Trofinetide for the Treatment of Girls Aged Two to Four Years With Rett Syndrome: Final Results From the Open-Label DAFFODIL Study

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BACKGROUND

- Rett syndrome (RTT) is a rare neurodevelopmental disorder characterized by loss of verbal communication with limited nonverbal skills, loss of fine and gross motor function, behavioral issues, seizures, hand stereotypies, and gastrointestinal problems[1,2]
- Trofinetide, a synthetic analog of glycine-proline-glutamate, was approved by the US Food and Drug Administration in March 2023 for the treatment of RTT in adults and pediatric patients aged ≥2 years[3]
  - The approval was based on the positive efficacy and safety findings from the 12-week, randomized, placebo-controlled, phase 3 LAVENDER study (NCT04181723) in females aged 5–20 years with RTT[4]
  - The safety and efficacy interim findings of the phase 2/3 DAFFODIL study (NCT04988867) in younger girls with RTT, aged 2–4 years, contributed to the indication being inclusive of ages 2 years and older[5]

OBJECTIVE

- To evaluate the final safety/tolerability and exploratory efficacy of long-term treatment with trofinetide in girls aged 2–4 years with RTT enrolled in DAFFODIL

METHODS

DAFFODIL Study Design

- DAFFODIL (NCT04988867) was a multicenter, open-label study of trofinetide in girls aged 2–4 years with RTT
  - The study included 2 periods: A (12 weeks) and B (~21 months)
- Trofinetide was administered twice daily (BID) orally or by gastrostomy tube and dosed according to body weight
  - Treatment began with trofinetide 2 g BID, with a dose increase to 4 g BID at the week 2 visit
  - At the week 4 visit, the dose was increased to the full dose: 5 g BID for participants who weighed ≥9 to <12 kg (baseline body weight), or 6 g BID for participants who weighed ≥12 to <20 kg

Study Population

- Eligible participants were girls with RTT aged 2–4 years with body weight ≥9 and <20 kg at screening; classic/typical RTT or possible RTT according to the Rett Syndrome Diagnostic Criteria; documented disease-causing mutation in the methyl-CpG-binding protein 2 (*MECP2*) gene; Clinical Global Impression–Severity (CGI-S)[6] score ≥4 at screening and baseline; and a stable pattern of seizures (or no seizures) within 8 weeks before screening

Endpoints

- Safety (treatment periods A and B): treatment-emergent adverse events (TEAEs)
- PK (treatment period A): steady-state exposures calculated using population PK modeling and Bayesian estimation to confirm target exposure range
- Exploratory efficacy (treatment periods A and B):
  - CGI–Improvement (CGI-I)[6]
  - CGI-S[6]
  - Caregiver Global Impression–Improvement (CaGI-I)
  - Overall Quality of Life Rating on the Impact of Childhood Neurologic Disability Scale (ICND-QoL)[7]
- Optional caregiver exit interviews (study conclusion)

RESULTS

Baseline Demographics and Clinical Characteristics

- In total, 15 participants were enrolled in DAFFODIL (**Table 1**)

Table 1. Baseline Demographics and Clinical Characteristics

Characteristic	Participants (N = 15)
Age, mean (SD), years	3.1 (0.8)
Age categories, 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, mean (SD), kg	13.5 (2.2)
MECP2 gene mutation severity, n (%)	
Mild	4 (26.7)
Moderate	0
Severe	11 (73.3)
Baseline ICND-QoL score, mean (SD)[a]	3.9 (0.9)
Baseline CGI-S score, mean (SD)[b]	4.7 (0.7)

[a]The numeric score of the child's overall quality of life ranges from 1 ("poor") to 6 ("excellent"). [b]Based on a 7-point scale (1 = "normal/not at all ill" to 7 = "extremely ill")
CGI-S, Clinical Global Impression–Severity; ICND-QoL, Overall Quality of Life Rating of the Impact of Childhood Neurologic Disability Scale; *MECP2*, methyl-CpG-binding protein 2 gene; SD, standard deviation

