

Trofinetide Use and Treatment Patterns Among Children Aged 2–4 Years with Rett Syndrome in the United States: A Retrospective Specialty Pharmacy Linked Claims Database Analysis

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Introduction: Rett syndrome (RTT) is a rare, X-linked neurodevelopmental disorder that primarily affects females. Trofinetide (TROF) was approved for RTT in individuals aged ≥ 2 years. Although the DAFFODIL trial examined TROF efficacy in children aged 2–4 years, real-world evidence in this age group remains limited.

Methods: A retrospective cohort study was conducted using linked medical and pharmacy claims from 01/01/2021–09/30/2024 (study period). Individuals aged 2–4 years with RTT who initiated TROF during 04/01/2023–03/31/2024 (identification period) were included (index date=first TROF RX). Outcomes included baseline characteristics, prescriber specialty, TROF persistence (≤ 90 -day allowable gap), dosing patterns based on shipped/dispensed RXs (BID, mg; % target daily dose [%TDD]), time on treatment, and restarts among non-persistent individuals. Variables were summarized descriptively. Kaplan–Meier analyses assessed the time to treatment non-persistence.

Results: Among 159 individuals, 65.4% were persistent and 34.6% were non-persistent; 14.5% of non-persistent individuals restarted TROF. Mean $\pm$ SD age was 3.2 $\pm$ 0.8 vs 3.3 $\pm$ 0.7 years in persistent vs non-persistent groups. Females comprised 95.2% vs 87.3%, respectively. Child neurology was the most common prescriber specialty (54.8% vs 63.6%). Non-persistent individuals had higher rates of dysphagia (34.5% vs 16.3%), gastrostomy (20.0% vs 3.8%), and breathing irregularities (16.4% vs 1.9%). Mean BID dose and %TDD were similar between groups across shipments. Median (IQR) time on treatment was 13.3 (6.1–17.2) months in the persistent group vs 4.4 (0.8–12.6) months in the non-persistent group. Kaplan–Meier analysis showed >87.5% remained on TROF beyond 3 months and >65.0% remained on TROF through end of available follow-up.

Conclusion: In routine US practice, approximately two-thirds of children aged 2–4 years initiating TROF remained persistent during available follow-up, with sustained use beyond 1 year and a subset (14.5% of non-persistent children) restarting after discontinuation. Non-persistent children had significantly higher baseline rates of dysphagia, gastrostomy, and breathing irregularities, suggesting that early disease-related multisystem complications may be associated with reduced treatment continuity. These findings complement DAFFODIL and provide early real-world evidence on TROF persistence, restarts, and dosing patterns in this young RTT population.

Plain Language Summary:

Why was the study done?

Rett syndrome is a rare genetic disorder that impacts brain development, primarily in young girls. In March 2023, the drug trofinetide became the first approved treatment for this condition in the United States. While clinical trials showed the drug is safe and effective for young children aged 2 to 4, doctors and families need real-world evidence to see how well children stick with the treatment in everyday life outside of strict trial settings.

What did the researchers do and find?

We analyzed health insurance and pharmacy data for 159 children aged 2 to 4 with Rett syndrome who started trofinetide between April 2023 and March 2024. We looked at how long they stayed on the medication, their daily dosages, and whether those who stopped eventually restarted.

Our study revealed that:

- Two-thirds of the children (65.4%) successfully stayed on their trofinetide treatment continuously for over a year.
- Children who stopped taking the medication usually did so around the 4-month mark. However, about 14.5% of those children eventually restarted the drug after a break.
- Children who stopped the medication had higher rates of other health issues before starting, such as stomach problems and seizures, compared to those who stayed on it.

What do these results mean?

Real-world data shows most young children with Rett syndrome stay on trofinetide long-term. Since those with more pre-existing health issues often stop treatment, doctors can use this information to closely support high-risk patients.

Keywords: rett syndrome, children, trofinetide, treatment patterns

Introduction

Rett syndrome (RTT) is a rare, debilitating X-linked neurodevelopmental disorder that primarily affects females. A recent global systematic review and meta-analysis estimated a worldwide birth prevalence of approximately 1 in 10,000–15,000 female live births.¹ RTT can also occur, less commonly, among males. A US real-world evidence study estimated an annual prevalence of approximately 0.08 to 0.10 per 10,000 in males between 2017 and 2019.^{1,2} RTT impairs neurologic function, with neurodevelopmental regression beginning around 6–18 months of age.³ This regression is characterized by loss of purposeful hand use and verbal communication as well as limited nonverbal skills, impaired motor skills, seizures, and behavioral and gastrointestinal issues.¹

Trofinetide (TROF) is a synthetic analog of glycine-proline-glutamate, the N-terminal tripeptide of insulin-like growth factor 1 (IGF-1), administered orally as a weight-based, twice-daily oral solution.⁴ In March 2023, TROF became the first and only FDA approved therapy in the United States (US) for RTT, based on the significant clinical benefit demonstrated in LAVENDER, LILAC, and DAFFODIL trials.^{4–8} All studies in the TROF clinical program including the 12-week, randomized, double-blind, placebo-controlled, Phase 3 LAVENDER trial among females aged 5 to 20 years;⁵ the 40-week LILAC-1,⁶ and the 32-month LILAC-2 open-label extension trials of LAVENDER have been conducted to support the efficacy and safety of TROF in RTT.⁷ In addition, an open-label Phase 2/3 DAFFODIL trial was conducted among fifteen 2–4-year-old females with RTT,⁸ to inform TROF dosing recommendations and evaluate its long-term safety, tolerability, and efficacy since RTT is commonly diagnosed at a median age of 2.7 years.⁹ Given the heterogeneous nature of RTT, it should be noted that all eligible participants in the LAVENDER trial were required to be at least in the 6-months post-regression phase, while participants in the DAFFODIL were allowed to be in the active regression phase or less than 6-months post-regression phase to ensure that patients in active or nonactive regression phases were studied. DAFFODIL results show that TROF had acceptable tolerability for up to 78 weeks and the safety results were consistent with the 12-week LAVENDER study and the 40-week LILAC-1 trials.^{5–8} The prescribed dosing in DAFFODIL also achieved the target exposure and was similar to the range of exposure reported in pediatric and adult participants with RTT from the LAVENDER study.^{5,8}

