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DAYBUE® (trofinetide): Results from the DAFFODIL™ Study

This letter is provided in response to your specific request for information regarding the final results from the Phase 2/3 clinical trial of trofinetide in girls aged 2–4 years with Rett syndrome (RTT).

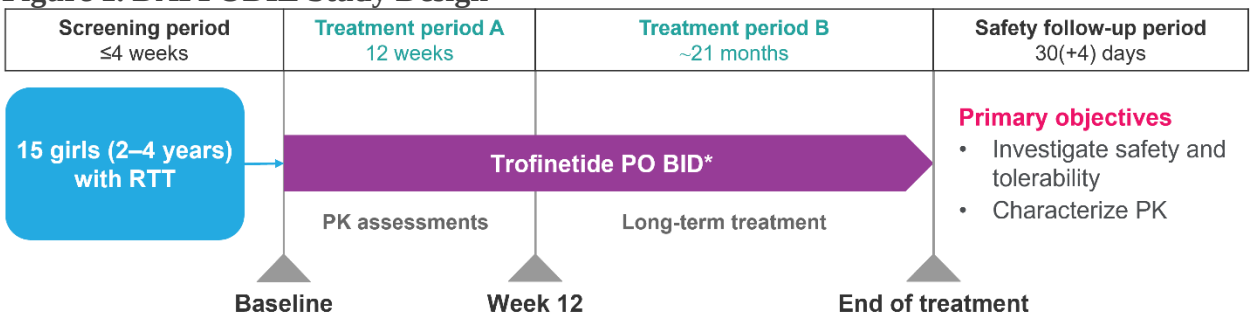
Summary

- 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.[1]
- Twelve (80.0%) participants were still **enrolled in the study when it was terminated** by the sponsor. Three (20.0%) participants terminated the study early: two (13.3%) due to an adverse event and one (6.7%) due to noncompliance with study drug.[1]
- 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.[1]
- Steady state exposure at the clinical doses fell within the target exposure range.[1]

DAFFODIL (ACP-2566-009)

This was a multicenter, open-label, Phase 2/3 safety, tolerability and PK study of trofinetide in girls (2–4 years of age) with diagnosed RTT (**Figure 1**). 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. Fifteen participants received trofinetide 2 g (10 mL) BID, with subsequent increases to the full weight-based dose at scheduled visits, depending on tolerability.[1]

Figure 1. DAFFODIL Study Design[1]



**2 g (10 mL) BID at baseline, 4 g (20 mL) BID at Week 2, and 5 g (25 mL) BID (≥9 to <12 kg) or 6 g (30 mL) BID (≥12 to <20 kg) at Week 4.*
Abbreviations: BID=twice a day; PK=pharmacokinetic(s); PO=oral; RTT=Rett syndrome.

Selected inclusion and exclusion criteria are shown in **Table 1**.

Table 1. Selected Inclusion and Exclusion Criteria[2]

Selected inclusion criteria

• Female participants:
  ○ 2 to 4 years of age and body weight ≥9 kg and <20 kg at screening, or
  ○ 5 years of age and body weight ≥9 kg and <12 kg at screening
• Could swallow the study medication provided as a liquid solution or take it by gastrostomy tube
• Classic/typical RTT or possible RTT according to the Rett Syndrome Diagnostic Criteria
• A documented disease-causing mutation in the *MECP2* gene
• CGI-S score of ≥4 at screening and baseline
• A stable pattern of seizures, or had no seizures, within 8 weeks prior to screening

Selected exclusion criteria

• Had been treated with insulin within 12 weeks of baseline
• Current clinically significant cardiovascular, endocrine (such as hypo- or hyperthyroidism, Type 1 diabetes mellitus, or uncontrolled Type 2 diabetes mellitus), renal, hepatic, respiratory or gastrointestinal disease (such as celiac disease or inflammatory bowel disease) or had major surgery planned during the study
• History of, or current, cerebrovascular disease or brain trauma
• Significant, uncorrected visual or uncorrected hearing impairment
• History of, or current, malignancy
• Had any of the following:
  ○ QTcF interval of >450 ms at screening or baseline
  ○ History of a risk factor for torsades de pointes (e.g., heart failure or family history of long QT syndrome)
  ○ History of clinically significant QT prolongation that was deemed to put the participant at increased risk of clinically significant QT prolongation
  ○ Other clinically significant finding on ECG at screening or baseline

Abbreviations: ECG=electrocardiogram; MECP2=methyl-CpG-binding protein 2; QTcF=corrected QT interval using Fridericia's correction method; RTT=Rett syndrome.

