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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 Development Program in Rett Syndrome

This letter is provided in response to your specific request for information regarding the trofinetide clinical development program in Rett syndrome (RTT).

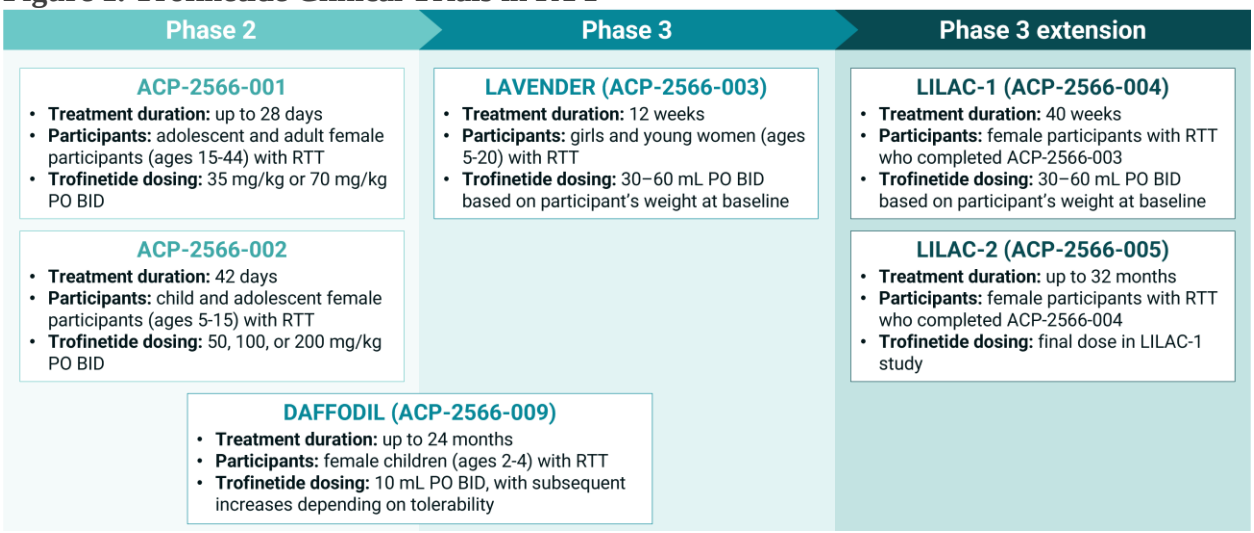
Summary

- Trofinetide was first assessed in an exploratory, dose-escalating, Phase 2 study (**ACP-2566-001**) in 56 adolescent/adult females with RTT.[1]
- A second exploratory Phase 2 study (**ACP-2566-002**) was conducted over 42 days in a cohort of 82 girls aged 5–15 years with RTT.[2]
- The 12-week Phase 3 **LAVENDER™** study evaluated the efficacy and safety of trofinetide in 187 female participants (5–20 years old) with RTT.[3]
    - A statistically significant improvement over placebo was demonstrated for both **co-primary endpoints**, the Rett Syndrome Behaviour Questionnaire (RSBQ) total score and Clinical Global Impression-Improvement (CGI-I) score.[3]
    - **Treatment-emergent adverse events** (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 treatment group.[3]
    - **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.[3]
- Participants who completed LAVENDER were eligible to enroll in the **LILAC-1™** and **LILAC-2™** open-label extension (OLE) studies.[4,5]
- The open-label, Phase 2/3 **DAFFODIL™** study evaluated the safety, tolerability and pharmacokinetics (PK) of trofinetide in 15 girls aged 2–4 years with RTT over two treatment periods for a total duration of up to 78 weeks.[6]
    - Overall, 93.3% of subjects reported **at least one TEAE**. The most common TEAEs were diarrhea (80.0%) and vomiting (53.3%), which were all mild or moderate in severity. Two participants (13.3%) discontinued due to TEAEs: 1 (6.7%) participant due to diarrhea and 1 (6.7%) participant due to vomiting.[6]

Clinical Studies in RTT

The efficacy and safety of trofinetide for the treatment of RTT have been evaluated in 3 placebo-controlled studies: two Phase 2 trials and one Phase 3 trial (**Figure 1**). In addition, two Phase 3 OLE studies and a Phase 2/3 open-label study have been completed.[7]

Figure 1. Trofinetide Clinical Trials in RTT[7]



Abbreviations: BID=twice daily; PO=oral; RTT=Rett syndrome.

