An Evaluation of Real-World Effectiveness and Safety of Trofinetide in Patients With Rett Syndrome: A Retrospective Chart Review

Constance Smith-Hicks,[1] Peter Heydemann,[2] Cary Fu,[3] Steven Skinner,[4] Arthur Beisang,[5] Amitha Ananth,[6] Davut Pehlivan,[7] David Lieberman,[8] Christopher W. Beatty,[9] Bernhard Suter,[7] Colleen Buhrfiend,[2] Ryan Bucco[10]

[1]Center for Synaptic Disorders, Rett and Related Disorders Clinic, Kennedy Krieger Institute, Johns Hopkins University School of Medicine, Baltimore, MD, USA; [2]Rush University Medical Center, Chicago, IL, USA; [3]Department of Pediatrics, Vanderbilt Kennedy Center, Vanderbilt University Medical Center, Nashville, TN, USA; [4]Greenwood Genetic Center, Greenwood, SC, USA; [5]Gillette Children's Specialty Healthcare, St Paul, MN, USA; [6]University of Alabama at Birmingham, Birmingham, AL, USA; [7]Section of Pediatric Neurology and Developmental Neuroscience, Department of Pediatrics, Baylor College of Medicine, Houston, TX, USA; [8]Department of Neurology, Boston Children's Hospital, Boston, MA, USA; [9]Department of Pediatrics, Division of Neurology, Nationwide Children's Hospital, the Ohio State University, Columbus, OH, USA; [10]Acadia Pharmaceuticals Inc., San Diego, CA, USA

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INTRODUCTION

- Rett syndrome (RTT) is a rare neurodevelopmental disease associated with developmental regression and difficulties with verbal communication, motor skills, and hand use[1]
  - Patients with RTT experience several comorbidities due to the disease, including seizures, scoliosis, issues with sleep, and behavioral and gastrointestinal issues[2,3]
- Trofinetide is approved for the treatment of RTT based on the efficacy and safety results of the phase 3 clinical trial program[4-7]
- Although trofinetide clinical trials have demonstrated the efficacy and safety of trofinetide in patients with RTT, real-world data are essential to understand its impact in routine clinical practice
  - In LOTUS, a phase 4 observational study of trofinetide use in the real world, caregivers indicated improvements in the symptoms of RTT with a safety profile consistent with previous trofinetide clinical trials[8]

OBJECTIVE

- To present the results of a retrospective chart review designed to evaluate the real-world effectiveness, safety, and treatment patterns of trofinetide in patients with RTT following its commercial availability in the US in April 2023

METHODS

Study Design

- This multi-site, non-interventional, observational, retrospective chart review study included patients with RTT aged ≥2 years across 10 clinical sites in the US
- Patients were categorized based on the timing of initiation of trofinetide: those who initiated trofinetide after commercial availability and those who initiated trofinetide during clinical trials

Study Assessments

- Data were extracted from electronic health records and included demographics, clinical characteristics, and safety outcomes
- Changes in the symptoms of RTT were assessed from baseline to 3, 6, and 12 months post initiation of commercial trofinetide
- RTT symptom domains used in this study were derived from the Rett Syndrome Behaviour Questionnaire (RSBQ) subdomains (general mood, breathing problems, hand behaviors, repetitive face movements, body rocking and expressionless face, nighttime behaviors, fear/anxiety, and walking/standing)[9] with some modifications to gather more detailed information
  - The RSBQ hand behaviors subdomain was divided into hand behaviors and fine motor skills; the nighttime behaviors subdomain was divided into nighttime behaviors and sleep
  - Three additional domains—communication, connectedness, and alertness/awareness—were added
- Safety endpoints included the incidence of adverse events (AEs)
- Descriptive statistics were used to analyze the data

