



acadia
medical affairs

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](#).

DAYBUE[®] (trofinetide): Adverse Events in Clinical Trials

This letter is provided in response to your specific request for information regarding the adverse events (AEs) experienced by participants in the clinical trials of trofinetide in Rett syndrome (RTT).

Relevant Labeling Information¹

- **Warnings and Precautions**

- In LAVENDER[™] and in long-term studies, 85% of patients treated with DAYBUE experienced diarrhea. In those treated with DAYBUE, 49% either had persistent diarrhea or recurrence after resolution despite dose interruptions, reductions, or concomitant antidiarrheal therapy. Diarrhea severity was of mild or moderate severity in 96% of cases. In LAVENDER, antidiarrheal medication was used in 51% of patients treated with DAYBUE.
- In LAVENDER, 12% of patients treated with DAYBUE experienced weight loss of greater than 7% from baseline, compared to 4% of patients who received placebo. In long-term studies, 2.2% of patients discontinued treatment with DAYBUE due to weight loss.
- In LAVENDER, vomiting occurred in 29% of patients treated with DAYBUE and in 12% of patients who received placebo. Patients with Rett syndrome are at risk for aspiration and aspiration pneumonia. Aspiration and aspiration pneumonia have been reported following vomiting in patients being treated with DAYBUE.

Summary

- The 12-week [Phase 3 LAVENDER study](#) evaluated the efficacy and safety of trofinetide in 187 female participants (5–20 years old) with RTT.²
 - [Treatment emergent AEs \(TEAEs\)](#) were reported in 92.5% of participants in the trofinetide arm (N=93) and 54.3% in the placebo arm (N=94), with TEAEs leading to discontinuation in 17.2% and 2.1%, respectively, and serious TEAEs in 3.2% of each group.²
 - The most [common TEAEs](#) were diarrhea (80.6% with trofinetide vs. 19.1% with placebo) and vomiting (26.9% with trofinetide vs. 9.6% with placebo). Most TEAEs of diarrhea and vomiting in the trofinetide group (97.3% and 96.0%, respectively) were characterized as mild-to-moderate. In the placebo group, 100% of diarrhea and vomiting TEAEs were characterized as mild-to-moderate.²
- In the 40-week [LILAC-1[™] open-label extension](#) (OLE) study (N=154), 92.9% of participants reported AEs, 12.3% reported serious AEs and 35.7% reported AEs leading to discontinuation. The most common AEs were diarrhea (74.7%) and vomiting (28.6%).³
- In the 32-month [LILAC-2[™] OLE study](#) (N=77), 93.5% reported AEs, 29.9% reported serious AEs and 11.7% reported AEs leading to discontinuation. The most common AEs were diarrhea (53.2%), COVID-19 (27.3%) and vomiting (19.5%). There were four deaths during the study, none of which were considered related to study drug.⁴

This was a 12-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group, Phase 3 study in 187 female participants (5–20 years old) with a diagnosis of typical RTT according to the Rett Syndrome Diagnostic Criteria and a documented disease-causing mutation in the *MECP2* gene (**Figure 1**).^{1,2} Participants received trofinetide 30–60 mL twice daily (BID) or placebo, based on their weight at baseline, administered orally or by gastrostomy tube. The primary objective of this study was to investigate the efficacy of treatment with oral trofinetide versus placebo in girls and women with RTT.^{2,6}

The flowchart illustrates the study design timeline:

- Screening period** (≤3 weeks): 187 female participants (5–20 years old) with Rett syndrome are recruited.
- Double-blind treatment period** (12 weeks): Participants are randomized to either Trofinetide PO BID* (N=93) or Placebo PO BID* (N=94).
- Safety follow-up period** (30(+4) days): The study concludes at Week 12.

Co-primary endpoints are measured at Week 12:

- RSBQ total score – change from baseline to Week 12
- CGI-I score at Week 12

Abbreviations: BID=twice a day; CGI-I=Clinical Global Impression-Improvement; PO=oral; RSBQ=Rettsyndrome Behaviour Questionnaire.

Baseline Characteristics

Treatment groups were well balanced for demographic and baseline characteristics.² In the Randomized Analysis Set (all randomized participants),⁶ the mean (standard deviation [SD]) age of participants was 11.0 (4.69) years in the trofinetide group (N=93) and 10.9 (4.57) in the placebo (N=94), with a mean (SD) baseline CGI-S score of 4.9 (0.77) and 4.9 (0.76), respectively. Most participants (88.2% of the trofinetide group and 95.7% of the placebo group) were White.²

In the Safety Analysis Set (all randomized participants who received ≥ 1 dose of study medication), 75.3% of participants in the trofinetide group (N=93) had a history of constipation, compared with 78.7% in the placebo group (N=94). Medical history of seizures was reported in