ACP-2566-001

This was an exploratory randomized, double-blind, placebo-controlled, multi-center, parallel-group, Phase 2 study.[1,8] Trofinetide was administered orally at doses of 35 mg/kg BID and 70 mg/kg BID for 28 days to 56 adolescent and adult participants (15–44 years of age) with RTT.[1] The primary objective was to assess the safety and tolerability in each dosing cohort comparing active with placebo treatment arms. Secondary objectives were to investigate measures of efficacy and to determine the blood pharmacokinetics.[8] The secondary measures of efficacy used in the study provided insight into potential efficacy measures for future studies.[1]

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.

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 versus 15% in the placebo group), irritability (22% in the 35 mg/kg group versus 15% in the placebo group), and somnolence (17% in the 70 mg/kg group versus 5% in the placebo group).[1] Three participants experienced serious TEAEs, none of which were deemed related to treatment with trofinetide. Most TEAEs were mild or moderate in intensity and were considered not related to study drug. One participant discontinued due to serious TEAEs. No deaths were reported during the study.[1]

Efficacy Results

The study was not designed or powered to detect a statistically significant difference between trofinetide and placebo on measures of efficacy. Results from the group-level analysis by individual cohort showed that trofinetide at 70 mg/kg BID exceeded the minimum requirement for efficacy based on prespecified criteria.[1]

ACP-2566-002

This was an exploratory, randomized, double-blind, placebo-controlled, multi-center, parallel-group, Phase 2 study with primary outcomes relating to assessment of safety and PK, and secondary outcomes relating to efficacy. Trofinetide was administered orally or via gastrostomy tube BID at doses of 50 mg/kg, 100 mg/kg, and 200 mg/kg for 42 days in girls (5–15 years of age) with RTT (N=82).[2]

A total of 82 participants were randomized in this study: 24 in the placebo group, 15 in the 50 mg/kg BID trofinetide group, 16 in 100 mg/kg BID trofinetide group, and 27 in the 200 mg/kg BID trofinetide group. The mean age of the cohort was 9.7 years (range 5.1–15.9 years) and 94% were white. Overall demographic characteristics for participants were balanced across the treatment groups.[2]

Safety Results

Only one participant (200 mg/kg BID group) was withdrawn from the study at the request of her parents because of increased mild gastroesophageal reflux, moderate diarrhea, and mild vomiting, which resolved uneventfully after discontinuation. Four SAEs occurred in 3 participants: 1 participant receiving placebo, 1 participant receiving 100 mg/kg bid, and 1 participant receiving 200 mg/kg BID. All the SAEs were deemed not related to study medication and resolved by the end of the study.

The most common AEs reported during the double-blind period across all treatment groups were diarrhea (27%), vomiting (15%), upper respiratory tract infection (12%), and pyrexia (10%) (**Table 1**). Most AEs were mild or moderate in intensity and most events were considered not related to study drug. There were no deaths reported in the study.[2]

Table 1. TEAEs in ≥2 Participants in Either Trofinetide Group and >Placebo (ACP-2566-002)[2]

System Organ Class Preferred Term	Number (%) of Participants			
	Placebo (n=24)	Trofinetide 50 mg/kg (n=15)	Trofinetide 100 mg/kg (n=16)	Trofinetide 200 mg/kg (n=27)
Reported ≥1 TEAE	14 (58)	8 (53)	11 (69)	19 (70)
Gastrointestinal disorders				
Diarrhea	1 (4)	4 (27)	2 (13)	15 (56)
Vomiting	3 (13)	1 (7)	2 (13)	6 (22)
Constipation	0 (0)	0 (0)	0 (0)	2 (7)
General disorders and administration site conditions				
Pyrexia	2 (8)	0 (0)	3 (19)	3 (11)
Infections and infestations				
Upper respiratory tract infection	3 (13)	1 (7)	0 (0)	5 (19)
Respiratory, thoracic, and mediastinal disorders				
Sinus congestion	0 (0)	0 (0)	1 (6)	2 (7)

Abbreviation: TEAE=treatment-emergent adverse event.

