

Real-World Benefits and Tolerability of Trofinetide in Rett Syndrome Patients Categorized as Atypical, Males, and Adults: The LOTUS Study

Veeral Gohil,¹ Mubeen F. Rafay,² Arthur Beisang,³ Jenny Downs,^{4,5} Loan Robinson,¹ Louise Cosand,¹ Ryan Bucco¹

¹Acadia Pharmaceuticals Inc., San Diego, CA, USA; ²Section of Pediatric Neurology, Department of Pediatrics and Child Health, University of Manitoba, Winnipeg, MB, Canada; ³Gillette Children’s Specialty Healthcare, St Paul, MN, USA; ⁴The Kids Research Institute Australia, The Centre for Child Health Research, University of Western Australia, Perth, WA, Australia; ⁵Curtin School of Allied Health, Faculty of Health Sciences, Curtin University, Perth, WA, Australia

INTRODUCTION

- Rett syndrome (RTT) is a rare neurodevelopmental disorder characterized by a regression in early childhood, predominantly observed in speech, fine motor hand skills, and ambulation¹
 - RTT is associated with a broad set of symptoms including deficits in communication, breathing, hand stereotypies, nighttime behaviors, vocalizations, facial expressions, mood, and seizures^{1,2}
- Trofinetide (DAYBUE®/DAYBUE® STIX [US], DAYBUE® [CAN], DAYBU® [EU]) is approved for the treatment of patients with RTT in the US, EU, Canada, and Israel³⁻⁶
- The approval of trofinetide was based on the efficacy and safety results of LAVENDER (NCT04181723), a 12-week, phase 3, randomized, placebo-controlled study of trofinetide in females with RTT;⁷ efficacy was demonstrated by 2 co-primary endpoints and 1 key secondary endpoint, all powered to show a difference from placebo and all statistically significant
 - LAVENDER enrolled female patients with classic RTT aged 5–20 years; male patients, patients with atypical RTT, and patients aged >20 years were excluded from the study⁷
- The real-world benefits and tolerability of trofinetide have been characterized in LOTUS, an observational, phase 4 study of trofinetide use in the real world⁸
 - LOTUS does not have exclusion criteria; male participants, participants with atypical RTT, and adult participants aged >20 years were included in the study⁸

OBJECTIVE

- To characterize the real-world benefits and tolerability of trofinetide in patients with atypical RTT, male patients with RTT, and adult patients aged >20 years with RTT enrolled in LOTUS

METHODS

LOTUS Study Design and Population

- LOTUS is an ongoing, phase 4, observational, real-world, prospective, online study involving caregivers of patients prescribed trofinetide under routine clinical care
 - LOTUS participation lasts for ≥12 months from trofinetide initiation, with the option to extend participation for an additional 12 months
 - Caregivers of any patients who were prescribed trofinetide under routine care are eligible for this study; there are no exclusion criteria
- ### Relevant Study Assessments
- The Behavioral Improvement Questionnaire (BIQ) is a novel measure that has been adapted from the Rett Syndrome Behavior Questionnaire (RSBQ), the top caregiver concerns from the US Natural History Study, and the RTT community list of symptoms in the Voice of the Patient Report;⁹⁻¹¹ it consists of questions soliciting a “yes” or “no” response from caregivers as to whether they observed new and/or maintained improvements following treatment with trofinetide compared with the period before starting trofinetide
 - A “yes” answer resulted in the opportunity to identify all areas of improvement from a checklist that included alertness, behavioral problems, breathing irregularities, communication tools, eating/swallowing, grinding teeth, mobility or balance, mood, muscle tone abnormalities, nonverbal communication, purposeful use of hands, repetitive movements, sleep, social interaction/connectedness, verbal communication, and other domains
 - The BIQ was assessed monthly for 6 months and every 3 months thereafter

