Acadia Pharmaceuticals Inc. is providing this letter in response to your unsolicited request for medical information. It is for scientific exchange and individual educational purposes only, and should not be copied or distributed. Information included in this letter may not be consistent with the US FDA-approved Prescribing Information for DAYBUE® (trofinetide) or may be related to unapproved uses of DAYBUE. This letter is not intended to advocate any unapproved or approved use, indication, dosage, or other treatment-related decision. Acadia strives to provide current, accurate, and fair-balanced information in compliance with current industry information dissemination guidelines.

For further information regarding Indication and Important Safety Information for DAYBUE, please click here: Prescribing Information.

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DAYBUE® (trofinetide): Outcomes from the LOTUS Study

This letter is provided in response to your specific request for information regarding outcomes from the ongoing Phase 4 LOTUS study of patients prescribed trofinetide under routine clinical care.

Dosing patterns observed in the LOTUS study are not consistent with the dosing recommendations in the FDA-approved Prescribing Information. Findings related to Rett symptom improvement assessments should be interpreted with caution and clinical conclusions should not be drawn due to study limitations. The efficacy of DAYBUE has only been demonstrated at the FDA-recommended weight-based dose. Improvements may not occur until the patient reaches the recommended dose and continues treatment. Diarrhea management considerations listed here may not be consistent with FDA-approved recommendations in the Prescribing Information.

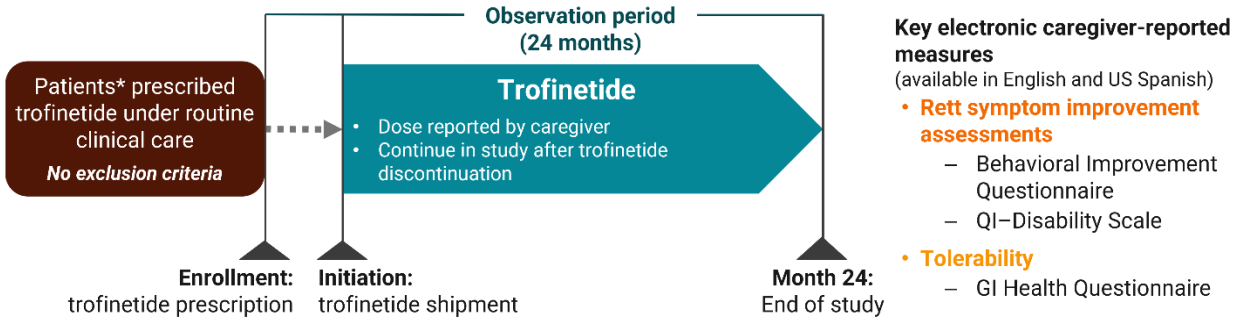
Summary

- **LOTUS** is an ongoing Phase 4, prospective, observational, real-world, open-label study involving caregivers of adults or pediatric patients of either sex who are prescribed trofinetide under routine clinical care.[1]
- **Interim analysis data** are available for 18 months of follow up (N=227). Owing to ongoing enrollment, data are presented up to 12 months since the initiation of trofinetide.[1]
    - The median (interquartile range [IQR]) **dose reported at Week 1** was 36% (20.0−76.0%) of labelled daily dose. By Week 10 onwards, ≥80% of the median target dose of trofinetide was administered.[1]
    - Overall, 71–90% of caregivers reported behavioral improvements that were new or maintained when compared with before trofinetide treatment on the **Behavioral Improvement Questionnaire** (BIQ) over the twelve monthly visits. The most frequently reported improvements were nonverbal communication, alertness, and social interaction/connectedness.[1]
    - The median (IQR) change in **Quality-of-Life Inventory–Disability (QI-Disability) total score** from baseline was 4.6 (-0.2−10.2) at Month 12.
    - Up to Month 12, **diarrhea and formed/normal stool** were both common, with constipation decreasing across early treatment weeks; vomiting was uncommon (<12% at any time point).[1]
    - One hundred and forty five **adverse events** (AEs) were reported among 60 participants (26.4%); the most common AEs were diarrhea (12.3%), vomiting (6.6%), and constipation (3.1%).[1]
- The results of this open-label, real-world study should be interpreted with recognition of its **limitations**.

