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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

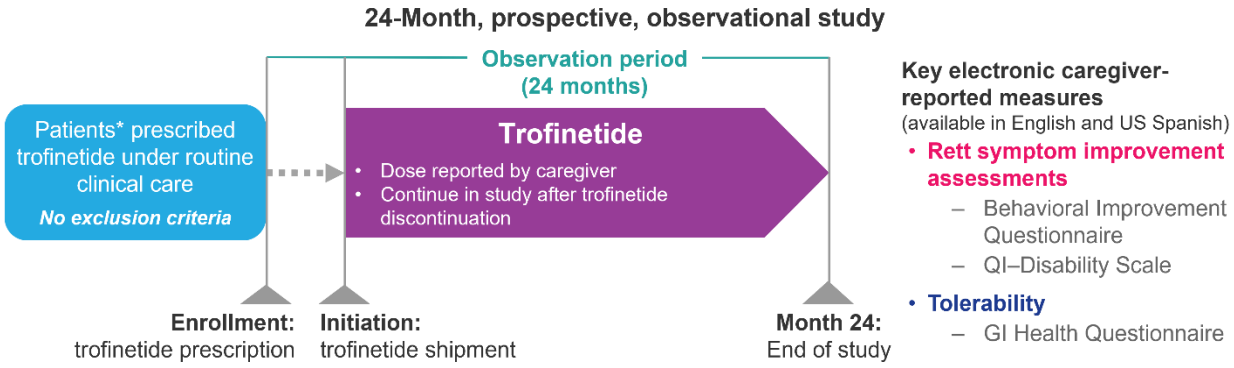
- **LOTUS** is an ongoing Phase 4, prospective, observational, real-world, open-label study involving caregivers of adults or pediatric patients of either sex who are prescribed trofinetide under routine clinical care.[1]
- **Interim analysis data** are available for 12 months of follow up (N=192). Owing to ongoing enrollment, data are presented up to 9 months since the initiation of trofinetide.[2]
    - The median (interquartile range [IQR]) **dose reported at Week 1** was 45% (20.0−76.0%) of labelled daily dose. By Week 9 onwards, ≥80% of the median target dose of trofinetide was administered.[2]
    - Overall, 69–81% of caregivers reported behavioral improvements that were new or maintained when compared with before trofinetide treatment on the **Behavioral Improvement Questionnaire** (BIQ) over the nine monthly visits. The most frequently reported improvements were nonverbal communication, alertness, and social interaction/connectedness.[2]
    - The median (IQR) **Quality-of-Life Inventory–Disability (QI-Disability) total score** was 55 (47.9−66.4) at baseline and 58.9 (53.5−69.9) at Month 9.[2]
    - Up to Month 9, **diarrhea and formed/normal stool** were both common, with constipation decreasing across early treatment weeks; vomiting was uncommon (<7% at any time point).[2]
    - Sixty **adverse events** (AEs) were recorded among 23 participants (12.0%); the most common AEs were diarrhea (5.2%), vomiting (4.2%), and constipation (1.6%).[3]
- 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**). 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[1,4,5]



**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.[4] The QI–Disability scale was developed by Downs et al.[6] as a measure of quality-of-life for children and adolescents with intellectual disability, and has been validated in individuals with Rett syndrome.[4] 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.[4]

