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

Louise Cosand,[1] Ryan Bucco[1]

[1]Acadia Pharmaceuticals Inc., San Diego, CA, USA

Poster #8

Scan the QR code to receive a PDF of the poster

INTRODUCTION

- 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]
  - Studies of animal models of RTT have demonstrated that the symptoms of RTT can be improved with treatment[2]
- Trofinetide is approved for the treatment of RTT in patients aged ≥2 years in the United States as well as some other countries[3]
- The trofinetide phase 3 clinical trial program enrolled patients with RTT aged 2–20 years,[4-7] yet adult patients constitute most patients with RTT
  - In the US Natural History study, 70% of patients were still alive at age 45 years,[8] and hence, RTT patients spend more time as adults than children
  - General neurologists sometimes consider the treatment of RTT in adult patients to be the domain of pediatric neurologists
- The results of LOTUS, an ongoing phase 4 observational, real-world study, confirm the improvements in the symptoms of RTT and tolerability profile of trofinetide from the trofinetide clinical program[9]
  - LOTUS does not have exclusion criteria for enrollment; hence, adult patients are included in the study

OBJECTIVE

- To characterize the real-world benefits and tolerability of trofinetide in the treatment of adults with RTT aged ≥20 years using the results of the 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 Quality-of-Life Inventory-Disability (QI-Disability) Questionnaire is a caregiver assessment designed to measure quality of life (QoL) for school-aged children and adolescents with intellectual disability over the past month[10-12]
  - Higher scores represent better QoL
  - The QI-Disability Questionnaire was assessed monthly for 6 months and every 3 months thereafter
- The Behavioral Improvement Questionnaire (BIQ) is a novel measure that has been adapted from the Rett Syndrome Behaviour Questionnaire, the top caregiver concerns from the US Natural History Study, and the RTT community list of symptoms in the Voice of the Patient Report[13-15]; 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, non-verbal 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 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 12 months since the initiation of trofinetide
- This analysis is focused on adult patients aged ≥20 years

RESULTS

Demographics and Baseline Characteristics

- Overall, 77 adult patients with RTT, aged 21–60 years, were included in this analysis (Table 1)

Trofinetide Dosing

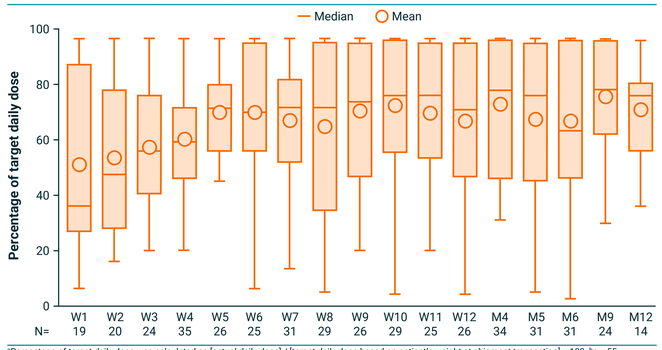
- Most patients (88.2–100.0%) took trofinetide twice daily, whereas others took it either 1 time per day (≤4.3%) or 3 times per day (2.5–10.3%)
- The median dose reported at week 1 was 50.3% of the target weight-banded label dose (Figure 1)
  - Dosing ranged from 53.0–75.0% of the target weight-banded label dose between week 2 and month 12

Table 1. Baseline Demographic and Clinical Characteristics

Characteristics	Adults in LOTUS (N = 77)
RTT type, n (%)	
Classic	40 (67.8)
Atypical	16 (27.1)
Does not meet diagnostic criteria for either	3 (5.1)
Missing	18 (23.4)
Sex, n (%)	
Male	2 (2.6)
Female	75 (97.4)
Median (IQR) age at time of RTT diagnosis, years[a]	4.5 (3.0–15.5)
Median (IQR) age at time of trofinetide initiation, years[b]	28.0 (24.0–33.0)

[a]n = 56. [b]Trofinetide initiation is the day of trofinetide shipment. **IQR**, interquartile range; **RTT**, Rett syndrome.