LOTUS (ACP-2566-014): Study Design

This is an ongoing Phase 4, observational, real-world, prospective, open-label study involving caregivers of patients prescribed trofinetide under routine clinical care in the United States. Participation in LOTUS lasts for ≥12 months from trofinetide initiation, with the option to extend participation for an additional 12 months (**Figure 1**). Caregivers of any adult or pediatric patients of any biological sex who were prescribed trofinetide under routine clinical care are eligible for this study; there are no exclusion criteria.[1]

Figure 1. LOTUS Study Design[1,2]



**Adult or pediatric patients of either sex.*
Abbreviations: GI=gastrointestinal; QI–Disability=Quality-of-Life Inventory–Disability; US=United States.

The study utilizes three electronic caregiver-reported measures, which are available in English and United States Spanish (**Table 1**). The BIQ and GI Health Questionnaire were developed by Acadia for the LOTUS study and have not been validated in individuals with Rett syndrome.[1] The QI–Disability scale was developed by Downs et al.[3] as a measure of quality-of-life for school-aged children and adolescents with intellectual disability, and has been validated for adults with Rett syndrome.[1] Caregivers can download their responses to these measures as PDFs to share with their Healthcare Providers.

This study was not designed to actively solicit AEs. Potential AEs reported by caregivers are identified incidentally by a medical monitor reviewing free text responses in the electronic caregiver-reported measures and interactions with the study call center.[1]

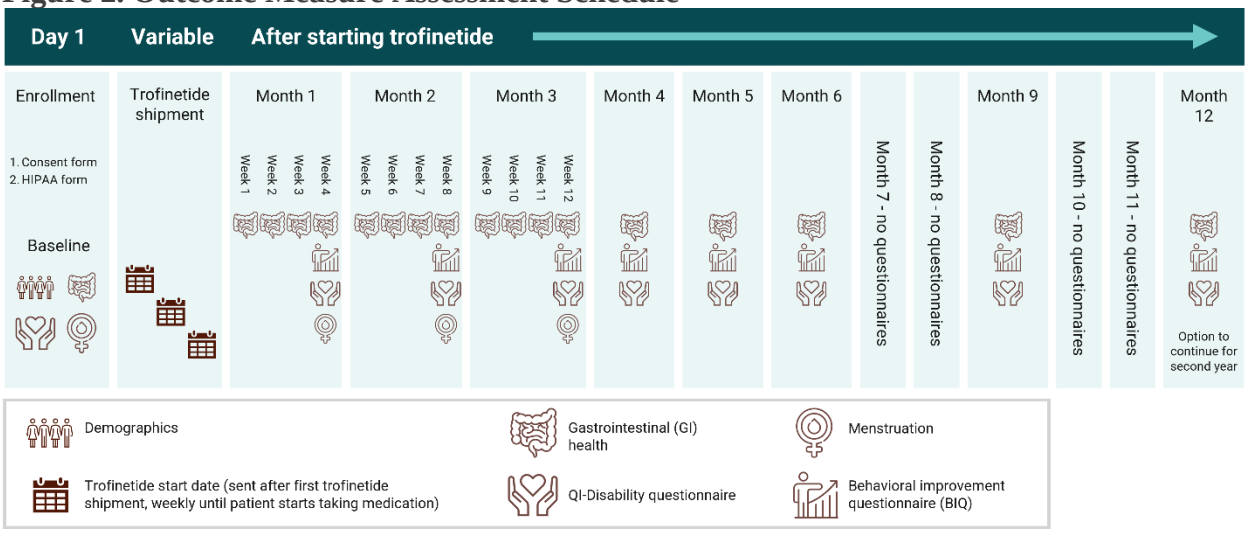
Table 1. Electronic Caregiver-reported Measures[2]

Electronic caregiver-reported measure	Description	Frequency
Behavioral Improvement Questionnaire (BIQ)	Selection of perceived behavioral improvements since starting trofinetide, across multiple domains	Collected monthly for 6 months, and every 3 months thereafter
QI–Disability scale[3]	A measure of quality-of-life for children and adolescents with intellectual disability	Collected monthly for 6 months, and every 3 months thereafter
GI Health Questionnaire	Information on GI symptoms occurrence, frequency, and management	Collected weekly for 12 weeks, then monthly for 3 months, then every 3 months

Abbreviations: GI=gastrointestinal; QI–Disability=Quality-of-Life Inventory–Disability.

