Poster #10

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Time to Response to Trofinetide in Patients With Rett Syndrome: Results From Trofinetide Clinical Trials

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DISCLOSURES

AP, LR, CZ, RR, and LC are employees and stakeholders in Acadia Pharmaceuticals Inc. **AA** has received funding for clinical trials from Anavex Life Sciences Corp. and Acadia Pharmaceuticals Inc.

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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 clinical trials with a manageable safety profile[3-5]
  - In LAVENDER, a phase 3, 12-week, randomized, double- blind study of trofinetide versus placebo in female participants with RTT aged 5–20 years, statistically significant improvements were observed in the caregiver- assessed Rett Syndrome Behaviour Questionnaire (RSBQ) and the clinician-assessed Clinical Global Impression– Improvement (CGI-I) scale[3]
  - Continued improvements in the core symptoms of RTT were observed with extended trofinetide treatment in LILAC and LILAC-2, phase 3, 40-week and 32-month open-label extension studies of LAVENDER, respectively[4,5]
  - The most common adverse event reported in LAVENDER, LILAC, and LILAC-2 was diarrhea[3-5]
- Anecdotal, real-world reports from RTT experts at US centers of excellence suggest that some patients require more than 12 weeks to respond to trofinetide

OBJECTIVES

- To estimate time to response (TTR) to trofinetide in patients with RTT using CGI-I scores in the Phase 3 clinical program
- To explore consistency of outcomes by repeating TTR analysis using RSBQ total score change from baseline

METHODS

Participants

- Participants of LAVENDER, LILAC, and LILAC-2 who received trofinetide for 12 months were included in this analysis (Figure 1)
- TTR periods included 0–3 months, 3–6 months, and 6–12 months; results are presented for participants randomized to trofinetide in LAVENDER, placebo in LAVENDER, and pooled

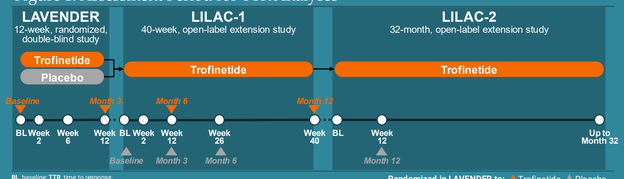
CGI-I TTR Analysis

- Participants were included if they had a CGI-I score available at month 3 and month 12
  - For those without response at month 3, but with response at month 12, the CGI-I score at month 6 was evaluated, if available
- CGI-I response criteria used for the TTR analysis was based on built-in responder status of the measure, rated as 1 = "very much improved," 2 = "much improved," 3 = "minimally improved," 4 = "no change," 5 = "minimally worse," 6 = "much worse," and 7 = "very much worse"[6]; the CGI-I response criteria accounted for randomization to trofinetide or placebo in LAVENDER (Table 1)

RBSQ TTR Analysis

- Participants were included if they had an RSBQ total score available at baseline, month 3, and month 12; RSBQ total score change from baseline was calculated for each time point
  - For those without response at month 3 but with response at month 12, the RSBQ total score change at month 6 was calculated and evaluated, if available
- RSBQ response criteria used for the TTR analysis was based on an approximated minimal clinically important difference (MCID) of 3- to 6- point change in total score[7] where a reduction in total score by ≥3 points indicated response (Table 2)

Figure 1. Assessment Period for TTR Analyses



BL, baseline; **TTR**, time to response. **Randomized in LAVENDER to:** ▲ Trofinetide ▲ Placebo

Table 1. Response Criteria for CGI-I TTR Analysis

	CGI-I response criteria					
	Trofinetide in LAVENDER			Placebo in LAVENDER		
TTR group	Month 3	Month 6	Month 12	Month 3	Month 6	Month 12
0–3 months	≤3	-	≤4	≤3	-	≤3
3–6 months	4	≤3	≤3	≥4	≤3	≤3
6–12 months	4	≥4	≤3	≥4	≥4	≤3

CGI-I, Clinical Global Impression–Improvement; **TTR**, time to response.

Table 2. Response Criteria for RSBQ TTR Analysis

	RSBQ score change response criteria		
TTR group	Month 3	Month 6	Month 12
0–3 months	≤-3	-	≤-3
3–6 months	≥-2	≤-3	≤-3
6–12 months	≥-2	≥-2	≤-3

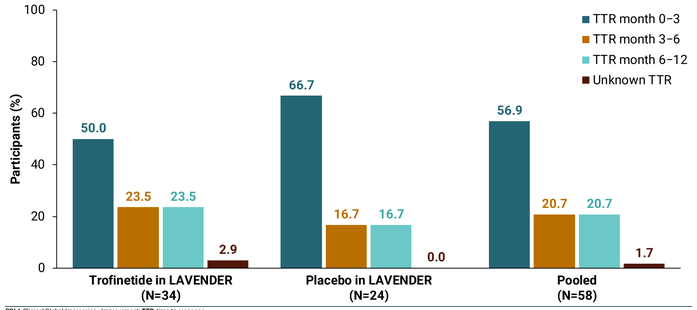
RSBQ, Rett Syndrome Behaviour Questionnaire; **TTR**, time to response.

