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DAYBUE™ (trofinetide): Concomitant Medications in the LAVENDER™ Study

This letter is provided in response to your specific request for information regarding the concomitant medications used by participants in the Phase 3 clinical trial of trofinetide in Rett syndrome (RTT).

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,[1] concomitant medications were used by 100% of participants on trofinetide (N=93) and 98.9% of participants on placebo (N=94).[2]
- **Drugs for constipation** were used by 60.2% of participants on trofinetide and 70.2% on placebo. The **antidiarrheal** loperamide was used in 50.5% of participants on trofinetide and 3.2% on placebo.[1]
- **Anti-epileptics** were used by 64.5% of participants in the trofinetide group and 72.3% of participants in the placebo group.[1]
- **Anxiolytics or antidepressants** were used by 22.6% of participants in the trofinetide group and 36.2% of participants in the placebo group.[2]

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**).[1,3] 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.[1,4]

Figure 1. LAVENDER Study Design[1,4]

**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.[5]

Participants were allowed to be on psychoactive medications, as well as other medication daily for chronic illness, but were required to be on a stable dose for 4 weeks prior to baseline, with no plans to change the dose.[1] Concomitant medications were defined as any medications that were ongoing at first dose of study drug or with a start date between the dates of the first and last doses of study drug, inclusive.[2]

Baseline Characteristics

Treatment groups were well balanced for demographic and baseline characteristics.[1] In the Randomized Analysis Set (all randomized participants),[4] 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.[1]

Selected Concomitant Medications

In the Safety Analysis Set (all randomized participants who received ≥1 dose of study medication),[1] concomitant medications were used by 100% of participants on trofinetide (N=93) and 98.9% of participants on placebo (N=94).[2]

Medications Related to Gastrointestinal Function

Drugs for constipation (65.2%) were one of the most frequently used concomitant medications in both treatment groups (**Table 1**). Loperamide was used in 50.5% of participants on trofinetide and 3.2% on placebo.[1]

Table 1. Concomitant Medications Related to Gastrointestinal Function Reported in ≥10% of Subjects in Either Treatment Group – Safety Analysis Set[2]

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 gastrointestinal 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	- -	25 (26.9)

WHO ATC Class Preferred Term	Placebo (N=94) n (%)	Trofinetide (N=93) n (%)
Plantago ovata	- -	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=gastro-esophageal reflux disease; NOS=not otherwise specified.

Antiemetics and antinauseants were used in 6.5% of participants on trofinetide and 4.3% on placebo (**Table 2**).[2]

Table 2. Concomitant Antiemetics and Antinauseants – Safety Analysis Set[2]

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)	--
Hyoscine	1 (1.1)	--

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

Anti-epileptic Medications

Anti-epileptics were one of the most frequently used concomitant medications in both treatment groups, used by 64.5% of participants in the trofinetide group and 72.3% of participants in the placebo group (**Table 3**).[1]

Table 3. Concomitant Anti-epileptic Medication – Safety Analysis Set[2]

WHO ATC Class Preferred Term	Placebo (N=94) n (%)	Trofinetide (N=93) n (%)
Anti-epileptics	68 (72.3)	60 (64.5)
Diazepam	28 (29.8)	17 (18.3)
Levetiracetam	24 (25.5)	19 (20.4)
Clonazepam	13 (13.8)	15 (16.1)
Lamotrigine	14 (14.9)	9 (9.7)
Oxcarbazepine	5 (5.3)	17 (18.3)
Cannabidiol	12 (12.8)	9 (9.7)
Valproate	10 (10.6)	12 (12.9)
Clobazam	13 (13.8)	4 (4.3)
Zonisamide	9 (9.6)	8 (8.6)
Topiramate	7 (7.4)	7 (7.5)
Lacosamide	2 (2.1)	6 (6.5)
Midazolam	5 (5.3)	3 (3.2)
Lorazepam	2 (2.1)	3 (3.2)
Rufinamide	4 (4.3)	- -
Carbamazepine	1 (1.1)	2 (2.2)
Cannabis sativa	2 (2.1)	- -
Gabapentin	2 (2.1)	- -
Phenobarbital	1 (1.1)	1 (1.1)
Brivaracetam	1 (1.1)	- -
Felbamate	- -	1 (1.1)

