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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): Impact of Dosing Below Prescribing Information Recommendations on Treatment Outcomes

This letter is provided in response to your specific request for information regarding the impact of dosing DAYBUE below Prescribing Information recommendations on treatment outcomes in individuals with Rett syndrome (RTT).

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.

Summary

- For LAVENDER™ participants who received trofinetide (N=93), 35.5% had a final dose that was below initial dose levels following **dose reductions** that were permitted for tolerability reasons. In the LILAC-1™ and LILAC-2™ open-label extension (OLE) studies, 39.0% of 154 participants and 7.2% of 69 participants had a final dose that was below initial dose levels, respectively.[1]
- In a **post hoc analysis** of LAVENDER, baseline demographic and clinical characteristics, medical history, and use of gastrointestinal (GI)-related medications were similar between participants with and without trofinetide dose reductions.[2]
    - The mean (standard error [SE]) change in **Rett Syndrome Behaviour Questionnaire (RSBQ) total score** from baseline to Week 12 was -3.3 (1.8) and -6.0 (1.2) for participants treated with trofinetide with dose reductions and no dose reductions, respectively.
    - The mean (SE) **Clinical Global Impression–Improvement (CGI-I) score** at Week 12 was 3.6 (0.15) and 3.5 (0.10) for participants treated with trofinetide with dose reductions and no dose reductions, respectively.
    - In participants with trofinetide dose reductions, the incidence of **treatment-emergent adverse events** (TEAEs) and early trofinetide termination were 97% and 33%, compared with 90% and 20% in participants without dose reductions, respectively.
    - In participants with trofinetide dose reductions, the **rate of diarrhea that recovered/resolved** was 69.7% compared with 43.3% in participants without dose reductions.
- The recommended weight-based dosing regimen for trofinetide assessed in LAVENDER, as per the Prescribing Information, was confirmed in population pharmacokinetic (popPK) analysis to achieve exposures consistent with the identified **target trofinetide exposure range**.[3]
- In **exposure-response (E-R) modeling,** the trofinetide exposures achieved in LAVENDER were confirmed to be predictive of efficacy: as trofinetide area under the concentration-time curve from 0 to 12 hours (AUC_{0-12}) increased, there was a reduction (improvement) in RSBQ total scores.[4]

- In **Study ACP-2566-002**, a nominally significant reduction in RSBQ total score and CGI-I score was observed at the 200 mg/kg twice daily (BID) trofinetide dose. However, trofinetide at doses of 50 mg/kg BID and 100 mg/kg BID did not show any effects on the exploratory effectiveness endpoints.[5]
- An **electronic prescribing experience survey** was completed by 22 prescribers from 16 United States (US) RTT centers of excellence. Trofinetide dose titration was reported by 95% of respondents, and 70–75% of patients were estimated to achieve their label dose following a titration protocol. Trofinetide discontinuation due to lack of efficacy was estimated to be approximately 5–8%.[6,7]

Background

In the Phase 2 study ACP-2566-002, a nominally significant reduction in RSBQ total score and CGI-I score at the 200 mg/kg 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.[5,8]

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.[9] 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[10] and are the dosing recommendations in the DAYBUE Prescribing Information.[11]

Table 1. DAYBUE Weight-based Dosage and Dose Range (mg/kg) Per BID Dose[11]*

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

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

Dose Reduction in Trofinetide Clinical Trials

In the LAVENDER, LILAC-1 and LILAC-2 clinical trials in individuals with RTT, dose reductions (to a dose as low as half the assigned dose in LAVENDER and LILAC-1, or as low as 3 g [15 mL] BID in LILAC-2) were permitted if participants could not tolerate administration of the full assigned dose. The dose was to be increased as soon as possible based on the clinical situation, with the aim of returning the originally assigned dose.[12-14]

For LAVENDER participants who received trofinetide (N=93), 35.5% had their dose reduced, and 25.8% had a final dose that was below initial dose levels (**Table 2**). In the LILAC-1 OLE (N=154), 51.3% of participants had their dose reduced and 39.0% had a final dose that was

below initial dose levels. In the LILAC-2 OLE (N=69), 8.7% of participants had their dose reduced and 7.2% had a final dose that was below initial dose levels.[1]

Table 2. Trofinetide Dose Reduction and Final Dose Status in Phase 3 and OLE Studies[1]

Study	Participants with dose reduction, n (%)	Final dose for participants whose dose was reduced, n (%)		
		Below initial dose levels	Equal to initial dose levels	Unknown
LAVENDER (N=93)	33 (35.5)	24 (25.8)	9 (9.7)	0
LILAC-1 (N=154)	79 (51.3)	60 (39.0)	14 (9.1)	5 (3.2)
LILAC-2 (N=69)	6 (8.7)	5 (7.2)	1 (1.4)	0

Abbreviation: OLE=open-label extension.

