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

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DAYBUE® (trofinetide): Clinical Trials and Observational Studies in Adult Patients with Rett Syndrome

This letter is provided in response to your specific request for information regarding the clinical trials and observational studies of trofinetide in adult patients with Rett syndrome (RTT).

Relevant Label Information[1]

- DAYBUE and DAYBUE® STIX (trofinetide) are indicated for the treatment of Rett syndrome in adults and pediatric patients 2 years of age and older.

Summary

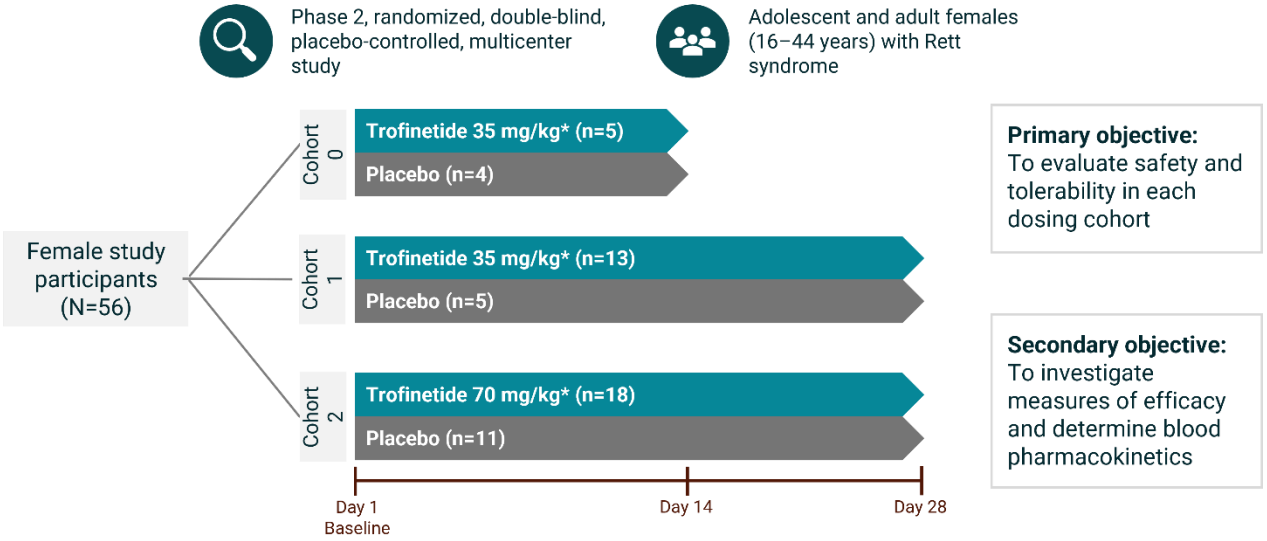
- The **ACP-2566-001 (Study 001)** was an exploratory, Phase 2, double-blind, placebo-controlled, dose-escalation study in 56 adolescent and adult female participants with RTT to assess the safety and tolerability of trofinetide.[2]
  - Trofinetide was administered orally at doses of 35 mg/kg twice daily and 70 mg/kg twice daily for up to 28 days.[2]
  - The **mean age** for all participants (modified intent to treat [mITT], N=55) was 25.3 years (range: 15.9 to 44.2 years). The maximum age in the trofinetide group was 40.8 years.[2]
  - **Trofinetide was tolerable over 28 days**; the most common reported treatment-emergent adverse event (TEAE) with a higher incidence vs placebo was diarrhea (39% [7/18] in the trofinetide 35 mg/kg twice daily group vs 15% [3/20] in the placebo group).[2]
- **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.[3] **Interim analysis data** up to 12 months since the initiation of trofinetide are available for 77 adult patients aged ≥20 years with RTT.[4]

Phase 2 Study 001

Study 001 was an exploratory randomized, double-blind, placebo-controlled, multicenter, parallel-group, Phase 2 study in adolescent and adult female participants with RTT (**Figure 1**).[2,5] The secondary measures of efficacy used in the study provided insight into potential efficacy measures for future studies.[2]

Initially, participants were randomly assigned in a 2:1 ratio to trofinetide or placebo for 14 days in the first of 2 sequential dose cohorts (35 mg/kg twice daily for cohort 1 and 70 mg/kg twice daily for cohort 2).[2] After 9 participants were enrolled in cohort 1 and following review by an independent Data and Safety Monitoring Committee, the protocol was amended to extend the treatment period to 28 days for cohort 1. The 9 participants receiving only 14 days of treatment are referred to as cohort 0. Selected inclusion and exclusion criteria for Study 001 are shown in **Table 1**.[5]