The schedule of outcome measure assessments is shown in **Figure 2**.

Figure 2. Outcome Measure Assessment Schedule[2]



Abbreviations: HIPAA=Health Insurance Portability and Accountability Act; QI–Disability=Quality-of-Life Inventory–Disability.

Interim 18-Month Follow-up Analysis

In total, 227 participants were included in this 18-month follow-up. Owing to ongoing enrollment, data are presented up to 12 months since the initiation of trofinetide. The BIQ, QI-Disability Questionnaire, and safety analyses were conducted using the safety analysis set, defined as all enrolled patients who were on active trofinetide treatment, allowing for treatment discontinuation and reinitiation. The GI Health Questionnaire analyses were conducted in the subset of patients from the safety analysis set who were taking trofinetide the day they filled out the questionnaire.[1]

Participant Characteristics

Caregivers reported that 65.0% of participants had classic Rett syndrome (RTT), while 27.7% of participants had atypical RTT (**Table 2**). Most participants were female (96.9%), and patient age ranged from 1 to 60 years.[1]

Table 2. Baseline Demographics and Characteristics (Safety Analysis Set)[1]

	Total (N=227)
Rett syndrome type, n (%)	
n	206
Classic	134 (65.0)
Atypical	57 (27.7)
Does not meet diagnostic criteria for either	15 (7.3)
Sex, n (%)	
n	227
Male	7 (3.1)
Female	220 (96.9)
Race, n (%)	
n	201
White	162 (80.6)

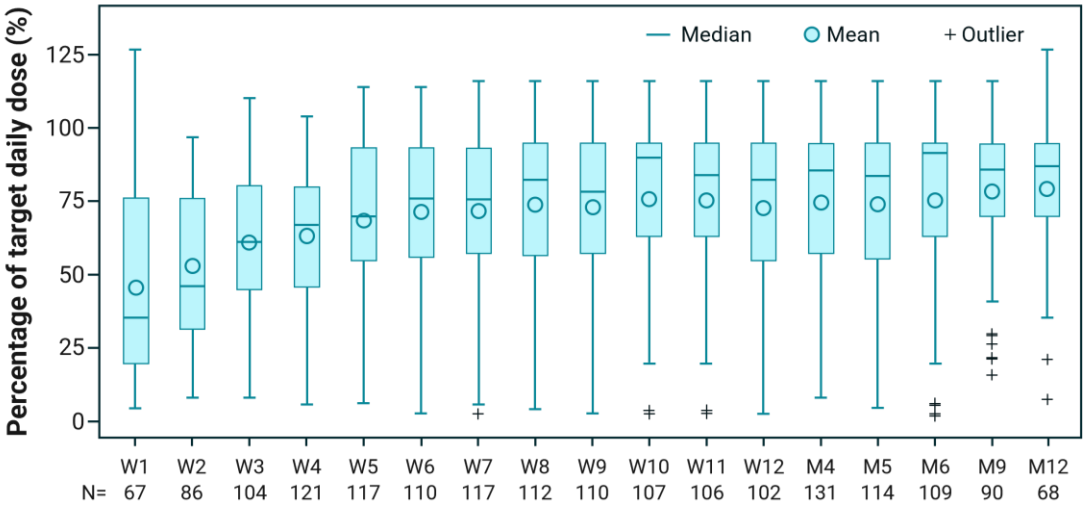
	Total (N=227)
Black or African American	17 (8.5)
Asian	10 (5.0)
American Indian or Alaska Native	2 (1.0)
Native Hawaiian or other Pacific Islander	1 (0.5)
Other	17 (8.5)
Did not wish to disclose	2 (1.0)
Age at the time of diagnosis, years	
n	190
Median (IQR)	3.0 (2.0–5.0)
Age at the time of trofinetide initiation*, years	
n	205
Median (IQR)	13.0 (6.0–22.0)

n-values may not be 227 because caregiver-reported assessments were optional, and data was not received for every patient for all timepoints.
**Trofinetide initiation is the day of trofinetide shipment.*
Abbreviation: IQR=interquartile range.