43.0% of participants in the trofinetide group and 50.0% of participants in the placebo group, and medical history of epilepsy was reported in 21.5% of participants in the trofinetide group and 17.0% of participants in the placebo group.²

Antiepileptics (68.4%) and drugs for constipation (65.2%) were the most frequently used concomitant medications in both treatment groups. Loperamide was used in 50.5% of participants on trofinetide and 3.2% on placebo.² Antiemetics and antinauseants were used in 6.5% of participants on trofinetide and 4.3% on placebo.⁸

Safety Results

In the respective trofinetide and placebo groups, at least one TEAE was reported in 86 (92.5%) and 51 (54.3%) participants (**Table 1**). No deaths were reported.²

Table 1. Summary of TEAEs (ACP-2566-003; Safety Analysis Set)⁸

	Placebo (N=94) n (%)	Trofinetide (N=93) n (%)
Any TEAE	51 (54.3)	86 (92.5)
Any serious TEAE	3 (3.2)	3 (3.2)
Any related TEAE	20 (21.3)	78 (83.9)
Any related serious TEAE	1 (1.1)	2 (2.2)
Any TEAE leading to drug withdrawn	2 (2.1)	16 (17.2)*
Any severe TEAE	3 (3.2)	6 (6.5)
Any fatal TEAE	0	0

*During the NDA review, the FDA assigned 2 additional discontinuations due to TEAEs based on participant narratives, to be 18 (19%). This was reviewed and agreed upon by Acadia.

Abbreviations: NDA=New Drug Application; TEAE=treatment-emergent adverse event.

The most common TEAEs were diarrhea and vomiting. Diarrhea was reported in 80.6% of participants treated with trofinetide and 19.1% of participants treated with placebo (**Table 2**). Of the TEAEs of diarrhea in the trofinetide arm, 97.3% were characterized as mild-to-moderate (severe diarrhea was observed in 2 participants; **Table 3**). In the placebo group, 100% (18/18) of diarrhea TEAEs were characterized as mild-to-moderate,² with the following definitions:⁶

- Mild: easily tolerated, causing minimal discomfort, and not interfering with normal everyday activities.
- Moderate: sufficiently discomforting to interfere with normal everyday activities.
- Severe: incapacitating and/or preventing normal everyday activities.

Vomiting was reported in 26.9% of participants treated with trofinetide and 9.6% of participants treated with placebo (**Table 2**). Of the TEAEs of vomiting in the trofinetide arm, 96% were characterized as mild-to-moderate (severe vomiting was observed in 1 participant; **Table 3**). In the placebo group, 100% (9/9) of vomiting TEAEs were characterized as mild-to-moderate.²

Table 2. TEAEs in ≥5% in Either Treatment Group (ACP-2566-003; Safety Analysis Set)²

Preferred Term	Placebo (N=94) n (%)	Trofinetide (N=93) n (%)
Diarrhea	18 (19.1)	75 (80.6)
Vomiting	9 (9.6)	25 (26.9)
Seizure	5 (5.3)	8 (8.6)
Pyrexia	4 (4.3)	8 (8.6)

Preferred Term	Placebo (N=94) n (%)	Trofinetide (N=93) n (%)
Decreased appetite	2 (2.1)	5 (5.4)
Irritability	0	6 (6.5)

Abbreviation: TEAE=treatment-emergent adverse event.

Table 3. TEAEs in $\geq 5\%$ in Either Treatment Group by Severity (ACP-2566-003; Safety Analysis Set)²

Preferred Term	Placebo (N=94) n (%)			Trofinetide (N=93) n (%)		
	Mild	Moderate	Severe	Mild	Moderate	Severe
Diarrhea	15 (16.0)	3 (3.2)	0	39 (41.9)	34 (36.6)	2 (2.2)
Vomiting	8 (8.5)	1 (1.1)	0	18 (19.4)	6 (6.5)	1 (1.1)
Seizure	3 (3.2)	2 (2.1)	0	3 (3.2)	5 (5.4)	0
Pyrexia	2 (2.1)	2 (2.1)	0	7 (7.5)	1 (1.1)	0
Decreased appetite	1 (1.1)	1 (1.1)	0	2 (2.2)	3 (3.2)	0
Irritability	0	0	0	3 (3.2)	2 (2.2)	1 (1.1)

Abbreviation: TEAE=treatment-emergent adverse event.

