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

12830 El Camino Real · Suite 400 · San Diego, California 92130 · USA · Tel. 858.558.2871 · Fax 858.558.2872 · acadia.com

DAYBUE® (trofinetide): Vomiting Adverse Events in Clinical Trials

This letter is provided in response to your specific request for information regarding adverse events (AEs) of vomiting in the trofinetide clinical trials in individuals with Rett syndrome (RTT). In the trofinetide clinical trials, management of vomiting was not protocolized, and was conducted per the discretion of the site primary investigator.

Relevant Label Information[1]

- **Warnings and Precautions**
  - 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.

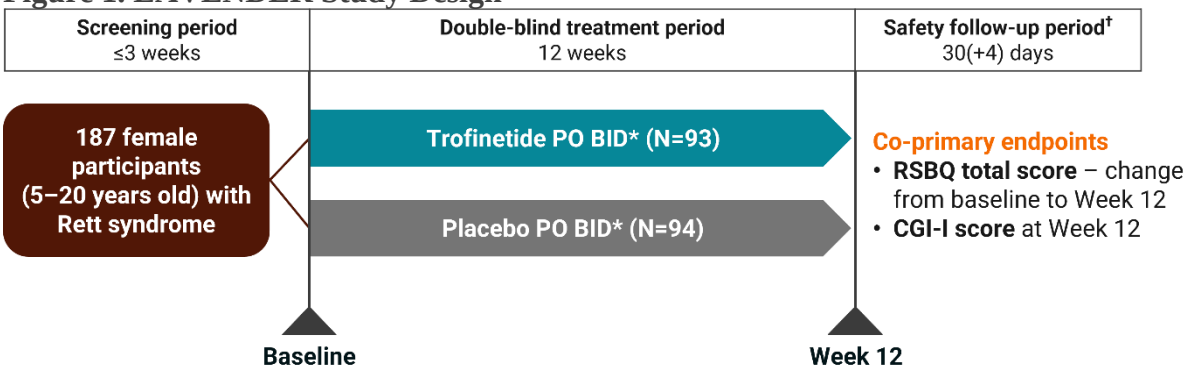
Summary

- In the 12-week **Phase 3 LAVENDER study** evaluating the efficacy and safety of trofinetide in 187 female participants (5–20 years old) with RTT, **treatment-emergent AEs (TEAEs) of vomiting** were reported in 26.9% of participants treated with trofinetide and 9.6% of participants treated with placebo.[2]
  - In the trofinetide arm, 96% (24/25) of vomiting TEAEs were characterized as mild-to-moderate; 1 participant experienced severe vomiting TEAEs. In the placebo arm, 100% (9/9) of vomiting TEAEs were characterized as mild-to-moderate.[2]
  - One participant (1.1%) in the trofinetide group and no participants in the placebo group experienced vomiting TEAEs leading to discontinuation of study drug.[2]
- In the **LILAC-1™** (N=154) and **LILAC-2™** (N=77) OLE studies evaluating the long-term safety and tolerability of trofinetide, AEs of vomiting were reported in 28.6% and 19.5% of participants, respectively.[3,4]
- The open-label, Phase 2/3 **DAFFODIL™** study evaluated the safety and tolerability of trofinetide in 15 girls aged 2–4 years for a total duration of up to 78 weeks. TEAEs of vomiting were reported in 53.3% of participants, all of which were characterized as mild-to-moderate.[5]

Phase 3 LAVENDER Study

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]

Figure 1. LAVENDER Study Design[2,6]



**Dose based on participant's body weight at baseline.*
†The LAVENDER follow-up visit does not take place if the participant rolls over into the open-label extension study.
Abbreviations: BID=twice a day; CGI-I=Clinical Global Impression-Improvement; PO=oral; RSBQ=Rett Syndrome Behaviour Questionnaire.

