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

This letter is provided in response to your specific request for information regarding diarrhea adverse events (AEs) in clinical trials of trofinetide in Rett syndrome (RTT). In the trofinetide clinical trials, management of diarrhea was not protocolized, and was conducted per the discretion of the site primary investigator. Recommendations for diarrhea management are included in the label for prescribers to consider when prescribing trofinetide.[1]

Relevant Labeling Information[1]

- **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.

Summary

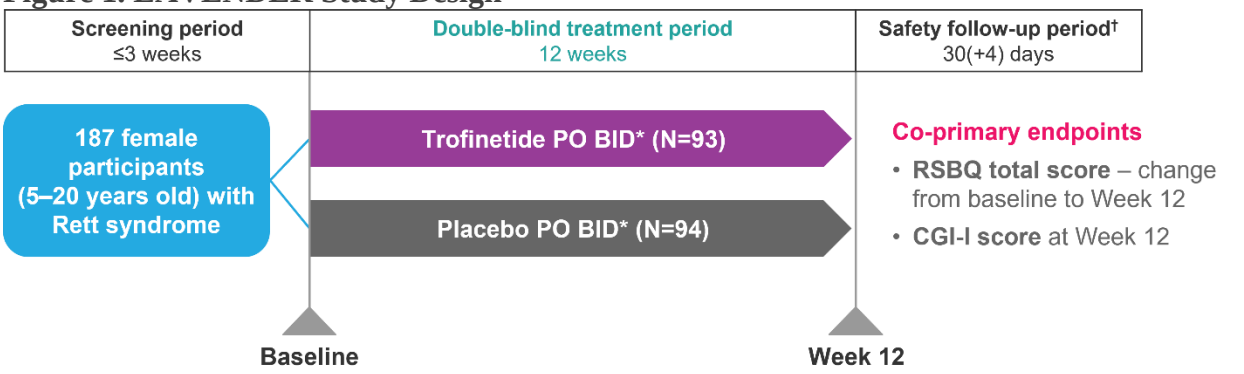
- In the 12-week **Phase 3 LAVENDER study** evaluating the efficacy and safety of trofinetide in 187 female participants (5–20 years old) with RTT, **treatment-emergent AEs (TEAEs) of diarrhea** were reported in 80.6% (75/93) of participants treated with trofinetide and 19.1% (18/94) of participants treated with placebo.[2]
  - In the trofinetide arm, 97.3% (73/75) of diarrhea TEAEs were characterized as mild-to-moderate; 2 participants experienced severe diarrhea TEAEs. In the placebo arm, 100% (18/18) of diarrhea TEAEs were characterized as mild-to-moderate.[2]
  - Twelve participants (12.9%) in the trofinetide group and no participants in the placebo group experienced diarrhea TEAEs leading to discontinuation of study drug.[2]
  - In **post-hoc analysis of diarrhea TEAEs** to assess for potential influence of selected participant and treatment characteristics in trofinetide-treated participants, no clear trends emerged.[3,4]
- In the **LILAC-1™ (N=154)** and **LILAC-2™ (N=77)** OLE studies evaluating the long-term safety and tolerability of trofinetide, AEs of diarrhea were reported in 74.7% and 53.2% of participants, respectively.[5,6]
- In **pooled analysis** of 178 participants who received trofinetide in LAVENDER and two long-term studies (LILAC-1 and LILAC-2), 85% of patients treated with trofinetide experienced diarrhea. In those treated with trofinetide, 49% either had persistent diarrhea or recurrence after resolution despite dose interruptions, reductions, or concomitant antidiarrheal therapy.[1,7]
- 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

diarrhea were reported in 80.0% of participants, all of which were characterized as mild-to-moderate.[8]

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.[2,9]

Figure 1. LAVENDER Study Design[2,9]



**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.[10]

Baseline Characteristics

Treatment groups were well balanced for demographic and baseline characteristics.[2] In the Randomized Analysis Set (all randomized participants),[9] 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) (**Table 1**).[2]

Table 1. Medical History of GI Disorders in ≥2% of Participants (ACP-2566-003; Safety Analysis Set)[11]

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)
GI hypomotility	0	2 (2.2)
Impaired gastric emptying	2 (2.1)	0

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

In the respective trofinetide and placebo groups, 40.9% and 41.5% of participants were administered study medication via gastrostomy tube.[2]

Selected Concomitant Medications

Drugs for constipation (65.2%) were one of the most frequently used concomitant medications in both treatment groups (**Table 2**). Loperamide was used in 50.5% of participants on trofinetide and 3.2% on placebo.[2]