Serious TEAEs were observed in 3.2% of study participants in both the trofinetide and placebo groups (**Table 1**).² Serious TEAEs were bacteremia/urinary tract infection/bronchiolitis (n=1), COVID-19 pneumonia (n=1), and seizure (n=1) in the participants treated with trofinetide, and respiratory distress (n=1), constipation (n=1), and pneumatosis intestinalis (n=1) in the participants treated with placebo.² For each of these participants, the TEAE was assessed as serious due to hospitalization.⁸

Eight severe TEAEs were observed in 6 (6.5%) participants in the trofinetide group: diarrhea (n=2), vomiting (n=1), bacteremia (n=1), urinary tract infection (n=1), COVID-19 pneumonia (n=1), irritability (n=1), and agitation (n=1). Three severe TEAEs were observed in 3 (3.2%) of participants in the placebo group: respiratory distress (n=1), constipation (n=1), and pneumatosis intestinalis (n=1).⁸

Study treatment discontinuation rates related to TEAEs were 17.2% in the trofinetide group as compared to 2.1% in the placebo group (**Table 4**). In the trofinetide group, TEAEs leading to discontinuation of study drug were most commonly reported for diarrhea (12.9%), decreased appetite (3.2%), and lethargy and seizure (2.2% each).² All of the TEAEs leading to discontinuation of study drug were considered related to study drug, except for 1 case of arthralgia in the placebo group.⁸

Changes in laboratory tests, electrocardiograms and vital signs were generally small and similar in the treatment groups; none were considered clinically meaningful.² Small, transient changes in alanine aminotransferase values were reported in seven of 92 (7.6%) and three of 93 (3.2%) participants in the trofinetide and placebo groups, respectively. These changes were not associated with notable changes in other liver function tests, and no instances met Hy's law criteria.^{2,9}

Table 4. TEAEs Leading to Discontinuation of Study Drug (ACP-2566-003; Safety Analysis Set)^{2,8}

MedDRA System Organ Class Preferred Term	Placebo (N=94)		Trofinetide (N=93)	
	Participants, n (%)	Events, n	Participants, n (%)	Events, n
Any TEAE leading to discontinuation of study drug	2 (2.1)	2	16 (17.2)*	23
Gastrointestinal disorders	1 (1.1)	1	14 (15.1)	15
Diarrhea	0	0	12 (12.9) [†]	12
Frequent bowel movements	0	0	1 (1.1)	1
Gastroesophageal reflux disease	0	0	1 (1.1)	1
Pneumatosis intestinalis	1 (1.1)	1	0	0
Vomiting	0	0	1 (1.1)	1
Investigations	0	0	1 (1.1)	1
Weight decreased	0	0	1 (1.1)	1
Metabolism and nutrition disorders	0	0	3 (3.2)	3
Decreased appetite	0	0	3 (3.2)	3
Musculoskeletal and connective tissue disorders	1 (1.1)	1	0	0
Arthralgia	1 (1.1)	1	0	0
Nervous system disorders	0	0	4 (4.3)	4
Lethargy	0	0	2 (2.2)	2
Seizure	0	0	2 (2.2)	2

*During the NDA review, the FDA assigned 2 additional discontinuations due to TEAEs based on participant narratives, to be 18 (19%). This was reviewed and agreed upon by Acadia.

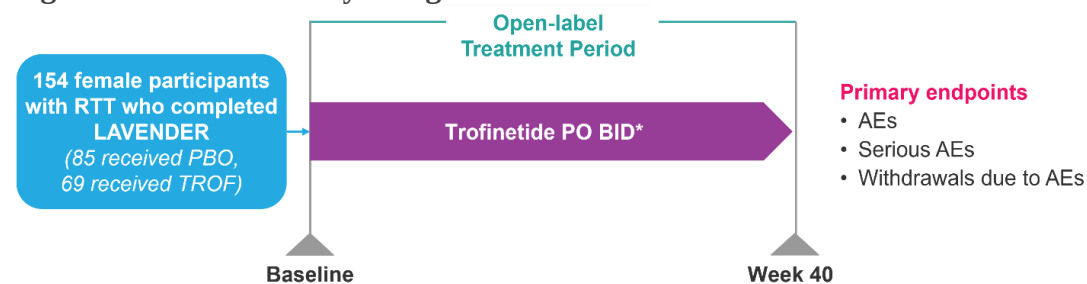
[†]During the NDA review, the FDA assigned 2 additional discontinuations due to TEAEs of diarrhea based on participant narratives, to be 14 (15%). This was reviewed and agreed upon by Acadia.

Abbreviations: NDA=New Drug Application; TEAE=treatment-emergent adverse event.

LILAC-1 (ACP-2566-004)

This was a 40-week, multicenter, OLE study to evaluate long-term safety and tolerability of trofinetide in the 154 girls and women with a diagnosis of typical RTT according to the Rett Syndrome Diagnostic Criteria with a documented disease-causing mutation in the *MECP2* gene, who elected to roll over into the study after completing the preceding double-blind Phase 3 study (LAVENDER) (**Figure 2**). The primary endpoint of LILAC-1 was the long-term safety and tolerability of trofinetide.³

Figure 2. LILAC-1 Study Design³



*Dose based on participant's body weight at baseline, except for participants whose assigned dose in LAVENDER was decreased for tolerability reasons who will remain on that same dose in LILAC-1 and have their dose increased during the study, if tolerated, to the appropriate dose level based on weight.