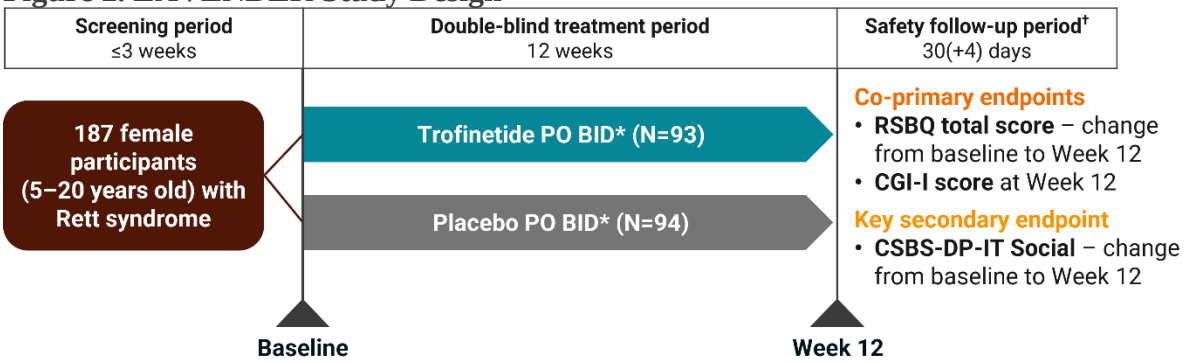
Efficacy Results

For the 200 mg/kg BID dose group, three of the five core endpoints showed a statistically significant difference from placebo: the RSBQ total score (p=0.042; Cohen's d = -0.487), the RTT-DSC total score (p=0.025; Cohen's d = -0.247), and the CGI-I scale (p=0.029; Cohen's d = -0.645). The 50 mg/kg BID and 100 mg/kg BID groups did not reach statistical significance.[2]

LAVENDER (ACP-2566-003)

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 2**).[3,9] Participants received trofinetide 30–60 mL BID or placebo, based on the participant's weight at baseline. The primary objective of this study was to investigate the efficacy of treatment with oral trofinetide versus placebo in girls and women with RTT.[3,10]

Figure 2. LAVENDER Study Design[3,10]



**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; CSBS-DP-IT Social=Communication and Symbolic Behavior Scales Developmental Profile™ Infant-Toddler Checklist – Social Composite Score; PO=oral; RSBQ=Rett Syndrome Behaviour Questionnaire.

Eligible participants had a score of 10–36 on the RTT Clinical Severity Scale, a Clinical Global Impression-Severity (CGI-S) score of ≥4 (moderate), were ≥6 months after regression at screening, and had a stable pattern of seizures or no seizures within 8 weeks of screening.[3]

Baseline Characteristics

Demographic and baseline disease characteristics were well balanced between the treatment groups.[3] In the Randomized Analysis Set (all randomized participants),[10] the mean (standard deviation [SD]) age of participants was 10.9 (4.62) years overall, with a mean (SD) baseline CGI-S score of 4.9 (0.76). Most participants (88.2% of the trofinetide group and 95.7% of the placebo group) were White (**Table 2**). In the respective trofinetide and placebo groups, 40.9% and 41.5% of participants were administered study medication via gastrostomy tube.[3]

Table 2. Baseline Demographics and Disease Characteristics – Randomized Analysis Set (ACP-2566-003)*[3]

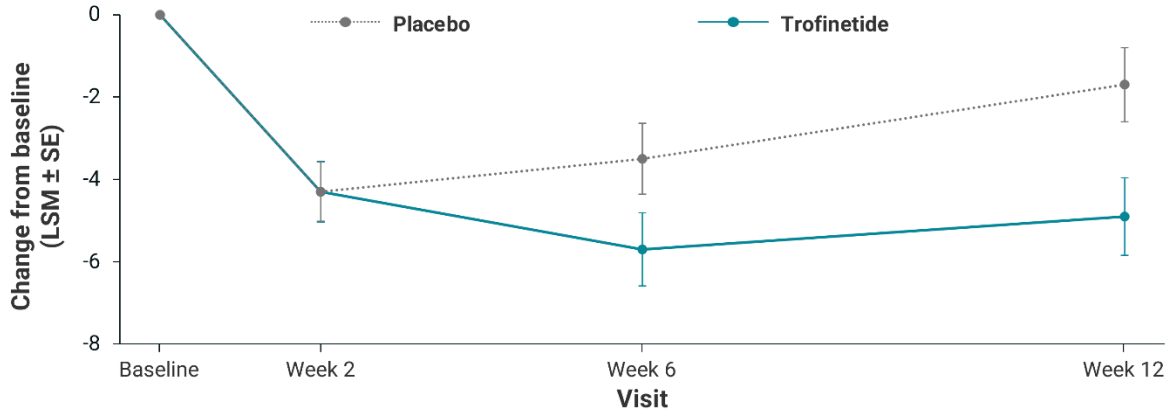
	Placebo (N=94)	Trofinetide (N=93)	Total (N=187)
Age, years (mean ± SD)	10.9 ± 4.57	11.0 ± 4.69	10.9 ± 4.62
Primary race, n (%)			
White	90 (95.7)	82 (88.2)	172 (92.0)
Black or African American	1 (1.1)	1 (1.1)	2 (1.1)
Asian	1 (1.1)	5 (5.4)	6 (3.2)
Native Hawaiian or other Pacific Islander	0	1 (1.1)	1 (0.5)
Other	2 (2.1)	4 (4.3)	6 (3.2)
RSBQ total score (mean ± SD)	44.4 ± 12.13	43.8 ± 11.42	44.1 ± 11.76
CGI-S score (mean ± SD)	4.9 ± 0.76	4.9 ± 0.77	4.9 ± 0.76