- The Quality-of-Life Inventory-Disability (QI Disability) Questionnaire is a caregiver assessment designed to measure quality of life (QoL) for school-aged children and adolescents with intellectual disability over the past month¹²⁻¹⁴
 - Higher scores represent better QoL
 - The QI-Disability Questionnaire was assessed monthly for 6 months and every 3 months thereafter
- The Gastrointestinal (GI) Health Questionnaire was designed to assess GI health including dosing timing and amount, incidence of diarrhea and vomiting, the type of stool formation over the past 3 days, and specifics about diarrhea frequency, as well as GI management strategies employed by caregivers for preventing or managing diarrhea
 - Weekly assessments were conducted for the first 12 weeks of the study, followed by once a month for the next 3 months, and quarterly at month 9
- All measures were completed by caregivers online
- Due to ongoing enrollment, data were presented up to 12 months since the initiation of trofinetide
- This analysis is focused on patients with atypical RTT, male patients with RTT, and adult patients aged >20 years with RTT, as reported by their caregivers

RESULTS

Demographics and Baseline Characteristics

- Overall, 227 patients aged 2–60 years were included in this follow-up; 56 patients’ caregivers reported them as having atypical RTT, 7 patients were male, and 77 patients were adults aged >20 years (**Table 1**)

Behavioral Improvements

- In all subgroups at all time points, ≥70% of caregivers reported improvements in symptoms of RTT in those they cared for
- Overall, 73–78% of caregivers of patients with atypical RTT, 75–100% of caregivers of male patients with RTT, 80–85% of caregivers of adults with RTT, and 84–90% of caregivers of patients in the complete LOTUS population reported behavioral improvements on the BIQ in the first year of trofinetide treatment that were new or maintained compared with before trofinetide treatment in patients who had taken ≥1 dose of trofinetide (**Figure 1A**)
- The most commonly reported behavioral improvements with BIQ in all populations in the first year of trofinetide treatment were nonverbal communication (atypical, 53–61%; males, 50–75%; adults, 56–57%; complete population, 59–71%), alertness (atypical, 46–68%; males, 75–80%; adults, 50–61%; complete population, 57–70%), and social interaction/connectedness (atypical, 44–56%; males, 40–75%; adults, 41–39%; complete population, 43–51%) (**Figure 1B, C, D, and E**)

Figure 1. Behavioral Improvements Reported by Caregivers With BIQ



BIQ, Behavioral Improvement Questionnaire; RTT, Rett syndrome
The LOTUS full population is inclusive of all subgroups

GI Health After Initiation of Trofinetide

- In all three subgroups, caregivers’ reports of normal stool were common (ie, no diarrhea or constipation) (**Supplemental Figure 1**)
- For all groups, there was a reduction in the incidence of constipation observed with trofinetide treatment (**Supplemental Figure 1**)
- The incidence of diarrhea in patients in all groups varied in the first year of trofinetide treatment (**Supplemental Figure 1**)
 - Most reports of diarrhea were contained inside the patient’s diaper (ie, loose and in diaper/watery stools) throughout this follow-up, with a lower incidence of diarrhea outside the patient’s diaper (ie, on clothes/watery and outside clothes/watery stools)

