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For further information regarding Indication and Important Safety Information for DAYBUE and DAYBUE STIX, please click here: [Prescribing Information](#).

DAYBUE® (trofinetide): Up-Titration of Dose During Treatment Initiation

This letter is provided in response to your specific request for information regarding up-titration of DAYBUE dosage during initiation of treatment. There are no recommendations for up-titration of DAYBUE dose in the Prescribing Information.¹ In the LAVENDER™ pivotal trial, there was no up-titration of dose and participants were started at the FDA-recommended weight-based dose as described in Table 1 of the Prescribing Information.^{1,2}

The efficacy of DAYBUE has only been demonstrated at the FDA-recommended weight-based dose. Improvements may not occur until the patient reaches the recommended dose and continues treatment. Always use clinical judgment to make sound decisions for individual patients, including reviewing the FDA-approved Prescribing Information prior to initiating DAYBUE, and appropriately monitoring patients as they initiate or continue treatment for Rett syndrome (RTT).

Summary

This document provides an overview of the following:

- Dosage recommendations from the [DAYBUE Prescribing Information](#)¹
- Up-titration approaches that were used in two trofinetide clinical trials in participants with RTT, the Phase 2 study [ACP-2566-002](#) in girls aged 5–15 years³ and the [DAFFODIL™ trial](#) in girls aged 2–4 years⁴
- Examples of up-titration schedules being used in clinical practice based on a [survey](#) of United States (US) RTT centers of excellence⁵
- Up-titration recommendations from an [expert consensus](#) on real-world use of trofinetide using a modified Delphi method⁶

Background

In the Phase 2 study ACP-2566-002, a nominally significant reduction in Rett Syndrome Behaviour Questionnaire (RSBQ) total score and Clinical Global Impression-Improvement (CGI-I) score at the 200 mg/kg twice daily (BID) dose of trofinetide was observed, while doses of 50 mg/kg BID and 100 mg/kg BID did not show any effects on the exploratory effectiveness endpoints. It was also observed that body weight had an influence on trofinetide exposure, with lower weight patients experiencing lower exposures at the same weight-based dosing.^{3,7}

Dose simulation modeling based on Study ACP-2566-002 data showed that a four-level model of weight-based dosing bands with fixed doses corresponding to different body weight ranges would result in an optimal percentage of subjects with exposures within the target range ($AUC_{0-12,ss} = 800$ to $1200 \mu g \cdot h/mL$) at body weights between 12 and 100 kg.⁸ These weight-based dosing bands for DAYBUE oral solution (200 mg/mL), which equate to doses between 200 mg/kg and 556 mg/kg (**Table 1**), were assessed in the pivotal LAVENDER study² and are the dosing recommendations in the DAYBUE Prescribing Information.¹

Table 1. DAYBUE Weight-based Dosage and Dose Range (mg/kg) Per BID Dose¹

Patient Weight	DAYBUE Dosage	DAYBUE Dose Range
9 kg to less than 12 kg	5,000 mg twice daily	417–556 mg/kg
12 kg to less than 20 kg	6,000 mg twice daily	300–500 mg/kg
20 kg to less than 35 kg	8,000 mg twice daily	229–400 mg/kg
35 kg to less than 50 kg	10,000 mg twice daily	200–286 mg/kg
50 kg or more	12,000 mg twice daily	≤240 mg/kg

Abbreviation: BID=twice daily.

Dosage Recommendations from the Prescribing Information

The recommended dosage of DAYBUE or DAYBUE® STIX (trofinetide) is based on patient weight (**Table 2**). Administer DAYBUE or DAYBUE STIX orally or via gastrostomy (G) tube twice daily, in the morning and evening, with or without food. Doses administered via gastrojejunal (GJ) tubes must be administered through the G-port.¹

Table 2. Recommended Dosage of DAYBUE or DAYBUE STIX in Patients 2 Years of Age and Older^{1*}

Patient Weight	Recommended Dosage
9 kg to less than 12 kg	5,000 mg twice daily
12 kg to less than 20 kg	6,000 mg twice daily
20 kg to less than 35 kg	8,000 mg twice daily
35 kg to less than 50 kg	10,000 mg twice daily
50 kg or more	12,000 mg twice daily

*Note: Dosage adjustment is recommended for patients with moderate renal impairment. Refer to the full Prescribing Information.