RESULTS

CGI-I TTR Analysis

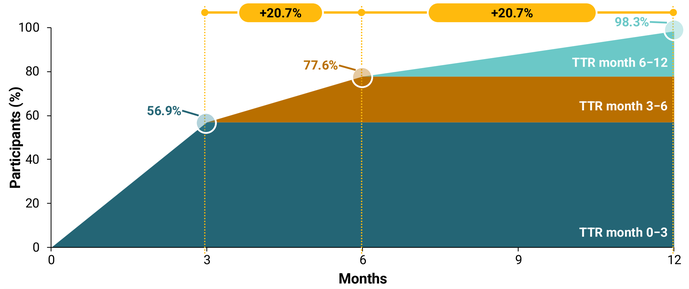
- Overall, 58 participants of the Phase 3 trofinetide clinical program met analysis criteria
- In total, 33 (56.9%) of pooled participants had a TTR of 0–3 months, 12 (20.7%) had a TTR of 3–6 months, and 12 (20.7%) had a TTR of 6–12 months (Figures 2 and 3)
  - Similar TTR trends were observed for participants randomized to trofinetide and placebo in LAVENDER (Figure 2)
  - There was 1 (1.7%) participant who improved after month 3 and by month 12, but TTR estimation was not possible due to missing month 6 value

Figure 2. Pooled TTR Status per CGI-I and by Randomization in LAVENDER



CGI-I, Clinical Global Impression–Improvement; **TTR**, time to response.

Figure 3. Pooled TTR Status per CGI-I

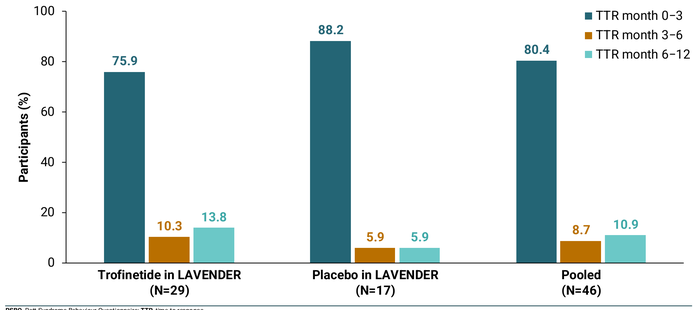


*While 100% responded by month 12, 98.3% had TTR estimation available. **CGI-I**, Clinical Global Impression–Improvement; **TTR**, time to response.

RSBQ TTR Analysis

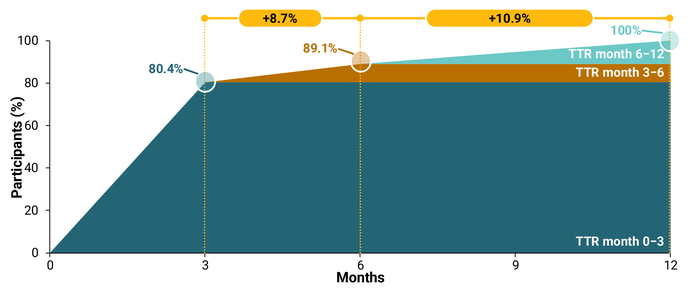
- Overall, 46 participants of the Phase 3 trofinetide clinical program met analysis criteria
- In total, 37 (80.4%) of pooled participants had a TTR of 0–3 months, 4 (8.7%) had a TTR of 3–6 months, and 5 (10.9%) had a TTR of 6–12 months (Figures 4 and 5)
- Similar TTR trends were observed for participants randomized to trofinetide and placebo in LAVENDER (Figure 4)

Figure 4. Pooled TTR Status per RSBQ and by Randomization in LAVENDER



RSBQ, Rett Syndrome Behaviour Questionnaire; **TTR**, time to response.

Figure 5. Pooled TTR Status Per RSBQ



RSBQ, Rett Syndrome Behaviour Questionnaire; **TTR**, time to response.

CONCLUSIONS

Approximately 56.9% of participants of the phase 3 trofinetide clinical trial program who responded to trofinetide by 12 months had a TTR within 3 months, based on CGI-I response criteria; approximately 80.4% had a TTR within 3 months, based on RSBQ response criteria

In turn, approximately 19.6% to 43.1% of participants did not experience onset of trofinetide response until sometime after month 3 of treatment, indicating that some patients may require a longer trofinetide trial period beyond 3 months to ensure proper assessment of efficacy

- These analyses also indicate that caregiver reports are an essential component of evaluating trofinetide efficacy, as caregivers were more likely to detect treatment response in early treatment months as compared with clinicians
- The difference in TTR observed with CGI-I and RSBQ can be attributed to the CGI-I instrument having response criteria built-in, whereas an approximate MCID had to be used for the RSBQ instrument
- Furthermore, the difference in TTR can be explained by the fact that the CGI-I measures global improvement in RTT through time, while the RSBQ measures improvement in individual symptoms of RTT at a specific time
- Finally, the TTR differences could also be explained by the RSBQ instrument being subject to floor and ceiling effects, while the CGI-I instrument is not

Direct comparison between, and pooling across, the group of participants randomized to trofinetide and placebo in LAVENDER should be interpreted with caution, as the first 12 weeks of trofinetide exposure in the participant group randomized to trofinetide in LAVENDER was blinded, whereas the trofinetide exposure in the participant group treated with trofinetide in LILAC/LILAC-2 was open-label