Early Utilization Patterns Among Individuals With Rett Syndrome Receiving Trofinetide After FDA Approval in the United States: A Sub-group Analysis of Individuals From LAVENDER and LILAC Trials

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BACKGROUND

- Trofinetide (TROF) was approved on March 10, 2023, by the FDA in the United States (US) for the treatment of Rett syndrome (RTT) in adult and pediatric patients aged 2 years and older [1-3].
- Patients participating in the 12-week double-blind placebo controlled pivotal trial (LAVENDER [NCT04181723]) were given the option to enroll in two open-label extension trials: 40-week LILAC-1 (NCT04279314) followed by 32-month LILAC-2 (NCT04776746) [4-6]. Due to the FDA approval for TROF during March 2023, LILAC-2 was terminated early.
- Understanding long-term TROF dosing patterns during early post-launch period among LAVENDER and LILAC patients who continued TROF (TROF Continuers) vs. those who did not continue TROF (TROF Non-Continuers) after FDA approval may provide important insights.

OBJECTIVES

- To understand the patient journey and generate post-launch data of TROF Continuers vs. TROF Non-Continuers after LILAC-2 in the real-world setting.

METHODS

Study Design and Data Source

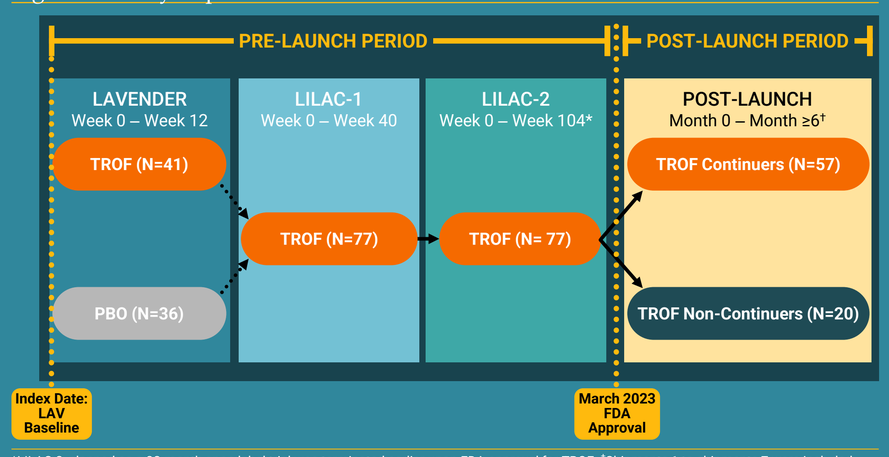
- A descriptive analysis of data from the patients of LAVENDER and LILAC trials linked with TROF prescription (RX) shipments data from a specialty pharmacy database that dispenses TROF RXs nationally in the US.

Study Population

- **Figure 1** shows the eligible study population comprising of patients from all three trials (LAVENDER, LILAC-1 and LILAC-2) who were grouped into:
  - TROF Continuers: those who continued TROF in the real-world setting after FDA approval (post-launch) for ≥6 months (i.e., ~7 TROF shipment/RX fills) with an allowable treatment gap of ≤60 days.
  - TROF Non-Continuers: those who did not continue TROF during the post-launch setting after FDA approval.

METHODS

Figure 1. Study Population



*LILAC-2, planned as a 32-month open-label trial was terminated earlier upon FDA approval for TROF. †Shipments 1 to shipments 7 were included based on available follow-up period at the time of analysis. **LAV**, LAVENDER; **PBO**, placebo; **TROF**, trofinetide.

Schedule of Assessments (Pre-launch & Post-launch)

- Assessments at predetermined time points included the following: pre-launch [LAVENDER (baseline, week 2, week 6, week 12), LILAC-1 (baseline, week 2, week 12, week 26, week 40), LILAC-2 (baseline, week 12, week 52)] for both groups and post-launch (months 0-≥6) for TROF continuers.

Time Periods

- Index Date: TROF or Placebo initiation date (i.e., LAVENDER trial baseline).
- Pre-launch: TROF use during 3 trials (LAVENDER, LILAC-1 and LILAC-2) before FDA approval.
- Post-launch: real-world TROF RX fills using shipment dates from specialty pharmacy database.

Baseline (Demographic and Clinical) Characteristics

- Patient characteristics: age, gender, race, weight (kg), height (cm), and body mass index (BMI, kg/m^2), and clinical comorbidities (e.g., constipation, epilepsy) were examined at index date among both groups.

Study Outcomes [Pre-launch & Post-launch]

- Time on treatment was evaluated among TROF Continuers vs. TROF Non-Continuers.

