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Analysis of the Effect of Trofinetide Treatment on the Domain and Item-Level Responses of the Rett Syndrome Behaviour Questionnaire Using Data From the LAVENDER Trial

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INTRODUCTION & OBJECTIVES

Introduction

- Rett syndrome (RTT) is a severe rare genetic neurodevelopmental disorder characterized by multiple (heterogeneous) neurological and behavioral impairments[1,2]
- The complex and heterogeneous nature of RTT has required multiple outcome measures to be developed and utilized by different clinical specialists, focusing on changes in clinician-assessed impairments and activities[3]
- For RTT in particular, patient-reported outcomes (measures or caregiver-reported) provide critical feedback on clinical interventions, such as the efficacy of drugs during clinical trials[4]
- Trofinetide was FDA-approved in 2023 for the treatment of RTT[5]; the Rett Syndrome Behaviour Questionnaire (RSBQ) was one of the co-primary efficacy assessments in the trofinetide pivotal LAVENDER trial[6,7]
- The RSBQ is a 45-item, caregiver-completed scale that assesses observable behaviors of individuals with RTT across 8 domains[8]
  - RSBQ assesses core RTT behaviors using a 3-point Likert scale (0 = behavior “not true,” 1 = behavior “somewhat/ sometimes true,” or 2 = behavior “often true”); with total score ranging from 0 to 90 (higher scores indicate increased severity)
- Presence of ceiling and floor effects have been reported with the RSBQ,[9] but it has not been reported how specific domains, individual items or the floor and ceiling effects impact treatment effects of medication

Objectives

- To examine the effect of trofinetide treatment at the domain- and item-level score changes of the caregiver-reported RSBQ among individuals with RTT in the LAVENDER study
- To evaluate floor and ceiling effects across domains and individual items at baseline and assess their impact on measured treatment response

METHODS

- Post hoc analysis of the 12-week, double-blind, randomized, placebo-controlled, phase 3 study (LAVENDER; NCT04181723) of trofinetide was conducted to examine domain- and item-level changes in the 45-item RSBQ
- The percentage of patients with at least a one-point reduction (improvement), no change, or increase (worsening) from baseline to week 12, was tabulated for the trofinetide and placebo study arms at the domain score level and for each individual item of the RSBQ
- For each domain and item, differences between percentage of patients improving and worsening were classified as net improvement (NI) or net worsening (NW), depending on the result, and are reported
- Results were also compared after accounting for floor and ceiling effects of RSBQ items
  - Basic descriptive and distributions of RSBQ responses at baseline were conducted to ascertain overall heterogeneity and presence of floor or ceiling effects using previously published tresholds[11]
    - Floor effect: >50% patients with a score of 0 (“not true as far as you know”; ie, patients cannot improve on the item score)
    - Ceiling effect: >50% patients with a score of 2 (“very true or often true”; ie, patients cannot get worse on the item score)

RESULTS

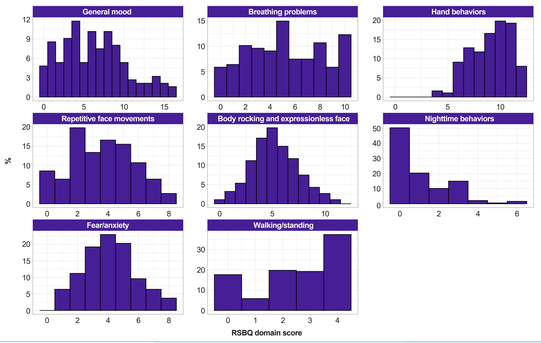
Demographics and Clinical Characteristics

- The 187 females from LAVENDER included in this analysis had a mean (SD) age of 10.9 (4.6) years and mean (SD) RSBQ scores of 44.4 (12.1) and 43.8 (11.4) at baseline for the trofinetide and placebo arms, respectively[7]

Overall Baseline RSBQ Score Descriptions and Distributions

- At baseline, the mean distribution of responses across all RSBQ items was 30.0% (score 0), 39.4% (score 1), and 30.6% (score 2)
- The response distribution across RSBQ domains is shown in **Figure 1**

Figure 1. Response Distribution by RSBQ Domain[a]



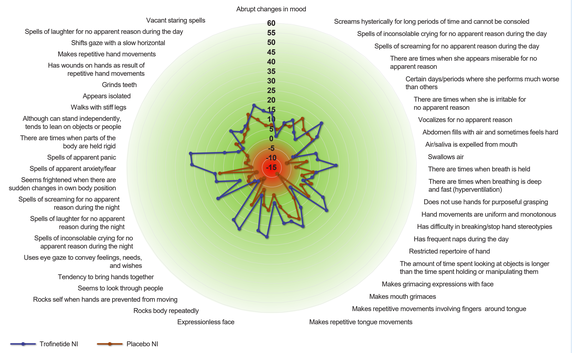
[a]Seven uncategorized RSBQ items do not belong to any domain listed above
RSBQ, Rett Syndrome Behaviour Questionnaire

