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THE PACIFIC STUDY: A PHASE 1B/2A STUDY TO INVESTIGATE THE SAFETY, TOLERABILITY, PHARMACOLOGY, AND EXPLORATORY EFFICACY OF LP352 IN PARTICIPANTS WITH DEVELOPMENTAL AND EPILEPTIC ENCEPHALOPATHIES

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Acknowledgments

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Additional information and resources regarding the PACIFIC study can be accessed at the QR code above.

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DEVELOPMENTAL AND EPILEPTIC ENCEPHALOPATHIES (DEEs)

- DEEs are a group of rare neurodevelopmental disorders characterized by early-onset seizures, abnormal electroencephalogram (EEG) activity, and developmental delay or regression[1-3]
  - Includes specific syndromes (eg, Dravet syndrome, Lennox-Gastaut syndrome) and uncharacterized DEE
  - Seizures are often resistant to current antiseizure therapy
  - DEE can profoundly impact quality of life and the emotional well-being of patients and their caregivers
- To date, trials in DEE have focused on patients with specific syndromes, rather than patients with uncharacterized DEE

LP352: A NOVEL 5-HT$_{2C}$ SUPERAGONIST

- Preclinical and clinical data support a role for the 5-hydroxytryptamine (5-HT)$_2$ receptor in modulating the frequency and threshold of seizure onset (**Figure 1**)[4-6]
  - 5-HT$_{2C}$ receptor agonists may increase seizure threshold and reduce seizure frequency, and may represent efficacious treatments for a variety of motor seizures and seizure disorders
- LP352 is a potent and selective 5-HT$_{2C}$ superagonist specifically designed for use in DEE (**Table 1**)
  - LP352 demonstrates >200-fold increased selectivity for the ligand binding site of 5-HT$_{2C}$ receptors versus 5-HT$_{2A}$ and 5-HT$_{2B}$, which is expected to minimize adverse effects seen with 5-HT$_{2A}$ and 5-HT$_{2B}$ agonism
- Prior double-blind, placebo-controlled studies of LP352 demonstrated[7,8]:
  - LP352 was rapidly absorbed into the systemic circulation following oral administration
  - There was no clinically meaningful food effect on systemic exposures
  - Prolactin (PRL) concentrations transiently increased in a dose-dependent manner following LP352 administration, indicating successful engagement of central 5-HT$_{2C}$ receptors
  - Single or multiple ascending doses of LP352 were generally well tolerated in most participants, with most treatment-emergent adverse events (TEAEs) reported as mild or moderate

Figure 1. LP352 Proposed Mechanism of Action

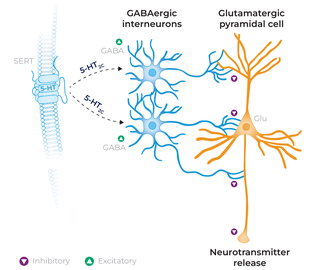


Table 1. Selectivity and Side Effects of 5-HT$_{2C}$ Agonists

	5-HT Receptor Subtype	EC$_{50}$, nM	Ki, nM	Selectivity: 5-HT$_{2C}$ vs 5-HT$_{2B}$	Selectivity: 5-HT$_{2C}$ vs 5-HT$_{2A}$	Noted Side Effects
LP352 5-HT$_{2C}$ Superagonist	5-HT$_{2C}$	~120	~50	>200×	>200×	Headache, nausea, weight loss
	5-HT$_{2B}$	>10,000	>10,000	—	—	—
	5-HT$_{2A}$	>10,000	>10,000	—	—	—
Nordexfenfluramine[a]	5-HT$_{2C}$	72.4	10.4	0.94×	11.5×	Headache, nausea, weight loss
	5-HT$_{2B}$	25.7	9.8	—	—	—
	5-HT$_{2A}$	1778	120.2	—	—	Insomnia
Lorcaserin	5-HT$_{2C}$	39	13	11.3×	7.1×	Headache, nausea, weight loss
	5-HT$_{2B}$	2380	147	—	—	—
	5-HT$_{2A}$	553	92	—	—	—

[a]Active metabolite of fenfluramine.

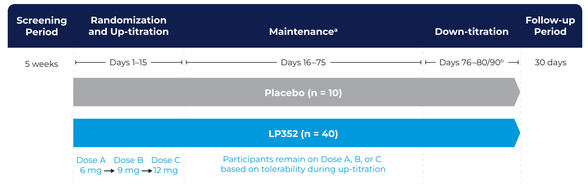
STUDY OBJECTIVES

- Primary objective
  - Investigate the safety, tolerability, and efficacy of multiple doses of LP352 in adults and adolescents with DEE
- Secondary objectives
  - Characterize the pharmacokinetics (PK) of LP352 in adults and adolescents with DEE
  - Characterize the pharmacodynamic (PD) effects of LP352 on PRL
  - Evaluate and characterize PK/PD relationships of LP352 for endpoints related to safety and seizures
  - Identify the optimal dose(s) of LP352 for future clinical studies

STUDY DESIGN

- Double-blind, placebo-controlled, parallel-group Phase 1b/2a dose-escalation study (**Figure 2**)
  - Initiated in March 2022 at ~25 US sites; will expand to Australia in Q1 2023
  - Expected to enroll ~50 male and female patients aged ≥12 to ≤65 years

Figure 2. PACIFIC Study Design



[a]Maintenance dose of LP352: Dose A, Dose B, Dose C, or placebo TID.
[b]Up to a 15-day down-titration/taper period (reducing dose every 5 days) depending on the last maintenance dose.