Given the small sample size, as well as the absence of males in the DAFFODIL trial, there is an unmet need for the RTT clinical community and caregivers to learn about TROF use among a large sample of patients aged 2–4 years (ie, females and males) in the post-launch setting. Therefore, this analysis examines the real-world demographic/clinical characteristics, dosing/titration patterns of TROF among children aged 2–4 years old in the US. Treatment persistence, generally defined as patients remaining on therapy over time without a clinically meaningful interruption, is an important real-world measure of treatment continuity and may be a reflection of multiple factors including treatment efficacy, safety, tolerability as well as dose titration issues, preference, and acceptability. In young children with RTT, multisystem complications, including gastrointestinal and respiratory complications, may further complicate medication administration and continuity of care, supporting the need to evaluate TROF persistence in routine clinical practice. Furthermore, this analysis was intended to expand our understanding of TROF's real-world treatment persistence and dosing patterns following TROF availability in routine clinical practice in the post-launch setting after the end of DAFFODIL trial.

Methods

Study Design and Data Source

A retrospective cohort analysis of claims was conducted using deidentified, tokenized, patient-level data from 01/01/2021 through 09/30/2024 (ie, study period). The tokenized data was an integration of linked medical and pharmacy claims from two data sources: IQVIA's Anonymized Patient Level Data and specialty-pharmacy data with TROF prescription (RX) shipment information. Linkage was performed using deidentified patient tokens generated before analytic access, and the analytic dataset did not contain direct patient identifiers or protected health information. IQVIA claims data is an open-source, administrative data that includes pre-adjudicated, de-identified healthcare claims information of over 130 million beneficiaries in the United States. It provided information about demographic characteristics, insurance enrollment information, as well as medical diagnostic and health care procedural claims. On the other hand, the specialty-pharmacy data provided information on patients who received a prescription for TROF along with dates of TROF shipment, information of prescription (RX, dose) claims, prescriber specialty, and shipment information. Data from the IQVIA and specialty pharmacy databases were obtained through a third-party vendor engaged on behalf of the study sponsor in accordance with applicable data use agreements and the Health Insurance Portability and Accountability Act (HIPAA). This was to ensure the privacy and security of all protected health information (PHI), with the overall study conducted in compliance with the ethical principles of the Declaration of Helsinki. Since the study involved de-identified, anonymized, patient-level secondary data without any identifiable PHI, patient consent was not required and the need for ethics committee approval was not applicable.

Study Population

Individuals aged 2–4 years with RTT (ICD-10-CM: F84.2) from the tokenized database during the study period were included. Eligible individuals who had a TROF RX during 04/01/2023 to 03/31/2024 (patient identification period) were included in the study. The index date was defined as the first TROF RX date during the patient identification period. Furthermore, the final study cohort was required to have ≥ 6 months of continuous enrollment during pre-index and ≥ 6 months of continuous enrollment during post-index. Patient baseline characteristics were evaluated during pre-index period and study outcomes were evaluated during post-index (Figure 1). The final study sample of 2–4-year-olds were categorized into TROF continuers (persistent) and TROF non-continuers (non-persistent).

Study Outcomes

The study outcomes among the two groups (persistent vs non-persistent) included baseline characteristics, prescriber specialty/provider type, TROF persistency rates, TROF dosage patterns, and time on TROF treatment. Additionally, we examined any individuals who restarted TROF among the non-persistent group and the time to restart.

Baseline demographics and clinical characteristics included age, gender, region, insurance type, selected differential diagnoses, and comorbidities during pre-index period. The comorbidities, selected pre-index diagnoses, and RTT-related clinical characteristics were identified using ICD-10-CM diagnosis codes in medical claims; prescriber specialty/provider

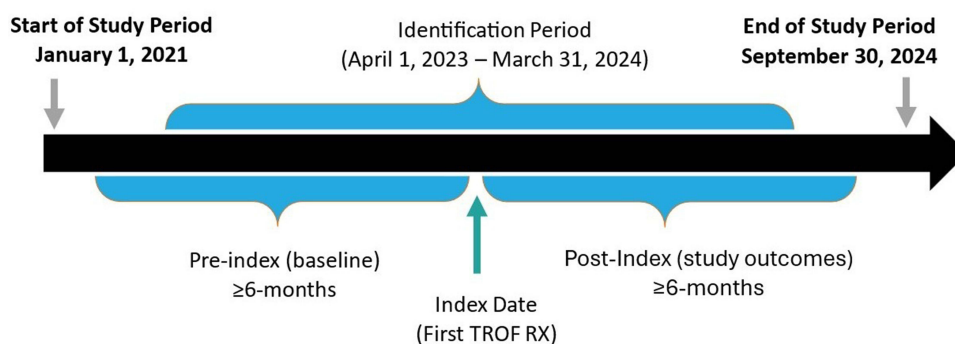


Figure 1 Study Design and Study Population.

Abbreviations: TROF, Trofinetide; RX, Prescription.

type was identified for those who were linked closest to the first TROF RX pharmacy claim. Treatment persistence was calculated using TROF RX shipment dates and days' supply, with an allowable treatment gap of ≤ 90 days between RX shipments after the expected end of days' supply. The persistent group was defined as the proportion of individuals on continuous TROF treatment with an allowable treatment gap of ≤ 90 days; and the non-persistent group was defined as the proportion of individuals with no TROF RX refill within the allowable treatment gap of ≤ 90 days. Among non-persistent individuals, those who had a TROF RX shipment after a >90 -day treatment gap was defined as restarts, while those without a TROF RX shipment after the >90 -day gap through the end of available follow-up were deemed to have discontinued TROF.

