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ALTERNATE DOSING REGIMENS FOR AN IMMEDIATE RELEASE FORMULATION OF THE NOVEL ANTISEIZURE MEDICATION LP352 BASED ON PHARMACOKINETICS (PLASMA AND CEREBROSPINAL FLUID [CSF]) AND PHARMACODYNAMICS (QEEG)

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LONGBOARD PHARMACEUTICALS

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BACKGROUND

- LP352 is a potent and highly selective 5-hydroxytryptamine (5-HT_{2C}) superagonist designed for the treatment of individuals with developmental and epileptic encephalopathies (DEEs)
  - LP352 elicits a greater response than serotonin at the 5-HT_{2C} receptor and has no detected activity at receptors associated with significant adverse side effects: 5-HT_{2A} (psychiatric: insomnia, hallucinations, euphoria)[1] and 5-HT_{2B} (valvular heart disease and pulmonary arterial hypertension)[2,3]
- Relative to dosing 3 times a day (TID),[4] dosing twice daily (BID) in patients with DEEs may lower the therapeutic burden by increasing patient adherence to treatment and easing delivery of treatment for caregivers

OBJECTIVE

- To evaluate the pharmacokinetics (PK) and pharmacodynamics (PD) of TID and BID doses of LP352

METHODS

- This was a phase 1, open-label, multiple-dose study in healthy adults between 18 and 55 years of age (n = 25; **Table 1**)
- Following an initial 2 to 4 days of up-titration (depending on target dose), volunteers were dosed for 6 to 8 days at the target doses of 12 mg, 15 mg, or 18 mg BID
- Serial plasma samples were obtained after a single dose and after multiple doses on days 8, 9, and 10
- Serial cerebrospinal fluid (CSF) samples were obtained at steady state on day 11
- Serial quantitative electroencephalograms (QEEGs) with eyes in the open and closed positions were recorded at baseline and days -1, 1, 3 or 5, 10, and 16 (at trough)
- LP352 concentrations were quantified in various clinical samples using validated bioanalytical methods
- Standard PK parameters were calculated
- All QEEG assessments used state-of-the-art recording instruments and were performed by qualified electroencephalogram technologists
- 18 mg BID exposure data was compared to previously reported 12 mg TID exposure data[4]

Table 1. Schedule of Dosing

● Serial EEGs
● Serial PK samples
● Serial CSF samples

Up-titration phase | Target dosing | Taper-down phase

Cohort (n = 25)	Dose #	D-1	D1	D2	D3[b]	D4	D5[b]	D6	D7	D8	D9	D10	D11	D12	D13	D14	D15	D16
3 (12 mg BID)	1	–	6	6	12	12	12	12	12	12	12	12	12	6	3	3	3	3
	2	–	6	6	12	12	12	12	12	12	12	12	6	6	3	3	–	–
4A (15 mg BID)[a]	1	–	6	6	12	12	15	15	15	15	15	15	15	9	4.5	4.5	4.5	4.5
	2	–	6	6	12	12	15	15	15	15	15	15	9	9	4.5	4.5	–	–
4B (18 mg BID)[a]	1	–	6	6	12	12	18	18	18	18	18	18	18	9	4.5	4.5	4.5	4.5
	2	–	6	6	12	12	18	18	18	18	18	18	9	9	4.5	4.5	–	–

[a]A minimum of 4 subjects (Cohort 4a) were up-titrated to 15 mg BID dose on day 5 and completed the day 11 morning dose before the remaining subjects (Cohort 4b) were up-titrated to the target 18 mg BID dose.
[b]Serial QEEGs were obtained on days 3 or 5.

RESULTS

Participants

- 25 healthy adult volunteers were included in this study (20 male and 5 female volunteers)
- The mean weight of volunteers was 73.5 kg, 77.8 kg, and 75.2 kg, for LP352 12 mg, 15 mg, and 18 mg BID, respectively

Pharmacokinetics

- Across BID dose ranges, the observed PK in both plasma and CSF was dose linear (**Table 2**)
- The CSF/plasma exposure ratio for area under the concentration-time curve from time zero to the end of the dosing interval (AUC_{tau}) was generally >0.84 at the 3 BID dose levels (**Table 2**)

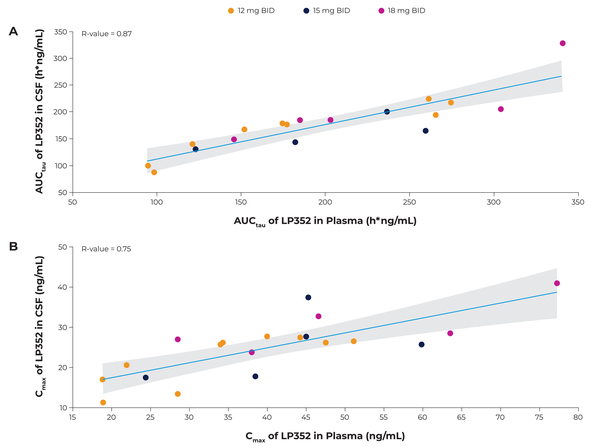
Table 2. Summary Statistics of LP352 12 mg, 15 mg, and 18 mg BID Plasma and CSF PK Parameters

