



## Original Research

Assessing Experiences With Trofinetide for Rett Syndrome: Interviews With Caregivers of Participants in Clinical Trials<sup>☆</sup>

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## ABSTRACT

**Purpose:** Rett syndrome (RTT) is a rare neurodevelopmental disorder that mainly affects girls and women. Trofinetide is approved for the treatment of RTT in adults and children aged  $\geq 2$  years. To gain insight into experiences with RTT and effects of trofinetide treatment at different stages of RTT, interviews with caregivers of individuals with RTT were conducted upon their exit from the open-label trofinetide trials.

**Methods:** Interviews were conducted with caregivers of participants in the LILAC/LILAC-2 open-label extension trials of the phase 3 LAVENDER trial in participants aged 5 to 20 years, and in DAFFODIL, an open-label trial in participants aged 2 to 4 years. Caregivers were asked about the RTT effects, experiences with trofinetide, meaningfulness of treatment effects, and satisfaction. Qualitative thematic analysis was performed.

**Findings:** Caregivers of 33 participants from the open-label trials were interviewed, including 26 from LILAC/LILAC-2 (mean age, 12.3 years) and 7 from DAFFODIL (mean age, 4.5 years). The most commonly reported effects of RTT in LILAC/LILAC-2 were no verbal communication (24/26 [92.3%]), unable to use hands (15/26 [57.7%]), repetitive hand movements (15/26 [57.7%]), unable to walk (15/26 [57.7%]), and seizures (14/26 [53.8%]). In DAFFODIL, the most commonly reported effects of RTT were no verbal communication (7/7 [100%]), impaired balance (4/7 [57.1%]), unable to use hands (3/7 [42.9%]), repetitive hand movements (3/7 [42.9%]), mood disturbance (3/7 [42.9%]), constipation (3/7 [42.9%]), and limited ability to use hands (3/7 [42.9%]). Caregivers most commonly reported improvements in hand use (11/26 [42.3%]), engagement with others (11/26 [42.3%]), eye gaze (8/26 [30.8%]), use of the Tobii eye tracking device (7/26 [26.9%]), and attention/focus/concentration (7/26 [26.9%]) in LILAC/LILAC-2. In DAFFODIL, caregivers reported improvements in new words (5/7 [71.4%]), hand use (4/7 [57.1%]), and eye contact (4/7 [57.1%]). Nearly all (31/32) caregivers were very satisfied or satisfied with trofinetide.

**Implications:** Caregivers of participants in open-label trofinetide trials reported improvements in RTT with meaningful impact in areas of motor function, communication, and engagement.

## Introduction

Rett syndrome (RTT) is a rare genetic neurodevelopmental disorder that predominantly affects females but may occur in males.<sup>1,2</sup> Most cases of RTT are caused by mutations in the *MECP2* gene, which encodes methyl-CpG-binding protein 2, a regulatory protein of gene expression.<sup>1</sup> The global prevalence of RTT has been estimated as 5 to 10 per 100,000 females with no significant regional variability.<sup>3</sup> Individuals with RTT

experience apparently normal development for approximately the first 6 months of life, followed by regression of fine motor and communication skills, typically between 6 and 18 months of age, then stabilization.<sup>4</sup> RTT is characterized by loss of spoken language and limited nonverbal communication ability, loss of purposeful hand use, stereotypic hand movements, severely impaired fine and gross motor skills, gait abnormalities, and gastrointestinal problems.<sup>2,5</sup> Other frequent manifestations include seizures, breathing abnormalities, and chewing and swallowing difficul-

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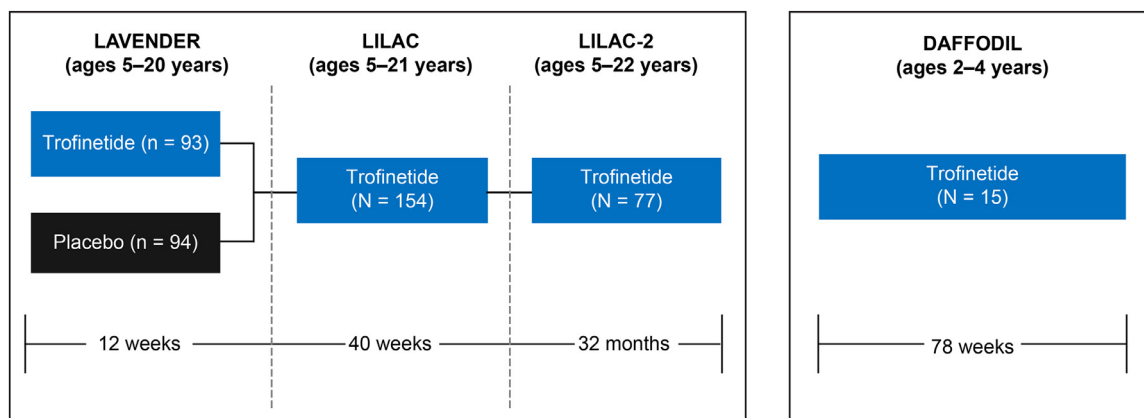