Figure 1. Study Design for Study 001[2,5]



**Treatments were given orally twice daily. Participants were up-titrated to their assigned dose based on a predefined dosing schedule.*

Table 1. Selected Inclusion and Exclusion Criteria for Study 001[5]

Selected inclusion criteria
• Classic RTT with a proven mutation in the *MECP2* gene • Aged between 16 years and 45 years • Severity rating on the Rett Syndrome Natural History/Clinical Severity Scale between 10 and 36 • CGI-S score of ≥4 • Stable on current concomitant medications for ≥4 weeks • Able to swallow the study drug provided as a liquid solution or via gastrostomy tube
Selected exclusion criteria
• No detectable abnormality of the EEG during screening assessment • Actively undergoing regression • Screening QT/QTcF interval >450 milliseconds • History of risk factors for torsade de pointes • Prior QT/QTcF prolongation that was controlled with medication, in which normal QT/QTcF intervals could only be achieved with medication • Previous clinically significant QT/QTcF prolongation that was deemed to presently put the participant at increased risk of clinically significant QT/QTcF prolongation • Current treatment with insulin

Abbreviations: CGI-S=Clinical Global Impression-Severity; EEG=electroencephalogram; MECP2=Methyl-CpG Binding Protein 2; QTcF=corrected QT interval using Fridericia's correction method; RTT=Rett syndrome.

Baseline Characteristics

The mean age of all participants in the mITT population was 25.3 years (range: 15.9 to 44.2 years); the maximum age in the trofinetide group was 40.8 years.[2] Most participants were White (89%, 49/55 participants); and the mean body mass index of all participants was 21.84 kg/m^2. Baseline severity on the Clinical Severity Scale (CSS) and Motor Behavior Assessment (MBA) total and change index scores was overall balanced between treatment groups within cohorts and across cohorts (**Table 2**).

Table 2. Baseline Demographics and Disease Characteristics in Study 001 (mITT population*)[2]

	Cohort 0		Cohort 1		Cohort 2	
	Placebo n=4	35 mg/kg n=5	Placebo n=5	35 mg/kg n=13	Placebo n=11	70 mg/kg n=17
Age, years						
Mean (SD)	22.43 (4.610)	26.65 (8.775)	32.09 (9.324)	22.62 (5.582)	27.09 (8.357)	24.52 (5.853)
Median	22.20	25.38	33.93	20.62	25.21	23.90
Min, Max	17.4, 27.9	17.6, 40.8	18.5, 44.2	15.9, 31.0	16.3, 43.9	17.1, 35.9
Ethnicity, n (%)						
Hispanic or Latino	2 (50)	0	1 (20)	0	0	2 (12)
Not Hispanic or Latino	2 (50)	5 (100)	4 (80)	13 (100)	11 (100)	15 (88)
Race, n (%)						
White	3 (75)	5 (100)	5 (100)	10 (77)	11 (100)	15 (88)
Black or African American	1 (25)	0	0	3 (23)	0	1 (6)
Asian	0	0	0	0	0	1 (6)
Severity scores, mean (SD)						
CSS total score	23.3 (6.29)	25.0 (3.46)	20.2 (8.11)	22.9 (7.98)	25.4 (6.22)	24.5 (6.64)
MBA total score	49.5 (9.33)	56.6 (8.53)	44.6 (13.41)	47.9 (15.29)	48.4 (8.50)	49.8 (12.37)
CSS change index score	8.3 (0.96)	7.8 (1.92)	8.2 (2.39)	8.4 (2.47)	9.1 (2.55)	8.4 (1.84)
MBA change index score	24.0 (4.83)	24.6 (3.65)	21.2 (5.81)	20.8 (5.81)	22.4 (3.80)	23.1 (5.97)

**One (1) participant discontinued the study before receiving any study medication.*
Abbreviations: CSS=Clinical Severity Scale; MBA=Motor Behavior Assessment Scale; mITT=modified intent to treat; SD=standard deviation.

