Poster # 3.485

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Epilepsy Rates Among Individuals Treated versus Untreated with Trofinetide for Rett Syndrome in the United States

Nazia Rashid,[1] Vinod Yakkala,[2] Daksha Gopal,[2] Krithika Rajagopalan[2]

[1]Acadia Pharmaceuticals Inc., San Diego, CA, USA;
[2]Anlitiks Inc., Windermere, FL, USA

INTRODUCTION

- Approximately 75% of individuals with Rett syndrome (RTT) have neurological comorbidities such as epilepsy that can often be refractory to multiple antiepileptic drugs; possibly increasing caregiver and health resource use burden.[1-3]
- The introduction of trofinetide (TROF) as the first FDA-approved therapy for RTT in March 2023 among individuals ≥2 years of age marked a paradigm shift to the RTT treatment landscape.[4]
- Concomitant epilepsy is common among individuals with RTT. Thus, it is important to understand the epilepsy occurrence patterns among those treated with TROF in the real-world setting.

OBJECTIVES

- To examine the differences in epilepsy rates between individuals with RTT who are treated with TROF compared to those who are not treated with TROF.

METHODS

Study Design & Data Source

- A retrospective cohort study using medical claims from IQVIA's Anonymized Patient Level Data linked with pharmacy claims from a specialty pharmacy database from January 01, 2021, to September 30, 2024 (i.e., study period) was conducted (Figure 1).

Study Population & Time Period Definitions

- Individuals with ≥1 medical claim diagnosis of RTT (ICD-10 code: F84.2) or ≥1 prescription (RX) claim for TROF (NDC: 63090-660-01, 63090-0660-01) were included.
- The eligible population was stratified into two groups based on TROF treatment status (i.e., treated or untreated) between April 1, 2023 (i.e., closest date to March 10, 2023, FDA approval date) through September 30, 2023 (i.e., identification period):
  - Treated: Individuals with ≥1 claims for TROF during the identification period:
    - Index date: first TROF RX fill date during the identification period.
  - Untreated: Individuals who did not initiate TROF during the identification period:
    - Index date: an assigned index date using a risk set sampling approach that is set to the elapsed time (in days) from RTT diagnosis to TROF initiation of every 1 treated individual to 5 untreated (1:5 ratio) individuals. This approach creates comparable person-time between groups and helps avoid immortal time bias.

Matching

- The treated and untreated (risk set sampled) individuals were also age, sex and index date matched using 1:1 Mahalanobis distance matching (without replacement).

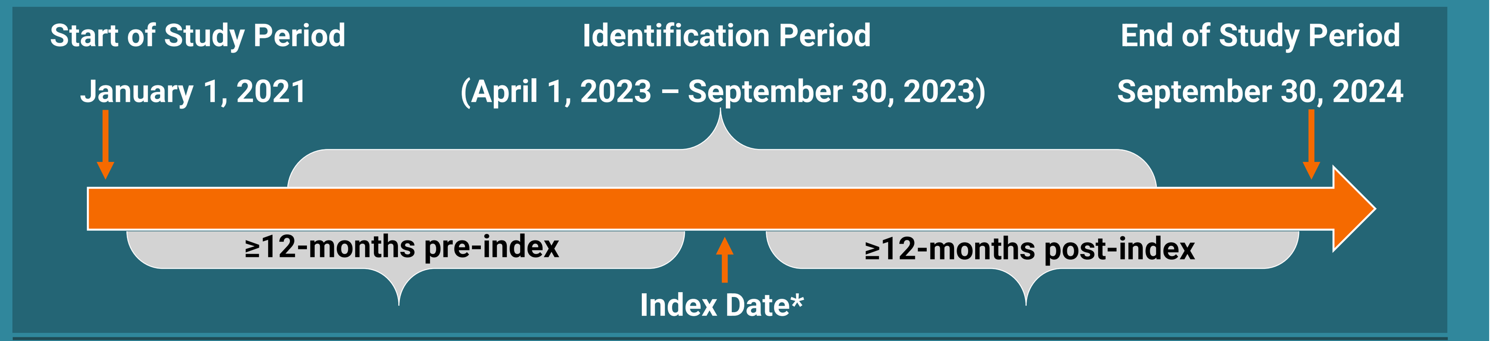
Study Measures: Baseline Characteristics

- Demographics such as age and gender at index date as well as selected clinical comorbidities (dysphagia, gastrostomy, etc.,) during pre-index were examined in the treated and untreated groups.
- Physician specialty (neurologists, pediatrician, etc.,) closest to treatment index and closest to RTT diagnosis was examined among treated and untreated groups, respectively.

