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

DAYBUE® (trofinetide): Impact of Up-Titration During Treatment Initiation on Tolerability

This letter is provided in response to your specific request for information regarding the impact of up-titration of DAYBUE dosage during initiation of treatment on tolerability in individuals with Rett syndrome (RTT). 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 impact of up-titration of DAYBUE dosage during initiation of treatment on tolerability has not been directly assessed in clinical studies. 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.

Relevant Labeling Information¹

• Warnings and Precautions

- In LAVENDER and in long-term studies, 85% of patients treated with DAYBUE experienced diarrhea. In those treated with DAYBUE, 49% either had persistent diarrhea or recurrence after resolution despite dose interruptions, reductions, or concomitant antidiarrheal therapy. Diarrhea severity was of mild or moderate severity in 96% of cases. In LAVENDER, antidiarrheal medication was used in 51% of patients treated with DAYBUE.
- In LAVENDER, 12% of patients treated with DAYBUE experienced weight loss of greater than 7% from baseline, compared to 4% of patients who received placebo. In long-term studies, 2.2% of patients discontinued treatment with DAYBUE due to weight loss.
- In LAVENDER, vomiting occurred in 29% of patients treated with DAYBUE and in 12% of patients who received placebo.
Patients with Rett syndrome are at risk for aspiration and aspiration pneumonia. Aspiration and aspiration pneumonia have been reported following vomiting in patients being treated with DAYBUE. Interrupt, reduce the dosage, or discontinue DAYBUE if severe diarrhea occurs, if dehydration is suspected, if significant weight loss occurs, or if vomiting is severe or occurs despite medical management.

Summary

- While treatment-emergent adverse events (TEAEs) by dose group are available from a [pooled analysis of safety data](#) from the Phase 2 and Phase 3 double-blind clinical studies,³ the impact of up-titration of DAYBUE dosage during initiation of treatment on tolerability has not been directly assessed in clinical trials.
- The open-label, Phase 2/3 [DAFFODIL™](#) study evaluated the safety, tolerability and pharmacokinetics (PK) of trofinetide in 15 girls aged 2–4 years with RTT over two treatment periods for a total duration of up to 78 weeks.⁴ For safety in the younger age group, trofinetide was titrated over a number of weeks.
 - Overall, 93.3% of subjects reported at least one [treatment-emergent adverse event](#) (TEAE). The most common TEAEs were diarrhea (80.0%) and vomiting (53.3%), which were all mild or moderate in severity. Two participants (13.3%) discontinued due to TEAEs: 1 (6.7%) participant due to TEAEs of diarrhea and 1 (6.7%) participant due to vomiting.⁴
- In [exposure-response \(E-R\) modeling](#) of select TEAEs using data from the trofinetide Phase 2 studies and pivotal Phase 3 trial in female participants with RTT, an E-R relationship was found for [diarrhea](#), [vomiting](#) and [weight decreased](#), but not for decreased appetite, irritability, or seizures.⁵
 - The model-predicted probability of diarrhea, vomiting and weight decreased was found to increase as trofinetide exposure increased.⁵
- An [electronic prescribing experience survey](#) was completed by 22 prescribers from 16 United States (US) RTT centers of excellence.^{6,7} Trofinetide dose titration was reported by 95% of respondents, with several different titration approaches being used.⁶
 - Survey respondents indicated that approximately 20% of patients may discontinue trofinetide due to tolerability issues.⁷

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 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.^{8,9}

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 $1200 \mu\text{g}\cdot\text{h/mL}$) at body weights between 12 and 100 kg.¹⁰ 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 Product Label.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.

