Efficacy and Safety of Trofinetide for the Treatment of Rett Syndrome: Results From the Phase 3 LAVENDER Study

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Disclosures

- Dr Neul has received research funding from the National Institutes of Health, International Rett Syndrome Foundation, and Rett Syndrome Research Trust; **personal consultancy for Acadia Pharmaceuticals Inc.,** AveXis, GW Pharmaceuticals, Roche, Neurogene, Taysha, Signant, and Analysis Group, and is on the Scientific Advisory Board of Alcyone Lifesciences. He has participated in DSMB for OVID and is a Scientific Cofounder of LizarBio.
- **Dr Neul does not own any assets (stocks, options, etc.) in Acadia Pharmaceuticals, Inc.**

Rett Syndrome: Significant Unmet Need

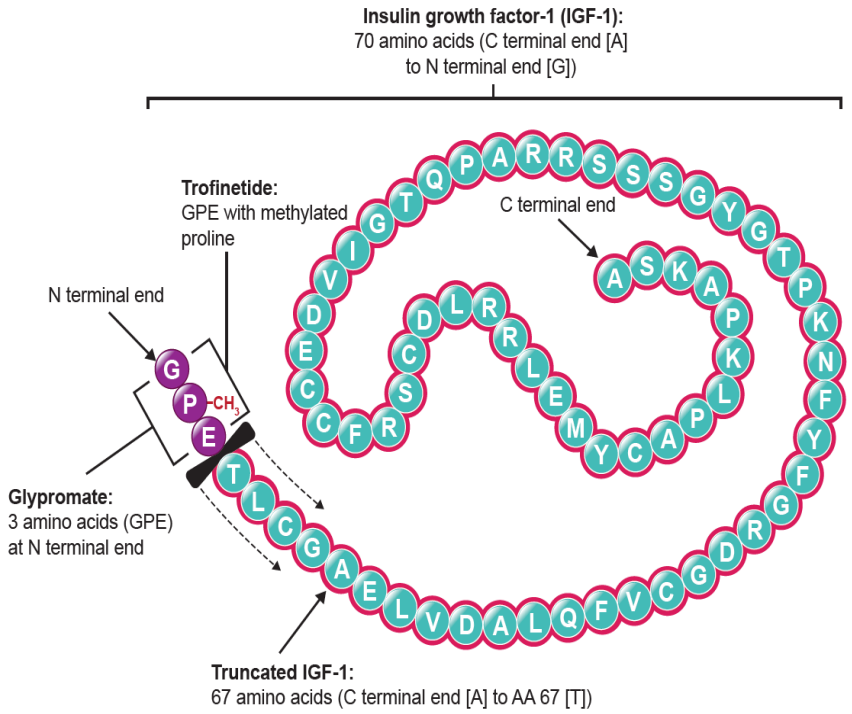
- Rett syndrome (RTT) is a rare, debilitating X-linked neurodevelopmental disorder for which there is no approved treatment
  - RTT primarily affects females (1 in 10,000 to 15,000 births; ~6000–9000 patients in the US)[1,2]
  - Most cases are caused by mutations in the *MECP2* gene, which encodes a DNA-binding protein that regulates gene expression[3]
- Regression around 6–18 months of age with loss of purposeful hand skills and spoken language as defining features of RTT[4-5]
- RTT symptoms include[5]
  - Fine and gross motor impairment
  - Loss of verbal and nonverbal communication
  - Hand stereotypies
  - Seizures
  - Gastrointestinal symptoms, including severe constipation

MECP2, methyl-CpG binding protein 2.

1. Fehr S, et al. *Pediatr Res*. 2011;70:313-19. 2. Estimate based on incidence rates from the National Institutes of Health – National Institute of Neurological Disorders and Stroke. 3. Amir RE, et al. *Nat Genet.* 1999;23:185-8. 4. Hagberg B. *Ment Retard Dev Disabil Res Rev*. 2002;8:61-5. 5. Neul JL, et al. *Ann Neurol.* 2010;68:944-50.

