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DAYBUE® (trofinetide) Clinical Trials and Observational Studies in Male Participants

This letter is provided in response to your specific request for information regarding clinical trials and observational studies of trofinetide conducted in male participants.

Relevant Label Information¹

- DAYBUE and DAYBUE® STIX (trofinetide) are indicated for the treatment of Rett syndrome in adults and pediatric patients 2 years of age and older.

Summary

- The trofinetide clinical development program for Rett syndrome (RTT) did not include data from male patients.
- [LOTUS](#) is an ongoing Phase 4, prospective, observational, real-world, open-label study involving caregivers of adults or pediatric patients of either sex who are prescribed trofinetide under routine clinical care.² [Interim analysis data](#) up to 12 months since the initiation of trofinetide are available for 7 male patients with RTT.³
- Male participants were included in [Phase 1 clinical studies](#) of healthy adult volunteers, a [Phase 2 study in fragile X syndrome](#) (FXS) and two [Phase 2 clinical studies in traumatic brain injury](#) (TBI).⁴

Background

RTT is a rare, debilitating neurological disorder that occurs primarily in females.⁵ The trofinetide clinical development program does not include data from male patients with RTT.⁴ The exclusion of males from the Phase 2 and Phase 3 clinical trials in RTT was based on considerations of study design to reduce variability in the population sample.⁶ Males with RTT were not enrolled due to the rarity of cases and difficulties inherent in adding another criterion for stratification.⁶ Male participants are, however, included in the ongoing Phase 4 LOTUS study involving caregivers of any adult or pediatric patients of any biological sex who were prescribed trofinetide under routine clinical care.³

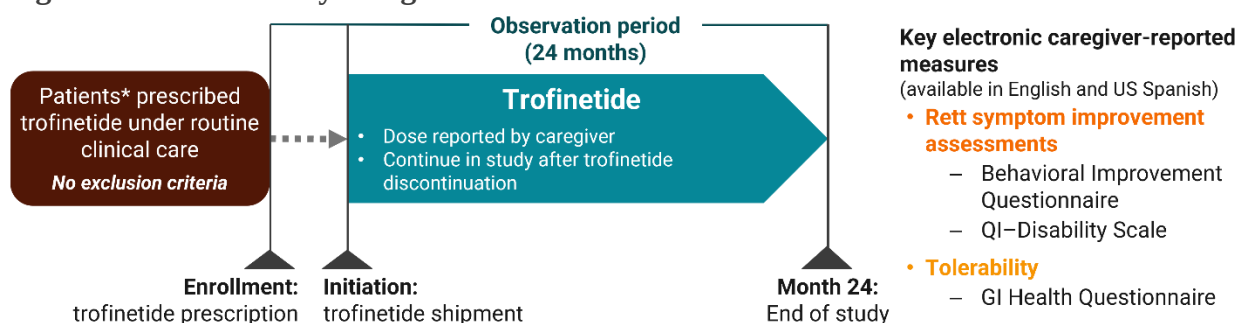
Male participants were included in Phase 1 clinical studies of healthy adult volunteers, a Phase 2 study in adolescent and adult males with FXS, and two Phase 2 clinical studies in adolescents and adults with TBI. Overall, 357 males have been exposed to trofinetide in clinical trials, including 189 who received trofinetide via IV infusion and 168 who received oral trofinetide.⁴

Phase 4 LOTUS Study (ACP-2566-014)

This is an ongoing Phase 4, observational, real-world, prospective, open-label study involving caregivers of patients prescribed trofinetide under routine clinical care in the United States. Participation in LOTUS lasts for ≥ 12 months from trofinetide initiation, with the option to extend participation for an additional 12 months (**Figure 1**). Caregivers of any adult or pediatric

patients of any biological sex who were prescribed trofinetide under routine clinical care are eligible for this study; there are no exclusion criteria.²

Figure 1. LOTUS Study Design^{2,7}



*Adult or pediatric patients of either sex.

Abbreviations: GI=gastrointestinal; QI-Disability=Quality-of-Life Inventory-Disability; US=United States.

The study utilizes three electronic caregiver-reported measures, which are available in English and United States Spanish (**Table 1**). The Behavioral Improvement Questionnaire (BIQ) and Gastrointestinal (GI) Health Questionnaire were developed by Acadia for the LOTUS study and have not been validated in individuals with Rett syndrome.² The QI-Disability scale was developed by Downs et al.⁸ as a measure of quality-of-life for school-aged children and adolescents with intellectual disability, and has been validated for adults with Rett syndrome (QI-Disability results have not yet been reported for male participants).^{2,3}

Table 1. Electronic Caregiver-reported Measures⁷

Electronic caregiver-reported measure	Description	Frequency
Behavioral Improvement Questionnaire (BIQ)	Selection of perceived behavioral improvements since starting trofinetide, across multiple domains	Collected monthly for 6 months, and every 3 months thereafter
QI-Disability scale ⁸	A measure of quality-of-life for children and adolescents with intellectual disability	Collected monthly for 6 months, and every 3 months thereafter
GI Health Questionnaire	Information on GI symptoms occurrence, frequency, and management	Collected weekly for 12 weeks, then monthly for 3 months, then every 3 months

Abbreviations: GI=gastrointestinal; QI-Disability=Quality-of-Life Inventory-Disability.