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 (**Table 2**), with 10 participants younger than 4 years of age at screening (4 participants were 2 years of age; 6 participants were 3 years of age; and 5 participants were 4 years of age). 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.[1,3]

Table 2. Baseline Demographics and Characteristics (Safety Analysis Set)[1]

Characteristic	Trofinetide (N=15)
Age at screening, years (mean ± SD)	3.1 ± 0.80
Age at screening category, n (%)	
<4 years	10 (66.7)
≥4 years	5 (33.3)
Primary race, n (%)	
Non-White	2 (13.3)
White	13 (86.7)
Weight at baseline, kg (mean ± SD)	13.5 ± 2.2
Age at RTT diagnosis, years (mean ± SD)	2.0 ± 0.4
RTT-CSS score at screening (mean ± SD)	23.4 ± 4.9
CGI-S score (mean ± SD)	4.7 ± 0.7

Characteristic	Trofinetide (N=15)
ICND-QoL	3.9 ± 0.9

Abbreviations: CGI-S=Clinical Global Impression-Severity; ICND-QoL=Overall Quality of Life rating on the Impact of Childhood Neurologic Disability Scale; RTT=Rett syndrome; RTT-CSS=Rett Syndrome-Clinical Severity Scale; SD=standard deviation.

The majority (93.3%) of participants had one *MECP2* mutation (one participant had >1 mutation). *MECP2* mutation severity was categorized as severe for 73.3% of participants (**Table 3**).[1] Overall, 66.7% of participants had a medical history of constipation.[3]

Table 3. *MECP2* Gene Mutation Severity and Selected Medical History (Safety Analysis Set)[1,3]

	Trofinetide (N=15) n (%)
***MECP2* gene mutation severity, n (%)**	
Mild	4 (26.7)
Moderate	0
Severe	11 (73.3)
Selected medical history, n (%)	
Constipation	10 (66.7)
Seizure	2 (13.3)
Gastrostomy	6 (40.0)

Abbreviation: MECP2=Methyl-CpG Binding Protein 2.

Selected Concomitant Medications

Overall, loperamide was used by 53.3% of participants, and 46.7% were taking osmotically acting laxatives (**Table 4**). No participants received concomitant antiemetics and antinauseants.[3]

Table 4. Selected Concomitant Medications Reported in ≥20% of Participants (Safety Analysis Set)[3]

WHO ATC Class Preferred Term	Trofinetide (N=15) n (%)
Antipropulsives	8 (53.3)
Loperamide	8 (53.3)
Contact laxatives	3 (20.0)
Inula helenium root; senna alexandrina leaf	3 (20.0)
Herbal intestinal adsorbents	3 (20.0)
Plantago ovata	3 (20.0)
Osmotically acting laxatives	7 (46.7)
Macrogol	5 (33.3)
Other antiepileptics	5 (33.3)
Levetiracetam	4 (26.7)
Other drugs for functional gastrointestinal disorders	3 (20.0)
Simeticone	3 (20.0)

Concomitant medication was defined as any medications that were ongoing at the first dose of study drug or with a start date between the dates of the first and last doses of study drug, inclusive.
Abbreviations: ATC=Anatomical Therapeutic Chemical; WHO=World Health Organization.