Analysis of dosage patterns were conducted on all individuals with TROF RX; and TROF dose was calculated as twice daily dose (BID) in milligrams (mg) and as percentage target daily dose (%TDD). In this analysis, TROF RX refers to TROF prescriptions that were shipped/dispensed and recorded in the specialty-pharmacy shipment data. To examine titration patterns (a dose change between RXs), we required individuals to have ≥ 2 TROF RXs where changes of dose could be examined between TROF RX fills. The dispensed dose was calculated as (number of bottles shipped per prescription $\times$ 450 mL per bottle). This dose was converted to total drug amount (mg) using the TROF concentration (200 mg/mL) and divided by the prescription days' supply to estimate the daily dose (mg/day); the daily dose was then divided by 2 to derive the BID dose (mg per dose). The mean %TDD was calculated as [actual daily dose (mL) received] / [target daily dose based on patient's weight from the label at shipment transaction] $\times$ 100. Label dose was estimated based on TROF package insert (weight-based dosing). Time on TROF treatment was calculated from index date to the date of non-persistence or the end of available follow-up or end of study time period (09/2024), whichever occurred first.

Statistical Analysis

Continuous variables were reported as mean, standard deviation (SD), median, interquartile range (IQR); categorical variables were reported as frequencies and percentages, n (%). The monthly TROF dose was shown by mean (volume [mg], % TDD) from TROF RX shipment data. Titration/dose change was reported as any change in dose (mg) between the TROF RX shipments. A Kaplan Meier analysis was used to estimate time to non-persistence, defined as a >90 -day treatment gap after the expected end of days' supply. Individuals without observed non-persistence were censored at the end of available follow-up or end of the study period, whichever occurred first. Between-group comparisons were conducted using chi-square or Fisher's exact tests ($n < 5$) for categorical variables, as appropriate based on cell counts, and t -tests or Wilcoxon rank-sum tests for continuous variables, as appropriate based on distributional assumptions. Statistical significance was determined using p -value < 0.05 . All statistical analyses were conducted using Anlitiks proprietary RapidAnalyzer™ analytic platform powered by R Studio. We used the STROBE reporting guideline to draft this manuscript, and the STROBE reporting checklist when editing, included in [Supplementary Table 1](#). Direct patient or public involvement in the study design, conduct, or dissemination was not feasible or appropriate for this research.

Results

A total of 1535 individuals with RTT and at least 1 TROF Rx were identified during the study period between 01/01/2021 to 09/30/2024. Over 13% ($n=203/1535$) of them were between the ages of 2–4 and 87% ($n=1331/1535$) were >4 years of age at TROF initiation. After additional exclusion criteria were applied, we identified 159 2–4-year-old individuals with RTT on TROF for the analysis ([Figure 2](#)). After applying the persistency calculation, two treatment groups based on persistence status were formed: 65.4% ($n=104$) as persistent and 34.6% ($n=55$) were non-persistent. Of those in the non-persistent group, 14.5% ($n=8$) restarted TROF ([Figure 2](#)).

Baseline Characteristics, Prescriber Specialty/Provider Type, and Comorbidities

In this study of a population of 2–4-year-olds on TROF, the mean (SD) age at baseline was similar for the persistent vs non-persistent group: 3.2 (0.8) vs 3.3 (0.7) years ([Table 1](#)). While the persistent group had 4.8% males, the non-persistent group had a higher proportion of males (12.7%) ([Table 1](#)). Approximately 40% of the persistent group resided in the South of the US, while similar proportion in the non-persistent group resided in the Midwest ([Table 1](#)). The most common prescriber

