# Trofinetide for the Treatment of Rett Syndrome: Long-Term Safety and Efficacy Results From the Open-Label LILAC-2 Study

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## BACKGROUND

- Rett syndrome (RTT) is a rare neurodevelopmental disorder characterized by a broad set of core symptoms, including deficits in breathing, hand movements or stereotypies, repetitive behaviors, nighttime behaviors, vocalizations, facial expressions, eye gaze, mood, and seizures[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]
  - In LAVENDER (NCT04181723), a 12-week, randomized, placebo-controlled, phase 3 study of trofinetide in RTT, significant differences were demonstrated between trofinetide and placebo in caregiver- and clinician-assessed efficacy endpoints relevant to RTT with an acceptable safety profile[4]
  - In LILAC (NCT04279314), a 40-week, open-label extension study of participants who completed LAVENDER, treatment with trofinetide continued to improve symptoms of RTT with a safety profile consistent with LAVENDER[5]
- Longer-term safety and efficacy data of trofinetide in RTT are important, as RTT is a chronic disorder that requires lifelong treatment[6]

## OBJECTIVE

- To evaluate the long-term safety and efficacy of trofinetide in girls and women with RTT

## METHODS

### LILAC-2 Study Design

- LILAC-2 (NCT04776746) was a 32-month, open-label extension study of trofinetide in females aged 5–22 years following completion of the LAVENDER and LILAC studies
- Trofinetide was given following weight-based dosing twice daily (morning and evening, ≥8 hours apart) orally or by gastrostomy tube (G-tube) (**Table 1**)

### Study Population

- Eligible participants were females aged 5–22 years who participated in the LAVENDER and LILAC studies and could swallow the study medication provided as a liquid solution or could take it by gastrostomy tube

### Endpoints

- The long-term safety and tolerability of trofinetide were assessed with the incidence of adverse events (AEs), which included both treatment-emergent AEs and events that began during LAVENDER and LILAC and were still ongoing at the baseline visit of LILAC-2
- The efficacy of trofinetide was assessed with the Rett Syndrome Behaviour Questionnaire (RSBQ) and the Clinical Global Impression–Improvement (CGI-I) scores
  - RSBQ is a 45-item caregiver-completed scale (items are grouped into 8 symptom domain subscales) that assesses a wide range of core RTT symptoms[7]
  - CGI-I is a clinician rating of illness improvement or worsening relative to the baseline visit using a 7-point scale with RTT-specific anchors[8]

### Statistical Analysis

- Safety and efficacy were analyzed in the Safety Analysis Set, which consisted of all participants who received ≥1 dose of trofinetide in LILAC-2

**Table 1. Trofinetide weight-based dosing schedule in LILAC-2**

| Participant weight, kg | Trofinetide dose, mg | Trofinetide volume, mL |
|---|---|---|
| 12–20 | 6000 BID | 30 BID |
| >20–35 | 8000 BID | 40 BID |
| >35–50 | 10,000 BID | 50 BID |
| >50 | 12,000 BID | 60 BID |

BID, twice daily

## RESULTS

### Demographics and Baseline Characteristics

- In total, 77 participants who completed LAVENDER and LILAC were enrolled in LILAC-2 and treated with open-label trofinetide; 36 and 41 participants were treated with placebo and trofinetide in LAVENDER, respectively
- In the total population, the overall mean (standard deviation [SD]) age was 12.0 (4.38) years; 51.9% of participants were aged 5–11 years (**Table 2**)
- The mean (SD) RSBQ and CGI-S scores at LILAC-2 baseline in the total population were 36.4 (12.68) and 4.8 (0.89), respectively (**Table 2**)
- Overall, 79.2% of participants completed the study
  - The mean (standard error [SE]) duration of exposure to trofinetide for LILAC-2 participants was 811.1 (23.16) and 692.3 (33.20) days for participants treated with trofinetide and placebo in LAVENDER, respectively; the duration of exposure to trofinetide was 755.6 (20.83) days in the LILAC-2 total group