Table 2. Concomitant Medications Related to GI Function in ≥10% of Participants (ACP-2566-003; Safety Analysis Set)[11]

WHO ATC Class Preferred Term	Placebo (N=94) n (%)	Trofinetide (N=93) n (%)
Antidiarrheal microorganisms	**7 (7.4)**	**10 (10.8)**
Antipropulsives	**3 (3.2)**	**47 (50.5)**
Loperamide	3 (3.2)	47 (50.5)
Drugs for constipation	**66 (70.2)**	**56 (60.2)**
Macrogol 3350	46 (48.9)	37 (39.8)
Sennoside A+B	12 (12.8)	8 (8.6)
Magnesium hydroxide	10 (10.6)	8 (8.6)
Macrogol	10 (10.6)	4 (4.3)
Drugs for functional GI disorders	**14 (14.9)**	**16 (17.2)**
Simethicone	13 (13.8)	10 (10.8)
Drugs for peptic ulcer and GERD	**33 (35.1)**	**28 (30.1)**
Lansoprazole	12 (12.8)	7 (7.5)
Intestinal adsorbents	**0**	**25 (26.9)**
Plantago ovata	0	22 (23.7)
Other alimentary tract and metabolism products	**22 (23.4)**	**18 (19.4)**
Probiotics NOS	12 (12.8)	9 (9.7)
Levocarnitine	11 (11.7)	5 (5.4)

Abbreviations: ATC=Anatomical/Therapeutic/Chemical; GERD=gastroesophageal reflux disease; GI=gastrointestinal; NOS=not otherwise specified; WHO=World Health Organization.

Diarrhea TEAEs

TEAEs of diarrhea were reported in 80.6% of participants treated with trofinetide and 19.1% of participants treated with placebo (**Table 3**). 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 4**). In the placebo group, 100% (18/18) of diarrhea TEAEs were characterized as mild-to-moderate,[2] with the following definitions:[9]

- 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 Diarrhea TEAEs (Safety Analysis Set)[11]

Preferred Term	Placebo (N=94)		Trofinetide (N=93)	
	Participants, n (%)	Events, n	Participants, n (%)	Events, n
TEAEs	18 (19.1)	20	75 (80.6)	103
Serious TEAEs	0	0	0	0
TEAEs leading to discontinuation	0	0	12 (12.9)*	12
Related TEAEs	12 (12.8)	14	74 (79.6)	100

**During the NDA review, the FDA assigned 2 additional discontinuations due to TEAEs of diarrhea based on subject narratives, to be 14 (15%). This was reviewed and agreed upon by Acadia.*
Abbreviation: TEAE=treatment-emergent adverse event.

Table 4. Diarrhea TEAEs by Severity (Safety Analysis Set)[2]

Placebo (N=94), n (%)			Trofinetide (N=93), n (%)		
Mild	Moderate	Severe	Mild	Moderate	Severe
15 (16.0)	3 (3.2)	0	39 (41.9)	34 (36.6)	2 (2.2)

Abbreviation: TEAE=treatment-emergent adverse event.

The mean first onset of diarrhea TEAEs was 6.5 days (range, 1 to 49 days) after starting trofinetide. The duration of diarrhea varied but resolved within a median of 3 days (range, 1 to 46 days) after stopping trofinetide.[3] None of the diarrhea TEAEs were associated with hospitalization; 1 occurred with the TEAE of dehydration, and 3 with the TEAE of weight loss.[11] In the trofinetide group, 10.7% of participants with diarrhea TEAEs experienced weight loss of ≥7% from baseline compared with 16.7% of those without diarrhea.[3]

Twelve participants (12.9%) in the trofinetide group and none of the participants in the placebo group experienced diarrhea TEAEs leading to discontinuation of study drug (**Table 3**).[2] Study-drug related diarrhea TEAEs were reported for 74 (79.6%) participants in the trofinetide group and 12 (12.8%) participants in the placebo group.[11]

Post-hoc Analysis of Diarrhea TEAEs in LAVENDER

Diarrhea TEAEs from the LAVENDER trial were further examined to assess for potential influence of selected participant and treatment characteristics in trofinetide-treated participants, with no clear trends emerging. Descriptive statistics (mean, median, standard deviation) are presented, but statistical testing was not performed because these data were not powered for statistical analysis, many sample sizes were small, and the analysis was post-hoc in nature.[4]

Post-hoc subgroup analysis was conducted by age (**Table 5**).

