# Weight-Based Banded Dosing to Achieve Target Exposure and Exposure-Response Efficacy Analyses to Support Trofinetide Treatment in Rett Syndrome

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## BACKGROUND

- Trofinetide is an investigational drug for the treatment of Rett syndrome (RTT), a debilitating genetic neurodevelopmental disorder caused by loss-of-function mutations in the X-linked methyl-CpG-binding protein 2 (*MECP2*) gene[1] that result in abnormal neuronal maturation and plasticity[2–4]
- Trofinetide is a synthetic analog of glycine-proline-glutamate (GPE), a naturally occurring tripeptide in the brain that is enzymatically cleaved from insulin-like growth factor 1[5,6]
  - In the *Mecp2*-deficient mouse model of RTT, GPE partially reversed RTT-like symptoms, improved survival, and enhanced synaptic morphology and function[7]
- 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 demonstrated an acceptable safety profile[8]
  - Previous phase 2 studies have also demonstrated trofinetide to be efficacious and well tolerated in the treatment of RTT[9,10]
- Weight-based dosing of trofinetide was used in LAVENDER to achieve the target exposure (area under the concentration-time curve over the dosing interval [12 hours] at steady state [$AUC_{0–12,ss}$] of 800–1200 µg•h/mL) that was previously identified in a phase 2 study[10]
- Initial exposure-response (E-R) modeling of the phase 2 studies in females with RTT using predicted exposure parameters and selected efficacy endpoints suggested a correlation between trofinetide $AUC_{0–12,ss}$ and magnitude of response on the Rett Syndrome Behaviour Questionnaire (RSBQ) and Clinical Global Impression–Improvement (CGI-I) scale, the coprimary endpoints in LAVENDER
  - The E-R RSBQ model was used to identify the target exposure and guide weight-banded dose selection for LAVENDER

## OBJECTIVES

- To refine the previous population pharmacokinetic (popPK) model by incorporating pooled data from 13 clinical studies, including LAVENDER
- 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 weight-based dosing used in LAVENDER would achieve target exposure in individuals with RTT aged 5–20 years
- To perform E-R analyses to characterize the relationships between exposure measures and the LAVENDER efficacy endpoints

## METHODS

### Target Exposure

- The refined popPK model included data from 442 participants from 13 trofinetide clinical trials:
  - Eight phase 1 studies in healthy participants
  - Two phase 2 studies (Neu-2566-Rett-001[9] and Neu-2566-Rett-002[10]) and a phase 3 study (LAVENDER[8]) 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 individual based on the final popPK model and individual empiric Bayesian pharmacokinetic (PK) parameter estimates. These exposure measures included $AUC_{0–12,ss}$ and $C_{max,ss}$ for participants in LAVENDER following per protocol body weight–banded dosing regimens:
  - 6 g, 8 g, 10 g, and 12 g twice daily (BID) for participants weighing ≥12 to <20 kg, ≥20 to <35 kg, ≥35 to <50 kg, and ≥50 kg, respectively
- The estimated exposure measures were used to generate plots that compare the distributions 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)

### Exposure-Efficacy Modeling

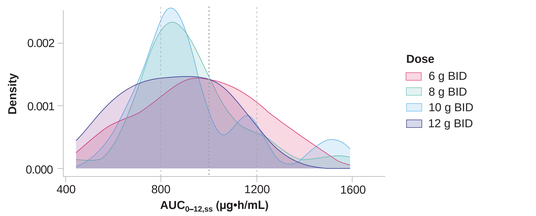
- Efficacy endpoints from LAVENDER that were included in the modeling were RSBQ and CGI-I (coprimary endpoints), Communication and Symbolic Behavior Scales-Developmental Profile™-Infant Toddler Checklist (CSBS-DP-IT) Social Composite score (key secondary endpoint), and the Rett Syndrome Clinician Rating of Ability to Communicate Choices (RTT-COMC; secondary endpoint)
- The E-R model for CGI-I scores was developed using data from LAVENDER and the two phase 2 studies (Neu-2566-Rett-001 and Neu-2566-Rett-002)
- E-R modeling for RSBQ scores used data from Neu-2566-Rett-002 and LAVENDER
- E-R modeling for CSBS-DP-IT Social Composite and RTT-COMC scores used data from LAVENDER
- Development of the E-R models involved the following procedure: (1) generation of individual estimates of exposure based on the popPK model; (2) exploratory data analysis; (3) base structural model development incorporating drug exposure effects; (4) evaluation of covariate effects; (5) final model refinement; and (6) model evaluation
- The final E-R efficacy models were validated using a simulation-based, visual predictive check methodology to assess concordance between the model-based simulated data and the observed data