Abbreviations: AE=adverse event; BID=twice a day; CGI-I=Clinical Global Impression-Improvement; PBO=placebo; PO=oral; RSBQ=Rett Syndrome Behaviour Questionnaire; RTT=Rett syndrome; TROF=trofinetide.

Baseline Characteristics

At LILAC-1 baseline, the mean (SD) overall age of participants was 11.0 (4.55) years, and 92.9% of participants were White. The mean (SD) baseline CGI-S score was 4.8 (0.78).³ Overall, 75.3% of participants had a medical history of constipation, 49.4% had a medical history of seizures and 20.8% had a medical history of epilepsy.¹⁰ All participants received at least 1 concomitant medication during the study. Antiepileptics (72.7%), antipropulsives (62.3%), and drugs for constipation (59.7%) were the most frequently used concomitant medications.³ Antiemetics and antinauseants were used in 14.9% of participants.¹⁰

Safety Results

Overall, 143 (92.9%) participants experienced AEs; 19 (12.3%) were serious AEs (**Table 5**).³ One participant experienced two serious AEs that were considered related to study drug (urinary tract infection and dehydration).¹⁰

Table 5. Summary of AEs (ACP-2566-004; Safety Analysis Set)¹⁰

	PBO in LAVENDER (N=85) n (%)	TROF in LAVENDER (N=69) n (%)	Total (N=154) n (%)
Any AE	82 (96.5)	61 (88.4)	143 (92.9)
Any serious AE	10 (11.8)	9 (13.0)	19 (12.3)
Any related AE	73 (85.9)	52 (75.4)	125 (81.2)
Any related serious AE	0	1 (1.4)	1 (0.6)
Any AE leading to discontinuation of study drug	36 (42.4)	19 (27.5)	55 (35.7)
Any severe AE	12 (14.1)	3 (4.3)	15 (9.7)
Any fatal AE	0	0	0

Abbreviations: AE=adverse event; PBO=placebo; TROF=trofinetide.

The most common AEs were diarrhea (74.7%) and vomiting (28.6%) (**Table 6**). Most reports of diarrhea were of mild or moderate severity (95.6%); all reports of vomiting were mild or moderate in severity.³

Table 6. AEs ≥5% in Total Group (ACP-2566-004; Safety Analysis Set)³

Preferred Term	PBO in LAVENDER (N=85) n (%)	TROF in LAVENDER (N=69) n (%)	Total (N=154) n (%)
Diarrhea	71 (83.5)	44 (63.8)	115 (74.7)
Vomiting	29 (34.1)	15 (21.7)	44 (28.6)
COVID-19	9 (10.6)	8 (11.6)	17 (11.0)
Seizure	9 (10.6)	5 (7.2)	14 (9.1)
Upper respiratory tract infection	9 (10.6)	4 (5.8)	13 (8.4)
Pyrexia	7 (8.2)	5 (7.2)	12 (7.8)
Decreased appetite	6 (7.1)	5 (7.2)	11 (7.1)
Irritability	4 (4.7)	6 (8.7)	10 (6.5)
Urinary tract infection	6 (7.1)	4 (5.8)	10 (6.5)
Weight decreased	5 (5.9)	4 (5.8)	9 (5.8)

Abbreviations: AE=adverse event; PBO=placebo; TROF=trofinetide.

It should be noted that 27 participants (17.5%) had an ongoing AE of diarrhea and 5 participants (3.2%) had an ongoing AE of vomiting at the start of LILAC-1 (Table 7).¹⁰

Table 7. Ongoing Pre-Treatment-Emergent AEs of Vomiting (ACP-2566-004; Safety Analysis Set)¹⁰

Preferred Term	PBO in LAVENDER (N=85) n (%)	TROF in LAVENDER (N=69) n (%)	Total (N=154) n (%)
Diarrhea	1 (1.2)	26 (37.7)	27 (17.5)
Vomiting	0	5 (7.2)	5 (3.2)

Abbreviations: AE=adverse event; PBO=placebo; TROF=trofinetide.

Serious AEs were reported in 19 participants (12.3%).³ The most frequently reported events were seizure (3.2%), pneumonia (2.6%), dehydration (1.9%), pyrexia, rhinovirus infection, viral infection, status epilepticus, and acute respiratory failure (1.3% each). For each of these participants, the AE was assessed as serious due to hospitalization.¹⁰

Diarrhea (n=33; 21.4%) was the most common AE leading to discontinuation of study drug, followed by vomiting (n=10; 6.5%) (Table 8).³

Table 8. AEs Leading to Discontinuation of Study Drug (ACP-2566-004; Safety Analysis Set)¹⁰