Study Participants

- Patients with specific syndromes or unclassified DEE are invited to participate, regardless of specific genotype or phenotype (**Figure 3 and Table 2**)

Figure 3. Key Inclusion and Exclusion Criteria

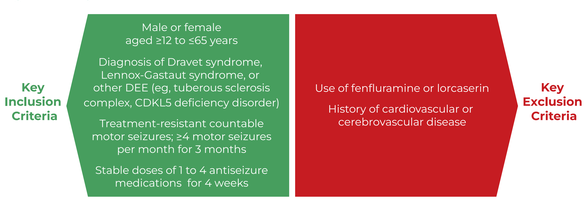


Table 2. Inclusion Criteria for Patients With Dravet, LGS, and Other DEEs

	Dravet	LGS	Other DEEs
Onset	Between 3 and 19 months	Before 8 years of age	Unprovoked seizures before 5 years
Seizure Type	Generalized tonic-clonic, unilateral clonic, or bilateral clonic seizures	Tonic or tonic/atonic seizures AND more than 1 type of generalized seizure (tonic-clonic, tonic-atonic, atonic, tonic, myoclonic, or drop)	Combined focal and generalized seizure types, or multiple generalized seizure types
Developmental History	Initially typical, then delayed	Delayed	Delayed
EEG	—	Consistent with LGS diagnosis[a]	Slow or disorganized
Additional Criteria	One of the following: • Emergence of another seizure type after the first • Induced by warm temperatures, fevers, or visual stimuli • Genetic test consistent with Dravet	More than 1 type of generalized seizure for ≥6 months before screening	No history of idiopathic generalized epilepsy

[a]Abnormal interictal EEG background activity with interictal slow spike-and-wave pattern ≤2.5 Hz or interictal generalized paroxysmal fast activity.

Outcome Measures

- Incidence and severity of TEAEs
- Changes from baseline on the Columbia-Suicide Severity Rating Scale
- Changes from baseline in the Patient Health Questionnaire-9
- Percentage change from baseline in observed countable motor seizure frequency (during treatment and maintenance periods)
- LP352 PK parameters
- Effects on PRL

KEY BENEFITS FOR PARTICIPANT

- Broad inclusion criteria allow patients with uncharacterized DEE to participate, regardless of genotype or diagnosis
- 4:1 randomization scheme ensures participants have an 80% chance of receiving LP352
- Medication can be taken orally or via feeding tube, allowing for patient flexibility
- Consenting participants have the option to receive free genetic epilepsy testing
- All participants completing the study have the opportunity to continue through the open-label extension and continue to receive LP352

ADVOCACY AND RESEARCH PARTNERS

We have engaged advocacy groups across the DEE landscape in order to optimize enrollment and design of the PACIFIC study

List of patient advocacy groups is not exhaustive.

PACIFIC STUDY COLLABORATORS

Dennis J. Dlugos, MD, MCSE

Dr. Dlugos is a professor of neurology and pediatrics at the Children's Hospital of Pennsylvania and the University of Pennsylvania School of Medicine. He currently holds the Tristram C. Colket, Jr. Endowed Chair in Pediatric Neurology. Dr. Dlugos is the Principal Investigator for the PACIFIC study.

Jacqueline French, MD

Dr. French is a professor of neurology at the New York University Langone Comprehensive Epilepsy Center. She is also the founder and director of the Epilepsy Study Consortium, Inc. (ESCI), which is being engaged as a partner in the conduct of the PACIFIC study.

CONCLUSIONS

- **5-HT$_{2C}$ receptor agonists may increase seizure threshold and reduce seizure frequency; LP352 has the potential to be the most highly selective 5-HT$_{2C}$–targeted therapy to reduce the occurrence of seizures in DEE**
- **The PACIFIC study will provide insight into the safety, tolerability, and PK/PD profile of 3 escalating doses of LP352 in a variety of DEE patients, while providing proof of concept for a more generalizable, non–syndrome-based DEE trial**
- **The data from this study should inform future clinical trials regarding dose selection, relevant efficacy measures, and the appropriate DEE study population**

PACIFIC Developmental and Epileptic Encephalopathies Study

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Abbreviations **5-HT**, 5-hydroxytryptamine; **DEE**, developmental and epileptic encephalopathy; **EC$_{50}$**, half maximal effective concentration; **EEG**, electroencephalogram; **GABA**, gamma aminobutyric acid; **Glu**, glutamate; **LGS**, Lennox-Gastaut syndrome; **PD**, pharmacodynamic; **PK**, pharmacokinetics; **PRL**, prolactin; **SERT**, serotonin reuptake transporter; **TEAE**, treatment-emergent adverse event **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.** Gharedaghi MH et al. *Exp Brain Res.* 2014;232:347-367. **5.** Bagdy G et al. *J Neurochem.* 2007;100:857-873. **6.** Sourbron J, Lagae L. *Epilepsia Open.* 2022;7:231-246. **7.** Parasrampuria DA et al. Single Ascending Dose Pharmacokinetics (PK), Pharmacodynamics (PD), and Tolerability of LP352 in Healthy Participants. Presented at the American Academy of Neurology 2022 Annual Meeting. **8.** Parasrampuria DA et al. A Randomized, Double-Blind, Placebo-Controlled, Multiple Ascending Dose Pharmacokinetics (PK), Pharmacodynamics (PD), and Tolerability Study of LP352 in Healthy Participants. Presented at the American Academy of Neurology 2022 Annual Meeting; April 2-7, 2022; Seattle, WA.