**No significant differences (p≤0.05) were detected between the study groups.*
Abbreviations: CGI-S=Clinical Global Impression-Severity; RSBQ=Rett Syndrome Behaviour Questionnaire; RTT=Rett syndrome; SD=standard deviation.

Efficacy Results

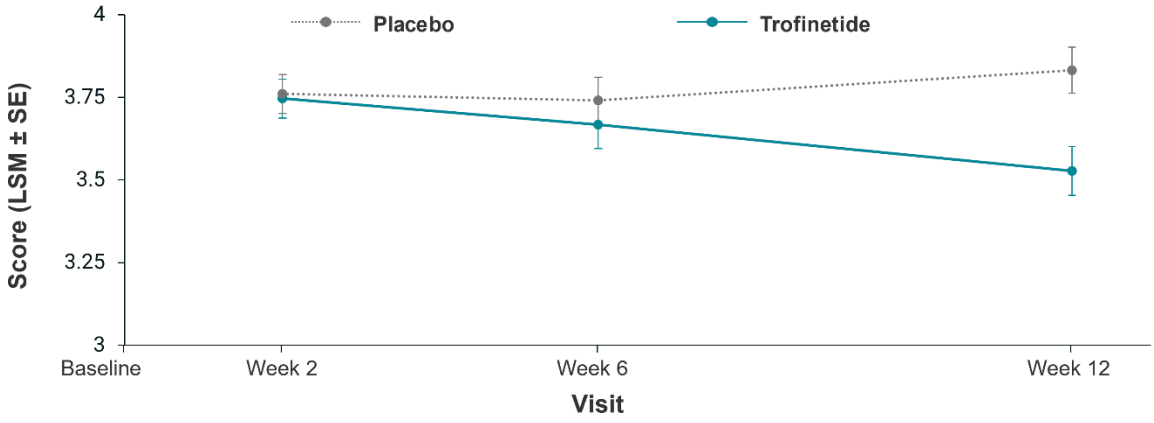
In the Full Analysis Set (all randomized participants who received ≥1 dose of study medication and who have both a baseline value and ≥1 post-baseline value for the RSBQ total score or who have ≥1 post-baseline value for the CGI-I score), a statistically significant improvement over placebo was demonstrated for both co-primary endpoints.[3,10] The mean (SE) change from baseline to Week 12 in the RSBQ total score was -5.1 (0.99) and -1.7 (0.98) in the trofinetide and placebo groups, respectively. Based on the MMRM analysis, the LSM change from baseline to Week 12 on the RSBQ was -4.9 vs. -1.7 for trofinetide and placebo, respectively (LSM treatment difference -3.2 [95% CI -5.7, -0.6]; p=0.018; effect size=0.37; **Figure 3**). The LSM CGI-I score at Week 12 was 3.5 vs. 3.8 for trofinetide and placebo, respectively (LSM treatment difference -0.3 [95% CI -0.5, -0.1]; p=0.003; effect size=0.47; **Figure 4** and **Figure 5**).[3,9]

Figure 3. RSBQ Change from Baseline by Visit (LSM ± SE) (OC; MMRM) – Full Analysis Set (ACP-2566-003)[3]



Abbreviations: LSM=least squares mean; MMRM=mixed model repeated measures; OC=observed cases; RSBQ=Rett Syndrome Behaviour Questionnaire; SE=standard error.