Caregiver-reported Dosing Patterns

The median dose reported at Week 1 was 36.0% of the target, weight-banded label dose with wide variability in dosing (IQR, 20.0–76.0% of labeled daily dose). By Week 10 onwards, ≥80% of the median target dose of trofinetide was administered (**Figure 3**). By Month 6, the median (IQR) dose was 92.0% (63.3−95.0%) of target.[1]

Figure 3. Percentage of Target Daily Dose (Safety Analysis Set)[1]



Abbreviations: M=month; W=week.

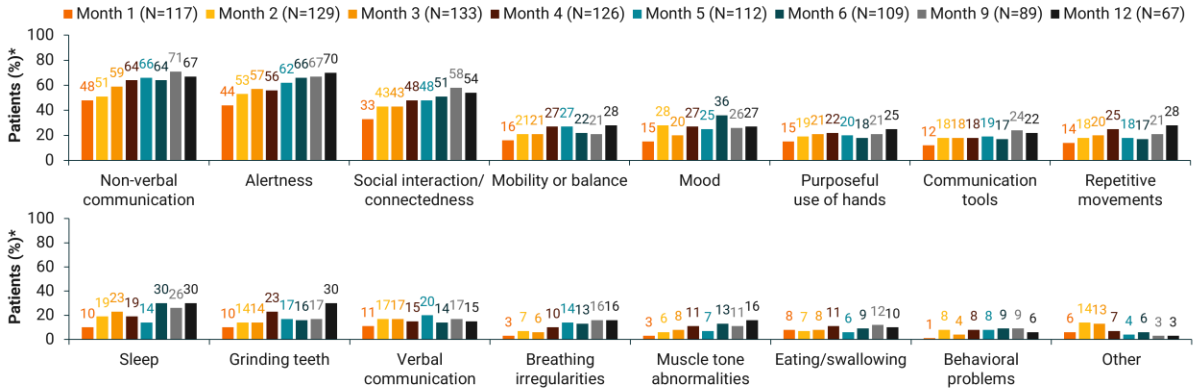
Most commonly, caregivers reported two doses administered per day (68.5−93.3% across time points). The maximum number of doses per day was four.[1]

Outcomes: Behavioral Improvement Questionnaire (BIQ)

In patients on active trofinetide treatment, 71−90% of caregivers reported behavioral improvements on the BIQ over the twelve monthly visits that were new or maintained compared with before trofinetide treatment. The most frequently reported improvements were nonverbal

communication (48–71%), alertness (44–70%), and social interaction/connectedness (33–58%) (**Figure 4**).[1] Findings from BIQ should be interpreted with caution given the study limitations. Caregiver observations may represent chance findings, and clinical conclusions cannot be drawn from these data.

Figure 4. Area of Caregiver-reported Improvements on the BIQ up to Month 12 (Safety Analysis Set)[1]