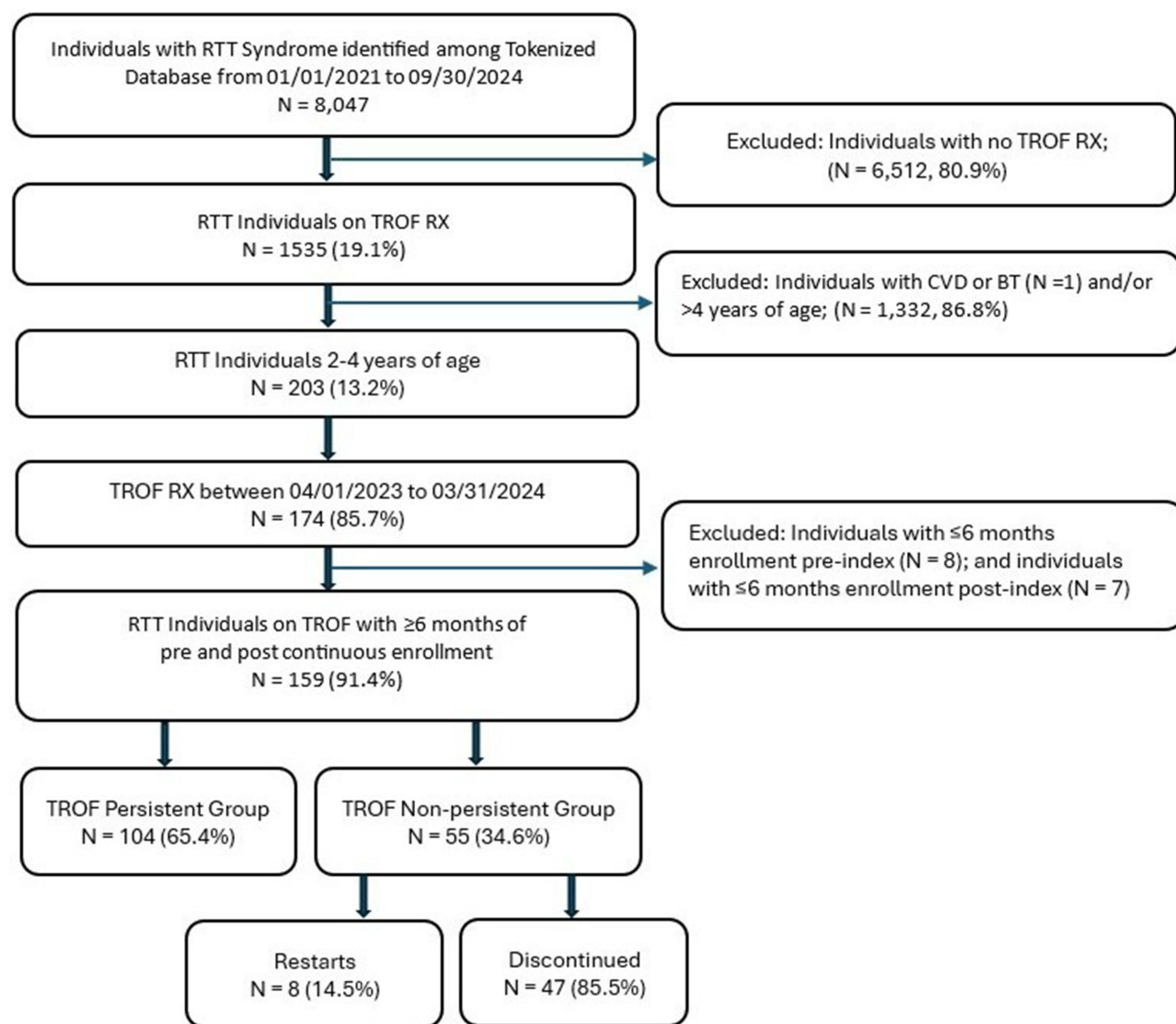


Figure 2 Cohort Attrition Flow Diagram.

Abbreviations: RTT, Rett syndrome; RX, Prescription; TROF, Trofinetide.

specialty/provider types in the persistent vs non-persistent group were child neurology (54.8% vs 63.6%), pediatrics (11.5% vs 14.5%), and nurse practitioners (9.6% vs 5.5%) (Table 1). Both persistent and non-persistent groups appeared to have higher rates of differential diagnosis prior to RTT diagnosis: non-specific developmental delays (48.1% vs 61.8%) followed by autism spectrum disorder (25.0% vs 27.3%) and cerebral palsy (4.8% vs 7.3%).

Overall, the persistent group had numerically lower rates of concomitant baseline comorbidities vs the non-persistent group (Table 2). Additionally, fewer patients in the persistent group reported pre-index gastrointestinal disorders, infections/viruses, scoliosis, neurological disorders (epilepsy, convulsion), and respiratory failure compared to those in the non-persistent group (Table 2). The RTT clinical features are also shown in Table 2, where a higher proportion of non-persistent patients had RTT-related symptoms compared with persistent patients.

Dosage Patterns of Trofinetide

The mean dispensed BID dose in mg was similar among the persistent and non-persistent group (Figure 3). The initial mean TROF RX BID dose was 5182.0 mg vs 5127.7 mg and increased to 5576.1 mg vs 5519.3 mg at TROF RX2 and remained similar across all the shipments during post-index. The mean %TDD was also similar among both the groups (Figure 4). The mean %

Table 1 Baseline Demographics and Characteristics

	Total	Persistent	Non-Persistent	p-value
	(n=159)	(n=104)	(n=55)	
Age at TROF Index Date (years)				
Mean (SD)	3.3 (0.8)	3.2 (0.8)	3.3 (0.7)	0.53
Median (IQR)	3 (1)	3 (1)	3 (1)	
Gender, n (%)				
Female	147 (92.5)	99 (95.2)	48 (87.3)	0.14
Male	12 (7.5)	5 (4.8)	7 (12.7)	0.14
Region, n (%)				
South	57 (35.8)	42 (40.4)	15 (27.3)	0.14
Midwest	51 (32.1)	30 (28.8)	21 (38.2)	0.31
West	22 (13.8)	13 (12.5)	9 (16.4)	0.67
Northeast	9 (5.7)	6 (5.8)	3 (5.5)	1.00
Unknown/Unspecified	20 (12.6)	13 (12.5)	7 (12.7)	1.00
Insurance Plan Type, n (%)[^]				
Third Party	126 (79.2)	84 (80.8)	42 (76.4)	0.66
Medicaid	19 (11.9)	9 (8.7)	10 (18.2)	0.13
Physician Specialty/Provider Type, n (%)				
Child Neurology	92 (57.9)	57 (54.8)	35 (63.6)	0.37
Pediatrics	20 (12.6)	12 (11.5)	8 (14.5)	0.77
Nurse Practitioner	13 (8.2)	10 (9.6)	3 (5.5)	0.54
Clinical Neurophysiology	8 (5.0)	7 (6.7)	1 (1.8)	0.26
Medical Genetics	8 (5.0)	7 (6.7)	1 (1.8)	0.26
Neurology	6 (3.8)	6 (5.8)	0 (0.0)	0.18
Other specialty*	12 (7.5)	8 (7.7)	7 (12.7)	0.39
Differential Diagnosis, n (%)				
NSDD	84 (52.8)	50 (48.1)	34 (61.8)	0.14
ASD	41 (25.8)	26 (25.0)	15 (27.3)	0.90
Cerebral palsy	9 (5.7)	5 (4.8)	4 (7.3)	0.50

Notes: *Other physician specialties/provider types were sleep medicine, developmental/behavioral pediatrics, neurodevelopmental disabilities, psychiatry, internal medicine. [^]Other insurance plan types were either cash (3.1%) or unknown (5.7%) of the total patients.

