Real-World Use of Trofinetide: A Survey of Dosing Strategies From US Rett Syndrome Centers of Excellence

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BACKGROUND

- Rett syndrome (RTT) is a rare neurodevelopmental disorder characterized by loss of verbal communication with limited nonverbal skills, loss of fine and gross motor function, behavioral issues, seizures, hand stereotypies, and gastrointestinal problems[1,2]
- Trofinetide was approved by the US Food and Drug Administration in March 2023 for the treatment of RTT in adults and pediatric patients aged ≥2 years[3]
- Trofinetide is recommended to be administered orally twice daily (BID), in the morning and evening, with or without food, according to patient weight (**Table 1**)[3]
- In LAVENDER, the randomized, placebo-controlled, phase 3 study of trofinetide in girls and women with RTT, approximately one-third of patients in the trofinetide arm had their dose adjusted for tolerability reasons[4] and evidence suggests that clinicians are using alternative dosing strategies in the real world[5]

Table 1. Trofinetide Weight-Based Dosing Recommendations

Patient weight, kg	Trofinetide dose (BID), mg	Trofinetide volume (BID), mL
9 – <12	5000	25
12 – <20	6000	30
20 – <35	8000	40
35 – <50	10,000	50
≥50	12,000	60

BID, twice daily

OBJECTIVE

- To explore real-world alternative dosing strategies of trofinetide in patients with RTT

METHODS

Survey Design

- An electronic prescriber experience survey was designed to collect real-world trofinetide dosing strategies, dosing considerations, and achievable dose
- The survey was sent in May 2024 to 33 prescribers at 18 US RTT centers of excellence (COEs) designated by the International Rett Syndrome Foundation

Data Analysis

- All results were summarized with descriptive statistics

RESULTS

Survey Participation

- Overall, 22 prescribers from 16 COEs completed the electronic survey
- The prescribers targeted for survey completion accounted for 38.1% of trofinetide prescriptions in the United States since approval (**Table 2**)

Table 2. Electronic Survey Participation and Representation

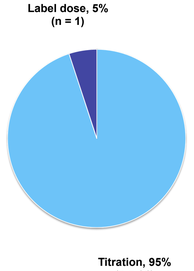
	US trofinetide prescribers (N = 697)[a]	US trofinetide prescriptions (N = 1553)[a]
Non-COE providers, n (%)	665 (95.4)	962 (61.9)
COE providers, n (%)	32 (4.6)[b]	591 (38.1)

[a]As of May 2024. [b]One eligible prescriber was associated with zero prescriptions
COE, center of excellence

Trofinetide Dosing at Treatment Initiation

- Most survey respondents (95%, n = 21) indicated that they titrate trofinetide in treatment-naïve patients with RTT rather than initiate at label dose (**Figure 1**)

Figure 1. Survey Respondents' Initial Trofinetide Dosing Strategy



Survey question:
How do you initiate trofinetide in a patient that has never received trofinetide before?

- Titration protocols included initiating trofinetide at a lower percentage of label dose (50%, n = 11) or lower milliliters than label dose (27%, n = 6), or were determined based on baseline conditions, such as diarrhea, constipation, and dose goal (14%, n = 3), or are unknown (9%, n = 2) (**Table 3**)
  - Most titration protocols start at 25–50% of the dose goal BID and increase by 5–10 mL BID every 1 to 2 weeks as tolerated
  - Slower titration protocols and titration protocols with lower dose increases were reported for patients with lower weight, younger patients, patients with a history of diarrhea, patients with history of poor trofinetide tolerability, and patients who experienced medication side effects
  - Faster titration protocols and titration protocols with higher dose increases were reported for patients with higher weight, older patients, patients with a history of constipation, and patients with history of acceptable trofinetide tolerability

Table 3. Trofinetide Titration Protocols Reported by Survey Respondents

Titration protocols by percentage of label dose (n = 11)	
Starting dose (BID)	**Titration**
25%	Increase by 25% every 2 weeks
25%	Increase by 5 mL BID every 1 to 2 weeks
33%	Increase by 33% weekly
25–33%	Increase by 5 mL weekly
25–50%	Increase by 5 mL BID weekly
50%	Increase by 25% weekly
50%	Increase by 25% weekly
50%	Increase by 5 mL BID weekly
50%	Increase by 5 mL BID every 1 to 2 weeks
50%	Increase by 5 mL BID every 2 weeks
50%	Increase by 5–10 mL weekly
Titration protocols by mL of label dose (n = 6)	
Starting dose (BID)	**Titration**
5 mL	Increase by 2.5 mL BID weekly
5 mL	Increase by 5 mL weekly
5 mL	Increase by 5 mL weekly
5 mL	Increase by 5 mL BID weekly
5 mL	Increase by 5 mL BID weekly
10–15 mL	Increase by 5 mL BID weekly