## RESULTS

### Target Exposure

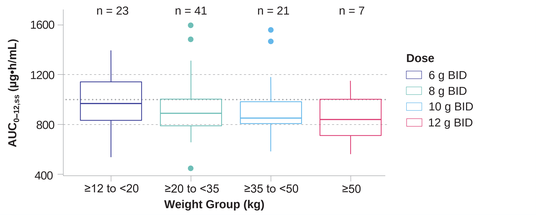
- The refined popPK model was similar to the previous popPK model developed, indicating consistency of the PK profile across studies
- A distribution plot (**Figure 1**) and boxplots (**Figure 2**) comparing $AUC_{0–12,ss}$ values for each body weight group with the previously identified target exposure range indicated that the median peak $AUC_{0–12,ss}$ values were largely contained within the target exposure range for all body weight ranges and that the distribution of $AUC_{0–12,ss}$ values overlapped with the target exposure range
  - Individuals in the lowest body weight band (who received 6 g BID) had slightly higher values of $AUC_{0–12,ss}$ compared with the other body weight bands (8 g, 10 g, and 12 g BID)

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



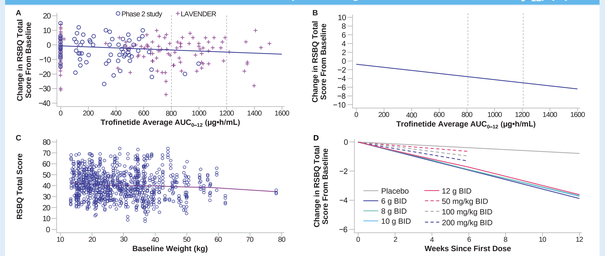

The dashed lines represent the target exposure range ($AUC_{0–12,ss}$ = 800–1200 µg•h/mL). The dotted line represents the median target exposure ($AUC_{0–12,ss}$ = 1000 µg•h/mL). The bottom and top of each box represent the 25th and 75th percentiles, respectively; the whiskers represent the 25th/75th percentile + 1.5 × IQR; the line within each box represents the median. The circles represent the values above/below the 25th/75th percentile + 1.5 × IQR
$AUC_{0–12,ss}$, 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

### Exposure-Efficacy Modeling

#### E-R Analysis of RSBQ

- The RSBQ E-R model included 264 participants with 1022 RSBQ total scores; the median (range) baseline RSBQ total score was 42 (13–74)
- An E-R relationship was identified for RSBQ total scores and was modeled as a linear time-course model including parameters estimating the baseline RSBQ total scores and the slope for time
- A linear function described the relationship between the trofinetide $AUC_{0–12}$ and slope whereby a higher trofinetide exposure was predictive of a reduction (improvement) in RSBQ total score
  - Average $AUC_{0–12}$ values of 800 and 1200 µg•h/mL resulted in reductions in model-predicted RSBQ total scores at Week 12 of 3.55 and 4.94, respectively, compared with 0.76 for placebo (**Figures 3A and 3B**)
- Baseline body weight was a significant covariate (heavier weight corresponding to larger reductions in RSBQ total scores; **Figure 3C**), and model-predicted change in RSBQ scores from baseline were dose-dependent and consistent across the 4 weight-based bands (**Figure 3D**)

**Figure 3. Scatterplot and model-predicted change in RSBQ total scores from baseline to end of treatment versus trofinetide $AUC_{0–12}$ (A and B). Scatterplot of RSBQ total scores versus baseline weight (C). Model-predicted change in RSBQ scores from baseline versus week for each dose level (assuming median trofinetide $AUC_{0–12}$) (D)**




In Panels A and B, the solid line represents the model-predicted change for the final E-R model; one placebo outlier (RSBQ score = 40) was excluded for graphical purposes. The dashed lines represent the target exposure range ($AUC_{0–12,ss}$ = 800–1200 µg•h/mL). In Panel C, the line represents a smoothing spline fit to the data. In Panel D, dose regimens of 50, 100, and 200 mg/kg BID were from the phase 2 study (Neu-2566-Rett-002), and doses of 6, 8, 10, and 12 g BID were from LAVENDER
$AUC_{0–12}$, area under the concentration-time curve over the dosing interval (12 hours); BID, twice daily; E-R, exposure-response; RSBQ, Rett Syndrome Behaviour Questionnaire

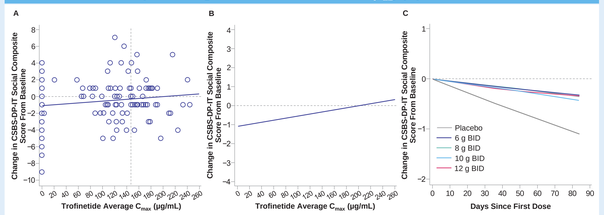
#### E-R Analysis of CGI-I

- The CGI-I E-R model included 316 participants with 989 CGI-I scores
- No E-R relationship was found for CGI-I scores