Abbreviations: ASD, Autism spectrum disorder; IQR, Inter-quartile range; RTT, Rett syndrome; SD, Standard deviation; TROF, Trofinetide; NSDD, Non-specific developmental delay.

TDD for TROF RX 1 among persistent vs non-persistent groups was 89.6% vs 87.7%, respectively; there was an increase in mean %TDD at TROF RX 2 for both the groups at 96.4% vs 94.7%; furthermore, both groups remained similar across all the shipments during post-index. Among those with at least 2 RXs (n=149), 39.6% (n=59) likely underwent dose titration and 60.4% (n=90) did not; approximately 72.9% (43/59) of those that underwent titration were in the persistent group. The titration (a dose

Table 2 Baseline Comorbidities and Rett Syndrome Related Clinical Characteristics

	Total	Persistent	Non-persistent	p-value
	(N=159)	(N=104)	(N=55)	
Comorbidities				
Gastrointestinal disorders, n (%)				
Dysphagia	36 (22.6)	17 (16.3)	19 (34.5)	<0.05
Constipation	25 (15.7)	13 (12.5)	12 (21.8)	0.19
Gastroesophageal reflux disorder	16 (10.1)	8 (7.7)	8 (14.5)	0.28
Vomiting	10 (6.3)	6 (5.8)	4 (7.3)	0.74
Gastrostomy	15 (9.4)	4 (3.8)	11 (20.0)	<0.05
Infections/Viruses, n (%)				
Upper respiratory tract infection	25 (15.7)	16 (15.4)	9 (16.4)	1.00
Fever	14 (8.8)	9 (8.7)	5 (9.1)	1.00
Lower respiratory tract infection	11 (6.9)	5 (4.8)	6 (10.9)	0.27
COVID-19	10 (6.3)	5 (4.8)	5 (9.1)	0.47
Neurological disorders, n (%)				
Epilepsy	27 (17.0)	13 (12.5)	14 (25.5)	0.06
Seizures	17 (10.7)	10 (9.6)	7 (12.7)	0.74
Respiratory Disorders, n (%)				
Cough	17 (10.7)	13 (12.5)	4 (7.3)	0.42
Aspiration	17 (10.7)	12 (11.5)	5 (9.1)	0.84
Rett Syndrome Related Characteristics				
Growth/Nutritional disorders, n (%)				
Nutritional deficiency	17 (10.7)	7 (6.7)	10 (18.2)	0.05
Growth abnormalities*	9 (5.7)	4 (3.8)	5 (9.1)	0.28
Neurodevelopmental disorders, n (%)				
Loss of acquired communication skills	48 (30.2)	33 (31.7)	15 (27.3)	0.69
Development progress delayed	31 (19.5)	20 (19.2)	11 (20.0)	1.00
Weakness/paralysis	25 (15.7)	20 (19.2)	5 (9.1)	0.15
Loss of acquired motor skills	34 (21.4)	19 (18.3)	15 (27.3)	0.27
Sleep dysfunction	13 (8.2)	9 (8.7)	4 (7.3)	1.00
Behavioral disorders/disturbance symptoms**	13 (8.2)	8 (7.7)	5 (9.1)	1.00
Respiratory Disturbances, n (%)				
Breathing irregularities	11 (6.9)	2 (1.9)	9 (16.4)	<0.05

Notes: *ie, underweight, short stature; ** ie, irritability, aggressive behavior, crying tantrums, self-mutilation, scratching, biting. All comorbidities and RTT-related clinical characteristics were identified using ICD-10-CM diagnosis codes.



Figure 3 Mean Twice Daily (BID) Dose (mg) among Persistent versus Non-Persistent Individuals.
Notes: The proportion of persistent and non-persistent individuals was shown only for the first 12 Shipments. The dispensed dose was calculated as (number of bottles shipped per prescription × 450 mL per bottle). This dose was converted to total drug amount (mg) using the TROF concentration (200 mg/mL) and divided by the prescription days' supply to estimate the daily dose (mg/day); the daily dose was then divided by 2 to derive the BID dose (mg per dose).
Abbreviations: BID, Twice daily; mg, Milligram; RX, Prescription.