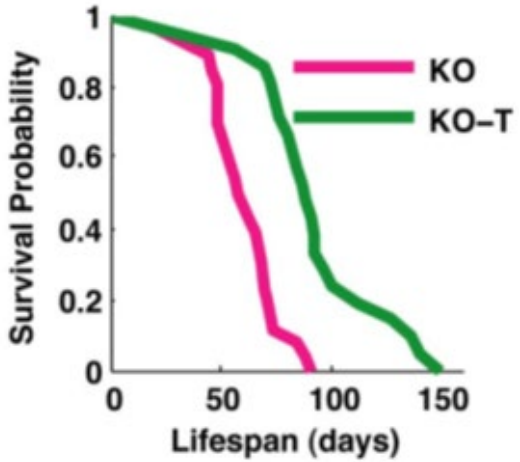
Introduction to Trofinetide

Trofinetide is an investigational drug and a novel synthetic analog of glycine-proline-glutamate (GPE), the amino-terminal tripeptide of insulin-like growth factor 1[1]

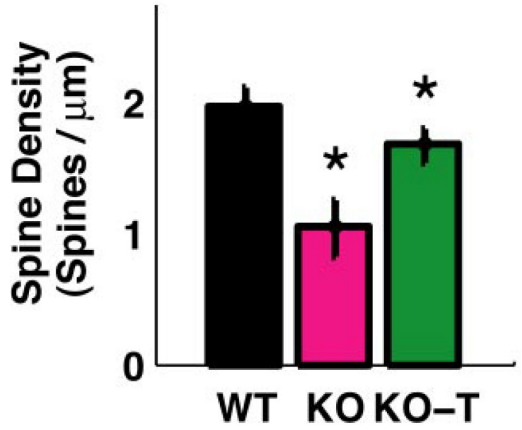


In a mouse model, treatment with GPE partially reverses the features of Rett syndrome compared with untreated mice, including **increases** in:[2]

- Lifespan



- Neuronal spine density



- Locomotor activity
- Brain weight

KO, *Mecp2* knockout mice; KO-T, *Mecp2* knockout mice treated with GPE; WT, wild-type mice.

1. Bickerdike MJ, et al. *J Neurol Sci.* 2009;278:85-90. 2. Tropea D, et al. *Proc Natl Acad Sci USA*. 2009;106:2029-34.

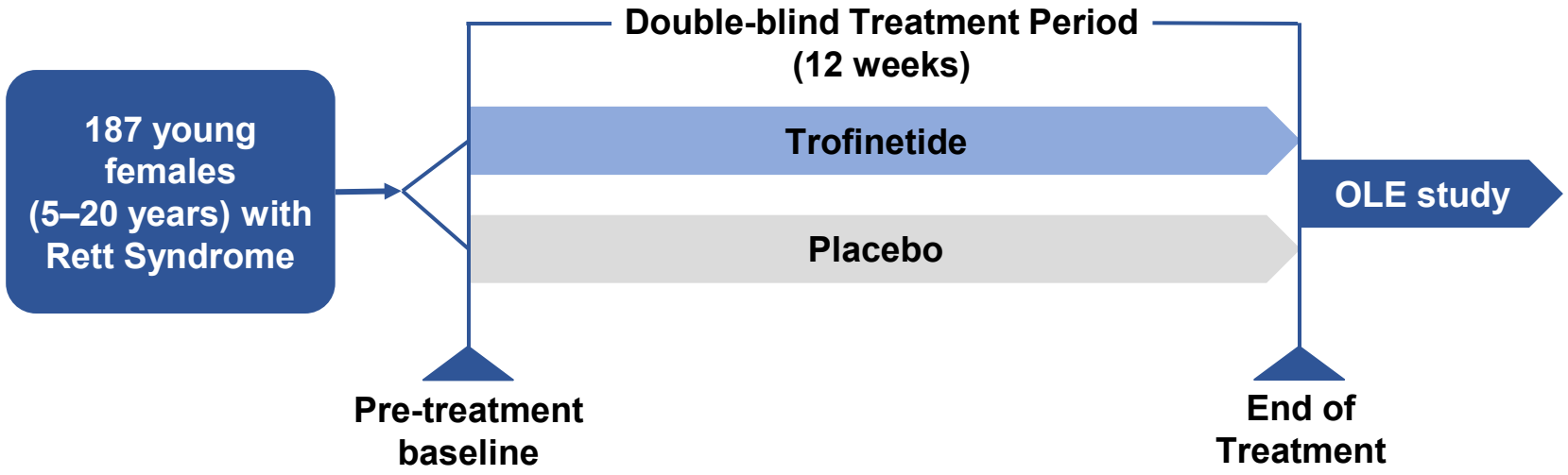
Efficacy Endpoints in Trofinetide RTT Studies

