Changes in Trofinetide Dosing Frequency and Administration With Rice Cereal to Manage Diarrhea in Patients With Rett Syndrome: Case Reports

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INTRODUCTION

- Trofinetide is approved for the treatment of Rett syndrome (RTT) in patients aged ≥2 years in the United States and patients aged ≥2 years weighing ≥9 kg in Canada[1,2]
- Trofinetide is disease specific and improves the core symptoms of RTT[3-6]
  - The most common adverse event reported in trofinetide clinical trials was diarrhea[3-6]
- The incidence and management of diarrhea with trofinetide in patients with RTT is burdensome to caregivers
  - Recommendations for the management of diarrhea with trofinetide include lifestyle and pharmacological interventions[7,8]
  - Clinicians and caregivers of patients with RTT remain interested in additional diarrhea management strategies to avoid trofinetide discontinuation

OBJECTIVES

- To describe the rationale for changing the trofinetide dosing schedule from the recommended twice a day (BID) dosing to three (TID) or four (QID) times a day, with or without rice cereal, to mitigate the incidence of diarrhea with trofinetide without the use of antidiarrheal medications
- To support this rationale with the presentation of 3 anecdotal patient cases

CHANGES TO TROFINETIDE DOSING AND ADMINISTRATION

- The incidence of diarrhea with trofinetide in patients with RTT can be managed by changing the dosing schedule from the recommended BID dosing to TID dosing while keeping the total daily trofinetide volume constant, after a period of titration
  - If diarrhea cannot be managed with TID dosing, QID dosing can be used
- Caregivers are also encouraged to add rice cereal to trofinetide if loose stools persist
  - The addition of rice cereal appears to be most helpful for patients with RTT with gastrostomy tubes
- In this scheme, trofinetide initiation follows a stepwise approach (**Figure 1**)
  - Discontinuation of all constipation medications
  - Initiation of trofinetide at 50% of the target daily dose, divided by the number of doses desired by day, wherever TID or QID
  - Increase trofinetide dose by 5 mL per dose at weekly intervals while keeping the TID or QID dosing, with the goal of reaching the patient's target daily dose
  - Addition of rice cereal at the first sign of loose stools
    - If stool remains loose after the addition of rice cereal, the titration protocol is paused until the loose stool stops and caregivers feel ready to restart
    - If diarrhea occurs abruptly during the titration protocol, trofinetide is discontinued for a few days and restarted at a lower dose
  - Some patients may not reach the target daily dose, yet they can still experience improvement in RTT symptoms at their lower trofinetide dose

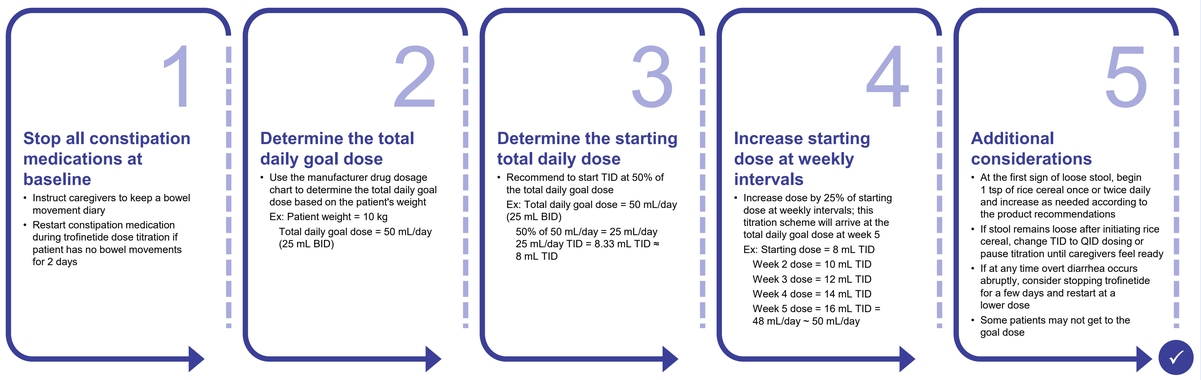
PHARMACOKINETIC AND MECHANISTIC RATIONALE FOR CHANGES TO TROFINETIDE DOSING AND ADMINISTRATION

