Poster #65

Three-Year Maintenance of RSBQ Domain Score Improvements with Trofinetide Treatment for Rett Syndrome: Longitudinal Analysis Across LAVENDER, LILAC-1 and LILAC-2 Trials

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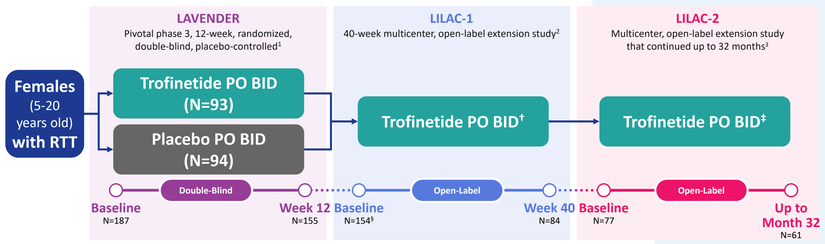
BACKGROUND

- Trofinetide (TROF) is the first and only FDA-approved treatment for Rett syndrome (RTT) based on the 12-week LAVENDER and long-term extension (40-week LILAC-1 and 32-month LILAC-2) trials. [1-3] [Figure1].
- TROF Clinical Program includes the below trials :
  - **LAVENDER** – A pivotal Phase 3, 12-week, randomized, double-blind, placebo-controlled trial. [1]
  - **LILAC-1** – A 40-week multicenter, open-label extension study. [2]
  - **LILAC-2** – A multicenter, open-label extension study that continued up to 32 months. [3]

Figure 1: Trofinetide Clinical Program



*Orally or by gastrostomy tube. †Dose based on participants body weight at baseline. Participants whose assigned dose in LAVENDER was decreased for tolerability were to remain on same dose in LILAC-1 with dose increased to level based on weight, if tolerable. ‡The assigned dose was the participants final dose from the antecedent study. If the dose was reduced in LILAC-1 for tolerability, the dose was increased during LILAC-2, if tolerated, to the appropriate dose level based on weight. §Of these participants, 85 received placebo and 69 received trofinetide during LAVENDER.

1. Neul JL, et al. Nat Med. 2023;29(6):1468-1475. 2. Percy AK, et al. Med. 2024;5(9):1178-1189.e3. 3. Percy AK, et al. Med. 2024;5(10):1275-1281.e2.

- Prior analysis of the TROF clinical trials shows that TROF demonstrates long-term improvements and maintenance of effect on the RSBQ total score. [1-3]
- However, long-term improvements and maintenance of effect with TROF on the specific core RTT symptoms, as measured by the eight RSBQ domains is required.

METHODS

Study Design and Population

- This analysis examined long-term improvements and maintenance of effect in RSBQ domain scores at 12-weeks of LAVENDER, 40-weeks in LILAC-1 (1-year), 52-weeks (2-years) of LILAC-2 and up to 104-weeks (3-years) in LILAC-2.
- **Analysis Population**: All LILAC-2 participants who have completed LAVENDER and LILAC-1.
- **Sensitivity analysis**: Domain specific improvements among participants who exhibited domain-level symptoms at LAVENDER baseline (i.e., no Domain-Level Baseline Ceiling Effect (no-DLBCE)) for each domain (results not presented here).
- The 8 RSBQ domains and the respective items in each domain are presented in Figure 2.

Study Measures & Outcomes

- Mean increase or decrease (change from baseline) in each of the eight RSBQ domain scores from LAVENDER baseline at every visit for 3-years.
- Higher scores also represents higher impairment; therefore, a reduction in scores from baseline suggest treatment effect (i.e., improvement).

