Weight-Based Banded Dosing to Achieve Target Exposure and Exposure-Response Safety Analyses to Support Trofinetide Treatment in Girls With Rett Syndrome Aged 2–4 Years

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BACKGROUND

- Trofinetide is an investigational drug for the treatment of Rett syndrome (RTT), a debilitating genetic neurodevelopmental disorder
- In the phase 3 LAVENDER™ study in females with RTT aged 5–20 years (NCT04181723), trofinetide provided statistically significant improvements over placebo in caregiver- and clinician-rated efficacy measures and had an acceptable safety profile[1]
- A previous population pharmacokinetic (popPK) model incorporating data from 13 studies confirmed that weight-based banded dosing in LAVENDER would achieve the target therapeutic exposure range (area under the concentration-time curve over the dosing interval [12 hours] at steady state [$AUC_{0–12,ss}$] = 800−1200 µg•h/mL), and safety exposure-response (E-R) modeling indicated that treatment-emergent adverse events (TEAEs) of diarrhea, vomiting, and decreased weight were exposure-dependent in LAVENDER
- In the United States, the median age of diagnosis of classic RTT is 2.7 years[2]; thus, the open-label, phase 2/3 DAFFODIL™ study (NCT04988867) was designed to evaluate long-term safety in a RTT population 2–4 years of age using weight-based trofinetide dosing (5 g twice daily [BID] for participants weighing ≥9 to <12 kg and 6 g BID for participants weighing ≥12 to <20 kg); Treatment Period A (12 weeks) has been completed, but Treatment Period B (~21 months) is ongoing

OBJECTIVES

- To refine the previous popPK model by incorporating data from the DAFFODIL study
- To use the updated popPK model to estimate individual steady-state exposure parameters (maximum observed drug concentration at steady state [$C_{max,ss}$] and $AUC_{0–12,ss}$) to confirm that the body weight–banded dosing used in DAFFODIL would achieve target exposure in girls ≤5 years of age with RTT
- To perform exploratory E-R safety analyses of select TEAEs using data from the DAFFODIL study for comparison with safety findings from LAVENDER

METHODS

Target Exposure

- The updated popPK model included 455 participants from 14 trofinetide clinical trials:
  - Eight phase 1 studies in healthy individuals
  - Two phase 2 studies, one phase 3 study (LAVENDER), and one phase 2/3 study (DAFFODIL) in participants with RTT
  - Two phase 2 studies in other disease conditions (fragile X syndrome and traumatic brain injury)
- Individual exposure measures were generated via integration of the predicted concentration-time profile for each participant based on the final popPK model and individual empiric Bayesian PK parameter estimates. These exposure measures included the $AUC_{0–12,ss}$ and $C_{max,ss}$ for participants in DAFFODIL and LAVENDER following per-protocol body weight–banded dosing regimens
- The estimated exposure measures were used to generate plots that compare the distribution of $AUC_{0–12,ss}$ values for each body-weight group with the target exposure range ($AUC_{0–12,ss}$ = 800–1200 µg•h/mL)

Exploratory E-R Safety Analyses

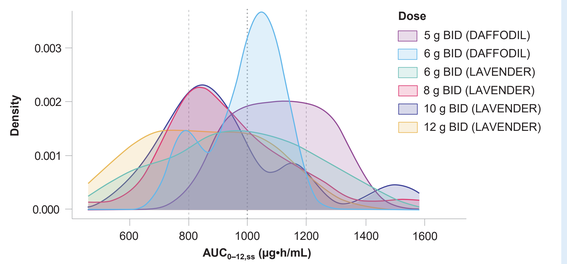
- Exploratory graphical analyses of the distributions of trofinetide exposure measures versus the observed occurrence of TEAEs of interest (decreased appetite, diarrhea, irritability, seizures, vomiting, and weight decreased) in DAFFODIL during Treatment Period A (12 weeks) were compared with data from LAVENDER
  - Due to the small number of patients available in DAFFODIL, no formal exposure-safety modeling was performed

RESULTS

Target Exposure

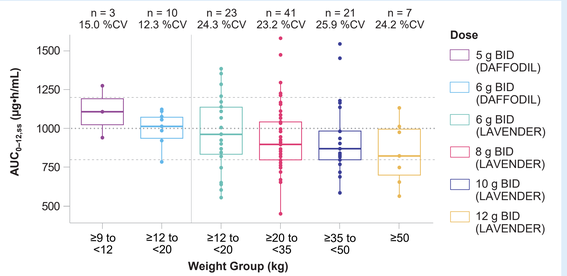
- The addition of data from DAFFODIL provided 13 additional female participants with RTT; study participants from DAFFODIL had a median (range) age of 3 (2–4) years and a median (range) body weight of 13.6 (9.8–18.1) kg
- Final PK parameter estimates between the previous model and the updated model were similar, indicating consistency of PK profile across studies
- A distribution plot (**Figure 1**) and a boxplot (**Figure 2**) comparing $AUC_{0–12,ss}$ values for each body-weight group to the previously identified target exposure range indicated that the distribution of $AUC_{0–12,ss}$ values overlapped with the target exposure range, and the median peak $AUC_{0–12,ss}$ values were largely contained within the target exposure range for all body-weight bands

Figure 1. Distributions of popPK model-predicted $AUC_{0–12,ss}$ values in DAFFODIL and LAVENDER study participants, by body weight–banded dosing regimen



The dashed lines represent the target exposure range ($AUC_{0–12,ss}$ = 800–1200 µg•h/mL). The dotted line represents the median target exposure ($AUC_{0–12,ss}$ = 1000 µg•h/mL)
$AUC_{0–12,ss}$, area under the concentration-time curve over the dosing interval (12 hours) at steady state; BID, twice daily; popPK, population pharmacokinetic