MedDRA System Organ Class Preferred Term	PBO in LAVENDER (N=85) n (%)	TROF in LAVENDER (N=69) n (%)	Total (N=154) n (%)
Any AE leading to drug withdrawn	36 (42.4)	19 (27.5)	55 (35.7)
Gastrointestinal disorders	28 (32.9)	12 (17.4)	40 (26.0)
Diarrhea	24 (28.2)	9 (13.0)	33 (21.4)
Vomiting	6 (7.1)	4 (5.8)	10 (6.5)
General disorders and administration site conditions	1 (1.2)	0	1 (0.6)
Screaming	1 (1.2)	0	1 (0.6)
Infections and infestations	1 (1.2)	1 (1.4)	2 (1.3)
Enterovirus infection	1 (1.2)	0	1 (0.6)
Gastroenteritis	0	1 (1.4)	1 (0.6)
Injury, poisoning and procedural complications	1 (1.2)	0	1 (0.6)
Product use complaint	1 (1.2)	0	1 (0.6)
Investigations	2 (2.4)	2 (2.9)	4 (2.6)
Weight decreased	2 (2.4)	1 (1.4)	3 (1.9)
Alanine aminotransferase increased	0	1 (1.4)	1 (0.6)
Metabolism and nutrition disorders	1 (1.2)	1 (1.4)	2 (1.3)
Decreased appetite	1 (1.2)	0	1 (0.6)
Feeding disorder	0	1 (1.4)	1 (0.6)
Nervous system disorders	3 (3.5)	2 (2.9)	5 (3.2)
Seizure	1 (1.2)	1 (1.4)	2 (1.3)
Seizure cluster	2 (2.4)	0	2 (1.3)
Gross motor delay	0	1 (1.4)	1 (0.6)
Psychiatric disorders	1 (1.2)	1 (1.4)	2 (1.3)
Agitation	1 (1.2)	0	1 (0.6)
Breath holding	0	1 (1.4)	1 (0.6)

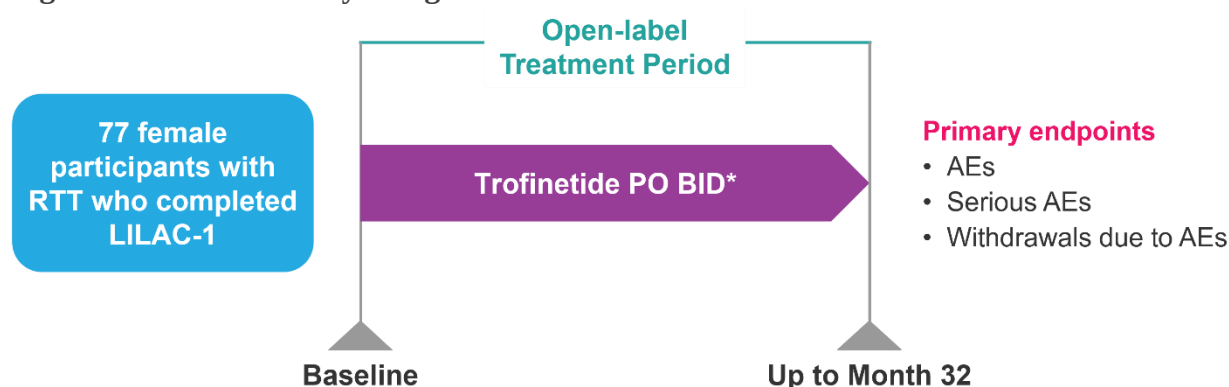
MedDRA System Organ Class Preferred Term	PBO in LAVENDER (N=85) n (%)	TROF in LAVENDER (N=69) n (%)	Total (N=154) n (%)
Respiratory, thoracic and mediastinal disorders	1 (1.2)	1 (1.4)	2 (1.3)
Acute respiratory failure	1 (1.2)	0	1 (0.6)
Aspiration	1 (1.2)	0	1 (0.6)
Cough	0	1 (1.4)	1 (0.6)
Oropharyngeal pain	0	1 (1.4)	1 (0.6)

Abbreviations: AE=adverse event; PBO=placebo; TROF=trofinetide.

LILAC-2 (ACP-2566-005)

This was a multicenter, open-label, long-term study (up to 32 months) of trofinetide to monitor the safety and efficacy of continuing trofinetide therapy for eligible participants who completed LILAC-1 (**Figure 3**). The primary endpoint of LILAC-2 was the long-term safety and tolerability of trofinetide.⁴

Figure 3. LILAC-2 Study Design⁴



*The assigned dose for this study was the participant's final dose from the antecedent study. If the dose was reduced in LILAC-1 for tolerability reasons, the dose was increased during LILAC-2, if tolerated, to the appropriate dose level based on weight. Abbreviations: AE=adverse event; BID=twice a day; PO=oral; RTT=Rett syndrome.