Study Measures: Clinical Outcomes

- Percentage (%) of individuals with ≥1 claim for epilepsy (ICD-10 code: G40) and seizure (ICD-10 code: R56) during pre- and post-index among treated vs. untreated individuals were examined in both unmatched and matched groups.
  - Among matched individuals with ≥1 claim for epilepsy during post-index, epilepsy history (≥1 claim for epilepsy during pre-index) was examined in both treated and untreated cohorts.
    - A subgroup of individuals in the treated group with ≥1 post-index epilepsy claim were stratified and examined if the epilepsy claim occurred during the TROF treatment duration (defined as the period from the first TROF prescription fill through the last prescription fill plus days' supply).

Figure 1. Study Design



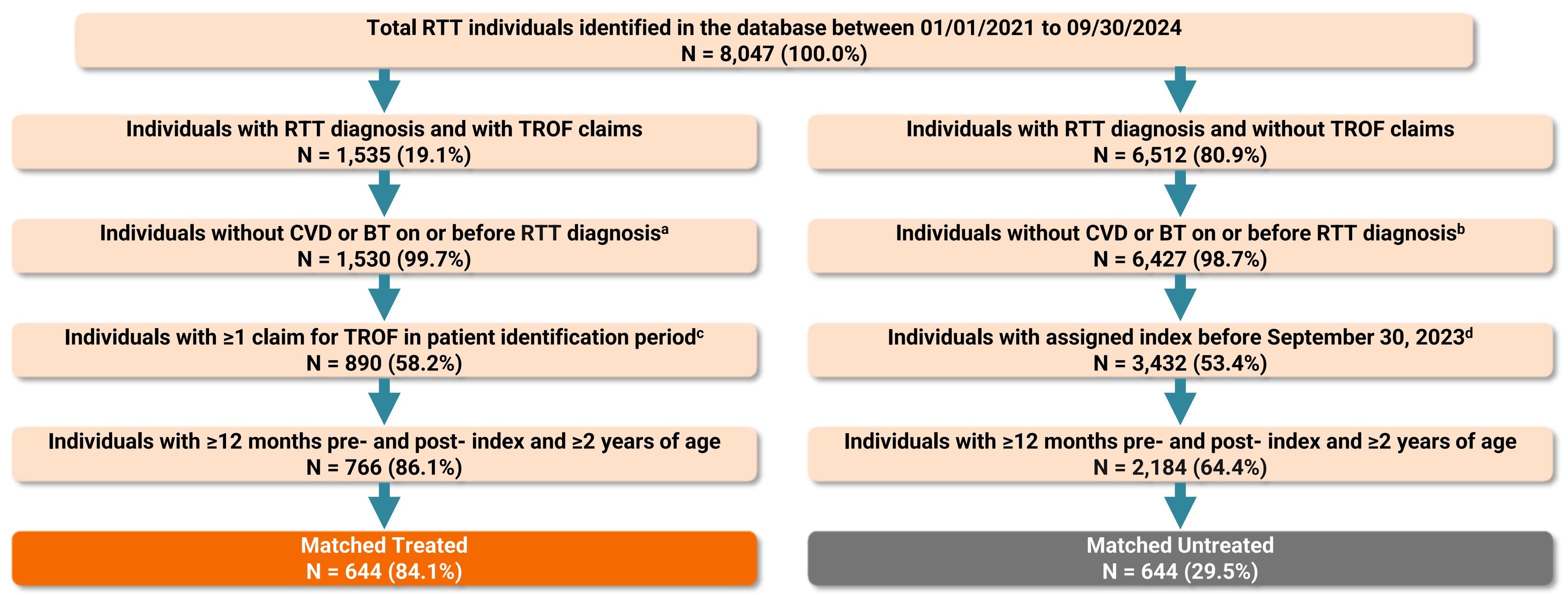
*Date of 1st TROF RX – treated group; Derived index date based on matched diagnosis-to-treatment – untreated group

RESULTS

Study Population

- Of 8,047 individuals with claims for RTT or TROF, 19.1% (n=1,535) were treated with TROF, while 80.9% (n=6,512) were not treated with TROF. After applying eligibility criteria, the final unmatched sample included 2,950 individuals, of which 25.9% (n=766) were treated with TROF and 74.1% (n=2,184) were untreated. Following 1:1 matching, both treated and untreated groups had 644 individuals (Figure 2).

