Trofinetide for the Treatment of Rett Syndrome: Results From the Open-label Extension LILAC Study

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BACKGROUND

- Trofinetide, a synthetic analog of glycine-proline-glutamate, was recently approved for the treatment of Rett syndrome (RTT) based on the results of the 12-week, randomized, placebo-controlled, phase 3 LAVENDER study (NCT04181723)[1,2]
  - In LAVENDER, significant differences were demonstrated between trofinetide and placebo in caregiver- and clinician-assessed efficacy endpoints relevant to RTT, and trofinetide had an acceptable safety profile[1]
  - The results of LAVENDER suggest trofinetide is capable of modifying core symptoms of the underlying pathophysiology of RTT[1]
- RTT is a chronic disorder that requires lifelong treatment[3]; hence, it is important to investigate the long-term efficacy and safety of trofinetide in patients with RTT

OBJECTIVE

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

METHODS

LILAC Study Design

- LILAC (NCT04279314) was an open-label extension study of trofinetide in females aged 5–21 years following the LAVENDER study
- The study consisted of an open-label trofinetide treatment period of 40 weeks and a safety follow-up period of 30 days for participants who did not enter LILAC-2, a 32-month, open-label extension trial (ClinicalTrials.gov NCT04776746)
- Trofinetide was given following weight-based dosing twice daily (morning and evening, at least 8 hours apart), orally or by gastrostomy tube (**Table 1**)

Table 1. Trofinetide weight-based dosing schedule in LILAC

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

BID, twice daily

Study Population

- Eligible participants were females aged 5–21 years who had participated in the LAVENDER study and could swallow the study medication as a liquid solution or could take it by gastrostomy tube

Endpoints

- The primary endpoint of LILAC was the long-term safety and tolerability of trofinetide in females with RTT
  - Adverse events (AEs) included both treatment-emergent AEs and events that began during LAVENDER and were still ongoing at the baseline visit of LILAC
- Secondary endpoints included change from baseline in the Rett Syndrome Behaviour Questionnaire (RSBQ) total score at Weeks 2, 12, 26, and 40; the Clinical Global Impression–Improvement (CGI-I) score at Weeks 2, 12, 26, and 40 compared with LILAC baseline status; and CGI-I responder rates (defined as CGI-I categories of "very much improved," "much improved," and "minimally improved," resulting in a score of ≤3) at Week 40
  - RSBQ is a 45-item, caregiver-completed scale (items are grouped into eight symptom domain subscales) that assesses a wide range of core RTT symptoms[4]
  - CGI-I is a clinician rating of illness improvement or worsening relative to the baseline visit using a seven-point scale with RTT-specific anchors[5]

Statistical Analysis

- Safety and efficacy were analyzed in the Safety Analysis Set, which consisted of all participants who received at least one dose of trofinetide in LILAC

RESULTS

Demographics and Baseline Characteristics

- In total, 154 participants were enrolled and treated with open-label trofinetide following the double-blind treatment of trofinetide (n = 69) or placebo (n = 85) received in LAVENDER
- In the total population, the overall mean (standard deviation) age was 11.0 (4.55) years; 59.7% of participants were aged 5–11 years (**Table 2**)

Table 2. Baseline demographic and clinical characteristics

	Placebo in LAVENDER (n = 85)	Trofinetide in LAVENDER (n = 69)	LILAC total (N = 154)
Age, years, mean (SD)	11.0 (4.51)	10.9 (4.63)	11.0 (4.55)
Age categories, years, n (%)			
5–11	51 (60.0)	41 (59.4)	92 (59.7)
12–16	20 (23.5)	17 (24.6)	37 (24.0)
17–21	14 (16.5)	11 (15.9)	25 (16.2)
Primary race, n (%)			
White	82 (96.5)	61 (88.4)	143 (92.9)
Black or African American	0	1 (1.4)	1 (0.6)
Asian	1 (1.2)	4 (5.8)	5 (3.2)
Native Hawaiian or other Pacific Islander	0	1 (1.4)	1 (0.6)
Other	2 (2.4)	2 (2.9)	4 (2.6)
LILAC baseline RSBQ total score, mean (SD)	42.8 (12.99)	39.5 (11.87)[a]	41.3 (12.57)
LILAC baseline RSBQ severity, n (%)			
<35	23 (27.1)	24 (34.8)	47 (30.5)
≥35	62 (72.9)	44 (63.8)	106 (68.8)
Missing	0	1 (1.4)	1 (0.6)
MECP2 gene mutation severity category, n (%)			
Mild	34 (40.0)	23 (33.3)	57 (37.0)
Moderate	8 (9.4)	10 (14.5)	18 (11.7)
Severe	40 (47.1)	32 (46.4)	72 (46.8)
Unknown	3 (3.5)	4 (5.8)	7 (4.5)

