# Real-World Trofinetide Dosing for Rett Syndrome: The LOTUS Study

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## BACKGROUND

- Rett syndrome (RTT) is a rare neurodevelopmental disorder characterized by a regression in early childhood, predominantly observed in speech, fine motor hand skills, and ambulation[1]
  - RTT is associated with a broad set of symptoms including deficits in communication, breathing, stereotypies, nighttime behaviors, vocalizations, facial expressions, mood, and seizures[1,2]
- Trofinetide was approved by the US Food and Drug Administration in March 2023 for the treatment of RTT in adults and pediatric patients aged ≥2 years[3]
  - Trofinetide is recommended to be dosed twice a day following weight-banded dosing[3]
  - In LAVENDER, a phase 3, randomized, placebo-controlled study of trofinetide in girls and women with RTT, the trial participants started trofinetide at their full weight-banded dose; dose reductions to manage tolerability were allowed[4]

## OBJECTIVE

- To characterize trofinetide dosing patterns in the real world with the 12-month follow-up of the LOTUS study

## METHODS

### LOTUS Study Design and Study Population

- LOTUS is an ongoing, phase 4, observational, real-world, prospective study involving caregivers of patients prescribed trofinetide under routine clinical care
- LOTUS participation lasts for ≥12 months from trofinetide initiation, with the option to extend participation for an additional 12 months
- Caregivers of any patients who were prescribed trofinetide under routine care are eligible for this study; there are no exclusion criteria

### Relevant Study Assessments

- Real-world dosing and gastrointestinal (GI) health were reported weekly for the first 3 months of the study and then monthly using a caregiver-reported questionnaire
  - Participants reporting zero doses of trofinetide on the date of the questionnaire are excluded from that timepoint
- Dosing was reported by caregivers using a dropdown menu that used 5-mL ranges; the middle of the range was used in analyses
- The first 12 weeks of dosing for both groups are shown, as the doses and metrics of GI function converge before the end of the 12-week sampling period
- Due to ongoing enrollment, data were presented up to 9 months since the initiation of trofinetide

## RESULTS

### Demographics and Baseline Characteristics

- In total, 192 participants, with ages ranging from 2 to 60 years, were included (**Table 1**)

**Table 1. Baseline Demographic and Clinical Characteristics**

| Characteristic | Total (N = 192) |
|---|---|
| RTT type, n (%)[a] | |
| Classic | 101 (66.0) |
| Atypical | 41 (26.8) |
| Does not meet diagnostic criteria for either | 11 (7.2) |
| Sex, n (%) | |
| Male | 8 (4.2) |
| Female | 183 (95.8) |
| Median (IQR) age at time of RTT diagnosis, years[b] | 3.0 (2.0–5.0) |
| Median (IQR) age at time of trofinetide initiation, years[c,d] | 15.0 (7.0–24.0) |

[a]n = 129. [b]n = 119. [c]n = 121. [d]Trofinetide initiation is the day of trofinetide shipment
IQR, interquartile range; RTT, Rett syndrome

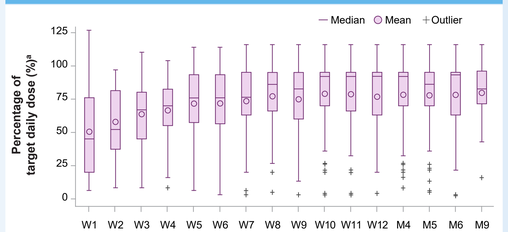
### Trofinetide Dosing

- Most participants (59.6–93.1%) took trofinetide twice a day, while others took it either 1 time per day (0–4.7%), 3 times per day (1.9–6.9%), or 4 times per day (0–1.3%)
- The median dose reported at week 1 was 45.0% of the target weight-banded label dose; by week 12, the median dose was 92.0% of target (**Figure 1**)
  - There was wide variability in dosing at week 1 (interquartile range [IQR], 20.0–76.0% of labeled daily dose), suggesting a variety of dosing approaches used when initiating trofinetide in real-world clinical practice

