Real-World Benefits and Tolerability of Trofinetide for the Treatment of Pediatric and Adult Patients With Rett Syndrome: The LOTUS Study

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BACKGROUND

- Rett syndrome (RTT) is a rare neurodevelopmental disorder associated with changes in the *MECP2* gene, characterized by developmental regression in early childhood, predominantly observed in speech, fine motor hand skills, and ambulation[1]
  - Caregivers have identified communication/speech impairment, seizures, impaired hand use or repetitive hand movements, gastrointestinal issues, and mobility and balance difficulties as the most troublesome RTT-related concerns[2]
- Trofinetide is approved for the treatment of RTT in patients aged ≥2 years in the United States and patients aged ≥2 years weighing ≥9 kg in Canada[3,4]
  - The primary clinical trial supporting the efficacy and safety of trofinetide in RTT was the 12-week, phase 3, placebo-controlled LAVENDER study in girls and women with RTT aged 5–20 years[5]; participants who completed the study could continue treatment in LILAC and LILAC-2, 40-week and 32-month open-label extension studies of LAVENDER, respectively[6,7]
  - Additionally, the tolerability and efficacy of trofinetide in girls with RTT aged 2–4 years was assessed in the open-label phase 2/3 DAFFODIL study[8]
- Although the efficacy and safety of trofinetide in adult patients with RTT aged into their forties was assessed in early phase 2 clinical trials,[9] the benefits and tolerability of trofinetide in patients with RTT have not been studied in patients younger than 2 years old
  - Associations between age and outcome measures in the clinical trial program suggested similar improvements in scores across age groups, although the studies were not powered to interpret age group–related results[5–7]

OBJECTIVE

- To characterize the benefits and tolerability of trofinetide in pediatric and adult patients with RTT using real-world 12-month follow-up data from the ongoing LOTUS study

METHODS

LOTUS Study Design and 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
- This subgroup analysis focused on pediatric (0–17 years of age) and adult (≥18 years of age) patient populations enrolled in the study

Relevant Study Assessments

- The Behavioral Improvement Questionnaire (BIQ) is a novel measure that has been adapted from the Rett Syndrome Behaviour Questionnaire (RSBQ), the top caregiver concerns from the US Natural History Study, and the RTT community list of symptoms in the Voice of the Patient Report[2,10,11]; it consists of questions soliciting a "yes" or "no" response from caregivers as to whether they observed new and/or maintained improvements following treatment with trofinetide compared with the period before starting trofinetide
  - A "yes" answer resulted in the opportunity to identify all areas of improvement from a checklist
  - The BIQ was assessed monthly for 6 months and every 3 months thereafter
- The Quality-of-Life Inventory-Disability (QI-Disability) Questionnaire is a caregiver assessment designed to measure quality of life (QoL) for school-age children and adolescents with intellectual disability over the past month[12–14]
  - Higher scores represent better QoL
  - The QI-Disability Questionnaire was assessed monthly for 6 months and every 3 months thereafter
- The Gastrointestinal (GI) Health Questionnaire was designed to assess GI health including dose timing and amount, incidence of diarrhea and vomiting, the type of stool formation over the past 3 days, specifics about diarrhea frequency, and GI management strategies for preventing or managing diarrhea employed by caregivers
  - Weekly assessments were conducted for the first 12 weeks of the study, followed by once a month for the next 3 months, and quarterly at month 9
- Due to ongoing enrollment, data were presented up to 9 months since the initiation of trofinetide

RESULTS

Demographics and Baseline Characteristics

- In total, 117 and 74 pediatric and adult patients, respectively, were included in this 12-month follow-up (**Table 1**)
  - The ages of patients in the pediatric population ranged from 2 to 17 years of age, while the age range in the adult population was 18 to 60 years of age

Trofinetide Dosing

- The median dose reported at week 1 was 45.0% and 41.0% of the target weight-banded label dose for pediatric and adult patients, respectively; by week 8, the median dose was at least 86.0% and 70.0% of target for pediatric and adult patients, respectively (**Figure 1A, B**)
  - The median dose varied at week 1 for pediatric (interquartile range [IQR], 20.0–70.0%) and adult (IQR, 28.0–93.0%) patients, suggesting that clinicians employ a variety of dosing approaches used when initiating trofinetide in real-world clinical practice

Behavioral Improvements

- Caregivers of pediatric (76–85%) and adult (59–77%) patients reported behavioral improvements on the BIQ during months 1–9 that were new or maintained compared with before trofinetide treatment in patients who had taken at least 1 dose of trofinetide (**Figure 2A, B**)
  - The greatest and most consistently reported improvements in pediatric and adult patients were nonverbal communication (pediatric: 53–64%; adult: 41–58%), alertness (pediatric: 50–69%; adult: 33–65%), and social interaction/connectedness (pediatric: 36–58%; adult: 26–46%)