Safety

- The most common TEAEs in treatment periods A and B were diarrhea (80.0%), vomiting (53.3%), and COVID-19 (46.7%) (**Table 2**)
  - Serious TEAEs (26.7%) were unrelated to treatment
- There were no deaths reported during the study (**Table 2**)

Table 2. Summary of TEAEs

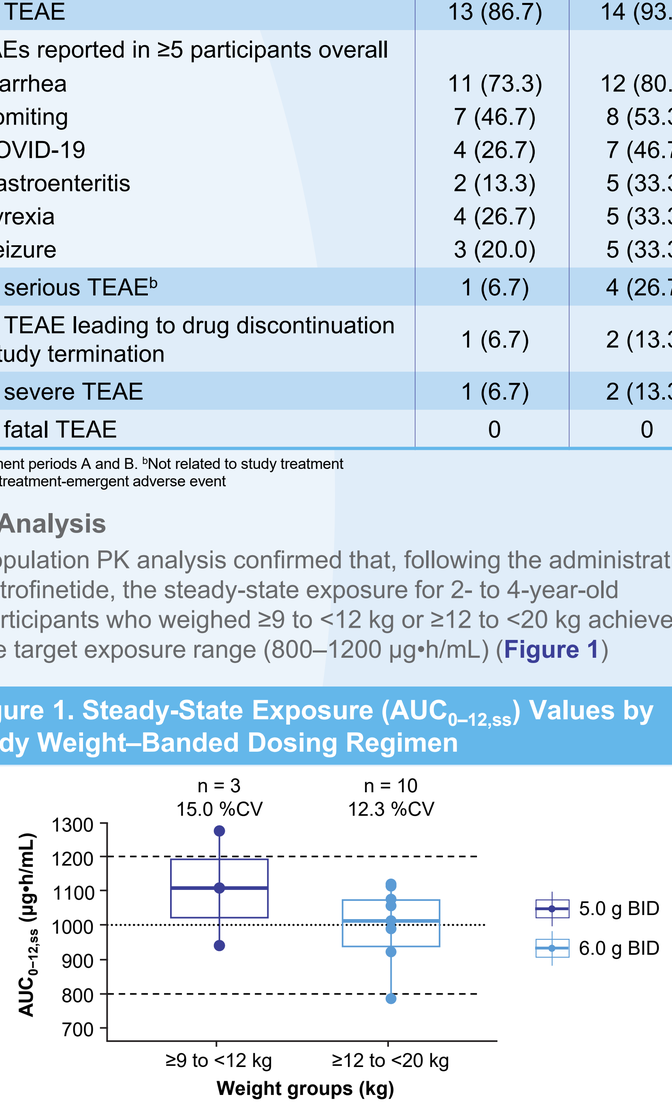
Preferred term, n (%)	Treatment period A (N = 15)	Overall[a] (N = 15)
Any TEAE	13 (86.7)	14 (93.3)
TEAEs reported in ≥5 participants overall		
Diarrhea	11 (73.3)	12 (80.0)
Vomiting	7 (46.7)	8 (53.3)
COVID-19	4 (26.7)	7 (46.7)
Gastroenteritis	2 (13.3)	5 (33.3)
Pyrexia	4 (26.7)	5 (33.3)
Seizure	3 (20.0)	5 (33.3)
Any serious TEAE[b]	1 (6.7)	4 (26.7)
Any TEAE leading to drug discontinuation or study termination	1 (6.7)	2 (13.3)
Any severe TEAE	1 (6.7)	2 (13.3)
Any fatal TEAE	0	0

[a]Treatment periods A and B. [b]Not related to study treatment
TEAE, treatment-emergent adverse event