Figure 2: Attrition Table



Abbreviations: APLD, Anonymized Patient Level Data; **BT,** Brain Trauma; **CVD,** Cerebrovascular Disease; **RTT,** Rett Syndrome; **TROF,** Trofinetide
[a]5 individuals were excluded from the treated cohort due to CVD and/or BT; [b]85 individuals were excluded from the untreated cohort due to diagnosis of CVD and/or BT prior to RTT diagnosis; [c]640 individuals were excluded from the treated cohort due to TROF claim outside of the patient identification period; [d]1,248 individuals were excluded from the untreated cohort due to assigned index prior to patient identification period (Sept 30, 2023); Post-index period includes index.

Baseline Characteristics

- The mean age at RTT diagnosis among the matched treated vs. untreated group was 13.7 years vs. 15.2 years, respectively and most individuals were females (>89%) in all groups (Table 1).
- Similar rates of pre-index seizures were observed among treated and untreated groups in the unmatched and matched cohorts (Table 1).
- Individuals in the unmatched treated cohort were more commonly seen by child neurologists (50.3%), followed by pediatricians (11.9%) and neurologists (8.2%). Physician specialty of nearly half of untreated individuals was unknown, the remaining 50% were more commonly seen by child neurologists (26.7%), pediatricians (14.4%) and neurologists (8.0%). Matched groups showed similar trends (Table 1).

Table 1. Demographics and Clinical Characteristics

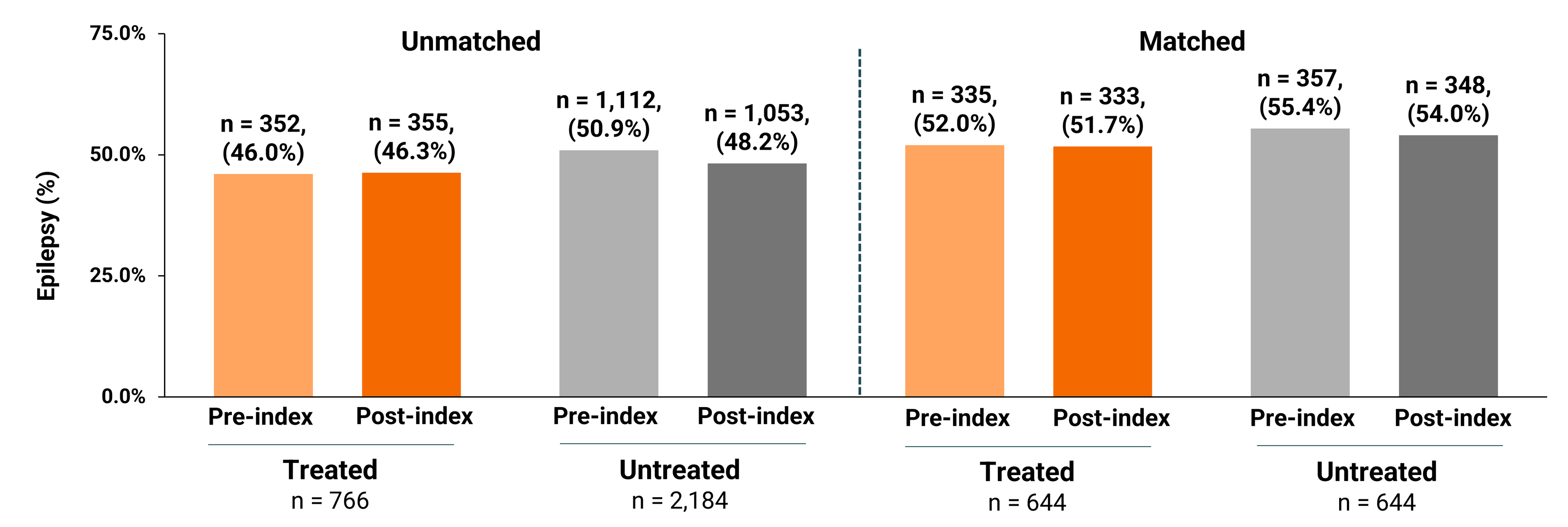
Characteristic	Unmatched		Matched	
	Treated (n = 766)	Untreated (n = 2,184)	Treated (n = 644)	Untreated (n = 644)
Age at RTT Diagnosis (years), mean ± SD	13.4 ± 10.3	21.7 ± 12.8	13.7 ± 10.2	15.2 ± 11.4
Gender, n (%)				
Male	35 (4.6%)	235 (10.8%)	25 (3.9%)	25 (3.9%)
Female	731 (95.4%)	1,949 (89.2%)	619 (96.1%)	619 (96.1%)
Age at Index (years), mean ± SD	15.4 ± 10.9	23.5 ± 12.8	15.4 ± 10.2	16.8 ± 11.3
Selected Clinical Comorbidities, n (%)				
Gastrostomy	220 (28.7%)	639 (29.3%)	212 (32.9%)	197 (30.6%)
Dysphagia	215 (28.1%)	555 (25.4%)	198 (30.7%)	161 (25.0%)
Constipation	195 (25.5%)	546 (25.0%)	183 (28.4%)	167 (25.9%)
Scoliosis	188 (24.5%)	536 (24.5%)	182 (28.3%)	171 (26.5%)
Seizures	186 (24.3%)	518 (23.7%)	178 (27.6%)	153 (23.8%)
Physician Specialty Type[a], n (%)				
Unknown	0 (0.0%)	1,055 (48.3%)	0 (0.0%)	261 (40.5%)
Known[b]	766 (100%)	1,129 (51.7%)	644 (100%)	383 (59.5%)
Child Neurologists	385 (50.3%)	302 (26.7%)	331 (51.4%)	121 (31.6%)
Pediatrician	91 (11.9%)	163 (14.4%)	79 (12.3%)	63 (16.4%)
Neurologists	63 (8.2%)	90 (8.0%)	56 (8.7%)	24 (6.3%)
Clinical Neurophysiologists	60 (7.8%)	58 (5.1%)	50 (7.8%)	25 (6.5%)
Nurse Practitioner	67 (8.7%)	66 (5.8%)	46 (7.1%)	17 (4.4%)
Family Medicine	21 (2.7%)	85 (7.5%)	16 (2.5%)	24 (6.3%)