WHO ATC Class Preferred Term	Placebo (N=94) n (%)	Trofinetide (N=93) n (%)
Herbal antiepileptics	- -	1 (1.1)
Perampanel	- -	1 (1.1)

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

Anxiolytic and Antidepressant Medications

In LAVENDER, 21 out of 93 trofinetide patients (22.6%) and 34 out of 94 placebo participants (36.2%) were taking anxiolytic or antidepressant medications (**Table 4**).[2] Some agents appear in both categories because classification was based on 'indication' noted by site primary investigators.

Table 4. Concomitant Anxiolytics and Antidepressants – Safety Analysis Set[2]

WHO ATC Class Preferred Term	Placebo (N=94) n (%)	Trofinetide (N=93) n (%)
Antidepressants	19 (20.2)	8 (8.6)
Trazodone	13 (13.8)	6 (6.5)
Citalopram	2 (2.1)	1 (1.1)
Escitalopram	2 (2.1)	1 (1.1)
Amitriptyline	1 (1.1)	- -
Lamotrigine	1 (1.1)	- -
Mirtazapine	1 (1.1)	- -
Anxiolytics	15 (16.0)	13 (14.0)
Escitalopram	7 (7.4)	6 (6.5)
Clonazepam	1 (1.1)	4 (4.3)
Lorazepam	1 (1.1)	3 (3.2)
Diazepam	- -	2 (2.2)
Sertraline	3 (3.2)	1 (1.1)
Buspirone	2 (2.2)	- -
Fluoxetine	2 (2.2)	- -

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

Other Common Concomitant Medications

Additional concomitant medications used by ≥10% of participants in either treatment group are summarized in **Table 5**.

Table 5. Other Common Concomitant Medications Reported in ≥10% of Participants in Either Treatment Group – Safety Analysis Set[2]

WHO ATC Class Preferred Term	Placebo (N=94) n (%)	Trofinetide (N=93) n (%)
Adrenergics, inhalants	12 (12.8)	15 (16.1)
Salbutamol	7 (7.4)	10 (10.8)
Antihistamines for systemic use	28 (29.8)	24 (25.8)
Anti-inflammatory and antirheumatic products, nonsteroids	27 (28.7)	30 (32.3)
Ibuprofen	25 (26.6)	30 (32.3)
Decongestants and other nasal preparations for topical use	11 (11.7)	11 (11.8)
Hypnotics and sedatives	27 (28.7)	22 (23.7)
Melatonin	24 (25.5)	20 (21.5)
Multivitamins, combinations	13 (13.8)	9 (9.7)

WHO ATC Class Preferred Term	Placebo (N=94) n (%)	Trofinetide (N=93) n (%)
Multivitamins, plain	28 (29.8)	29 (31.2)
Vitamins NOS	28 (29.8)	29 (31.2)
Muscle relaxants, centrally acting agents	14 (14.9)	6 (6.5)
Baclofen	13 (13.8)	6 (6.5)
Other analgesics and antipyretics	30 (31.9)	24 (25.8)
Paracetamol	26 (27.7)	22 (23.7)
Other mineral supplements	11 (11.7)	6 (6.5)
Other nutrients	11 (11.7)	13 (14.0)
Other plain vitamin preparations	14 (14.9)	6 (6.5)
Pyridoxine hydrochloride	11 (11.7)	3 (3.2)
Psychostimulants, agents used for ADHD and nootropics	11 (11.7)	16 (17.2)
Clonidine	7 (7.4)	12 (12.9)
Vitamin A and D, incl. combinations of the two	27 (28.7)	32 (34.4)
Colecalciferol	19 (20.2)	16 (17.2)
Vitamin D NOS	12 (12.8)	20 (21.5)

Abbreviations: ADHD=attention deficit hyperactivity disorder; ATC Class=Anatomical/Therapeutic/Chemical Class level 3; incl.=including; NOS=not otherwise specified; WHO=World Health Organization.

References

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2. Acadia Pharmaceuticals Inc. Data on File. ACP-2566-003 Clinical Study Report. 2022.
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5. 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]**