Table 5. Incidence, Severity, Time to Onset, and Duration of Diarrhea TEAEs by Age Group at Baseline (ACP-2566-003; Safety Analysis Set)[4]

Treatment and Age Group, y	n	Participants with diarrhea, n (%)	Diarrhea events, n	Maximum severity			Mean time to onset, days (min, max)	Mean event duration, days (min, max)
				Mild n (%)	Moderate n (%)	Severe n (%)		
Placebo								
5–10	52	10 (19.2)	11	9 (17.3)	1 (1.9)	0	11.8 (2, 33)	13.8 (1, 78)
11–15	24	4 (16.7)	4	3 (12.5)	1 (4.2)	0	23.0 (1, 78)	5.8 (2, 12)
16–20	18	4 (22.2)	5	3 (16.7)	1 (5.6)	0	19.0 (8, 36)	33.5 (3, 77)
Trofinetide								
5–10	49	39 (79.6)	48	26 (53.1)	13 (26.5)	0	6.6 (1, 38)	52.2 (1, 92)
11–15	25	22 (88.0)	28	9 (36.0)	12 (48.0)	1 (4.0)	8.4 (1, 49)	50.6 (4, 89)
16–20	19	14 (73.7)	27	4 (21.1)	9 (47.4)	1 (5.3)	3.4 (1, 8)	50.6 (8, 84)

Abbreviation: TEAE=treatment-emergent adverse event.

In trofinetide-treated participants, diarrhea TEAE rates were compared according to history of constipation and route of administration (**Table 6**).

Table 6. Incidence of Diarrhea TEAEs by History of Constipation and Route of Trofinetide Administration (ACP-2566-003; Safety Analysis Set)[3,4]

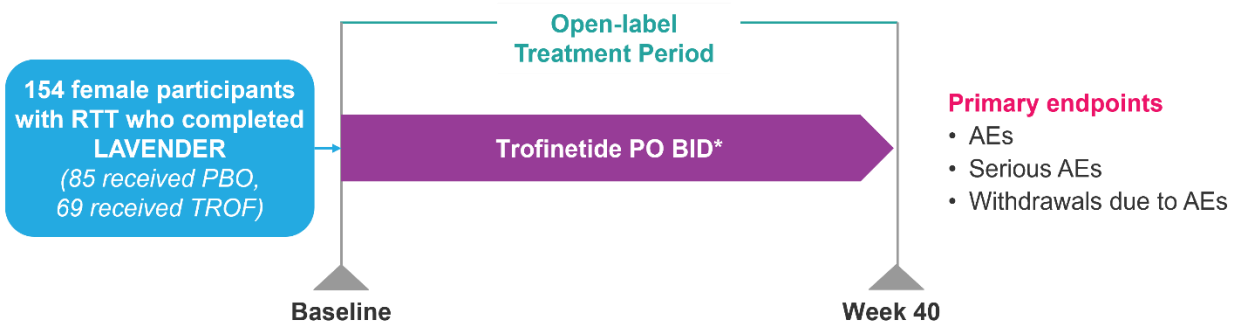
	Statistic	Placebo (N=94)	Trofinetide (N=93)
History of Constipation			
No	N	20	23
	n (%)	3 (15.0)	19 (82.6)
Yes	N	74	70
	n (%)	15 (20.3)	56 (80.0)
Route of Study Drug Administration			
G-Tube	N	39	38
	n (%)	6 (15.4)	34 (89.5)
Oral	N	55	55
	n (%)	12 (21.8)	41 (74.5)

Abbreviations: G-tube=gastrostomy tube; 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.[5]

Figure 2. LILAC-1 Study Design[5]



**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).[5] Overall, 75.3% of participants had a history of constipation (**Table 7**); 42.2% of participants had a medical history of gastrostomy.[12]

Table 7. Medical History of GI Disorders in ≥2% of Participants (ACP-2566-004; Safety Analysis Set)[12]

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 and loperamide was used in 62.3% of participants (**Table 8**). Drugs for constipation were used in 59.7% of participants.[5,12]

Table 8. Concomitant Medications Related to GI Function Reported in ≥10% of Participants (ACP-2566-004; Safety Analysis Set)[12]

WHO ATC Class Preferred Term	PBO in LAVENDER (N=85) n (%)	TROF in LAVENDER (N=69) n (%)	Total (N=154) n (%)
Antidiarrheal microorganisms	**9 (10.6)**	**8 (11.6)**	**17 (11.0)**