TROF Dosing Patterns

- Mean BID dose by volume was expressed in mL.
- Mean BID dose by weight was expressed in mg/kg and was calculated by multiplying the administered volume (mL) by 200, since each mL contains 200 mg of drug, and dividing by the individual's weight at the respective visits (pre-launch) or monthly TROF RX shipment date (post-launch).
- Mean percentage target daily dose (%TDD) was calculated as actual dose (mL) received and divided by the label recommended dose (mL), multiplied by 100.

Adverse events (AEs)

- Using the AE reporting definitions of LAVENDER trial, differences in percentage of patients with AEs (severity [mild, moderate, severe]) during LILAC-2 between the two groups were identified.
- To summarize the AE data, if a patient reported the same AE of varying severity at different visits during LILAC-2, then the patient was assumed to have the highest reported AE severity, and we counted this one for the analyses.

Statistical Analysis

- All continuous variables were reported as mean (SD) and categorical variables were reported as frequences and percentages, n (%).
- Time on TROF treatment was summarized as mean (range) in years and days while dose was shown by mean (volume, weight, % target daily dose [TDD]) at each schedule of assessment.

RESULTS

- Of the 77 patients [LILAC-2] who were included in this analysis, 74% (n=57) were categorized as TROF Continuers vs. 26% (n=20) were TROF Non-Continuers during post-launch (**Figure 1**).
  - Forty-one (53.2%) patients were on TROF during LAVENDER and 36 (46.8%) patients were on PBO during LAVENDER.

Patient Characteristics

- Mean age (SD) among TROF Continuers vs. TROF Non-Continuers was similar: 10.5 (4.4) vs. 11.9 (4.1) years, respectively; majority were White (89.5% vs. 100%) in both groups (**Table 1**).
- TROF Continuers vs. TROF Non-Continuers reported the following rates of comorbidities at index date: constipation (71.9% vs. 65.0%), GERD (45.6% vs. 25.0%), scoliosis (40.4% vs. 50.0%), and epilepsy (31.6% vs. 20.0%).

Study Outcomes [Pre-launch & Post-launch]

- During the pre-launch period, mean (range) time on TROF treatment was 2.2 yrs (1.6-2.9); [801 days (567–1051)] among TROF Continuers vs. 1.7 yrs (0.8-3.3); [625 days (310–1190)] among TROF Non-Continuers.
- In the post-launch period, all TROF Continuers remained on treatment for at least 6 months, with a mean (range) time on treatment of 0.5 yrs (0.4-0.9); [196 days (139–321)].

TROF Dosing Patterns

- Among TROF Continuers, mean dose by volume decreased from index date to week 52 of LILAC-2 (40.9 mL to 36.6 mL) and increased to 39.8 mL for the first RX in the post-launch setting; this remained stable thereafter (~40.0 mL). On the other hand, mean dose by volume fluctuated during the pre-launch period, from index date to end of LILAC-2, among TROF Non-Continuers (**Figure 2**).
- Similar trend was observed with mean dose by weight in both groups (**Figure 3**).
- During pre-launch, the mean %TDD decreased from index date (99.7% vs. 99.0%) to week 12 of LILAC-2 (84.6% vs. 85.9%) in both TROF Continuers and TROF Non-Continuers, respectively (**Figure 4**).
- During the post-launch setting, mean %TDD was 92.7% at shipment 1 and slightly decreased to 91.5% by shipment 7 (**Figure 4**).

Adverse Events

- **Table 2** provides the details of AEs stratified by severity during LILAC-2 for both TROF Continuers and TROF Non-Continuers.
- During LILAC-2, TROF Continuers had higher rates of COVID-19 (28.1% vs. 20.0%), diarrhea (19.3% vs. 10.0%), UTI (17.6% vs. 10.0%), and URTI (15.8% vs. 0.0%); however, TROF Non-Continuers had higher rates of vomiting (7.0% vs. 35.0%), pyrexia (14.0% vs. 25.0%), and constipation (20.0% vs. 8.8%).
- Diarrhea, URTI, pyrexia, seizures and constipation events were of mild to moderate severity; with no severe cases observed among patients in both, TROF Continuers and TROF Non-Continuers, for these specific events.

