

Treatment With Trofinetide Shows Benefit Compared With Placebo in the Ability to Communicate in Individuals With Rett Syndrome

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BACKGROUND

- Rett syndrome (RTT), a debilitating genetic neurodevelopmental disorder that is usually caused by loss-of-function mutations in the X-linked gene methyl-CpG-binding protein 2 (*MECP2*),¹ is characterized by several core features, including loss of verbal communication and limited nonverbal skills²
- The ability to communicate is consistently found to be among the greatest concerns of parents and caregivers of people with RTT,^{3–5} and benefit in the ability to communicate is often identified as the most important goal for caregivers in the treatment of RTT⁵
- Many people with RTT are able to communicate choices to caregivers using modalities such as eye gaze, body movements, and gestures, and this approach has become a focus of research on how to measure improvements in the functional ability to communicate^{6,7}
- The phase 3 LAVENDER study investigated the efficacy and safety of trofinetide treatment for 12 weeks in females with RTT aged 5–20 years and demonstrated statistically significant and clinically meaningful differentiation from placebo for the coprimary efficacy endpoints—the Rett Syndrome Behaviour Questionnaire (RSBQ) and Clinical Global Impression–Improvement (CGI-I) scale—and demonstrated an acceptable safety profile for trofinetide⁸

OBJECTIVE

- The objective of this analysis of secondary endpoints in LAVENDER was to report on those endpoints that were developed or adapted to assess the ability to communicate

METHODS

LAVENDER Study Design

- Study participants were stratified by age (5–10, 11–15, and 16–20 years) and baseline RSBQ severity (<35 and ≥35 total score) and randomized 1:1 to twice daily oral trofinetide or placebo using weight-based dosing
- The study consisted of 3 periods: screening (≤3 weeks), double-blind treatment (12 weeks), and safety follow-up for 30 days (for participants who did not continue into the open-label extension LILAC study)
- Communication-related assessments were conducted at baseline and Weeks 2, 6, and 12 (or end of treatment) and included the caregiver-rated Communication and Symbolic Behavior Scales–Developmental Profile™–Infant Toddler Checklist (CSBS-DP-IT) Social Composite score and 2 novel RTT-specific clinician rating scales that measured the ability to communicate choices using nonverbal modalities (Rett Syndrome Clinician Rating of Ability to Communicate Choices [RTT-COMC]) and verbal communication (Rett Syndrome Clinician Rating of Verbal Communication [RTT-VCOM])⁹

Communication-Related Assessments

- The 13 items of the CSBS-DP-IT Social Composite score are divided into 3 skill areas: “Emotion and Eye Gaze” (items 1–4), “Communication” (items 5–8), and “Gestures” (items 9–13), each scored as 0 (“not yet”), 1 (“sometimes”), or 2 (“often”) points; total scores range from 0 to 26, and higher scores indicate a better ability to communicate
- The RTT-COMC assesses the individual’s ability to communicate their choices or preferences, which can include the use of nonverbal means, such as eye contact or gestures, using an 8-point Likert scale (0 [normal] to 7 [most severe impairment])
- The RTT-VCOM assesses the individual’s ability to communicate verbally using an 8-point Likert scale (0 [normal functioning] to 7 [most severe impairment])
- All 3 communication endpoints were based on the change from baseline to Week 12; the CSBS-DP-IT Social Composite score was the key secondary efficacy endpoint, and the RTT-COMC and RTT-VCOM were other secondary efficacy endpoints in LAVENDER

Statistical Analysis

- The LAVENDER study used a hierarchical sequential gatekeeper procedure such that the key secondary efficacy endpoint was tested providing the primary analyses of the coprimary efficacy endpoints (RSBQ and CGI-I) reached statistical significance (p≤0.05)
- The communication-related endpoints were analyzed using the mixed-effects model for repeated measures (MMRM) method, assuming data missing at random
- For the CSBS-DP-IT Social Composite score and RTT-COMC, a subgroup analysis examined treatment effects by age, baseline RSBQ severity, and *MECP2* mutation severity categorized according to the RTT Natural History Study¹⁰

RESULTS

Demographic and Baseline Characteristics

- Overall, 187 participants were randomized to trofinetide (n = 93) or placebo (n = 94); the Full Analysis Set included 184 participants (trofinetide, n = 91; placebo, n = 93)
- Treatment groups were well balanced for demographic and baseline characteristics, including baseline scores for the CSBS-DP-IT, RTT-COMC, and RTT-VCOM (Table 1)
- Baseline scores indicate that communication was moderately to severely affected

