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

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BACKGROUND

- Rett syndrome (RTT) is a rare neurodevelopmental disorder that primarily affects females[1] and is characterized by a broad set of core symptoms, including irregular breathing; partial or complete loss of acquired spoken language and hand function skills; and development of hand stereotypies, gait abnormalities, nighttime behaviors, eye gaze, and seizures[2]
- Trofinetide, a synthetic analog of glycine-proline-glutamate, became the first FDA-approved treatment for RTT (indicated in adults and pediatric patients aged ≥2 years) on the basis of the results of the 12-week, randomized, placebo-controlled, phase 3 LAVENDER study (NCT04181723)[3,4]
  - 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[3]
  - The results of LAVENDER suggest trofinetide is capable of modifying core symptoms of the underlying pathophysiology of RTT[3]
- RTT is a chronic disorder that requires lifelong treatment[5]; hence, it is important to investigate the long-term efficacy and safety of trofinetide in patients with RTT

OBJECTIVE

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

METHODS

Study Design

- LILAC (NCT04279314) was an open-label extension study of trofinetide in females aged 5–21 years who were previously treated in the LAVENDER study
  - The study consisted of a treatment period for 40 weeks and a safety follow-up period of 30 days for participants who did not enter LILAC-2
- 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 Dosing

- In LILAC and LILAC-2, trofinetide was administered 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 and LILAC-2

Participant weight, kg	Trofinetide dose (BID), mg	Trofinetide volume (BID), mL
12–20	6,000	30
>20–35	8,000	40
>35–50	10,000	50
>50	12,000	60

BID, twice daily

Safety Assessments

- Adverse events (AEs) in LILAC included treatment-emergent AEs during LILAC and events that began during LAVENDER and were still ongoing at the baseline visit of LILAC
- AEs in LILAC-2 included treatment-emergent AEs during LILAC-2 and events that began during LAVENDER and LILAC and were still ongoing at the baseline visit of LILAC-2

Efficacy Assessments

- Efficacy was assessed during LILAC and LILAC-2 using the Rett Syndrome Behaviour Questionnaire (RSBQ) total score and the Clinical Global Impression–Improvement (CGI-I) score
  - 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[6]
  - 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[7]

RESULTS

Demographics and Baseline Characteristics

- In the LILAC study, 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
- The LILAC-2 study consisted of 77 participants who were treated with open-label trofinetide and had completed LAVENDER (placebo n = 36 and trofinetide n = 41) and LILAC
- The mean ages (standard deviation [SD]) in the LILAC and LILAC-2 populations were 11.0 (4.6) and 12.0 (4.4) years, respectively, and the majority were aged between 5 and 11 years (**Table 2**)

Table 2. Baseline Demographic and Clinical Characteristics

Characteristics	LILAC (N = 154)	LILAC-2 (N = 77)
Age, years, mean (SD)	11.0 (4.6)	12.0 (4.4)
Age categories, years, n (%)		
5–11	92 (59.7)	40 (51.9)
12–16	37 (24.0)	22 (28.6)
≥17[a]	25 (16.2)	15 (19.5)
Primary race, n (%)		
White	143 (92.9)	71 (92.2)
Black or African American	1 (0.6)	1 (1.3)
Asian	5 (3.2)	1 (1.3)
Other	5 (3.2)	4 (5.2)
Baseline RSBQ total score,[b] mean (SD)	41.3 (12.6)	36.4 (12.7)
Baseline RSBQ severity, n (%)		
<35	47 (30.5)	36 (46.8)
≥35	106 (68.8)	40 (51.9)
Missing	1 (0.6)	1 (1.3)
Baseline CGI-S score,[c] mean (SD)	4.8 (0.8)	4.8 (0.9)

[a]Age limit 21 years in LILAC and 22 years in LILAC-2. [b]45 items, rated as 0 = "not true", 1 = "somewhat or sometimes true" or 2 = "very true", with a total score ranging from 0–90 (maximum severity). [c]7-point scale (1 = normal/not at all ill; 2 = borderline ill; 3 = mildly ill; 4 = moderately ill; 5 = markedly ill; 6, = severely ill; 7=extremely ill)
CGI-S, Clinical Global Impression–Severity; RSBQ, Rett Syndrome Behaviour Questionnaire; SD, standard deviation