Table 1. Patient Demographics and Clinical Characteristics [LAVENDER]*

	TROF Continuers (n = 57)	TROF Non-Continuers (n = 20)
Mean (SD) Age, years	10.5 (4.4)	11.9 (4.0)
Female, n (%)	57 (100.0%)	20 (100.0%)
Race, n (%)		
White	51 (89.5%)	20 (100.0%)
Black or African American	1 (1.7%)	0 (0.0%)
Asian	1 (1.7%)	0 (0.0%)
Other	4 (7.0%)	0 (0.0%)
Mean (SD) Height, cm	126.9 (16.3)	133.1 (13.2)
Mean (SD) Weight, kg	29.5 (11.0)	31.9 (8.5)
Mean (SD) BMI, (kg/m^2)	17.5 (3.1)	17.4 (3.9)
Comorbidities, n (%)		
Constipation	**43 (75.4%)**	13 (65.0%)
GERD	**26 (45.6%)**	5 (25.0%)
Scoliosis	23 (40.4%)	**10 (50.0%)**
Seizure	**20 (35.1%)**	8 (40.0%)

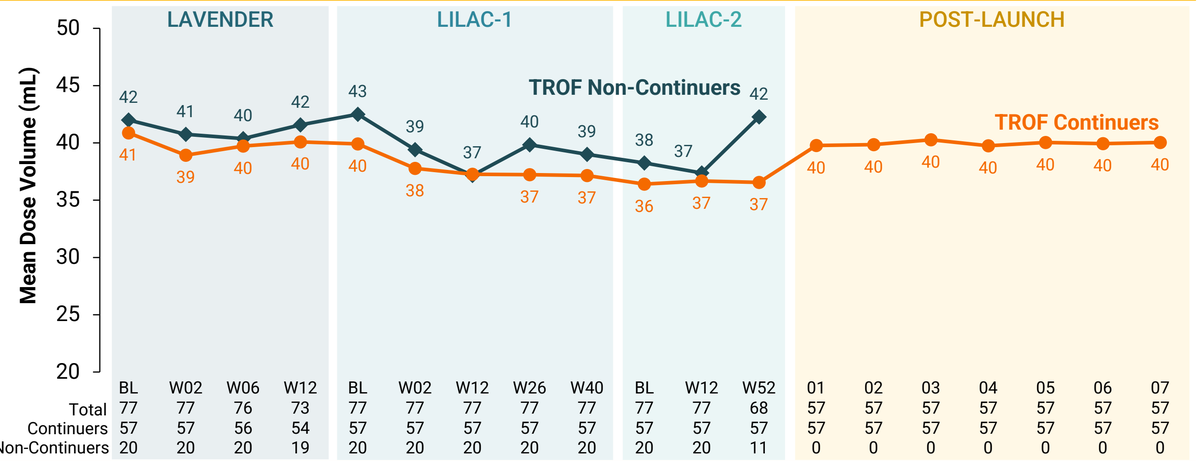
*At LAVENDER baseline. **GERD,** gastroesophageal reflux disease; **SD,** standard deviation.

Table 2. AEs Stratified by Severity during LILAC-2

n (%)	Mild	Moderate	Severe	Total
TROF Continuers (n = 57)				
Covid-19	12	4	0	**16 (28.0%)**
Diarrhea	8	3	0	**11 (19.3%)**
UTI	6	3	1	**10 (17.6%)**
URTI	9	0	0	**9 (15.8%)**
Pyrexia	5	3	0	8 (14.1%)
Seizure	5	3	0	8 (14.1%)
Influenza	4	1	1	**6 (10.6%)**
Constipation	2	3	0	5 (8.8%)
Pharyngitis streptococcal	5	0	0	**5 (8.8%)**
Pneumonia	2	3	0	**5 (8.8%)**
Vomiting	3	1	0	4 (7.1%)
TROF Non-Continuers (n = 20)				
Covid-19	3	1	0	4 (20.0%)
Diarrhea	1	1	0	2 (10.0%)
UTI	1	1	0	2 (10.0%)
URTI	0	0	0	0 (0.0%)
Pyrexia	2	3	0	**5 (25.0%)**
Seizure	0	3	0	3 (15.0%)
Influenza	0	0	1	1 (5.0%)
Constipation	3	1	0	**4 (20.0%)**
Pharyngitis streptococcal	0	1	0	1 (5.0%)
Pneumonia	0	0	0	0 (0.0%)
Vomiting	5	1	1	**7 (35.0%)**