### Trofinetide Dosing and Stool Type

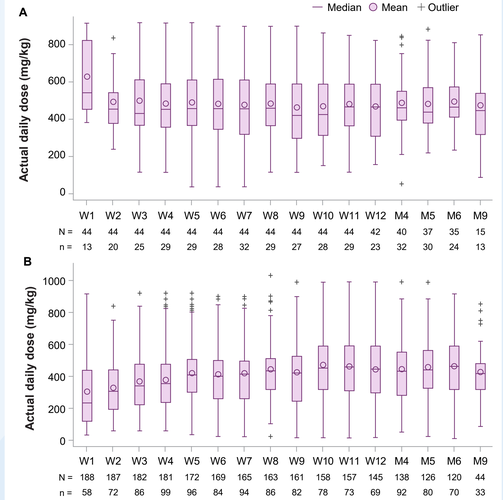
- Despite different initial trofinetide dosing strategies, the mean trofinetide doses over time converged for the participants who received <75% versus ≥75% of trofinetide target dose as the first recorded dose (**Figure 2**)
- The incidence of diarrhea was lower in participants who received <75% versus ≥75% of target dose as first recorded dose at early weeks of treatment, yet most participants did not experience diarrhea regardless of dose (**Figure 3**)
- The frequency of diarrhea was similar between participants who received <75% versus ≥75% of target dose as first recorded dose, but the <75% group had fewer clothing changes compared with the ≥75% group over the first 12 weeks of treatment (**Figure 4**)

**Figure 1. Percentage of Target Daily Dose**



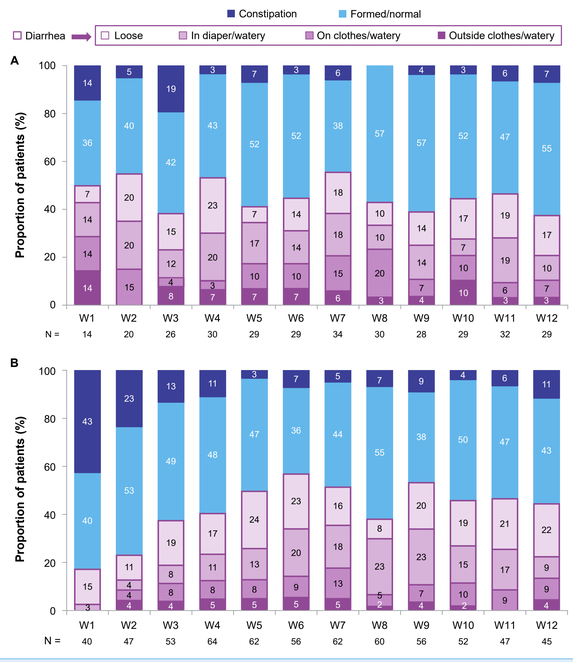

[a]Percentage of target daily dose was calculated as [actual daily dose] / [target daily dose based on patient's weight at shipment transaction] × 100
M, month; W, week

**Figure 2. Trofinetide Dosing Reported by Caregivers of Participants Who Received ≥75% (A) and <75% (B) of Target Dose as First Recorded Dose**




M, month; W, week

**Figure 3. Stool Type Reported by Caregivers of Participants Who Received ≥75% (A) and <75% (B) of Target Dose as First Recorded Dose**

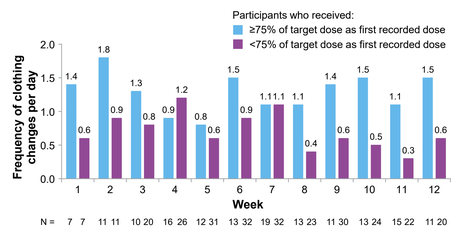



W, week

## CONCLUSIONS

- Based on this 12-month interim analysis, most participants of LOTUS initiated trofinetide at a lower dose than suggested in the label but increased their dose close to target dose by week 12 of treatment
- Trofinetide dose titration did not influence the overall prevalence of diarrhea and vomiting but might improve user experience by reducing their incidence in early weeks
  - The lower number of clothing changes in the titrating group suggests that families may find it easier to navigate a slower onset of diarrhea
- The results of this 12-month follow-up are limited by caregiver-reported observations, participant enrollment, and the online nature of this study; further analysis will occur as more participants are enrolled in the study

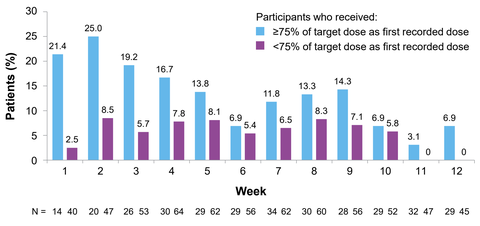
**Figure 4. Frequency of Clothing Changes Required Due to Diarrhea Reported by Caregivers**




### Trofinetide Dosing and Vomiting

- The proportion of participants who experienced vomiting was lower in participants who received <75% versus ≥75% of target dose as first recorded dose over the first 12 weeks of treatment (**Figure 5**)

**Figure 5. Frequency of Vomiting Reported by Caregivers**

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## DISCLOSURES

**LC** and **VA** are employees and stakeholders in Acadia Pharmaceuticals Inc.
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