Safety Results

The most commonly reported TEAEs (i.e. >2 participants in either active treatment group) with a higher incidence compared with the placebo group were diarrhea (39% in the 35 mg/kg group vs 15% in the placebo group), irritability (22% in the 35 mg/kg group vs 15% in the placebo group), and somnolence (17% in the 70 mg/kg group vs 5% in the placebo group; **Table 3**).[2]

Table 3. Incidence of TEAEs by Combined Cohorts During the Treatment Period in Study 001 (ITT Population)*[2]

System Organ Class Preferred Term, n (%)	Placebo (n=20)	35 mg/kg (n=18)	70 mg/kg (n=18)	Total (N=56)
Reported ≥1 TEAE	15 (75)	17 (94)	10 (56)	42 (75)
Gastrointestinal disorders				
Diarrhea	3 (15)	7 (39)	2 (11)	12 (21)
Vomiting	0	0	2 (11)	2 (4)
General disorders and administration site conditions				
Pyrexia	4 (20)	2 (11)	0	6 (11)
Infections and infestations				
Upper respiratory tract infection	1 (5)	1 (6)	2 (11)	4 (7)
Injury, poisoning, and procedural complications				
Fall	3 (15)	1 (6)	0	4 (7)
Nervous system disorders				

System Organ Class Preferred Term, n (%)	Placebo (n=20)	35 mg/kg (n=18)	70 mg/kg (n=18)	Total (N=56)
Somnolence	1 (5)	0	3 (17)	4 (7)
Drooling	0	1 (6)	2 (11)	3 (5)
Tremor	2 (10)	1 (6)	0	3 (5)
Complex partial seizures	0	0	2 (11)	2 (4)
Convulsion	2 (10)	0	0	2 (4)
Psychiatric disorders				
Irritability	3 (15)	4 (22)	0	7 (13)
Agitation	1 (5)	2 (11)	1 (6)	4 (7)
Insomnia	0	2 (11)	2 (11)	4 (7)
Hypervigilance	2 (10)	1 (6)	0	3 (5)
Mood swings	0	2 (11)	0	2 (4)
Sleep disorder	0	1 (6)	1 (6)	2 (4)
Respiratory, thoracic, and mediastinal disorders				
Cough	1 (5)	1 (6)	0	2 (4)
Skin and subcutaneous tissue disorders				
Rash	2 (10)	0	0	2 (4)

**TEAEs reported in at least 2 participants in either active treatment group.*
Abbreviations: ITT=intent to treat; TEAE=treatment-emergent adverse event.

Three (3) participants experienced serious TEAEs, none of which were deemed related to treatment with trofinetide.[2] One (1) participant discontinued due to serious TEAEs. Most TEAEs were mild or moderate in intensity and were not considered related to study drug. No deaths were reported during the study. Clinical laboratory tests, electrocardiograms, vital signs, and physical examinations (including fundoscopy and tonsil hypertrophy) indicated no time-dependent or dose-dependent trends.

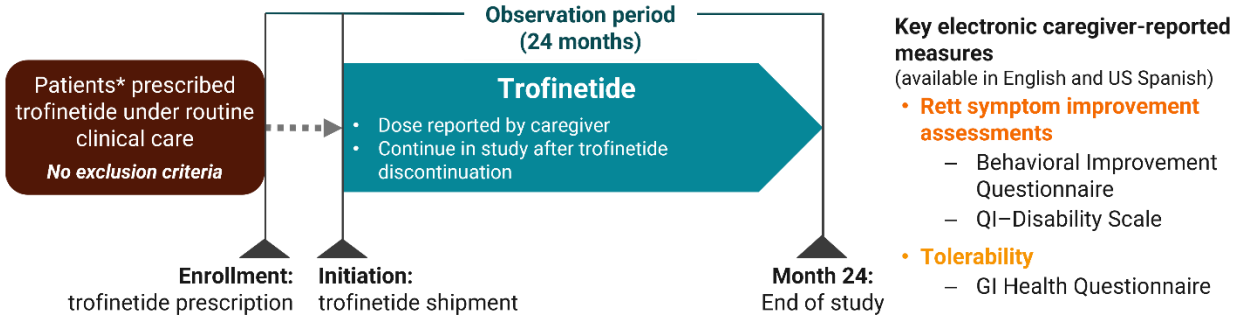
Efficacy Results

Results from the group-level analysis by individual cohort showed that trofinetide at 70 mg/kg twice daily exceeded the minimum requirement for efficacy based on prespecified criteria.

Phase 4 LOTUS Study (ACP-2566-014)

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 2**). 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.[3]

Figure 2. LOTUS Study Design[3,6]



**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 4**). The Behavioral Improvement Questionnaire (BIQ) and Gastrointestinal (GI) Health Questionnaire were developed by Acadia for the LOTUS study and have not been validated in individuals with Rett syndrome.[3] The QI–Disability scale was developed by Downs et al.[7] 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.[3]

Table 4. Electronic Caregiver-reported Measures[6]

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[7]	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.