Participants were ≥12 kg with classic/typical RTT and documented disease-causing mutation in the *MECP2* gene, and were ≥6 months post regression at screening. Additional eligibility criteria included an RTT Clinical Severity Scale rating of 10–36, CGI-S score of ≥4, and a stable pattern of seizures, or no seizures, within 8 weeks of screening.[7]

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),[2] 2.2% of participants in the trofinetide group (N=93) had a history of vomiting, compared with 2.1% in the placebo group (N=94) (**Table 1**).[8]

Table 1. Medical History of GI Disorders in ≥2% of Participants (ACP-2566-003; Safety Analysis Set)[8]

Preferred Term	Placebo (N=94) n (%)	Trofinetide (N=93) n (%)
Constipation	74 (78.7)	70 (75.3)
GERD	41 (43.6)	42 (45.2)
Dysphagia	3 (3.2)	6 (6.5)
Aerophagia	4 (4.3)	4 (4.3)
Flatulence	6 (6.4)	2 (2.2)
Diarrhea	3 (3.2)	3 (3.2)
Salivary hypersecretion	3 (3.2)	2 (2.2)
Abdominal distension	2 (2.1)	2 (2.2)
Malpositioned teeth	4 (4.3)	0
Vomiting	2 (2.1)	2 (2.2)

Preferred Term	Placebo (N=94) n (%)	Trofinetide (N=93) n (%)
GI hypomotility	0	2 (2.2)
Impaired gastric emptying	2 (2.1)	0

Abbreviations: GERD=gastroesophageal reflux disease; GI=gastrointestinal.

Selected Concomitant Medications

Overall, antiemetics and antinauseants were used concomitantly in 6 (6.5%) participants in the trofinetide group and 4 (4.3%) participants in the placebo group (**Table 2**).[8]

Table 2. Concomitant Antiemetics and Antinauseants (ACP-2566-003; Safety Analysis Set)[8]

WHO ATC Class Preferred Term	Placebo (N=94) n (%)	Trofinetide (N=93) n (%)
Antiemetics and antinauseants	4 (4.3)	6 (6.5)
Ondansetron	2 (2.1)	6 (6.5)
Dronabinol	1 (1.1)	0
Hyoscine	1 (1.1)	0

Abbreviations: ATC=Anatomical/Therapeutic/Chemical; WHO=World Health Organization.

Vomiting TEAEs

TEAEs of vomiting were reported in 26.9% of participants in the trofinetide and 9.6% of participants in the placebo arm (**Table 3**). Of these, 96% were characterized as mild-to-moderate in the trofinetide group (1 participant experienced severe vomiting TEAEs), and 100% were characterized as mild-to-moderate in the placebo group (**Table 4**),[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.

Table 3. Summary of Vomiting TEAEs (ACP-2566-003; Safety Analysis Set)[8]

Preferred Term	Placebo (N=94)		Trofinetide (N=93)	
	Participants, n (%)	Events, n	Participants, n (%)	Events, n
TEAEs	9 (9.6)	11	25 (26.9)	28
Serious TEAEs	0	0	0	0
TEAEs leading to discontinuation	0	0	1 (1.1)	1
Related TEAEs	1 (1.1)	1	16 (17.2)	17

Abbreviation: TEAE=treatment-emergent adverse event.

Table 4. Vomiting TEAEs by Severity (ACP-2566-003; Safety Analysis Set)[2]

Placebo (N=94), n (%)			Trofinetide (N=93), n (%)		
Mild	Moderate	Severe	Mild	Moderate	Severe
8 (8.5)	1 (1.1)	0	18 (19.4)	6 (6.5)	1 (1.1)

Abbreviation: TEAE=treatment-emergent adverse event.