Abbreviations: SD, Standard Deviation; **TROF,** Trofinetide
[a]Physician specialty type was seen closest to index date in the treated group and closest to the diagnosis date in the untreated group; [b]The percentages were based on known physician specialty.

Clinical Outcomes

- In the eligible unmatched (766 vs. 2,184) groups, the percentage of individuals with epilepsy was 46.0% (n=352) pre-index and 46.3% (n=355) post-index among the treated; it was 50.9% (n=1,112) pre-index and 48.2% (n=1,053) post-index among the untreated (Figure 3).
- In the matched groups, percentage of individuals with epilepsy was 52.0% (n=335) pre-index and 51.7% (n=333) post-index among the treated; it was 55.4% (n=357) pre-index and 54.0% (n=348) post-index among the untreated (Figure 3).
- Post-index seizure rates were 23.5% (n=180) among treated and 22.3% (n=488) among untreated group in the unmatched cohort. Similar results for seizures were also observed in the matched cohort among both treated and untreated groups.

Figure 3. Pre-index and Post-index Epilepsy rates among Unmatched and Matched Groups



Epilepsy History

- Among those with post-index epilepsy in both groups, 82.0% (273/333) vs. 85.3% (297/348) had pre-index epilepsy among treated vs. untreated, respectively (Figure 4).
- Of those who reported post-index epilepsy in the treated group, 287 reported it during TROF treatment. Of those who reported it during TROF treatment, 84.3% (n=242) reported it during pre-index as well (Figure 5).