Table 1. Baseline demographics and clinical characteristics

	Randomized Analysis Set	
	Placebo (n = 94)	Trofinetide (n = 93)
Mean (SD) age, years	10.9 (4.57)	11.0 (4.69)
Age categories, ^a years, n (%)		
5–11	55 (58.5)	53 (57.0)
12–16	24 (25.5)	23 (24.7)
17–20	15 (16.0)	17 (18.3)
Baseline RSBQ total score ^b		
Mean (SD)	44.4 (12.13)	43.8 (11.42)
Median (min, max)	43.0 (14, 69)	42.0 (21, 74)
Baseline CGI-S score ^c		
Mean (SD)	4.9 (0.76)	4.9 (0.77)
Median (min, max)	5 (4, 7)	5 (4, 6)
Baseline CSBS-DP-IT Social Composite score ^d		
Mean (SD)	8.9 (3.23)	8.7 (3.32)
Median (min, max)	9.0 (2, 16)	9.0 (2, 16)
Baseline RTT-COMC ^e		
Mean (SD)	3.3 (1.75)	3.5 (1.55)
Median (min, max)	4.0 (1, 7)	4.0 (1, 7)
Baseline RTT-VCOM ^f		
Mean (SD)	5.5 (0.96)	5.5 (1.02)
Median (min, max)	6.0 (2, 7)	6.0 (2, 7)

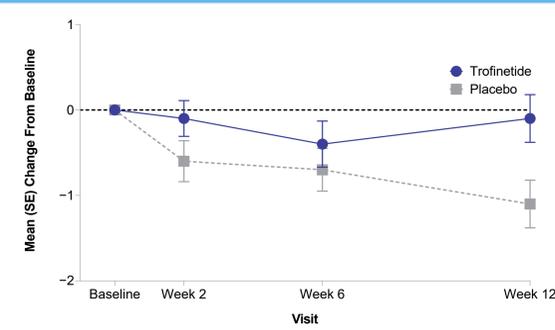
^aU.S. Food & Drug Administration–recommended age groups were used for the subgroup analyses; ^bRSBQ consists of 45 items rated as 0 (“not true”), 1 (“somewhat or sometimes true”), or 2 (“very true”) that can be grouped into 8 symptom domain subscales graded on a scale of 0–90 (maximum severity).¹¹ The score for item 31 (“uses eye gaze to convey feelings, needs, and wishes”) was reversed in the calculations of total score and subscores for all analyses; ^cCGI-S score uses a Likert scale (1 [normal] to 7 [among the most extremely ill patients]); ^dCSBS-DP-IT Social Composite score consists of 13 caregiver-rated items, each scored 0 (“not yet”), 1 (“sometimes”), or 2 (“often”), and ranges from 0 to 26 (an increasing score indicates better social communication development); ^eRTT-COMC uses an 8-point Likert scale (0 [normal] to 7 [most severe impairment]); ^fRTT-VCOM uses an 8-point Likert scale (0 [normal] to 7 [most severe impairment]).

CSBS, Clinical Global Impression–Severity; CSBS-DP-IT, Communication and Symbolic Behavior Scales–Developmental Profile™–Infant Toddler Checklist; RSBQ, Rett Syndrome Behaviour Questionnaire; RTT-COMC, Rett Syndrome Clinician Rating of Ability to Communicate Choices; RTT-VCOM, Rett Syndrome Clinician Rating of Verbal Communication; SD, standard deviation

CSBS-DP-IT Social Composite Score

- The mean (standard error [SE]) change from baseline to Week 12 in the CSBS-DP-IT Social Composite score was −1.1 (0.28) in the placebo group and −0.1 (0.28) in the trofinetide group (Figure 1)
- Based on the MMRM analysis, the change from baseline to Week 12 in the CSBS-DP-IT Social Composite score demonstrated a statistically significant difference in favor of the trofinetide group compared with the placebo group (least squares mean [LSM] difference: 1.0; 95% confidence interval [CI]: 0.3 to 1.7; p=0.0064; Cohen’s *d* effect size: 0.43)

Figure 1. Mean (SE) Change From Baseline by Visit for the CSBS-DP-IT Social Composite Score (Full Analysis Set)