Quality-of-Life Improvements

- The median change from baseline in QI-Disability total score was positive at all time points for pediatric and adult patients, indicating improvements in quality of life in all months of trofinetide treatment (**Figure 3A, B**)

GI Health After Initiation of Trofinetide

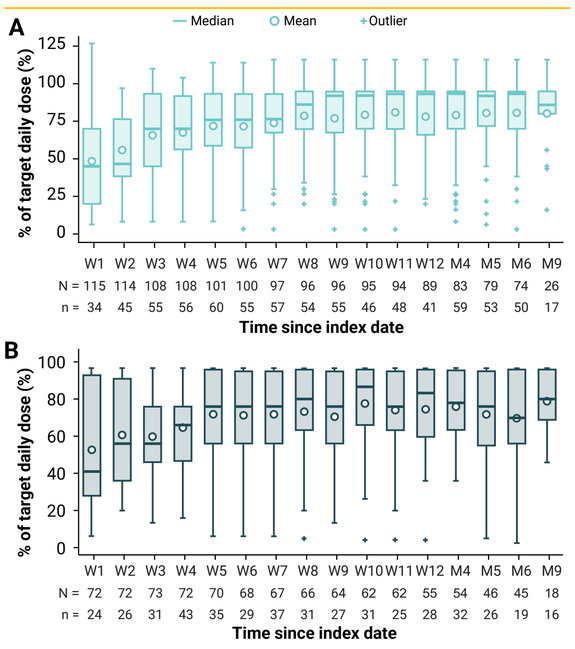
- Caregivers reported that pediatric and adult patients were most likely to void normal stools over the last 3 days before completing the GI assessment (**Figure 4A, B**)
- The highest incidence of diarrhea was reported at week 5 (56%) and week 6 (59%) in the pediatric and adult populations, respectively (**Figure 4A, B**)
  - Most reports of diarrhea were contained inside the patient's diaper (ie, loose and in diaper/watery stools), with a lower incidence of diarrhea outside the patient's diaper (ie, on clothes/watery and outside clothes/watery stools)
  - The most common diarrhea management strategies employed in the week prior to completing the GI assessment in pediatric and adult patients were using no constipation medications (pediatric: 43–71%; adult: 41–66%), increasing fluids to maintain hydration (pediatric: 6–45%; adult: 16–35%), and consuming supplementary fiber (pediatric: 18–35%; adult: 15–44%)
- Vomiting was uncommon in the pediatric (<16%) and adult (<12%) populations
  - Among pediatric and adult patients who experienced vomiting, the frequency in the previous 24 hours before reporting by caregivers ranged from 1 to 8 occurrences; most patients experienced 1–3 occurrences

Table 1. Baseline Demographic and Clinical Characteristics

Characteristics	Pediatric population (N = 117)	Adult population (N = 74)
Sex		
Male	5 (4.3)	3 (4.1)
Female	111 (95.7)[a]	71 (95.9)
Median (IQR) age at time of RTT diagnosis, years	3.0 (2.0–4.0)[b]	4.0 (2.0–14.0)[c]
Median (IQR) age at time of trofinetide initiation, years[d]	9.0 (5.0–13.0)	25.0 (21.0–33.0)