Figure 4. Epilepsy History in Matched Groups

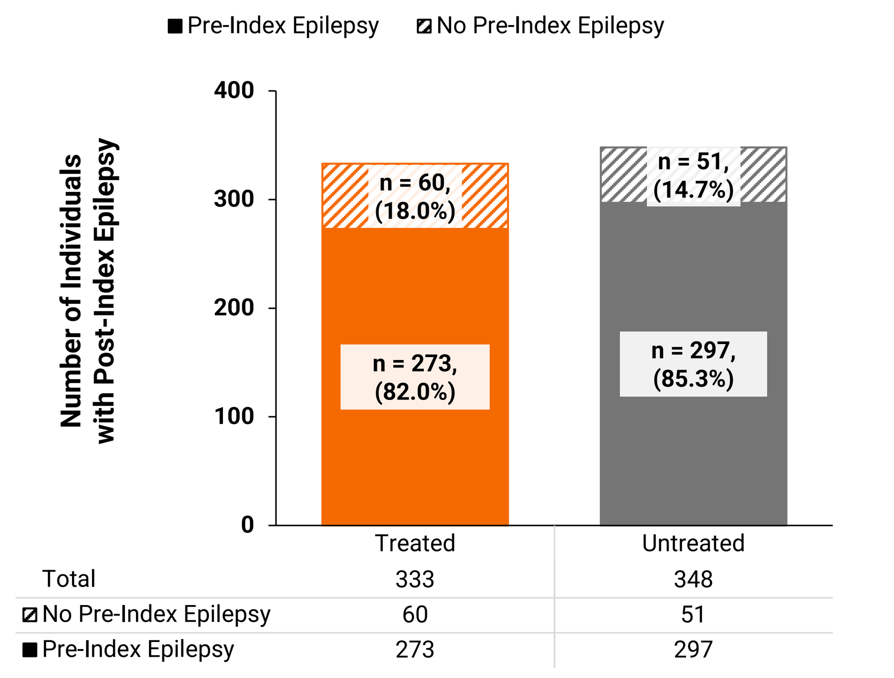
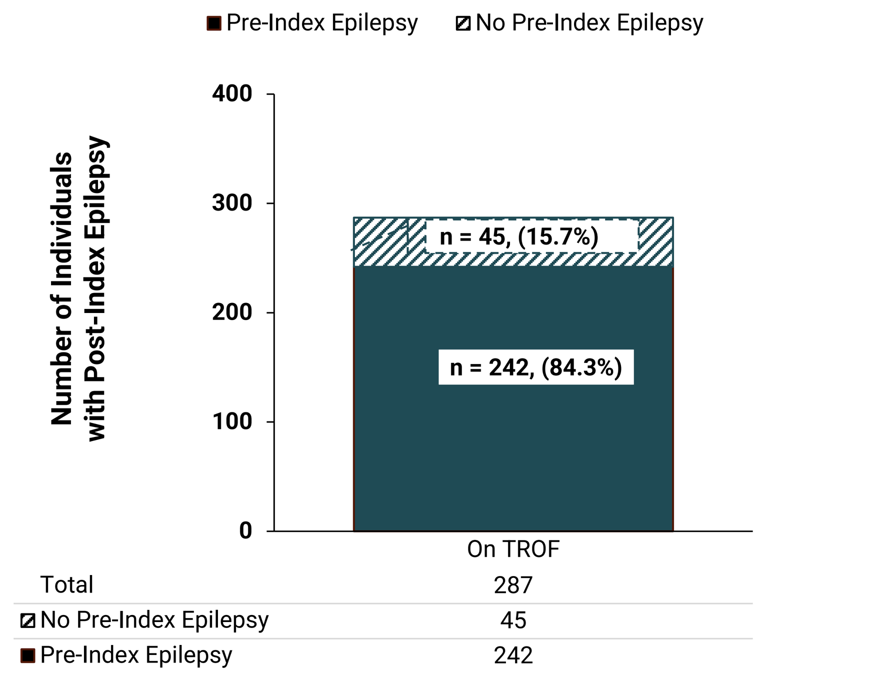


Figure 5. Epilepsy During TROF Treatment



Abbreviations: TROF, trofinetide
*Date of epilepsy diagnostic claim was during TROF treatment period (duration from first TROF RX fill through last RX fill + days' supply)

CONCLUSIONS

Overall, this real-world study showed similar epilepsy rates during the 12-month pre- and post-index periods in both TROF treated vs. untreated RTT groups.

The unmatched and matched TROF treated groups exhibited slightly lower 12-month post-index epilepsy rates compared to untreated groups.

Among individuals with post-index epilepsy, most already had a history of epilepsy, suggesting that post-index epilepsy occurrence is driven by pre-existing epilepsy and/or the underlying RTT pathology in both groups.

Our results suggest that TROF has a balanced neurological adverse event profile and represents a potentially safe treatment option among RTT individuals, regardless of prior epilepsy status.

DISCLOSURES

The study was supported by Acadia Pharmaceuticals Inc. (San Diego, CA, USA).

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