- Rett Syndrome Behaviour Questionnaire (RSBQ)
  - Assesses a wide range of core symptoms impaired in RTT[1]
  - 45-item caregiver-completed scale
  - Each item scored as 0 = not true, 1 = somewhat or sometimes true, or 2 = very true
- Clinical Global Impression-Improvement (CGI-I)
  - Clinician assessment of how much the participant's illness has improved or worsened
  - 7-point scale with RTT-specific anchors[2]
- Communication and Symbolic Behavior Scales-Developmental Profile™-Infant Toddler Social Composite score (CSBS-DP-IT Social)
  - Previously used in neurodevelopmental disorders including RTT[3]
  - Assesses communication and pre-linguistic skills
  - 13 items rated by the caregiver

1. Mount RH, et al. *J Child Psychol Psychiatry*. 2002;43(8):1099-110. 2. Neul JL, et al. *J Child Neurol* 2015;30:1743-8. 3. O'Leary HM, et al. *Ann Clin Transl Neurol*. 2018;5(3):323-32.

Phase 3 LAVENDER Study (NCT04181723)

Randomized, Double-blind, Placebo-controlled, Multi-center Study



Co-primary efficacy endpoints

- RSBQ (caregiver): change from baseline at Week 12
- CGI-I (clinician): score at Week 12

Key secondary efficacy endpoint

- CSBS-DP-IT Social Composite (caregiver): change from baseline at Week 12

- Participants randomized 1:1 with randomization stratified by age group and baseline RSBQ severity
- Treatment given orally or via gastrostomy tube (38%) using weight-based dosing

CGI-I, Clinical Global Impression – Improvement; CSBS-DP-IT, Communication and Symbolic Behavior Scales-Developmental Profile-Infant Toddler; OLE, open-label extension; RSBQ, Rett Syndrome Behaviour Questionnaire.

Key Inclusion Criteria

- Female, 5–20 years of age, inclusive, at screening
- Body weight ≥12 kg at screening
- Post-regression at screening (i.e., no loss or degradation in ambulation, hand function, speech, nonverbal communicative or social skills within 6 months of screening)
- Classic/typical RTT
- Documented disease-causing mutation in the *MECP2* gene
- Severity rating of 10–36, inclusive, on the RTT Clinical Severity Scale[1] at screening
- Stable pattern of seizures, or had no seizures, within 8 weeks of screening

MECP2, methyl-CpG binding protein 2; RTT, Rett syndrome.

1. Neul JL, et al. *Neurology*. 2008;70(16):1313-21.

Baseline Characteristics and Medical History

	Full Analysis Set[a]		
	Placebo (n = 93)	Trofinetide (n = 91)	Total (N = 184)
Mean (SD) age, years	10.8 (4.57)	11.0 (4.73)	10.9 (4.64)
Age categories, n (%)			
5 to 11 years	55 (59.1)	52 (57.1)	107 (58.2)
12 to 16 years	23 (24.7)	22 (24.2)	45 (24.5)
17 to 20 years	15 (16.1)	17 (18.7)	32 (17.4)
Baseline CGI-S category, n (%)			
4 = moderately ill	32 (34.4)	31 (34.1)	63 (34.2)
5 = markedly ill	42 (45.2)	37 (40.7)	79 (42.9)
6 = severely ill	18 (19.4)	23 (25.3)	41 (22.3)
7 = among the most extremely ill patients	1 (1.1)	0	1 (0.5)
***MECP2* gene mutation severity, n (%)[b]**			
Mild	37 (39.4)	30 (32.3)	67 (35.8)
Moderate	8 (8.5)	13 (14.0)	21 (11.2)
Severe	46 (48.9)	46 (49.5)	92 (49.2)
RTT-related medical history, n (%)[b]			
Constipation	74 (78.7)	70 (75.3)	144 (77.0)
Seizure	47 (50.0)	40 (43.0)	87 (46.5)

[a]Participants who were randomized, received at least one dose of study drug, and had both a baseline value and at least one postbaseline value for the RSBQ total score or had at least one CGI-I score after taking study medication.

[b]Mutation severity and medical history based on the Safety Analysis Set (N = 187; placebo n = 94 and trofinetide n = 93).