PK Analysis

- Population PK analysis confirmed that, following the administration of trofinetide, the steady-state exposure for 2- to 4-year-old participants who weighed ≥9 to <12 kg or ≥12 to <20 kg achieved the target exposure range (800–1200 µg•h/mL) (**Figure 1**)

Figure 1. Steady-State Exposure ($AUC_{0–12,ss}$) Values by Body Weight–Banded Dosing Regimen

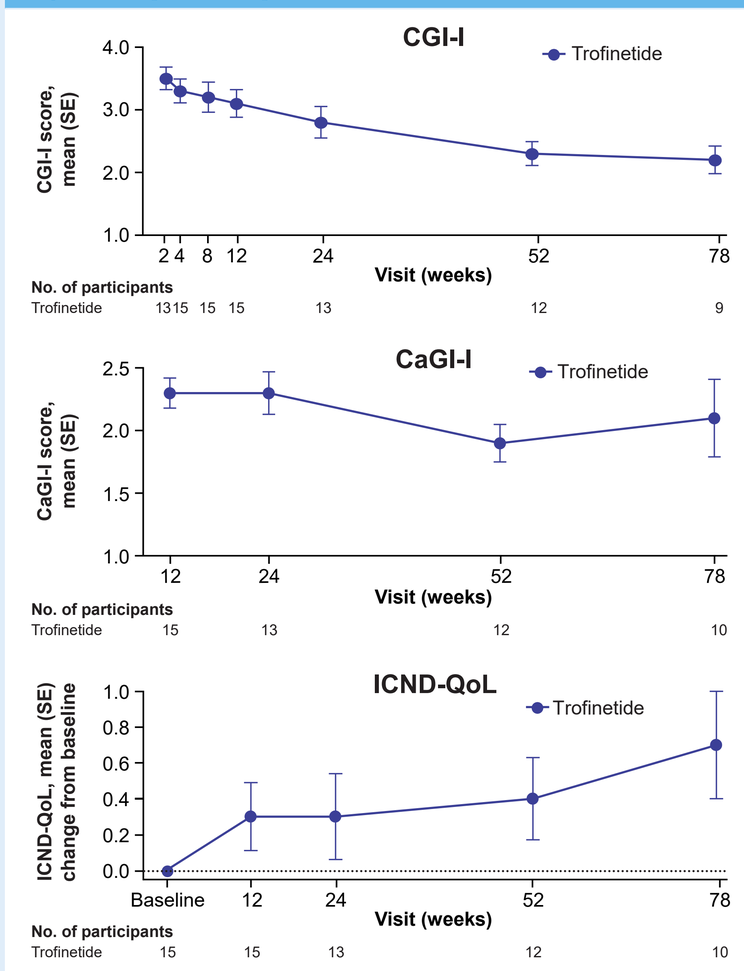


Dashed lines represent the target exposure range ($AUC_{0–12,ss}$= 800–1200 µg•h/mL). The dotted line represents the median target exposure ($AUC_{0–12,ss}$= 1000 µg•h/mL)
$AUC_{0–12,ss}$, area under the concentration-time curve over the dosing interval (12 hours) at steady state; BID, twice daily; %CV,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