Figure 1. Percentage of Target Daily Dose[a,b]

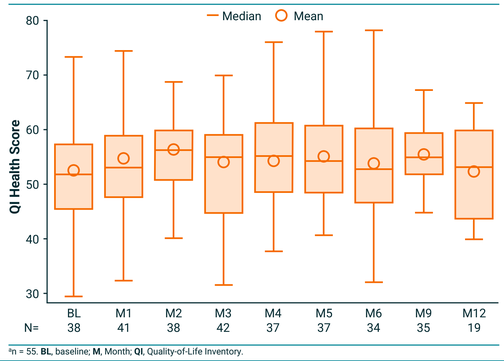


[a]Percentage of target daily dose was calculated as [actual daily dose] / [target daily dose based on patient's weight at shipment transaction] × 100. [b]n = 55. **M**, Month; **W**, Week.

Quality-of-Life Improvements

- The QI-Disability questionnaire median total score increased from baseline (52.1 [IQR, 45.5–57.3]) at nearly every measured timepoint in patients who had taken at least 1 dose of trofinetide, indicating modest improvement in quality of life with trofinetide (Figure 2)

Figure 2. QI-Disability Total Score Over Time[a]

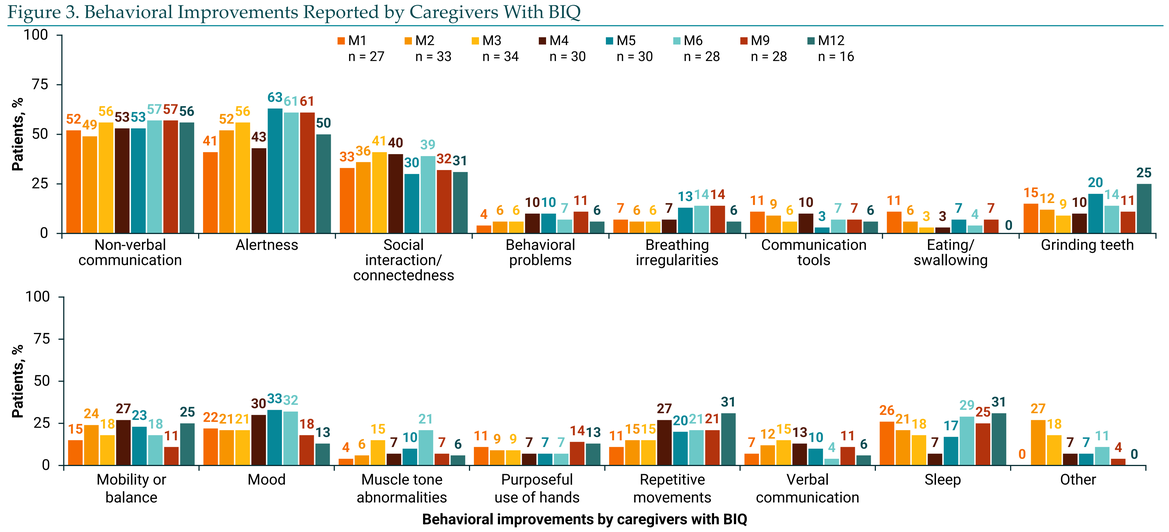


[a]n = 55. **BL**, baseline; **M**, Month; **QI**, Quality-of-Life Inventory.

Behavioral Improvements

- Overall, 75–85% of caregivers reported behavioral improvements on the BIQ during months 1–12 that were new or maintained compared with before trofinetide treatment in patients who had taken at least 1 dose of trofinetide (Figure 3)
  - The most commonly reported behavioral improvements with BIQ were nonverbal communication (49–57%), alertness (41–63%), and social interaction/connectedness (30–41%)