RESULTS

Demographics, Baseline Characteristics, Dosing, and Patient Disposition

- In total, 85 patients who initiated trofinetide after commercial availability and 14 patients who initiated trofinetide during clinical trials participated in the study (Table 1)
  - The median (interquartile range [IQR]) age of trofinetide initiation was 8.3 (4.6–20.1) years in patients who initiated trofinetide after commercial availability and 8.3 (5.3–11.0) years in patients who initiated trofinetide during clinical trials
  - All patients were female and had a pathogenic variant in the *MECP2* gene
- The median (IQR) trofinetide dose at baseline as percentage of the label recommended dose was 33.3% (25.0–100.0) and 100.0% (62.5–100.0) in patients who initiated trofinetide after commercial availability and during clinical trials, respectively (Table 2)
  - In patients who initiated trofinetide after commercial availability, 30 (35.3%) patients interrupted trofinetide and 23 (27.1%) patients discontinued trofinetide
  - In patients who initiated trofinetide during clinical trials, 2 (14.3%) patients interrupted trofinetide and 4 (28.6%) patients discontinued trofinetide
  - Most discontinuations in both groups were related to AEs

Table 1. Baseline Demographic and Clinical Characteristics

Characteristics	Trofinetide initiation: After commercial availability (n = 85)	Trofinetide initiation: During clinical trials (n = 14)
Sex, n (%)		
Female	85 (100)	14 (100)
Race, n (%)		
White	67 (78.8)	14 (100)
Black or African American	4 (4.7)	0
Asian	2 (2.4)	0
American Indian or Alaska Native	2 (2.4)	0
Other	4 (4.7)	0
Unknown	8 (9.4)	0
Confirmed *MECP2* mutation, n (%)	85 (100)	14 (100)
Median (IQR) age at time of RTT diagnosis, years	2.5 (2.0–4.0)	2.0 (1.1–2.5)
Median (IQR) age at time of trofinetide initiation, years	8.3 (4.6–20.1)	8.3 (5.3–11.0)

IQR, interquartile range; **RTT**, Rett syndrome.

Table 2. Dosing and Patient Disposition

Characteristics	Trofinetide initiation: After commercial availability (n = 85)	Trofinetide initiation: During clinical trials (n = 14)
Median (IQR) dose at baseline as a percentage of label recommended dose (%)	33.3 (25.0–100.0)	100.0 (62.5–100.0)
Dosing frequency, n (%)		
BID	84 (98.8)	14 (100)
TID	1 (1.2)	0
Discontinuation/interruption status, n (%)		
Never discontinued/interrupted	45 (52.9)	8 (57.1)
Interrupted	30 (35.3)	2 (14.3)
Discontinued	23 (27.1)	4 (28.6)
Discontinued with interruptions[a]	13 (56.5)	0
Discontinued without interruptions[a]	10 (43.5)	4 (100)
Reason for discontinuation (with or without interruptions), n (%)[a]		
AE	12 (52.2)	3 (75.0)
Efficacy	0	0
Other	5 (21.7)	1 (25.0)
Unknown	6 (26.1)	0

[a]Percentages are based on the total number of patients who discontinued trofinetide during study period.
AE, adverse event; **BID**, 2 times a day; **IQR**, interquartile range; **TID**, 3 times a day.

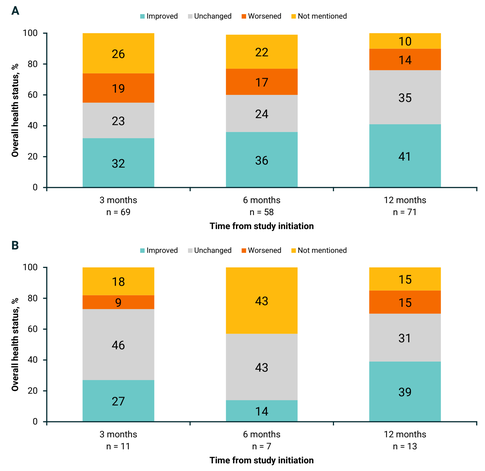
Baseline RTT Symptom Severity Across Domains

- The most commonly reported severe RTT symptoms at baseline in patients who initiated trofinetide after commercial availability and during clinical trials included issues with fine motor skills, gross motor skills (walking/standing), communication, hand behaviors, and breathing problems (Figure 1A and B)

Overall Health Status Compared With Baseline

- Patients who initiated trofinetide after commercial availability and during clinical trials experienced overall health improvements from months 3 to 12 (Figure 2A and B)