Figure 2: Eight RSBQ Domains Assess Core RTT Features

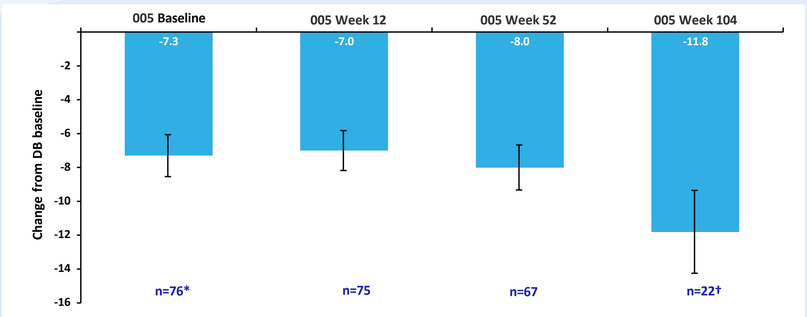
Note: Unspecified domain not included for the purpose of this analysis

RESULTS

Demographic and Clinical Characteristics

- Of the 77 LILAC-2 participants, mean age was 12 years, over 92% were white; mean TROF exposure from LAVENDER baseline was nearly 756 days [Table 1].

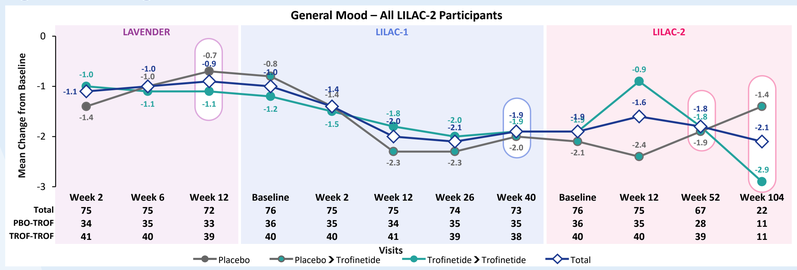
Figure 3: RSBQ Total Score Improvements



*RSBQ assessment was available for 76 participants only at LILAC-2 baseline
†The study was terminated early by the sponsor following FDA-approval and commercial availability of TROF.
At the time the study was terminated, only 22 participants had reached the Week 104 visit.

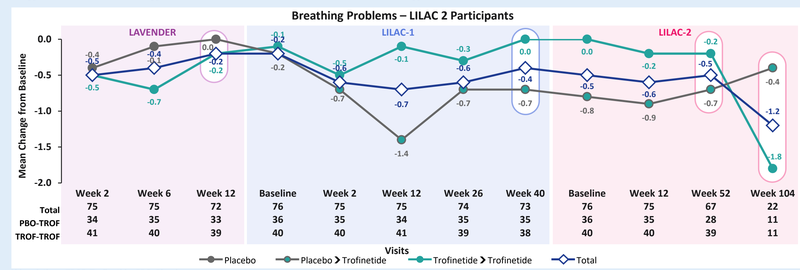
RESULTS

Figure 3a: Change From Baseline on General Mood Domain



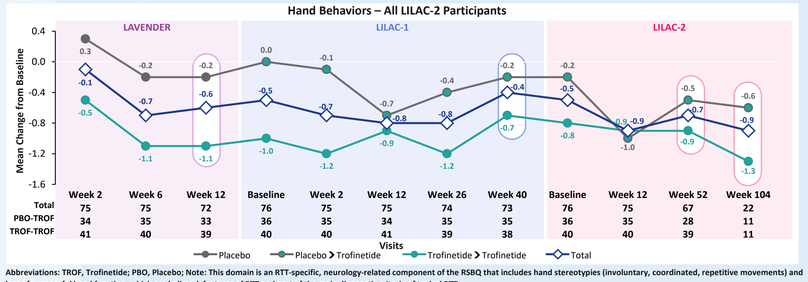
Abbreviations: TROF, Trofinetide; PBO, placebo;
Note: The general mood domain includes items related to unexpected periods of crying, screaming, irritability, and vocalization that are characteristic in RTT particularly during the regression period

Figure 3b: Change From Baseline on Breathing Problems Domain



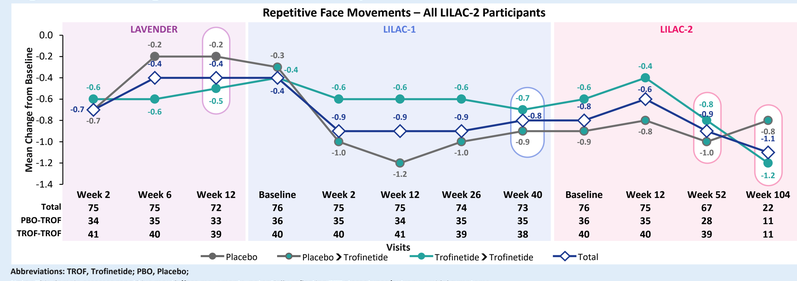
Abbreviations: TROF, Trofinetide; PBO, Placebo
Note: Items in this domain of the RSBQ are related to hyperventilation, air swallowing, and breath holding