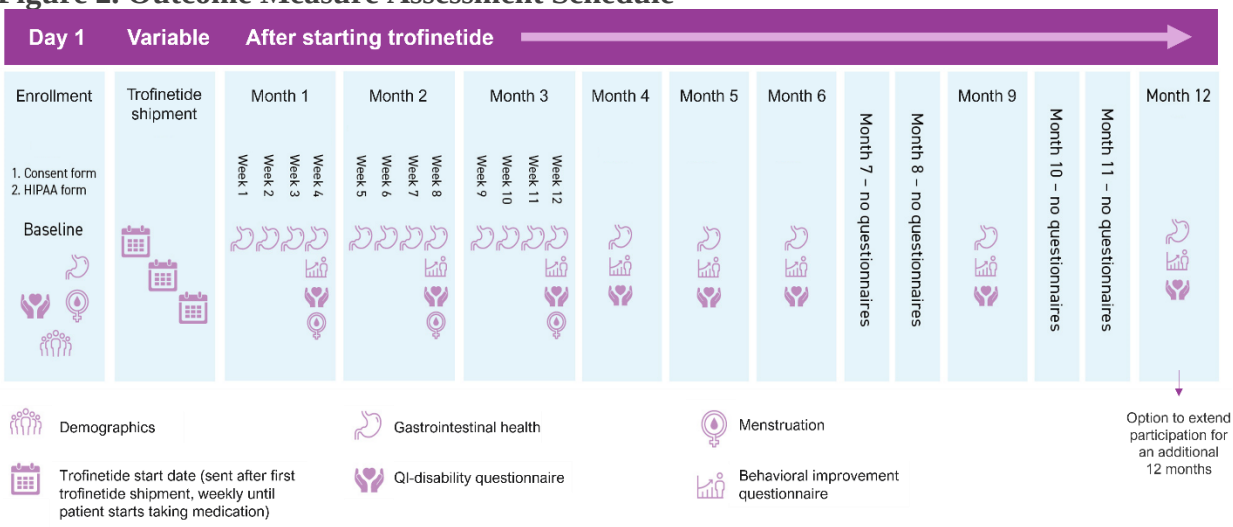
Table 1. Electronic Caregiver-reported Measures[4]

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[6]	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[1,4]



Interim 12-Month Follow-up Analysis

In total, 192 participants were included in this 12-month follow-up. Owing to ongoing enrollment, data are presented up to 9 months since the initiation of trofinetide.[2]

Participant Characteristics

Caregivers reported that 66.0% of participants had classic Rett syndrome (RTT), while 26.8% of participants had atypical RTT (**Table 2**). Most participants were female (95.8%), and patient age ranged from 2 to 60 years.[2]

Table 2. Baseline Demographics and Characteristics[2]

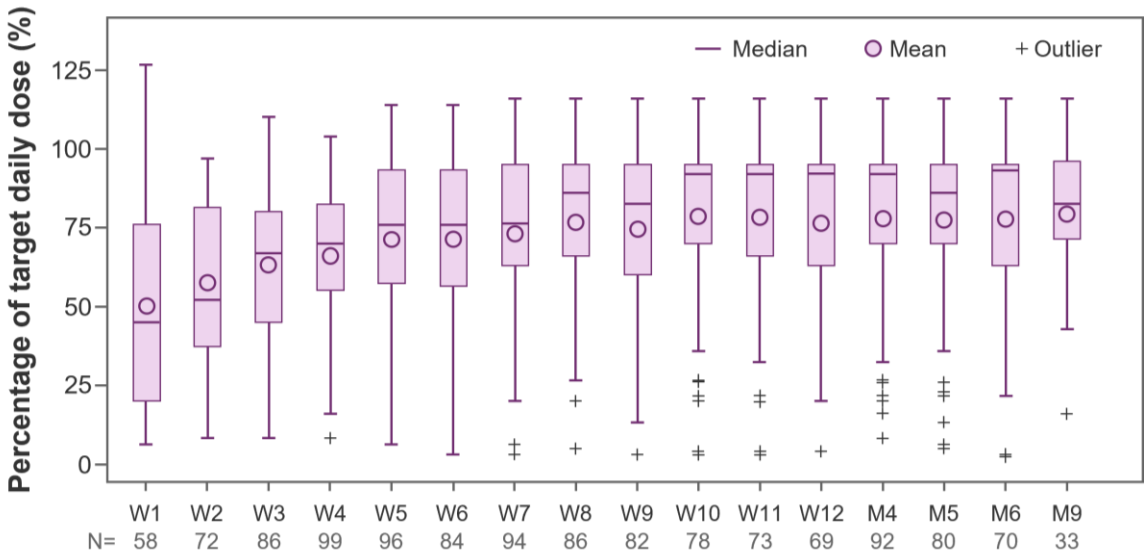
	Total (N=192)
Rett syndrome type, n (%)	
n	153
Classic	101 (66.0)
Atypical	41 (26.8)
Does not meet diagnostic criteria for either	11 (7.2)
Sex, n (%)	
n	191
Male	8 (4.2)
Female	183 (95.8)
Age at the time of diagnosis, years	
n	141
Median (IQR)	3.0 (2.0–5.0)
Age at the time of trofinetide initiation*, years	
n	135
Median (IQR)	15.0 (7.0–24.0)

