Real-World Benefits and Tolerability of Trofinetide for the Treatment of Rett Syndrome: Interim Analysis of 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 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 efficacy and safety of trofinetide were established in LAVENDER and maintained over LILAC and LILAC-2, open-label extension studies of LAVENDER[5-7]
- Results from quantitative measures from trofinetide clinical trials have generated interest among clinicians and families in practical, real-world outcomes associated with trofinetide treatment
  - Outcomes of interest include RTT-symptom improvement and diarrhea characterization in the real world, impact on older patients, and effects on quality of life

OBJECTIVE

- To characterize the benefits and tolerability of trofinetide in the treatment of RTT using the first 9 months of real-world data from the ongoing LOTUS study

METHODS

LOTUS Study Design and Population

- LOTUS is an ongoing, phase 4, observational, real-world, prospective, online 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

- 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[8-10]; 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 that included alertness, behavioral problems, breathing irregularities, communication tools, eating/swallowing, grinding teeth, mobility or balance, mood, muscle tone abnormalities, nonverbal communication, purposeful use of hands, repetitive movements, sleep, social interaction/connectedness, verbal communication, and other domains
  - 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[11-13]
  - 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 dosing 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
- All measures were completed by caregivers online
- Due to ongoing enrollment, data were presented up to 9 months since the initiation of trofinetide

RESULTS

Demographics and Baseline Characteristics

- In total, 192 patients, with ages ranging from 2 to 60 years, were included in this 12-month follow-up (**Table 1**)

Table 1. Baseline Demographic and Clinical Characteristics

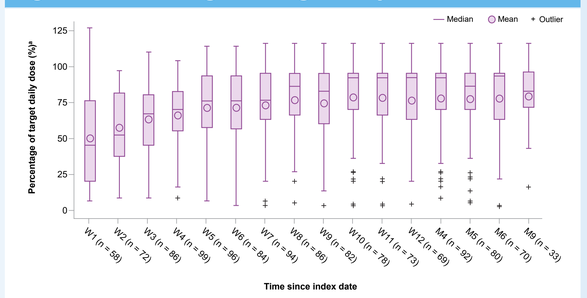
Characteristics	Total (N = 192)
RTT type, n (%)[a]	
Classic	101 (66.0)
Atypical	41 (26.8)
Does not meet diagnostic criteria for either	11 (7.2)
Sex, n (%)[b]	
Male	8 (4.2)
Female	183 (95.8)
Median (IQR) age at time of RTT diagnosis, years[c]	3.0 (2.0–5.0)
Median (IQR) age at time of trofinetide initiation,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

[a]n = 153. [b]n = 191. [c]n = 141. [d]n = 135. [e]Trofinetide initiation is the day of trofinetide shipment
IQR, interquartile range; RTT, Rett syndrome

Trofinetide Dosing

- Most patients (59.6–93.1%) took trofinetide twice daily, whereas others took it either 1 time per day (0–4.7%), 3 times per day (1.2–6.9%), 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 9 onwards, the median dose was at least 80.0% 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

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

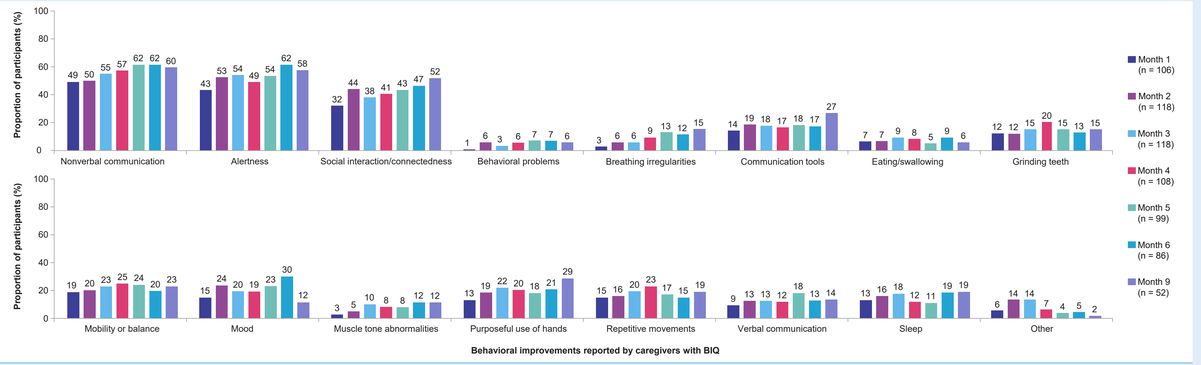
Behavioral Improvements

- Overall, 69–81% of caregivers 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 2**)
  - The greatest and most consistently reported improvements were nonverbal communication (49–62%), alertness (43–62%), and social interaction/connectedness (32–52%)

