EFFICACY AND SAFETY OF BEXICASERIN (LP352) IN ADOLESCENT AND **ADULT PARTICIPANTS** WITH DEVELOPMENTAL AND EPILEPTIC **ENCEPHALOPATHIES: RESULTS OF THE PHASE 1B/2A PACIFIC STUDY**

Randall Kaye,¹ Chad Orevillo,¹ Dennis J. Dlugos,² Ingrid E. Scheffer³

¹Longboard Pharmaceuticals, La Jolla, CA, USA; ²Children's Hospital of Philadelphia (CHOP), Philadelphia, PA, USA; ³The University of Melbourne, Austin Health, Melbourne, VIC, Australia

NGBOARD



DLongboard Pharmaceuticals. copies of this poster obtained through de are for personal use only nd may not be reproduced without permission of the authors.

Scan to download a reprint of this poster

Acknowledgments

This study was sponsored by Longboard Pharmaceuticals, Inc. (La Jolla, CA, USA). Medical writing assistance was provided by ApotheCom (San Diego, CA, USA) and funded by Longboard Pharmaceuticals.

Presented at the 76th Annual Meeting of American Academy of Neurology; April 13-18, 2024; Denver, CO.

BACKGROUND

- DEEs are the most severe group of epilepsies and are characterized by drug-resistant seizures, epileptiform abnormalities, and developmental slowing or regression¹⁻³
- DEE trials have focused on patients with specific epilepsy syndromes, including Dravet Syndrome, tuberous sclerosis complex, and LGS; the latter has etiologic heterogeneity
- Bexicaserin is a potent and selective 5-HT_{2C} receptor superagonist specifically designed for use in patients with DEE
- Preclinical and clinical data support the use of 5-HT_{2C} receptor superagonists in modulating the frequency and threshold of seizure onset⁴⁻⁶
- Bexicaserin was generally well tolerated in double-blind, placebo-controlled studies^{7,8}
- Here, we present the key findings from the phase 1b/2a study of participants with DEEs treated with bexicaserin

OBJECTIVE

• To assess the safety, tolerability, pharmacokinetics, and efficacy of bexicaserin for treatment of seizures in participants with DEEs

METHODS

Study Design

- This was a randomized, double-blind, placebo-controlled, parallel-group, dose-escalation study in participants ≥12 to ≤65 years of age with DEEs (PACIFIC, NCT05364021)
- Participants were randomly assigned (4:1) to receive bexicaserin or placebo
- Following a 15-day flexible titration period (maximum dose of 12 mg TID, based on tolerability), participants went through a 60-day maintenance period and a 5- to 15-day tapering period (**Figure 1**)
- Key inclusion criteria included the following:
- DEEs with average of ≥4 motor seizures per 4-week period during the 12 weeks before screening and ≥ 4 motor seizures in the 4-week period of screening
- Additional criteria for participants with Dravet Syndrome, LGS, and DEE Other are found in **Table 1** • Key exclusion criteria included the use of fenfluramine and lorcaserin

Outcome Measures

- The primary safety endpoint was safety measured through the incidence and severity of TEAEs and other safety parameters
- No echocardiogram monitoring was required
- The primary efficacy endpoint was the percentage change from baseline in observed countable motor seizure frequency during the treatment period

Figure 1. PACIFIC Study Design **Treatment Period** Screening | Randomization and Follow-up Period **Up-Titration** Titration Maintenance^a Period Days 16-75 Days 76-80/90⁵ Days 1-15 Weeks Bexicaserin (n = 43) $6 \text{ mg} \rightarrow 9 \text{ mg} \rightarrow 12 \text{ mg}$ Participant remained or 6, 9, or 12 mg based on pen-Lab tolerability during up-titration Placebo (n = 9) ^aMaintenance dose of bexicaserin: 6 mg, 9 mg, 12 mg, or placebo TID. ^bUp to a 15-day down-titration/taper period (reducing dose every 5 days) depending on the last maintenance dose.

Table 1. Diagnostic Eligibility Criteria by Participant Subgroup			
	Dravet Syndrome	LGS	DEE Other
Onset	Between 3–19 months of age	Before 8 years of age	Unprovoked seizures before 5 years of age
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 normal, then delayed	Delayed	Delayed
Electroencephalography		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 Syndrome 	More than 1 type of generalized seizure for ≥6 months before screening	No history of idiopathic generalized seizures

^aAbnormal inter-ictal electroencephalography background activity with inter-ictal slow spike-and-wave pattern <2.5 Hz or inter-ictal generalized paroxysmal fast activity.