n-values may not be 192 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 45.0% of the target, weight-banded label dose with wide variability in dosing (IQR, 20.0–76.0% of labeled daily dose). By Week 9 onwards, ≥80% of the median target dose of trofinetide was administered (**Figure 3**).[2] By Week 12, the median dose was 92.0% of target.[7]

Figure 3. Percentage of Target Daily Dose[2]



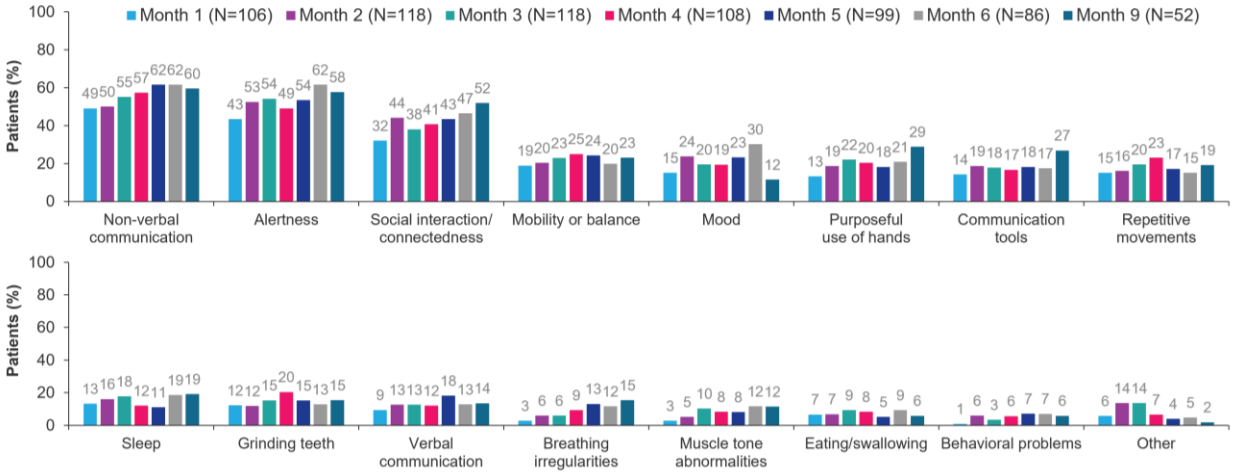
Percentage of target daily dose was calculated as: prescribing info (per label) of trofinetide [percentage of target daily dose] is [actual daily dose]/[target daily dose based on patient's weight at shipment transaction]×100.
Abbreviations: M=month; W=week.

Most commonly, caregivers reported two doses administered per day (59.6−93.1% across time points). The maximum number of doses per day was four.[2]

Outcomes: Behavioral Improvement Questionnaire (BIQ)

In patients on active trofinetide treatment, 69−81% of caregivers reported behavioral improvements on the BIQ over the nine monthly visits that were new or maintained compared with before trofinetide treatment. The most frequently reported improvements were nonverbal communication (49–62%), alertness (43–62%), and social interaction/connectedness (32–52%) (**Figure 4**).[2] 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 9[2]