Safety

- The most common AEs in the respective populations of LILAC and LILAC-2 were diarrhea (74.7% and 53.2%), vomiting (28.6% and 19.5%), and COVID-19 (11.0% and 27.3%) (**Table 3**)
- Overall, 70 (46.0%) and 16 (20.8%) participants discontinued treatment during LILAC and LILAC-2, respectively
  - AEs leading to study drug discontinuation or termination of study participation were reported in 55 (35.7%) participants in LILAC and 9 (11.7%) participants in LILAC-2
  - Diarrhea (21.4%) and vomiting (2.6%) were the most common AEs leading to discontinuation in LILAC and LILAC-2, respectively
- Four participants died during the LILAC-2 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) following surgical placement of gastrostomy tube
  - Deaths were not considered related to study drug by the investigator or sponsor

Table 3. Summary of AEs

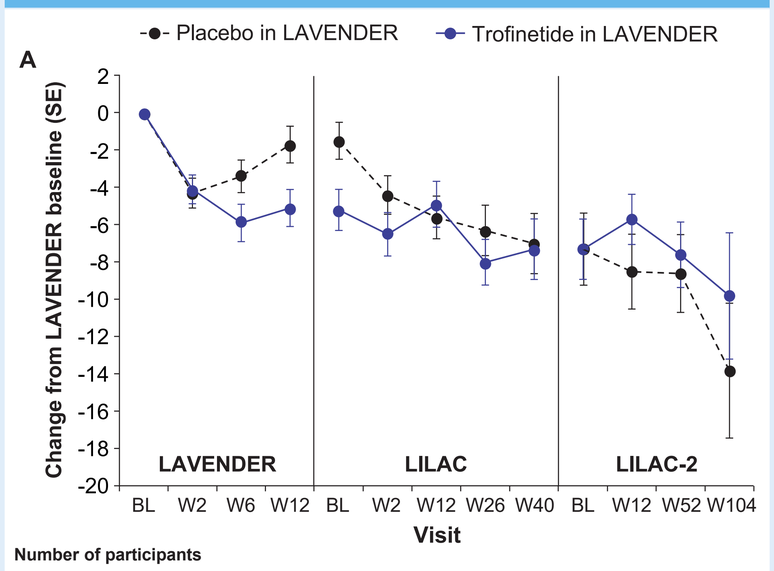
AEs and preferred term, n (%)	LILAC (N = 154)	LILAC-2 (N = 77)
Any AE	143 (92.9)	72 (93.5)
Most common AEs reported in LILAC and/or LILAC-2		
Diarrhea	115 (74.7)	41 (53.2)
Vomiting	44 (28.6)	15 (19.5)
COVID-19	17 (11.0)	21 (27.3)
Seizure	14 (9.1)	11 (14.3)
Upper respiratory tract infection	13 (8.4)	9 (11.7)
Pyrexia	12 (7.8)	13 (16.9)
Decreased appetite	11 (7.1)	4 (5.2)
Irritability	10 (6.5)	5 (6.5)
Urinary tract infection	10 (6.5)	13 (16.9)
Weight decreased	9 (5.8)	4 (5.2)
Serious AEs	19 (12.3)	23 (29.9)
AEs leading to drug withdrawal	55 (35.7)	9 (11.7)
AEs leading to drug withdrawal in ≥2% of participants		
Diarrhea	33 (21.4)	1 (1.3)
Vomiting	10 (6.5)	2 (2.6)
Fatal AEs	0	4 (5.2)

AE, adverse event

Efficacy

- In LILAC, treatment with trofinetide for 40 weeks resulted in improved RSBQ and CGI-I scores
  - The mean (standard error [SE]) change in the RSBQ from the LAVENDER baseline to Week 40 in the LILAC study was −7.3 (1.6) and −7.0 (1.6) for participants treated with trofinetide and placebo in LAVENDER, respectively, and was −7.1 (1.1) in the LILAC total group (**Figure 1A**)
  - Mean (SE) CGI-I scores compared with the LILAC baseline at Week 40 were 3.1 (0.1) and 3.2 (0.1) for participants treated with trofinetide and placebo in LAVENDER, respectively, and the score in the LILAC total group was 3.1 (0.1) (**Figure 1B**)
- In LILAC-2, treatment with trofinetide for up to 32 months resulted in continued improvement in RSBQ scores and sustained improvement in CGI-I scores
  - The mean (SE) change in the RSBQ from the LAVENDER baseline to Week 104 in the LILAC-2 study was −9.8 (3.4) and −13.8 (3.6) in participants treated with trofinetide and placebo in LAVENDER, respectively, and was −11.8 (2.5) in the LILAC-2 total group (**Figure 1A**)
  - The mean (SE) CGI-I score relative to LILAC baseline at Week 12 was 3.2 (0.1) and 3.0 (0.2) for participants treated with trofinetide and placebo in LAVENDER, respectively; the score in the LILAC-2 total group was 3.1 (0.1) (**Figure 1B**)