- Pharmacokinetic rationale
  - Trofinetide has linear kinetics, with no time- or dose-dependent effect on pharmacokinetic parameters; systemic exposure to trofinetide is dose proportional, with minimal to no accumulation observed after multiple-dose administration[1]
  - Changing the dosing frequency of trofinetide from BID to TID or QID, while maintaining total daily dose, will alter some pharmacokinetic parameters, such as maximum concentration (C_{max}), but should not result in clinically meaningful changes in the total exposure, known as area under the curve (AUC)
- Mechanistic rationale
  - Trofinetide is a small, osmotically active molecule that could potentially cause diarrhea in the large intestine
    - Although the specific route of absorption of trofinetide is unknown, it is possible that it is actively transported by peptide transporter 1 (PEPT1), given the chemical similarity to other actively transported tripeptides and cephalosporin compounds[9]
    - Changing the dosing schedule of trofinetide from the recommended BID schedule to TID or QID schedules reduces the amount of trofinetide consumed in 1 dosing, which could allow for better absorption of trofinetide in the small intestine and potentially spare saturation of the PEPT1 transporter, thereby reducing the potential for osmotic diarrhea
  - The trofinetide formulation includes maltitol, a sugar alcohol used as a sweetening and bulking agent
    - Maltitol is converted to glucose and sorbitol in the small intestine[10]
      - Glucose is actively absorbed in the small intestine; sorbitol is passively absorbed[10]
      - Sorbitol that is not absorbed in the small intestine moves to the colon, where it can act osmotically to pull extra water into the colon and cause loose stool[10]
  - The consumption of rice cereal at the time of trofinetide dosing might decrease the incidence of diarrhea by increasing the absorption of maltitol and sorbitol in the small intestine by potentially slowing gastrointestinal transit time

CASE PRESENTATIONS

- Dosing frequency was changed from the recommended BID schedule to TID or QID schedules and administration was supplemented with rice cereal for 3 female patients with RTT, aged 17, 25, and 37 years at the time of trofinetide initiation (**Table 1**)
- In all cases, changes in dosing frequency and/or addition of rice cereal with trofinetide administration resulted in diarrhea cessation (**Figure 2**) and improvement in symptoms of RTT (**Table 1**)

Figure 1. Trofinetide Dose Titration Protocol



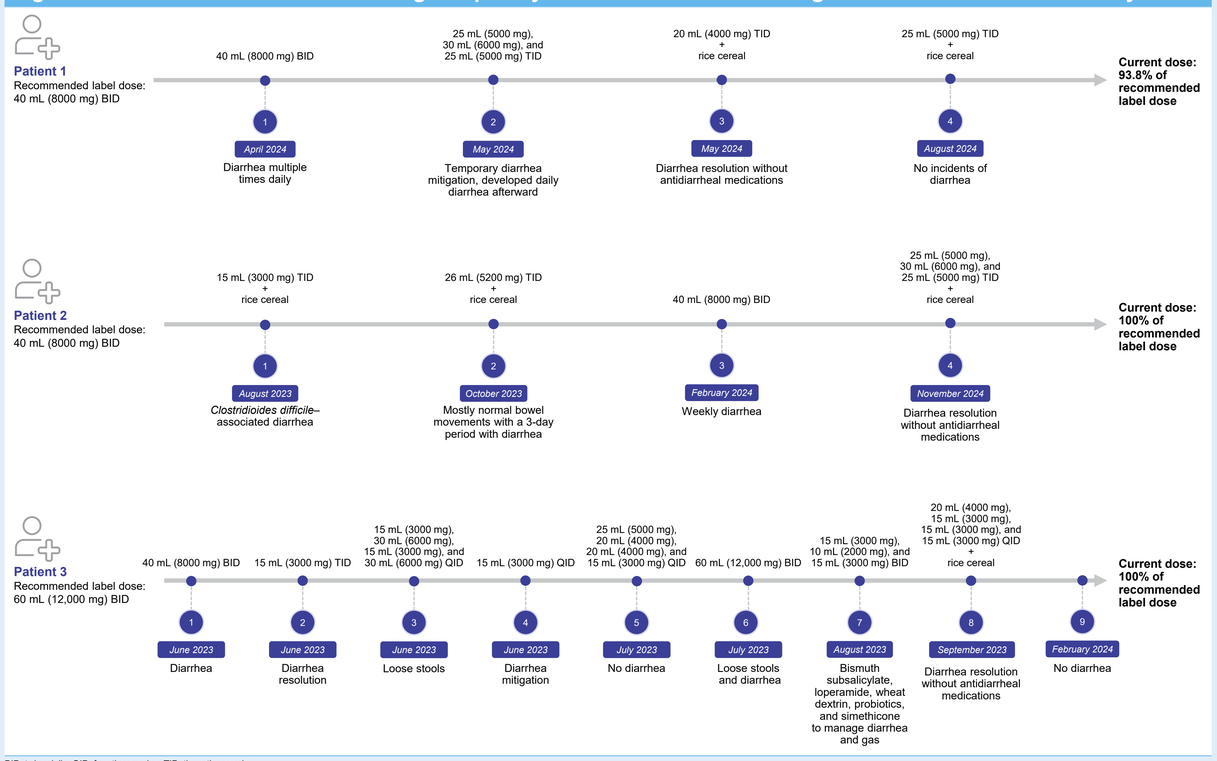
BID, twice a day; QID, four times a day; TID, three times a day