LAVENDER Post Hoc Efficacy Analysis by Dose Reduction

Methods

A post hoc analysis of the Phase 3 LAVENDER study assessed the efficacy of trofinetide in participants who did and did not experience trofinetide dose reductions. Dose reduction was defined as a reduction relative to any previous dose. Groups were analyzed by baseline demographic and clinical characteristics, medical history, and use of GI-related medications. Efficacy assessments included change in RSBQ score from baseline and CGI-I scores at Weeks 2, 6, and 12. Other assessments included the percentage of target dose reached at each interval between visits, overall incidence of TEAEs, and rates of early termination from LAVENDER.[2]

Baseline Characteristics

Overall, 33 and 60 participants of LAVENDER did and did not experience dose reduction, respectively. Baseline demographic and clinical characteristics, and medical history, were similar between participants with and without trofinetide dose reductions (**Table 3**).[2]

Table 3. Baseline Demographics and Characteristics[2]

	Trofinetide dose reduction (N=33)	Trofinetide no dose reduction (N=60)
Mean (SE) age, years	11.8 (0.8)	10.6 (0.6)
Age categories, n (%)		
5–10 years	17 (51.5)	32 (53.3)
11–15 years	8 (24.2)	17 (28.3)
16–20 years	8 (24.2)	11 (18.3)
Weight categories, n (%)		
12–20 kg	4 (12.1)	19 (31.7)
>20–35 kg	20 (60.6)	22 (36.7)
>35–50 kg	6 (18.2)	15 (25.0)
>50 kg	3 (9.1)	4 (6.7)
***MECP2* gene mutation severity, n (%)**		
Mild	8 (24.2)	22 (36.7)
Moderate	6 (18.2)	7 (11.7)
Severe	17 (51.5)	29 (48.3)
Unknown	2 (6.1)	2 (3.3)
RSBQ total score, mean (SE)	45.0 (2.1)	43.1 (1.4)
RSBQ severity, n (%)		
<35	6 (18.2)	12 (20.0)
≥35	27 (81.8)	48 (80.0)

CGI-S score, mean (SE)	5.1 (0.1)	4.8 (0.1)
CGI-S category, n (%)		
1–3	0	0
4	6 (18.2)	26 (43.3)
5	19 (57.6)	19 (31.7)
6	8 (24.2)	15 (25.0)
RTT-CSS score, mean (SE)	25.3 (1.0)	23.5 (0.9)

Abbreviations: CGI-S=Clinical Global Impression–Severity; MECP2=methyl-CpG-binding protein 2; RSBQ=Rett Syndrome Behaviour Questionnaire; RTT-CSS=Rett Syndrome-Clinical Severity Scale; SE=standard error.

Both groups had a similar history of GI disorders at baseline (84.8% and 88.3% in the dose reduction and no dose reduction groups, respectively); the most common GI disorders in both groups included constipation, gastroesophageal reflux disease, and dysphagia. The most common medications used at baseline and throughout the trial to manage GI disorders in both groups were antipropulsives and drugs for constipation.[2]

Efficacy Results

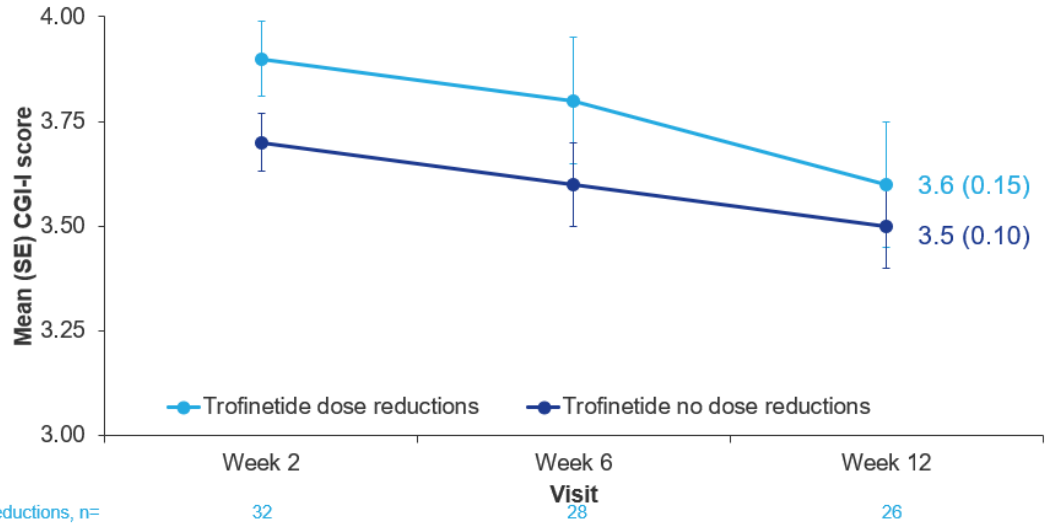
Mean (SE) change in RSBQ total score from baseline to Week 12 of LAVENDER was -3.3 (1.8) and -6.0 (1.2) for participants treated with trofinetide with dose reductions and no dose reductions, respectively (**Figure 1**). Mean (SE) CGI-I score compared with the LAVENDER baseline at Week 12 was 3.6 (0.15) and 3.5 (0.10) for participants treated with trofinetide with dose reductions and no dose reductions, respectively (**Figure 2**).[2]