Topline Efficacy Results
Full Analysis Set

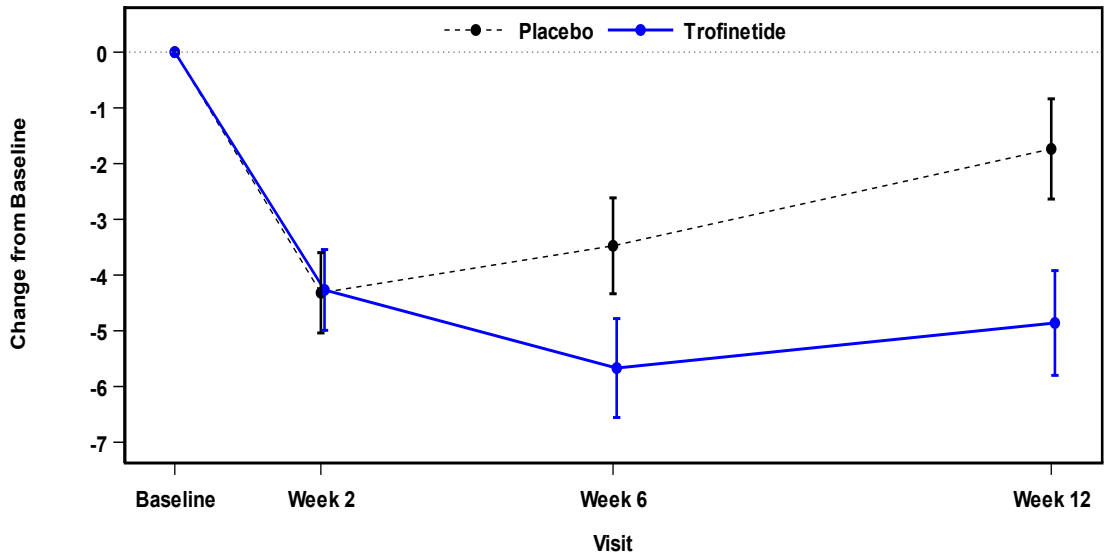
	Placebo	Trofinetide
Primary Endpoints		
RSBQ Change from baseline to week 12, Mean (SE)	-1.7 (0.98)	-5.1 (0.99)
Two-sided p-value		***0.0175****
Cohen's *d* effect size		**0.37**
CGI-I Score at week 12, Mean (SE)	3.8 (0.06)	3.5 (0.08)
Two-sided p-value		***0.0030****
Cohen's *d* effect size		**0.47**
Key Secondary Endpoint		
CSBS-DP-IT Social Composite Score Change from baseline to week 12, Mean (SE)	-1.1 (0.28)	-0.1 (0.28)
Two-sided p-value		***0.0064****
Cohen's *d* effect size		**0.43**

CGI-I, Clinical Global Impression – Improvement; CSBS-DP-IT, Communication and Symbolic Behavior Scales-Developmental Profile-Infant Toddler Checklist-Social; RSBQ, Rett Syndrome Behaviour Questionnaire; SE, standard error.

**p*-values based on least squares mean from the mixed-effects model for repeated measures analysis.

Co-primary Endpoints
Full Analysis Set

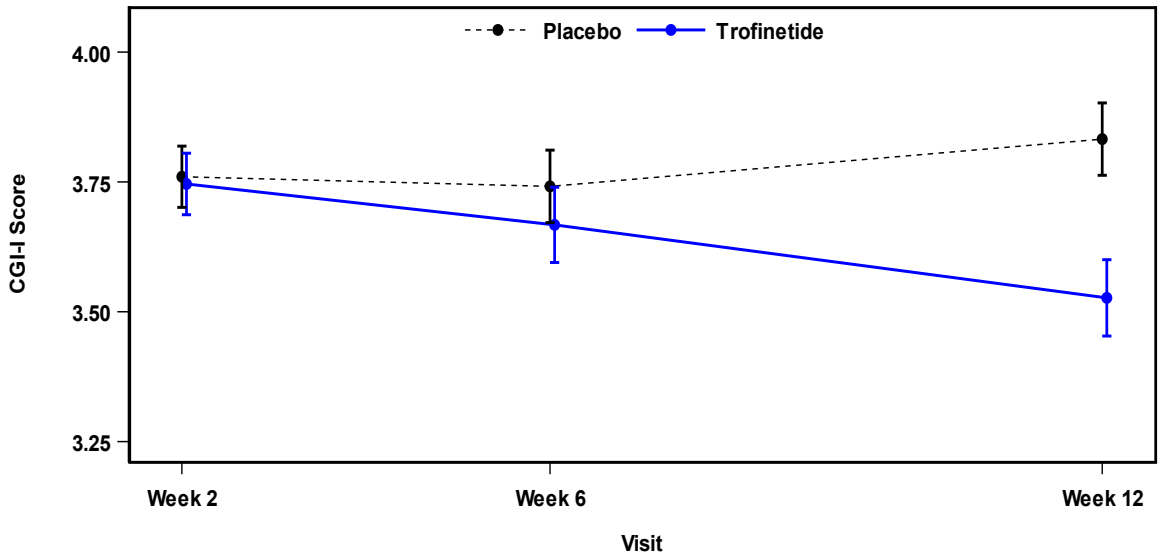
Rett Syndrome Behaviour Questionnaire (RSBQ)



