Poster #6

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Trofinetide for the Treatment of Rett Syndrome: Efficacy in Participants of the LAVENDER Study Who Had Dose Reductions

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DISCLOSURES

EO'CP has received consulting fees from Acadia Pharmaceuticals Inc. **RR, LC,** and **AP** are employees and stakeholders in Acadia Pharmaceuticals Inc.

ACKNOWLEDGMENTS

The study was supported by Acadia Pharmaceuticals Inc. (San Diego, CA, USA). Medical writing support was provided by Juan Sanchez-Cortes, PhD, of Evidence Scientific Solutions, Inc., and funded by Acadia Pharmaceuticals Inc.

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Presented at National Association of Pediatric Nurse Practitioners (NAPNAP) 47th National Conference 2026
18-21 March 2026 | Pittsburgh, PA

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INTRODUCTION

- Trofinetide is approved for the treatment of Rett syndrome (RTT) in patients aged ≥2 years in the US and patients aged ≥2 years weighing ≥9 kg in Canada[1,2]
- Trofinetide improved the core symptoms of RTT in LAVENDER, a phase 3, 12-week, randomized, double-blind study of trofinetide versus placebo in female participants with RTT aged 5–20 years[3]
  - Statistically significant improvements were observed for trofinetide versus placebo in the caregiver-assessed Rett Syndrome Behaviour Questionnaire (RSBQ) and the clinician-assessed Clinical Global Impression–Improvement (CGI-I) scale[3]
  - The most common adverse event with trofinetide was diarrhea[3]
- Trofinetide is recommended to be administered using weight-banded dosing,[1,2] yet approximately one-third of participants in the trofinetide arm of LAVENDER had their dose adjusted for tolerability reasons
- Exposure-response data from phase 2 clinical trials suggest that the relationship between trofinetide dose and efficacy may be linear rather than via threshold effect[4,5]

OBJECTIVE

- To assess the efficacy of trofinetide in participants of LAVENDER who did and did not experience trofinetide dose reductions

METHODS

Study Design

- LAVENDER (NCT04181723) was a 12-week, randomized, double-blind, placebo-controlled study of trofinetide in females aged 5–20 years with RTT[3]
  - Study participants had classic/typical RTT, a documented disease-causing mutation in the *MECP2* gene, a severity rating of 10–36 (inclusive) on the RTT-Clinical Severity Scale, and a stable pattern of seizures or no seizures within 8 weeks of screening[3]
- The coprimary efficacy endpoints were the caregiver-assessed RSBQ and the clinician-assessed CGI-I scale[3]
  - 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 baseline using a 7-point scale with RTT-specific anchors[7]
- The LAVENDER protocol permitted dose adjustments (as low as 50% of assigned weight-banded dose) up until week 6 of the study
  - Investigators were able to increase previously reduced doses, as tolerated, up to week 6 of the study

Post Hoc Efficacy Analysis by Dose Reduction

- Participants of LAVENDER treated with trofinetide were grouped into those with and without dose reductions
  - A dose reduction was defined as a reduction relative to any previous dose
- Groups were analyzed by baseline demographic and clinical characteristics, medical history, and use of gastrointestinal (GI)-related medications in LAVENDER
- Efficacy assessments included change in RSBQ score from baseline and CGI-I scores at weeks 2, 6, and 12 of LAVENDER
- Other assessments included the percentage of target dose reached at each interval between visits, overall incidence of treatment-emergent adverse events (TEAEs), and rates of early termination from LAVENDER
  - Percentage of target dose was calculated as

% Target Daily Dose

$$= \left(\frac{\text{Sum of the actual daily dose within a visit interval}}{\text{Number of days during a visit interval} \times \text{Recommended weight-banded dose}} \right) \times 100$$

RESULTS

Baseline Demographic and Clinical Characteristics

- Overall, 33 and 60 participants of LAVENDER did and did not experience dose reductions (Table 1)

