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A PHASE 1 STUDY OF 5-HT$_{2C}$ SUPERAGONIST BEXICASERIN SHOWS ROBUST BRAIN PENETRATION, A STRONG CORRELATION BETWEEN PLASMA AND CSF PHARMACOKINETICS AND QEEG CHANGES REFLECTING RECEPTOR ENGAGEMENT

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BACKGROUND

- Developmental and epileptic encephalopathies (DEEs) are rare neurodevelopmental disorders characterized by early-onset seizures that are often difficult to control, accompanied by abnormal electroencephalogram activity and developmental delay or regression[1-3]
- Bexicaserin is a potent and highly selective 5-hydroxytryptamine (5-HT)$_{2C}$ superagonist designed for the treatment of DEEs
  - Bexicaserin 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)[4] and 5-HT$_{2B}$ (valvular heart disease and pulmonary arterial hypertension)[5,6]
- The first-in-human study showed rapid oral absorption of bexicaserin with attainment of peak levels within 1-2 hours of dosing in circulation that resulted in an early pharmacodynamic (prolactin) effect[7]

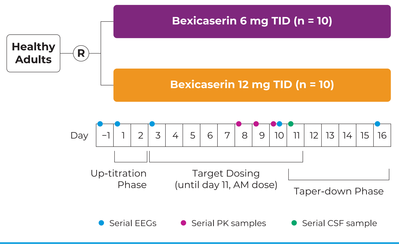
OBJECTIVES

- To evaluate the relative plasma and cerebrospinal fluid (CSF) pharmacokinetics (PK) of multiple oral doses of bexicaserin, while assessing the accompanying effects on quantitative electroencephalogram (QEEG) activity

METHODS

- This was a phase 1, open-label, multiple-dose study in healthy adults between 18 to 55 years of age (n = 20; **Figure 1**)
- Participants received liquid oral doses of bexicaserin 6 mg or 12 mg 3 times daily (TID)
  - Dose regimens included up-titration (days 1 and 2) followed by target dosing for 8 days
- Serial plasma samples were obtained after single dose and selected multiple dose days (days 8-10)
- Serial CSF samples were obtained at steady state (day 11)
- Serial EEGs with eyes in open and closed positions were recorded at baseline and days –1, 1, 3, 10, and 16
- Protein unbound fraction of bexicaserin was determined from steady state plasma samples at multiple timepoints
- Validated triple-quad liquid chromatography mass-spectrometric methods were used for the quantitation of bexicaserin in various clinical samples
- The concentration data of bexicaserin (plasma and CSF) were subjected to standard non-compartmental PK analysis

Figure 1. Study Design



RESULTS

Participants

- 20 healthy adult volunteers were included in this study (10 participants in the bexicaserin 6 mg TID and 10 participants in the bexicaserin 12 mg TID groups)
- There were 60% male versus 40% female participants in the bexicaserin 6 mg TID group and 70% male versus 30% female participants in the bexicaserin 12 mg TID group (**Table 1**)

Table 1. Participant Characteristics

Characteristic	Bexicaserin 6 mg TID n = 10	Bexicaserin 12 mg TID n = 10
Age, mean (SD), years[a]	40.7 (7.48)	34.9 (6.98)
Sex, n (%)		
Male	6 (60.0)	7 (70.0)
Female	4 (40.0)	3 (30.0)
Race/Ethnicity, n (%)		
Asian	1 (10.0)	2 (20.0)
Black or African American	3 (30.0)	0
White	6 (60.0)	8 (80.0)
Native Hawaiian or Other Pacific Islander	0	0
Other	0	0
Hispanic or Latino	4 (40.0)	0
Not Hispanic or Latino	6 (60.0)	10 (100.0)
BMI, mean (SD)	25.6 (3.822)	24.89 (2.512)

[a]Age was derived from date of birth to the date of informed consent.

