HT$_{2C}$ than lorcaserin (**Table 2, Figure 5**)
  - The mean average serum concentration ($C_{avg}$) of 6 mg and 12 mg LP352 doses in CSF samples reached approximately 0.6-fold and 1.7-fold, respectively, of the Ki value (14.4 ng/mL) for 5-HT$_{2C}$ agonism
  - In contrast, the mean $C_{avg}$ CSF concentration of lorcaserin 10 mg twice daily (BID) reached approximately 0.3-fold of the Ki value (2.5 ng/mL) for 5-HT$_{2C}$ agonism

### Figure 5. Comparison of Relative In Vivo 5-HT$_{2C}$ Agonism




### Table 2. Mean Pharmacokinetic Parameters

| | LP352 6 mg TID | LP352 12 mg TID | Lorcaserin 10 mg BID[7,8] |
|---|---|---|---|
| $C_{max}$, ng/mL | | | |
| Mean | 12.29 | 30.36 | 0.95 |
| Mean/Ki | 0.85 | 2.10 | 0.38 |
| $C_{avg}$, ng/mL | | | |
| Mean | 9.26 | 24.36 | 0.78 |
| Mean/Ki | 0.64 | 1.70 | 0.31 |
| $AUC_{tau}$, h·ng/mL | 74.06 | 194.88 | 9.31 |

Published lorcaserin data are from a separate study.

Reference value for LP352 Ki = 14.4 ng/mL. Reference value for lorcaserin Ki = 2.5 ng/mL.

$C_{avg}$ was calculated by dividing $AUC_{tau}$ by tau (tau = 8 h for LP352; tau = 12 h for lorcaserin).

## CONCLUSIONS

- **LP352 6 mg and 12 mg TID resulted in robust CSF concentrations, with the potential for clinically meaningful engagement of 5-HT$_{2C}$ receptors**
- **In lieu of the observed clinical activity of lorcaserin in certain DEEs, CSF data suggest that both LP352 doses achieve target exposures in the brain for potential clinical activity**
- **Overall, these data support the hypothesis that LP352 achieves relatively high CSF levels and may offer the opportunity to optimize dosing during the clinical development of LP352**

**Abbreviations** **5-HT**, 5-hydroxytryptamine; **AUC**, area under the curve; **BID**, twice daily; **BMI**, body mass index; **$C_{avg}$**, average serum concentration; **$C_{max}$**, maximum serum concentration; **CSF**, cerebrospinal fluid; **DEE**, developmental and epileptic encephalopathy; **GABA**, gamma aminobutyric acid; **Ki**, binding constant; **PK**, pharmacokinetics; **SERT**, serotonin transporter; **TID**, 3 times daily.

**References** **1.** Scheffer IE et al. *Epilepsia.* 2017;58:512-521. **2.** Scheffer IE, Liao J. *Eur J Paediatr Neurol.* 2020;24:11-14. **3.** Gallop K et al. *Epilepsy Behav.* 2021;124:108324. **4.** López-Giménez J, González-Maeso J. *Curr Top Behav Neurosci.* 2018;36:45-73. **5.** Higgins GA et al. *Pharmacol Ther.* 2020:107417. **6.** Hutcheson JD et al. *Pharmacol Ther.* 2011;132:146-157. **7.** Lorcaserin. FDA Clinical Pharmacology and Biopharmaceutics Review SBA; application number: 022529Orig1s000.022529Orig1s000. **8.** BELVIQ/BELVIQ XR. Prescribing Information. Eisai Inc. Revised May 2017.