Figure 1. RSBQ Change from Baseline in LAVENDER Participants With and Without Trofinetide Dose Reductions[2]

Trofinetide dose reductions, n=	33	32	28	25
Trofinetide no dose reductions, n=	58	58	55	51

Abbreviations: RSBQ=Rett Syndrome Behaviour Questionnaire; SE=standard error.

Figure 2. CGI-I Score in LAVENDER Participants With and Without Trofinetide Dose Reductions[2]

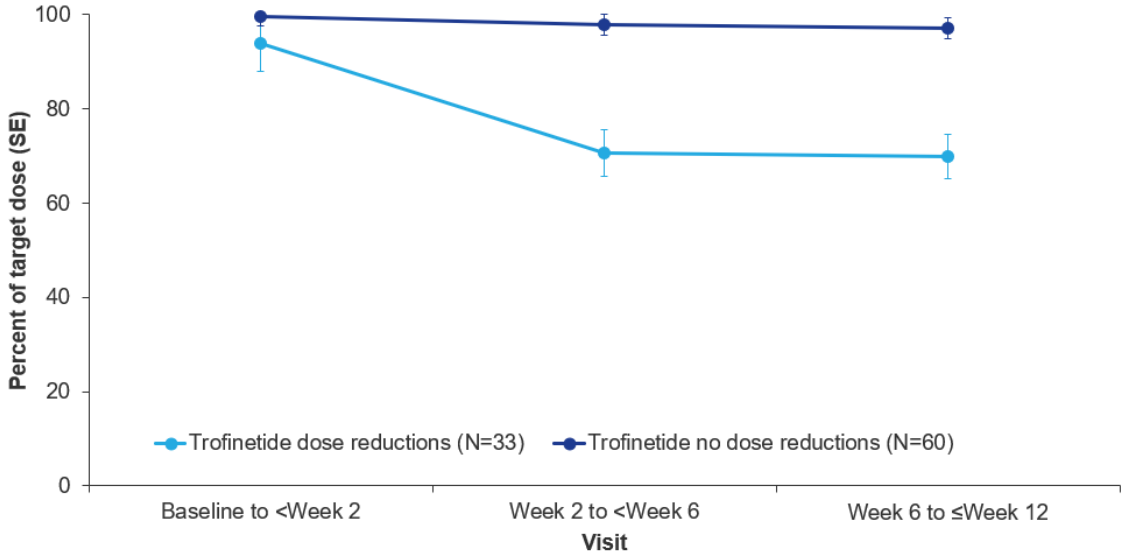


	Week 2	Week 6	Week 12
Trofinetide dose reductions, n=	32	28	26
Trofinetide no dose reductions, n=	58	55	51

Abbreviations: CGI-I=Clinical Global Impression–Improvement; SE=standard error.