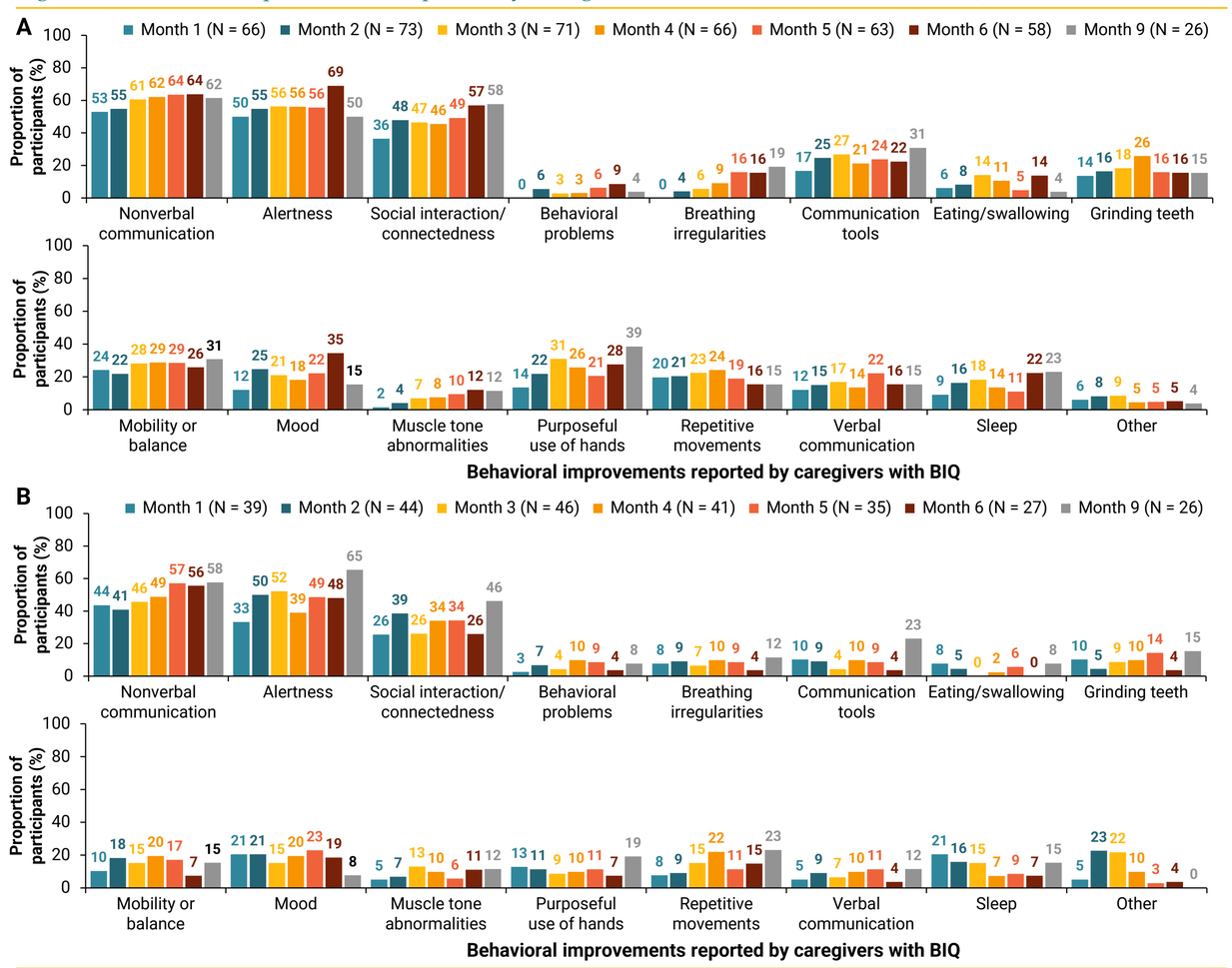
[a]n = 116. [b]n = 83. [c]n = 58. [d]Trofinetide initiation is the day of trofinetide shipment.
IQR, interquartile range; RTT, Rett syndrome.

Figure 1. Percentage of Target Daily Dose in (A) Pediatric and (B) Adult Patients



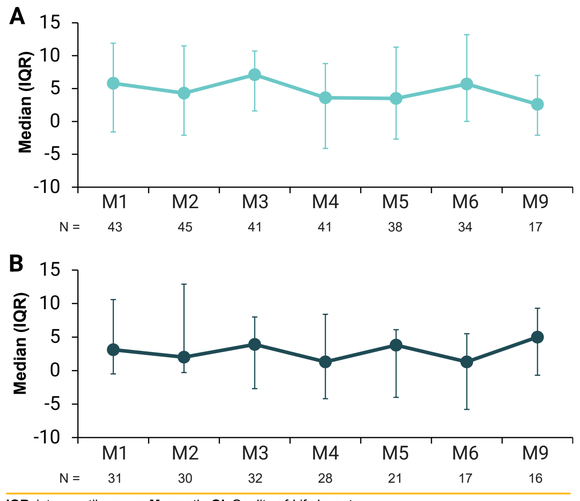
Percentage of target daily dose was calculated as [actual daily dose] / [target daily dose based on patient's weight at shipment transaction] × 100. **M**, month; **W**, week.