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)
Antipropulsives	**58 (68.2)**	**38 (55.1)**	**96 (62.3)**
Loperamide	58 (68.2)	38 (55.1)	96 (62.3)
Drugs for constipation	**59 (69.4)**	**33 (47.8)**	**92 (59.7)**
Macrogol	47 (55.3)	20 (29.0)	67 (43.5)
Glycerol	10 (11.8)	8 (11.6)	18 (11.7)
Sennoside A+B	9 (10.6)	7 (10.1)	16 (10.4)
Drugs for functional GI disorders	**15 (17.6)**	**15 (21.7)**	**30 (19.5)**
Simethicone	14 (16.5)	10 (14.5)	24 (15.6)
Drugs for peptic ulcer and GERD	**29 (34.1)**	**22 (31.9)**	**51 (33.1)**
Omeprazole	8 (9.4)	11 (15.9)	19 (12.3)
Lansoprazole	11 (12.9)	6 (8.7)	17 (11.0)
Intestinal adsorbents	**30 (35.3)**	**19 (27.5)**	**49 (31.8)**
Plantago ovata	27 (31.8)	17 (24.6)	44 (28.6)
Other alimentary tract and metabolism products	**21 (24.7)**	**12 (17.4)**	**33 (21.4)**
Probiotics NOS	12 (14.1)	7 (10.1)	19 (12.3)

Abbreviations: ATC=Anatomical/Therapeutic/Chemical; GERD=gastroesophageal reflux disease; GI=gastrointestinal; NOS=not otherwise specified; PBO=placebo; TROF=trofinetide; WHO=World Health Organization.

Diarrhea AEs

AEs of diarrhea were reported in 74.7% of participants overall (**Table 9**). Most reports of diarrhea were of mild or moderate severity (95.6%). Diarrhea was the most common AE leading to discontinuation.[5]

Table 9. Summary of Diarrhea AEs (ACP-2566-004; Safety Analysis Set)[5,12]

	PBO in LAVENDER (N=85) n (%)	TROF in LAVENDER (N=69) n (%)	Total (N=154) n (%)
AEs	71 (83.5)	44 (63.8)	115 (74.7)
Serious AEs	0	0	0
AEs leading to discontinuation	24 (28.2)	9 (13.0)	33 (21.4)

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

It should be noted that 27 participants (17.5%) had an ongoing AE of diarrhea at the start of LILAC-1 (**Table 10**).[12]

Table 10. Ongoing Pre-Treatment-Emergent AEs of Diarrhea (ACP-2566-004; Safety Analysis Set)[12]

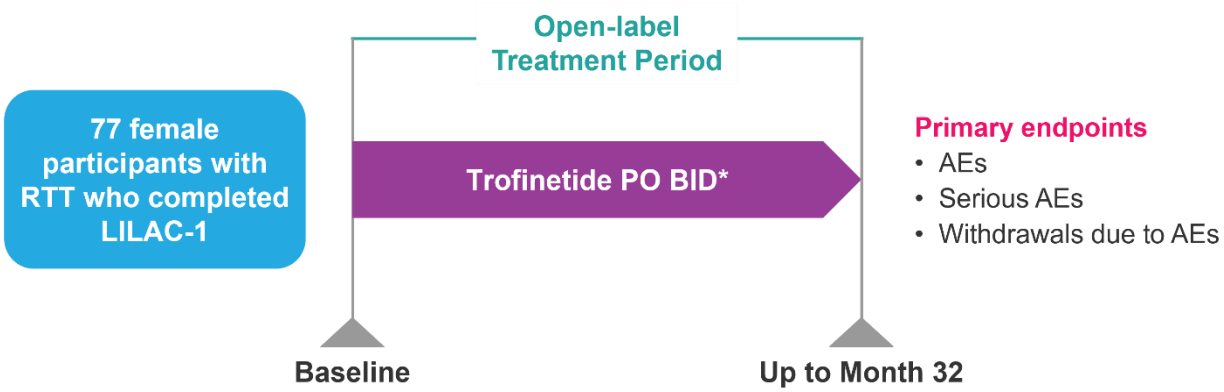
Preferred Term	PBO in LAVENDER (N=85) n (%)	TROF in LAVENDER (N=69) n (%)	Total (N=154) n (%)
Diarrhea	1 (1.2)	26 (37.7)	27 (17.5)

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.[6]

Figure 3. LILAC-2 Study Design[6]



**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).[6] Overall, 72.7% of participants had a history of constipation (**Table 11**); 48.1% of participants had a medical history of gastrostomy.[13]