Figure 2. Boxplot of popPK model-predicted $AUC_{0–12,ss}$ values in DAFFODIL and LAVENDER study participants, by body weight–banded dosing regimen

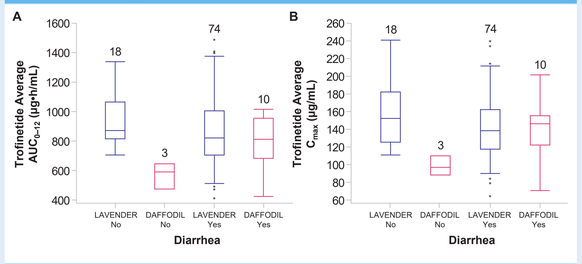


The dashed lines represent the target exposure range ($AUC_{0–12,ss}$ = 800–1200 µg•h/mL). The dotted line represents the median target exposure ($AUC_{0–12,ss}$ = 1000 µg•h/mL). The bottom and top of each box represent the 25th and 75th percentiles, respectively; the whiskers represent the 25th/75th percentiles + 1.5 × IQR; the line within each box represents the median. The circles represent the values above/below the 25th/75th percentiles + 1.5 × IQR
%CV, coefficient of variation expressed as a percentage; $AUC_{0–12,ss}$, area under the concentration-time curve over the dosing interval (12 hours) at steady state; BID, twice daily; IQR, interquartile range; n, number of participants; popPK, population pharmacokinetic

Exploratory E-R Safety Analyses

- No TEAEs of decreased appetite, irritability, or body weight decreased occurred in DAFFODIL during the 12 weeks of Treatment Period A
- Overall, 10 out of 13 participants (76.9%) with TEAEs of interest had ≥1 occurrence of diarrhea
  - The majority of the first occurrences of diarrhea TEAEs (~90%) occurred during the first 60 days of treatment
  - The majority of diarrhea TEAEs (90%) were mild; 10% were moderate
  - The range of exposures for participants with and without TEAEs of diarrhea in DAFFODIL was similar and within the range of exposures from LAVENDER (**Figure 3**)

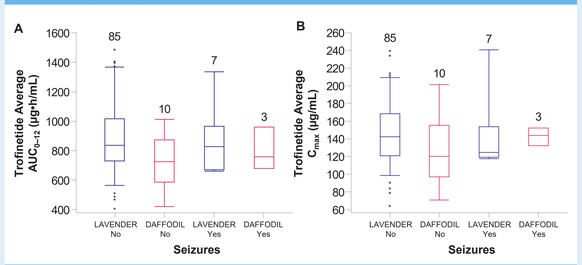
Figure 3. Trofinetide $AUC_{0–12}$ (A) and C_{max} (B) versus the occurrence of diarrhea, by study



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

- Overall, 3 out of 13 participants (23.1%) had ≥1 occurrence of seizures during the 12 weeks of Treatment Period A of DAFFODIL
  - Approximately 67% of the first occurrences of seizure TEAEs occurred during the first 80 days of treatment
  - All seizure TEAEs were of moderate severity
  - The range of exposures for participants with and without TEAEs of seizures in DAFFODIL was similar and within the range of exposures from LAVENDER (**Figure 4**)

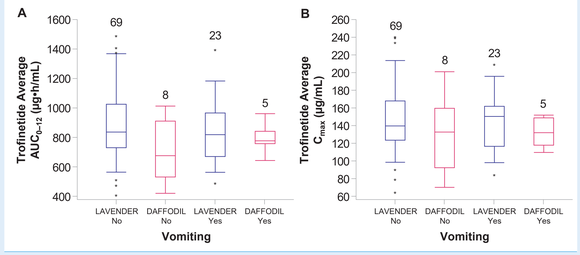
Figure 4. Trofinetide $AUC_{0–12}$ (A) and C_{max} (B) versus the occurrence of seizures, by study



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

- Overall, 5 out of 13 participants (38.5%) had ≥1 occurrence of vomiting during the 12 weeks of Treatment Period A in DAFFODIL
  - The majority of the first occurrences of vomiting TEAEs (~80%) occurred during the first 60 days of treatment
  - The majority of vomiting TEAEs (80%) were mild; 20% were moderate
  - The range of exposures for participants with and without TEAEs of vomiting in DAFFODIL was similar and within the range of exposures from LAVENDER (**Figure 5**)

Figure 5. Trofinetide $AUC_{0–12}$ (A) and C_{max} (B) versus the occurrence of vomiting, by study



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

CONCLUSIONS

- Weight-based banded trofinetide dosing for girls 2–4 years of age with RTT in the DAFFODIL study achieved the target exposure as evaluated in LAVENDER; thus, the proposed dosing regimen in DAFFODIL is adequate to achieve target exposure in girls with RTT aged 2–4 years
- There were no new safety concerns in the DAFFODIL study
- The range of exposures in the DAFFODIL study in girls with and without TEAEs of diarrhea, vomiting, and seizures was similar and within the range of exposure reported in females 5–20 years of age in LAVENDER

REFERENCES

1. Neul JL, et al. *Neurology*. 2022;99(3):e304.
2. Banerjee A, et al. *Brain*. 2019;142(2):239–248.

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DISCLOSURES

MD, **HBr**, and **KMB** are employees of and stockholders in Acadia Pharmaceuticals Inc. **KM**, **JP**, and **HBa** are employees of and hold stock in Simulations Plus.

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