Pharmacokinetics

- There was a dose linear increase between maximum concentration (C_{max}), area under the concentration-time curve from time zero to the end of the dosing interval (AUC_{tau}), and average concentration (C_{avg}) of bexicaserin 6 mg and 12 mg TID in both plasma (days 8, 9, and 10) and CSF (day 11), while time to maximum concentration (T_{max}) was consistent at the 2 dose levels across the various days (**Table 2**)
- Based on the similarity in the exposures of bexicaserin across days 8-10, steady state in plasma was attained by day 8 at either 6 mg or 12 mg TID doses (**Table 2**)
- There was a dose linear increase between C_{max}, AUC_{tau}, and C_{avg} of bexicaserin 6 mg and 12 mg TID in both plasma and CSF samples, while T_{max} was similar between the 2 doses but appeared to be at least 1 hour longer as compared to plasma (**Table 3**). The half-life ($t_{1/2}$) values were similar between 6 mg and 12 mg doses and comparable to $t_{1/2}$ values reported for bexicaserin in plasma (approximately 6 hours)[7]

Table 2. Summary Statistics of Bexicaserin 6 mg and 12 mg TID Plasma PK Parameters Following Multiple Doses of Bexicaserin

	Day 8				Day 9				Day 10			
Dose	C_{max} (ng/mL)	AUC_{tau} (h*ng/mL)	T_{max} (h)	C_{avg} (ng/mL)	C_{max} (ng/mL)	AUC_{tau} (h*ng/mL)	T_{max} (h)	C_{avg} (ng/mL)	C_{max} (ng/mL)	AUC_{tau} (h*ng/mL)	T_{max} (h)	C_{avg} (ng/mL)
Bexicaserin 6 mg TID												
n	10.0	10.0	10.0	10.0	10.0	10.0	10.0	10.0	10.0	10.0	10.0	10.0
Mean	17.0	79.6	1.50	9.95	19.1	88.1	1.20	11.0	16.9	85.4	1.30	10.7
SD	3.75	21.5	0.667	2.69	5.69	27.0	0.587	3.37	4.46	22.0	0.483	2.75
Bexicaserin 12 mg TID												
n	10.0	10.0	10.0	10.0	10.0	10.0	10.0	10.0	9.00	9.00	9.00	9.00
Mean	40.3	210	1.35	26.2	48.3	218	1.05	27.2	45.3	222	1.22	27.8
SD	20.8	118	0.709	14.7	23.1	137	0.369	17.1	31.3	148	0.441	18.5

Table 3. Summary Statistics of Bexicaserin 6 mg and 12 mg TID CSF PK Parameters Following Multiple Doses of Bexicaserin (Day 11)

	Day 11				
Dose	AUC_{tau} (h*ng/mL)	C_{max} (ng/mL)	T_{max} (h)	C_{avg} (ng/mL)	$t_{1/2}$ (h)
Bexicaserin 6 mg TID					
n	9	9	9	9	8
Mean	74.059	12.287	2.944	9.257	5.385
SD	18.135	3.345	1.310	2.267	1.060
Bexicaserin 12 mg TID					
n	7	7	7	7	7
Mean	194.877	30.357	2.786	24.360	6.257
SD	142.992	21.526	0.699	17.874	1.489

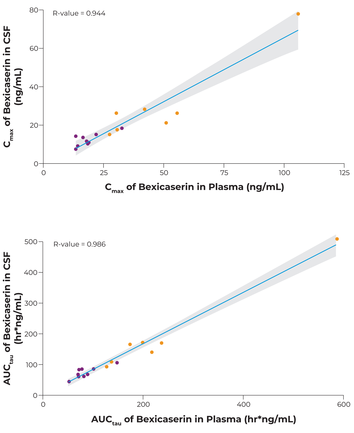
Table 4. CSF (Day 11) and Plasma (Day 10) PK Ratio of Bexicaserin 6 mg and 12 mg TID[a]

	Day 11	Day 10	PK Ratio
Dose	Mean AUC_{tau} in CSF (h*ng/mL)	Mean AUC_{tau} in Plasma (ng/mL)	Ratio CSF/Plasma
Bexicaserin 6 mg TID	74.1	85.4	0.86
Bexicaserin 12 mg TID	194.9	222.4	0.88

[a]n = 8 paired data for ratio calculation.

