P082

SAFETY AND TOLERABILITY OF BEXICASERIN IN ADOLESCENTS AND ADULTS WITH DEVELOPMENTAL AND EPILEPTIC ENCEPHALOPATHIES: INTERIM RESULTS OF THE PHASE 1B/2A PACIFIC STUDY OPEN-LABEL EXTENSION

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BACKGROUND

- Patients with developmental and epileptic encephalopathies (DEEs) are a rare, underserved population, with more than 20 DEEs identified to date[1-5]
- DEEs are the most severe group of epilepsies and are characterized by drug-resistant seizures, epileptiform abnormalities, and developmental slowing or regression. As such, patients with DEEs often have complex polypharmacy[1]
- With improved seizure control, it is hypothesized that the aspects of developmental delay driven by uncontrolled seizures also could improve.[1] However, randomized controlled trials have historically focused on Dravet Syndrome (DS), Tuberous Sclerosis Complex, CDKL5 Deficiency Disorder (CDD), and Lennox-Gastaut Syndrome (LGS), leaving numerous patients with other DEEs without any approved therapies[3,5,6]
- Bexicaserin is a new molecule that is a superagonist at the 5-hydroxytryptamine 2C (5-HT_{2C}) receptor[7]
  - The precise pharmacology at the 5-HT_{2C} receptor may offer advantages in optimizing seizure reduction in patients with DEEs while reducing the potential for adverse effects observed with other non-selective (serotonergic) anti-seizure medications (ASMs)[8]
- PACIFIC was a 4:1 randomized, double-blind, placebo-controlled, DEE-inclusive study (NCT05364021) in 52 participants with DS, LGS, and 'DEE Other,' who had ≥4 countable motor seizures (CMS) during their 28-day screening, while on a stable regimen of 1 to 4 concomitant ASMs[7,9]
  - Bexicaserin was well tolerated, exhibited an excellent safety profile, and resulted in clinically meaningful CMS reductions from baseline that were comparable in all subgroups (DS, −74.6%; LGS, −50.8%; and 'DEE Other,' −65.5%)[7,9]
  - Common treatment-emergent adverse events (TEAEs; reported in ≥10% of participants receiving bexicaserin) included somnolence, decreased appetite, constipation, and diarrhea[7,9]
- Patients who successfully completed the PACIFIC study were eligible to participate in an open-label extension (OLE) study[7] for up to 52 weeks (1 year; NCT05626634)
- In this poster, we present the interim analysis of the safety and tolerability data of adolescent and adult participants with DEEs who have received bexicaserin for at least 6 months in the OLE study

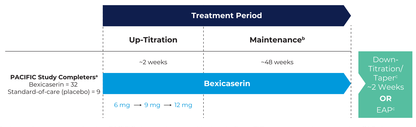
OBJECTIVE

- To assess the long-term safety and tolerability of bexicaserin in adolescent and adult participants with DEEs

METHODS

- Eligibility criteria included participants who were ≥12 to ≤65 years of age at enrollment of the PACIFIC study, received ≥1 dose of bexicaserin, and enrolled in the OLE (safety analysis set)
- All participants entering the OLE received bexicaserin 6 mg three times daily (TID), including those who had received standard-of-care (placebo arm) in the PACIFIC study (**Figure 1**)
  - Titration was at the investigator's discretion in the first 15 days (2 weeks), with a maximum dose of 12 mg TID based on tolerability
  - The maintenance period is ongoing and is planned for 48 weeks
  - Down-titration (taper) will occur during the last 2 weeks of the study for participants not entering the early access program (EAP)
- Safety is evaluated by the incidence and severity of TEAEs throughout the study

Figure 1. Study Design



[a]Participants who completed the PACIFIC study with down-titration to 6 mg TID were eligible to enroll in the OLE study.
[b]The dose of bexicaserin was escalated at 5-day intervals or per the discretion of the investigator based on tolerability.
[c]15-day down-titration/taper, reduction of 3 mg every 5 days. This does not apply to participants that elect to enter the EAP.

RESULTS

Participants

- As of May 22, 2024 (data cutoff date), a total of 41 participants (100% of participants who completed the PACIFIC study) enrolled in the OLE and received ≥1 dose of bexicaserin (safety analysis set; **Figure 2**)
- Demographics and baseline characteristics of participants in the PACIFIC study are provided in **Table 1**

Figure 2. Participants Enrolled in the OLE by Subtype

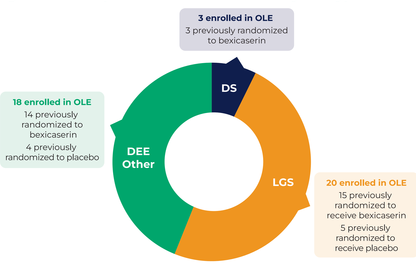


Table 1. Demographics and Baseline Characteristics of Participants in the PACIFIC Study

	Overall N = 52
Age, mean (SD), years	24.3 (9.3)
Min, max	12, 55
Sex, n (%)	
Male	28 (53.8)
Female	24 (46.2)
BMI, median (min, max), kg/m^2	23.0 (17, 35)
Baseline countable motor seizures	38.2
Concomitant medications, n (%)	
Clobazam	23 (44.2)
Valproate	23 (44.2)
Cannabidiol	17 (32.7)
Lamotrigine	17 (32.7)
Levetiracetam	17 (32.7)

