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DAYBUE® (trofinetide): Impact on Seizures

This letter is provided in response to your specific request for information regarding the impact of trofinetide on seizures or seizure burden in patients with Rett syndrome (RTT).

In the pivotal LAVENDER™ study and open-label extension (OLE) studies LILAC-1™ and LILAC-2™, and the open-label DAFFODIL™ study,[1-4] the impact of trofinetide on seizures or seizure burden was not assessed as a clinical endpoint. However, data were collected on seizure as a treatment-emergent adverse event (TEAE).

Summary

- Trofinetide clinical studies were not designed to assess the impact of trofinetide on seizures or seizure burden.
- The 12-week Phase 3 **LAVENDER study** evaluated the efficacy and safety of trofinetide in 187 female participants (5–20 years old) with RTT.[5] **Seizure was reported as a TEAE** in 5 of 94 participants (5.3%) in the placebo group and 8 of 93 participants (8.6%) in the trofinetide group.[5] All but 2 participants (1 in the trofinetide group and 1 in the placebo group) with a seizure-related TEAE had a history of seizures or epilepsy.[6]
- The 40-week OLE study **LILAC-1** evaluated the safety of long-term treatment with trofinetide in 154 female participants who chose to enroll after completing LAVENDER. **Seizure was reported as an adverse event (AE)** in 14 (9.1%) participants, of whom, all but 1 had a medical history of seizures or epilepsy.[7,8]
- The 32-month OLE **study LILAC-2** evaluated the safety of continued long-term treatment with trofinetide in 77 female participants who chose to enroll after completing LILAC-1. **Seizure was reported as an AE** in 11 (14.3%) participants, of whom, all but 2 had a medical history of seizures or epilepsy.[9,10]
- In the open-label, **Phase 2/3 DAFFODIL** study that evaluated the safety and tolerability of trofinetide in 15 girls aged 2–4 years for a total duration of up to 78 weeks, **seizure was reported as a TEAE** in 5 (33.3%) participants.[11]

Background

RTT is known to cause epileptic seizures from an early age, with a range of different seizure types observed.[12,13] The median age of onset of epilepsy in RTT is 4 or 5 years,[12,13] with a cumulative risk of developing epilepsy of approximately 90% over the lifespan. The course of seizure occurrence and remission in individuals with RTT is highly variable.[14]

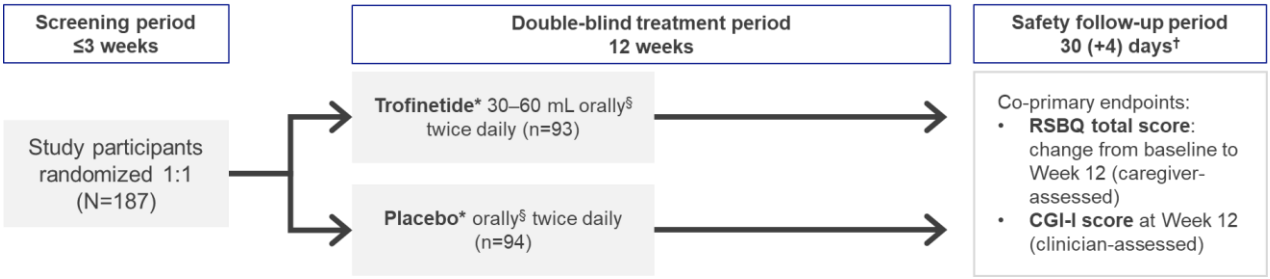
LAVENDER Study

LAVENDER Study Design[1,5,15]

Phase 3, 12-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group study

Female participants (5–20 years) diagnosed with typical RTT according to the Rett Syndrome Diagnostic Criteria and a documented disease-causing mutation in the *MECP2* gene

Primary objective: To investigate the efficacy of treatment with oral trofinetide vs placebo in girls and women with RTT



**Dose based on participant's body weight at baseline. §Medication was administered orally or by gastrostomy tube. †The LAVENDER follow-up visit does not take place if the participant rolls over into the open-label extension study.*
Abbreviations: CGI-I=Clinical Global Impression-Improvement; MECP2=methyl CpG binding protein 2; RSBQ=Rett Syndrome Behaviour Questionnaire.

Participants were ≥12 kg with classic/typical RTT, had a documented disease-causing mutation in the *MECP2* gene, and were ≥6 months post regression at screening.[16] Other selected inclusion criteria were: an RTT Clinical Severity Scale rating of 10–36, Clinical Global Impression-Severity (CGI-S) score of ≥4, and a stable pattern of seizures, or no seizures, within 8 weeks of screening.