Advise patients to stop laxatives before starting DAYBUE or DAYBUE STIX. Interrupt, reduce dose, or discontinue DAYBUE or DAYBUE STIX if severe diarrhea occurs, if dehydration is suspected, or if significant weight loss occurs.¹

If vomiting occurs after DAYBUE or DAYBUE STIX administration, an additional dose should not be taken. Instead, continue with the next scheduled dose. Interrupt, reduce dose, or discontinue DAYBUE or DAYBUE STIX if vomiting is severe or occurs despite medical management.¹

Dose Titration Schedule from Study ACP-2566-002

This was an exploratory, randomized, double-blind, placebo-controlled, Phase 2 study with primary outcomes relating to assessment of safety and PK, and secondary outcomes relating to efficacy. Trofinetide was administered BID at doses of 50 mg/kg, 100 mg/kg, and 200 mg/kg for 42 days in girls (5–15 years of age) with RTT (N=82). While a nominally significant reduction in RSBQ total score and CGI-I score at the 200 mg/kg BID dose trofinetide was observed, doses of 50 mg/kg BID and 100 mg/kg BID did not show any effects on the exploratory effectiveness endpoints.³

The 50 mg/kg group was up-titrated over 2 days, the 100 mg/kg group over 3 days, and the 200 mg/kg group over 5 days (**Table 3**).³

Table 3. Study ACP-2566-002 Dose Titration Schedule³

Dose Level	Dose Commences	Dose	Total Daily Dose	Proportion of Full Dose
50 mg/kg BID	Day 1	8.5 mg/kg BID	17 mg/kg	17%
	Day 2	35 mg/kg BID	70 mg/kg	70%
	Day 3	50 mg/kg BID	100 mg/kg	100%
100 mg/kg BID	Day 1	17.5 mg/kg BID	35 mg/kg	17.5%
	Day 2	35 mg/kg BID	70 mg/kg	35%
	Day 3	50 mg/kg BID	100 mg/kg	50%
	Day 4	100 mg/kg BID	200 mg/kg	100%
200 mg/kg BID	Day 1	17.5 mg/kg BID	35 mg/kg	9%
	Day 2	35 mg/kg BID	70 mg/kg	17.5%
	Day 3	50 mg/kg BID	100 mg/kg	25%
	Day 4	100 mg/kg BID	200 mg/kg	50%
	Day 5	150 mg/kg BID	300 mg/kg	75%
	Day 6	200 mg/kg BID	400 mg/kg	100%

Abbreviation: BID=twice daily.

Dose Titration Schedule from the DAFFODIL Study

The open-label, Phase 2/3 DAFFODIL study evaluated the safety, tolerability and pharmacokinetics of trofinetide in 15 girls aged 2–4 years with RTT over two treatment periods for up to 78 weeks. Based on study eligibility requirements, participants had a body weight ≥ 9 kg and < 20 kg at screening.⁴ For safety in this younger age group, trofinetide was titrated over a number of weeks.

The dose titration schedule for DAFFODIL was updated in a protocol amendment;⁹ both the original and amended schedules are provided.

Original Protocol

As per the original trial protocol, treatment was started with trofinetide 2 g BID, increased to the full dose of 5 g BID over an 8-week period (**Table 4**). In each case, the dose was increased only if the Investigator judges that the participant was showing acceptable tolerability of the treatment.⁹

Table 4. Original Protocol: DAFFODIL Study Dose Titration Schedule⁹

Dose Commences	Dose	Total Daily Dose	Proportion of Full Dose
Day 1	10 mL (2 g) BID	20 mL (4 g)	40%
Week 2	15 mL (3 g) BID	30 mL (6 g)	60%
Week 4	20 mL (4 g) BID	40 mL (8 g)	80%
Week 8	25 mL (5 g) BID	50 mL (10 g)	100%

Abbreviation: BID=twice daily.

Protocol Amendment

Following a protocol amendment, treatment was started with trofinetide 2 g BID, and increased to the full dose, according to baseline body weight, over a 4-week period (**Table 5** and **Table 6**). In each case, the dose was increased only if the Investigator judges that the participant was showing acceptable tolerability of the treatment.⁹

Table 5. Protocol Amendment: DAFFODIL Study Dose Titration Schedule For Participants Weighing ≥ 9 to <12 kg⁹

Dose Commences	Dose	Total Daily Dose	Proportion of Full Dose
Day 1	10 mL (2 g) BID	20 mL (4 g)	40%
Week 2	20 mL (4 g) BID	40 mL (8 g)	80%
Week 4	25 mL (5 g) BID	50 mL (10 g)	100%

Abbreviation: BID=twice daily.