Number of Subjects				
Placebo	93	90	92	85
Trofinetide	91	90	83	76

RSBQ change from baseline to week 12:
p-value = 0.0175*
Effect Size = 0.37

Clinical Global Impression – Improvement (CGI-I)

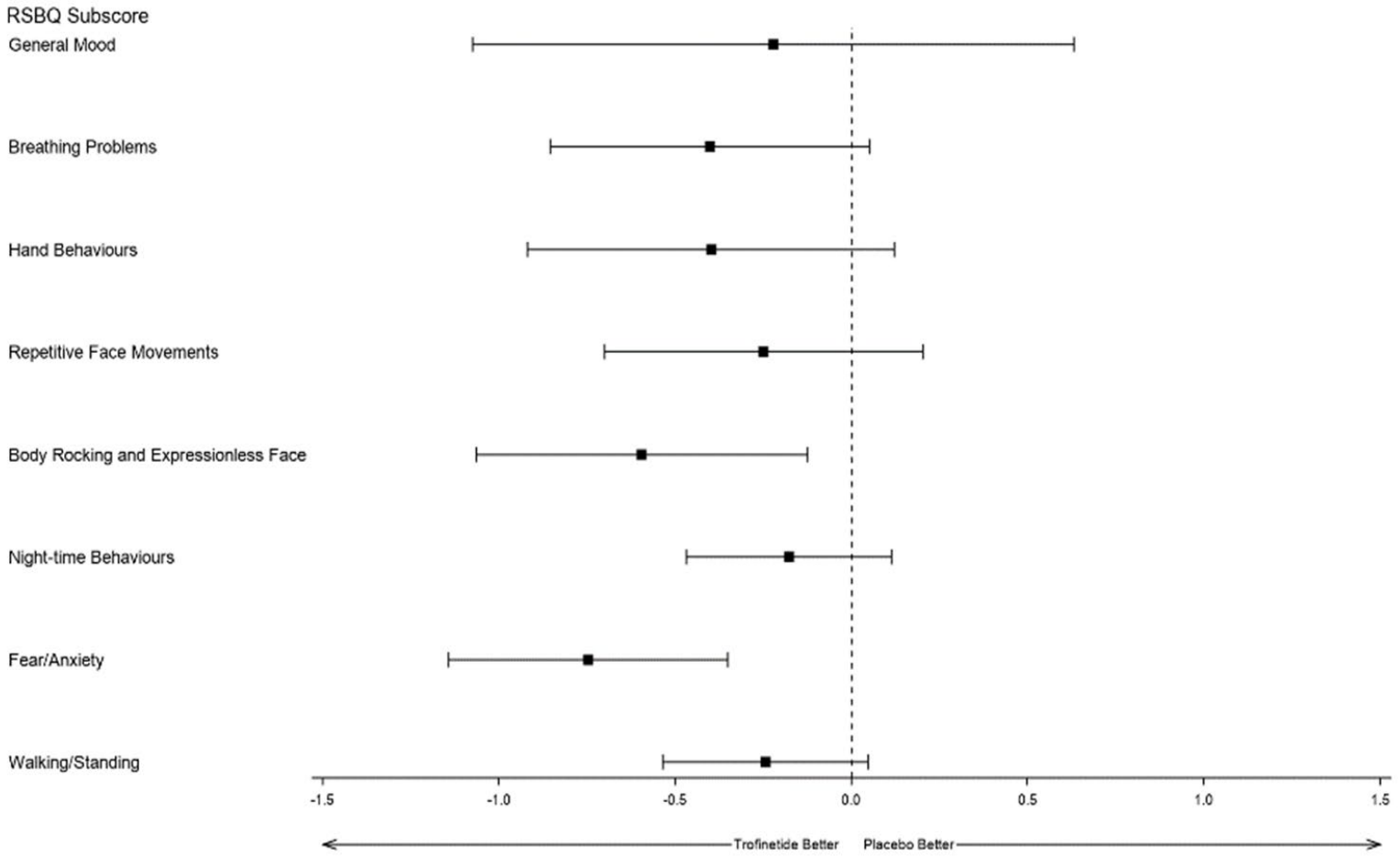


Number of Subjects			
Placebo	90	92	86
Trofinetide	90	83	77

CGI-I at Week 12:
p-value = 0.0030*
Effect Size = 0.47