Exploratory Efficacy

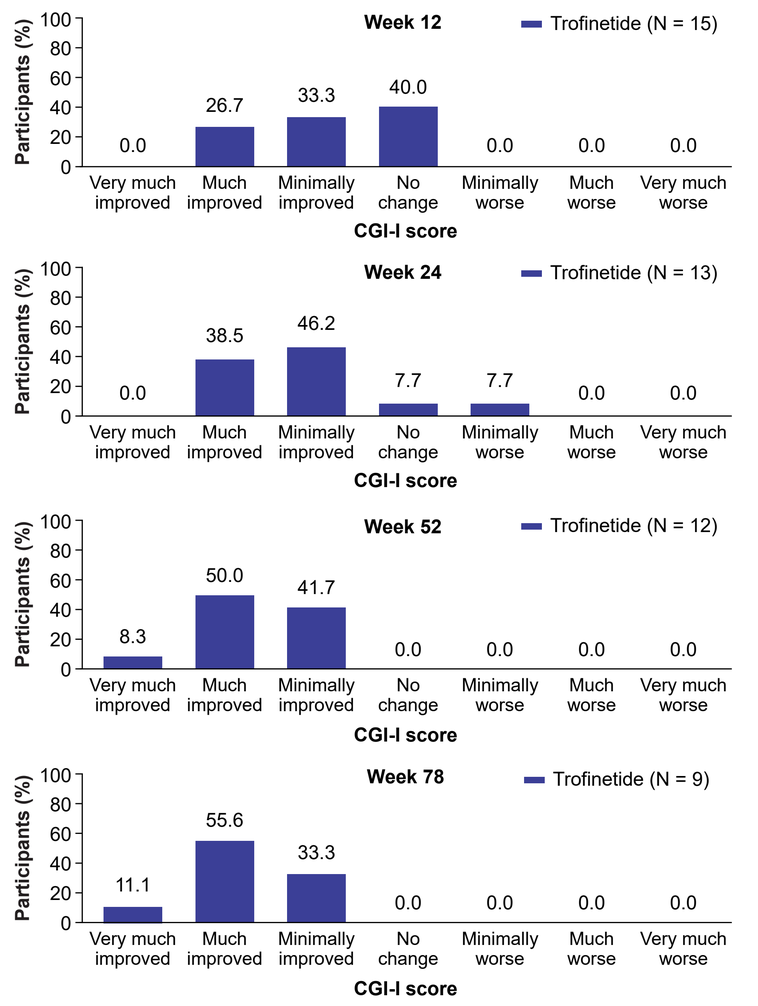
- Symptoms of RTT were improved throughout the study as measured by the CGI-I, CaGI-I, and change from baseline in the ICND-QoL (**Figure 2**)
- In the post hoc CGI-I responder analysis, the percentage of participants with a "much improved" CGI-I score of 2 increased throughout the study (**Figure 3**)
- There were no changes in CGI-S scores at each study visit

Figure 2. (A) CGI-I, (B) CaGI-I, and (C) ICND-QoL Exploratory Efficacy Results



CaGI-I, Caregiver Global Impression–Improvement; CGI-S, Clinical Global Impression–Severity; ICND-QoL, Overall Quality of Life Rating of the Impact of Childhood Neurologic Disability Scale; SE, standard error

Figure 3. Post Hoc CGI-I Responder Analysis



CGI-I, Clinical Global Impression–Improvement

Caregiver Exit Interviews

- In total, 7 caregivers of participants in DAFFODIL completed caregiver exit interviews
  - The inability to communicate was the most impactful symptom of RTT reposted by caregivers (n = 3; 42.9%)
  - Improved communication was the most desired treatment effect by caregivers (n = 5; 71.4%)
  - Verbal communication was the most frequently observed improvement with trofinetide by caregivers (n = 5; 71.4%)
  - All 7 caregivers were "satisfied" (n = 4) or "very satisfied" (n = 3) with the benefits of trofinetide

CONCLUSIONS

- Trofinetide had acceptable tolerability for up to 78 weeks in girls 2–4 years of age with RTT; safety results were consistent with the 12-week LAVENDER study and the 40-week LILAC open-label extension study[4,8]
- The prescribed dosing in DAFFODIL achieved the target exposure and was similar to the range of exposure reported in pediatric and adult participants with RTT from the LAVENDER study
- Improvements in caregiver- and clinician-rated efficacy endpoints related to the global impression of RTT symptoms and quality of life were sustained up to 78 weeks
- All caregivers reported they were "satisfied" or "very satisfied" with the benefits provided by trofinetide
- These findings together with the LAVENDER results support the approval of trofinetide in adults and pediatric patients 2 years of age or older

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