Table 1. Baseline Demographic and Clinical Characteristics

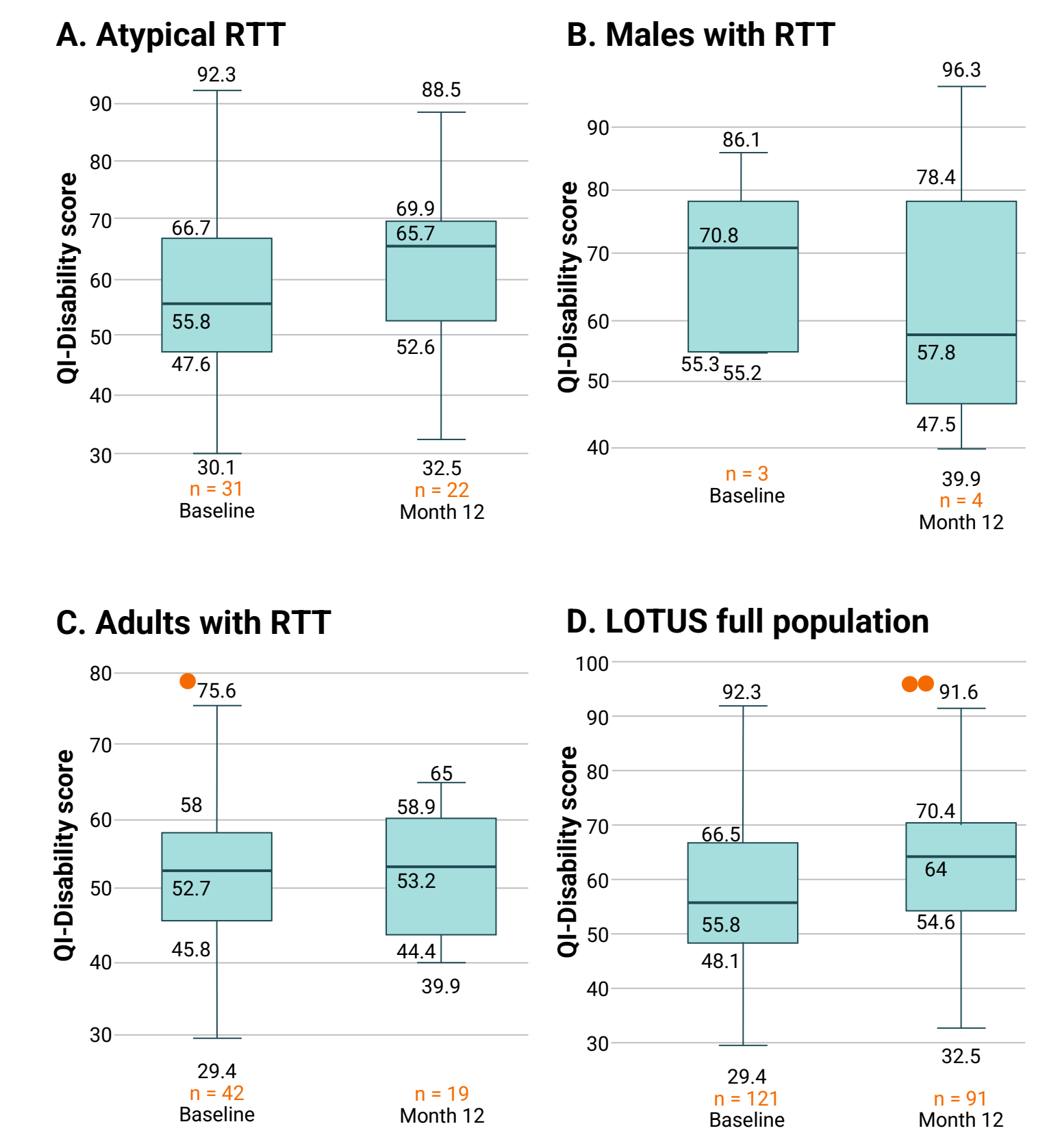
Characteristic	LOTUS atypical RTT (n = 56)	LOTUS males with RTT (n = 7)	LOTUS adults with RTT (n = 77)	LOTUS complete population (N = 227)
Sex, n (%)				
Female	56 (100)	0	75 (97.4)	220 (96.9)
Male	0 ^a	7 (100)	2 (2.6)	7 (3.1)
Median (IQR) age at time of RTT diagnosis, years^b	4 (2–6)	7 (1–25)	4.5 (3.0–15.5)	3 (2–5)
Median (IQR) age at time of trofinetide initiation, years^{c,d}	10 (6–18)	8 (3–19)	28 (24–33)	13 (6–22)

^aOne male patient with atypical RTT was excluded from the analysis as they had non-MECF2 genetic mutation. ^bn = 55 for atypical RTT population, n = 3 for males with RTT, n = 56 for adults with RTT, n = 190 for LOTUS complete population. ^cn = 55 for atypical RTT population, n = 205 for LOTUS complete population. ^dTrofinetide initiation is the day of trofinetide shipment
IQR, interquartile range; RTT, Rett syndrome

QoL Improvements

The QI-Disability median total score remained stable or increased from baseline to month 12 in patients with atypical RTT, males with RTT, adults with RTT, and in the complete LOTUS population who had taken ≥1 dose of trofinetide, indicating improvement in QoL (**Figure 2**)

Figure 2. QI-Disability Total Score Over Time in Patients With



RTT, Rett syndrome
The LOTUS full population is inclusive of all subgroups. Boxes show median and interquartile range (IQR); whiskers are 1.5 x IQR; outliers are displayed separately (orange dots)

CONCLUSIONS

- ✧ The real-world benefits and tolerability of trofinetide in subpopulations of LOTUS not included in the phase 3 trofinetide clinical program followed similar trends to the overall LOTUS study population
- ✧ Within the first year of treatment, most caregivers characterized improvements as nonverbal communication, attention, and social interaction/connectedness irrespective of patient subtype