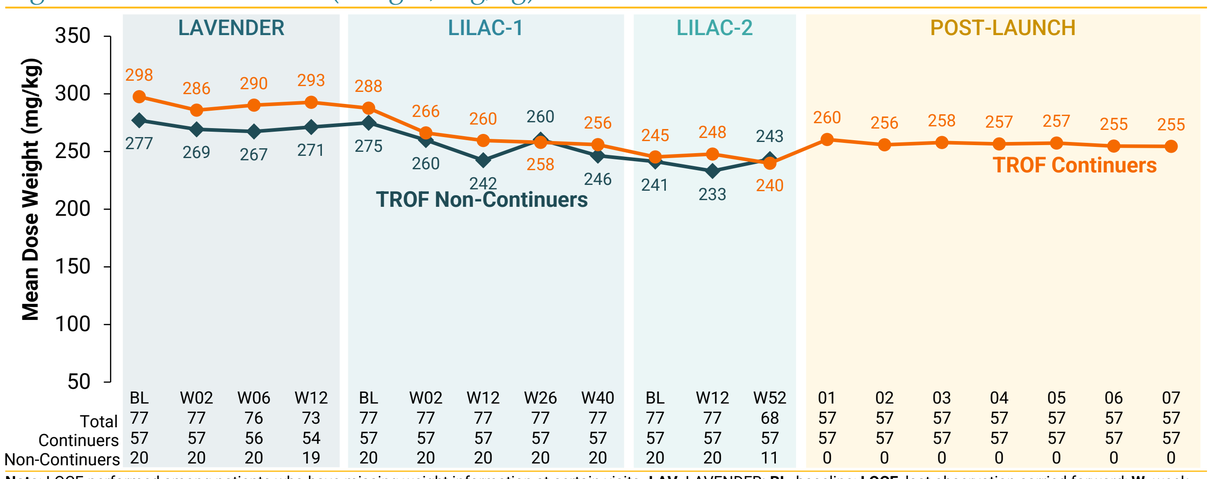
Note: Only top 10 most frequently occurring AEs were reported. **UTI,** urinary tract infection; **AE,** adverse event; **URTI,** upper respiratory tract infection.

Figure 2. Mean BID Dose (Volume, mL)



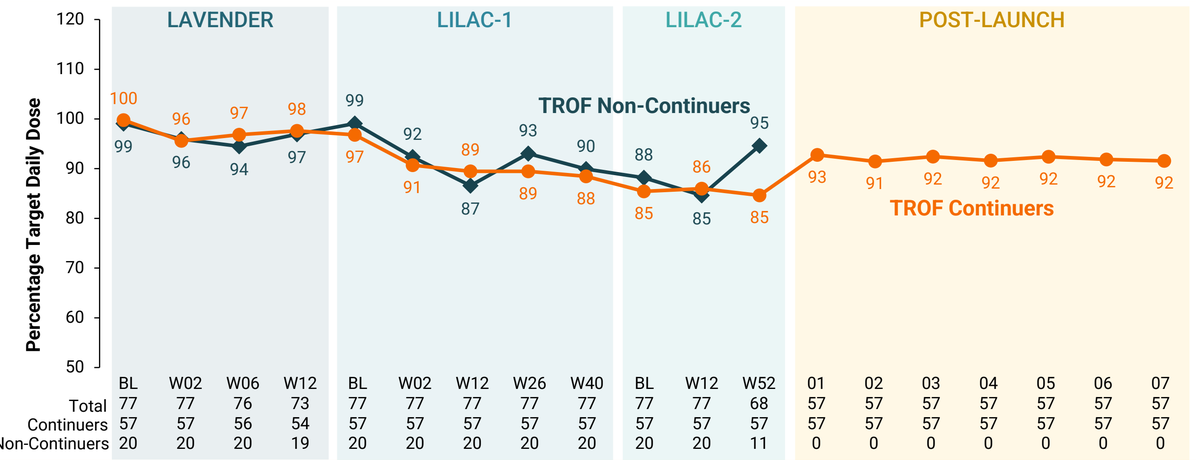
LAV, LAVENDER; **BL,** baseline; **W,** week.

Figure 3. Mean BID Dose (Weight, mg/kg)



Note: LOCF performed among patients who have missing weight information at certain visits**. LAV,** LAVENDER; **BL,** baseline; **LOCF**, last observation carried forward; **W,** week.

Figure 4. Mean Percentage Target Daily Dose



Note: LOCF performed among patients who have missing weight information at certain visits. **LAV,** LAVENDER; **BL,** baseline; **LOCF**, last observation carried forward; **W,** week.

CONCLUSIONS

- **This is the first analysis to demonstrate the characteristics and long-term dosing patterns of TROF Continuers from pre-launch clinical trial setting through post-launch (>3 years) real-world setting.**
- **Approximately three-quarters (74.0%) of patients continued TROF post-launch, suggesting TROF persistence following clinical trial participation among the real-world setting.**
- **The mean dose in volume (mL) was similar among TROF Continuers vs. TROF Non-Continuers, however, during pre-launch period, TROF Non-Continuers exhibited more fluctuation with their dosages.**
- **Despite the higher rates of AEs during LILAC-2 among TROF Continuers, all of them persisted on TROF therapy and continued TROF during post-launch for ≥6 months which is suggestive of a balanced tolerability-efficacy profile for TROF. Additionally, TROF Continuers had higher baseline comorbidity burden.**
- **Further real-world studies with longer follow-up are being conducted to demonstrate the value of TROF use among all patients as well as among male individuals with RTT and adult individuals with RTT (>20 years of age) to inform the RTT community.**

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DISCLOSURES

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