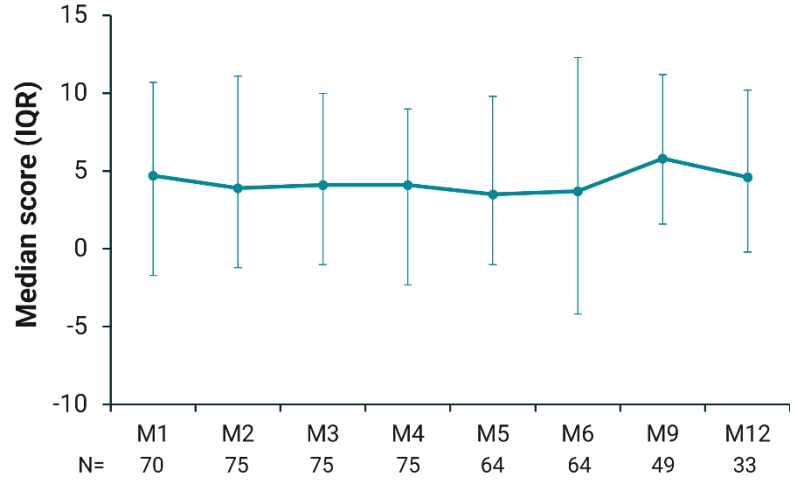


**Percentages are calculated using the number of patients whose caregiver's reported improvements.*
Abbreviation: BIQ=Behavioral Improvement Questionnaire.

Outcomes: Quality-of-Life Inventory–Disability (QI-Disability)

The median (IQR) change from baseline in QI-Disability total score was score was 4.6 (-0.2–10.2) for those patients (n=33) who had both baseline and 12-month assessments (**Figure 5**).[1] These findings are subject to limitations of the study and QI-Disability questionnaire.

Figure 5. Median QI-Disability Absolute Change in Total Score From Baseline up to Month 12 (Safety Analysis Set)[1]

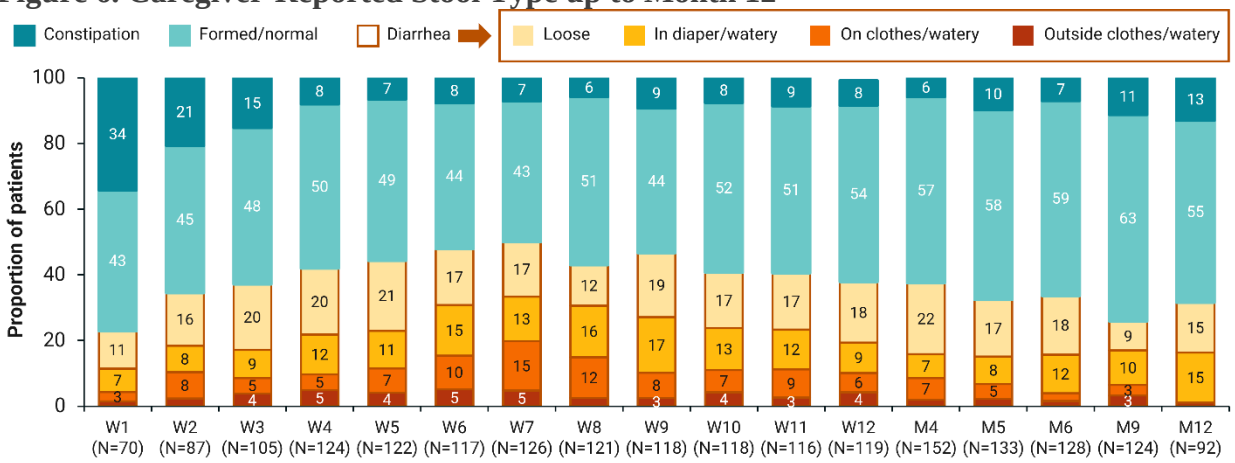


Score 0-100: Higher scores represent better Quality of Life.
Abbreviations: IQR=interquartile range; M=month; QI-Disability=Quality-of-Life Inventory–Disability.

Tolerability: GI Health Questionnaire

Diarrhea and formed/normal stool were both common, with constipation decreasing across early treatment weeks (**Figure 6**). The incidence of diarrhea varied from Weeks 1 to 12 (23−50%) and Months 4 to 12 (26−38%), with the highest incidence of diarrhea reported at Week 7 by 50% of caregivers. Most reports of diarrhea were contained inside the patient's diaper throughout this follow-up. The most common diarrhea management strategies were avoiding constipation medications (40−63%), increasing fluids to maintain hydration (21−36%), and consuming supplementary fiber (17−29%).[1]

Figure 6. Caregiver-Reported Stool Type up to Month 12*†[1]



Note, data values of ≤2 are not labeled.
**Over the last 3 days immediately prior to completing the GI assessment.*
†Subset of patients taking trofinetide on the day of the assessment.
Abbreviations: GI=gastrointestinal; M=month; W=week.