LAVENDER participants with trofinetide dose reductions reached 70.6% and 69.9% of their target daily dose by Week 2 to <Week 6 and Week 6 to ≤Week 12, respectively; participants without dose reductions reached 97.9% and 97.1% of their target daily dose by Week 2 to <Week 6 and Week 6 to ≤Week 12, respectively (**Figure 3**). There were 9 patients in the dose reduction group with their last recorded dose equal to their initial dose (i.e., weight-banded dose).[2]

Figure 3. Percentage of Target Daily Dose in LAVENDER Participants With and Without Trofinetide Dose Reductions[2]

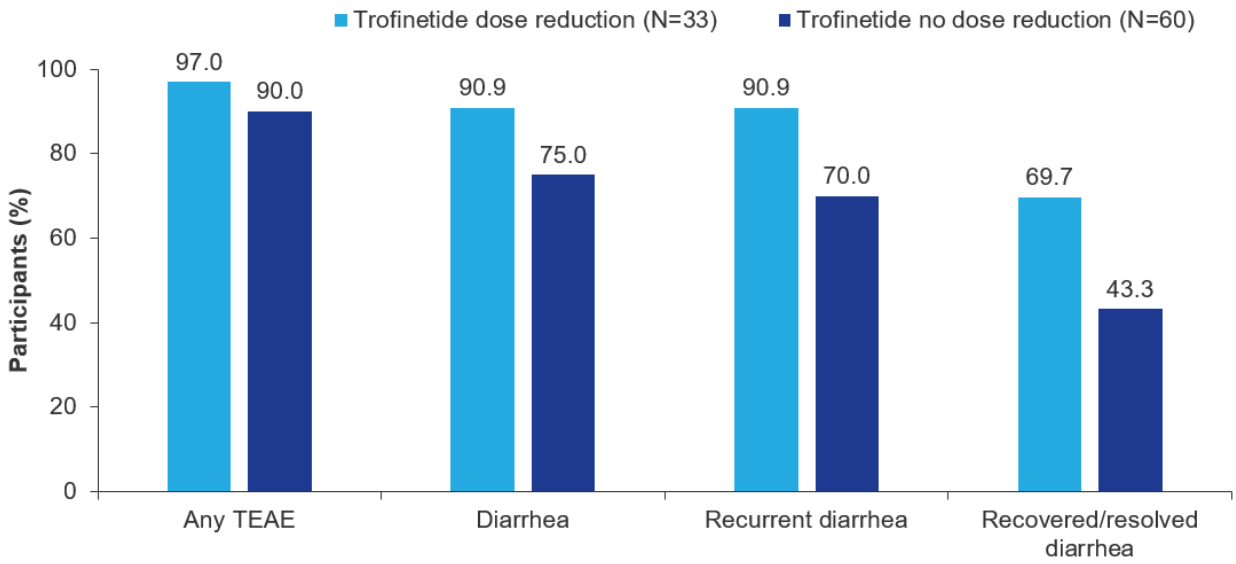


Abbreviation: SE=standard error.

Safety Results

Overall, 97.0% and 90.0% TEAEs were reported for participants treated with trofinetide with and without dose reductions, respectively. The incidence of diarrhea was 90.9% and 75.0% in participants treated with trofinetide with and without dose reductions, respectively. In total, 90.9% and 70.0% of participants with and without trofinetide dose reductions experienced recurrent diarrhea. The rate of recovered/resolved diarrhea was 69.7% and 43.3% in participants treated with trofinetide with and without dose reductions, respectively (**Figure 4**).[2]

Figure 4. Incidence of TEAEs in LAVENDER Participants Treated With Trofinetide With and Without Dose Reductions[2]



Abbreviation: TEAE=treatment-emergent adverse event.

Trofinetide early termination rates were 33.3% and 20.0% in participants treated with trofinetide with and without dose reductions, respectively (**Table 4**).[2]

Table 4. Trofinetide Early Termination in LAVENDER Participants With and Without Trofinetide Dose Reductions[2]

	Trofinetide dose reduction (N=33)	Trofinetide no dose reduction (N=60)
Early termination, n (%)	11 (33.3)	12 (20.0)
Baseline to <Week 2	2 (18.2)	4 (33.3)
Week 2 to <Week 6	5 (45.5)	5 (41.7)
Week 6 to <Week 12	4 (36.4)	3 (25.0)

Limitations

This post hoc analysis is limited by the following:[2]

- Presentation of non-prespecified outcomes; LAVENDER was not powered to detect differences between these groups
- No minimum amount of time that a LAVENDER participant had to take a reduced dose of trofinetide to be included in the dose reduction group