#### E-R Analysis of CSBS-DP-IT Social Composite Score

- The CSBS-DP-IT Social Composite E-R model included 182 participants with 679 CSBS-DP-IT Social Composite scores; the median (range) baseline CSBS-DP-IT Social Composite score was 9 (2–16)
- An E-R relationship was identified for CSBS-DP-IT Social Composite scores and was modeled as an exponential time-course model including parameters estimating the baseline CSBS-DP-IT Social Composite scores and the rate for time
- A higher trofinetide exposure ($C_{max}$) was predictive of an increase (improvement) in model-predicted CSBS-DP-IT Social Composite score
  - A linear function described the relationship between the trofinetide $C_{max}$ and rate of change in the CSBS-DP-IT Social Composite score over time
  - A median trofinetide $C_{max}$ of 147 µg/mL resulted in a reduction in model-predicted CSBS-DP-IT Social Composite score at Week 12 of 0.33, smaller than the reduction of 1.09 for placebo, indicating treatment with trofinetide resulted in less deterioration of the CSBS-DP-IT Social Composite score compared with placebo (**Figures 4A and 4B**)
  - Model-predicted reductions in CSBS-DP-IT Social Composite scores were consistent across the 4 weight-based bands (**Figure 4C**)

**Figure 4. Scatterplot and model-predicted change in CSBS-DP-IT Social Composite scores from baseline to end of treatment versus trofinetide $C_{max}$ (A and B). Model-predicted change in CSBS-DP-IT Social Composite scores from baseline versus day for each dose level (assuming median trofinetide $AUC_{0–12}$) (C)**

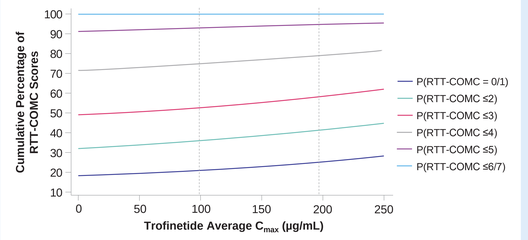



In Panel A, the dashed vertical line represents median $C_{max}$ of 147 µg/mL. In Panels A and B, the solid line represents the model-predicted change for the final E-R model. In Panels A, B, and C, the dashed horizontal line represents no change in CSBS-DP-IT Social Composite score
$AUC_{0–12}$, area under the concentration-time curve over the dosing interval (12 hours); BID, twice daily; $C_{max}$, maximum observed drug concentration; CSBS-DP-IT, Communication and Symbolic Behavior Scales-Developmental Profile™-Infant Toddler Checklist; E-R, exposure-response

#### E-R Analysis of RTT-COMC Scores

- The RTT-COMC E-R model included 181 participants with 672 RTT-COMC scores; the median (range) baseline RTT-COMC score was 4 (1–7)
- An E-R relationship was identified for RTT-COMC scores and was modeled as a proportional odds model with 2 additive components on the logit scale: baseline RTT-COMC score and the drug effect
- A higher trofinetide exposure ($C_{max}$) was predictive of a higher probability of lower RTT-COMC scores (improvement)
- A median trofinetide $C_{max}$ of 147 µg/mL resulted in a model-predicted cumulative probability of RTT-COMC score ≤3 of 0.55, compared with 0.49 for placebo (**Figure 5**)

**Figure 5. Model-predicted cumulative percentage of RTT-COMC scores versus trofinetide $C_{max}$ for the final E-R model for RTT-COMC scores**




Dashed vertical lines represent the 25th and 75th percentiles of $C_{max}$ for the target dose
$C_{max}$, maximum observed drug concentration; E-R, exposure-response; P, probability; RTT-COMC, Rett Syndrome Clinician Rating of Ability to Communicate Choices

## CONCLUSIONS

- The proposed weight-based banded dosing regimen in the LAVENDER study achieved the targeted trofinetide exposure range ($AUC_{0–12,ss}$ = 800–1200 µg•h/mL), confirming that the proposed dosing regimen in females with RTT aged 5–20 years is adequate to achieve target exposure
- The E-R relationship was significant and demonstrated that higher trofinetide exposures are associated with improved RSBQ, CSBS-DP-IT Social Composite, and RTT-COMC scores
  - Significant differences in these efficacy endpoints in favor of trofinetide versus placebo were observed in the LAVENDER study, confirming the findings of the E-R model

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## DISCLOSURES

**MD**, **JMY**, **HB**, and **KMB** are employees of and stakeholders in Acadia Pharmaceuticals Inc. **JP** and **KM** are employees of and hold stock in Simulations Plus.

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