Safety

- All 9 participants who were newly exposed to bexicaserin in the OLE still remain on bexicaserin
- Of the 41 participants, 2 (4.9%) have discontinued treatment with bexicaserin, both in the LGS subgroup (**Table 2**):
  - 1 participant due to a TEAE of lethargy
  - 1 participant withdrew consent
- Overall, 7 participants (17.1%) reported a serious TEAE (3 participants [7.3%] with pneumonia; 1 participant [2.4%] each with bacterial pneumonia, change in seizure presentation, seizures, and agitation, **Table 2**)
- Bexicaserin has been well tolerated and the most commonly reported TEAEs include upper respiratory tract infection, COVID-19, pneumonia, sinusitis, seizure, and decreased appetite (**Table 3**)

Table 2. Summary of Safety Results

n (%)	Overall N = 41
Participants with ≥1 TEAE	30 (73.2)
Drug-related TEAE[a]	11 (26.8)
Serious TEAE	7 (17.1)
Drug-related serious TEAE[a]	1 (2.4)
TEAE leading to study drug discontinuation	1 (2.4)
TEAE leading to dose modification	5 (12.2)
TEAE leading to death	0
TEAE leading to study discontinuation	1 (2.4)

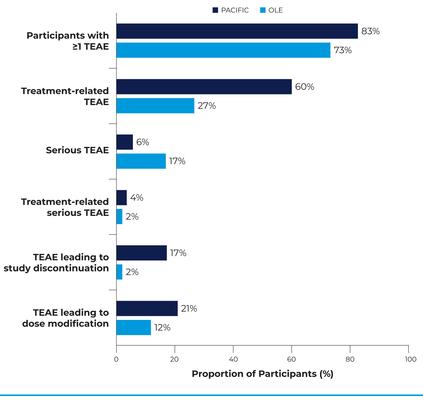
[a]Drug-related TEAEs are defined as TEAEs deemed probably or possibly related to bexicaserin by the investigator.

Table 3. Common TEAEs (Occurring in ≥5% of Participants) by Preferred Term

n (%)	Overall N = 41
Upper respiratory tract infection	5 (12.2)
COVID-19	3 (7.3)
Pneumonia	3 (7.3)
Sinusitis	3 (7.3)
Seizure	3 (7.3)
Decreased appetite	3 (7.3)

- In the OLE, the proportion of treatment-related TEAEs, TEAEs leading to study discontinuation, and TEAEs leading to dose modification occurred with lower frequency compared with that reported in the PACIFIC study (**Figure 3**)
  - In the PACIFIC study, 7 participants randomized to bexicaserin discontinued due to a TEAE during the up-titration phase
  - In the OLE, 1 participant discontinued due to a TEAE of lethargy during the up-titration phase

Figure 3. Summary of Safety Results: PACIFIC[7,9] and OLE



CONCLUSIONS

- **Bexicaserin continues to exhibit a favorable safety and tolerability profile at 6 months based on data from this OLE interim analysis**
- **No new or unexpected safety signals were observed**
- **100% of eligible PACIFIC participants chose to enroll in the OLE, with 2 discontinuations (4.9%) at 6 months (1 participant during dose escalation, 1 participant during maintenance). Both discontinuations were in participants who had received bexicaserin in the PACIFIC study**
- **The subset of participants newly exposed to bexicaserin in the OLE (n = 9) had no significant adverse events leading to discontinuation at 6 months, further reinforcing that in the context of a flexible titration process, bexicaserin is well tolerated in a DEE-inclusive population**
- **Moreover, somnolence was a common TEAE reported as a reason for discontinuation for participants in the PACIFIC study during the up-titration period, which was not observed in the OLE**
- **Results from this OLE interim analysis and the PACIFIC study are supportive of further investigation of the efficacy and safety of bexicaserin for the management of seizures in patients with DS, LGS, and a variety of other DEEs in a Phase 3 study**

Abbreviations **5-HT$_{2C}$**, 5-hydroxytryptamine 2C; **ASM**, anti-seizure medication; **BMI**, body-mass index; **CDD**, CDKL5 Deficiency Disorder; **CMS**, countable motor seizure; **DEE**, developmental and epileptic encephalopathy; **DS**, Dravet Syndrome; **EAP**, early access program; **LGS**, Lennox-Gastaut Syndrome; **n/N**, number of participants; **OLE**, open-label extension; **SD**, standard deviation; **TEAE**, treatment-emergent adverse event; **TID**, three 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.** Johannesen Landmark C, et al. *Epilepsia*. 2021;62(4):857-873. **4.** Strzelczyk A, Schubert-Bast S. *CNS Drugs*. 2022;36(10):1079-1111. **5.** Guerrini R, et al. *Physiol Rev*. 2023;103(1):433-513. **6.** Sills GJ. *Ther Adv Neurol Disord*. 2023;16:17562864231191000. **7.** Dell'Isola GB, et al. *Expert Opin Pharmacother*. 2024;25(9):1121-1130. **8.** Lagae L, et al. *Lancet*. 2019;394(10216):2243-2254. **9.** Kaye R, et al. Presented at the 76th Annual Meeting of American Academy of Neurology; April 13-18, 2024; Denver, CO.

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LONGBOARD PHARMACEUTICALS

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