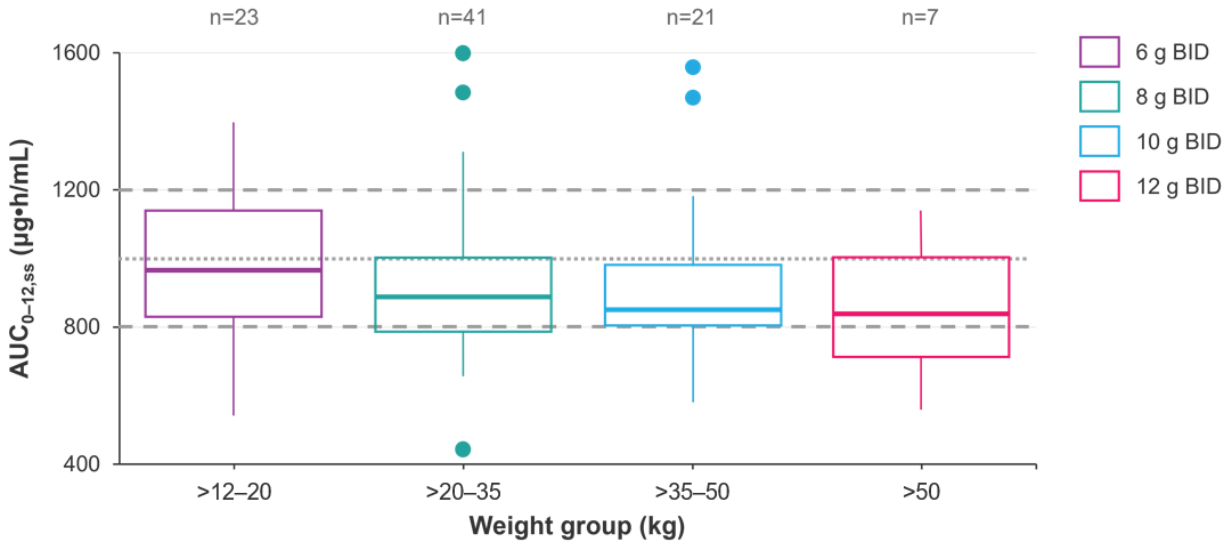
- Prescribers in real-world clinical practice may not rechallenge patients at higher doses after a dose reduction, as was seen among the investigators in LAVENDER

Target Exposure Range for Trofinetide

A target trofinetide exposure range of $AUC_{0–12,ss}$ = 800 to 1200 µg•h/mL was identified based on popPK analysis and E-R modeling using data from five Phase 1 studies and four Phase 2 studies, including ACP-2566-001 and ACP-2566-002. The popPK model has since been refined to include data from 442 participants from 13 clinical trials, including LAVENDER, with results similar to the previous popPK model.[3]

The banded weight-based dosing regimen used in LAVENDER, as per the DAYBUE Prescribing Information, was confirmed in the refined popPK analysis to achieve exposures consistent with this identified target exposure range (**Figure 5**).[3]

Figure 5. Boxplot of PopPK Model-predicted $AUC_{0–12,ss}$ Values in LAVENDER Study Participants by Body Weight–banded Dosing Regimen[3]



The dashed lines represent the target exposure range ($AUC_{0–12,ss}$ = 800–1200 µg•h/mL). The dotted line represents the median target exposure ($AUC_{0–12,ss}$ = 1000 µg•h/mL).
The bottom and top of each box represent the 25th and 75th percentiles, respectively; the whiskers represent the 25th/75th percentile + 1.5 × IQR; the line within each box represents the median. The circles represent the values above/below the 25th/75th percentile + 1.5 × IQR
Abbreviations: $AUC_{0–12,ss}$=area under the concentration-time curve over the dosing interval (12 hours) at steady state; BID=twice daily; IQR=interquartile range; n=number of participants; popPK=population pharmacokinetic.

Exposure-Response (E-R) Modeling

Methods

E-R modeling was conducted for RSBQ total score using data from the Phase 2 study ACP-2566-002 and the pivotal LAVENDER Phase 3 trial assessing trofinetide in female participants with RTT. E-R modeling for CGI-I score used data from two Phase 2 studies (ACP-2566-001 and ACP-2566-002) and LAVENDER. Baseline age, weight, and body mass index were included in the evaluation of covariate effects. For each efficacy analysis, the baseline value of