[a]n = 68
MECP2, methyl-CpG-binding protein 2 gene; RSBQ, Rett Syndrome Behaviour Questionnaire; SD, standard deviation

Safety

- The most common AEs in the total population were diarrhea (74.7%), vomiting (28.6%), and COVID-19 (11.0%) (**Table 3**)
  - Most reports of diarrhea were of mild or moderate severity (95.6%); all reports of vomiting were mild or moderate in severity
- Overall, 46.0% of participants discontinued treatment during the study
  - Diarrhea (21.4%) was the most common AE leading to treatment discontinuation (**Table 3**)
  - Three participants (1.9%) discontinued due to an AE of weight decreased; in general, weight loss was not specifically associated with diarrhea or vomiting (**Table 3**)

Table 3. Summary of AEs

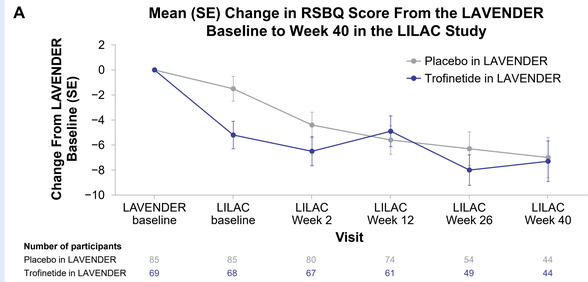
AEs and preferred term, n (%)	Placebo in LAVENDER (n = 85)	Trofinetide in LAVENDER (n = 69)	LILAC total (N = 154)
Any AE	82 (96.5)	61 (88.4)	143 (92.9)
AEs reported in ≥5% of participants in the LILAC total group			
Diarrhea	71 (83.5)	44 (63.8)	115 (74.7)
Vomiting	29 (34.1)	15 (21.7)	44 (28.6)
COVID-19	9 (10.6)	8 (11.6)	17 (11.0)
Seizure	9 (10.6)	5 (7.2)	14 (9.1)
Upper respiratory tract infection	9 (10.6)	4 (5.8)	13 (8.4)
Pyrexia	7 (8.2)	5 (7.2)	12 (7.8)
Decreased appetite	6 (7.1)	5 (7.2)	11 (7.1)
Irritability	4 (4.7)	6 (8.7)	10 (6.5)
Urinary tract infection	6 (7.1)	4 (5.8)	10 (6.5)
Weight decreased	5 (5.9)	4 (5.8)	9 (5.8)
Serious AEs	10 (11.8)	9 (13.0)	19 (12.3)
AEs leading to drug withdrawal	36 (42.4)	19 (27.5)	55 (35.7)
AEs leading to drug withdrawal in >2% of participants in the LILAC total group			
Diarrhea	24 (28.2)	9 (13.0)	33 (21.4)
Vomiting	6 (7.1)	4 (5.8)	10 (6.5)
Fatal AEs	0	0	0

AE, adverse event

Efficacy

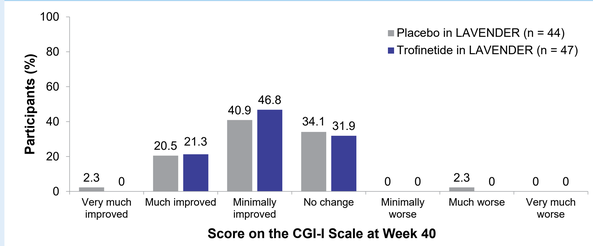
- After 40 weeks of treatment, trofinetide improved RSBQ and CGI-I scores
  - The mean (standard error [SE]) change from the LAVENDER baseline to Week 40 in the LILAC study in RSBQ was −7.3 (1.62) for participants treated with trofinetide in LAVENDER and −7.0 (1.61) for participants treated with placebo in LAVENDER (**Figure 2A**); the score in the LILAC total group was −7.1 (1.13)
  - Mean (SE) CGI-I scores compared with the LILAC baseline at Week 40 were 3.1 (0.11) and 3.2 (0.14) for participants treated with trofinetide and placebo in LAVENDER, respectively (**Figure 2B**); the score in the LILAC total group was 3.1 (0.09)
- At Week 40, 65.9% of the LILAC total group showed improvement in CGI-I compared with the LILAC baseline, with 68.1% treated with trofinetide in LAVENDER showing improvement and 63.7% treated with placebo in LAVENDER showing improvement (**Figure 3**)

Figure 2. RSBQ and CGI-I Scores



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

Figure 3. CGI-I Responder Rates at Week 40



CGI-I, Clinical Global Impression–Improvement

CONCLUSIONS

- Open-label treatment with trofinetide in LILAC continued to improve symptoms of RTT
- There were no new safety concerns reported in LILAC, and the safety profile of trofinetide in LILAC was consistent with LAVENDER

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DISCLOSURES

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