**p*-values based on least squares mean from the mixed-effects model for repeated measures analysis.

RSBQ Subscores Treatment Difference
Full Analysis Set



LS mean change in subscore from BL to Week 12 with 95% CI

Trofinetide n = 76

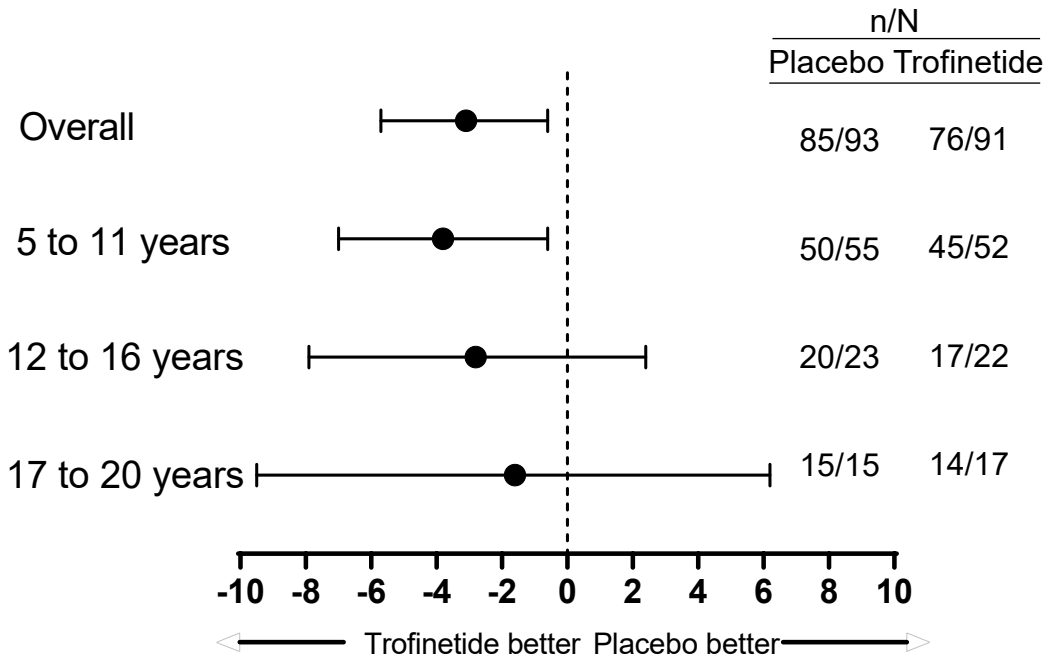
Placebo n = 85

- All domains directionally in favor of trofinetide
- Overall effect not driven by 1 or 2 domains