Pooled Analysis of Double-Blind Clinical Studies in RTT

The efficacy and safety of trofinetide for the treatment of RTT have been evaluated in 3 double-blind, placebo-controlled studies that assessed different doses of trofinetide: two Phase 2 trials, ACP-2566-001 and ACP-2566-002, and one Phase 3 trial, LAVENDER.^{2,8,11} All clinical study participants had a diagnosis of typical RTT according to the Rett Syndrome Diagnostic Criteria and a documented disease-causing mutation in the *MECP2* gene.^{1,12,13}

ACP-2566-001 and -002 were both exploratory randomized, double-blind, placebo-controlled, Phase 2 studies with primary objectives related to the assessment of the safety and tolerability of trofinetide in individuals with RTT.^{8,11} In Study 001, trofinetide was administered orally at doses of 35 mg/kg twice daily (BID) and 70 mg/kg BID for 28 days to 56 adolescent and adult participants (15–44 years of age) with RTT. Trofinetide doses were up-titrated over 2 days.¹¹ In Study 002, 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 to girls (5–15 years of age) with RTT (N=82). 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.⁸

LAVENDER was a 12-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group, Phase 3 study in 187 female participants (5–20 years old) with RTT.^{1,2} The primary objective of this study was to investigate the efficacy of treatment with oral trofinetide versus placebo in girls and women with RTT.^{2,14} Participants received trofinetide 30–60 mL twice daily (BID) or placebo, based on their weight at baseline, administered orally or by gastrostomy tube. There was no up-titration of dose and participants were started at the recommended dose.²

Pooled Safety Results

Overall, for the pooled population, 59.4% (79/133) of placebo-treated participants experienced TEAEs compared with 83.0% (146/176) of trofinetide-treated participants. The most common TEAEs (>2% for trofinetide overall) by dose group are summarized in **Table 2**. For the TEAEs selected for further analysis in [E-R modeling](#), diarrhea was reported for 56.8% of the trofinetide-treated participants overall (N=176), with vomiting reported for 19.9%, irritability for 6.8%, seizure for 5.7%, decreased appetite for 4.0%, and weight decreased for 1.7% (compared with 16.5% for diarrhea, 9.0% for vomiting, 2.3% for irritability, 6.0% for seizure, 2.3% for decreased appetite, and 0% for weight decreased in the placebo group).³

Table 2. TEAEs in >2% of Participants Receiving Trofinetide, by Dose Group (Pooled Safety Analysis Set)³

Preferred Term	Placebo (N=133)	Trofinetide BID (mg/kg)			
		<200 (N=67)	200 to <300 (N=75)	300 to <400 (N=36)	400 to 500 (N=6)
Any TEAE	79 (59.4)	47 (70.1)	62 (82.7)	36 (100.0)	5 (83.3)
Diarrhea	22 (16.5)	14 (20.9)	54 (72.0)	31 (86.1)	4 (66.7)
Vomiting	12 (9.0)	4 (6.0)	16 (21.3)	13 (36.1)	2 (33.3)
Pyrexia	12 (9.0)	5 (7.5)	7 (9.3)	5 (13.9)	0
Irritability	3 (2.3)	5 (7.5)	4 (5.3)	2 (5.6)	1 (16.7)
Seizure	8 (6.0)	2 (3.0)	4 (5.3)	3 (8.3)	1 (16.7)
Upper respiratory tract infection	8 (6.0)	3 (4.5)	5 (6.7)	2 (5.6)	0
Decreased appetite	3 (2.3)	2 (3.0)	4 (5.3)	1 (2.8)	0
Somnolence	2 (1.5)	5 (7.5)	1 (1.3)	1 (2.8)	0
Dermatitis diaper	1 (0.8)	1 (1.5)	2 (2.7)	3 (8.3)	0
Gastroesophageal reflux disease	1 (0.8)	1 (1.5)	2 (2.7)	2 (5.6)	0
Insomnia	0	4 (6.0)	1 (1.3)	0	0
Nasopharyngitis	3 (2.3)	2 (3.0)	3 (4.0)	0	0
Pharyngitis streptococcal	1 (0.8)	1 (1.5)	1 (1.3)	3 (8.3)	0
Bruxism	0	1 (1.5)	3 (4.0)	0	0
Fall	4 (3.0)	1 (1.5)	1 (1.3)	2 (5.6)	0
Nasal congestion	2 (1.5)	2 (3.0)	2 (2.7)	0	0
Retching	1 (0.8)	0	1 (1.3)	3 (8.3)	0

Abbreviations: BID=twice daily; TEAE=treatment-emergent adverse event.