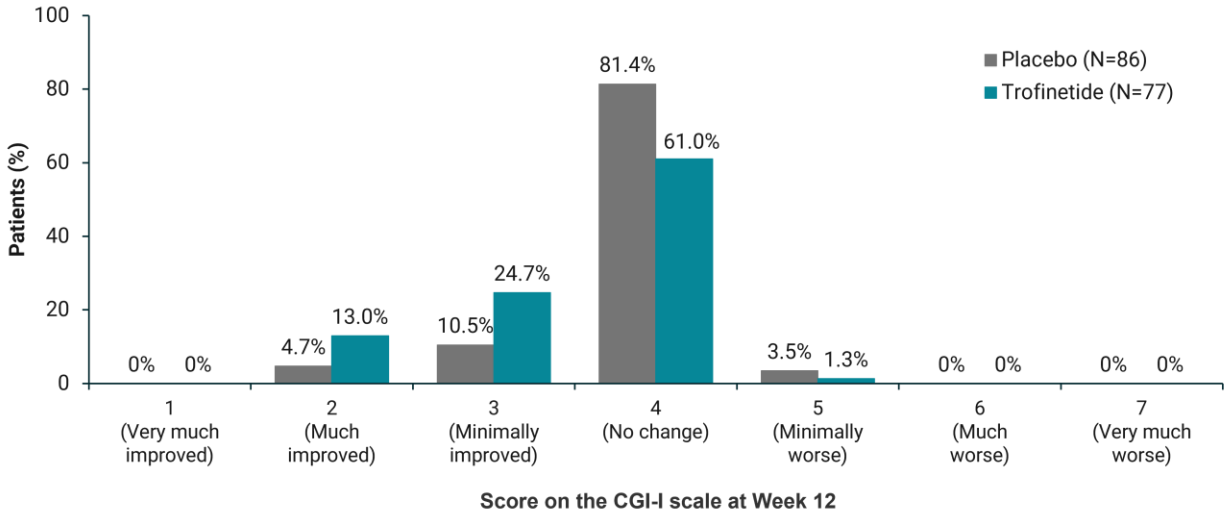
Figure 4. CGI-I Score by Visit (LSM ± SE) (OC; MMRM) – Full Analysis Set (ACP-2566-003)[3]



Placebo, n=	90	92	86
Trofinetide, n=	90	83	77

Abbreviations: CGI-I=Clinical Global Impression-Improvement; LSM=least squares mean; MMRM=mixed model repeated measures; OC=observed cases; SE=standard error.

Figure 5. Distribution of CGI-I Scores for Patients Completing LAVENDER – Full Analysis Set (ACP-2566-003)[9]



Abbreviation: CGI-I=Clinical Global Impression-Improvement.

Safety Results

In the Safety Analysis Set (all randomized participants who received ≥1 dose of study medication), in the respective trofinetide and placebo groups, at least one TEAE was reported in 86 (92.5%) and 51 (54.3%) participants (**Table 3**). No deaths were reported.[3]

Table 3. Summary of TEAEs – Safety Analysis Set (ACP-2566-003)[11]

	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 TEAE leading to drug withdrawn	2 (2.1)	16 (17.2)*
Any fatal TEAE	0	0

**During the NDA review, the FDA assigned 2 additional discontinuations due to TEAEs based on subject narratives, to be 18 (19%). This was reviewed and agreed upon by Acadia.*
Abbreviations: NDA=New Drug Application; TEAE=treatment-emergent adverse event.

TEAEs ≥5% in either treatment group are shown in **Table 4**. The most common TEAEs were diarrhea (80.6% with trofinetide vs. 19.1% with placebo), of which 97.3% in the trofinetide arm were characterized as mild-to-moderate, and vomiting (26.9% with trofinetide vs. 9.6% with placebo), of which 96% in the trofinetide arm were characterized as mild-to-moderate,[3] with the following definitions:[10]

- 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 4. TEAEs in ≥5% in Either Treatment Group – Safety Analysis Set (ACP-2566-003)[3]

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)
Decreased appetite	2 (2.1)	5 (5.4)
Irritability	0	6 (6.5)

Abbreviation: TEAE=treatment-emergent adverse event.

