Trofinetide for the Treatment of Rett Syndrome: An Open-label Study in Girls 2 to 4 Years of Age

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BACKGROUND

- Rett syndrome (RTT) is a rare, debilitating, X-linked neurodevelopmental disorder[1]
  - RTT primarily affects females (1 in 10,000–15,000 births)[2]
  - RTT causes problems with neurologic function, with regression beginning around age 6–18 months[3]
  - This regression is characterized by loss of purposeful hand use and verbal communication as well as limited nonverbal skills, impaired motor skills, seizures, and behavioral and gastrointestinal issues[1]
- Trofinetide is a novel synthetic analog of a tripeptide (glycine-proline-glutamate) that is enzymatically cleaved from the N-terminus of insulin-like growth factor-1[4]
- In the randomized, double-blind, placebo-controlled, phase 3 LAVENDER™ study (ClinicalTrials.gov identifier: NCT04181723) in girls and women with RTT, weight-based dosing with twice-daily (BID) oral trofinetide for 12 weeks demonstrated statistically significant improvement over placebo in the coprimary (Rett Syndrome Behaviour Questionnaire, Clinical Global Impression–Improvement [CGI-I] score) and in the key secondary (Communication and Symbolic Behavior Scales–Developmental Profile™–Infant Toddler Checklist Social Composite score) efficacy endpoints and had an acceptable safety profile[5]
- In the United States, RTT is commonly diagnosed at a median age of 2.7 years,[6] so data are needed to inform trofinetide dosing recommendations and to evaluate its long-term safety in this population aged ≤5 years

OBJECTIVE

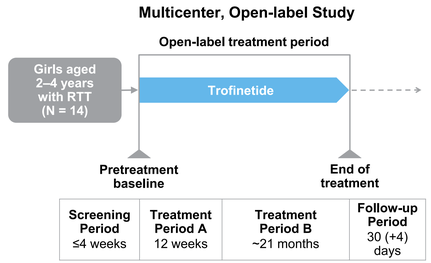
- To evaluate the safety/tolerability, preliminary efficacy, and pharmacokinetics (PK) of trofinetide in girls aged 2–5 years with RTT

METHODS

Study Design and Participants

- DAFFODIL™ (ClinicalTrials.gov identifier: NCT04988867) is a multicenter, open-label study of trofinetide open to girls aged 2–5 years with RTT
- The study has completed the planned enrollment of girls with RTT who met the inclusion criteria: aged 2–4 years with body weight ≥9 and <20 kg at screening; girls aged 5 years with body weight ≥9 and <12 kg at screening were also eligible; 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)[7] score ≥4 at screening and baseline; and stable pattern of seizures (or no seizures) within 8 weeks before screening
- The duration of participation is ≤26 months and consists of screening, 2 treatment periods, and follow-up (**Figure 1**)
  - Treatment Period A was designed for evaluating the dosing, safety/tolerability, and PK and lasts 12 weeks, the same length as the phase 3 LAVENDER study of trofinetide in girls and women aged 5–20 years with RTT[5]
    - Interim data from a database cutoff date of March 14, 2022, are presented for Treatment Period A
  - Treatment Period B (about 21 months) was designed to assess the safety of long-term treatment with trofinetide
    - This treatment period is ongoing and thus not reported here

Figure 1. Study Design



RTT, Rett syndrome

Dosing of Study Drug

- Trofinetide BID was administered 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 Endpoints

- Primary endpoints: safety
  - Treatment-emergent adverse events (TEAEs)
  - Serious TEAEs
  - Withdrawals due to TEAEs
  - Potentially clinically important changes in other safety assessments (vital signs, electrocardiograms, laboratory evaluations [clinical chemistry, urinalysis, hematology])
- Exploratory efficacy endpoints
  - CGI-I score,[7] scored from 1 (very much improved) to 7 (very much worse), such that a lower score indicates improvement
  - Caregiver's Global Impression–Improvement (CaGI-I) score, scored from 1 (much improved from baseline) to 5 (much worse from baseline), such that a lower score indicates improvement
  - Overall Quality of Life rating on the Impact of Childhood Neurologic Disability scale (ICND-QoL)[8]
    - The child's overall quality of life is ranked from 1 (poor) to 6 (excellent), such that a higher score indicates improvement
  - CGI-S score,[7] scored from 1 (normal, not at all ill) to 7 (among the most extremely ill), such that a lower score indicates improvement
- PK endpoints
  - Whole blood concentration of trofinetide
    - Blood samples were collected at each visit during Treatment Period A
  - Trofinetide PK parameters using the population PK approach[9]

RESULTS

- Fourteen participants were enrolled and 10 completed Treatment Period A
- Baseline demographic and disease characteristics and RTT-related medical history are shown in **Table 1**