Participant Disposition

Thirteen (86.7%) participants completed Treatment Period A (**Table 5**). Reasons for early termination from Treatment Period A were adverse event (n=1) and noncompliance with study

drug (n=1). During Treatment Period B, 1 participant terminated the study early due to an adverse event. The remaining 12 (80.0%) participants terminated early due to study termination by the sponsor, and all 12 participants took commercially marketed trofinetide within 30 days after study completion. The overall study duration was up to 78 weeks.[1]

Table 5. Participant Disposition (Safety Analysis Set)[1]

	Trofinetide (N=15), n (%)	
	Treatment Period A	Overall: Treatment Periods A and B
Completed the study	13 (86.7)	0
Early termination of the study	2 (13.3)	15 (100.0)
Adverse event	1 (6.7)	2 (13.3)
Noncompliance with study drug	1 (6.7)	1 (6.7)
Study terminated by Sponsor	0	12 (80.0)

Safety Results

Overall, 14 participants (93.3%) reported any TEAE (**Table 6**). No deaths were reported.[1]

Table 6. Summary of TEAEs (Safety Analysis Set)[1]

	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.

TEAEs that were reported in ≥2 participants are summarized in **Table 7**. Overall, diarrhea and vomiting were the most common TEAEs, reported in 80.0% and 53.3% of participants, respectively.[1] Diarrhea was mild for 7 (46.7%) participants and moderate for 5 (33.3%) participants; vomiting was mild for 6 (40.0%) participants and moderate for 2 (13.3%) participants. Diarrhea was considered a related TEAE for 10 (66.7%) participants, and vomiting was considered a related TEAE for 5 (33.3%) participants.[3]

Table 7. TEAEs Reported in ≥2 Participants Overall (Safety Analysis Set)[1]

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)

Preferred Term	Trofinetide (N=15), n (%)	
	Treatment Period A	Overall: Treatment Periods A and B
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.

Serious TEAEs were reported by 4 (26.7%) participants overall: gastroenteritis sapovirus in 1 (6.7%) participant in Treatment Period A, and seizure (n=2 [13.3%]), altered state of consciousness (n=1 [6.7%]) and dysphagia (n=1 [6.7%]) in Treatment Period B. None of the events were considered related to study drug; all events required hospitalization but fully resolved and participants fully recovered.[1]

Overall, 2 (13.3%) participants discontinued from the study drug due to TEAEs (**Table 8**). One participant discontinued during Treatment Period A due to a TEAE of diarrhea that was moderate in severity and considered related to study drug. During Treatment Period B, one participant was discontinued from the study due to a TEAE of vomiting which was mild in severity and considered related to the study drug.[1,3]

Table 8. TEAEs Leading to Discontinuation (Safety Analysis Set)[3]

System Organ Class Preferred Term	Trofinetide (N=15), n (%)	
	Treatment Period A	Overall: Treatment Periods A and B
Any TEAE leading to discontinuation	1 (6.7)	2 (13.3)
Gastrointestinal disorders	1 (6.7)	2 (13.3)
Diarrhea	1 (6.7)	1 (6.7)
Vomiting	0	1 (6.7)

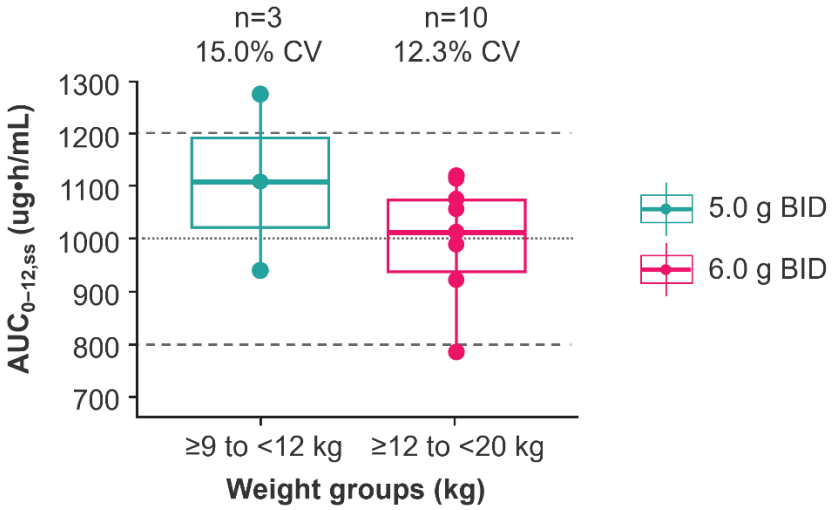
Abbreviation: TEAE=treatment-emergent adverse event.