Baseline Characteristics

Treatment groups were well balanced for demographic and baseline characteristics.[5] In the randomized analysis set (all randomized participants), the mean (standard deviation [SD]) age of participants was 11.0 (4.69) years in the trofinetide group and 10.9 (4.57) in the placebo, with a mean (SD) baseline CGI-S score of 4.9 (0.77) and 4.9 (0.76), respectively.[6] Most participants (88.2% [82/93] of the trofinetide group and 95.7% [90/94] of the placebo group) were White.[5] In the safety analysis set (all randomized participants who received ≥1 dose of study medication), 43% (40/93) of participants in the trofinetide group had a history of seizures vs 50% (47/94) of participants in the placebo group (**Table 1**).[5,6]

Table 1. Selected Medical History (Safety Analysis Set; LAVENDER)[5]

n (%)	Placebo (n=94)	Trofinetide (n=93)
Seizure	47 (50.0)	40 (43.0)
Epilepsy	16 (17.0)	20 (21.5)
Focal dyscognitive seizures	1 (1.1)	2 (2.2)
Partial seizures	1 (1.1)	2 (2.2)
Status epilepticus	2 (2.1)	1 (1.1)

Concomitant Antiepileptic Medication

Antiepileptics were a frequently used concomitant medication in both treatment groups (**Table 2**).[5]

Table 2. Concomitant Antiepileptic Medication (Safety Analysis Set; LAVENDER)[6]

WHO ATC Class Preferred Term	Placebo (n=94) n (%)	Trofinetide (n=93) n (%)	Total (N=187) n (%)
Antiepileptics	68 (72.3)	60 (64.5)	128 (68.4)
Diazepam	28 (29.8)	17 (18.3)	45 (24.1)
Levetiracetam	24 (25.5)	19 (20.4)	43 (23.0)
Clonazepam	13 (13.8)	15 (16.1)	28 (15.0)
Lamotrigine	14 (14.9)	9 (9.7)	23 (12.3)
Oxcarbazepine	5 (5.3)	17 (18.3)	22 (11.8)
Cannabidiol	12 (12.8)	9 (9.7)	21 (11.2)
Valproate	10 (10.6)	12 (12.9)	22 (11.8)
Clobazam	13 (13.8)	4 (4.3)	17 (9.1)
Zonisamide	9 (9.6)	8 (8.6)	17 (9.1)
Topiramate	7 (7.4)	7 (7.5)	14 (7.5)
Lacosamide	2 (2.1)	6 (6.5)	8 (4.3)
Midazolam	5 (5.3)	3 (3.2)	8 (4.3)
Lorazepam	2 (2.1)	3 (3.2)	5 (2.7)
Rufinamide	4 (4.3)	0	4 (2.1)
Carbamazepine	1 (1.1)	2 (2.2)	3 (1.6)
Cannabis sativa	2 (2.1)	0	2 (1.1)
Gabapentin	2 (2.1)	0	2 (1.1)
Phenobarbital	1 (1.1)	1 (1.1)	2 (1.1)
Brivaracetam	1 (1.1)	0	1 (0.5)
Felbamate	0	1 (1.1)	1 (0.5)
Herbal antiepileptics	0	1 (1.1)	1 (0.5)
Perampanel	0	1 (1.1)	1 (0.5)

Abbreviations: ATC Class=Anatomical/Therapeutic/Chemical Class level 3; WHO=World Health Organization.

Seizure TEAEs

TEAEs of seizure are summarized in **Table 3**.[6] In a post hoc analysis, the difference between the rates of seizure TEAEs for placebo and trofinetide groups was not significant.[5] One (1) TEAE of partial seizures occurred in the placebo group, compared with none in the trofinetide group. All participants but 1 in the trofinetide group and 1 in the placebo group with a seizure-related TEAE (seizure or partial seizures) had a history of epilepsy or seizures.[6]

Table 3. Summary of Seizure TEAEs (Safety Analysis Set; LAVENDER)[6]

	Placebo (n=94)		Trofinetide (n=93)	
	Participants, n (%)	Events, n	Participants, n (%)	Events, n
TEAEs*	5 (5.3)	5	8 (8.6)	11
Serious TEAEs	0	0	1 (1.1)	1
TEAEs leading to discontinuation	0	0	2 (2.2)	2
Related TEAEs	1 (1.1)	1	2 (2.2)	2

**p=0.3775, based on a post hoc analysis using Chi-square test of association.[5]*
Abbreviation: TEAE=treatment-emergent adverse event.