Baseline Characteristics

At LILAC-2 baseline, the mean (SD) overall age of participants was 12.0 (4.4) years, and 92.2% of participants were White. The mean (SD) baseline CGI-S score was 4.8 (0.9).⁴ Overall, 72.7% of participants had a medical history of constipation, 40.3% had a medical history of seizures, and 29.9% had a medical history of epilepsy. All participants received at least one concomitant medication during the study; antiepileptics (77.9%), other analgesics and antipyretics (61.0%), drugs for constipation, (55.8%), anti-inflammatory and antirheumatic products, non-steroids (50.6%), and antipropulsives (45.5%) were the most frequently used concomitant medications. Overall, antiemetics and antinauseants were used in 16.9% of participants.¹¹

Safety Results

Overall, 72 (93.5%) participants experienced AEs; 23 (29.9%) were serious AEs (**Table 9**). No participants experienced a serious AE that was considered related to study drug. There were four deaths during the study, none of which were considered related to study drug. One participant experienced two fatal AEs, vomiting and aspiration, following the surgical placement of a

gastrostomy tube. The remaining fatal AEs were experienced by one participant each: cardiac arrest, gastric ulcer hemorrhage, and sudden unexplained death in epilepsy.^{4,11}

Table 9. Summary of AEs (ACP-2566-005; Safety Analysis Set)¹¹

	Trofinetide (N=77) n (%)
Any AE	72 (93.5)
Any serious AE	23 (29.9)
Any related AE	42 (54.5)
Any related serious AE	0
Any AE leading to discontinuation of study drug	9 (11.7)
Any severe AE	10 (13.0)
Any fatal AE	4 (5.2)

Abbreviation: AE=adverse event.

The most common AEs were diarrhea (53.2%), COVID-19 (27.3%) and vomiting (19.5%) (**Table 10**). All reports of diarrhea were of mild or moderate severity; most reports of vomiting (n=14; 93.3%) were mild or moderate in severity.⁴

Table 10. AEs in ≥5% of Participants (ACP-2566-005; Safety Analysis Set)¹¹

Preferred Term	Trofinetide (N=77) n (%)
Diarrhea	41 (53.2)
COVID-19	21 (27.3)
Vomiting	15 (19.5)
Pyrexia	13 (16.9)
Urinary tract infection	13 (16.9)
Seizure	11 (14.3)
Constipation	9 (11.7)
Upper respiratory tract infection	9 (11.7)
Influenza	7 (9.1)
Cough	6 (7.8)
Pharyngitis streptococcal	6 (7.8)
Pneumonia	5 (6.5)
Irritability	5 (6.5)
Gastroenteritis viral	4 (5.2)
Viral upper respiratory tract infection	4 (5.2)
Nasal congestion	4 (5.2)
Flatulence	4 (5.2)
Electrocardiogram QT prolonged	4 (5.2)
Weight decreased	4 (5.2)
Decreased appetite	4 (5.2)
Dehydration	4 (5.2)
Lethargy	4 (5.2)

Abbreviation: AE=adverse event.

Seizure (n=5; 6.5%) was the most common serious AE, followed by vomiting, pneumonia, urinary tract infection and acute respiratory failure, which were each reported in 2 (2.6%) participants. Other serious AEs were reported in 1 participant each, including cardiac arrest,

abdominal pain, gastric perforation, gastric ulcer, gastric ulcer hemorrhage, pneumoperitoneum, pyrexia, sudden unexplained death in epilepsy, COVID-19, enterovirus infection, influenza, parainfluenzae virus infection, pharyngitis streptococcal, pneumonia viral, pyelonephritis, rhinovirus infection, staphylococcal infection, urinary tract infection fungal, procedural pain, renal procedural complication, dehydration, hypokalaemia, hyponatraemia, disturbance in attention, dystonia, dystonic tremor, generalised tonic-clonic seizure, status epilepticus, pelvic fluid collection, aspiration, respiratory distress.¹¹

Vomiting (n=2; 2.6%) was the most common AE leading to discontinuation of study drug. Other AEs leading to discontinuation of study drug were reported in 1 participant each (**Table 11**).⁴