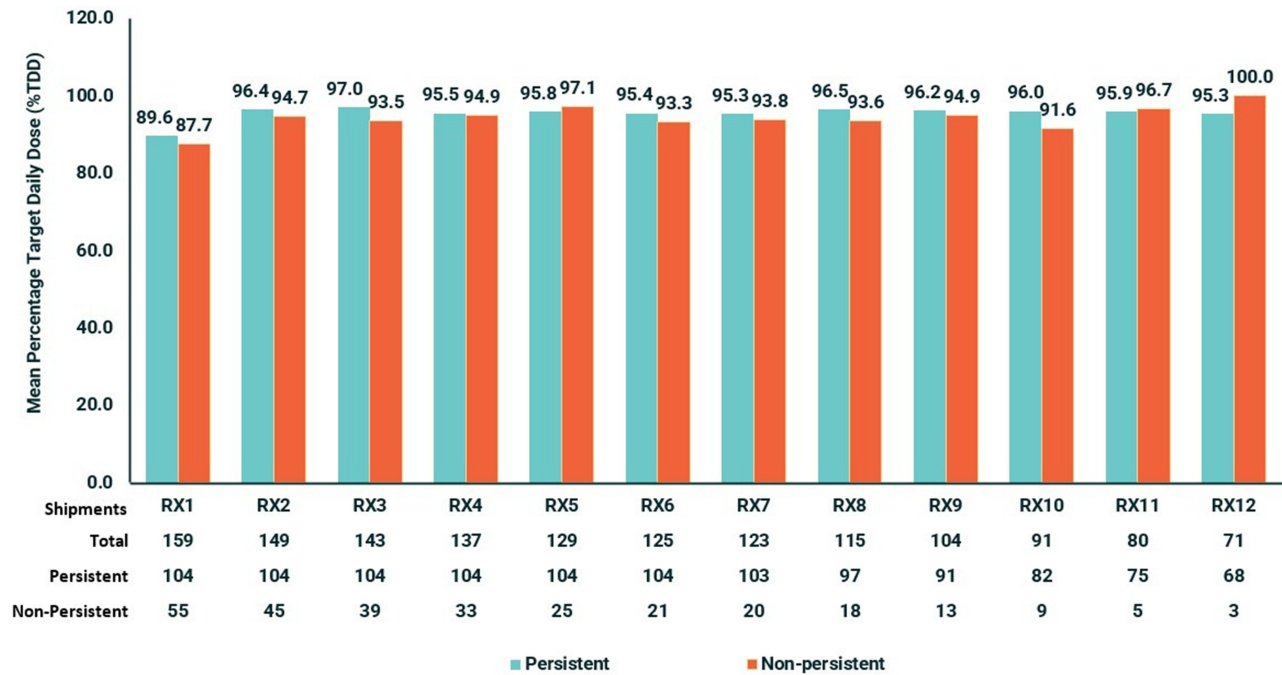


Figure 4 Mean Percentage Target Daily Dose (%TDD) among Persistent versus Non-Persistent Individuals.
Note: The proportion of persistent and non-persistent individuals were shown only for the first 12 Shipments.
Abbreviations: RX, Prescription; TDD, Target daily dose.

change) was seen primarily between the first two RXs between the two groups, where persistent vs non-persistent had ~1000 mg increase (940 mg vs 1140 mg) from TROF RX 1 to TROF RX 2 (Figure 5). Overall, the persistent group was able to reach a steady individual TROF dose with minimal fluctuations in dose across shipments.

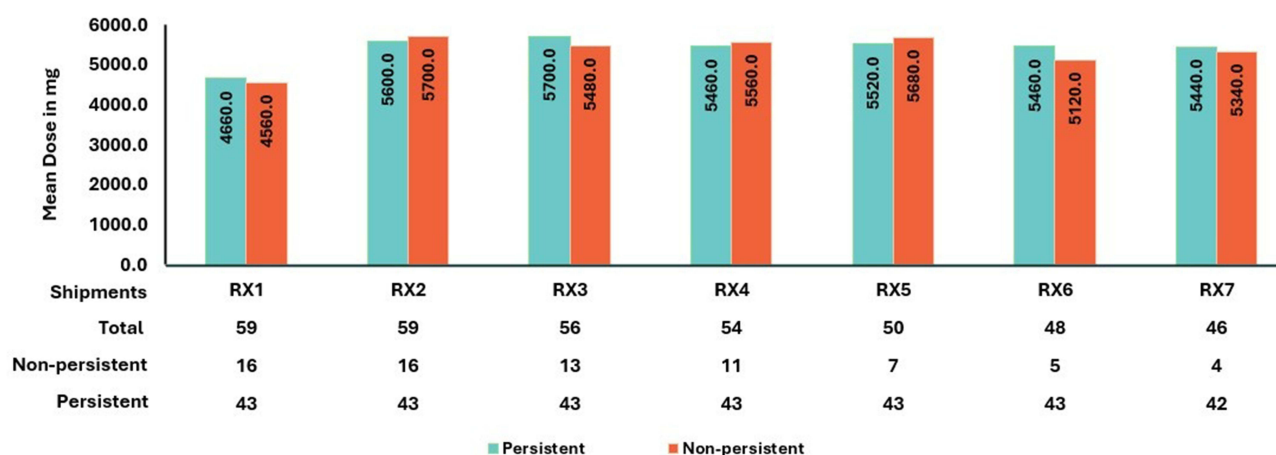


Figure 5 Dose Differences Among Titrated Patients by Persistency Status (n=59).

Note: The proportion of persistent and non-persistent individuals and titration were shown only for the first 7 Shipments.

Abbreviations: RX, Prescription; mg, Milligram.

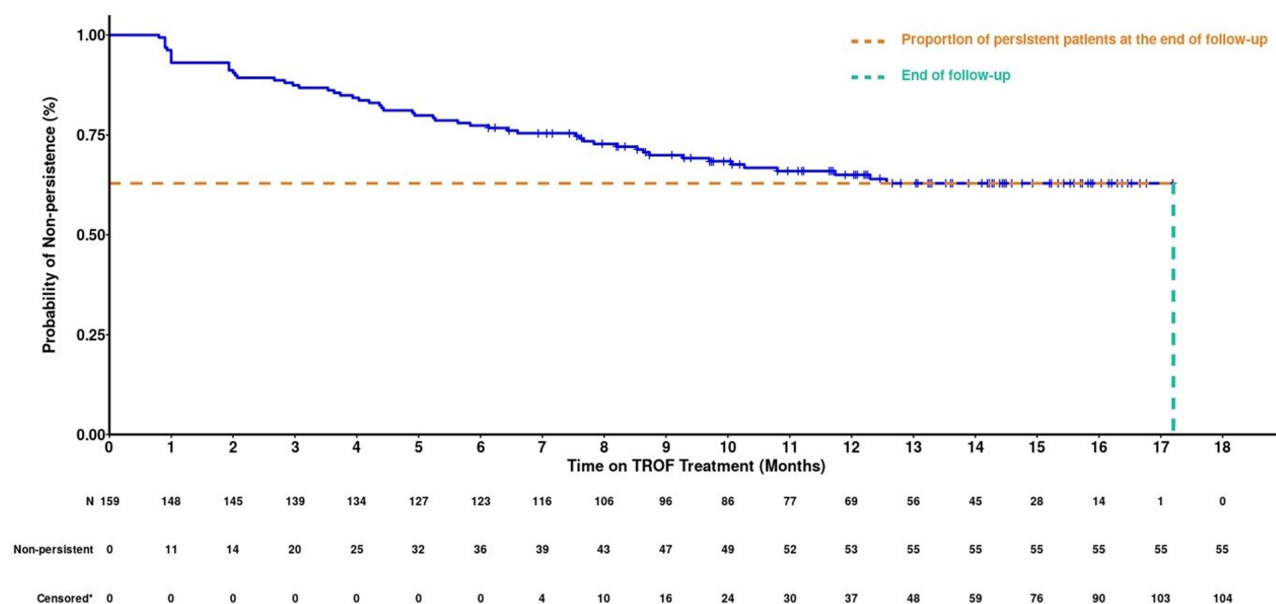


Figure 6 Time on Treatment among Rett Individuals with Trofinetide - Kaplan Meier Curve.