Table 1. Patient Characteristics and Improvement With Trofinetide

	Patient 1	Patient 2	Patient 3
RTT medical history			
Approximate age at diagnosis	3 years	3 years	4 years
MECP2 mutation	916-C>T	p.S49X	c.908 T>G
Comorbidities and symptoms	• Lower extremity flexion contractures, impaired mobility, seizures, and deep vein thrombosis • Inability to walk and form words, required wearing diapers, G-tube placement for feeding, and posterior spinal fusion for scoliosis	• Movement disorders (eg, tremors, hand stereotypies, focal dystonia of left lower extremity, left neck tilt, and Parkinsonism) • Respiratory disorders (eg, breath holding and tachypnea) • Scoliosis	• Decreased verbal skills, fine motor skills, and gait • Stereotypic hand tapping motions with the left hand over the right hand
Trofinetide for the treatment of RTT			
Approximate age at initiation	25 years	17 years	37 years
Administration route	G-tube	G-tube	G-tube
Clinical improvement	• Increased alertness and emotional expression • Increased attention was observed within 6 weeks of trofinetide initiation • Increased vocalizations and improvement in gross motor movements	• Lower irritability and increased alertness • Improvement in breath holding, eye gaze communication, and fine motor skills	• Increased alertness and social interaction • Increased verbalization and improvements in use of Tobii communication device • Increased eye contact with people • Improvements in motor skills • Cessation of breath holding

G-tube, gastrostomy tube; RTT, Rett syndrome

Figure 2. Timeline of Trofinetide Dosing Frequency and Administration Changes With Effects on Tolerability



BID, twice daily; QID, four times a day; TID, three times a day

CONCLUSIONS

- **Division of the trofinetide dosing schedule and/or the addition of rice cereal at the time of administration reduced the incidence of diarrhea in patients with RTT, allowing the patients to tolerate and continue treatment**
- **Patients with RTT who take trofinetide at a different dosing schedule and/or with rice cereal are still able to experience improvements in symptoms associated with RTT, including improvements in alertness, social interaction/connectedness, communication, and motor skills, while mitigating the incidence of diarrhea without the use of antidiarrheal medications**
  - **The similarity of benefits observed in the anecdotal patient cases presented here with the improvements reported in the LAVENDER, LILAC, LILAC-2, DAFFODIL, and LOTUS studies[3-6,11] suggest that changing the dosing schedule of trofinetide or the addition of rice cereal does not impact the efficacy of trofinetide**
- The anecdotal cases presented are limited to medical history information available for each case
  - Future studies are needed to address the mechanism of diarrhea with trofinetide, the contribution of trofinetide and other formulation agents in the mechanism of diarrhea, and the generalizability of the effect of changing trofinetide dosing frequency and addition of rice cereal with administration to a larger patient cohort

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DISCLOSURES

AB is a consultant to Acadia Pharmaceuticals Inc.

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