Table 1. Percentage of Patients With NI or NW

	NI, %		NW, %		NI or NW,%	
Full analysis	**Trofinetide (N = 76)**	**Placebo (N = 85)**	**Trofinetide (N = 76)**	**Placebo (N = 85)**	**Trofinetide (N = 76)**	**Placebo (N = 85)**
All RSBQ items	21.0	15.9	10.4	12.2	10.6	3.7
RSBQ domains						
Body rocking and expressionless face	22.4	13.0	10.1	12.9	12.3	0.1
Breathing problems	17.9	13.2	9.5	13.2	8.4	0.0
Fear/anxiety	26.3	16.2	5.6	16.5	20.7	-0.3
General mood	22.4	21.0	12.5	11.6	9.9	9.4
Hand behaviors	20.2	14.5	11.0	12.2	9.2	2.3
Nighttime behaviors	12.3	8.7	7.0	10.2	5.3	-1.5
Repetitive face movements	24.0	17.7	11.2	9.7	12.8	8.0
Walking/standing	17.1	12.4	9.9	14.1	7.2	-1.7
Uncategorized items	22.8	19.0	11.1	10.4	11.7	8.6
Floor and ceiling adjusted analysis	**NI, %**		**NW, %**		**NI or NW, %**	
	Trofinetide (N = 76)	**Placebo (N = 85)**	**Trofinetide (N = 76)**	**Placebo (N = 85)**	**Trofinetide (N = 76)**	**Placebo (N = 85)**
All RSBQ items	31.7	24.1	16.9	19.7	14.8	4.4
RSBQ domains						
Body rocking and expressionless face	32.2	21.0	15.2	18.1	17.0	2.9
Breathing problems	24.8	19.5	14.5	19.7	10.3	-0.2
Fear/anxiety	36.6	21.4	8.5	23.9	28.1	-2.5
General mood	36.9	33.6	15.2	15.0	21.7	18.6
Hand behaviors	22.8	17.5	33.8	35.0	-11.0	-17.5
Nighttime behaviors	38.0	26.6	7.1	11.0	30.9	15.6
Repetitive face movements	36.4	25.3	14.5	13.2	21.9	12.1
Walking/standing	23.9	16.3	19.6	29.4	4.3	-13.1
Uncategorized items	32.0	26.7	17.0	15.8	15.0	10.9

NI, net improvement; NW, net worsening; RSBQ, Rett Syndrome Behaviour Questionnaire

Figure 2. Percentage of Patients With NI or NW on RSBQ Items



NI, net improvement; NW, net worsening.

- Five domains and 15 out of 45 questions exhibited floor or ceiling effects at baseline
  - Two domains, general mood (3 items) and nighttime behavior (3 items), had 6 times the floor effects at baseline
  - Three domains, hand behavior (5 items), walking/standing (1 item), and body rocking & expressionless face (2 items) had items with ceiling effects and 1 additional item that was part of the 7 uncategorized items

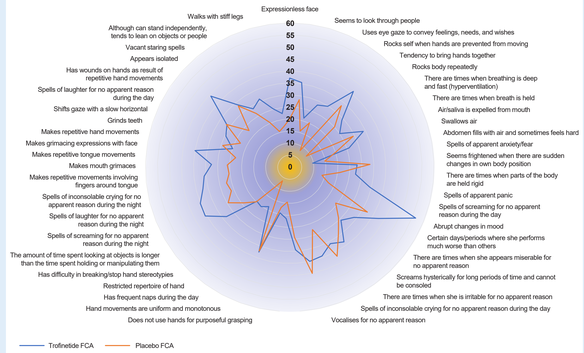
Domain and Item-level Response Results at Week 12

- At 12 weeks, the mean distribution of responses across all RSBQ items was 35.7% (score 0), 39.9% (score 1), and 24.3% (score 2) in the trofinetide group and 32.3% (score 0), 40.3% (score 1), and 27.5% (score 2) in the placebo group, respectively
- Patients on trofinetide had a NI on all 8 domain scores, including the uncategorized items, while those in the placebo arm had NI on 3 domain scores (**Table 1**)
  - The top 3 domains with the greatest numerical difference versus placebo included fear/anxiety (21.0%), body rocking and expressionless face (12.2%), and walking/standing (8.9%)
- Patients on trofinetide had a NI on 41 of 45 items, while those in the placebo arm had NI on 29 of 45 individual items (**Figure 2**)
  - The numerical magnitude of NI was higher for trofinetide than for placebo on the majority of domains, items, and overall score

Ceiling and Floor Adjusted Response Results at Week 12

- After adjusting for ceiling and floor effects, trofinetide had similar NI results, but with a slightly higher magnitude of difference versus placebo (**Table 1**)
  - Patients on trofinetide had a NI on 7 of 8 domain scores, while the placebo arm had NI on 4 domain scores (**Table 1**)
- The top 3 domains with >15% change versus placebo included fear/anxiety (30.6%), walking/standing (17.4%), and nighttime behaviors (15.3%)
- Patients on trofinetide had a NI on 39 out of 45 items, while the placebo arm had NI on 31 of 45 individual items (**Figure 3**)
  - The numerical magnitude of NI was higher for trofinetide than for placebo on the majority domains, items, and overall score

Figure 3. Percentage of Patients With NI or NW on RSBQ Items Adjusted for Floor and Ceiling Effects



NI, net improvement; NW, net worsening.

LIMITATIONS

- As is common in rare disease research, available results are important to provide additional context of treatment effects and are not intended to be comparative claims

CONCLUSIONS

- These findings provide additional insights into the meaningfulness of trofinetide treatment when considering the narrow response options available on the RSBQ
- Our analyses are consistent with the main LAVENDER study findings and further support trofinetide’s potential to improve RTT across RSBQ domain and item-level changes
- Based on these analyses, the domains where caregivers may observe the greatest potential for improvement with trofinetide include fear/anxiety, body rocking and expressionless face, walking/standing, and nighttime behaviors
- The high number of items (41 of 45) showing potential for improvement further supports the complex and heterogeneous nature of RTT and importance of evaluating patients broadly from the caregiver perspective

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ACKNOWLEDGMENTS

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

DISCLOSURES

MVS, **NR**, and **JMY** are employees and stakeholders in Acadia Pharmaceuticals Inc. **ML**, **SC**, **EW**, and **BGF** are employees of Cencora. **KR** is the owner of ANLITIKS.

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Presented at The International Society for Pharmacoeconomics and Outcomes Research 2025 Congress, May 13–16, Montreal, QC, Canada

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