Figure 2. Overall Health Status Compared With Baseline in (A) Patients Who Initiated Trofinetide After Commercial Availability and (B) Patients Who Initiated Trofinetide During Clinical Trials



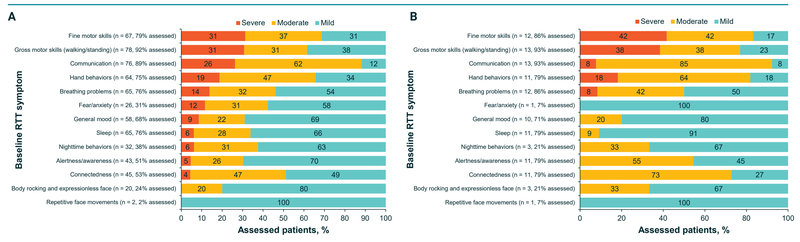
Change in Symptoms of RTT From Baseline to Month 12 of Trofinetide Treatment

- Improvements in the symptoms of RTT were consistently reported in the subdomains of communication, gross motor skills, alertness/awareness, connectedness, fine motor skills, general mood, and hand behaviors for both patient groups (Figure 3A and B)

Safety

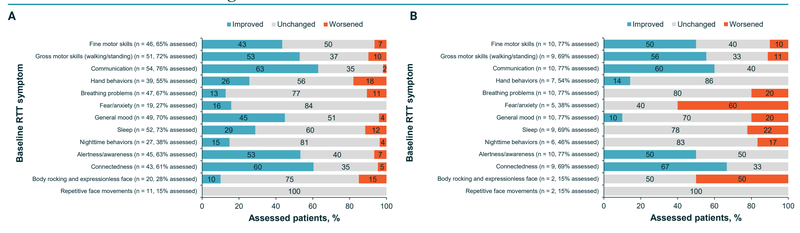
- AEs were reported for 71 (83.5%) and 11 (78.6%) patients who initiated trofinetide after commercial availability and during clinical trials, respectively (Table 3)
  - The most commonly reported AEs in both groups were diarrhea and vomiting

Figure 1. Baseline RTT Symptom Severity Across Domains in (A) Patients Who Initiated Trofinetide After Commercial Availability and (B) Patients Who Initiated Trofinetide During Clinical Trials[a]



[a]Patients without domain assessments or in which no issues were noted are not shown. Percentages shown in vertical axis correspond to patients assessed in each domain; percentages in bars correspond to symptom severity in assessed patients.
RTT, Rett syndrome.

Figure 3. Change in Symptoms of RTT From Baseline to Month 12 of Trofinetide Treatment in (A) Patients Who Initiated Trofinetide After Commercial Availability and (B) Patients Who Initiated Trofinetide During Clinical Trials[a]



[a]Patients without domain assessments or in which no issues were noted are not shown. Percentages shown in vertical axis correspond to patients assessed in each domain; percentages in bars correspond to symptom improvement in assessed patients.
RTT, Rett syndrome.

Table 3. Incidence of AEs[a]

n (%)	AEs in ≥5% of patients: Trofinetide initiation: After commercial availability (n = 85)	AEs in ≥5% of patients: Trofinetide initiation: During clinical trials (n = 14)	AEs possibly/probably related: Trofinetide initiation: After commercial availability (n = 85)	AEs possibly/probably related: Trofinetide initiation: During clinical trials (n = 14)	AEs that led to dose interruption: Trofinetide initiation: After commercial availability (n = 85)	AEs that led to dose interruption: Trofinetide initiation: During clinical trials (n = 14)	AEs that led to discontinuation: Trofinetide initiation: After commercial availability (n = 85)	AEs that led to discontinuation: Trofinetide initiation: During clinical trials (n = 14)
Any AE	71 (83.5)	11 (78.6)	-	-	-	-	-	-
Diarrhea	59 (69.4)	10 (71.4)	57 (67.1)	10 (71.4)	15 (17.6)	1 (7.1)	11 (12.9)	3 (21.4)
Vomiting	20 (23.5)	1 (7.1)	15 (17.6)	1 (7.1)	7 (8.2)	1 (7.1)	5 (5.9)	0
Seizure	12 (14.1)	0	4 (4.7)	0	3 (3.5)	0	3 (3.5)	0
Decreased appetite	8 (9.4)	0	8 (9.4)	0	3 (3.5)	0	2 (2.4)	0
Constipation	7 (8.2)	0	4 (4.7)	0	1 (1.2)	0	1 (1.2)	0
Weight decreased	6 (7.1)	0	6 (7.1)	0	1 (1.2)	0	3 (3.5)	0
Flatulence	4 (4.7)	0	3 (3.5)	0	0	0	0	0
Pneumonia	4 (4.7)	0	1 (1.2)	0	0	0	1 (1.2)	0
Irritability	2 (2.4)	1 (7.1)	2 (2.4)	1 (7.1)	1 (1.2)	0	1 (1.2)	1 (7.1)