Table 6. Protocol Amendment: DAFFODIL Study Dose Titration Schedule For Participants Weighing 12 to <20 kg⁹

Dose Commences	Dose	Total Daily Dose	Proportion of Full Dose
Day 1	10 mL (2 g) BID	20 mL (4 g)	33%
Week 2	20 mL (4 g) BID	40 mL (8 g)	67%
Week 4	30 mL (6 g) BID	60 mL (12 g)	100%

Abbreviation: BID=twice daily.

Up-Titration Schedules Used in Clinical Practice: Electronic Prescribing Experience Survey

An electronic survey on prescribing experience was sent in May 2024 to 33 prescribers at 18 US RTT centers of excellence designated by the International Rett Syndrome Foundation. The survey was completed by 22 prescribers from 16 centers of excellence. Most survey respondents (95%, n=21) indicated that they use an up-titration approach for trofinetide in treatment-naïve patients with RTT rather than initiate at the FDA-recommended dose in the Prescribing Information.^{5,10}

Titration protocols (dosing approaches and schedules used at different centers) 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). 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 (Table 7).⁵

Table 7. Trofinetide Titration Approaches Reported by Survey Respondents⁵

Survey question: Please enter your titration protocol(s) for those newly starting trofinetide. Please include dose, frequency of administration, and titration interval.¹⁰

Frequency of administration, and titration interval.		
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 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% TID	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 weekly over 4 steps	
–	Patient-specific and based on tolerability	

Abbreviations: BID = twice daily; TID = three times daily.

Please note, survey results may be inconsistent with findings from the clinical trials. These results, based on prescriber opinion, should be interpreted with caution and may represent chance findings. Clinical conclusions cannot be drawn given lack of clinical/patient data to validate survey results. Survey respondents were compensated for their participation.

The decision to up-titrate the dose of DAYBUE when initiating treatment is based on the clinical judgment of the Healthcare Provider in consultation with the caregiver. When choosing to up-titrate, the dosing schedule should be individualized for each patient. The safety and efficacy of the up-titration approaches created by treatment centers have not been assessed in clinical trials.

Expert Consensus on Real-World Use of Trofinetide Using a Modified Delphi Method

A modified Delphi process was conducted in the United States to establish consensus recommendations for the practical use of trofinetide in the treatment of RTT. This modified Delphi method involved the development and refinement of a set of 72 statements by a multidisciplinary steering group of five trofinetide-experienced RTT experts practicing at US RTT Centers of Excellence, followed by assessment and rating of the statements by a panel of trofinetide-experienced RTT experts also practicing at a US RTT Centers of Excellence. Two rounds of assessments were completed by 25 respondents in each round, resulting in consensus (i.e. 75% agreement) being reached across the final statement set.⁶ This differs from the standard Delphi process where all statements are generated by the entire group of participants, and the process is strictly survey-based.¹¹

The consensus recommendations support the initiation of trofinetide at a low dose, titrating slowly, and tailoring the dose to the patient's needs, as outlined in **Table 8**.⁶

Table 8. Selected Consensus Statements Relating to Up-Titration of Trofinetide at Initiation of Treatment⁶

Statement:	Strongly agree	Tend to agree	Tend to disagree	Strongly disagree	Overall agreement
A dose titration schedule should be created prior to initiation, with flexibility to adapt as needed based on tolerability	84%	16%	0%	0%	100%
Titration should be adapted based on the patient's individual tolerance of the dose	92%	8%	0%	0%	100%
Particularly if there are tolerability concerns (e.g., GI comorbidities), most physicians initiate trofinetide at either 5-10 mL (1000-2000 mg) BID or 25-50% of the recommended weight-banded dose BID and titrate thereafter; however, the starting dose should be individualized, taking into account factors such as the ability to consume liquids	56%	28%	16%	0%	84%
Flexibility in management approaches is essential to accommodate individual patient history, tolerability, and clinical needs when initiating and titrating trofinetide	80%	20%	0%	0%	100%
Patients should be titrated at a rate of 5 mL (1000 mg) per dose every 1-2 weeks, if they are tolerating trofinetide well	32%	44%	20%	4%	76%
For patients unable to tolerate titration of 5-10 mL (1000-2000 mg) per dose every 1-2 weeks, slower titrations should be considered	60%	32%	4%	4%	92%
Dosage should be reassessed at every visit and ideally, every six months, until reaching target dose	68%	28%	0%	4%	96%
Dosage should be reassessed once the patient progresses to the next weight band	72%	24%	4%	0%	96%
Periodic dose re-challenges to achieve recommended weight-banded dose are encouraged, particularly if patients have been tolerating their current dose	52%	40%	8%	0%	92%