TEAEs leading to discontinuation by dose group for the pooled population are summarized in **Table 3**.

Table 3. TEAEs Leading to Discontinuation by Dose Group (Pooled Safety Analysis Set)³

Preferred Term	Placebo (N=133)	Trofinetide BID (mg/kg)			
		<200 (N=67)	200 to <300 (N=75)	300 to <400 (N=36)	400 to 500 (N=6)
Any TEAE leading to discontinuation	2 (1.5)	2 (3.0)	9 (12.0)	6 (16.7)	1 (16.7)
Diarrhea	0	0	9 (12.0)	4 (11.1)	0
Decreased appetite	0	0	3 (4.0)	0	0
Lethargy	0	0	2 (2.7)	0	0
Seizure	0	0	0	1 (2.8)	1 (16.7)
Vomiting	0	0	1 (1.3)	1 (2.8)	0
Altered state of consciousness	0	1 (1.5)			
Frequent bowel movements	0	1 (1.5)	0	0	0
Pulmonary embolism	0	1 (1.5)	0	0	0
Gastroesophageal reflux disease	0	0	1 (1.3)	0	0
Weight decreased	0	0	1 (1.3)	0	0
Pneumatosis intestinalis	1 (0.8)	0	0	0	0
Arthralgia	1 (0.8)	0	0	0	0

Abbreviations: BID=twice daily; TEAE=treatment-emergent adverse event.

DAFFODIL (ACP-2566-009)

This was a multicenter, open-label, Phase 2/3 safety, tolerability and PK study of trofinetide in 15 girls (2–4 years of age) with diagnosed RTT. Based on study eligibility requirements, participants had a body weight ≥ 9 kg and < 20 kg at screening. The planned total duration of the trial was up to 26 months, with a screening period, two treatment periods (periods A and B), and a safety follow-up period. Period A was designed for evaluation of the dosing, tolerability, PK, and exploratory efficacy of trofinetide over approximately 12 weeks. Period B was designed to assess the safety and exploratory efficacy of long-term treatment with trofinetide for up to 21 months. The primary objectives of the study were to investigate the safety and tolerability of treatment with oral trofinetide in this population, and to characterize the PK.⁴

For safety in this younger age group, trofinetide was titrated over a number of weeks. As per the original trial protocol, treatment was started with trofinetide 10 mL (2 g) BID, and increased by increments of 5 mL (1 g) at Weeks 2 and 4 until the full dose of 25 mL (5 g) BID was reached at Week 8. Following a protocol amendment, treatment was started with trofinetide 10 mL (2 g) BID, and increased to the full dose, according to baseline body weight, over a 4-week period (**Table 4** and **Table 5**). In each case, the dose was increased only if the Investigator judged that the participant was showing acceptable tolerability of the treatment.¹⁵

Table 4. Protocol Amendment: DAFFODIL Study Dose Titration Schedule For Participants Weighing ≥ 9 to < 12 kg¹⁵

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 5. Protocol Amendment: DAFFODIL Study Dose Titration Schedule For Participants Weighing 12 to < 20 kg¹⁵

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.