Ten serious AEs occurred in 6 patients. These comprised 3 serious AEs of pneumonia, 1 of urinary tract infection, 4 of seizures or status epilepticus, 1 of femur fracture, and 1 of skin irritation/folliculitis. Two of these serious AEs (pneumonia and skin irritation/folliculitis) were possibly/probably related to trofinetide. All serious AEs involved hospitalization but were not considered life-threatening.
AE, adverse event.

CONCLUSIONS

The results of this chart review provide valuable insight into the real-world use of trofinetide in patients with RTT, including its effectiveness and safety
- **Patients with severe RTT symptoms at baseline experienced improvements in the symptoms of the disease that may help reduce caregiver burden**

The results of the chart review follow similar trends to the results of the trofinetide clinical program and the real-world LOTUS study[4-8]
- **This chart review study complements the LOTUS study, which includes caregiver-reported assessments, by providing clinician-reported assessments**

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ACKNOWLEDGMENTS

The study was supported by Acadia Pharmaceuticals Inc. (San Diego, CA, USA). Medical writing support was provided by Juan Sanchez-Cortes, PhD, of Evidence Scientific Solutions, Inc., and funded by Acadia Pharmaceuticals Inc.

DISCLOSURES

CS-H serves on the Acadia Pharmaceuticals Inc. advisory board and receives research support from the Kennedy Krieger Institute, which has an institutional agreement with Acadia Pharmaceuticals Inc. **PH** has no disclosures. **CF** has received funding for clinical trials from Zogenix Pharmaceuticals and consultancy fees from Acadia Pharmaceuticals Inc. **SS** was a site PI for Acadia Pharmaceuticals Inc., is a consultant with Acadia Pharmaceuticals Inc., and serves as a member of a data safety monitoring board for clinical trials conducted by Taysha Gene Therapies. **AB** is a consultant to Acadia Pharmaceuticals Inc. and Taysha Therapeutics. **AA** has received funding for clinical trials from Acadia Pharmaceuticals Inc., Neurogene, Taysha Therapeutics, and UCB. **DP** is supported by the Doris Duke Charitable Foundation (#2023-0235) and NINDS 1K23 NS125126-01A1, and is a consultant to Ionis Pharmaceuticals. **DL** has received funding for clinical trials from Acadia Pharmaceuticals Inc., Anavex Life Sciences, GW Pharmaceuticals, Neurogene, the Rett Syndrome Research Trust, and Taysha Gene Therapies; he has received consultancy fees from Acadia Pharmaceuticals Inc., Neurogene, and Taysha Gene Therapies. **CWB** is a consultant and advisor to Acadia Pharmaceuticals Inc. **BS** has received funding for clinical trials from Acadia Pharmaceuticals Inc., Anavex Life Sciences, Neurogene, the Rett Syndrome Research Trust and Grace Science Foundation; he has received consultancy fees from Acadia Pharmaceuticals Inc., Neurogene, and Taysha Gene Therapies. **CB** is a consultant and advisor to Acadia Pharmaceuticals Inc. **RB** is an employee and stakeholder in Acadia Pharmaceuticals Inc.

Presented at the 2026 International Rett Syndrome Foundation (IRSF) Rett Syndrome Scientific Meeting | June 29–July 1, 2026 | Prior Lake, MN, USA

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