Trofinetide Treatment of Rett Syndrome Is Not Associated With Increased Seizure Incidence or Interactions With Antiepileptic Drugs

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BACKGROUND

- Rett syndrome (RTT) is a debilitating neurodevelopmental disorder associated with a range of symptoms, including seizures[1]
- Seizures affect between 50% and 90% of individuals with RTT[2] and are managed using antiepileptic drugs, which are known to interact with a wide range of medications[3]
- Based on the findings of the phase 3 LAVENDER study (ClinicalTrials.gov identifier: NCT04181723),[4] trofinetide (DAYBUE™) became the first drug to be approved for the treatment of RTT; it is approved in patients 2 years of age and older
- Almost half of the 187 participants (n = 87; 46.5%) in the LAVENDER study had a history of seizures, which was reflected by the frequent use of concomitant antiepileptic medications in the trofinetide (64.5%) and placebo (72.3%) groups during the study
- Seizure was reported as a treatment-emergent adverse event (TEAE) in LAVENDER at a similar incidence in the trofinetide group (n = 8; 8.6%) and placebo group (n = 5; 5.3%), and of the 13 participants with a seizure TEAE, all but 1 participant in each treatment group had a history of seizures[4]

OBJECTIVES

- To explore the relationship between seizures and trofinetide exposure, pharmacokinetic and exposure-response (ER) modeling were used to correlate trofinetide exposure parameters and seizure incidence, and to assess whether there is the potential for a drug interaction between trofinetide and antiepileptic medications

METHODS

Predicted Trofinetide Exposure

- A population pharmacokinetic model for trofinetide was used to generate pharmacokinetic parameter estimates using a Bayesian approach for each individual in the analysis dataset
  - The population pharmacokinetic model included 13 clinical studies of trofinetide (8 phase 1 studies in healthy subjects; 2 phase 2 studies in RTT [RTT-001[5] and RTT-002[6]], 1 phase 2 study in fragile X syndrome, 1 phase 2 study in traumatic brain injury; 1 phase 3 study in RTT [LAVENDER[4]])
  - Individual trofinetide exposure measures included area under the concentration-time curve for the dosing interval of 0 to 12 hours ($AUC_{0–12}$), average drug concentration (C_{avg}), and maximum drug concentration (C_{max})
  - These trofinetide exposure measures were used in the exposure-response models to correlate exposure and seizure incidence

Exposure-Response Modeling

- Pooled safety data, which included participants who received placebo or trofinetide with available trofinetide exposure measures, were derived from the phase 3 LAVENDER study[4] and 2 phase 2 studies (RTT-001[5] and RTT-002[6]) that investigated trofinetide in RTT
- ER modeling of seizure incidence involved (1) exploratory data analysis; (2) base structural model development incorporating drug exposure; (3) evaluation of covariate effects; (4) model refinement; and (5) model evaluation
  - Linear and exponential logistic regression models were used to estimate the probability of seizures for each predicted drug exposure
- Model evaluation was performed using the final model to simulate 500 replicates of the analysis dataset
  - The simulated and observed proportions of participants with seizures were plotted versus trofinetide exposure groups to visually assess concordance between the model-based simulated data and the observed data
- Potential drug-drug interactions (DDIs) were investigated by comparing the AUC in study participants with and without coadministered antiepileptic drug

Statistical Analysis

- Exploratory data analyses were performed using SAS Version 9.4 (SAS Institute, Cary, NC, USA) and KIWI Version 4 202111 (Cognigen division of Simulations Plus, Inc., Buffalo, NY, USA)
- ER modeling was performed using the computer program NONMEM, Version 7, Level 3.0 (ICON Development Solutions, Hanover, MD, USA) using the Laplacian estimation method

RESULTS

Dataset for Modeling

- The pooled safety dataset from the phase 2 studies (RTT-001[5] and RTT-002[6]) and the phase 3 LAVENDER study[4] included 323 participants (trofinetide n = 185 and placebo n = 138)
  - RTT-001: 56 adolescent or adult females with RTT (16–45 years of age) were randomized to placebo (n = 20), trofinetide 35 mg/kg (n = 18), or trofinetide 70 mg/kg (n = 18) and treated twice daily for 4 weeks
  - RTT-002: 82 pediatric and adolescent females with RTT (5–15 years of age) were randomized to placebo (n = 24), trofinetide 50 mg/kg (n = 15), trofinetide 100 mg/kg (n = 16), or trofinetide 200 mg/kg (n = 27) and treated twice daily for 6 weeks
  - LAVENDER: 187 females with RTT (5–20 years of age) were randomized to placebo (n = 94) or trofinetide (n = 93) and treated twice daily for 12 weeks using weight-based dosing (≥12 to <20 kg [6 g], ≥20 to <35 kg [8 g)], ≥35 to <50 kg [10 g], and ≥50 kg [12 g])

Seizure Incidence

- Based on the pooled dataset, a total of 16 participants (5.0%) had at least 1 seizure TEAE during the treatment period, and the incidence of seizure TEAEs was comparable between placebo-treated (n = 6; 4.3%) and trofinetide-treated participants (n = 10; 5.4%)
  - Seizure TEAEs in participants administered trofinetide ranged from 0% to 12% across the different dose groups (**Table 1**)
  - Approximately 56% of seizure TEAEs were observed during the first 30 days of treatment
  - The majority of seizure TEAEs were mild (43.8%) or moderate (43.8%), and 12.5% were severe