Figure 3. Behavioral Improvements Reported by Caregivers With BIQ

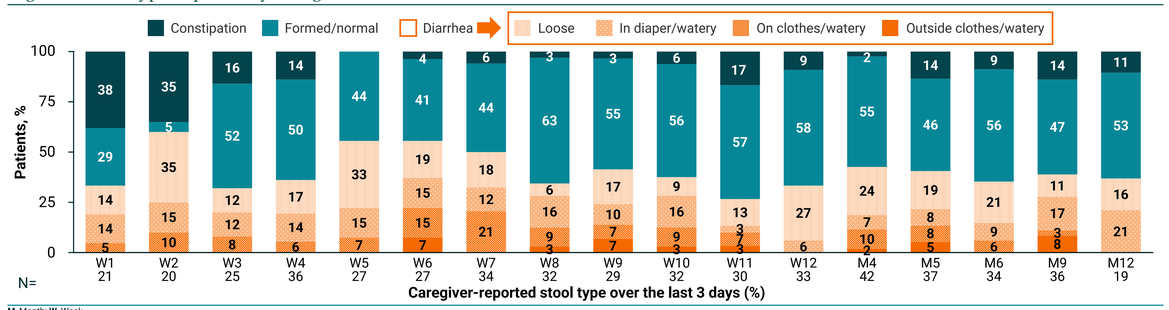


BIQ, Behavioral Improvement Questionnaire; **BL**, baseline; **M**, Month.

GI Health After Initiation of Trofinetide

- Caregivers reported that patients voided normal stools over the last 3 days before completing the GI assessment (ie, no diarrhea or constipation) from weeks 1–12 (5–63%) and months 4–12 (46–56%) (Figure 4)
- The incidence of diarrhea varied from weeks 1–12 (26–60%) and months 4–12 (36–43%), with the highest incidence of diarrhea reported at week 2 by 60% 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 skipping trofinetide doses (22–40%), taking a lower dose of trofinetide (8–29%), and increasing fluids to maintain hydration (8–16%)

Figure 4. Stool Type Reported by Caregivers



M, Month; **W**, Week.

CONCLUSIONS

Caregivers of adult patients treated with trofinetide reported improvements in symptoms of RTT

The real-world benefits and tolerability of trofinetide in adults with RTT in LOTUS followed similar trends to the overall LOTUS population

REFERENCES

1. Neul JL, et al. *Ann Neurol.* 2010;68(6):944–950. **2.** Guy J, et al. *Science*. 2007;315(5815):1143–1147. **3.** DAYBUE (trofinetide) [package insert]. San Diego, CA: Acadia Pharmaceuticals; 2024. **4.** Neul JL, et al. *Nat Med.* 2023;29(6):1468–1475. **5.** Percy AK, et al. *Med.* 2024;5(9):1178–1189.e3. **6.** Percy AK, et al. *Med.* 2024:5(10):1275–1281.e2. **7.** Percy AK, et al. *Med.* 2025:6(6):100608. **8.** Tarquinio DC, et al. *Pediatr Neurol*. 2015;53(5):402–411. **9.** Cosand L, et al. *Dev Med Child Neurol.* 2026;68(3):407–417. **10.** Mendoza J, et al. *J Med Genet*. 2021;58(9):637–644. **11.** Jacoby P, et al. *J Dev Behav Pediatr*. 2020;41(7):534–539. **12.** Downs J, et al. *Qual Life Res*. 2019;28(3):783–794. **13.** International Rett Syndrome Foundation, Rett Syndrome Research Trust. Voice of the Patient Report: Rett Syndrome Externally-Led Patient-Focused Drug Development Meeting. https://rettpfdd.org/site/assets/files/1/2022-rett-syndrome-voice-of-the-patient-report.pdf. Accessed March 16, 2026. **14.** Neul JL, et al. *J Neurodev Disord*. 2023;15(1):33. **15.** Mount RH, et al. *J Child Psychol Psychiatry*. 2002;43(8):1099–1010.

ACKNOWLEDGMENTS

The study was supported by Acadia Pharmaceuticals Inc. (San Diego, CA, USA). Medical writing support was provided by Juan Sanchez-Cortes, PhD, employee of Envision Spark, an Envision Medical Communications agency, a part of Envision Pharma Group, and funded by Acadia Pharmaceuticals Inc.

DISCLOSURES

LC and RB are employees and stakeholders in Acadia Pharmaceuticals Inc.

Presented at the International Rett Syndrome Foundation (IRSF) Annual Scientific Meeting | Prior Lake, MN | June 29-July 1, 2026

ACADIA®