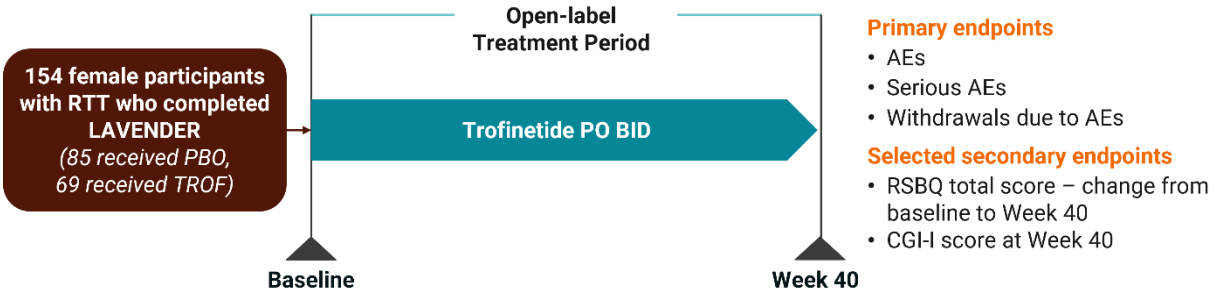
Serious TEAEs were observed in 3.2% of study participants in both the trofinetide and placebo groups.[3] Serious TEAEs were bacteremia/urinary tract infection/bronchiolitis (n=1), COVID-19 pneumonia (n=1), and seizure (n=1) in the participants treated with trofinetide, and respiratory distress (n=1), constipation (n=1), and pneumatosis intestinalis (n=1) in the participants treated with placebo.[3]

Study treatment discontinuation rates related to TEAEs were 17.2% in the trofinetide group as compared to 2.1% in the placebo group. 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).[3] 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.[11]

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 6**). The primary endpoint of LILAC-1 was the long-term safety and tolerability of trofinetide.[4]

Figure 6. LILAC-1 Study Design[4]



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.

Participants received trofinetide 30–60 mL twice daily (BID), based on their weight at baseline of the present study. However, participants whose assigned dose in LAVENDER was decreased for tolerability reasons were to 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.[4]

Baseline Characteristics

At LILAC-1 baseline, the mean (standard deviation [SD]) overall age of participants was 11.0 (4.55) years, and 92.9% of participants were White. The mean (SD) baseline RSBQ total score was 41.3 (12.57), and the mean (SD) baseline CGI-S score was 4.8 (0.78).[4]

Participant Disposition

Overall, 70 (46%) participants discontinued the study; 36% discontinued due to an adverse event and 3% due to lack of efficacy.[4]

Safety Results

Overall, 143 (92.9%) participants experienced AEs; 19 (12.3%) were serious AEs (**Table 5**).[4] One participant experienced two serious AEs that were considered related to study drug (urinary tract infection and dehydration).[12]

Table 5. Summary of Adverse Events – Safety Analysis Set (ACP-2566-004)[4]

	PBO in LAVENDER (N=85)	TROF in LAVENDER (N=69)	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 AE leading to discontinuation of study drug	36 (42.4)	19 (27.5)	55 (35.7)

	PBO in LAVENDER (N=85)	TROF in LAVENDER (N=69)	Total (N=154) n (%)
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.[4]

Table 6. Adverse Events ≥5% in Total Group – Safety Analysis Set (ACP-2566-004)[4]

	PBO in LAVENDER (N=85)	TROF in LAVENDER (N=69)	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: PBO=placebo; TROF=trofinetide.

Diarrhea (n=33; 21.4%) was the most common AE leading to discontinuation of study drug, followed by vomiting (n=10; 6.5%).[4] Other AEs leading to discontinuation of study drug that were reported in more than 1 participant were weight decreased (n=3; 1.9%), seizure (n=2; 1.3%), and seizure cluster (n=2; 1.3%).[12]

Efficacy Results

Open-label treatment with trofinetide in LILAC-1 continued to improve symptoms of RTT, as measured by the RSBQ total score and CGI-I score (secondary endpoints), including those who transitioned from placebo in the LAVENDER study (**Table 7**).[4]

Table 7. RSBQ Change from Baseline and CGI-I Score at Week 40 – Safety Analysis Set (ACP-2566-004)[4,12]