Baseline Characteristics

A total of 15 participants received at least one dose of study drug and were included in the Safety Analysis Set. The overall mean (SD) age was 3.1 (0.80) years, with 10 participants younger than 4 years of age at screening. The overall mean (SD) age at RTT diagnosis for all participants was 2.0 (0.4) years and ranged from 1.1 to 3.0 years.⁴

Safety Results

Overall, 14 participants (93.3%) reported any TEAE (**Table 6**). Serious TEAEs were reported by 4 (26.7%) participants overall. Overall, 2 (13.3%) participants discontinued from the study drug due to TEAEs. No deaths were reported.⁴

Table 6. Summary of TEAEs (Safety Analysis Set)⁴

	Trofinetide (N=15), n (%)	
	Treatment Period A	Overall: Treatment Periods A and B
Any TEAE	13 (86.7)	14 (93.3)
Any serious TEAE	1 (6.7)	4 (26.7)
Any related TEAE*	11 (73.3)	13 (86.7)
Any related serious TEAE*	0	0
Any TEAE leading to study drug discontinuation	1 (6.7)	2 (13.3)
Any severe TEAE [†]	1 (6.7)	2 (13.3)
Any fatal TEAE	0	0

*Events with missing relationship were counted as related. [†]Events with missing severity were counted as severe.

Abbreviation: TEAE=treatment-emergent adverse event.

Overall, diarrhea and vomiting were the most common TEAEs, reported in 80.0% and 53.3% of participants, respectively (Table 7).⁴

Table 7. TEAEs Reported in ≥2 Participants Overall (Safety Analysis Set)⁴

Preferred Term	Trofinetide (N=15), n (%)	
	Treatment Period A	Overall: Treatment Periods A and B
Diarrhea	11 (73.3)	12 (80.0)
Vomiting	7 (46.7)	8 (53.3)
COVID-19	4 (26.7)	7 (46.7)
Gastroenteritis	2 (13.3)	5 (33.3)
Pyrexia	4 (26.7)	5 (33.3)
Seizure	3 (20.0)	5 (33.3)
Upper respiratory tract infection	1 (6.7)	4 (26.7)
Cough	2 (13.3)	3 (20.0)
Influenza	1 (6.7)	3 (20.0)
Nasal congestion	3 (20.0)	3 (20.0)
Conjunctivitis	1 (6.7)	2 (13.3)
Dermatitis diaper	2 (13.3)	2 (13.3)
Ear infection	1 (6.7)	2 (13.3)
Epilepsy	1 (6.7)	2 (13.3)
Feeding disorder	2 (13.3)	2 (13.3)
GERD	1 (6.7)	2 (13.3)
Somnolence	2 (13.3)	2 (13.3)
Weight decreased	2 (13.3)	2 (13.3)

Abbreviations: GERD=gastroesophageal reflux disease; TEAE=treatment-emergent adverse event.

Exposure-Response (E-R) Modeling

The E-R modeling dataset included the Safety Analysis populations of two Phase 2 studies (ACP-2566-001 and ACP-2566-002) and one Phase 3 study (ACP-2566-003) in individuals with RTT, receiving either placebo or trofinetide with available trofinetide exposure measures.⁵ The exposure-response analyses included select TEAEs: decreased appetite, diarrhea, irritability, seizures, vomiting, and weight decreased. Only those TEAEs with a ≥5% occurrence rate were formally modeled. Baseline age, weight, and body mass index were included in the evaluation of

covariate effects. Exposure estimates evaluated included the average of daily C_{max} , AUC_{0-12} , and C_{avg} from first to last dose date for all patients. Trofinetide exposure measures were set to zero for placebo patients.⁵

Baseline Demographics

The E-R dataset included 323 female participants with RTT. The population was primarily white (92.0%); 3.1% of patients were Asian, 2.5% were black or African American, 2.2% were categorized as “other” race, and 0.3% were native Hawaiian or other Pacific Islander. The patients ranged from 5 to 44 years of age with a median age of 11 years. The median body weight at baseline was 29.2 kg with a range of 13.3 to 79.0 kg.⁵

Results

Occurrence rates for the TEAEs of interest for the E-R dataset are shown in **Table 8**.