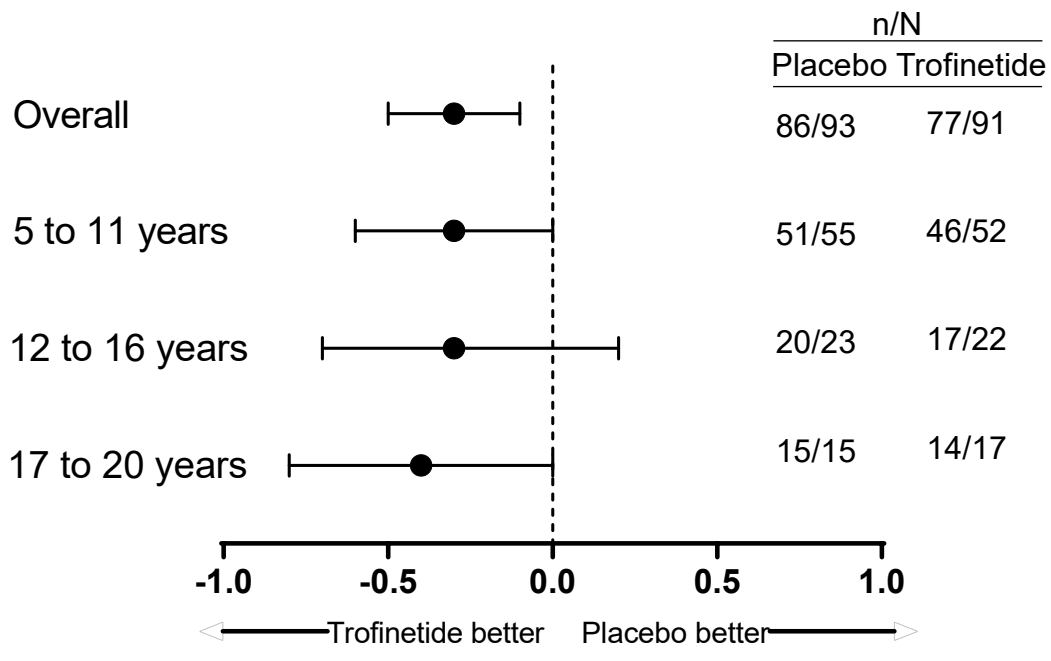
BL, baseline; CI, confidence interval; LS, least squares; RSBQ, Rett Syndrome Behaviour Questionnaire.

Subgroup Analysis by Age
Full Analysis Set

Rett Syndrome Behaviour Questionnaire (RSBQ)



Clinical Global Impression – Improvement (CGI-I)

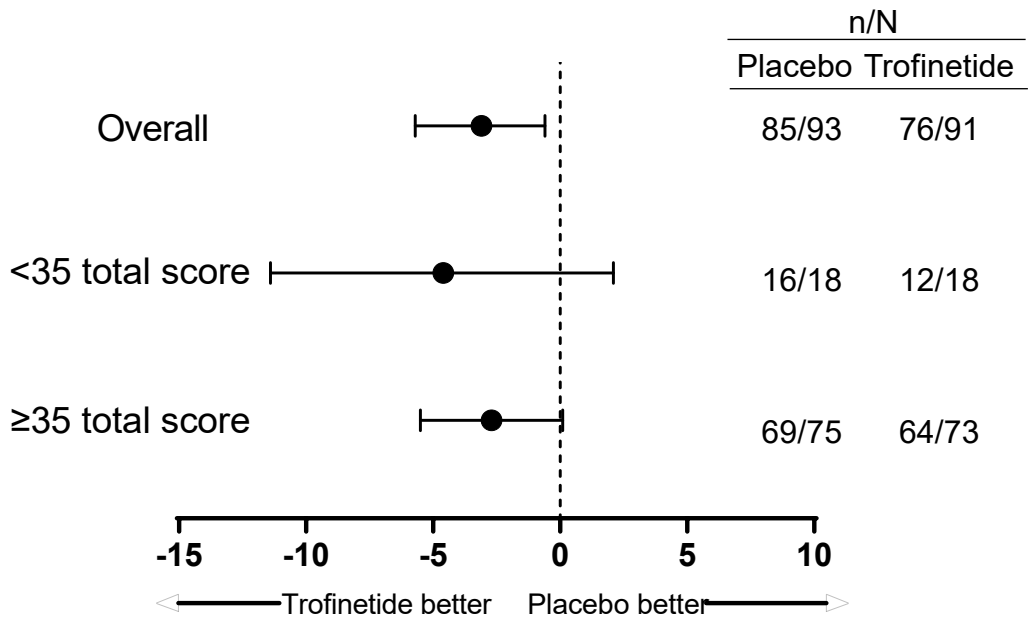


CI, confidence interval; LS, least squares.