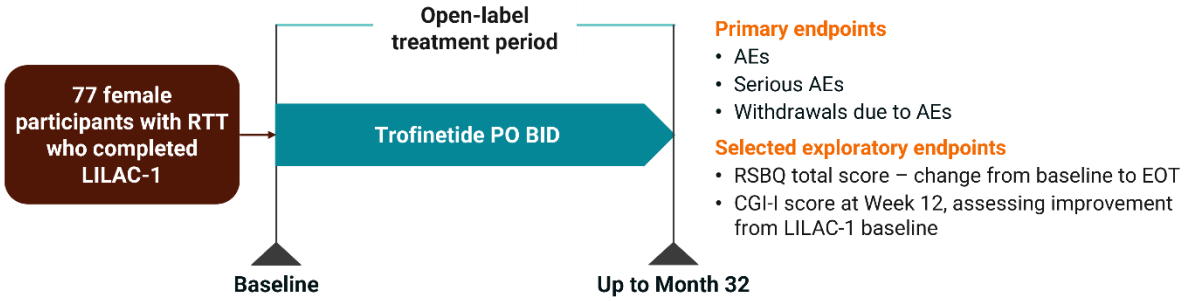
Week 40 endpoint measure	PBO in LAVENDER	TROF in LAVENDER	Total
RSBQ total score, change from LAVENDER baseline			
N	44	44	88
Mean (SE)	-7.0 (1.61)	-7.3 (1.62)	-7.1 (1.13)
CGI-I score*			
N	44	47	91
Mean (SE)	3.2 (0.14)	3.1 (0.11)	3.1 (0.9)

**Clinician rated improvement or worsening relative to LILAC-1 baseline.*
Abbreviations: CGI-I=Clinical Global Impression-Improvement; PBO=placebo; RSBQ=Rett Syndrome Behaviour Questionnaire; SE=standard error; 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 77 participants who previously completed a Phase 3 trofinetide treatment study (LAVENDER) and the LILAC-1 OLE study (**Figure 7**). The primary endpoint of LILAC-2 was the long-term safety and tolerability of trofinetide.[5]

Figure 7. LILAC-2 Study Design[5,13]



Abbreviations: AE=adverse event; BID=twice a day; CGI-I=Clinical Global Impression-Improvement; EOT=end of treatment; PO=oral; RSBQ=Rett Syndrome Behaviour Questionnaire; RTT=Rett syndrome.

A participant's assigned dose for this study was their final dose from the antecedent study (LILAC-1). If the participant's weight at LILAC-2 baseline, or after 52 weeks in the LILAC-2 study, put them in a new weight category, the Investigator could decide to increase the dose accordingly. 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.[5,13]

Exposure to Trofinetide

For participants in LILAC-2, the mean (SE) durations of exposure to trofinetide (including LAVENDER and LILAC-1) were 755.6 (20.8) days for the overall study population, 811.1 (23.2) days for participants who were treated with trofinetide in LAVENDER and LILAC-1, and 692.3 (33.2) days for participants who received placebo in LAVENDER and were switched to trofinetide in LILAC-1.[5]

Baseline Characteristics

In the total population for LILAC-2, the overall mean (SD) age was 12.0 (4.4) years with 42.9% of participants aged 5–10 years; 92.2% of participants were White. The mean (SD) RSBQ total score and CGI-S score at LILAC-2 baseline in the total population was 36.4 (12.7) and 4.8 (0.9), respectively.[5,14]

Participant Disposition

All 77 participants received at least one dose of trofinetide in LILAC-2 and were included in the safety analysis set; 61 (79.2%) completed the study while 16 (20.8%) discontinued. Reasons for discontinuation included an AE (n=5; 6.5%), death (n=4; 5.2%), and lack of efficacy (n=3; 3.9%).[5]

Safety Results

Overall, 72 (93.5%) participants experienced AEs; 23 (29.9%) were serious AEs (**Table 8**). 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.[5,14]

Table 8. Summary of Adverse Events – Safety Analysis Set (ACP-2566-005)[5]

	Trofinetide (N=77) n (%)
Any AE	72 (93.5)
Any serious AE	23 (29.9)
Any AE leading to discontinuation of study drug	9 (11.7)
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 9**). All reports of diarrhea were of mild or moderate severity; most reports of vomiting (n=14; 93.3%) were mild or moderate in severity.[5]

Table 9. Adverse Events in ≥10% of Participants – Safety Analysis Set (ACP-2566-005)[5]

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)

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.[5]