Table 8. Occurrence Rates for TEAEs of Interest (E-R Dataset)⁵

Preferred Term	Placebo (N=138) n (%)	Trofinetide (N=185) n (%)	Total (N=323) n (%)
Decreased appetite	3 (2.2)	7 (3.8)	10 (3.1)
Diarrhea	22 (15.5)	104 (56.2)	126 (39.0)
Irritability	1 (0.7)	10 (5.4)	11 (3.4)
Seizures	6 (4.4)	10 (5.4)	16 (5.0)
Vomiting	12 (8.7)	33 (17.8)	45 (13.9)
Weight decreased	6 (4.4)	17 (9.2)	23 (7.1)

Abbreviations: E-R=exposure-response; TEAE=treatment-emergent adverse event.

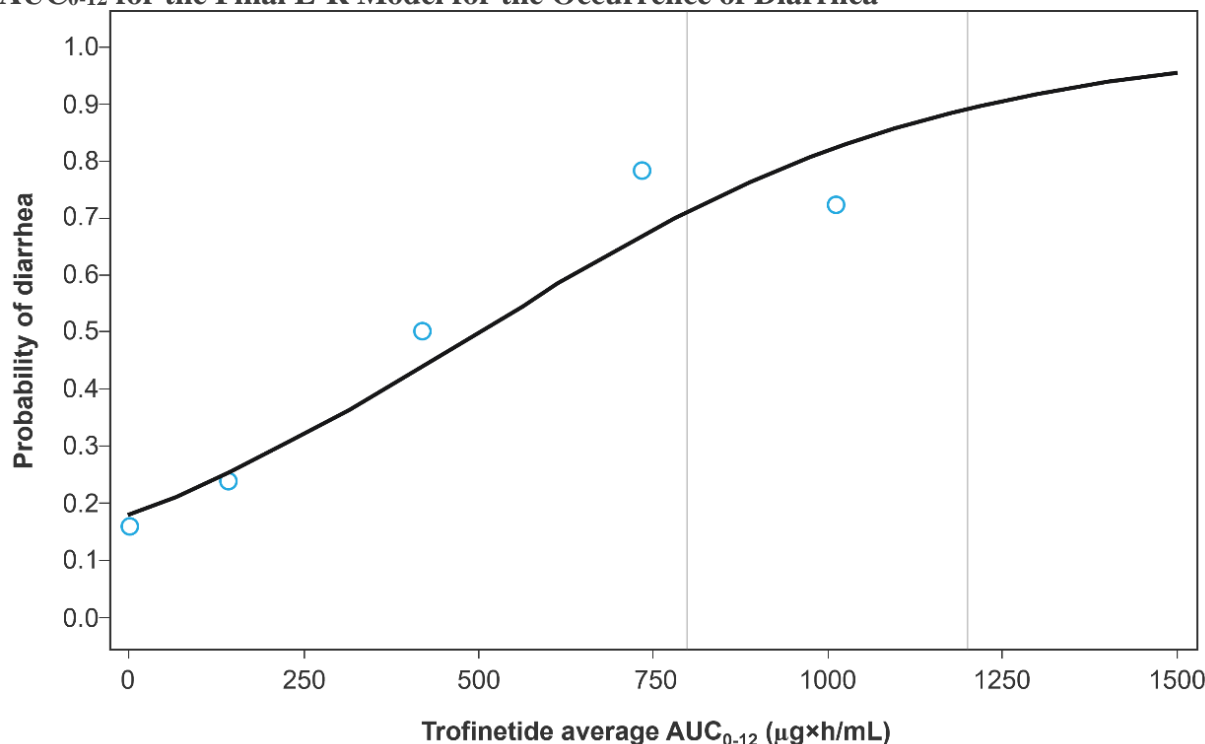
In exploratory graphical analyses for TEAEs of decreased appetite, irritability, and seizures, there was a relatively flat occurrence across trofinetide exposure measures indicating no E-R relationship. Due to the low incidence of decreased appetite and irritability TEAEs, no formal E-R modeling was performed. In base E-R modeling for seizures, none of the exposure measures evaluated were found to be a statistically significant predictor of the probability of seizures, so no further E-R modeling was performed.⁵