Titration protocols by baseline conditions (n = 3)		
Baseline condition	**Starting dose**	**Titration**
(+) Diarrhea history	60% TID	Increase by 5 mL TID weekly
(−) Diarrhea history	60% BID	Increase by 5 mL BID weekly
(+) Constipation history	50% BID	Increase by 10 mL BID weekly
(−) Constipation history	10 mL BID	Increase by 10 mL BID weekly
Goal dose ≤30 mL BID	5 mL BID	Increase by 5 mL BID weekly
Goal dose ≥40 mL BID	10 mL BID	Increase by 10 mL BID weekly

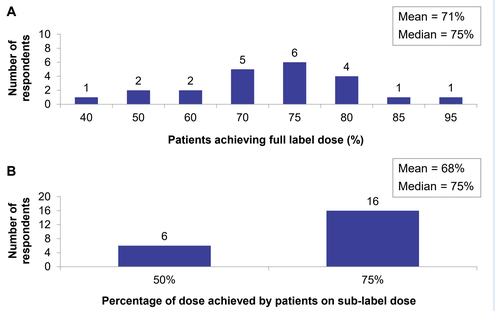
Unknown titration protocols (n = 2)	
Starting dose	**Titration**
–	Increase by 5–10 mL over 4 steps
–	Patient-specific and based on tolerability

Survey question: Please enter your titration protocol(s) for those newly starting trofinetide. Please include dose, frequency of administration, and titration interval
BID, twice daily; TID, three times daily

Achievement of Trofinetide Label Dose With Titration

- Overall, respondents estimated 70–75% of patients achieve their label dose following a titration protocol (**Figure 2A**)
- Of the 25–30% of patients who do not achieve their label dose with a titration protocol, the majority can tolerate approximately 75% of their label dose (**Figure 2B**)

Figure 2. Achievement of Trofinetide Label Dose With Titration: (A) Estimated Percentage of Patients Achieving Label Dose; (B) Estimated Percentage of Dose Achieved by Patients on Sub-label Doses

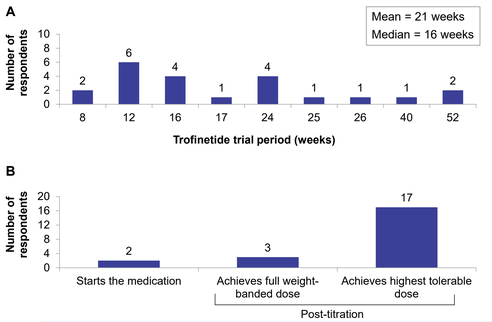


Survey question:
Based on your experience, approximately what percentage of patients are able to achieve their full weight-banded dose after titrating? If you answered less than 100%, for those unable to achieve full dose, approximately what percentage of the full weight-banded dose are the majority able to achieve?

Trofinetide Trial Period

- Survey respondents encourage families to allow 4–5 months to determine trofinetide efficacy (**Figure 3A**)
  - For most, this period of evaluation begins after the patient arrives at their highest tolerable dose after titration (**Figure 3B**)

Figure 3. Trofinetide Trial Period: (A) Number of Weeks to Try Trofinetide; (B) When Trofinetide Trial Period Begins



Survey question:
What is the minimum amount of time that you recommend patients trial trofinetide prior to determining lack of efficacy? Does the minimum amount of time begin when patient starts the medication, achieves full weight-banded dose, or achieves their highest tolerable dose (which may be lower than full weight-banded dose)?

CONCLUSIONS

- Trofinetide dose titration is a common practice among providers at RTT COEs, with several titration strategies available
- Experts reported that dose titration allows for most patients to reach their label dose while experiencing treatment benefit
- Experts evaluate trofinetide efficacy for 4–5 months after the patient achieves their highest tolerable dose after titration
- The clinical approaches reported here correspond with dose adjustments observed in LOTUS, an ongoing real-world evidence study of trofinetide in patients with RTT[5]

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DISCLOSURES

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