Table 1. Baseline Demographic and Clinical Characteristics

	Trofinetide Dose Reduction (N = 33)	Trofinetide No Dose Reduction (N = 60)
Mean (SE) age, years	11.8 (0.8)	10.6 (0.6)
Age categories, n (%)		
5–10 years	17 (51.5)	32 (53.3)
11–15 years	8 (24.2)	17 (28.3)
16–20 years	8 (24.2)	11 (18.3)
Weight categories, n (%)		
12–20 kg	4 (12.1)	19 (31.7)
>20–35 kg	20 (60.6)	22 (36.7)
>35–50 kg	6 (18.2)	15 (25.0)
>50 kg	3 (9.1)	4 (6.7)
***MECP2* gene mutation severity, n (%)**		
Mild	8 (24.2)	22 (36.7)
Moderate	6 (18.2)	7 (11.7)
Severe	17 (51.5)	29 (48.3)
Unknown	2 (6.1)	2 (3.3)
Mean (SE) baseline RSBQ total score	45.0 (2.1)	43.1 (1.4)
Baseline RSBQ severity, n (%)		
<35	6 (18.2)	12 (20.0)
≥35	27 (81.8)	48 (80.0)
Mean (SE) baseline CGI-S score	5.1 (0.1)	4.8 (0.1)
Baseline CGI-S severity, n (%)		
1–3	0	0
4	6 (18.2)	26 (43.3)
5	19 (57.6)	19 (31.7)
6	8 (24.2)	15 (25.0)
Mean (SE) baseline RTT-CSS score	25.3 (1.0)	23.5 (0.9)

CGI-I, Clinical GI-S, Clinical Global Impression–Severity; **RSBQ,** Rett Syndrome Behaviour Questionnaire; **RTT-CSS,** Rett Syndrome-Clinical Severity Scale; **SE,** standard error.

GI Medical History and GI-Related Medications

- Both groups had a similar history of GI disorders at baseline (84.8% and 88.3% in the dose reduction and no dose reduction groups, respectively); the most common GI disorders in both groups included constipation, gastroesophageal reflux disease, and dysphagia (Table 2)
- The most common medications used at baseline and throughout the trial to manage GI disorders in both groups were antipropulsives and drugs for constipation (Table 2)

Table 2. GI Medical History and GI-Related Medications

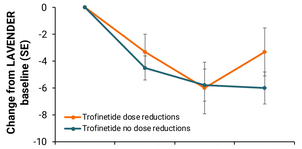
	Trofinetide Dose Reduction (N = 33)	Trofinetide No Dose Reduction (N = 60)
Any GI disorder, n (%)	28 (84.8)	53 (88.3)
GI disorders in ≥5% of participants in any group, n (%)		
Constipation	25 (75.8)	45 (75.0)
Gastroesophageal reflux disease	13 (39.4)	29 (48.3)
Dysphagia	2 (6.1)	4 (6.7)
Aerophagia	1 (3.0)	3 (5.0)
Diarrhea	0	3 (5.0)
Gastrointestinal hypomotility	2 (6.1)	0
Medications to manage GI disorders in ≥5% of participants in any group, n (%)		
Antipropulsives	21 (63.6)	26 (43.3)
Drugs for constipation	21 (63.6)	35 (58.3)
Drugs for functional GI disorders	6 (18.2)	10 (16.7)
Intestinal adsorbents	11 (33.3)	14 (23.3)
Other alimentary tract and metabolism products	5 (15.2)	13 (21.7)
Antidiarrheal microorganisms	3 (9.1)	7 (11.7)

GI, gastrointestinal.

Efficacy in LAVENDER Participants With and Without Trofinetide Dose Reductions

- Mean (standard error [SE]) change in RSBQ total score from baseline to week 12 of LAVENDER was -3.3 (1.8) and -6.0 (1.2) for participants treated with trofinetide with dose reductions and no dose reductions, respectively (Figure 1)
- Mean (SE) CGI-I score compared with the LAVENDER baseline at week 12 was 3.6 (0.15) and 3.5 (0.10) for participants treated with trofinetide with dose reductions and no dose reductions, respectively (Figure 2)

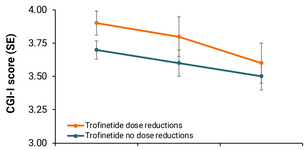
Figure 1. RSBQ Change From Baseline in LAVENDER Participants With and Without Trofinetide Dose Reductions



Number of participants				
Trofinetide dose reductions	33	32	28	25
Trofinetide no dose reductions	58	58	55	51

RSBQ, Rett Syndrome Behaviour Questionnaire; **SE,** standard error.