Table 11. Medical History of GI Disorders in ≥2% of Participants (ACP-2566-005; Safety Analysis Set)[13]

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 and loperamide was used in 45.5% of participants (**Table 12**). Drugs for constipation were used in 55.8% of participants.[13]

Table 12. Concomitant Medications Related to GI Function in ≥10% of Participants (ACP-2566-005; Safety Analysis Set)[13]

WHO ATC Class Preferred Term	Trofinetide (N=77) n (%)
Antidiarrheal microorganisms	**11 (14.3)**
Antiemetics and antinauseants	**13 (16.9)**
Ondansetron	12 (15.6)
Antipropulsives	**35 (45.5)**
Loperamide	35 (45.5)
Drugs for constipation	**43 (55.8)**
Macrogol	28 (36.4)
Glycerol	10 (13.0)
Sennoside A+B	9 (11.7)
Drugs for functional GI disorders	**23 (29.9)**
Simethicone	16 (20.8)
Drugs for peptic ulcer and GERD	**28 (36.4)**
Omeprazole	11 (14.3)
Lansoprazole	10 (13.0)
Esomeprazole	8 (10.4)
Intestinal adsorbents	**16 (20.8)**
Plantago ovata	16 (20.8)
Other alimentary tract and metabolism products	**19 (24.7)**
Levocarnitine	10 (13.0)
Probiotics NOS	10 (13.0)

Abbreviations: ATC=Anatomical/Therapeutic/Chemical; GERD=gastroesophageal reflux disease; GI=gastrointestinal; NOS=not otherwise specified; WHO=World Health Organization.

Diarrhea AEs

AEs of diarrhea were reported in 53.2% of participants overall; all reports of diarrhea were of mild or moderate severity.[6] One participant discontinued due to an AE of diarrhea (**Table 13**).[13]

Table 13. Summary of Diarrhea AEs (ACP-2566-005; Safety Analysis Set)[6,13]

	Total (N=77) n (%)
AEs	41 (53.2)
Serious AEs	0
AEs leading to discontinuation	1 (1.3)

Abbreviation: AE=adverse event.

Pooled Analysis of Any Diarrhea TEAEs in LAVENDER and Long-term Studies

Diarrhea resolution status, dose modification, and concomitant antidiarrheal treatment was summarized for 178 participants who received trofinetide in LAVENDER and two long-term, OLE studies, LILAC-1 and LILAC-2 (**Table 14**).[7]

In the pooled analysis, 85% of patients treated with trofinetide experienced diarrhea. In those treated with trofinetide, 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.[1] Any diarrhea TEAEs were not associated with

hospitalization for any of the participants. Forty-four participants (24.7%) in the pooled analysis experienced any diarrhea TEAEs leading to discontinuation of study drug.[7]

Table 14. Summary of Diarrhea Resolution Status, Dose Modification, and Concomitant Antidiarrheal Treatment (Pooled Analysis)[7]

Parameter	Trofinetide (N=178)
Any diarrhea TEAEs*, n (%)	151 (84.8)
Diarrhea resolved after last dose of trofinetide and did not recur, n (%)	13 (7.3)
Diarrhea resulted with drug withdrawn and did not recur, n (%)	27 (15.2)
Diarrhea completely resolved while on trofinetide and did not recur, n (%)	24 (13.5)
Duration of diarrhea (days), mean	64.2
Dose interrupted for any reason [1], n (%)	6 (3.4)
Duration dose interrupted (days), mean	7.8
Dose reduced for any reason [1], n (%)	10 (5.6)
Duration dose reduced (days), mean	110.6
Amount of dose reduction (%), mean	47.2
Dose returned to (%), mean	60.9
Concomitant antidiarrheal treatment [2], n (%)	18 (10.1)
Duration of concomitant antidiarrheal treatment (days), mean	244.5
Diarrhea did not resolve while on trofinetide or recurred after resolution, n (%)	87 (48.9)
Diarrhea recurred after resolution, n (%)	60 (33.7)
Duration of diarrhea (days), mean	110.6
Dose interrupted for any reason [1], n (%)	17 (9.6)
Duration dose interrupted (days), mean	11.5
Dose reduced for any reason [1], n (%)	58 (32.6)
Duration dose reduced (days), mean	137.9
Amount of dose reduction (%), mean	51.5
Dose returned to (%), mean	74.5
Concomitant antidiarrheal treatment [2], n (%)	75 (42.1)
Duration of concomitant antidiarrheal treatment (days), mean	245.5