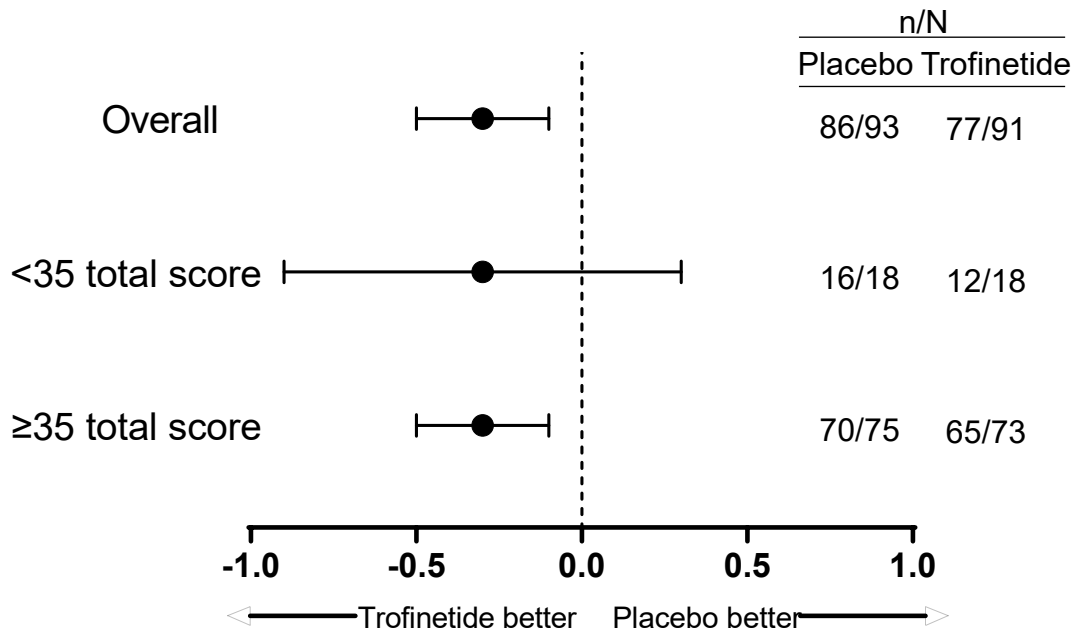
Forest plots of treatment difference in LS mean change from baseline to Week 12 in RSBQ Total Score or CGI-I and corresponding 95% CI (mixed-effect model for repeated measures).

Subgroup Analysis by Baseline RSBQ Severity
Full Analysis Set

Rett Syndrome Behaviour Questionnaire (RSBQ)



Clinical Global Impression – Improvement (CGI-I)



CI, confidence interval; LS, least squares.

Forest plots of treatment difference in LS mean change from baseline to Week 12 in RSBQ Total Score or CGI-I and corresponding 95% CI (mixed-effect model for repeated measures).

Summary of Treatment-Emergent Adverse Events
Safety Analysis Set

TEAE, n (%)	Placebo (n = 94)	Trofinetide (n = 93)
Any TEAE	51 (54.3)	86 (92.5)
Serious TEAE	3 (3.2)	3 (3.2)
TEAE leading to drug withdrawal	2 (2.1)	16 (17.2)
Fatal TEAE	–	–

TEAE, treatment-emergent adverse event.

Treatment-Emergent Adverse Events ≥5% in Either Treatment Group by Severity

Safety Analysis Set

Preferred term	Placebo (N = 94) n (%)			Trofinetide (N = 93) n (%)		
	Mild	Moderate	Severe	Mild	Moderate	Severe
Diarrhea	15 (16.0)	3 (3.2)	–	39 (41.9)	34 (36.6)	2 (2.2)
Vomiting	8 (8.5)	1 (1.1)	–	18 (19.4)	6 (6.5)	1 (1.1)
Seizure	3 (3.2)	2 (2.1)	–	3 (3.2)	5 (5.4)	–
Pyrexia	2 (2.1)	2 (2.1)	–	7 (7.5)	1 (1.1)	–
Decreased appetite	1 (1.1)	1 (1.1)	–	2 (2.2)	3 (3.2)	–
Irritability	–	–	–	3 (3.2)	2 (2.2)	1 (1.1)

Conclusions

- In this phase 3 study, trofinetide demonstrated a statistically significant difference from placebo at Week 12 in:
  - RSBQ and CGI-I, as assessed by caregivers and clinicians, respectively
    - Similar benefit was observed irrespective of age and baseline RSBQ severity
    - All RSBQ subscores directionally favored trofinetide; overall effect was not driven by 1 or 2 domains
  - CSBS-DP-IT Social Composite Score, measuring the ability to communicate
- An acceptable safety profile was observed for trofinetide
  - The most common TEAE was diarrhea, as expected from the phase 2 study[1]
  - Most (97.3%) TEAEs of diarrhea were of mild or moderate severity

1. Glaze DG, et al. *Neurology.* 2019;92:e1912-25.

CGI-I, Clinical Global Impression – Improvement; CSBS-DP-IT, Communication and Symbolic Behavior Scales-Developmental Profile-Infant Toddler; RSBQ, Rett Syndrome Behaviour Questionnaire; TEAE, treatment-emergent adverse event.