Figure 2. CGI-I Score in LAVENDER Participants With and Without Trofinetide Dose Reductions



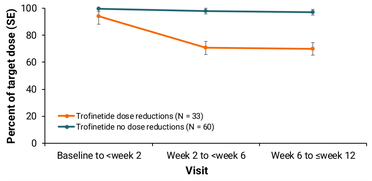
Number of participants			
Trofinetide dose reductions	32	28	26
Trofinetide no dose reductions	58	55	51

CGI-I, Clinical Global Impression–Improvement; **SE,** standard error.

Percentage of Target Daily Dose in LAVENDER Participants With and Without Trofinetide Dose Reductions

- LAVENDER participants with trofinetide dose reductions reached 70.6% and 69.9% of their target daily dose by week 2 to <week 6 and week 6 to ≤week 12, respectively; participants without dose reductions reached 97.9% and 97.1% of their target daily dose by week 2 to <week 6 and week 6 to ≤week 12, respectively (Figure 3)
  - There were 9 patients in the dose reduction group with their last recorded dose equal to their initial dose (ie, weight-banded dose)

Figure 3. Percentage of Target Daily Dose in LAVENDER Participants With and Without Trofinetide Dose Reductions



SE, standard error.

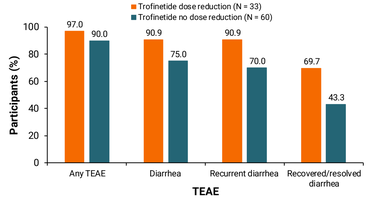
Safety

- Overall, 97.0% and 90.0% TEAEs were reported for participants treated with trofinetide with and without dose reductions, respectively (Figure 4)

Safety *(continued)*

- The incidence of diarrhea was 90.9% and 75.0% in participants treated with trofinetide with and without dose reductions, respectively (Figure 4)
- In total, 90.9% and 70.0% of participants with and without trofinetide dose reductions experienced recurrent diarrhea (Figure 4)
- The rate of recovered/resolved diarrhea was 69.7% and 43.3% in participants treated with trofinetide with and without dose reductions, respectively (Figure 4)

Figure 4. Incidence of TEAEs in LAVENDER Participants Treated With Trofinetide With and Without Dose Reductions



TEAE, treatment-emergent adverse event.

Trofinetide Early Termination in LAVENDER Participants With and Without Trofinetide Dose Reductions

- Trofinetide early termination rates were 33.3% and 20.0% in participants treated with trofinetide with and without dose reductions, respectively (Table 3)

Table 3. Trofinetide Early Termination in LAVENDER Participants With and Without Trofinetide Dose Reductions

	Trofinetide Dose Reduction (N = 33)	Trofinetide No Dose Reduction (N = 60)
Early termination, n (%)	11 (33.3)	12 (20.0)
Baseline to <week 2	2 (18.2)	4 (33.3)
Week 2 to <week 6	5 (45.5)	5 (41.7)
Week 6 to <week 12	4 (36.4)	3 (25.0)

CONCLUSIONS

There were no differences in LAVENDER participants with and without trofinetide dose reductions in terms of baseline demographic and clinical characteristics, medical history, and use of GI-related medications in LAVENDER

LAVENDER participants without trofinetide dose reductions showed better improvement in RSBQ and CGI-I scores than participants with dose reductions, yet the latter group still experienced treatment benefit beyond that observed in the placebo group in LAVENDER

- Both groups experienced RSBQ improvements within the approximated minimal clinically important difference of 3- to 6-point change in RSBQ total score,[8] while the placebo group did not

LAVENDER participants with trofinetide dose reductions took approximately 70% of their target daily dose from week 6 to 12

- This percentage of target dose is consistent with real-world reports from RTT experts at US centers of excellence in those who cannot tolerate full weight-banded dose[9]

The incidence of TEAEs, including diarrhea, and early trofinetide termination were higher in LAVENDER participants with trofinetide dose reductions

- The participants with dose reductions had a higher rate of diarrhea that recovered/resolved

This post hoc analysis is limited by

- Presentation of non-prespecified outcomes; LAVENDER was not powered to detect differences between these groups
- No minimum amount of time that a LAVENDER participant had to take a reduced dose of trofinetide to be included in the dose reduction group
- Prescribers in real-world clinical practice may not rechallenge patients at higher doses after a dose reduction, as was seen among the investigators in LAVENDER