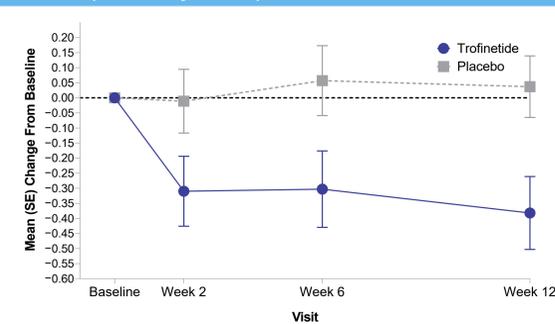


Higher CSBS-DP-IT Social Composite scores indicate improvement; CI, confidence interval; CSBS-DP-IT, Communication and Symbolic Behavior Scales–Developmental Profile™–Infant Toddler Checklist; SE, standard error

RTT-COMC

- The mean (SE) change from baseline at Week 12 in the RTT-COMC in the respective trofinetide and placebo groups was −0.4 (0.12) and 0.0 (0.10) (Figure 2)
- Based on the MMRM analysis, the change from baseline at Week 12 showed a nominal significant difference in favor of trofinetide compared with placebo (LSM difference: −0.3; 95% CI: −0.6 to −0.0; p=0.0257; Cohen’s *d* effect size: 0.36)

Figure 2. Mean (SE) Change From Baseline by Visit in the RTT-COMC (Full Analysis Set)



Lower scores for RTT-COMC indicate improvement; RTT-COMC scores at each study visit are reported to 2 decimal places

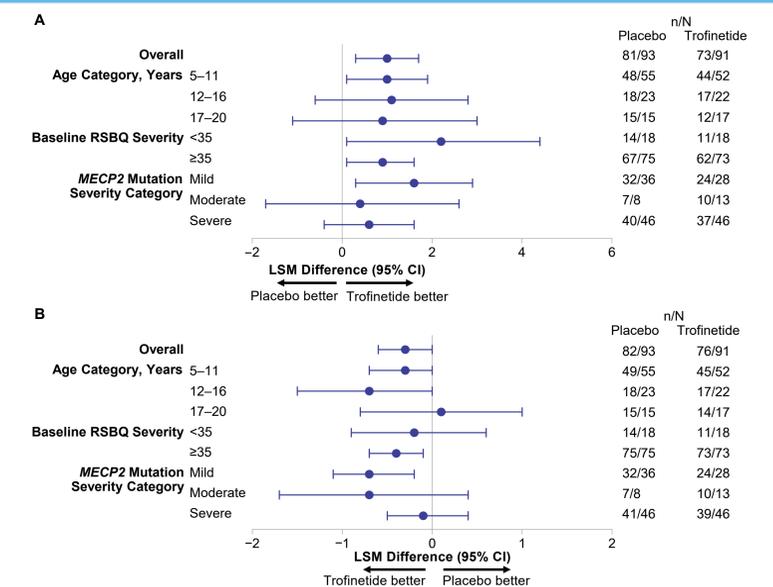
RTT-VCOM

- The mean change from baseline in the RTT-VCOM was 0 at each study visit in both the trofinetide and placebo groups
- Based on the MMRM analysis, there was no treatment difference for the change from baseline to Week 12 (LSM difference: 0.0; 95% CI: −0.2 to 0.2; p=0.9799; Cohen’s *d* effect size: 0.00)

Subgroup Analyses

- Treatment differences in favor of trofinetide for both the CSBS-DP-IT Social Composite score and RTT-COMC were observed irrespective of age (with the exception of the older age group for the RTT-COMC), baseline RSBQ severity, and category of *MECP2* mutation severity (Figure 3)

Figure 3. Forest Plots of Subgroup Analyses for CSBS-DP-IT Social Composite Score (A) and RTT-COMC (B) by Age, Baseline RSBQ Severity, and Category of *MECP2* Mutation Severity (MMRM Analysis; Full Analysis Set)



Higher scores in the CSBS-DP-IT Social Composite score and lower scores in the RTT-COMC are indicative of improvement

CI, confidence interval; CSBS-DP-IT, Communication and Symbolic Behavior Scales–Developmental Profile™–Infant Toddler Checklist; LSM, least squares mean; MMRM, mixed-effects model for repeated measures; RSBQ, Rett Syndrome Behaviour Questionnaire; RTT-COMC, Rett Syndrome Clinician Rating of Ability to Communicate Choices

CONCLUSIONS

- Significant treatment benefit for trofinetide versus placebo was observed in scales measuring the ability to communicate
 - The benefit in the ability to communicate was unaffected by age, disease severity at baseline, or mutation severity category
- These communication scales may be appropriate for future clinical studies in RTT and other neurodevelopmental disorders

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DISCLOSURES

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