All of the seizure TEAEs were mild to moderate in severity (**Table 4**).[5] The TEAE of partial seizures was mild in severity.

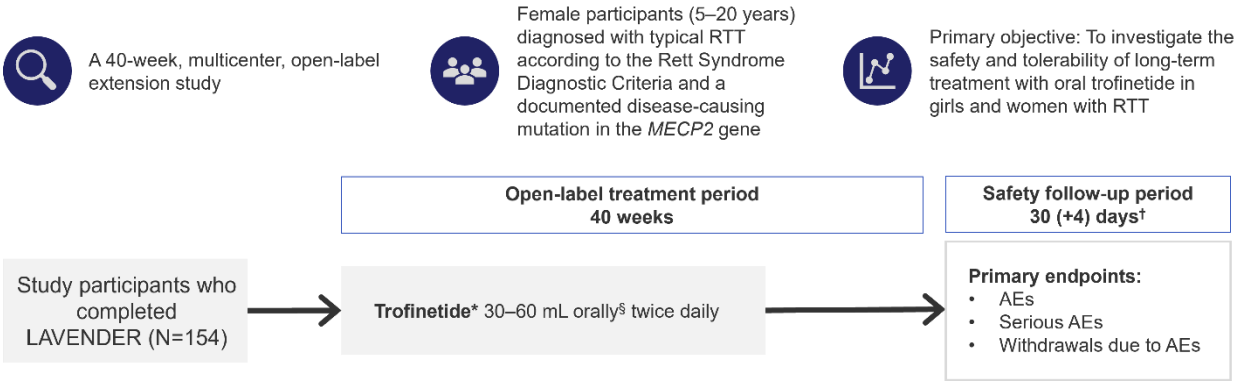
Table 4. Seizure TEAEs by Severity* (Safety Analysis Set; LAVENDER)[5]

Placebo (n=94), n (%)			Trofinetide (n=93), n (%)		
Mild	Moderate	Severe	Mild	Moderate	Severe
3 (3.2)	2 (2.1)	0	3 (3.2)	5 (5.4)	0

**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.[1]*
Abbreviation: TEAE=treatment-emergent adverse event.

LILAC-1 OLE Study

LILAC-1 Study Design[2,8]



**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. †The LILAC-1 follow-up visit does not take place if the participant rolls over into the LILAC-2 open-label extension study. §Orally or by gastrostomy tube.*
Abbreviations: AE=adverse event; MECP2=methyl CpG binding protein 2; RTT=Rett syndrome.

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).[8] In the safety analysis set, overall, 49% (76/154) of participants had a history of seizures (**Table 5**).[7]

Table 5. Selected Medical History (Safety Analysis Set; LILAC-1)[7]

	PBO in LAVENDER (n=85), n (%)	TROF in LAVENDER (n=69), n (%)	Total (N=154), n (%)
Seizure	44 (51.8)	32 (46.4)	76 (49.4)
Epilepsy	16 (18.8)	16 (23.2)	32 (20.8)
Focal dyscognitive seizures	0	2 (2.9)	2 (1.3)
Partial seizures	1 (1.2)	1 (1.4)	2 (1.3)
Status epilepticus	2 (2.4)	1 (1.4)	3 (1.9)

Abbreviations: PBO=placebo; TROF=trofinetide.

Concomitant Antiepileptic Medication

Antiepileptics were a frequently used concomitant medication in LILAC-1 (**Table 6**).[8]

Table 6. Concomitant Antiepileptic Medication (Safety Analysis Set; LILAC-1)[7]