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.[3]

Interim 18-Month Follow-up Analysis in Adult Participants

In total, 77 adult participants aged ≥20 years were included in this 18-month follow-up, with ages ranging from 21 to 60 years (**Table 5**). Owing to ongoing enrollment, data are presented up to 12 months since the initiation of trofinetide. The median trofinetide dose at Week 1 was 50.3% of the target weight-banded label dose. Dosing ranged from 53.0–75.0% of the target weight-banded label dose between Week 2 and Month 12. Trofinetide was administered twice daily in 88.2–100.0% of participants, once daily in ≤4.3% of participants or 3 times per day in 2.5–10.3% of participants.[4]

Table 5. Baseline Demographics and Characteristics[4]

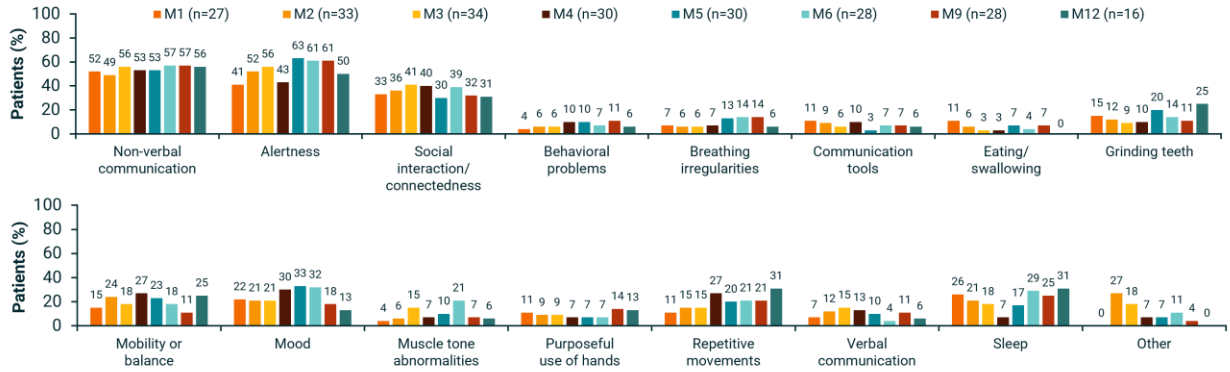
Characteristics	Adult LOTUS participants (N=77)
RTT type, n (%)	
Classic	40 (67.8)
Atypical	16 (27.1)
Does not meet diagnostic criteria for either	3 (5.1)
Missing	18 (23.4)
Sex, n (%)	
Male	2 (2.6)
Female	75 (97.4)
Median (IQR) age at time of RTT diagnosis, years*	4.5 (3.0–15.5)
Median (IQR) age at time of trofinetide initiation, years†	28.0 (24.0–33.0)

**n=56.*
†Trofinetide initiation is the day of trofinetide shipment.
Abbreviations: IQR=interquartile range; RTT = Rett syndrome.

Outcomes: Behavioral Improvement Questionnaire (BIQ)

Overall, in adult participants who had taken ≥1 dose of trofinetide, 75–85% of caregivers reported behavioral improvements on the BIQ over the visits through to Month 12 that were new or maintained compared with before trofinetide treatment. The most frequently reported improvements were nonverbal communication (49–57%), alertness (41–63%), and social interaction/connectedness (30–41%) (**Figure 3**).[4] 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 3. Area of Caregiver-reported Improvements on the BIQ up to Month 12[4]

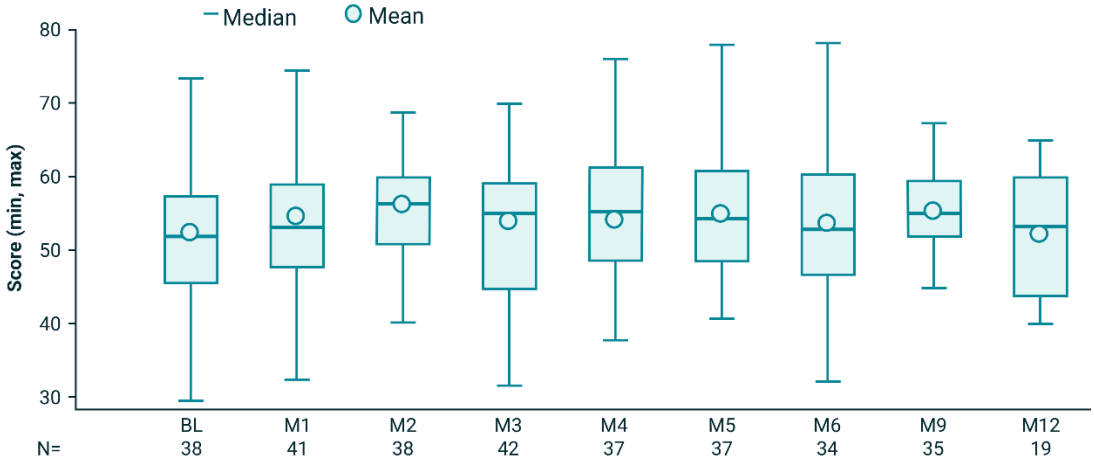


**Percentages are calculated using the number of patients whose caregiver's reported improvements.*
Abbreviations: BIQ=Behavioral Improvement Questionnaire; M=Month