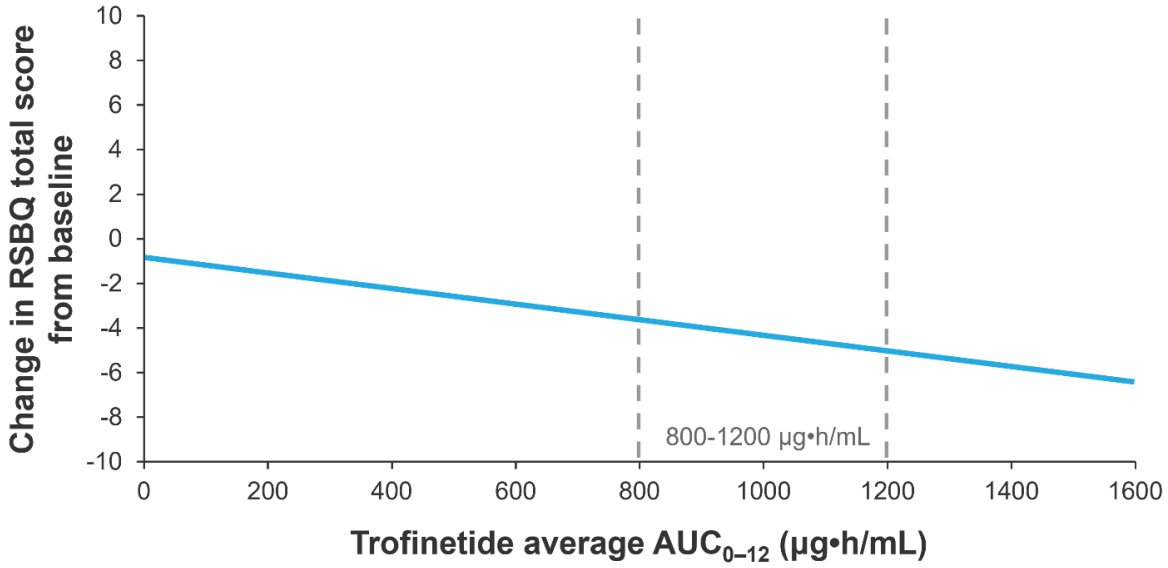
the endpoint was also evaluated as a covariate. The measures of trofinetide exposure evaluated included the average daily consecutive between-visit exposure estimates of C_{max}, AUC_{0-12}, and C_{avg}.[4]

Results: RSBQ Total Score

The RSBQ E-R model included 264 participants with 1022 RSBQ total scores; the median (range) baseline RSBQ total score was 42 (13–74). An E-R relationship was identified for RSBQ total scores and was modeled as a linear time-course model including parameters estimating the baseline RSBQ total scores and the slope for time. Baseline body weight was a significant covariate (heavier weight corresponding to larger reductions in RSBQ total scores).[4]

A linear function described the relationship between the trofinetide $AUC_{0–12}$ and slope whereby a higher trofinetide exposure was predictive of a reduction (improvement) in RSBQ total score (**Figure 6**).[4]

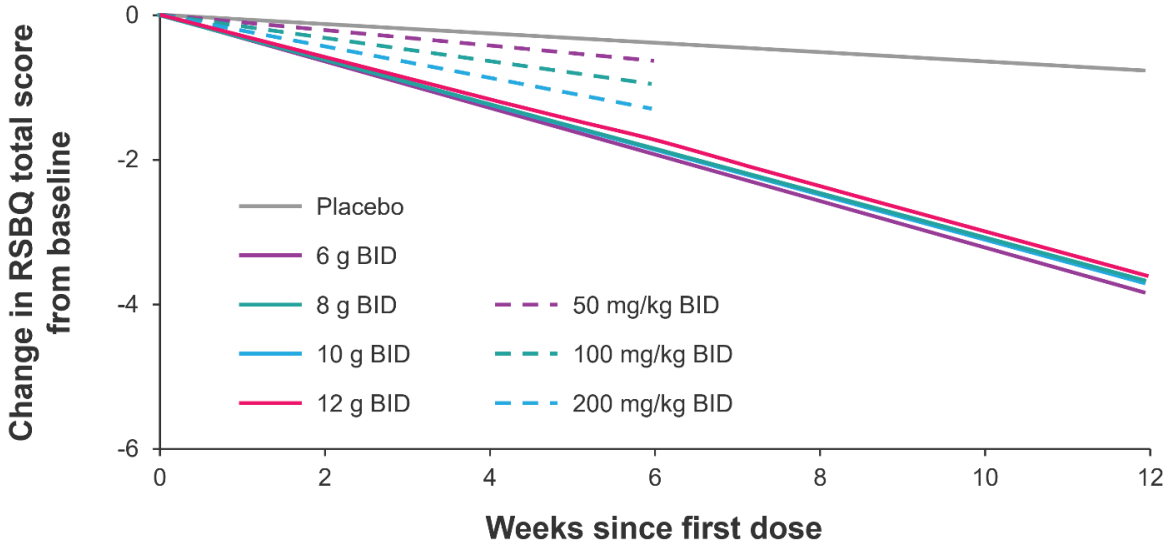
Figure 6. Model-predicted Change in RSBQ Total Scores from Baseline to End of Treatment (Week 12) vs. Trofinetide AUC_{0-12}[4]



Abbreviations: AUC_{0-12}=area under the concentration-time curve from time 0 to 12 hours; RSBQ=Rett Syndrome Behaviour Questionnaire.