RESULTS

Participants

• 52 participants (43 bexicaserin, 9 placebo) were randomly assigned to treatment (29 LGS, 4 Dravet Syndrome, and 19 DEE Other) across 34 sites (**Tables 2** and **3**)

Table 2. Participant Disposition

Parameter n (%)	Bexicaserin (n = 43)	Placebo (n = 9)
Safety set	43 (100)	9 (100)
Full analysis set	35 (81.4)	9 (100)
Participants completed	32 (74.4)	9 (100)

Table 3. Demographics and Baseline Characteristics

	Bexicaserin (n = 43)	Placebo (n = 9)	Overall (N = 52)
Age, mean (SD), years	23.8 (9.62)	26.7 (7.73)	24.3 (9.31)
Min, max	12, 55	19, 41	12, 55
Sex, n (%)			
Male	21 (48.8)	7 (77.8)	28 (53.8)
Female	22 (51.2)	2 (22.2)	24 (46.2)
BMI, median (min, max), kg/m²	22.4 (17, 35)	28.1 (19, 34)	23.0 (17, 35)
Baseline countable motor seizures	40.0	24.1	38.2
Concomitant medications, n (%)			
Clobazam	21 (48.8)	2 (22.2)	23 (44.2)
Valproate	17 (39.5)	6 (66.7)	23 (44.2)
Cannabidiol	14 (32.6)	3 (33.3)	17 (32.7)
Lamotrigine	13 (30.2)	4 (44.4)	17 (32.7)
Levetiracetam	16 (37.2)	1 (11.1)	17 (32.7)

• 35 participants received bexicaserin in the full analysis set; 30 (85.7%) reached the highest dose (12 mg TID) and 27 (77.1%) reached and tolerated the maximum dosing through the maintenance period (**Table 4**)

Table 4. Highest Tolerated Dose Achieved and Maintained for the Maintenance Period

n (%)	Bexicaserin	Placebo	Overall
All participants	35	9	44
6 mg	4 (11.4)	Ο	4 (9.1)
9 mg	4 (11.4)	ר.רר) ר	5 (11.4)
12 mg	27 (77.1)	8 (88.9)	35 (79.5)

Safety

• The most common TEAEs were somnolence, decreased appetite, constipation, diarrhea, lethargy,

tremor, urinary tract infection, fatigue, pyrexia, agitation, and hypotension (**Table 5**)

• Three participants (7.0%) in the bexicaserin group reported an SAE (ankle fracture × 2, constipation, and increased seizures)

• During the titration period, 16.3% of bexicaserin-treated participants discontinued due to an AE, while during the maintenance period, 4.7% of bexicaserin-treated participants discontinued due to an AE

Table 5. Summary of Safety Results

n (%)	Bexicaserin (n = 43)	Placebo (n = 9)	Overall (N = 52)
Participants with ≥1 TEAE	35 (81.4)	8 (88.9)	43 (82.7)
TEAEs by SOC ^a			
Nervous system disorders			
Somnolence	12 (27.9)	1 (11.1)	13 (25.0)
Lethargy	4 (9.3)	0	4 (7.7)
Tremor	3 (7.0)	0	3 (5.8)
Gastrointestinal disorders			
Constipation	6 (14.0)	0	6 (11.5)
Diarrhea	5 (11.6)	0	5 (9.6)
Infections and infestations			
Urinary tract infection	3 (7.0)	0	3 (5.8)
General disorders and administration site conditions			
Fatigue	3 (7.0)	Ο	3 (5.8)
Pyrexia	3 (7.0)	Ο	3 (5.8)
Metabolism and nutrition disorders			
Decreased appetite	9 (20.9)	Ο	9 (17.3)
Psychiatric disorders			
Agitation	3 (7.0)	0	3 (5.8)
Vascular disorders			
Hypotension	3 (7.0)	0	3 (5.8)

^aOver 5% of bexicaserin participants and greater than placebo







Figure 4. The Overall Pattern of Response in the LGS Group Was Highly Similar to the DEE Other Group





Figure 6. Higher Proportion of Participants in the Bexicaserin Group Had a ≥ 50% Reduction in Frequency of (A) Observed Countable Motor Seizures and (B) Total Seizures Versus Placebo During Treatment Period



CONCLUSIONS

- In this study, bexicaserin exhibited a favorable safety and tolerability profile in a broad DEE population
- Treatment with bexicaserin reduced seizures in all participant subgroups, including LGS and DEE Other
- Efficacy was demonstrated in participants with a polytherapy background, including multiple antiseizure medications, including cannabidiol

Abbreviations 5-HT, 5-hydroxytryptamine; AE, adverse event; BMI, body mass index; DEE, Developmental and Epileptic Encephalopathy; LGS, Lennox-Gastaut Syndrome; SAE, serious adverse event; SD, standard deviation; SOC, system organ class; **TEAE**, treatment-emergent adverse event; **TID**, 3 times daily.

References

1. Scheffer IE et al. Epliepsia. 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; April 2-7, 2022; Seattle, WA. 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.