Diarrhea

The majority of the first occurrences of diarrhea TEAEs (approximately 85%) occurred during the first 20 days of treatment. Overall, 67.5% of diarrhea TEAEs were mild, 31% were moderate, and 1.6% were severe.⁵

The final E-R model for the probability of diarrhea was a logistic regression model with 2 additive components on the logit scale including placebo response and the drug effect described by a linear function of trofinetide AUC_{0-12} (**Figure 1**). As trofinetide AUC_{0-12} increased, the model-predicted probability of diarrhea increased. Using the target trofinetide AUC_{0-12} range of 800 and 1200 $\mu\text{g} \times \text{h/mL}$, the model-predicted probability of diarrhea was 0.71 and 0.89, respectively, compared to 0.18 in a placebo-treated patient.⁵

Figure 1. Observed and Model-Predicted Probability of Diarrhea vs. Trofinetide Average AUC₀₋₁₂ for the Final E-R Model for the Occurrence of Diarrhea⁵



The line represents the model-based predicted probability of diarrhea. The circles represent the associated observed probabilities for placebo and at the median exposure of each group.

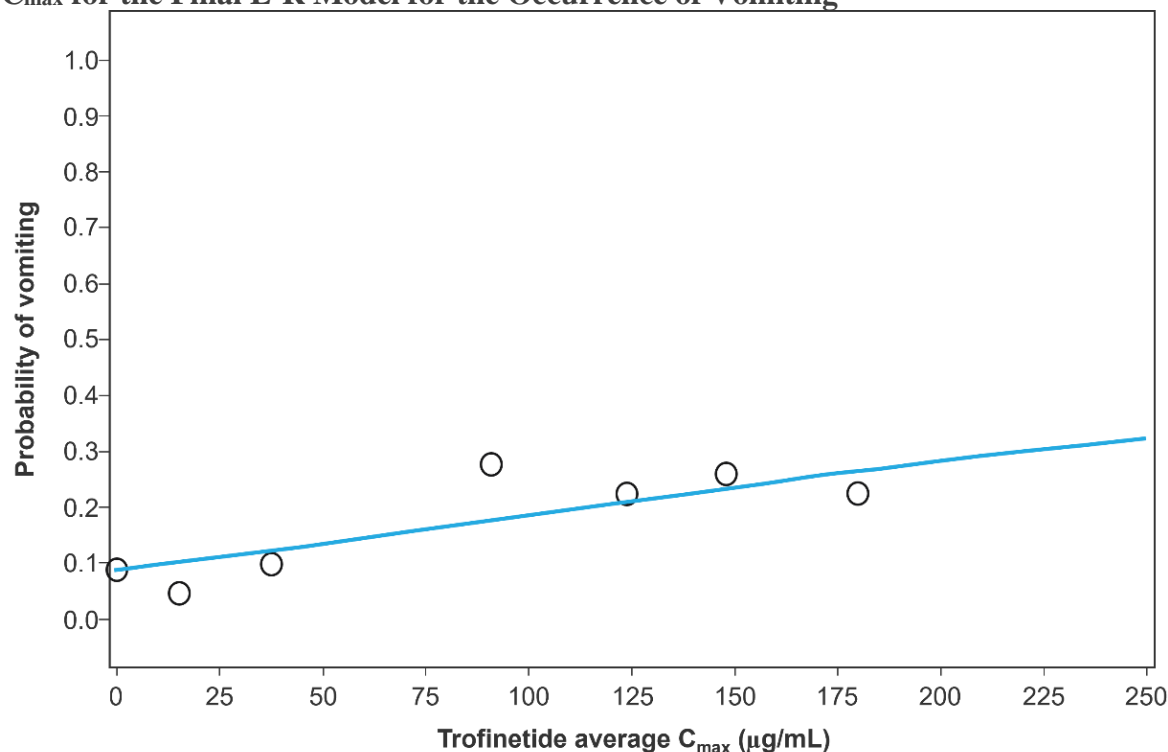
Abbreviations: AUC₀₋₁₂=area under the concentration-time curve from time 0 to 12 hours; E-R=exposure-response.