	PBO in LAVENDER (n=85), n (%)	TROF in LAVENDER (n=69), n (%)	Total (n=154), n (%)
Antiepileptics	**63 (74.1)**	**49 (71.0)**	**112 (72.7)**
Diazepam	28 (32.9)	15 (21.7)	43 (27.9)
Levetiracetam	25 (29.4)	16 (23.2)	41 (26.6)
Clonazepam	16 (18.8)	14 (20.3)	30 (19.5)
Lamotrigine	15 (17.6)	7 (10.1)	22 (14.3)
Valproic acid	11 (12.9)	10 (14.5)	21 (13.6)
Cannabidiol	9 (10.6)	11 (15.9)	20 (13.0)
Oxcarbazepine	6 (7.1)	14 (20.3)	20 (13.0)
Zonisamide	10 (11.8)	9 (13.0)	19 (12.3)
Clobazam	13 (15.3)	5 (7.2)	18 (11.7)
Topiramate	5 (5.9)	4 (5.8)	9 (5.8)
Lorazepam	4 (4.7)	3 (4.3)	7 (4.5)
Lacosamide	2 (2.4)	4 (5.8)	6 (3.9)
Midazolam	4 (4.7)	2 (2.9)	6 (3.9)
Gabapentin	1 (1.2)	2 (2.9)	3 (1.9)
Rufinamide	3 (3.5)	0	3 (1.9)
Carbamazepine	1 (1.2)	1 (1.4)	2 (1.3)
Brivaracetam	1 (1.2)	0	1 (0.6)
Fosphenytoin	1 (1.2)	0	1 (0.6)
Perampanel	0	1 (1.4)	1 (0.6)
Phenobarbital	1 (1.2)	0	1 (0.6)

Abbreviations: PBO=placebo; TROF=trofinetide.

Seizure AEs

Seizure AEs are summarized in **Table 7**. Of the 14 participants with seizure AEs, all but 1 had a medical history of seizures or epilepsy. A serious AE of seizure was reported in 5 participants, including 2 participants with increase in seizure, 1 participant with increased seizure frequency, and 2 participants with breakthrough seizures. Status epilepticus was reported as a serious AE in 2 participants. All serious AEs resolved except one serious AE (status epilepticus) was resolved with sequelae. AEs leading to discontinuation of study drug that were related to seizures included seizure in 2 participants and seizure cluster in 2 participants.[7]

Table 7. Summary of Seizure AEs (Safety Analysis Set; LILAC-1)[7]

	PBO in LAVENDER (n=85), n (%)	TROF in LAVENDER (n=69), n (%)	Total (N=154), n (%)
AEs	9 (10.6)	5 (7.2)	14 (9.1)
Serious AEs	2 (2.4)	3 (4.3)	5 (3.2)
AEs leading to discontinuation	1 (1.2)	1 (1.4)	2 (1.3)

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

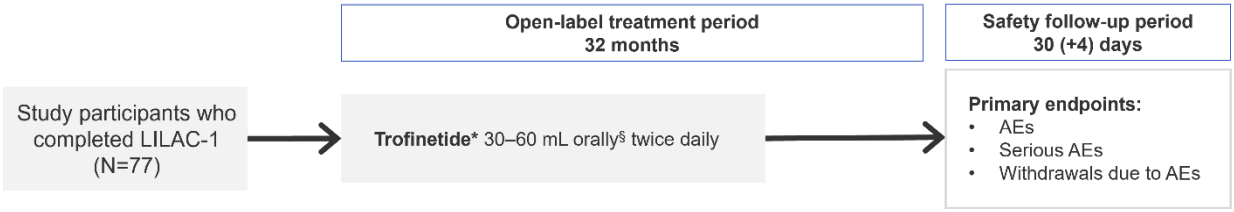
LILAC-2 OLE Study

LILAC-2 Study Design[3,10]

A long-term, multicenter, open-label extension study

Female participants (5–20 years) diagnosed with typical RTT according to the Rett Syndrome Diagnostic Criteria and a documented disease-causing mutation in the *MECP2* gene

Primary objective: To investigate the safety and tolerability of continued long-term treatment with oral trofinetide in girls and women with RTT



**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.*
§Orally or by gastrostomy tube.
Abbreviations: AE=adverse event; MECP2=methyl CpG binding protein 2; 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).[10] In the safety analysis set, overall, 40% (31/77) of participants had a history of seizures (**Table 8**).[9]

Table 8. Selected Medical History (Safety Analysis Set; LILAC-2)[9]

	Trofinetide (N=77), n (%)
Seizure	31 (40.3)
Epilepsy	23 (29.9)
Focal dyscognitive seizures	2 (2.6)
Partial seizures	2 (2.6)
Status epilepticus	2 (2.6)

Concomitant Antiepileptic Medication

Antiepileptics were a frequently used concomitant medication in LILAC-2 (**Table 9**).[10]

Table 9. Concomitant Antiepileptic Medication (Safety Analysis Set; LILAC-2)[10]

	Trofinetide (N=77), n (%)
Antiepileptics	**60 (77.9)**
Diazepam	24 (31.2)
Levetiracetam	21 (27.3)
Clonazepam	19 (24.7)
Lamotrigine	13 (16.9)
Zonisamide	13 (16.9)
Oxcarbazepine	12 (15.6)
Valproic acid	10 (13.0)
Clobazam	8 (10.4)
Cannabidiol	7 (9.1)
Lacosamide	7 (9.1)
Lorazepam	7 (9.1)
Topiramate	6 (7.8)