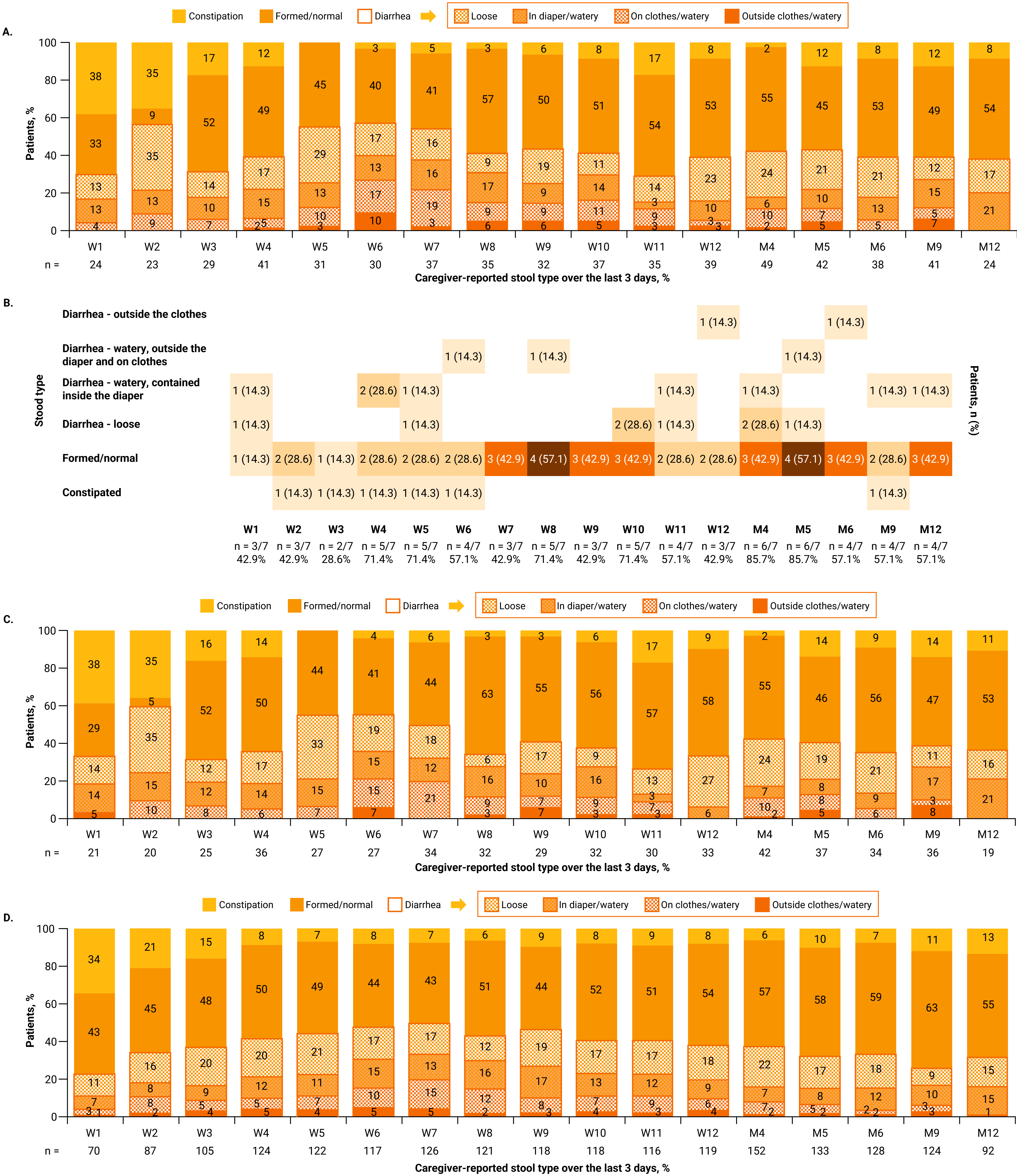
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RESULTS

Supplemental Figure 1. Stool Type Reported by Caregivers in Patients With (A) Atypical RTT, (B) Males With RTT, (C) Adults with RTT, and (D) LOTUS Full Population.



RTT, Rett syndrome; W, week; M, month.