Figure 1. Trofinetide clinical trial disposition and timing.

ties that result in feeding tube placement.<sup>2,5</sup> Individuals with RTT need lifelong 24-hour care and have complex medical needs.<sup>6</sup>

In March 2023, the US Food and Drug Administration (FDA) approved the first pharmacologic RTT treatment, trofinetide\* oral solution, for adults and children aged  $\geq 2$  years with RTT. The efficacy and safety of trofinetide in RTT were reported in the large, randomized, placebo-controlled phase 3 LAVENDER trial of girls and women aged 5 to 20 years (those in the stable stage of RTT).<sup>7</sup> In LAVENDER, statistically significant improvements over placebo were reported in the coprimary end points Rett Syndrome Behavioral Questionnaire (RSBQ), a caregiver-reported outcome measure ( $P = 0.018$ ), and the clinician-rated Clinical Global Impression–Improvement (CGI-I) scale with RTT-specific anchors ( $P = 0.003$ ).<sup>7</sup> Results from LILAC and LILAC-2, the open-label extension trials of LAVENDER, affirm the long-term safety and continued effectiveness of trofinetide treatment in girls and women with RTT.<sup>8,9</sup> In addition, data from the open-label DAFFODIL trial in girls aged 2 to 4 years support the long-term safety and effectiveness of trofinetide in younger children who are experiencing the regression stage of RTT.<sup>10</sup>

In recent patient-focused drug development guidance documents, the US FDA has recommended that manufacturers consider and provide relevant information on the patient experience, including patients' perspectives, needs, and priorities, throughout the drug development process,<sup>11,12</sup> particularly in the development of treatments for rare diseases.<sup>13</sup> With conditions such as RTT, in which the patient is unable to self-report, eliciting the caregiver's observations of the patient's experience is acceptable.<sup>12</sup>

Limited qualitative research describing the effects of RTT on individuals and their caregivers has been published. In one of the phase 2 trofinetide trials, caregivers were asked to rate their RTT symptoms of most concern,<sup>14</sup> and a recent study identified the key concerns of caregivers of individuals with RTT from US Natural History Study data.<sup>15</sup> Another study asked caregivers of individuals with RTT how they would view changes in the symptoms covered in the RSBQ,<sup>16</sup> a caregiver-completed questionnaire with 45 items.<sup>17</sup> Consistently across these qualitative studies, caregivers indicated that their most desired improvements from treatment for RTT would be in communication, mobility, and functional hand use.

Here, we present the results of optional exit interviews with caregivers of participants from the LILAC/LILAC-2 and DAFFODIL clinical trials, conducted to explore participants' experiences with RTT and with trofinetide treatment. The objectives of the exit interviews were to document caregiver-reported signs and impacts of RTT, elicit caregiver reports of the participant experience and any changes in RTT effects noted over the course of the clinical trials, and explore the meaningfulness of

changes experienced and satisfaction with the efficacy of the medication.

## Methods

### Study Design and Population

All adult caregivers of participants enrolled in the LILAC/LILAC-2 (ClinicalTrials.gov identifiers NCT04279314 and NCT04776746; 40-week and 32-month open-label extensions of the LAVENDER trial, respectively) or DAFFODIL (ClinicalTrials.gov identifier NCT04988867; 78-week open-label study) clinical trials in the US (Figure 1) at the time the qualitative study was conducted (at the end of LILAC-2 or DAFFODIL) were eligible and invited to participate in an optional interview. Interviews were conducted on or before the end-of-treatment visit date of participants in DAFFODIL or LILAC-2. Both trials were terminated as planned when trofinetide received US FDA approval. At the time interviews were conducted, treatment assignment from LAVENDER was blinded for all parties, including the interviewers.

Interview study approval was obtained from relevant institutional review boards (IRBs) for all participating study sites. Caregivers who volunteered to be interviewed provided written informed consent. Two qualitative researchers conducted individual, in-depth interviews with caregivers via telephone using an IRB-approved semistructured interview guide. Each interview lasted approximately 60 minutes.