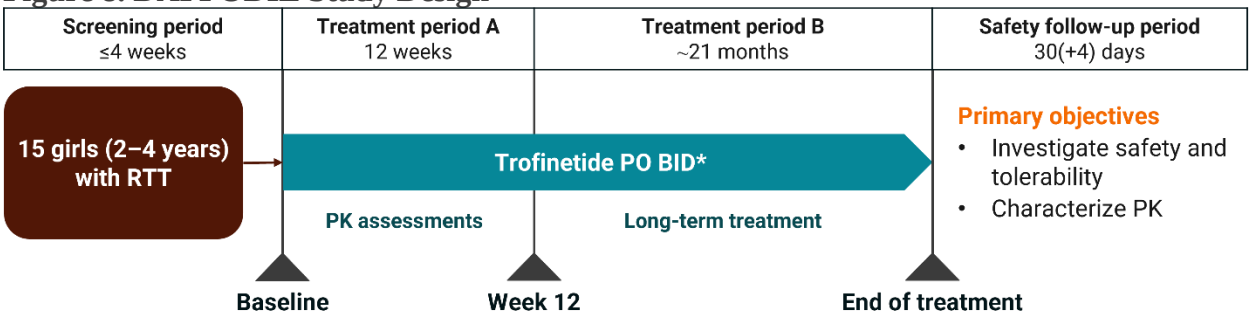
Efficacy Results

Open-label treatment with trofinetide in LILAC-2 continued to improve symptoms of RTT, as measured by the RSBQ total score and CGI-I score (exploratory endpoints). Overall, the mean (SE) change in RSBQ total score from LAVENDER baseline to Week 104 of LILAC-2 was -11.8 (2.45). For participants treated with trofinetide and placebo in LAVENDER, the mean (SE) change in RSBQ total score from the LAVENDER baseline to Week 104 in LILAC-2 was -9.8 (3.38) and -13.8 (3.61), respectively. The mean (SE) CGI-I score compared with the LILAC-1 baseline at Week 12 of LILAC-2 for the overall population was 3.1 (0.10).[5]

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 8**). The planned total duration of the trial was up to 26 months, with a screening period, two treatment periods (periods A and B), and a safety follow-up period. Period A was designed for evaluation of the dosing, tolerability, PK, and exploratory efficacy of trofinetide over approximately 12 weeks. Period B was designed to assess the safety and exploratory efficacy of long-term treatment with trofinetide for up to 21 months. Fifteen participants received trofinetide 2 g (10 mL) BID, with subsequent dose increases at scheduled visits, depending on tolerability.[6]

Figure 8. DAFFODIL Study Design[6]



**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.[6]

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).[6]

Safety Results

Overall, 14 participants (93.3%) reported any TEAE (**Table 10**). No deaths were reported.[6]

Table 10. Summary of TEAEs – Safety Analysis Set (ACP-2566-009)[6]

	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 TEAE leading to study drug discontinuation	1 (6.7)	2 (13.3)
Any fatal TEAE	0	0

Abbreviation: TEAE=treatment-emergent adverse event.

Overall, diarrhea and vomiting were the most common TEAEs, reported in 80.0% and 53.3% of participants, respectively (**Table 11**).[6] 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.[15]

Table 11. TEAEs Reported in >2 Participants Overall – Safety Analysis Set (ACP-2566-009)[6]

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)

Abbreviation: TEAE=treatment-emergent adverse event.

Serious TEAEs were reported by 4 (26.7%) participants overall: seizure (n=2 [13.3%]) altered state of consciousness (n=1 [6.7%]), dysphagia (n=1 [6.7%]), and gastroenteritis sapovirus. None of the events were considered related to study drug; all events required hospitalization but fully resolved and participants fully recovered. Overall, 2 (13.3%) participants discontinued from the study drug due to TEAEs: diarrhea (n=1 [6.7%]) and vomiting (n=1 [6.7%]).[6]

Exploratory Efficacy Results

The following efficacy measures were assessed as exploratory endpoints: CGI-I score, CGI-S score, Caregiver's Global Impression–Improvement (CaGI-I) score, and overall Quality of Life rating on the Impact of Childhood Neurologic Disability Scale (ICND-QoL).[6]

- The mean (SE) CGI-I score showed improvement at Week 4 (3.3 [0.19]), Week 12 (3.1 [0.22]) and through Week 78 (2.2 [0.22]), whereas there was no change from baseline in the mean CGI-S score at any post-baseline visit.
- The mean (SE) CaGI-I scores at Week 12 and Week 78 were 2.3 (0.12) and 2.1 (0.31), respectively.
- The mean (SE) of the ICND QoL scores increased from baseline by 0.3 (0.19) at Week 12 and 0.7 (0.30) at Week 78.

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