# Design and Outcome Measures of an Open-label Study of Trofinetide for the Treatment of Girls 2–5 Years of Age With Rett Syndrome

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## BACKGROUND

- Rett syndrome (RTT) is a rare, debilitating X-linked neurodevelopmental disorder for which there is no approved treatment[1]
  - RTT primarily affects females (1 in 10,000 to 15,000 births)[2]
  - RTT causes problems in neurological function, with regression beginning around 18–30 months of age[3]
  - This regression is characterized by loss of purposeful hand use and verbal/nonverbal communication as well as 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 insulin-like growth factor 1[4]
- In the pivotal phase 3 LAVENDER study in girls and women with RTT, weight-based dosing with twice-daily oral trofinetide for 12 weeks demonstrated statistically significant improvement over placebo in the co-primary (Rett Syndrome Behaviour Questionnaire and Clinical Global Impression-Improvement [CGI-I] scores) 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 US, RTT is commonly diagnosed as early as 18 months to 2 years of age, so data are needed to inform trofinetide dosing recommendations and to evaluate its long-term safety in this patient population aged ≤5 years

## OBJECTIVE

- To present the design of an open-label study to investigate the pharmacokinetics (PK) and long-term safety and tolerability of trofinetide in girls 2–5 years of age with RTT

## METHODS

### Study Design

- DAFFODIL (ClinicalTrials.gov identifier: NCT04988867) is a multicenter, open-label study of trofinetide in girls 2–5 years of age with RTT
- The study has completed the planned enrollment of 15 girls with RTT who met the inclusion criteria (**Table 1**)
- The duration of participation will be 26 months and will consist of 3 periods (**Figure 1**):
  - Screening (≤4 weeks)
  - Treatment (≤24 months)
    - Treatment period A (12 weeks) is designed for evaluation of the dosing, safety/tolerability, and PK and will last 12 weeks, the same length as the phase 3 LAVENDER study of trofinetide in girls and women 5–20 years of age with RTT[6]
    - Treatment period B (about 21 months) is designed to assess the safety of long-term treatment with trofinetide
  - Safety follow-up (30 + 4 days)

**Figure 1. Study design**

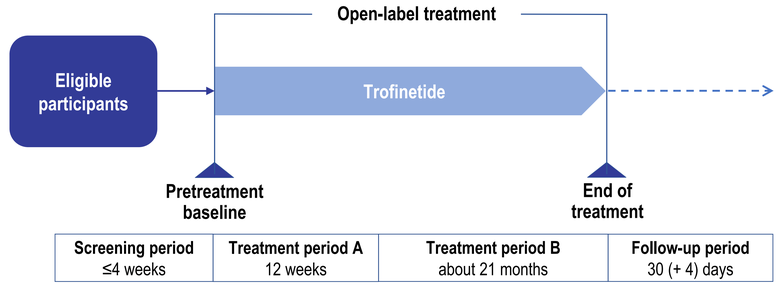



**Table 1. DAFFODIL key inclusion and exclusion criteria**

| Inclusion criteria | Exclusion criteria |
|---|---|
| • Female, 2–4 years of age with body weight ≥9 and <20 kg at screening OR 5 years of age with body weight ≥9 and <12 kg at screening<br>• Can swallow liquid study medication or receive it via gastrostomy tube<br>• Classic/typical RTT or possible RTT according to the Rett Syndrome Diagnostic Criteria<br>• Documented disease-causing mutation in *MECP2* gene<br>• CGI-S score ≥4 at screening and baseline<br>• Stable pattern of seizure, or no seizures, within 8 weeks prior to screening | • Treated with growth hormone, IGF-1, or insulin within 12 weeks of baseline<br>• Current clinically significant cardiovascular, endocrine (such as hypothyroidism or hyperthyroidism, type 1 diabetes, or uncontrolled type 2 diabetes), renal, hepatic, respiratory, or gastrointestinal (such as celiac or inflammatory bowel) disease, or major surgery planned during the study<br>• QTcF interval of >450 ms at screening or baseline<br>• History of clinically significant QT prolongation deemed to put the patient at risk of clinically significant QT prolongation |

CGI-S, Clinical Global Impression-Severity; IGF-1, insulin-like growth factor 1; *MECP2*, methyl-CpG-binding protein 2; QTcF, QT interval corrected using Fridericia's correction method; RTT, Rett syndrome

### Dosing of Study Drug

- Trofinetide will be administered twice daily and will be up-titrated as tolerated up to the Week 4 visit (**Table 2**)

**Table 2. Dosing schedule for trofinetide**

| Dose commences (treatment period A visit) | Weight at baseline | Dose | Total daily dose |
|---|---|---|---|
| Day 1 | Any | 10 mL (2 g) BID | 20 mL (4 g) |
| Week 2 | Any | 20 mL (4 g) BID | 40 mL (8 g) |
| Week 4 | 9 to <12 kg | 25 mL (5 g) BID | 50 mL (10 g) |
| | 12 to <20 kg | 30 mL (6 g) BID | 60 mL (12 g) |

BID, twice daily

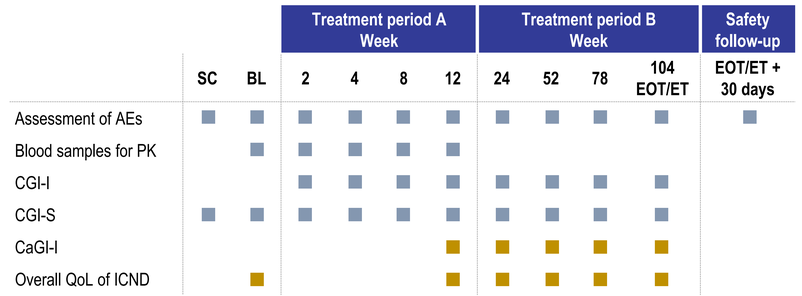
### Study Endpoints

- Primary endpoints
  - Safety endpoints
    - Treatment-emergent adverse events (AEs)
    - Serious AEs
    - Withdrawals due to AEs
    - Potentially clinically important changes in other safety assessments (vital signs, electrocardiograms, laboratory evaluations [clinical chemistry, urinalysis, hematology])
  - PK endpoints
    - Whole blood concentration of trofinetide
      - Blood samples will be collected at each visit during treatment period A
    - Trofinetide PK parameters using the population PK approach
- Exploratory efficacy endpoints include the CGI-I score,[7] Clinical Global Impression-Severity (CGI-S) score,[7] Caregiver's Global Impression-Improvement (CaGI-I) score, and Overall Quality of Life rating on the Impact of Childhood Neurologic Disability (ICND) scale[8]

### Assessment Schedule

- Assessments will be conducted at times indicated in **Figure 2**

**Figure 2. Timing of assessments and assessors in DAFFODIL**




AE, adverse event; BL, baseline; CaGI-I, Caregiver's Global Impression-Improvement; CGI-I, Clinical Global Impression-Improvement; CGI-S, Clinical Global Impression-Severity; EOT, end of treatment; ET, early termination; ICND, Impact of Childhood Neurologic Disability; PK, pharmacokinetics; QoL, quality of life; SC, screening

## CONCLUSIONS

- Using the design and outcome measures presented here, this study will assess the safety/tolerability and PK of open-label trofinetide in girls 2–5 years of age with RTT
- The findings will help inform appropriate dosing and safety in younger patients with RTT and extend what is known about trofinetide beyond the older children and adults already studied

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## DISCLOSURES

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