At trofinetide target AUC_{0-12} values of 800-1200 µg•h/mL, the reductions (improvement) in model-predicted RSBQ total scores at Week 12 were 3.55 and 4.94, respectively, compared to a reduction of 0.76 for placebo. Based on the dose regimen used in the Phase 2 study and the LAVENDER study, the model-predicted change in RSBQ total scores from baseline increased in a linear and dose-proportional manner (**Figure 7**).[4]

Figure 7. Model-predicted Change in RSBQ Total Scores from Baseline vs. Weeks Since First Dose[4]



Abbreviations: AUC_{0-12}=area under the concentration-time curve from time 0 to 12 hours; BID=twice daily; RSBQ=Rett Syndrome Behaviour Questionnaire.
Note: The model-predicted lines assume the median trofinetide AUC_{0-12} at each week for each dose level.

Results: CGI-I Score

E-R analysis of CGI-I scores was performed to describe the effect of trofinetide exposure on the efficacy endpoint CGI-I scores collected from 316 patients with 989 CGI-I scores from Studies ACP-2566-001, ACP-2566-002, and LAVENDER. No E-R relationship was found for CGI-I scores.[4]

Phase 2 Study Results: ACP-2566-002

This was an exploratory, randomized, double-blind, placebo-controlled, multi-center, parallel-group, Phase 2 study with primary outcomes relating to assessment of safety and PK, and secondary outcomes relating to efficacy. Trofinetide was administered orally or via gastrostomy tube 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).[5]

A total of 82 participants were randomized in this study: 24 in the placebo group, 15 in the 50 mg/kg BID trofinetide group, 16 in 100 mg/kg BID trofinetide group, and 27 in the 200 mg/kg BID trofinetide group. The mean age of the cohort was 9.7 years (range 5.1–15.9 years) and 94% were white. Overall demographic characteristics for participants were balanced across the treatment groups.[5]

Safety Results

Only one participant (200 mg/kg BID group) was withdrawn from the study at the request of her parents because of increased mild gastroesophageal reflux, moderate diarrhea, and mild vomiting, which resolved uneventfully after discontinuation. Four SAEs occurred in 3 participants: 1 participant receiving placebo, 1 participant receiving 100 mg/kg bid, and 1

participant receiving 200 mg/kg BID. All the SAEs were deemed not related to study medication and resolved by the end of the study.

The most common AEs reported during the double-blind period across all treatment groups were diarrhea (27%), vomiting (15%), upper respiratory tract infection (12%), and pyrexia (10%) (**Table 5**). Most AEs were mild or moderate in intensity and most events were considered not related to study drug. There were no deaths reported in the study.[5]

Table 5. TEAEs in ≥2 Participants in Either Trofinetide Group and >Placebo (ACP-2566-002)[5]

System Organ Class Preferred Term	Number (%) of Participants			
	Placebo (n=24)	Trofinetide 50 mg/kg (n=15)	Trofinetide 100 mg/kg (n=16)	Trofinetide 200 mg/kg (n=27)
Reported ≥1 TEAE	14 (58)	8 (53)	11 (69)	19 (70)
Gastrointestinal disorders				
Diarrhea	1 (4)	4 (27)	2 (13)	15 (56)
Vomiting	3 (13)	1 (7)	2 (13)	6 (22)
Constipation	0 (0)	0 (0)	0 (0)	2 (7)
General disorders and administration site conditions				
Pyrexia	2 (8)	0 (0)	3 (19)	3 (11)
Infections and infestations				
Upper respiratory tract infection	3 (13)	1 (7)	0 (0)	5 (19)
Respiratory, thoracic, and mediastinal disorders				
Sinus congestion	0 (0)	0 (0)	1 (6)	2 (7)

Abbreviation: TEAE=treatment-emergent adverse event.

