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

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BACKGROUND

- DEEs are the most severe group of epilepsies and are characterized by drug-resistant seizures, epileptiform abnormalities, and developmental slowing or regression[1-3]
- 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 onset[4-6]
  - 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

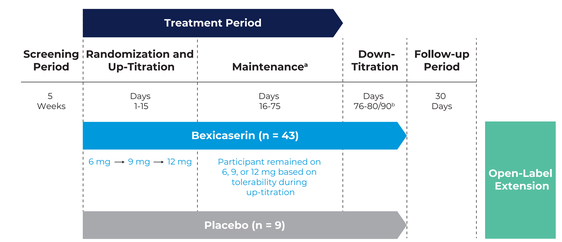
Study Design

- 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



[a]Maintenance dose of bexicaserin: 6 mg, 9 mg, 12 mg, or placebo TID.
[b]Up 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

[a]Abnormal 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)	0	4 (9.1)
9 mg	4 (11.4)	1 (11.1)	5 (11.4)
12 mg	27 (77.1)	8 (88.9)	35 (79.5)

Safety

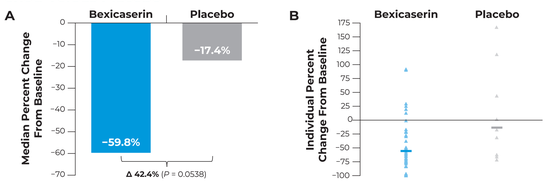
- The most common TEAEs were somnolence, decreased appetite, constipation, diarrhea, lethargy, tremor, urinary tract infection, fatigue, pyrexia, agitation, and hypotension (**Table 5**)
- Three participants (7.0%) in the bexicaserin group reported an SAE (ankle fracture × 2, constipation, and increased 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)	0	3 (5.8)
Pyrexia	3 (7.0)	0	3 (5.8)
Metabolism and nutrition disorders			
Decreased appetite	9 (20.9)	0	9 (17.3)
Psychiatric disorders			
Agitation	3 (7.0)	0	3 (5.8)
Vascular disorders			
Hypotension	3 (7.0)	0	3 (5.8)

[a]Over 5% of bexicaserin participants and greater than placebo.

Figure 2. Participants Receiving Bexicaserin Had a Greater Reduction in Observable Countable Motor Seizure Frequency During the Treatment Period Versus Placebo



Bexicaserin Achieved Placebo Adjusted Mean Seizure Reduction of 51.9% (P = 0.0206, post hoc exploratory analysis)

Figure 3. Countable Motor Seizures Were Reduced in All 3 Groups

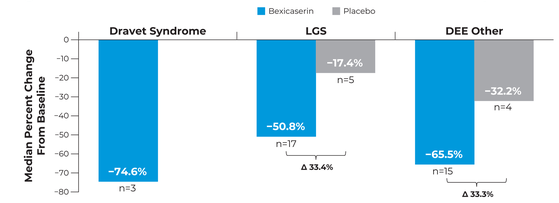


Figure 4. The Overall Pattern of Response in the LGS Group Was Highly Similar to the DEE Other Group

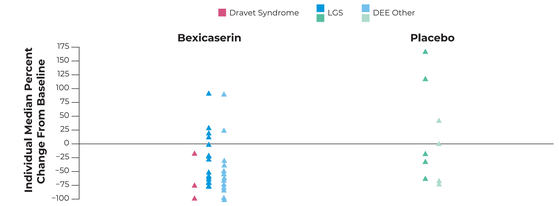


Figure 5. Participants in the Bexicaserin Group Had a Greater Reduction in Total Seizure Frequency During Treatment Period Versus Placebo

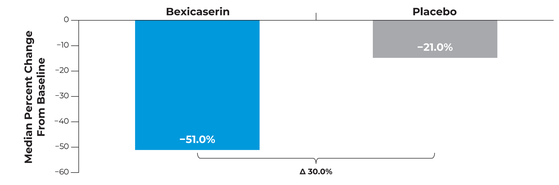
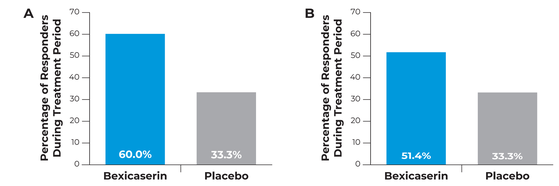


Figure 6. Higher Proportion of Participants in the Bexicaserin Group Had a ≥ 50% Reduction in Frequency of (A) Observed Countable Motor Seizures and (B) Total Seizures Versus Placebo During Treatment Period



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. *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; 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.