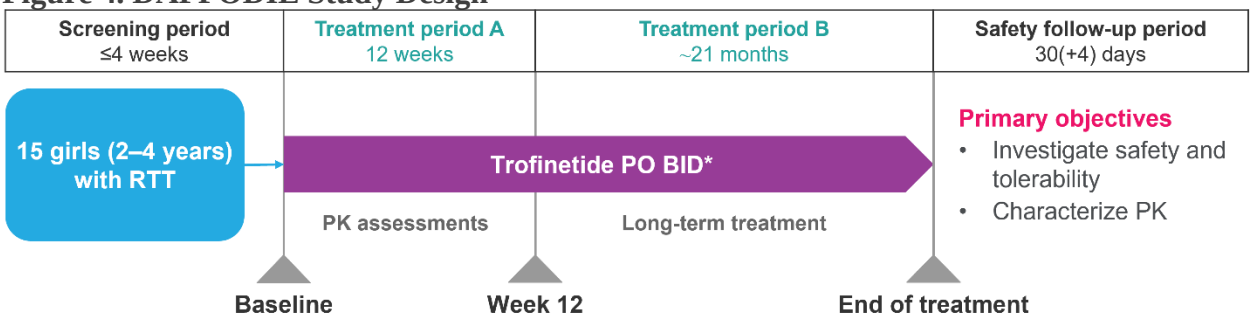
**Diarrhea, feces soft, frequent bowel movements.*
[1] If morning and evening doses in the dose modification log were both 0 or HELD, it was considered as a dose interruption; else if either morning or evening doses were less than the initial dose, it was considered as a dose reduction. A participant can be counted as both a dose reduction and a dose interruption.
[2] The concomitant antidiarrheal treatment includes loperamide; loperamide hydrochloride; loperamide hydrochloride; simethicone; plantago ovata; and fibre, dietary.
Abbreviation: TEAE=treatment-emergent 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.[8]

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.[8]

Figure 4. DAFFODIL Study Design[8]



**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

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).[8] Overall, 66.7% had a history of constipation (**Table 15**); 40.0% of participants had a medical history of gastrostomy.[14]

Table 15. Medical History of GI Disorders in ≥2% of Participants (ACP-2566-009; Safety Analysis Set)[14]

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

Overall, loperamide was used in 53.3% of participants, while osmotically acting laxatives were used in 46.7% of participants (**Table 16**). No participants received concomitant antiemetics and antinauseants.[14]

Table 16. Concomitant Medications Related to GI Function in ≥20% of Participants (ACP-2566-009; Safety Analysis Set)[14]

WHO ATC Class Preferred Term	Trofinetide (N=15) n (%)
Antipropulsives	**8 (53.3)**
Loperamide	8 (53.3)
Contact laxatives	**3 (20.0)**
Inula helenium root; senna alexandrina leaf	3 (20.0)
H_2-receptor antagonists	**4 (26.7)**
Famotidine	4 (26.7)
Herbal intestinal adsorbents	**3 (20.0)**
Plantago ovata	3 (20.0)
Osmotically acting laxatives	**7 (46.7)**
Macrogol	5 (33.3)
Other drugs for functional gastrointestinal disorders	**3 (20.0)**

WHO ATC Class Preferred Term	Trofinetide (N=15) n (%)
Simeticone	3 (20.0)
Proton pump inhibitors	**4 (26.7)**

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

Diarrhea TEAEs

Diarrhea TEAEs were reported in 80.0% of participants (**Table 17**). No serious TEAEs of diarrhea were reported.[8] Diarrhea was considered a related TEAE for 10 (66.7%) participants.[14]

Table 17. Summary of Diarrhea TEAEs (ACP-2566-009; Safety Analysis Set)[8]

	Trofinetide (N=15) n (%)
TEAEs	12 (80.0)
Serious TEAEs	0
TEAEs leading to discontinuation	1 (6.7)

Abbreviation: TEAE=treatment-emergent adverse event.

Diarrhea TEAEs were either of mild or moderate severity (**Table 18**).[8]

Table 18. Diarrhea TEAEs by Maximum Severity (Safety Analysis Set)[14]

Preferred Term	Trofinetide (N=15), n (%)		
	Mild	Moderate	Severe
Diarrhea	7 (46.7)	5 (33.3)	0

Abbreviation: TEAE=treatment-emergent adverse event.

One participant discontinued during Treatment Period A due to a TEAE of diarrhea that was moderate in severity and considered related to study drug.[8,14]

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