Table 1. Baseline characteristics for participants in the DAFFODIL study

Characteristic	Participants (N = 14)
Age, years	3.1 (0.83)
Age at RTT diagnosis, years	1.99 (0.42)
Race, n (%)	
White	13 (92.9)
Asian	1 (7.1)
Weight at baseline, kg	13.6 (2.3)
CGI-S score	4.6 (0.74)
MECP2 mutation severity, n (%)	
Mild	4 (28.6)
Moderate	0
Severe	9 (64.3)
Missing	1 (7.1)
RTT-related medical history, n (%)	
Constipation	9 (64.3)
Vomiting	2 (14.3)
Seizure	2 (14.3)

Data are presented as mean (standard deviation) unless otherwise specified
CGI-S, Clinical Global Impression–Severity; *MECP2*, methyl-CpG-binding protein 2; RTT, Rett syndrome

Safety

- Twelve participants (85.7%) reported ≥1 TEAE (**Table 2**); all were of mild or moderate severity
  - Diarrhea (64.3%) and vomiting (35.7%) were the most common TEAEs
  - No serious TEAEs or deaths were reported
  - One participant withdrew due to a TEAE (diarrhea)
- No clinically significant or potentially clinically important laboratory values were observed at Week 12 for chemistry, hematology, or urinalysis
- No participants exhibited any potentially clinically important electrocardiogram values up to and including Week 12

Efficacy

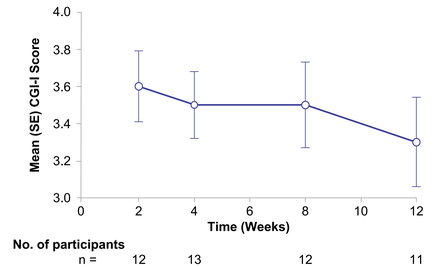
- Participants' scores improved on the CGI-I, with a mean (standard error [SE]) score of 3.6 (0.19) at Week 2 and 3.3 (0.24) at Week 12 (**Figure 2**)
- The mean (SE) CaGI-I score was 2.2 (0.13) at Week 12, indicating an improvement from baseline
- The mean (SE) ICND-QoL score improved from a baseline of 3.9 (0.25) to 4.2 (0.44) at Week 12
- The mean (SE) CGI-S score at Week 12 was 4.7 (0.24) and was unchanged from the earlier timepoints, including baseline

Table 2. TEAEs in the 12-week Treatment Period A

TEAEs, n (%)	Participants (N = 14)			
Any TEAEs	12 (85.7)			
Serious TEAEs	0			
Treatment-related TEAEs	8 (57.1)			
TEAEs leading to withdrawal	1 (7.1)			
Diarrhea	1 (7.1)			
TEAEs by preferred term in >1 participant and maximum severity, n (%)	**Total**	**Mild**	**Moderate**	**Severe**
Diarrhea	9 (64.3)	6 (42.9)	3 (21.4)	0
Vomiting	5 (35.7)	4 (28.6)	1 (7.1)	0
COVID-19	4 (28.6)	4 (28.6)	0	0
Pyrexia	4 (28.6)	4 (28.6)	0	0
Cough	2 (14.3)	2 (14.3)	0	0
Dermatitis, diaper	2 (14.3)	2 (14.3)	0	0
Seizure	2 (14.3)	0	2 (14.3)	0
Somnolence	2 (14.3)	2 (14.3)	0	0

TEAE, treatment-emergent adverse event

Figure 2. Mean CGI-I Score by Visit

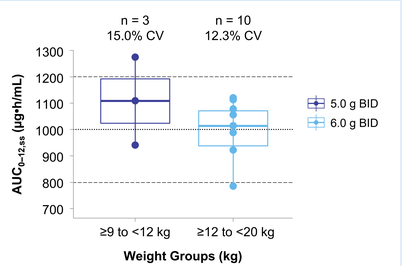


Scoring ranges from 1 (very much improved) to 7 (very much worse), such that lower scores indicate improvements
CGI-I, Clinical Global Impression–Improvement; SE, standard error

Pharmacokinetics

- Population PK analysis confirmed that, following the administration of trofinetide, the steady-state exposure for 2–4-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 3**)

Figure 3. 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 curve from 0–12 hours at steady state; BID, twice daily; CV, coefficient of variation

CONCLUSIONS

- Trofinetide was well tolerated in girls aged 2–4 years
- Trends toward improvements in efficacy, as assessed by CGI-I, CaGI-I, and ICND-QoL, were observed by Week 12 of trofinetide treatment
- PK informs appropriate trofinetide dosing for girls aged 2–4 years with RTT

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