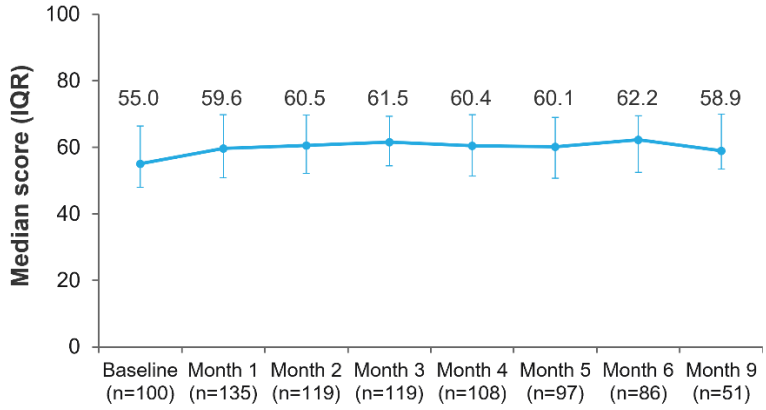


Percentages are calculated using the number of patients whose caregiver's reported improvements.
Abbreviation: BIQ=Behavioral Improvement Questionnaire.

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

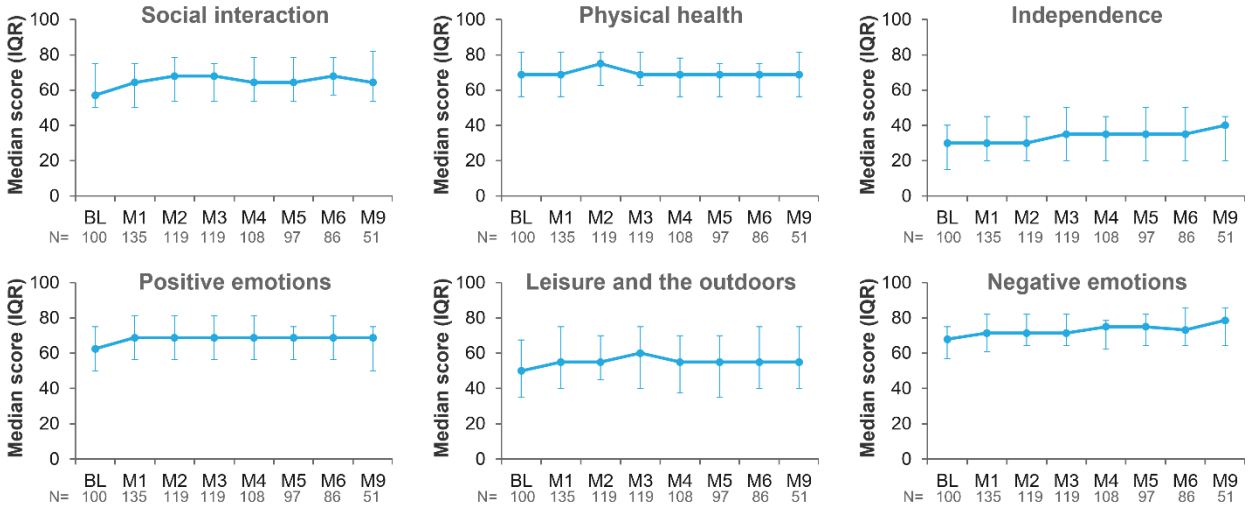
The median (IQR) QI-Disability total score was 55.0 (47.9−66.4) at baseline and 58.9 (53.5−69.9) at Month 9 (**Figure 5**). Individual QI-Disability domain scores over time are shown in **Figure 6**.[2] These findings are subject to limitations of the study and QI-Disability questionnaire.

Figure 5. Median QI-Disability Total Score Over Time up to Month 9[2]



Score 0-100: Higher scores represent better Quality of Life.[8]
Abbreviations: IQR=interquartile range; QI-Disability=Quality-of-Life Inventory–Disability.