Overall, laboratory results were generally within normal range. One participant had potentially clinically important and significant elevations (≥3 × upper limit of normal U/L) in alanine aminotransferase and aspartate aminotransferase at study termination on day 77 that returned to normal at a follow-up visit on Day 93. Changes in vital signs and electrocardiogram parameters were not clinically significant. Criteria for potentially clinically important changes from baseline in weight (i.e., ≥7% or ≤7%) were met at some point during the study by 13 (86.7%) participants who had a weight increase of ≥7%, and 2 (13.3%) participants who had a weight decrease of ≥7%.[1] No corrected QT interval using Fridericia's correction method (QTcF) potentially clinically important values were noted.[3]

PK Results

The PK analysis confirmed that trofinetide exposure in study participants fell within the target exposure range of $AUC_{0–12,ss}$ of 800–1200 µg•h/mL (**Figure 2**). The range of exposures in girls aged 2–4 years with diarrhea, vomiting, and seizures was similar to, and within, the range of exposure reported in females aged 5–20 years in LAVENDER™.[1]

Figure 2. Steady-state Exposure Values by Body Weight-banded Dosing Regimen (PK Analysis Set)[1]

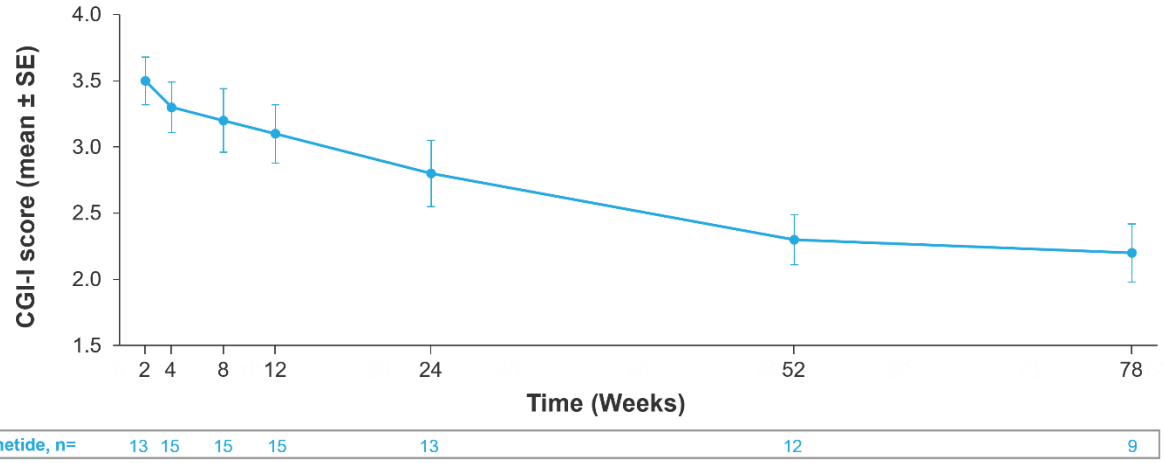


Dashed lines represent the target exposure range ($AUC_{0–12,ss}$= 800–1200 µg•h/mL). The dotted line represents the median target exposure ($AUC_{0–12,ss}$= 1000 µg•h/mL).
Abbreviations: $AUC_{0-12,ss}$= area under the concentration-time curve for the 0 to 12 hour dosing interval at steady state; BID=twice daily; %CV=coefficient of variation expressed as a percent; PK=pharmacokinetic.