Table 11. AEs Leading to Discontinuation (ACP-2566-005; Safety Analysis Set)¹¹

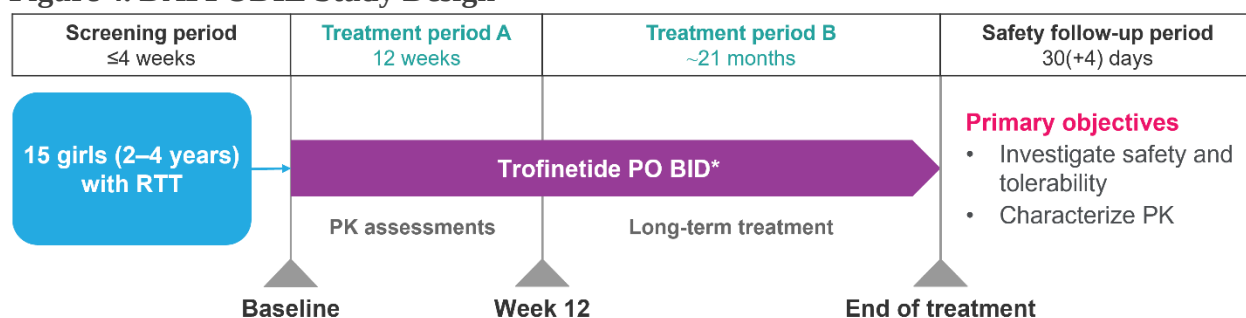
MedDRA System Organ Class Preferred Term	Trofinetide (N=77) n (%)
Any AE leading to drug withdrawn	9 (11.7)
Cardiac disorders	1 (1.3)
Cardiac arrest	1 (1.3)
Gastrointestinal disorders	5 (6.5)
Vomiting	2 (2.6)
Diarrhea	1 (1.3)
Gastric ulcer hemorrhage	1 (1.3)
Retching	1 (1.3)
General disorders and administration site conditions	1 (1.3)
Sudden unexplained death in epilepsy	1 (1.3)
Infections and infestations	1 (1.3)
COVID-19	1 (1.3)
Nervous system disorders	1 (1.3)
Seizure	1 (1.3)
Respiratory, thoracic and mediastinal disorders	2 (2.6)
Aspiration	1 (1.3)
Pneumonia aspiration	1 (1.3)

Abbreviation: AE=adverse event.

DAFFODIL (ACP-2566-009)

This was a multicenter, open-label, Phase 2/3 safety, tolerability and PK study of trofinetide in girls (2–4 years of age) with diagnosed RTT (**Figure 4**). The primary objectives of the study were to investigate the safety and tolerability of treatment with oral trofinetide in this population, and to characterize the PK. Fifteen participants received trofinetide 2 g (10 mL) BID, with subsequent dose increases at scheduled visits, depending on tolerability.⁵

Enrolled participants were required to meet the following inclusion criteria: 2–4 years of age with body weight ≥ 9 and < 20 kg at screening, or 5 years of age with body weight ≥ 9 and < 12 kg at screening; classic/typical RTT or possible RTT according to the Rett Syndrome Diagnostic Criteria; documented disease-causing mutation in the *MECP2* gene; CGI-S score ≥ 4 at screening and baseline; and stable pattern of seizures (or no seizures) within 8 weeks before screening.⁵

Figure 4. DAFFODIL Study Design⁵


*2 g (10 mL) BID at baseline, 4 g (20 mL) BID at Week 2, and 5 g (25 mL) BID (≥9 to <12 kg) or 6 g (30 mL) BID (≥12 to <20 kg) at Week 4.

Abbreviations: BID=twice a day; PK=pharmacokinetic(s); PO=oral; RTT=Rett syndrome.

Baseline Characteristics

A total of 15 participants received at least one dose of study drug and were included in the Safety Analysis Set. The overall mean (SD) age was 3.1 (0.80) years, and 86.7% were White. The mean CGI-S score at baseline was 4.7 (0.7).⁵ Overall, 66.7% had a medical history of constipation, 13.3% had a medical history of seizures, and 13.3% had a medical history of vomiting. All participants received at least one concomitant medication during the study; loperamide was used by 53.3% of participants, and 46.7% were taking osmotically acting laxatives. None of the participants were taking antiemetics and antinauseants.¹²

Safety Results

Overall, 14 participants (93.3%) reported any TEAE (Table 12). No deaths were reported.⁵

Table 12. Summary of TEAEs (ACP-2566-009; Safety Analysis Set)⁵

	Trofinetide (N=15), n (%)	
	Treatment Period A	Overall: Treatment Periods A and B
Any TEAE	13 (86.7)	14 (93.3)
Any serious TEAE	1 (6.7)	4 (26.7)
Any related TEAE*	11 (73.3)	13 (86.7)
Any related serious TEAE*	0	0
Any TEAE leading to study drug discontinuation	1 (6.7)	2 (13.3)
Any severe TEAE [†]	1 (6.7)	2 (13.3)
Any fatal TEAE	0	0

*Events with missing relationship were counted as related. [†]Events with missing severity were counted as severe.

Abbreviation: TEAE=treatment-emergent adverse event.