Efficacy Results

For the 200 mg/kg BID dose group, three of the five core endpoints showed a statistically significant difference from placebo: the RSBQ total score (p=0.042; Cohen's d = -0.487), the RTT-DSC total score (p=0.025; Cohen's d = -0.247), and the CGI-I scale (p=0.029; Cohen's d = -0.645). The 50 mg/kg BID and 100 mg/kg BID groups did not reach statistical significance.[5]

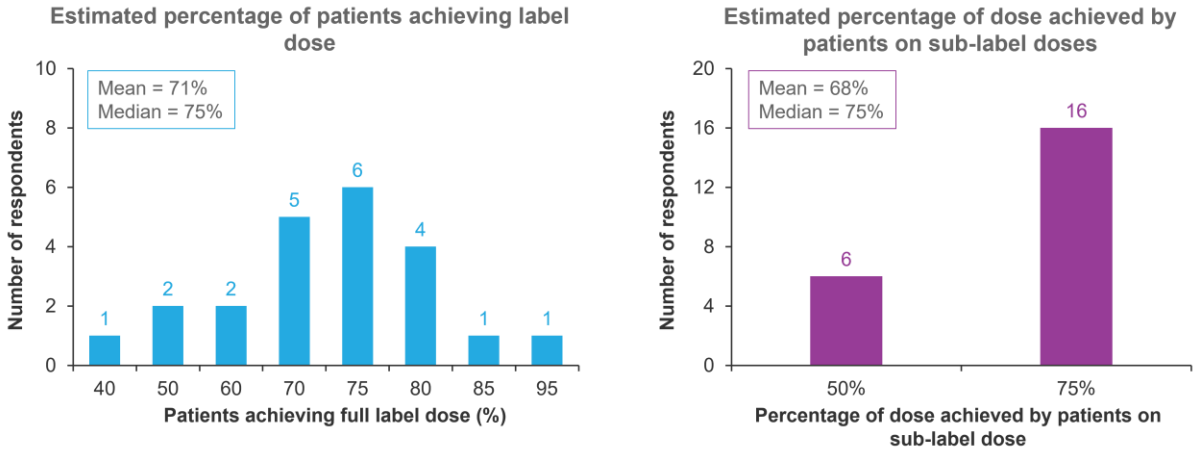
Electronic Prescribing Experience Survey

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.[6,7]

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. Overall, respondents estimated 70–75% of patients achieve their label dose following a titration protocol (**Figure 8**). 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.[6]

Figure 8. Achievement of Trofinetide Label Dose with Titration[6]

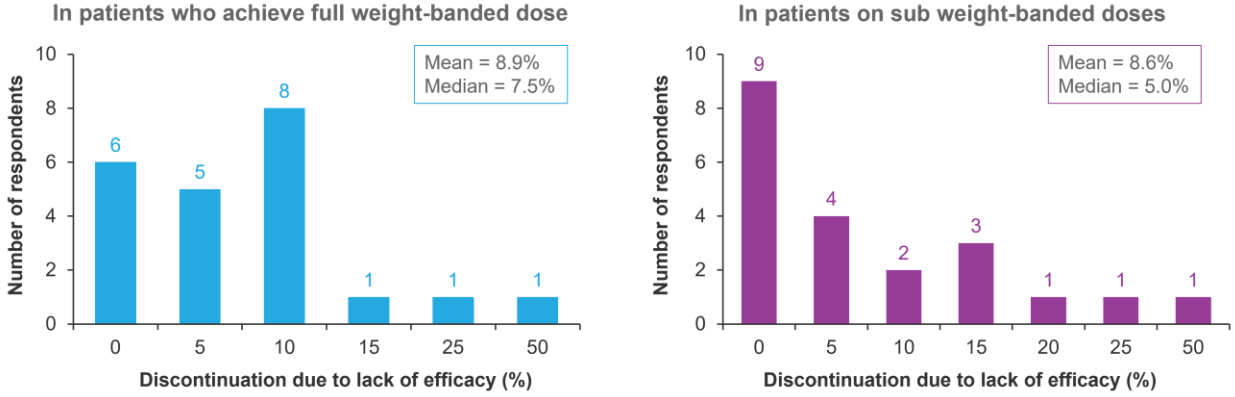
Survey question: Based on your experience, approximately what percentage of patients are able to achieve their full weight-banded dose after titrating? If you answered less than 100%, for those unable to achieve full dose, approximately what percentage of the full weight-banded dose are the majority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



Trofinetide discontinuation due to lack of efficacy was estimated to be approximately 5–8% (**Figure 9**).[7]

Figure 9. Trofinetide Discontinuation Due to Lack of Efficacy[7]

Survey question: Have you or do you currently have any patients on a full weight-banded dose? If yes, based on your experience, approximately what percentage of patients on full weight-banded dose discontinue due to lack of efficacy? Have you or do you currently have any patients on a sub weight-banded dose? If yes, based on your experience, approximately what percentage of patients on sub weight-banded dose discontinue due to lack of efficacy?



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.

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