Abbreviations: BID=twice daily; GI=gastrointestinal.

Consensus statements regarding treatment initiation are not consistent with the weight-based dosing recommendations in the FDA-approved Prescribing Information. Starting patients on a lower dose of trofinetide and titrating them to a tolerable dose over time has not been approved by the FDA, and the efficacy and safety of such approach have not been established. The efficacy of trofinetide has only been demonstrated at the FDA-recommended weight-based dose. Improvements may not occur until patient reaches the recommended dose and continues treatment. The Delphi consensus process was supported by Acadia Pharmaceuticals Inc. All steering group members received honoraria from Acadia while undertaking this work.

The decision to up-titrate the dose of DAYBUE when initiating treatment is based on the clinical judgment of the Healthcare Provider in consultation with the caregiver. When choosing to up-titrate, the dosing schedule should be individualized for each patient.

Additional Resources

The International Rett Syndrome Foundation (IRSF) has created a resource that allows Healthcare Providers to address questions to experts treating patients with RTT. The IRSF Collaboration Portal can be accessed using this [link](#). Healthcare Providers are required to register prior to accessing the portal.

References

1. DAYBUE® (trofinetide) [package insert]. San Diego, CA. Acadia Pharmaceuticals Inc. [\[Link\]](#)
2. Neul JL, Percy AK, Benke TA, et al. Trofinetide for the treatment of Rett syndrome: a randomized phase 3 study. *Nat Med*. 2023;29(6):1468-1475. [\[PubMed\]](#)
3. Glaze DG, Neul JL, Kaufmann WE, et al. Double-blind, randomized, placebo-controlled study of trofinetide in pediatric Rett syndrome. *Neurology*. 2019;92(16):e1912-e1925. [\[PubMed\]](#)
4. Percy AK, Ryther R, Marsh ED, et al. Results from the phase 2/3 DAFFODIL study of trofinetide in girls aged 2-4 years with Rett syndrome. *Med*. 2025;6(6):100608. [\[PubMed\]](#)
5. Prange E, Lieberman D, Correa G, et al. Real-world use of trofinetide: a survey of practices from prescribers at Rett syndrome centers of excellence in the United States. *Future Rare Diseases*. 2025;5(1):2597031. [\[Link\]](#)
6. Prange EOC, Beisang A, Pehlivan D, Suter B, Schleifer P. Expert Consensus on Real-World Use of Trofinetide for Rett Syndrome Using a Modified Delphi Method. *Annals of the Child Neurology Society*. 2026;4(1):38-51. [\[Link\]](#)
7. U.S. Food and Drug Administration. DAYBUE (trofinetide) Clinical Review. March 10, 2023. [\[Link\]](#).
8. Acadia Pharmaceuticals Inc. Data on File. ACP-2566-003 Clinical Study Report. 2022.
9. Percy AK, Ryther R, Marsh ED, et al. Results from the phase 2/3 DAFFODIL study of trofinetide in girls aged 2-4 years with Rett syndrome. Supplementary Information. *Med*. 2025;6(6):100608. [\[Link\]](#)
10. Prange E, Lieberman D, Correa G, et al. Real-world use of trofinetide: a survey of practices from prescribers at Rett syndrome centers of excellence in the United States. Supplemental Material. *Future Rare Diseases*. 2025;5(1):2597031. [\[Link\]](#)

11. Varndell W, Fry M, Elliott D. Applying real-time Delphi methods: development of a pain management survey in emergency nursing. *BMC Nurs.* 2021;20(1):149. [\[PubMed\]](#)