Table 1. Summary statistics of the occurrence of seizures, by regimen

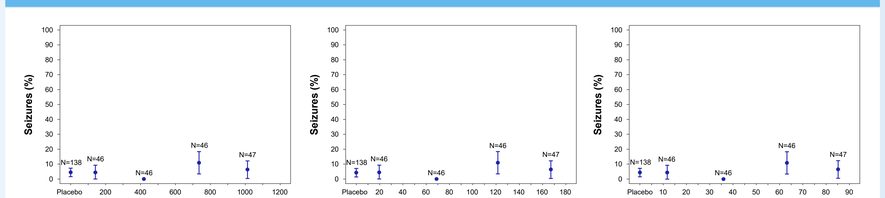
			Twice-daily trofinetide dosing in phase 2 studies					Twice-daily trofinetide dosing in LAVENDER				
Endpoint		PBO	35 mg/kg	50 mg/kg	70 mg/kg	100 mg/kg	200 mg/kg	6 g	8 g	10 g	12 g	Overall
Seizure adverse event occurrence, n (%)	No	132 (95.7)	18 (100.0)	15 (100.0)	15 (88.2)	16 (100.0)	26 (96.3)	21 (91.3)	38 (92.7)	19 (90.5)	7 (100.0)	307 (95.0)
	Yes	6 (4.3)	0	0	2 (11.8)	0	1 (3.7)	2 (8.7)	3 (7.3)	2 (9.5)	0	16 (5.0)

PBO, placebo

Exposure-Response Modeling of Seizures

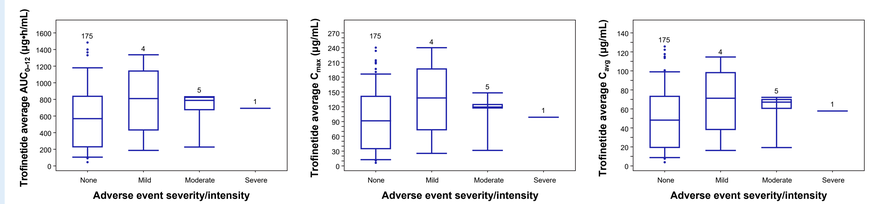
- Exploratory ER analyses demonstrated that the occurrence of seizures was consistently low across trofinetide exposure measures (**Figure 1**), and the range of trofinetide exposures overlapped across the seizure severity categories of mild, moderate, and severe (**Figure 2**), indicating no relationship between trofinetide exposures and seizures
- ER assessments using linear and exponential logistic regression models showed none of the exposure measures were statistically significant predictors ($\alpha = 0.05$) of the probability of seizures, confirming the lack of correlation

Figure 1. Percentage of Participants With Seizures Versus Trofinetide Exposure Measures



The circles and bars represent the observed probabilities and 90% CI, respectively, for placebo and at the median exposure of each quartile
$AUC_{0–12}$, area under the concentration-time curve for the dosing interval of 0 to 12 hours; C_{avg}, average drug concentration; CI, confidence interval, C_{max}, maximum drug concentration

Figure 2. Boxplots of Trofinetide Exposure Measures Versus the Severity of Seizures

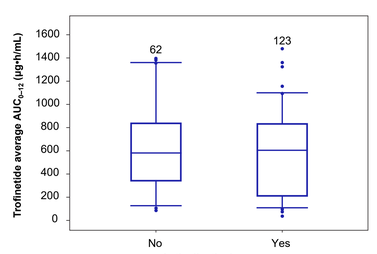


Boxes are 25th, 50th, and 75th percentiles; whiskers are 5th and 95th percentiles. Circles show data points outside this range. The number of participants is above each box
$AUC_{0–12}$, area under the concentration-time curve for the dosing interval of 0 to 12 hours; C_{avg}, average drug concentration; C_{max}, maximum drug concentration

Potential DDI With Antiepileptic Drugs

- Comparing exposure parameter ($AUC_{0–12}$) in participants receiving trofinetide showed a complete overlap in exposures between participants with and without antiepileptic drugs, indicating a lack of effect of antiepileptic medication on trofinetide exposure (**Figure 3**)

Figure 3. Trofinetide Exposure ($AUC_{0–12}$) in Participants With and Without Antiepileptic Drugs



Boxes are 25th, 50th, and 75th percentiles; whiskers are 5th and 95th percentiles. Circles show data points outside this range. The number of participants is above each box
$AUC_{0–12}$, area under the concentration-time curve for the dosing interval of 0 to 12 hours

CONCLUSIONS

- ER safety modeling confirms that there is no relationship between the probability of seizure TEAEs and trofinetide exposures based on the doses used in LAVENDER and the phase 2 studies
- There is no potential DDI between trofinetide and antiepileptic drugs that are commonly used to manage seizures in RTT
- These findings confirm that trofinetide, the first approved treatment for RTT, is not associated with increased seizure incidence and can be coadministered with antiepileptic drugs without any safety concerns

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DISCLOSURES

MD, **JMY**, and **KMB** are employees of and hold stock in Acadia Pharmaceuticals Inc.
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