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

Sunita Bond Haya Mayman Jenny Downs Louise Cosand

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]

OBJECTIVES

- 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 (Click to Expand)

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

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

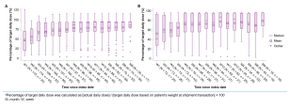
Trofinetide Dosing

- 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** and **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** and **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%)

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



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** and **B**)

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

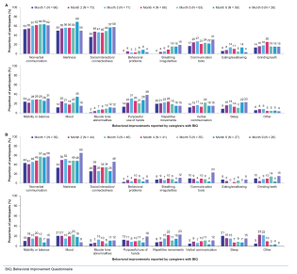
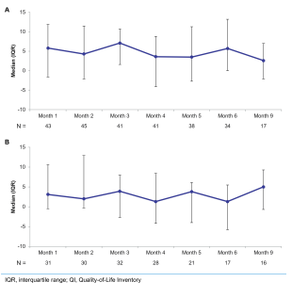
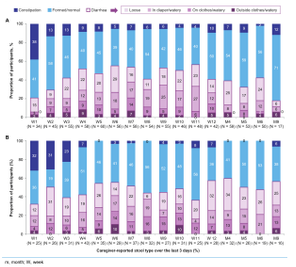


Figure 3. QI-Disability Absolute Change From Baseline in Total Score in (A) Pediatric and (B) Adult Patients



IQR, interquartile range; QI, Quality-of-Life Inventory

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



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** and **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** and **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

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 the stool 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

REFERENCES

ACKNOWLEDGMENTS

DISCLOSURES