Figure 3c: Change From Baseline on Hand Behaviors Domain



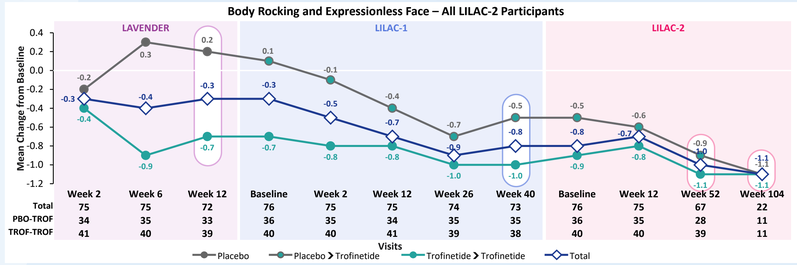
Abbreviations: TROF, Trofinetide; PBO, Placebo; Note: This domain is an RTT-specific, neurology-related component of the RSBQ that includes hand stereotypies (involuntary, coordinated, repetitive movements) and loss of purposeful hand function, which are hallmark features of RTT and part of the main diagnostic criteria of typical RTT

Figure 3d: Change From Baseline on Repetitive Face Movements Domain



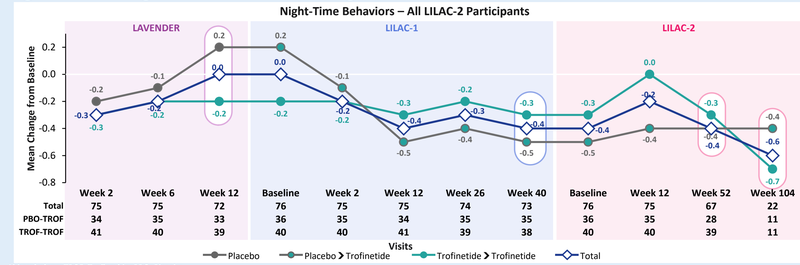
Abbreviations: TROF, Trofinetide; PBO, Placebo;
Note : This domain assesses repetitive mouth/face movements, potentially reflecting RTT stereotypes/extrapyramidal symptoms

Figure 3e: Change From Baseline on Body Rocking and Expressionless Face Domain



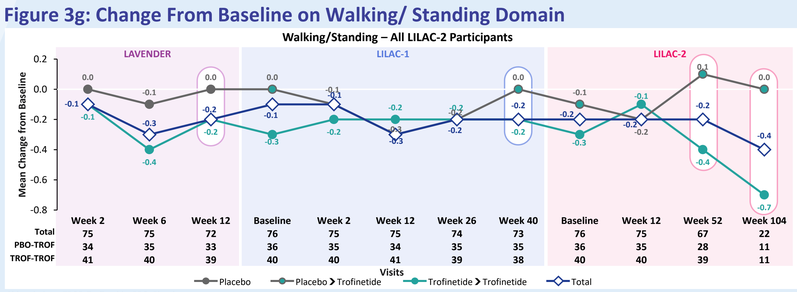
Abbreviations: TROF, Trofinetide; PBO, Placebo;
Note: This domain is heterogeneous in its inclusion of both eye gaze and expressionless face with the former included in the supportive criteria for atypical RTT

Figure 3f: Change From Baseline on Night-Time Behaviors Domain



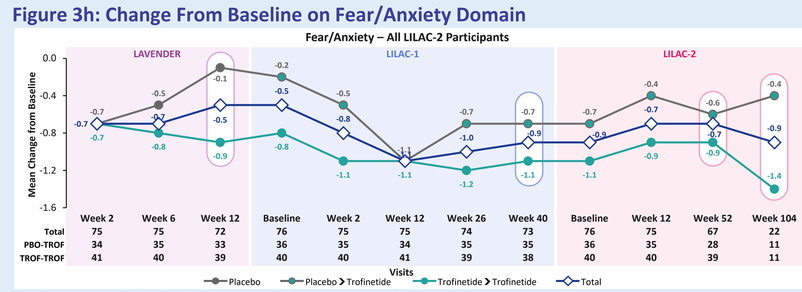
Abbreviations: TROF, Trofinetide; PBO, Placebo;
Note: Each of the 3 items in this domain relate to episodes of crying, laughing, or screaming during the night, which are recognized features of RTT