Interim 18-Month Follow-up Analysis in Male Participants

In total, 7 male participants were included in this 18-month follow-up, with ages ranging from 2–33 years (**Table 2**). Owing to ongoing enrollment, data are presented up to 12 months since the initiation of trofinetide. The median trofinetide dose at Week 1 was 38.9% of the target dose and increased to over 89.2% by Week 12.³

Table 2. Baseline Demographics and Characteristics³

Male LOTUS participants (N=7)	
Rett syndrome type, n (%)	
Classic	2 (28.6)

Male LOTUS participants (N=7)	
Atypical	1 (14.3)
Unknown	4 (57.1)
Ethnicity, n (%)	
Non-Hispanic	7 (100)
Median (IQR) age at time of RTT diagnosis, years (n=3)	7 (1–25)
Median (IQR) age at time of trofinetide initiation, years*	8 (3–19)

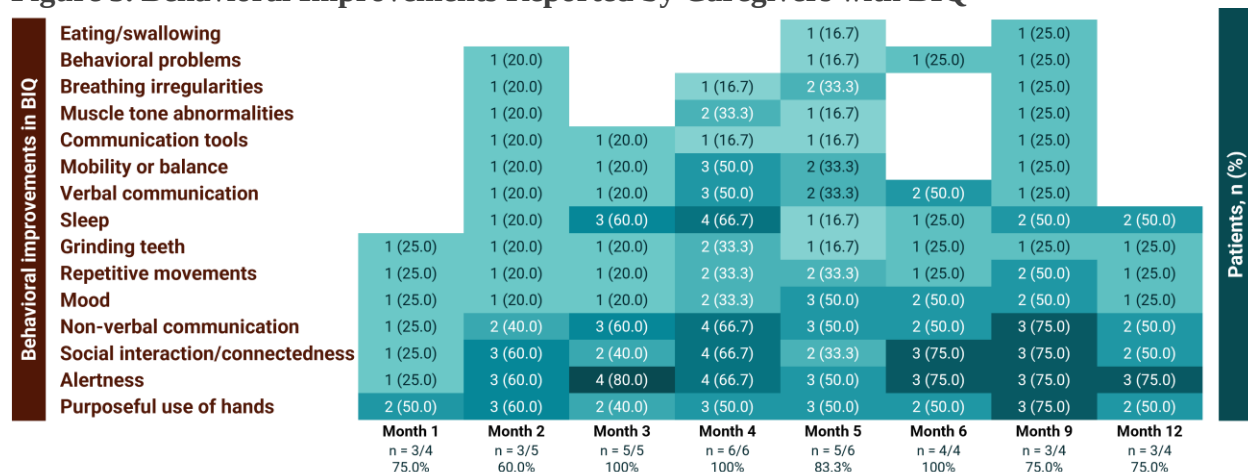
*Trofinetide initiation is the day of trofinetide shipment.

Abbreviations: IQR=interquartile range; RTT=Rett syndrome.

Outcomes: Behavioral Improvement Questionnaire (BIQ)

The behavioral improvements repeatedly reported by caregivers on the BIQ from Months 1 to 12 included alertness, mood, purposeful use of hands, repetitive movements, grinding teeth, non-verbal communication, and social interaction/connectedness (**Figure 3**).³ Findings from the BIQ should be interpreted with caution given the study limitations. Caregiver observations may represent chance findings, and clinical conclusions cannot be drawn from these data.