	Trofinetide (N=77), n (%)
Gabapentin	3 (3.9)
Midazolam	3 (3.9)
Carbamazepine	2 (2.6)
Cenobamate	1 (1.3)
Eslicarbazepine acetate	1 (1.3)
Fosphenytoin	1 (1.3)
Perampanel	1 (1.3)
Phenobarbital	1 (1.3)
Rufinamide	1 (1.3)

Seizure AEs

Seizures reported as AEs are summarized in **Table 10**. Of the 11 participants with seizure AEs, all but 2 had a medical history of seizures or epilepsy. In addition to serious AEs of seizure in 5 participants, generalized tonic-clonic seizure and status epilepticus were each reported as serious AEs in 1 participant. One participant experienced a fatal AE of sudden unexplained death in epilepsy.[10]

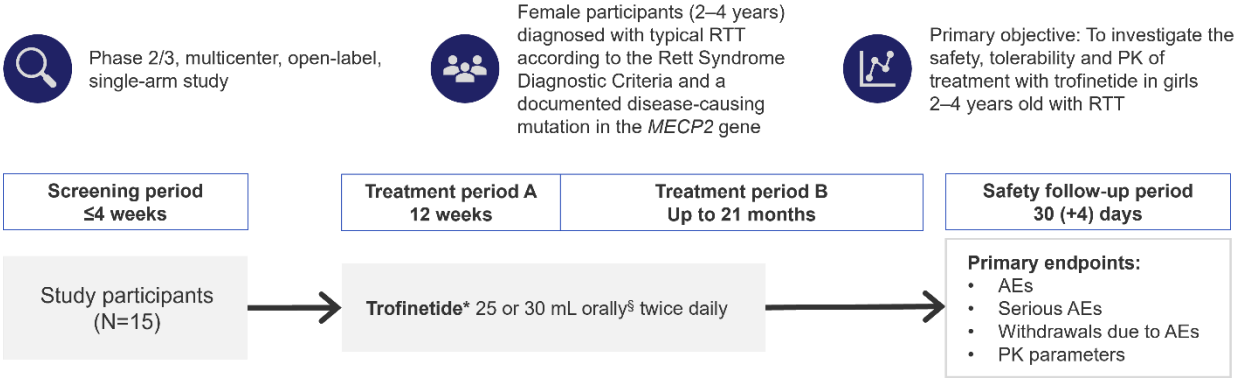
Table 10. Summary of Seizure AEs (Safety Analysis Set; LILAC-2)[10]

	Trofinetide (N=77), n (%)
AEs	11 (14.3)
Serious AEs	5 (6.5)
AEs leading to discontinuation	1 (1.3)

Abbreviation: AE=adverse event.

DAFFODIL Study

DAFFODIL Study Design[11,17]



**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. §Orally or by gastrostomy tube.*
Abbreviations: AE=adverse event; MECP2=methyl CpG binding protein 2; 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; CGI-S score ≥4 at screening and baseline; and stable pattern of seizures (or no seizures) within 8 weeks before screening.[11]

Baseline Characteristics

A total of 15 participants received at least one dose of study drug and were included in the Safety

Analysis Set. 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).[11] Two (13.3%) participants had a medical history of seizures.[18]

Concomitant Antiepileptic Medication

Five (33.3%) participants were taking antiepileptics as a concomitant medication (**Table 11**).[18]

Table 11. Concomitant Antiepileptic Medication (Safety Analysis Set; DAFFODIL)[18]

	Trofinetide (N=15), n (%)
Other Antiepileptics	5 (33.3)
Levetiracetam	4 (26.7)
Zonisamide	2 (13.3)

Seizure TEAEs

Seizures reported as AEs are summarized in **Table 12**. Of the 5 reported TEAEs of seizure, 1 was categorized as mild, 3 as moderate, and 1 as severe; none were considered related to study drug. There were 2 serious TEAEs of seizure: 1 was categorized as moderate and 1 as severe; neither was considered related to study drug.[18]

Table 12. Summary of Seizure TEAEs (Safety Analysis Set; DAFFODIL)[11]

	Trofinetide (N=15), n (%)
TEAEs	5 (33.3)
Serious TEAEs	2 (13.3)
TEAEs leading to discontinuation	0

Abbreviation: TEAE=treatment-emergent adverse event.

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