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

The QI-Disability questionnaire median total score was higher than the baseline of 52.1 (IQR, 45.5–57.3) at nearly every measured timepoint in patients who had taken ≥1 dose of trofinetide (**Figure 4**).[4] These findings are subject to limitations of the study and QI-Disability questionnaire.

Figure 4. Box Plot of QI-Disability Total Score up to Month 12*†[4]

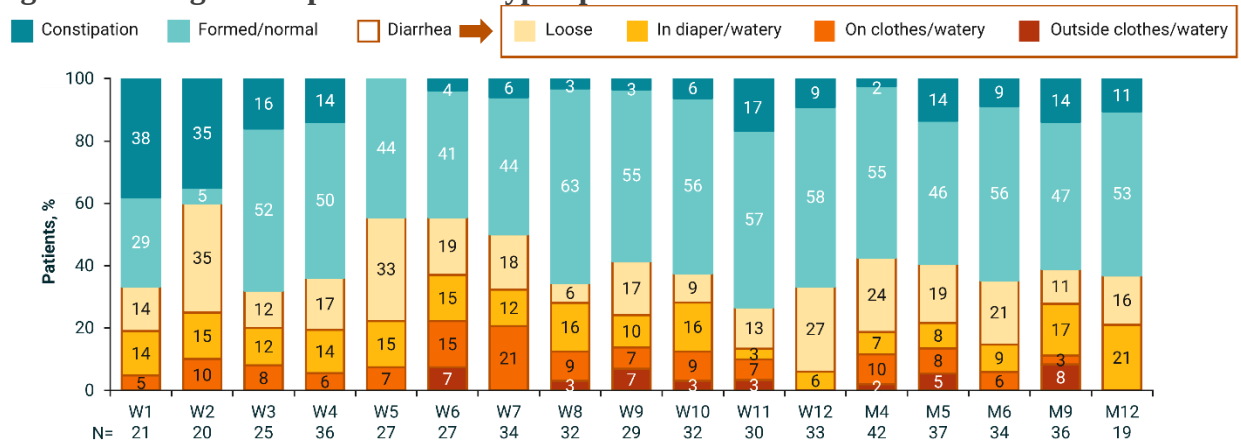


**n=55.*
†Score 0-100: Higher scores represent better Quality of Life.
Abbreviations: BL=baseline; M=month; QI-Disability=Quality-of-Life Inventory–Disability.

Tolerability: GI Health Questionnaire

Caregivers reported that adult patients were most likely to void normal stools over the last 3 days before completing the GI assessment (**Figure 5**). The highest incidence of diarrhea was reported at Week 2 (60%). Most reports of diarrhea were contained inside the patient's diaper throughout this follow-up. The most common diarrhea management strategies employed in the week prior to completing the GI assessment were skipping trofinetide doses (22–40%), taking a lower dose of trofinetide (8–29%), and increasing fluids to maintain hydration (8–16%).[4] Findings from the GI Health Questionnaire should be interpreted with caution due to study limitations.

Figure 5. Caregiver-Reported Stool Type up to Month 12*[4]



**Over the last 3 days immediately prior to completing the GI assessment.*
Abbreviations: GI=gastrointestinal; M=month; W=week.

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.[3] 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. DAYBUE® (trofinetide) [package insert]. San Diego, CA. Acadia Pharmaceuticals Inc. **[Link]**
2. Glaze DG, Neul JL, Percy A, et al. A Double-Blind, Randomized, Placebo-Controlled Clinical Study of Trofinetide in the Treatment of Rett Syndrome. *Pediatr Neurol.* 2017;76:37-46. **[PubMed]**
3. 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.* 2026;68(3):407-417. **[PubMed]**
4. Cosand L, Bucco R. Real-World Benefits and Tolerability of Trofinetide for the Treatment of Adults With Rett Syndrome: The LOTUS Study. Poster presented at the American Academy of Neurology (AAN) Annual Meeting, April 18–22, 2026.
5. Acadia Pharmaceuticals Inc. Data on File. In. San Diego, CA.
6. 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.* 2026;68(3):407-417. **[Link]**
7. 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]**