Vomiting

The majority of the first occurrences of vomiting TEAEs (approximately 78%) occurred during the first 30 days of treatment. The majority of vomiting TEAEs (84.4%) were considered mild, 13.3% were moderate, and 2.2% were severe.⁵

The final E-R model for the probability of vomiting was a logistic regression model with 3 components on the logit scale including placebo response, the drug effect described by an exponential function of trofinetide C_{max}, and a linear effect of age on placebo response (**Figure 2**). As trofinetide C_{max} increased, the model-predicted probability of vomiting increased. Younger patients also had a higher model-predicted probability of vomiting compared to older patients. Assuming the median trofinetide C_{max} of 147 µg/mL and the median age of 11 years, the model-predicted probability of vomiting was 0.23, compared to 0.09 in a placebo-treated patient.⁵

Figure 2. Observed and Model-Predicted Probability of Vomiting vs. Trofinetide Average C_{max} for the Final E-R Model for the Occurrence of Vomiting⁵



The line represents the model-based predicted probability of vomiting. The circles represent the median trofinetide average C_{max} values and associated observed probabilities.

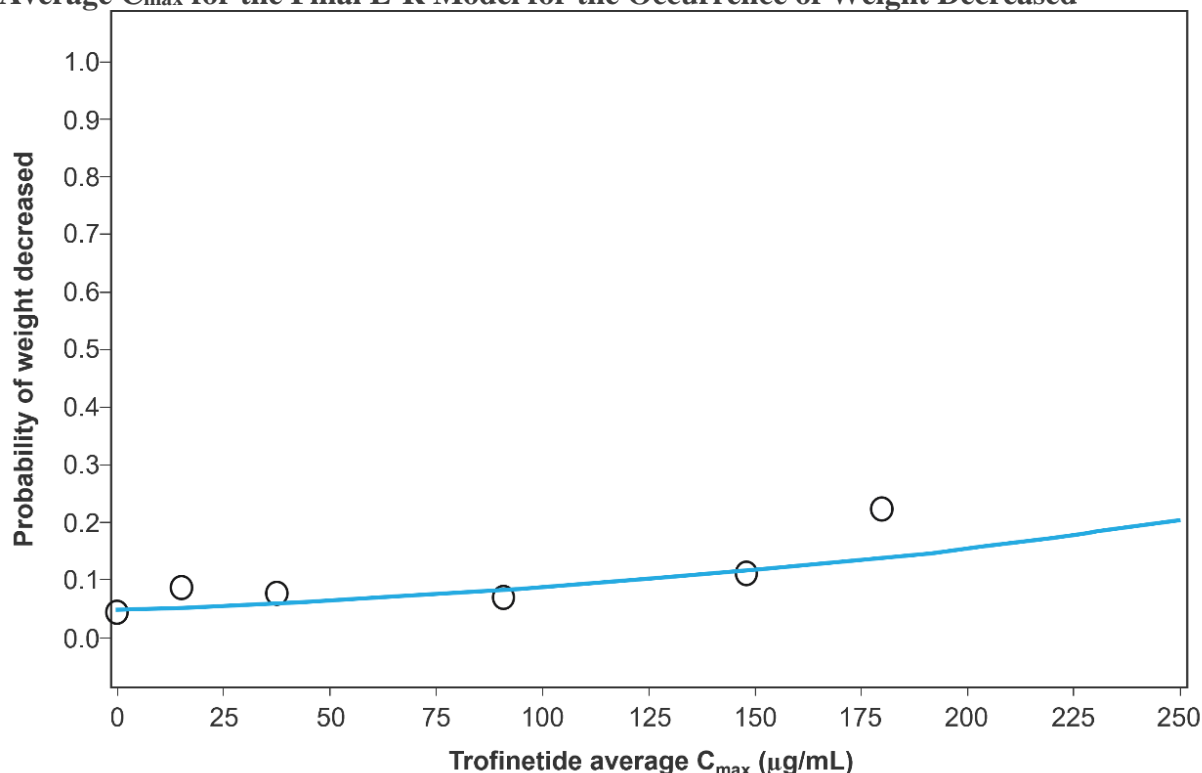
Abbreviations: C_{max} =maximum observed drug concentration; E-R=exposure-response.