Exploratory Efficacy Results

The following efficacy measures were assessed as exploratory endpoints: Clinical Global Impression–Improvement (CGI-I) score, Clinical Global Impression–Severity (CGI-S) score, Caregiver's Global Impression–Improvement (CaGI-I) score, and overall Quality of Life rating on the Impact of Childhood Neurologic Disability Scale (ICND-QoL). The mean (SE) CGI-I score showed improvement at Week 4 (3.3 [0.19]), Week 12 (3.1 [0.22]) and through Week 78 (2.2 [0.22]) (**Figure 3**).[1]

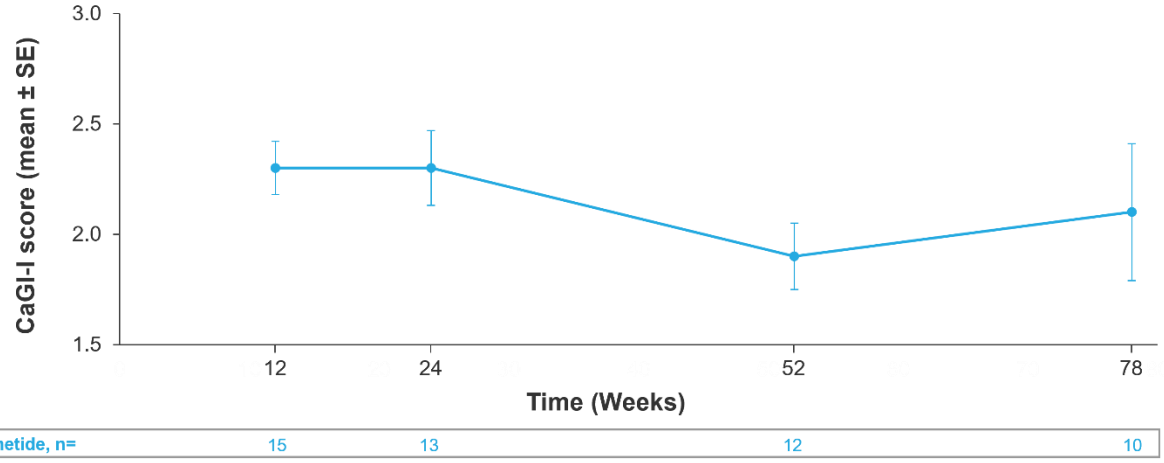
Figure 3. CGI-I Score by Visit (Safety Analysis Set)[1]



The CGI-I is scored from 1 (very much improved) to 7 (very much worse), such that a lower score indicates improvement.
Abbreviations: CGI-I=Clinical Global Impression-Improvement; SE=standard error.

The mean (SE) CaGI-I scores at Week 12 and Week 78 were 2.3 (0.12) and 2.1 (0.31), respectively (**Figure 4**).[1]

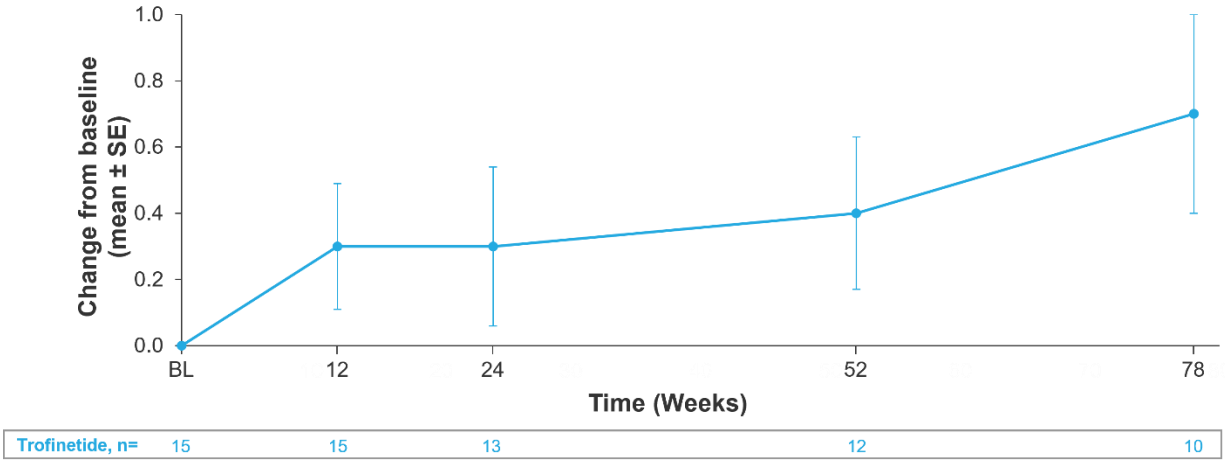
Figure 4. CaGI-I Score by Visit (Safety Analysis Set)[1]