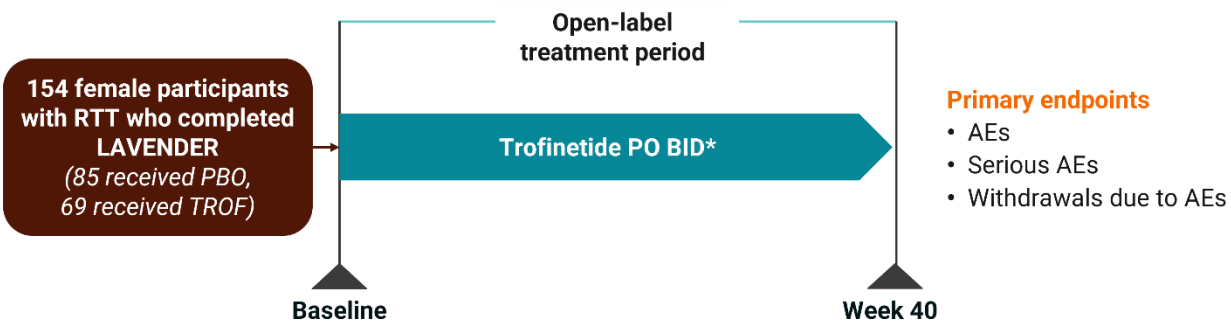
None of the vomiting TEAEs were associated with hospitalization.[8] One participant (1.1%) in the trofinetide group and none of the participants in the placebo group experienced vomiting TEAEs leading to discontinuation of study drug (**Table 3**).[2] Study-drug related vomiting TEAEs

were reported for 16 (17.2%) participants in the trofinetide group and 1 (1.1%) participant in the placebo group.[8]

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 Design[3]



**Dose based on participant's body weight at baseline, except for subjects 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 dose level based on weight.*
Abbreviations: AE=adverse event; BID=twice a day; PBO=placebo; PO=oral; 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, 2.6% of participants had a history of vomiting (**Table 5**).[9]

Table 5. Medical History of GI Disorders in ≥2% of Participants (ACP-2566-004; Safety Analysis Set)[9]

Preferred Term	PBO in LAVENDER (N=85) n (%)	TROF in LAVENDER (N=69) n (%)	Total (N=154) n (%)
Constipation	66 (77.6)	50 (72.5)	116 (75.3)
GERD	37 (43.5)	31 (44.9)	68 (44.2)
Diarrhea	18 (21.2)	31 (44.9)	49 (31.8)
Dysphagia	3 (3.5)	6 (8.7)	9 (5.8)
Aerophagia	4 (4.7)	3 (4.3)	7 (4.5)
Flatulence	5 (5.9)	2 (2.9)	7 (4.5)
Abdominal distension	3 (3.5)	2 (2.9)	5 (3.2)
Malpositioned teeth	4 (4.7)	0	4 (2.6)
Vomiting	3 (3.5)	1 (1.4)	4 (2.6)

Abbreviations: GERD=gastroesophageal reflux disease; GI=gastrointestinal; PBO=placebo; TROF=trofinetide.

Selected Concomitant Medications

Overall, antiemetics and antinauseants were used in 14.9% of participants (**Table 6**).[9]

Table 6. Concomitant Antiemetics and Antinauseants (ACP-2566-004; Safety Analysis Set)[9]

WHO ATC Class Preferred Term	PBO in LAVENDER (N=85) n (%)	TROF in LAVENDER (N=69) n (%)	Total (N=154) n (%)
Antiemetics and antinauseants	16 (18.8)	7 (10.1)	23 (14.9)
Ondansetron	15 (17.6)	7 (10.1)	22 (14.3)
Diphenhydramine	1 (1.2)	0	1 (0.6)
Dronabinol	1 (1.2)	0	1 (0.6)
Hyoscine	0	1 (1.4)	1 (0.6)
Promethazine hydrochloride	1 (1.2)	0	1 (0.6)

Abbreviations: ATC=Anatomical/Therapeutic/Chemical; PBO=placebo; TROF=trofinetide; WHO=World Health Organization.

