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For further information regarding Indication and Important Safety Information for DAYBUE, please click here: Prescribing Information.

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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]

This document provides an overview of the **dosage recommendations from the Prescribing Information**, the up-titration approaches that were used in two trofinetide clinical trials in participants with Rett syndrome (RTT): the **Phase 2 study ACP-2566-002** in girls aged 5–15 years,[3] the **DAFFODIL™ trial** in girls aged 2–4 years,[4] and some **examples** of up-titration schedules being used in clinical practice based on a **survey of United States (US) RTT centers of excellence**.[5] 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 RTT.

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.[3,6]

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 ($AUC_{0\text{-}12,ss}$= 800 to 1200 µg•h/mL) at body weights between 12 and 100 kg.[7] 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 study[2] and are the dosing recommendations in the DAYBUE Prescribing Information.[1]

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

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 oral solution (200 mg/mL) is BID, morning and evening, according to patient weight (**Table 2**).[1]

Table 2. DAYBUE Weight-based Dosage and Volume[1]*

Patient Weight	DAYBUE Dosage	DAYBUE Volume
9 kg to less than 12 kg	5,000 mg twice daily	25 mL twice daily
12 kg to less than 20 kg	6,000 mg twice daily	30 mL twice daily
20 kg to less than 35 kg	8,000 mg twice daily	40 mL twice daily
35 kg to less than 50 kg	10,000 mg twice daily	50 mL twice daily
50 kg or more	12,000 mg twice daily	60 mL 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. Interrupt, reduce the dosage, or discontinue DAYBUE if severe diarrhea occurs, if dehydration is suspected, or if significant weight loss occurs.[1]

If vomiting occurs after DAYBUE administration, an additional dose should not be taken. Instead, continue with the next scheduled dose. Interrupt, reduce dose, or discontinue DAYBUE 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 Schedule[3]

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;[8] 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.[8]

Table 4. Original Protocol: DAFFODIL Study Dose Titration Schedule[8]

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.[8]

Table 5. Protocol Amendment: DAFFODIL Study Dose Titration Schedule For Participants Weighing ≥9 to <12 kg[8]

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 kg[8]

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

Based on data from the specialty pharmacy that distributes DAYBUE and the preference of some prescribing physicians and caregivers to initiate DAYBUE treatment at low doses and titrate upwards to the recommended dose, several Centers of Excellence have created up-titration schedules. These dosing schedules are based on the clinical experience of experts treating patients with RTT and vary across treatment centers and individual patients. Information on real-world alternative dosing approaches of trofinetide in patients with RTT has been collected in an electronic prescriber experience survey.[5]

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]

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]

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 7**).[5]

Table 7. Trofinetide Titration Approaches Reported by Survey Respondents[5]

Survey question: Please enter your titration protocol(s) for those newly starting trofinetide. Please include dose, 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 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

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.

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

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