The CaGI-I is scored from 1 (much improved from baseline) to 5 (much worse from baseline), such that a lower score indicates improvement.
Abbreviations: CaGI-I=Caregiver's Global Impression-Improvement; SE=standard error.

The mean (SE) ICND-QoL scores increased from 3.9 (0.24) at baseline to 4.2 (0.31) at Week 12 and 4.6 (0.31) at Week 78, with mean (SE) changes from baseline of 0.3 (0.19) and 0.7 (0.30), respectively (**Figure 5**).[1]

Figure 5. ICND-QoL Score Change from Baseline by Visit (Safety Analysis Set)[1]



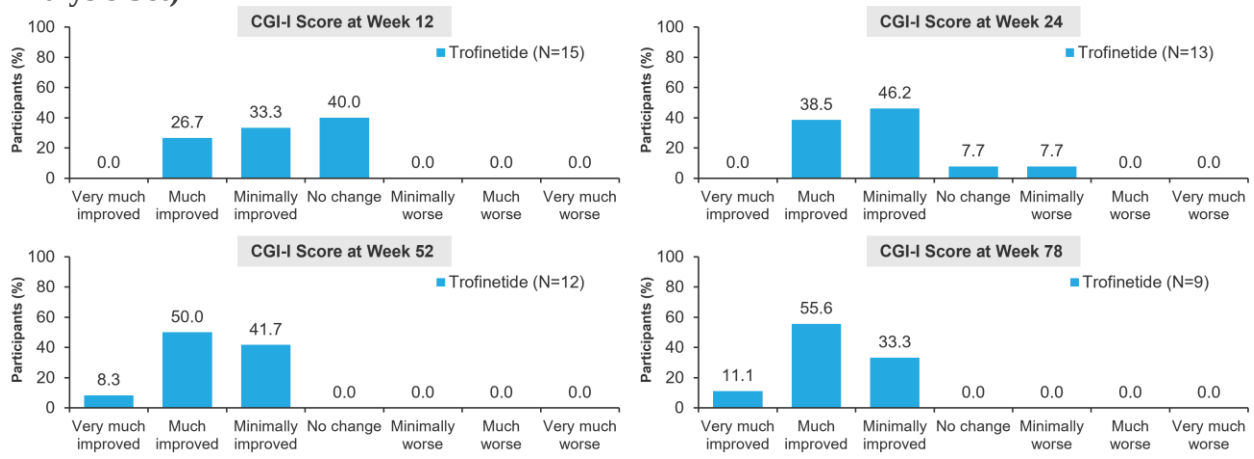
With the ICND-QoL, the child's overall quality of life is ranked from 1 (poor) to 6 (excellent), such that a higher score indicates improvement.
Abbreviations: ICND-QoL=Overall Quality of Life rating on the Impact of Childhood Neurologic Disability Scale; SE=standard error.

The mean (SE) change from baseline in CGI-S score was 0.0 (0.00) for all post-baseline visits.[1]

Post Hoc Responder Analysis

In a post hoc responder analysis of CGI-I score, the percentage of participants with a "much improved" CGI-I score of 2 increased throughout the study (**Figure 6**).[1]

Figure 6. Percentage of Participants with CGI-I Scores at Weeks 12, 24, 52 and 78 (Safety Analysis Set)[1]



Abbreviation: CGI-I=Clinical Global Impression-Improvement.

References

1. 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. **[Link]**
2. Acadia Pharmaceuticals Inc. Data on File. ACP-2566-009 Protocol. 2020.
3. Acadia Pharmaceuticals Inc. Data on File. ACP-2566-009 Clinical Study Report. 2023.