Vomiting AEs

AEs of vomiting were reported in 28.6% of participants overall (**Table 7**). All reports of vomiting were of mild or moderate severity.[3]

Table 7. Summary of Vomiting AEs (ACP-2566-004; Safety Analysis Set)[3,9]

	PBO in LAVENDER (N=85) n (%)	TROF in LAVENDER (N=69) n (%)	Total (N=154) n (%)
AEs	29 (34.1)	15 (21.7)	44 (28.6)
Serious AEs	0	0	0
AEs leading to discontinuation	6 (7.1)	4 (5.8)	10 (6.5)

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

It should be noted that 5 participants (3.2%) had an ongoing AE of vomiting at the start of LILAC-1 (**Table 8**).[9]

Table 8. Ongoing Pre-Treatment-Emergent AEs of Vomiting (ACP-2566-004; Safety Analysis Set)[9]

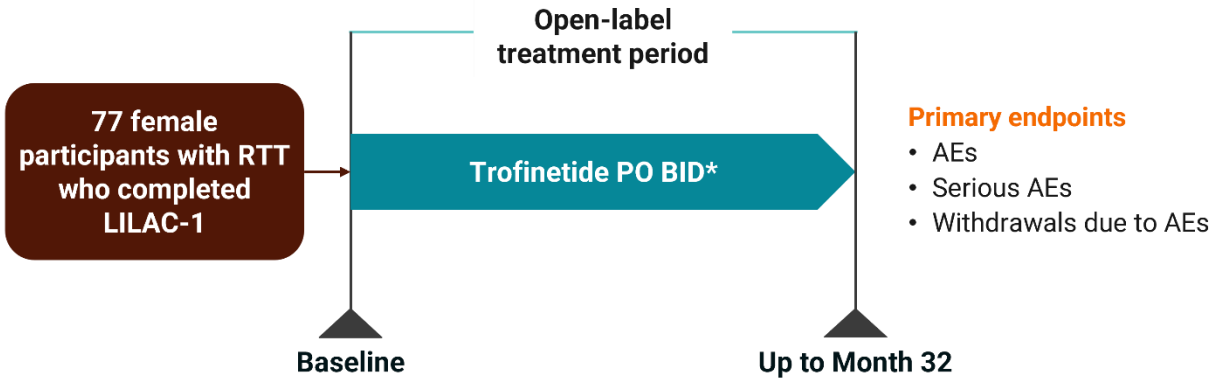
Preferred Term	PBO in LAVENDER (N=85) n (%)	TROF in LAVENDER (N=69) n (%)	Total (N=154) n (%)
Vomiting	0	5 (7.2)	5 (3.2)

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 Design[4]



**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, 3.9% of participants had a history of vomiting (**Table 9**).[10]

Table 9. Medical History of GI Disorders in ≥2% of Participants (ACP-2566-005; Safety Analysis Set)[10]

Preferred Term	Total (N=77) n (%)
Constipation	56 (72.7)
GERD	38 (49.4)
Diarrhea	34 (44.2)
Dysphagia	7 (9.1)
Flatulence	4 (5.2)
Vomiting	3 (3.9)
Aerophagia	2 (2.6)
Malpositioned teeth	2 (2.6)
Salivary hypersecretion	2 (2.6)

Abbreviations: GERD=gastroesophageal reflux disease; GI=gastrointestinal.

Selected Concomitant Medications

Overall, antiemetics and antinauseants were used in 16.9% of participants (**Table 10**).[10]

Table 10. Concomitant Antiemetics and Antinauseants (ACP-2566-005; Safety Analysis Set)[10]

WHO ATC Class Preferred Term	Trofinetide (N=77) n (%)
Antiemetics and antinauseants	13 (16.9)
Ondansetron	12 (15.6)
Hyoscine	1 (1.3)

Abbreviation: ATC=Anatomical/Therapeutic/Chemical; WHO=World Health Organization.