Figure 3g: Change From Baseline on Walking/ Standing Domain



Abbreviations: TROF, Trofinetide; PBO, Placebo;
Note: The RSBQ's Walking/Standing domain captures gait abnormalities, a key RTT criterion, and characterizes motor impairment/spasticity in RTT.

Figure 3h: Change From Baseline on Fear/Anxiety Domain



Abbreviations: DLBCE, Domain level baseline ceiling effects; RFM, Repetitive face movements; TROF, Trofinetide; PBO, Placebo;
Note: This RTT feature may link to autonomic issues; though not a diagnostic criterion, fear and anxiety are common in RTT individuals

Table 1: Demographics and Clinical Characteristics

	Overall cohort N=77*
Age, years (mean ± SD)	12.0 ± 4.38
Primary race, n (%)	
White	71 (92.2)
Black or African American	1 (1.3)
Asian	1 (1.3)
Other	4 (5.2)
RSBQ total score (mean ± SD)	36.4 ± 12.68
CGI-S score (mean ± SD)	4.8 ± 0.89
Duration of exposure (days)	
Mean ± SD	755.6 ± 182.76
Median	769.0
Min, Max	310, 1190
Duration of exposure categorical, n (%)	
<12 weeks	--
12 to <52 weeks	1 (1.3)
52 to <104 weeks	32 (41.6)
104 to <130 weeks	28 (36.4)
≥130 weeks	16 (20.8)

Abbreviations: IQR, Interquartile range; SD, Standard deviation * Safety Analysis set

Domain Outcomes

- All 8 RSBQ domains showed improvements at week 12 of LAVENDER and also at 1 year of LILAC-1, these improvements were maintained across 2 and 3 years [Figure 3a - 3h].

Domain Sensitivity Analysis

- Similarly, the sensitivity analysis among no-DLBCE participants also showed improvements on all 8 domains at week 12 of LAVENDER and also at 1 year of LILAC-1, these improvements were maintained across 2 and 3 years [Results not shown here].

CONCLUSIONS

- Long-term total score improvements and maintenance of effect reported previously was similarly observed on all 8 RSBQ domains by "LILAC-2 participants" across the TROF trials.
- The greatest improvements were seen in general mood, fear/anxiety, repetitive face movements, body rocking and expressionless face domains at one year of treatment (LAVENDER week 12 and LILAC-1 week 40).
- These improvements in total RSBQ and domain scores were maintained consistently over 2-years and 3-years until week 104 of LILAC-2.

LIMITATIONS

- This analysis was performed especially among participants who participated in all the 3 trials in order to estimate the long-term maintenance effects.
- The TROF safety profile and common adverse reactions have been previously reported for all three trials, including the cohort presented here. [1-3]

REFERENCES

1. Neul JL, Percy AK, Benke TA, et al. Trofinetide for the treatment of Rett syndrome: a randomized phase 3 study. Nat Med. 2023;29(6):1468-1475
2. Percy AK, Neul JL, Benke TA, Berry-Kravis EM, Glaze DG, Marsh ED, An D, Bishop KM, Youakim JM. Trofinetide for the treatment of Rett syndrome: Results from the open-label extension LILAC study. Med. 2024 Sep 13;5(9):1178-1189.e3. doi: 10.1016/j.medj.2024.05.018. Epub 2024 Jun 24. PMID: 38917793.
3. Percy AK, Neul JL, Benke TA, Berry-Kravis EM, Glaze DG, Marsh ED, Barrett AM, An D, Bishop KM, Youakim JM. Trofinetide for the treatment of Rett syndrome: Long-term safety and efficacy results of the 32-month, open-label LILAC-2 study. Med. 2024 Oct 11;5(10):1275-1281.e2. doi: 10.1016/j.medj.2024.06.007. Epub 2024 Jul 17. PMID: 39025065.

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