Real-World Benefits and Tolerability of Trofinetide for the Treatment of 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 breathing, stereotypies, repetitive behaviors, nighttime behaviors, vocalizations, facial expressions, mood, and seizures[1,2]
- Trofinetide, a synthetic analog of glycine-proline-glutamate, was approved by the US Food and Drug Administration in March 2023 for the treatment of RTT in adults and pediatric patients ≥2 years of age[3]
- Results from quantitative measures from trofinetide clinical trials have generated interest among clinicians and families in practical, real-world outcomes associated with trofinetide treatment

OBJECTIVES

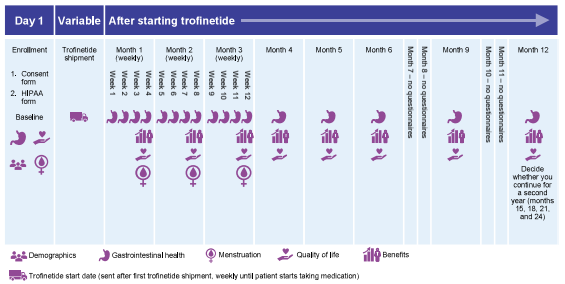
- To characterize benefits and tolerability of trofinetide, including behavioral improvements and dosing, at 9 months, using real-world follow-up data from the ongoing LOTUS study

METHODS

LOTUS Study Design and Study Population

- LOTUS is an ongoing phase 4, observational, real-world, prospective study of patients prescribed trofinetide under routine clinical care
- Participants are observed in LOTUS for ≥12 months from trofinetide initiation, with the option to extend participation for an additional 12 months (**Figure 1**)
- Adult or pediatric patients of any biological sex who were prescribed trofinetide under routine clinical care are eligible for this study; there are no exclusion criteria

Figure 1. LOTUS Study Design



Study Assessments

- Assessments developed for LOTUS include the Behavioral Improvement Questionnaire (BIQ) and the Gastrointestinal (GI) Health Questionnaire (**Figure 1**)
  - BIQ: A *yes/no* question about whether caregivers observed new and/or maintained improvements compared with before starting trofinetide. A *yes* answer resulted in the opportunity to identify all areas of improvement from a checklist, including nonverbal and verbal communication, use of communication tools, alertness, social interaction/connectedness, purposeful use of hands, muscle tone abnormalities, mobility or balance, sleep, breathing irregularities, behavioral problems, mood, eating/swallowing, grinding teeth, and other (with free-text field); assessed monthly for 6 months and every 3 months thereafter
  - GI Health Questionnaire: GI health assessment, including dosing timing and amount, incidence of diarrhea and vomiting, stool formation over the past 3 days and specifics about diarrhea frequency and severity, and GI management strategies for preventing or managing diarrhea employed by caregivers; assessed weekly for the first 12 weeks of the study, followed by once a month for the next 3 months, and quarterly at month 9

Statistical Analysis

- Categorical outcomes are summarized by the number and percentage of participants in each category
- Continuous outcomes are summarized with medians and interquartile ranges
- Owing to ongoing enrollment, data are presented from months 1–6

RESULTS

Demographics and Baseline Characteristics

- In total, 154 participants were included in this 9-month follow-up (**Table 1**)
  - Caregivers reported that the majority of participants had classic RTT (66.7%); 25.6% of participants had atypical RTT
  - Most participants were female (96.1%); 3.9% of participants were male
  - Patient age ranged from 2 to 60 years
  - The median (interquartile range [IQR]) age of RTT diagnosis was 3.0 (2.0–5.0) years, whereas the median age (IQR) of trofinetide initiation was 15.0 (7.0–24.0) years

Trofinetide Dosing

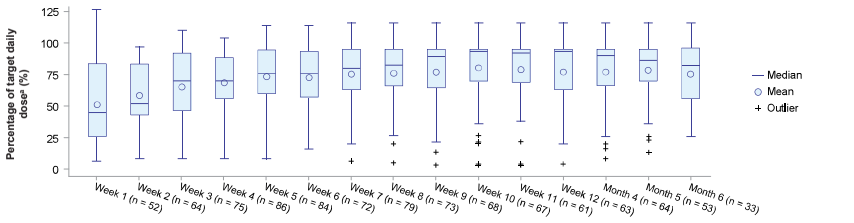
- The median dose reported at week 1 was 45.0% of the target, weight-banded label dose; by week 12, the median dose was 93.0% of target (**Figure 2**)
- There was wide variability in dosing at week 1 (IQR, 26.0–83.5% of labeled daily dose), suggesting a variety of dosing approaches used when initiating trofinetide in real-world clinical practice