Quality-of-Life Improvements

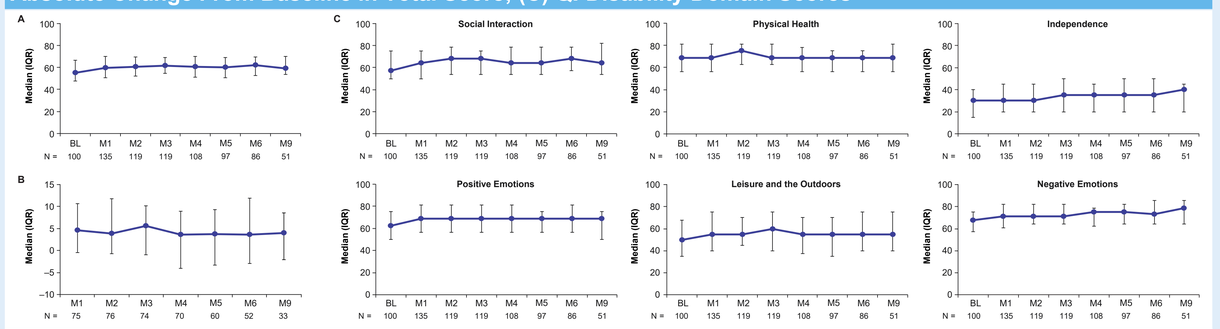
- The QI-Disability questionnaire median total score increased from baseline (55.0 [IQR, 47.9–66.4]) to month 9 (58.9 [IQR, 53.5–69.9) in patients who had taken at least 1 dose of trofinetide, indicating overall improvement in QoL with trofinetide treatment (**Figure 3A**)
- The median change from baseline in QI-Disability total score ranged from 4.6 (IQR, −0.5 to 10.7) to 4.0 (IQR, −2.1 to 8.5) from months 1–9, indicating that the improvements in QoL were reported in all months of trofinetide treatment (**Figure 3B**)
- Similar trends were observed for the social interaction, physical health, independence, positive emotions, leisure and the outdoors, and negative emotions individual domains scores of the QI-Disability questionnaire (**Figure 3C**)

Figure 2. Behavioral Improvements Reported by Caregivers With BIQ



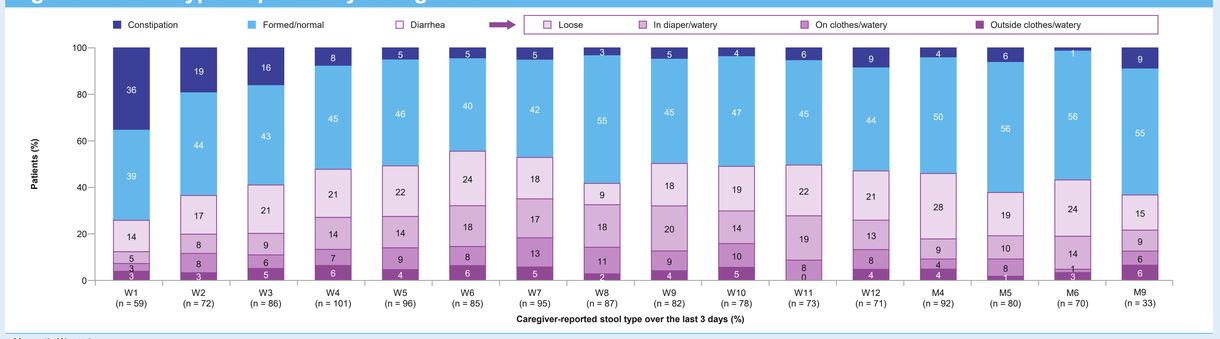
BIQ, Behavioral Improvement Questionnaire

Figure 3. QI-Disability Total and Domain Scores Over Time: (A) QI-Disability Total Score; (B) QI-Disability Absolute Change From Baseline in Total Score; (C) QI-Disability Domain Scores[a]



[a]Increase in negative emotion score corresponds to lower levels of negative emotion
BL, baseline; IQR, interquartile range; M, month; QI, Quality-of-Life Inventory

Figure 4. Stool Type Reported by Caregivers



M, month; W, week

GI Health After Initiation of Trofinetide

- Caregivers reported that patients were most likely to void normal stools over the last 3 days before completing the GI assessment (ie, no diarrhea or constipation) from weeks 1–12 (39–55%) and months 4–9 (50–56%) (**Figure 4**)
- The incidence of diarrhea varied from weeks 1–12 (25–55%) and months 4–9 (36–46%), with the highest incidence of diarrhea reported at week 6 by 55% of caregivers (**Figure 4**)
  - Most reports of diarrhea were contained inside the patient's diaper (ie, loose and in diaper/watery stools) throughout this follow-up, 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 reported in this follow-up were using no constipation medications (42–61%), increasing fluids to maintain hydration (18–39%), and consuming supplementary fiber (18–31%)
- Vomiting was uncommon throughout this follow-up (<7% at any timepoint)
  - Among patients who experienced vomiting, the frequency in the previous 24 hours before reporting by caregivers ranged from 1 occurrence to 1 report of more than 8 occurrences; most patients experienced 1–3 occurrences

CONCLUSIONS

- Caregivers of more than 87% of patients reported behavioral improvements of RTT symptoms at all timepoints, starting at the first timepoint
  - Nonverbal communication, alertness, and social interaction/connectedness were the most frequently reported improvements
- Consistent with behavioral improvements, caregivers reported improvements in QoL of patients starting at the first time point
- Diarrhea and formed/normal stool were both common, with diarrhea most commonly categorized as "loose" or "watery, contained inside the diaper"
- 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. **HM** is a consultant for 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 2025 IRSF Rett Syndrome Scientific Meeting, June 9–11, 2025, Boston, MA, USA

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