- An overlay of plasma and CSF curves showed similarity in the absorption, distribution, and elimination phases at 6 mg and 12 mg TID doses for either plasma or CSF (**Figure 2**)
- A strong correlation was observed between bexicaserin plasma and CSF PK parameters, with R-value = 0.944 for $C_{max,ss}$ and R-value = 0.986 for AUC_{tau} (**Figure 2**)

Figure 2. C_{max} and AUC_{tau} CSF versus Plasma PK Correlations for Bexicaserin 6 mg and 12 mg TID Dosing



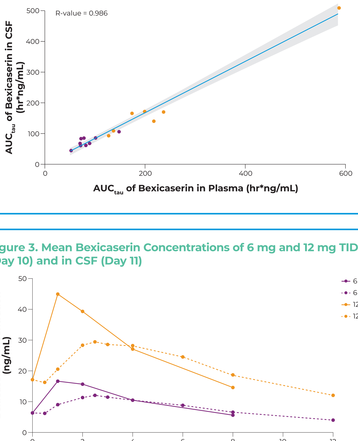


Figure 3. Mean Bexicaserin Concentrations of 6 mg and 12 mg TID in Plasma (Day 10) and in CSF (Day 11)

- Regardless of 6 mg or 12 mg TID doses, the unbound protein fraction of bexicaserin was very high and consistent at various times of measurements (**Table 5**)

Table 5. Unbound Fraction of Bexicaserin 6 mg and 12 mg TID Pre-Dose, 2- and 8-hours After Dosing[a]

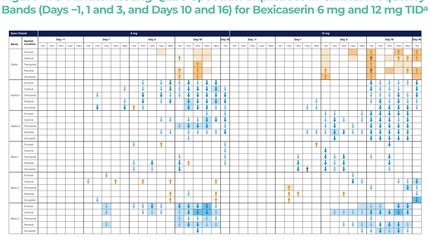
Dose	Pre-Dose	2 hours	8 hours
Bexicaserin 6 mg TID			
Mean	0.969	0.990	0.946
SD	0.035	0.013	0.050
Bexicaserin 12 mg TID			
Mean	0.961	0.969	0.976
SD	0.066	0.047	0.024

[a]n = 8 data points for each analysis.

QEEG Assessments

- Changes in cerebral activity, measured by QEEG, in the eyes open or eyes closed states, occurred across multiple spectral bands (eg, increases in diffuse delta, and decreases in theta, alpha, and beta frequency band amplitudes), indicating a clinical effect on the brain (**Figure 4**). Furthermore, there was a trend of time- and dose-dependency in the observed QEEG changes

Figure 4. 5-Minute Resting QEEG Spectral Amplitudes in Clinical Frequency Bands (Days –1, 1 and 3, and Days 10 and 16) for Bexicaserin 6 mg and 12 mg TID[a]



[a]Similar QEEG changes were observed for eyes closed measurements.

Safety

- Treatment-emergent adverse events were mild-to-moderate and consistent with earlier studies[7]
- There were no serious adverse events

CONCLUSIONS

- **Similarity in the absorption, distribution, and elimination profiles of bexicaserin in plasma or CSF at steady state were confirmed for the 6 mg and 12 mg TID doses**
- **Bexicaserin has negligible protein binding and readily crosses the blood brain barrier, which are highly desirable properties for compounds in the central nervous system domain**
- **Bexicaserin exhibits dose linear PK not only in the plasma but also in the brain**
- **Consistent with the rapid brain entry, bexicaserin leads to changes in cerebral EEG activity, which was observed to be time- and dose-dependent**

Abbreviations **5-HT**, 5-hydroxytryptamine; **AUC_{tau}**, area under the concentration-time curve from time zero to the end of the dosing interval; **C_{avg}**, average concentration; **C_{max}**, maximum concentration; **CSF**, cerebrospinal fluid; **DEEs**, developmental and epileptic encephalopathies; **EEG**, electroencephalogram; **PK**, pharmacokinetics; **QEEG**, quantitative EEG; **SD**, standard deviation; **$t_{1/2}$**, half-life; **TID**, 3 times daily; **T_{max}**, time to C_{max}.

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.** López-Giménez J, González-Maeso J. *Curr Top Behav Neurosci.* 2018;36:45-73. **5.** Higgins GA et al. *Pharmacol Ther.* 2020;207:1477. **6.** Hutcheson JD et al. *Pharmacol Ther.* 2011;132:146-157. **7.** Parasrampuria D et al. *Neurology.* 2022;98(18):1771.

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