**Table 2. Baseline demographic and clinical characteristics**

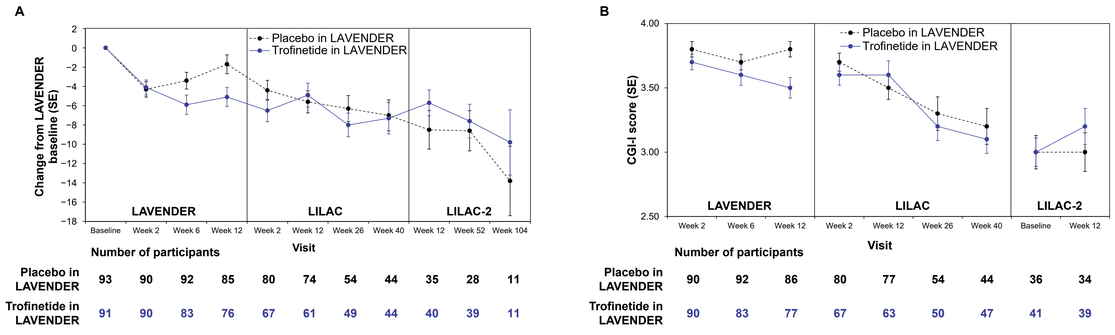
| Characteristics | LILAC-2 total (N = 77) |
|---|---|
| Mean (SD) age, years | 12.0 (4.38) |
| Age categories, n (%) | |
| 5–11 years | 40 (51.9) |
| 12–16 years | 22 (28.6) |
| 17–22 years | 15 (19.5) |
| Primary race, n (%) | |
| White | 71 (92.2) |
| Black or African American | 1 (1.3) |
| Asian | 1 (1.3) |
| Other | 4 (5.2) |
| LILAC-2 baseline RSBQ total score, mean (SD) | 36.4 (12.68) |
| LILAC-2 baseline RSBQ severity, n (%) | |
| <35 | 36 (46.8) |
| ≥35 | 40 (51.9) |
| Missing | 1 (1.3) |
| LILAC-2 baseline CGI-S score, mean (SD) | 4.8 (0.89) |

CGI-S, Clinical Global Impression-Severity; RSBQ, Rett Syndrome Behaviour Questionnaire; SD, standard deviation

### Safety

- The most common AEs in the total population were diarrhea (53.2%), COVID-19 (27.3%), and vomiting (19.5%) (**Table 3**)
- Overall, 20.8% of participants discontinued during the study
  - In total, 5 (6.5%), 4 (5.2%), 3 (3.9%), 2 (2.6%), and 2 (2.6%) participants discontinued the study owing to AEs, death, lack of efficacy, noncompliance with study drug, and other reasons, respectively
- Four participants died during the study
  - Cause of death was reported as cardiac arrest (n = 1), gastric ulcer hemorrhage (n = 1), sudden unexplained death in epilepsy (n = 1), and vomiting and aspiration (n = 1)
  - Deaths were not considered related to study drug by the investigator or sponsor

**Figure 1. RSBQ and CGI-I Scores. (A) Mean (SE) change in RSBQ score from the LAVENDER baseline to Week 104 in the LILAC-2 study. (B) Mean (SE) CGI-I scores in the LAVENDER, LILAC, and LILAC-2 studies relative to individual study baseline**




Number of participants

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Placebo in LAVENDER | 93 | 90 | 92 | 85 | 80 | 74 | 54 | 44 | 35 | 28 | 11 |
| Trofinetide in LAVENDER | 91 | 90 | 83 | 76 | 67 | 61 | 49 | 44 | 40 | 39 | 11 |

Number of participants

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Placebo in LAVENDER | 90 | 92 | 86 | 80 | 77 | 54 | 44 | 36 | 34 |
| Trofinetide in LAVENDER | 90 | 83 | 77 | 67 | 63 | 50 | 47 | 41 | 39 |

CGI-I, Clinical Global Impression-Improvement; RSBQ, Rett Syndrome Behaviour Questionnaire; SE, standard error

**Table 3. Summary of AEs**

| AEs and preferred term, n (%) | LILAC-2 total (N = 77) |
|---|---|
| Any AE | 72 (93.5) |
| AEs reported in ≥10% of participants in LILAC-2 total group | |
| Diarrhea | 41 (53.2) |
| COVID-19 | 21 (27.3) |
| Vomiting | 15 (19.5) |
| Pyrexia | 13 (16.9) |
| Urinary tract infection | 13 (16.9) |
| Seizure | 11 (14.3) |
| Constipation | 9 (11.7) |
| Upper respiratory tract infection | 9 (11.7) |
| Serious AEs | 23 (29.9) |
| AEs leading to drug withdrawal | 9 (11.7) |
| AEs leading to drug withdrawal in ≥2 participants | |
| Vomiting | 2 (2.6) |
| Fatal AEs | 4 (5.2) |

AE, adverse event

### Efficacy

- Trofinetide improved RSBQ and CGI-I scores in LILAC-2
  - The mean (SE) change in RSBQ total score from the LAVENDER baseline to Week 104 in LILAC-2 was −9.8 (3.38) and −13.8 (3.61) for participants treated with trofinetide and placebo in LAVENDER, respectively (**Figure 1A**); the score in the LILAC-2 total group was −11.8 (2.45)
  - Mean (SE) CGI-I scores compared with the LILAC baseline at Week 12 of LILAC-2 were 3.2 (0.14) and 3.0 (0.15) for participants treated with trofinetide and placebo in LAVENDER, respectively (**Figure 1B**); the score in the LILAC-2 total group was 3.1 (0.10)

## CONCLUSIONS

- Open-label treatment with trofinetide for up to 32 months in LILAC-2 continued to improve symptoms of RTT
- The safety profile of trofinetide in LILAC-2 was consistent with the safety results of LAVENDER and LILAC

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## DISCLOSURES

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