Table 1. Baseline Demographic and Clinical Characteristics

Characteristics	Total (N = 154)
RTT type, n (%)[a]	
Classic	86 (66.7)
Atypical	33 (25.6)
Does not meet diagnostic criteria for either	10 (7.8)
Sex, n (%)	
Male	6 (3.9)
Female	148 (96.1)
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)
Median (IQR) weight at trofinetide initiation, kg	34.5 (21.3–45.4)

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

Figure 2. Percentage of Target Daily Dose

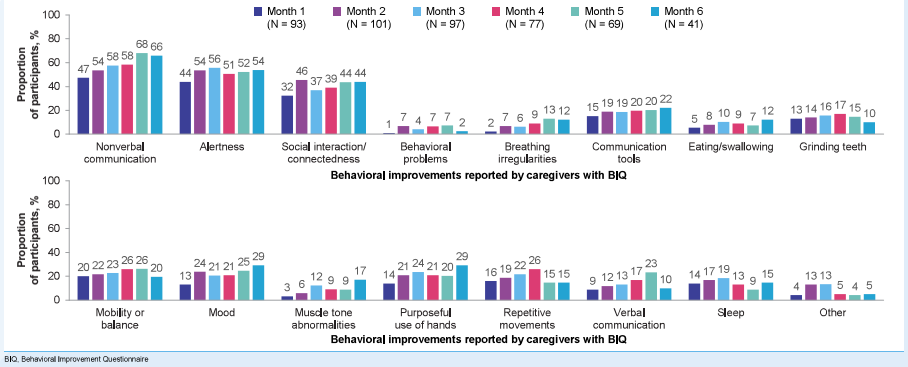


[a]Percentage of target daily dose was calculated as [actual daily dose] / [target daily dose based on patient's weight at shipment transaction] × 100

Behavioral Improvements

- Overall, 67.7–82.2% of caregivers reported behavioral improvements with trofinetide treatment on the BIQ during months 1–6 (**Figure 3**)
  - The most consistently reported improvements were nonverbal communication (47.3–68.1%), alertness (44.1–55.7%), and social interaction/connectedness (32.3–45.5%)

Figure 3. Behavioral Improvements Reported by Caregivers With BIQ

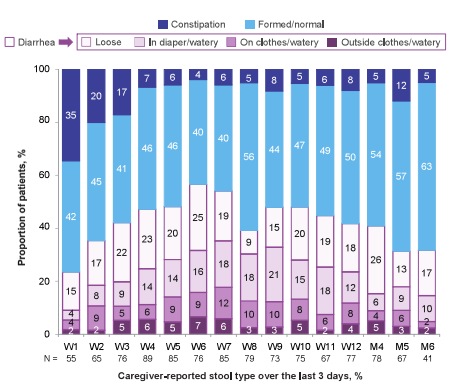


BIQ, Behavioral Improvement Questionnaire

GI Health After Initiation of Trofinetide

- The incidence of diarrhea varied from months 1–6 (23.6–56.6%), with diarrhea reported by 31.7% of caregivers at month 6 (**Figure 4**). At month 6:
  - Diarrhea was contained inside the participant's diaper for the majority (84.6%) who reported diarrhea (**Figure 4**)
  - The most common diarrhea management strategies were avoiding constipation medications (58.5%), taking a lower trofinetide dose or skipping doses (34.1%), and increasing fluid intake (29.3%)
  - Use of antidiarrheal medications and consumption of supplementary fiber were reported by 9.8% and 22.0% of caregivers, despite recommendations listing them as options for managing diarrhea[4]
- Vomiting/retching/dry heaves were uncommon from months 1–6 (<12%)
  - Among participants with vomiting/retching/dry heaves, the frequency ranged from 1 to one report of more than 8 occurrences; most experienced 1–3 occurrences

Figure 4. Stool Type Reported by Caregivers With the GI Health Questionnaire



GI, gastrointestinal

CONCLUSIONS

- Caregivers of more than 67% of participants reported 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
- Diarrhea and formed/normal stool were both common, with constipation decreasing across early treatment weeks
- Participants who reported diarrhea most commonly categorized the stool as "loose" or "watery, contained inside the diaper"
- Data suggest that diarrhea prevention and management strategies were used by small proportions of participants,[4] highlighting opportunities to leverage those strategies to further mitigate diarrhea
- The results of this 9-month follow-up are limited by 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 participants are enrolled in the study

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DISCLOSURES

LC and **VA** are employees and stakeholders in Acadia Pharmaceuticals Inc. **HM** is a consultant for Acadia Pharmaceuticals Inc. **JD** has been a consultant for Acadia Pharmaceuticals Inc., AveXis, Marinus Pharmaceuticals, 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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