Figure 2. Behavioral Improvements Reported by Caregivers With BIQ in (A) Pediatric and (B) Adult Patients



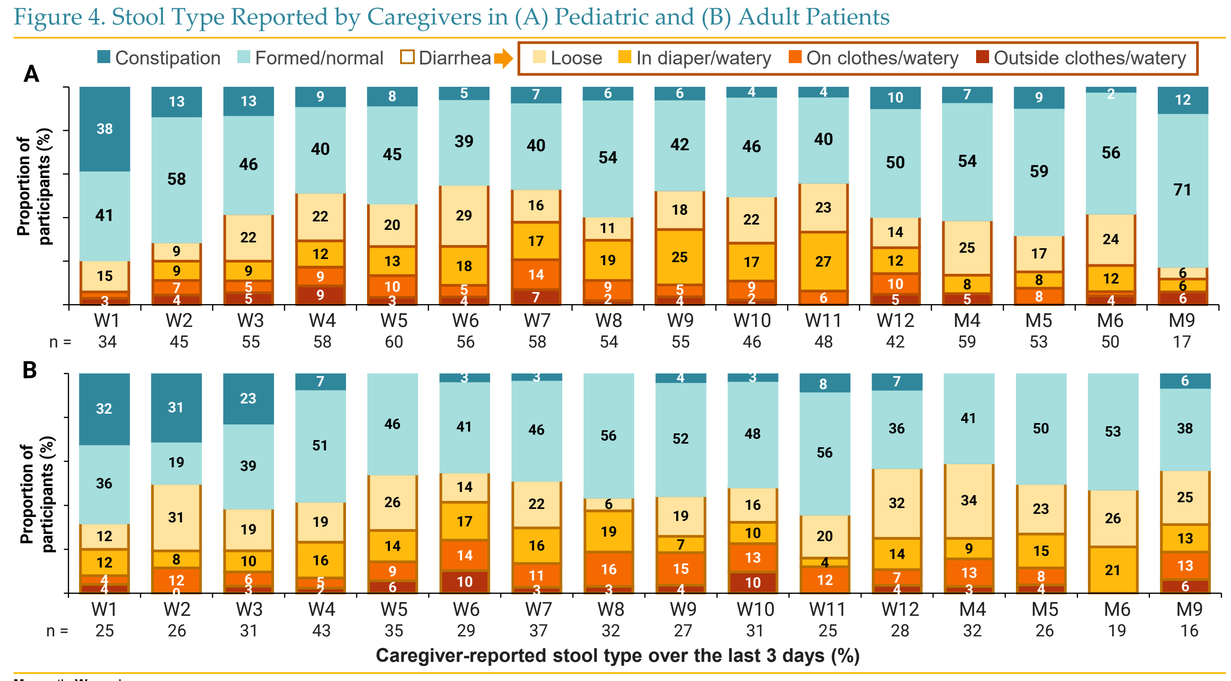
BIQ, Behavioral Improvement Questionnaire.

Figure 3. QI-Disability Absolute Change From Baseline in Total Score in (A) Pediatric and (B) Adult Patients



IQR, interquartile range; **M**, month; **QI**, Quality-of-Life Inventory.

Figure 4. Stool Type Reported by Caregivers in (A) Pediatric and (B) Adult Patients



M, month; **W**, week.

CONCLUSIONS

- **Caregivers of pediatric and adult patients with RTT in LOTUS reported behavioral and QoL improvements consistent with the general population of the study**
  - Both pediatric and adult patients had similar response patterns, suggesting that trofinetide responses do not clearly differ across age groups
- **Diarrhea and formed/normal stool were both common, with diarrhea most commonly categorized as "loose" or "watery, contained inside the diaper"**
  - These results are consistent with the 12-month follow-up of the general population of the LOTUS study[15]
- **The phase 4 LOTUS study includes an age range of 2–60 years old and provides a new opportunity to observe, without statistical inference, how caregivers of different-age patients taking trofinetide respond on outcome measures**
  - Future follow-ups with larger pediatric and adult populations might elucidate age-related differences in outcomes of trofinetide treatment in patients with RTT
  - The results of this 12-month follow-up are limited by caregiver reports, the number of patients who have reached later time points, missing data, and the online nature of this study; further analysis will occur as more patients are enrolled in the study

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ACKNOWLEDGMENTS

The study was supported by Acadia Pharmaceuticals Inc. (San Diego, CA, USA). Medical writing support was provided by Juan Sanchez-Cortes, PhD, of Evidence Scientific Solutions, Inc., and funded by Acadia Pharmaceuticals Inc.

DISCLOSURES

LC is an employee and stakeholder in Acadia Pharmaceuticals Inc. **JD** has been a consultant for Acadia Pharmaceuticals Inc., AveXis, Marinus Pharmaceuticals, Neurogene Inc., Orion, Taysha Gene Therapies, and Ultragenyx, and contributed to Anavex Life Sciences and Newron Pharmaceuticals clinical trials. All consultancies are unrelated to this work and all remuneration has been made to her department.

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Presented at the 54th Annual Meeting of the Child Neurology Society (CNS) | October 8-11, 2025 | Charlotte, NC, USA

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