Vomiting AEs

AEs of vomiting were reported in 19.5% of participants overall; 93.3% of vomiting AEs were mild or moderate in severity. Two participants discontinued due to an AE of vomiting (**Table 11**). One participant experienced a fatal AE of vomiting (co-occurring with a fatal AE of aspiration) which was not considered related to study drug.[4]

Table 11. Summary of Vomiting AEs (ACP-2566-005; Safety Analysis Set)[4,10]

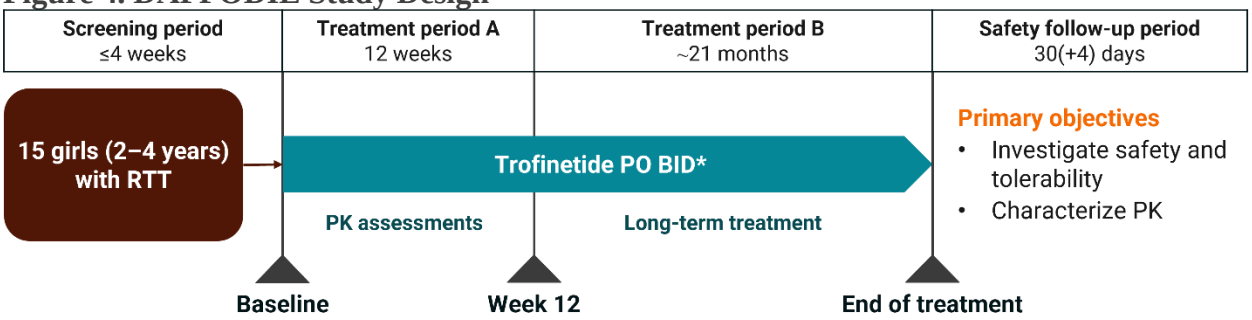
	Total (N=77) n (%)
AEs	15 (19.5)
Serious AEs	2 (2.6)
AEs leading to discontinuation	2 (2.6)
Fatal AEs	1 (1.3)

Abbreviation: AE=adverse event.

DAFFODIL (ACP-2566-009)

This was a multicenter, open-label, Phase 2/3 safety, tolerability and pharmacokinetic (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.[5]

Figure 4. DAFFODIL Study Design[5]



**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.

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]

Baseline Characteristics

The mean (SD) age of participants was 3.1 (0.8), and 86.7% were White. The mean (SD) baseline CGI-S score was 4.7 (0.7).[5] Overall, 13.3% had a history of vomiting (**Table 12**).[11]

Table 12. Medical History of GI Disorders in ≥2% of Participants (ACP-2566-009; Safety Analysis Set)[11]

Preferred Term	Trofinetide (N=15) n (%)
Constipation	10 (66.7)
GERD	5 (33.3)
Dysphagia	2 (13.3)
Vomiting	2 (13.3)

Abbreviations: GERD=gastroesophageal reflux disease; GI=gastrointestinal.

Selected Concomitant Medications

None of the participants were taking antiemetics and antinauseants.[11]

Vomiting TEAEs

Vomiting TEAEs were reported in 53.3% of participants (**Table 13**). No serious TEAEs of vomiting were reported.[5] Vomiting was considered a related TEAE for 5 (33.3%) participants.[11]

Table 13. Summary of Vomiting TEAEs (ACP-2566-009; Safety Analysis Set)[5]

	Trofinetide (N=15) n (%)
TEAEs	8 (53.3)
Serious TEAEs	0
TEAEs leading to discontinuation	1 (6.7)

Abbreviation: TEAE=treatment-emergent adverse event.

Vomiting TEAEs were either of mild or moderate severity (**Table 14**).[5]

Table 14. Vomiting TEAEs by Maximum Severity (ACP-2566-009; Safety Analysis Set)[11]

Preferred Term	Trofinetide (N=15), n (%)		
	Mild	Moderate	Severe
Vomiting	6 (40.0)	2 (13.3)	0

Abbreviation: TEAE=treatment-emergent adverse event.

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.[5,11]

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