Weight Decreased

For patients who experienced an AE of weight decreased, there was an even distribution of AEs of weight decreased across time.⁵

The final E-R model for the probability of AEs of weight decreased was a logistic regression model with 2 additive components on the logit scale including placebo response and the drug effect described by a linear function of trofinetide C_{max} . As trofinetide- C_{max} increased, the model predicted an increased probability of an AE of weight decreased (**Figure 3**). Using the model-predicted median trofinetide C_{max} of 147 $\mu\text{g/mL}$, the model-predicted probability of an AE of weight decreased was 0.11 compared to a 0.05 probability of an AE of weight decreased in a patient-administered placebo.⁵

Figure 3. Observed and Model-Predicted Probability of Weight Decreased vs. Trofinetide Average C_{max} for the Final E-R Model for the Occurrence of Weight Decreased⁵



The line represents the model-based predicted probability of weight decreased. The circles represent the median trofinetide average C_{max} values and associated observed probabilities.

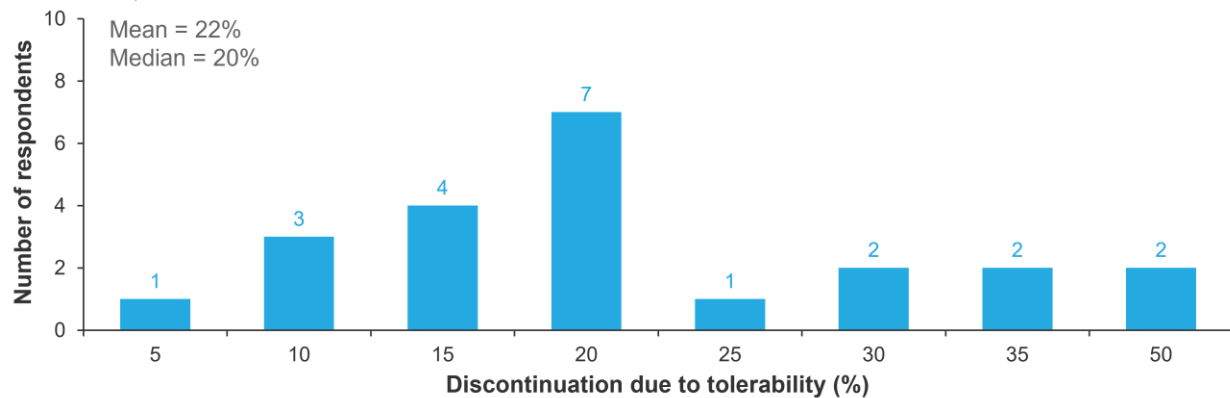
Abbreviations: C_{max} =maximum observed drug concentration; E-R=exposure-response.

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.⁶ Survey respondents indicated that approximately 20% of patients may discontinue trofinetide due to tolerability issues (**Figure 4**).⁷

Figure 4. Trofinetide Tolerability-Related Discontinuation⁷

Survey question: Based on your experience, approximately what percentage of patients discontinue trofinetide due to tolerability issues?



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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