Dose (mg)	AUC_{tau} in CSF (h*ng/mL)	AUC_{tau} in Plasma (h*ng/mL)	CSF/Plasma Ratio[a]
12 mg BID	165.1	169.7	0.973
15 mg BID	175.6	200.4	0.876
18 mg BID	210.1	235.6	0.892

[a]Computed using the CSF AUC_{tau}/plasma AUC_{tau} (total).

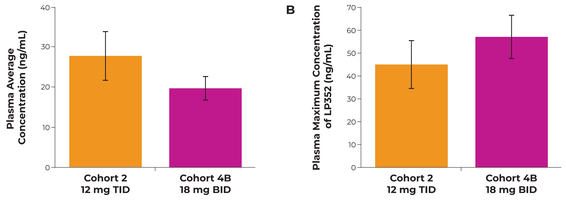
- There was a strong correlation of plasma and CSF PK parameters, including maximum concentration (C_{max}) and AUC_{tau} (**Figure 1**)

Figure 1. AUC_{tau} (A) and C_{max} (B) of LP352 12 mg, 15 mg, and 18 mg BID in Plasma PK Samples



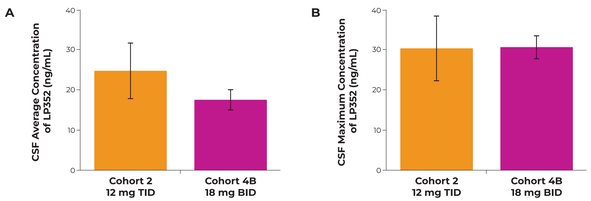
- Average plasma concentrations over the dosing interval were comparable (~28%) between the 18 mg BID and 12 mg TID dose groups (**Figure 2**)

Figure 2. Plasma Average (A) and Maximum Concentrations (B) of LP352 12 mg TID and 18 mg BID



- In the CSF, LP352 concentrations generally exceeded the Ki value (~14 ng/mL) for 5-HT_{2C} agonism by ~2-fold in both the 18 mg BID and 12 mg TID dosing groups (**Figure 3**)

Figure 3. CSF Average (A) and Maximum Concentration (B) of LP352 12 mg TID and 18 mg BID



Pharmacodynamics

- Similar to TID dosing, the QEEG data across multiple spectral bands for BID dosing of LP352 was consistent, with successful receptor engagement in the brain,[4] and as observed previously, there was evidence of time and dose dependency of the effect

Safety

- The 3-step up-titration approach to reach the highest target dose of 18 mg BID was found to be safe and tolerable, with patients experiencing generally mild to moderate treatment-emergent adverse events (TEAEs)
- The most common TEAEs were nausea, vomiting, headache, and dizziness, which are consistent with earlier TID studies[4]
- There was a single serious adverse event, which was not drug-related
- Overall, the safety and tolerability of BID dosing of LP352 was comparable to TID dosing regimen as previously observed[4-6]

CONCLUSIONS

- **The plasma and CSF PK data of LP352, in conjunction with the observed PD QEEG changes, demonstrate that BID dosing of LP352 is a viable alternative option for use in future clinical studies**
- **Using an up-titration dose escalation scheme, the safety, tolerability, and general TEAE profile of LP352 for the BID regimen were comparable to those previously observed for the TID regimen**

Abbreviations **5-HT**, 5-hydroxytryptamine; **AUC_{tau}**, area under the concentration-time curve from time zero to the end of the dosing interval; **BID**, twice daily; **C_{max}**, maximum serum concentration; **CSF**, cerebrospinal fluid; **D**, day; **DEE**, developmental and epileptic encephalopathy; **PD**, pharmacodynamics; **PK**, pharmacokinetics; **QEEG**, quantitative electroencephalogram; **TEAE**, treatment-emergent adverse event; **TID**, 3 times daily.

References **1.** López-Giménez J, González-Maeso J. *Curr Top Behav Neurosci.* 2018;36:45-73. **2.** Higgins GA et al. *Pharmacol Ther.* 2020:107417. **3.** Hutcheson JD et al. *Pharmacol Ther.* 2011;132:146-157. **4.** Srinivas N et al. *Clin Pharmacol Drug Dev.* 2023;12(1):52-53. **5.** Parasrampuria D et al. *Neurology.* 2022;98(18):1750. **6.** Parasrampuria D et al. *Neurology.* 2022;98(18):1771.