Figure 3. Behavioral Improvements Reported by Caregivers with BIQ³

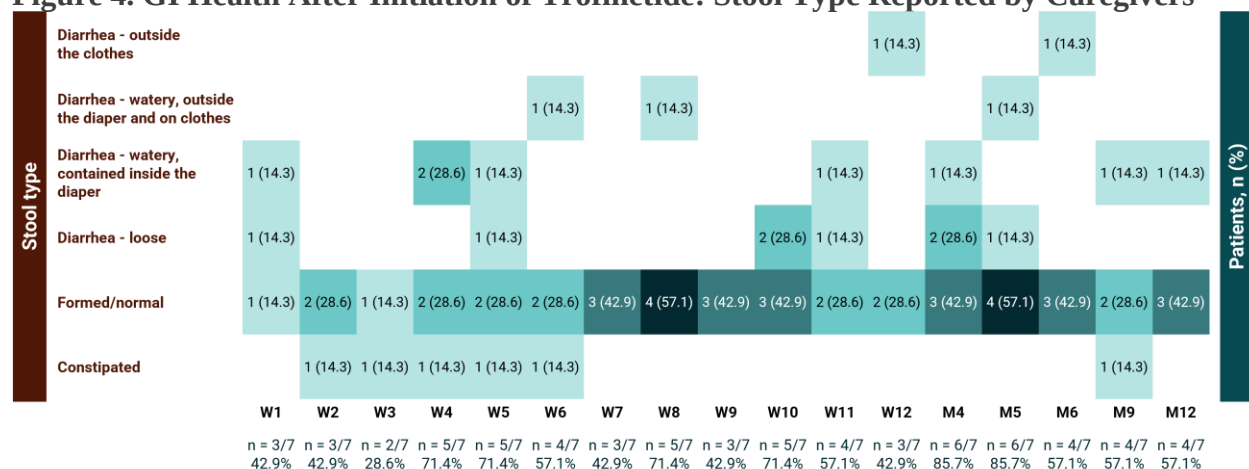


Abbreviation: BIQ=Behavioral Improvement Questionnaire.

Tolerability: GI Health Questionnaire

Most caregivers reported formed/normal stools throughout the follow-up; most reports of diarrhea were contained inside the patients' diaper (**Figure 4**). The most common diarrhea management strategies reported by caregivers were increased fluid intake, trofinetide dose reductions, and temporary trofinetide discontinuation.³ Findings from the GI Questionnaire should be interpreted with caution due to study limitations.

Figure 4. GI Health After Initiation of Trofinetide: Stool Type Reported by Caregivers³



Abbreviation: GI=gastrointestinal; M=month; W=week.

Adverse Events

Adverse events (AEs) were identified incidentally by a medical monitor reviewing free text responses and interactions with the study call center. Overall, 3 AEs were recorded among the 7 participants (Table 3).³

Table 3. Overview of Adverse Events³

Male LOTUS participants (N=7)	
Adverse events, n (%)	3 (42.9)
Pneumonia	1
Sapovirus	1
Weight Loss	1

Limitations

The results of this interim analysis are limited by the number of patients who had reached later time points, which resulted in the data being restricted to 12 months, the lack of a placebo arm, missing data, lack of validation of the BIQ and GI Health questionnaires, reliance solely on caregiver reports, the use of descriptive statistics, and the online nature of this study.² Further limitations of LOTUS include the following:

- The study is based on caregiver-reported questionnaires and clinician assessment of improvements in Rett symptoms was not obtained.
- Due to the open-label nature of the study, direct causation between a drug and reported findings cannot be established.
- This is an interim analysis of an ongoing study, so some participants have not progressed to later timepoints.

Phase 1 Studies in Healthy Adult Volunteers

Overall, 151 healthy adult male participants have been exposed to trofinetide in Phase 1 clinical studies. In a Phase 1 study of oral trofinetide in 9 men and 9 women, no between-sex differences in the pharmacokinetics (PK) of trofinetide were observed. No treatment- or dose-related patterns were evident across Phase 1 studies in the incidence of treatment-emergent adverse events (TEAEs).⁴

Phase 2 Study in FXS: NEU-2566-FXS-001

The safety and tolerability of oral trofinetide (35 mg/kg or 70 mg/kg twice daily [BID]) was studied in 72 adolescent and adult males (12–41 years old) with FXS in a Phase 2 randomized, double-blind, placebo-controlled study (Neu-2566-FXS-001).⁹ Incidences of TEAEs were generally comparable between the trofinetide and placebo groups. The most common TEAEs overall were upper respiratory tract infection (7%) and diarrhea (6%).⁹

Phase 2 Studies in TBI

The majority of participants in the two randomized, double-blind, placebo-controlled Phase 2 studies assessing trofinetide in participants with TBI were male: 88.1% in Neu-2566-TBI-001/002 (N=251) and 87.1% in Neu-2566-TBI-003 (N=31).⁴

In Neu-2566-TBI-001/002, a dose escalation study of trofinetide administered via IV infusion (1, 3 or 6 mg/kg/h) in participants with moderate to severe TBI (16–72 years old), the incidence of TEAEs and serious TEAEs did not differ meaningfully between trofinetide and placebo, except for serious TEAEs of prolonged electrocardiogram (ECG) QT (trofinetide, 4.2%; placebo, none).⁴

Neu-2566-TBI-003, a study in participants with mild TBI (19–40 years old) treated with orally administered trofinetide (35 mg/kg and 70 mg/kg BID), was stopped early due to slow enrollment. There was no clear relationship of incidence of specific TEAEs to either treatment or dose; the most frequent TEAEs were headache and dizziness.⁴

Pooled Analysis of Double-blind Oral-treatment Studies in Males

In a pooled safety analysis of data from male participants in double-blind studies of oral trofinetide (Neu-2566-FXS-001 and Neu-2566-TBI-003), headache (16.7%), vomiting (6.7%), diarrhea (6.7%) and fatigue (6.7%) were the most frequent TEAEs with trofinetide (N=60) occurring more than placebo (N=35).¹⁰

References

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