Note: *Individuals were censored at the date of last available TROF RX claim + end of days supply or end of follow-up or end of study period, whichever occurred first.

Abbreviation: TROF, Trofinetide.

Time on Trofinetide Treatment

The median (IQR) months on TROF for persistent vs non-persistent groups were 13.3 (6.1–17.2) months and 4.4 (0.8–12.6) months, respectively. The Kaplan Meier analysis showed that >87.5% of TROF patients remained on treatment beyond 3 months, ~80% remained on treatment beyond 6 months, and over two-thirds (>65%) continued treatment through the end of available study follow-up (6.0–18.2 months) (Figure 6).

Restarts

Of those in the non-persistent group, 14.5% (n=8) restarted TROF where the mean BID dose before discontinuation was 5500 mg and mean BID dose at restart was 5160 mg. The mean (SD) age was 3.6 (0.5) years, 100% were female, and

were reinitiated on TROF by child neurologists (62.5%) or nurse practitioners (25.0%). The mean (SD) time to restart among the non-persistent group was 164 (80) days; median (IQR) time to restart was 4.4 (3.1–10.7) months.

Discussion

This analysis is among the first real-world studies of TROF use among children aged 2–4 years, including both males and females. In a rare disease field where the entire clinical trial evidence base for this age group rests on the fifteen patients from the DAFFODIL trial, our real-world cohort of 159 children aged 2–4 years is genuinely meaningful in relative terms. This analysis also addresses a critical gap in the literature on real-world treatment persistence, which often serves as a measure of treatment continuity and reflects a composite of multiple factors such as efficacy, safety, tolerability, preference, and acceptability of TROF among children aged 2–4 years with RTT. In this study, we found that nearly 2 out of 3 individuals with RTT were persistent on TROF during available follow-up, with a median of 13 months of TROF treatment among the persistent individuals. More than 87.5% of RTT individuals remained on TROF treatment beyond first three months, whereas approximately 80% remained on TROF treatment for at least first six months and over 65% of these RTT individuals persisted through the end of the study period or end of follow-up. This study confirmed high rates of persistence and demonstrated long term persistence among children with RTT aged 2–4 years. Given the estimated time of onset of RTT around 2 years of age, it is possible that a majority of 2–4-year-olds in this real-world analysis are in a dynamic and active regression and/or <6 months post-regression stage of the disease. These high rates of persistence with TROF during a potentially active stage of the disease may help demonstrate TROF's acceptable clinical benefits and manageable tolerability profile.

Of the 35% who remained non-persistent, the median time to discontinuation was approximately 4 months from TROF initiation. While our claims-based dataset did not directly capture the underlying clinical reasons for discontinuation, prior Delphi consensus statements and the published results of the RTT Centers of Excellence (COE) survey on TROF treatment have noted that the early treatment period is frequently associated with weight-based dose titration and management of tolerability effects. Thus, it is possible that tolerability or adverse event management, dose adjustment, or titration during the first few months after TROF initiation in this cohort may be associated with lack of persistence.^{10–12} In our analysis, we observed some RTT individuals restarted TROF after a period of non-persistence, potentially suggesting that patients may restart TROF after their tolerability/adverse effects have subsided. Overall, these findings suggest that a majority of young children who initiated TROF were able to remain on treatment during the available follow-up period in routine clinical practice. As such, persistence among TROF-treated patients should be interpreted as a measure of real-world treatment continuation rather than as a direct assessment of the benefit-risk profile of TROF. While sustained persistence may serve as a behavioral marker of treatment continuation, these findings complement the safety and tolerability evidence generated by the LAVENDER, LILAC, and DAFFODIL clinical trials. These results complement recent studies such as LOTUS, COE Survey and consensus guidelines on TROF treatment.^{10–12} However, the reasons for discontinuation and restart were not available in the linked claims and shipment data.

The mean dispensed TROF dose and mean %TDD were similar among the two groups. It is important to note that management of the persistent group may support the longer use and tolerability of TROF; additionally, RTT is a heterogeneous disease with multisystem comorbidities and complications, thus individualized management is needed.¹³ These findings also reinforce the possibility of maintaining long-term effectiveness of TROF through potentially individualized treatment protocols that balance TROF's efficacy, safety, and tolerability effects. Further evaluation examining if persistent individuals are managed by RTT centers of excellence would also provide clinical decision-making insights about individualizing RTT management when TROF is initiated. Such insights may also help develop customized TROF treatment management protocols that would be useful for effective management of children aged 2–4 years. Future studies are needed to better understand the reasons other than tolerability issues that may drive TROF discontinuation to ensure the long-term treatment success of TROF in real-world settings.

Children in the non-persistent group had higher baseline clinical burden than those in the persistent group, including approximately two-fold higher rates of dysphagia, more than five-fold higher rates of gastrostomy, and nearly nine-fold higher rates of breathing irregularities. Taken together, this comorbidity profile is consistent with a more advanced or severe RTT phenotype in the non-persistent group, characterized by greater multisystem complexity. These descriptive

findings suggest that children with greater pre-existing disease burden and multisystem complications may be at higher risk for non-persistence in real-world practice. Other non-persistence drivers may include specialty pharmacy delays, prior authorization, insurance coverage gaps, and re-authorization barriers.