Figure 1. RSBQ (A) and CGI-I (B) Scores in LILAC and LILAC-2



[a]Score relative to study baseline. [b]Score relative to LILAC study baseline.
BL, baseline; CGI-I, Clinical Global Impression–Improvement; RSBQ, Rett Syndrome Behaviour Questionnaire; SE, standard error; W, week

CONCLUSIONS

- Symptoms of RTT continued to improve in LAVENDER study participants following open-label trofinetide treatment for 40 weeks in LILAC and up to 32 months in LILAC-2
- There were no new safety concerns reported in LILAC and LILAC-2, and the safety profile of trofinetide in the LILAC studies was consistent with LAVENDER

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ACKNOWLEDGMENTS

The study was supported by Acadia Pharmaceuticals Inc. (San Diego, CA, USA). Medical writing support was provided by Stuart Murray, MSc, of Evidence Scientific Solutions, Inc., and funded by Acadia Pharmaceuticals Inc.

DISCLOSURES

AKP is co-editor of *Translational Science of Rare Diseases*; received research funding from the National Institutes of Health; and is a consultant for Acadia Pharmaceuticals Inc., Anavex Life Sciences Corp., AveXis, and GW Pharmaceuticals, as well as adviser to the International Rett Syndrome Foundation. **JLN** has received research funding from the International Rett Syndrome Foundation, the National Institutes of Health, and Rett Syndrome Research Trust; has received personal consultancy fees from Acadia Pharmaceuticals Inc., Analysis Group, AveXis, F. Hoffmann-La Roche, GW Pharmaceuticals, Myrtelle, Neurogene, Newron Pharmaceuticals, Signant Health, and Taysha Gene Therapies, and for the preparation of CME activities for Medscape and PeerView Institute; is on the scientific advisory board of Alcyone Lifesciences; is a scientific cofounder of LizarBio Therapeutics; and was a member of a data safety monitoring board for clinical trials conducted by Ovid Therapeutics. **TAB** has received research funding from GRIN2B Foundation, the International Foundation for CDKL5 Research, Loulou Foundation, the National Institutes of Health, and Simons Foundation; has received consultancy fees from Alcyone, GRIN Therapeutics, the International Rett Syndrome Foundation, Marinus Pharmaceuticals, Neurogene, Takeda Pharmaceutical Company Limited, Ultragenyx, and Zogenix/UCB; and has participated in clinical trials with Acadia Pharmaceuticals Inc., GW Pharmaceuticals, Marinus Pharmaceuticals, Ovid Therapeutics, and Rett Syndrome Research Trust; all remuneration has been made to his department. **EMB-K** has received funding from Acadia Pharmaceuticals Inc., Alcobra Pharmaceuticals, AMO Pharma, Asuragen, AveXis, Biogen, BioMarin, Cydan Development, Inc., EryDel, Fulcrum Therapeutics, GeneTx, GW Pharmaceuticals, Ionis Pharmaceuticals, Jaguar Health, Lumos Pharma, Marinus Pharmaceuticals, Neuren Pharmaceuticals, Neurogene, Neurotrope, Novartis, Orphazyme, Ovid Therapeutics, Retrophin, Roche, Seaside Therapeutics, Taysha Gene Therapies, Tetra Bio-Pharma, Ultragenyx, Vtesse/Sucampo/Mallinckrodt Pharmaceuticals, Yamo Pharmaceuticals, and Zynerba Pharmaceuticals to consult on trial design or run clinical or lab validation trials in genetic neurodevelopmental or neurodegenerative disorders, all of which is directed to Rush University Medical Center in support of rare disease programs; has received no personal funds, and Rush University Medical Center has no relevant financial interest in any of the commercial entities listed. **DGG** has received personal compensation and research support from Acadia Pharmaceuticals, Neuren Pharmaceuticals, and Newron Pharmaceuticals. **EDM** has received research support from Eagles Autism Foundation, the International CDKL5 Research Foundation, the International Rett Syndrome Foundation, the Loulou Foundation, the National Institute of Child Health and Human Development, the National Institute of Neurological Disorders and Stroke, Penn Orphan Disease Center, and Rett Syndrome Research Trust; has been a site principal investigator for trials for Acadia Pharmaceuticals Inc., GW Pharmaceuticals, Marinus Pharmaceuticals, Stoke Therapeutics, and Zogenix; has received personal compensation for consulting from Acadia Pharmaceuticals Inc. and Stoke Therapeutics. **AL**, **DA**, and **JMY** are employees of and stakeholders in Acadia Pharmaceuticals Inc. **KMB** was an employee of Acadia Pharmaceuticals while the LILAC and LILAC-2 studies were conducted.

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Presented at the 9th World Rett Syndrome Congress, October 2–5, 2024, Gold Coast, QLD, Australia

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