Vomiting was <12% at any given time point throughout this follow-up. Among participants with vomiting, the frequency ranged from one occurrence to one report of more than eight occurrences; one to three occurrences were most commonly reported.[1]

Adverse Events

AEs were identified incidentally by a medical monitor reviewing free text responses and interactions with the study call center. In the Safety Analysis Set (N=227), 145 AEs were recorded among 60 participants (26.4%) who were on active trofinetide treatment, of which, diarrhea, vomiting, and constipation were the most common (**Table 3**). Nineteen serious AEs were reported among ten patients (4.4%).[1]

Table 3. Incidence of AEs (Safety Analysis Set)[1]

AEs and Preferred Term, n (%)	LOTUS total (N=227)
Participants with ≥1 AE	**60 (26.4)**
AEs reported in >1 LOTUS participants	
Diarrhea	28 (12.3)
Vomiting	15 (6.6)
Constipation	7 (3.1)
Dehydration	4 (1.8)
Cough	3 (1.3)
COVID-19	3 (1.3)

AEs and Preferred Term, n (%)	LOTUS total (N=227)
Drooling	3 (1.3)
Fatigue	3 (1.3)
Insomnia	3 (1.3)
Somnolence	3 (1.3)
Weight decreased	3 (1.3)
Eating disorder	2 (0.9)
Gastroenteritis viral	2 (0.9)
Lethargy	2 (0.9)
Nasopharyngitis	2 (0.9)
Pneumonia	2 (0.9)
Product dose omission issue	2 (0.9)
Rash	2 (0.9)
Retching	2 (0.9)
Seizure	2 (0.9)
Taste disorder	2 (0.9)
Participants with ≥1 serious AEs	**10 (4.4)**
Serious AEs reported in LOTUS participants	
Dehydration	3 (1.3)
Diarrhea	3 (1.3)
Constipation	2 (0.9)
Pneumonia	2 (0.9)
Aspiration	1 (0.4)
Dysphagia	1 (0.4)
Gastritis	1 (0.4)
Gastroenteritis viral	1 (0.4)
Hypophagia	1 (0.4)
Pancreatitis	1 (0.4)
Pneumonia aspiration	1 (0.4)
Seizure	1 (0.4)
Vomiting	1 (0.4)

Abbreviation: AE=adverse event.

Limitations

The results of this interim analysis are limited by the number of patients who had reached later time points, which resulted in the data being restricted to 12 months, the lack of a placebo arm, missing data, lack of validation of the BIQ and GI Health questionnaires, reliance solely on caregiver reports, the use of descriptive statistics, and the online nature of this study.[1] Further limitations of LOTUS include the following:

- The study is based on caregiver-reported questionnaires and clinician assessment of improvements in Rett symptoms was not obtained.
- Due to the open-label nature of the study, direct causation between a drug and reported findings cannot be established.
- This is an interim analysis of an ongoing study, so some participants have not progressed to later timepoints.

References

1. Cosand L, Mayman H, Downs J, Abler V. Real-world benefits and tolerability of trofinetide for the treatment of Rett syndrome: The LOTUS study. *Dev Med Child Neurol.* 2025. doi: 10.1111/dmcn.16482. **[PubMed]**
2. Cosand L, Mayman H, Downs J, Abler V. Real-world benefits and tolerability of trofinetide for the treatment of Rett syndrome: The LOTUS study. Supporting Information. *Dev Med Child Neurol.* 2025. doi: 10.1111/dmcn.16482. **[Link]**
3. Downs J, Jacoby P, Leonard H, et al. Psychometric properties of the Quality of Life Inventory-Disability (QI-Disability) measure. *Qual Life Res.* 2019;28(3):783-794. **[PubMed]**