Figure 6. Median QI-Disability Domain Scores Over Time up to Month 9[2]

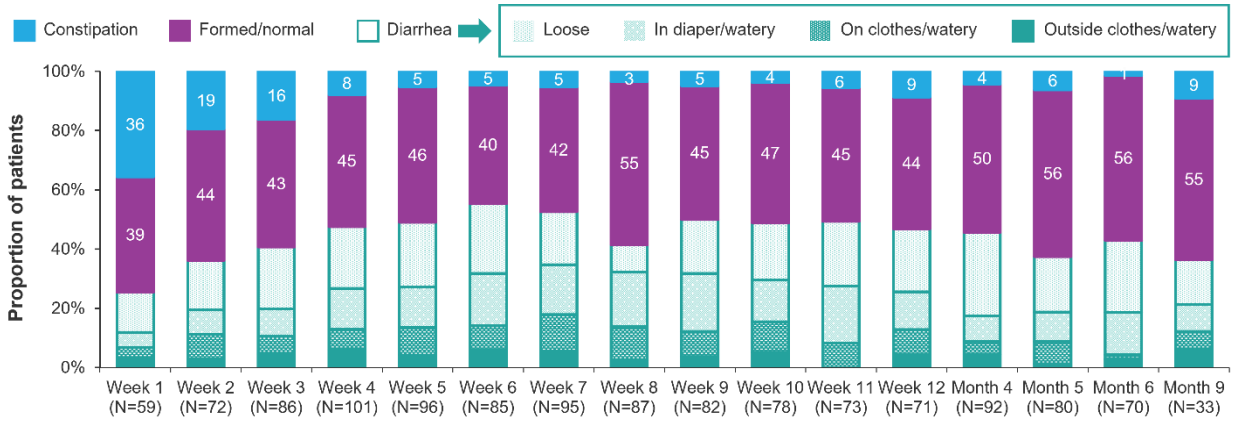


Score 0-100: Higher scores represent better Quality of Life.[8] Increase in negative emotion score corresponds to lower levels of negative emotion.
Abbreviations: BL=baseline; IQR=interquartile range; M=month; QI-Disability=Quality-of-Life Inventory–Disability.

Tolerability: GI Health Questionnaire

Diarrhea and formed/normal stool were both common, with constipation decreasing across early treatment weeks (**Figure 7**). The incidence of diarrhea varied from Weeks 1 to 12 (25−55%) and Months 4 to 9 (36−46%), with the highest incidence of diarrhea reported at Week 6 by 55% 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 (42−61%), increasing fluids to maintain hydration (18−39%), and consuming supplementary fiber (18−31%).[2]

Figure 7. Caregiver-Reported Stool Type up to Month 9*[2]



**Over the last 3 days immediately prior to completing the GI assessment.*

Vomiting was <7% 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.[2]

Adverse Events

AEs were identified incidentally by a medical monitor reviewing free text responses and interactions with the study call center.[4] In the Safety Analysis Set (N=192), i.e., all enrolled patients who received at least one dose of trofinetide, 60 AEs were recorded among 23 participants (12.0%) who were on active trofinetide treatment, of which, diarrhea, vomiting, and constipation were the most common (**Table 3**). Ten serious AEs were reported among six patients (3.1%).[3]

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

AEs and Preferred Term, n (%)	LOTUS total (N=192)
Participants with ≥1 AE	**23 (12.0)**
AEs reported in >1 LOTUS participants	
Diarrhea	10 (5.2)
Vomiting	8 (4.2)
Constipation	3 (1.6)
Insomnia	3 (1.6)
Drooling	2 (1.0)
Retching	2 (1.0)
Somnolence	2 (1.0)
Taste disorder	2 (1.0)
Participants with ≥1 serious AEs	**6 (3.1)**
Serious AEs reported in LOTUS participants	
Constipation	2 (1.0)
Diarrhea	2 (1.0)
Dehydration	1 (0.5)
Gastroenteritis viral	1 (0.5)
Pneumonia	1 (0.5)
Pneumonia aspiration	1 (0.5)
Vomiting	1 (0.5)

Abbreviation: AE=adverse event.

Limitations

The results of this interim analysis are limited by the lack of a placebo arm, missing data, lack of validation of the BIQ and GI Health questionnaires, and the online nature of this study. 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

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2. Mayman H, et al. Real-world benefits and tolerability of trofinetide for the treatment of Rett syndrome: Interim analysis of the LOTUS study. Poster presented at the International Rett Syndrome Foundation's Scientific Meeting (IRSF); June 9–11, 2025.
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