Real-world treatment persistence with high-cost specialty therapies such as TROF is influenced by a range of payer- and access-related factors that are not directly observable in claims data. TROF is distributed exclusively through specialty pharmacy channels and carries a substantial wholesale acquisition cost, which typically necessitates payer prior authorization, periodic re-authorization, and ongoing benefits verification. In our cohort, approximately 11.9% of children were covered by Medicaid, a payer category for which authorization criteria, formulary placement, and step-therapy requirements may differ from commercial (third-party) coverage, which represented the majority (79.2%) of our cohort. Additional logistical factors-including specialty pharmacy refill coordination, weight-based dose re-authorization at growth-related dose changes, and the need for ongoing caregiver engagement with multiple stakeholders-may also contribute to gaps in TROF supply that are recorded as non-persistence in claims-based definitions. Future studies that link claims data with payer-policy variables and patient-support program data could help disentangle clinical from non-clinical drivers of TROF non-persistence in young children with RTT.

The results of our analysis are consistent with findings from DAFFODIL trial which demonstrated similar dosing patterns among 2–4-year-old female children treated with TROF. Interestingly, the caregivers (n=7) who provided an exit interview on behalf of RTT participants from DAFFODIL when TROF was approved during March 2023 reported satisfaction with the benefits of TROF.¹⁴ All these findings together provide evidence about the clinical value proposition and effectiveness of TROF in real-world settings.

There are several limitations typical of real-world claims analyses that should be noted. Comorbidities and selected differential diagnoses were identified from ICD-10-CM codes and may be misclassified or incompletely captured. Claims data also cannot reliably determine the true age at clinical or molecular RTT diagnosis, because the first observed RTT diagnosis code may not represent the actual diagnosis date. However, given the narrow age range of this cohort, 2–4 years, any potential misclassification of age at diagnosis is unlikely to materially affect the interpretation of the study findings. Persistence was defined using dispensing records using a pre-defined definition of ≤ 90 -day allowable gap, after the expected end of supply. This definition was considered reasonable for assessing TROF persistence because it may account for treatment interruptions related to weight-based dose titration or dose adjustment, temporary dose delays or reductions to manage adverse events, specialty-pharmacy refill coordination, and other real-world factors. The use of an allowable gap is a well-known methodology used in claims studies to define persistence. Individual patient weight was not available in the linked dataset but in categories; therefore, %TDD (which is weight-based) relied on these categories. Additionally, while this study used linked medical claims and specialty-pharmacy shipment data of children aged 2–4 years initiating TROF, it is possible that this cohort may not represent all US children aged 2–4 years with RTT, particularly those without continuous observable insurance coverage or those not captured through the specialty-pharmacy distribution channel. Insurance type was assessed at the time of index, with most individuals having third-party insurance and 11.9% having Medicaid; however, the dataset did not capture changes in insurance coverage over time, prior authorization requirements, medication costs or cost-sharing, pharmacy coordination delays, or caregiver-reported access barriers. Therefore, the potential influence of payer coverage, affordability, and specialty-pharmacy logistics on TROF persistence could not be directly evaluated. Another limitation is the absence of data enumerating the specific reasons for discontinuing TROF, such as intolerability (eg, diarrhea), lack of perceived benefit, or other administrative or logistical barriers (eg, insurance denials or supply interruptions). Future real-world studies that integrate caregiver-reported outcomes, chart or clinic notes captured in electronic medical record narratives, or specialty pharmacy adherence-counseling notes will be needed to characterize the specific drivers of TROF discontinuation in this young RTT population. Nonetheless, the linked claims and dispensing data offer valuable real-world insight into TROF persistence and dosing patterns in 2–4 years RTT population.

Conclusions

To complement the DAFFODIL trial, we conducted this analysis to understand TROF persistence in the real-world setting, additionally including male patients and evaluating a larger sample of children with RTT. The majority

(approximately 7 in 10) of children aged 2–4 years with RTT remained persistent on TROF during the available follow-up, with more than half remaining on treatment for at least 13 months at the end of study follow-up. Mean dose and percentage target daily dose among persistent and non-persistent children were similar, with modest dose increases observed primarily between the first and second shipments. Among non-persistent children, 14.5% restarted TROF after a treatment gap, with a median time to restart of approximately 4.4 months. Notably, non-persistent children had significantly higher baseline rates of dysphagia, gastrostomy, and breathing irregularities, suggesting that early disease-related multisystem complications may be associated with reduced treatment continuity in real-world practice, a finding with direct clinical implications for individualized treatment support in children with more complex baseline phenotypes. While more research is needed to understand the role of physician specialty, demographics, comorbidities, dosing patterns, adverse effects, and reasons for discontinuation, these findings provide the first real-world evidence on TROF persistence and dosing patterns among male and female children aged 2–4 years in usual care practice.

Data Sharing Statement

The data sources used in this analysis are not publicly available, and the databases are syndicated and available upon use with a data license fee.

Ethics Approval and Consent to Participate

This real-world claim database study was conducted in accordance with the HIPAA Security Act of 1996 and complies with the Declaration of Helsinki as it relates to informed consent of participants. Since the study involved de-identified, anonymized, patient-level secondary data without any identifiable protected health information (PHI), patient consent was not required and the need for ethics committee approval was not applicable.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agreed to be accountable for all aspects of the work.

Funding

This study was sponsored by Acadia Pharmaceuticals Inc., San Diego, CA, USA; no grant number applicable.

Disclosure

Nazia Rashid and Dilesh Doshi are employees of and report stock options from Acadia Pharmaceuticals, San Diego, CA, USA. Krithika Rajagopalan and Vinod Yakkala are current employees of Anlitiks Inc., a company that received funding from Acadia Pharmaceuticals to conduct this study. The authors report no other conflicts of interest in this work.

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