TEAEs that were reported in ≥2 participants are summarized in Table 13. Overall, diarrhea and vomiting were the most common TEAEs, reported in 80.0% and 53.3% of participants, respectively.⁵ Diarrhea was mild for 7 (46.7%) participants and moderate for 5 (33.3%) participants; vomiting was mild for 6 (40.0%) participants and moderate for 2 (13.3%) participants. Diarrhea was considered a related TEAE for 10 (66.7%) participants, and vomiting was considered a related TEAE for 5 (33.3%) participants.¹²

Table 13. TEAEs Reported in ≥ 2 Participants Overall (ACP-2566-009; Safety Analysis Set)⁵

Preferred Term	Trofinetide (N=15), n (%)	
	Treatment Period A	Overall: Treatment Periods A and B
Diarrhea	11 (73.3)	12 (80.0)
Vomiting	7 (46.7)	8 (53.3)
COVID-19	4 (26.7)	7 (46.7)
Gastroenteritis	2 (13.3)	5 (33.3)
Pyrexia	4 (26.7)	5 (33.3)
Seizure	3 (20.0)	5 (33.3)
Upper respiratory tract infection	1 (6.7)	4 (26.7)
Cough	2 (13.3)	3 (20.0)
Influenza	1 (6.7)	3 (20.0)
Nasal congestion	3 (20.0)	3 (20.0)
Conjunctivitis	1 (6.7)	2 (13.3)
Dermatitis diaper	2 (13.3)	2 (13.3)
Ear infection	1 (6.7)	2 (13.3)
Epilepsy	1 (6.7)	2 (13.3)
Feeding disorder	2 (13.3)	2 (13.3)
GERD	1 (6.7)	2 (13.3)
Somnolence	2 (13.3)	2 (13.3)
Weight decreased	2 (13.3)	2 (13.3)

Abbreviations: GERD=gastroesophageal reflux disease; TEAE=treatment-emergent adverse event.

Serious TEAEs were reported by 4 (26.7%) participants overall: gastroenteritis sapovirus in 1 (6.7%) participant in Treatment Period A, and seizure (n=2 [13.3%]), altered state of consciousness (n=1 [6.7%]) and dysphagia (n=1 [6.7%]) in Treatment Period B. None of the events were considered related to study drug; all events required hospitalization but fully resolved and participants fully recovered.⁵

Overall, 2 (13.3%) participants discontinued from the study drug due to TEAEs (**Table 14**). One participant discontinued during Treatment Period A due to a TEAE of diarrhea that was moderate in severity and considered related to study drug. During Treatment Period B, one participant was discontinued from the study due to a TEAE of vomiting which was mild in severity and considered related to the study drug.^{5,12}

Table 14. TEAEs Leading to Discontinuation (ACP-2566-009; Safety Analysis Set)¹²

System Organ Class Preferred Term	Trofinetide (N=15), n (%)	
	Treatment Period A	Overall: Treatment Periods A and B
Any TEAE leading to discontinuation	1 (6.7)	2 (13.3)
Gastrointestinal disorders	1 (6.7)	2 (13.3)
Diarrhea	1 (6.7)	1 (6.7)
Vomiting	0	1 (6.7)

Abbreviation: TEAE=treatment-emergent adverse event.

References

1. DAYBUE™ (trofinetide) [package insert]. San Diego, CA. Acadia Pharmaceutical Inc. [\[Link\]](#)
2. Neul JL, Percy AK, Benke TA, et al. Trofinetide for the treatment of Rett syndrome: a randomized phase 3 study. *Nat Med*. 2023;29(6):1468-1475. [\[PubMed\]](#)
3. Percy AK, Neul JL, Benke TA, et al. Trofinetide for the treatment of Rett syndrome: Results from the open-label extension LILAC study. *Med*. 2024;5(9):1178-1189 e1173. [\[PubMed\]](#)
4. Percy AK, Neul JL, Benke TA, et al. Trofinetide for the treatment of Rett syndrome: Long-term safety and efficacy results of the 32-month, open-label LILAC-2 study. *Med*. 2024;5(10):1275-1281 e1272. [\[PubMed\]](#)
5. Percy AK, Ryther R, Marsh ED, et al. Results from the phase 2/3 DAFFODIL study of trofinetide in girls aged 2–4 years with Rett syndrome. *Med*. 2025. [\[Link\]](#)
6. Acadia Pharmaceuticals Inc. Data on File. ACP-2566-003 Protocol. 2020.
7. Neul JL, Percy AK, Benke TA, et al. Design and outcome measures of LAVENDER, a phase 3 study of trofinetide for Rett syndrome. *Contemp Clin Trials*. 2022;114:106704. [\[PubMed\]](#)
8. Acadia Pharmaceuticals Inc. Data on File. ACP-2566-003 Clinical Study Report. 2022.
9. Temple R. Hy's law: predicting serious hepatotoxicity. *Pharmacoepidemiol Drug Saf*. 2006;15(4):241-243. [\[PubMed\]](#)
10. Acadia Pharmaceuticals Inc. Data on File. ACP-2566-004 Clinical Study Report. 2023.
11. Acadia Pharmaceuticals Inc. Data on File. ACP-2566-005 Clinical Study Report. 2024.
12. Acadia Pharmaceuticals Inc. Data on File. ACP-2566-009 Clinical Study Report. 2023.