Each interview began with a brief overview of the qualitative study and questions about symptoms and impacts of RTT. The terms “symptoms” and “impacts,” which are often used to describe disease-related concepts, are somewhat difficult to delineate for RTT. The caregiver-reported results are presented as a unified, comprehensive list of symptoms, signs, and impacts of RTT that caregivers reported their child experienced, referred to here as RTT effects. Caregivers were given the opportunity to list as many RTT effects as they could and were asked about their expectations before entering the trial, their child's experiences with the study drug, including changes observed in their child during the phase 3 and open-label trials, the importance and meaningfulness of those changes, and their satisfaction with the efficacy of the study drug. Concept elicitation focused on gathering only the spontaneous reports of caregivers. Follow-up probe questions, such as whether the participant experienced a potential symptom or treatment effect that the caregiver did not initially mention, were not included as part of data collection. This focus on spontaneous reporting allowed interviewers to explore the widest range of experiences in the caregiver's own words.

Caregivers of participants in LILAC/LILAC-2 were asked first about their child's experiences in the phase 3, double-blinded trial (LAVENDER) and then in the open-label extensions (LILAC and LILAC-2). For some, LAVENDER was completed as many as 2 years before the con-

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duct of the interview. Caregivers were assured that recalling the time course of improvements was less important than describing the specific improvements their child experienced.

With the caregiver’s permission, an audio recording of each interview was created. Exit interview data were also systematically captured as field notes in Microsoft Excel (US) by 1 of the 2 interviewers. After interviews concluded, all audio files were transcribed verbatim and anonymized, and the transcripts and Excel qualitative database were prepared for qualitative analysis.

Analysis

Interview results were analyzed using a thematic analysis approach.<sup>18</sup> The qualitative analysis was conducted based on an a priori coding framework that was adapted as emerging themes were incorporated. Using the transcripts and interviewer field notes, dominant trends were identified and compared across interviews.<sup>19</sup> This analytic process generated themes or patterns in the way interview participants described their observations of the experiences of their child.

Analysis of results also included counts of improvements in RTT effects by type of improvement and total counts of improvements per trial, based on an a priori coding framework that was augmented to include emerging information. Results of the LILAC/LILAC-2 and DAFFODIL caregiver interviews are presented separately and in combination to highlight similarities and differences in experiences of RTT and trofine-tide treatment among individuals in the regression or stable stages of RTT.

Results

Participants

Across the clinical trials, a total of 34 caregivers from LILAC/LILAC-2 (n = 27) and DAFFODIL (n = 7) participated in an interview (Table 1). Two caregivers of 1 LILAC/LILAC-2 participant were interviewed together, but information from this interview was handled as 1 caregiver report for participant-related frequency counts and analyses. All participants with RTT were female, consistent with the clinical trial inclusion criteria. Participants from the LILAC/LILAC-2 trial were a mean of 12.3 years of age (range, 6 to 22 years) at the time of the interview versus 4.5 years (range, 4 to 5.5 years) for DAFFODIL. Clinical and demographic characteristics of the participants of LILAC/LILAC-2 and DAFFODIL who were represented in the interview study were similar to the characteristics of the overall population of the clinical studies (see Supplemental Tables I and II in the online version at doi:10.1016/j.clinthera.2024.12.012).

**Table 1**  
Caregiver and clinical trial participant characteristics: LILAC/LILAC-2 and DAF-FODIL exit interviews.

Characteristic	LILAC/LILAC-2	DAFFODIL
Caregivers, n	27*	7
Sex, n (%)		
Female	24 (88.9)	6 (85.7)
Male	3 (11.1)	1 (14.3)
Participants with RTT, n	26	7
Sex, n (%)		
Female	26 (100)	7 (100)
Male	0	0
Age at the time of interview (y)		
Mean (SD)	12.3 (4.7)	4.5 (0.6)
Range	6, 22	4, 5.5
Age at diagnosis (y)		
Mean (SD)	2.7 (1.3)	2.1 (0.7)
Range	0.6, 7	1, 2.1

RTT = Rett syndrome.  
\* Both parents of 1 trial participant simultaneously took part in an interview.

**Table 2**  
Most frequently reported RTT effects before entering clinical studies.

RTT Effect,* n (%)	LILAC/LILAC-2 (n = 26)	DAFFODIL (n = 7)
No verbal communication	24 (92.3)	7 (100)
Unable to use hands	15 (57.7)	3 (42.9)
Repetitive hand movements	15 (57.7)	3 (42.9)
Unable to walk	15 (57.7)	0
Seizures	14 (53.8)	0
Unable to perform self-care	12 (46.1)	2 (28.6)
Impaired social function/engagement	10 (38.5)	2 (28.6)
Mood disturbance	8 (30.8)	3 (42.9)
Constipation	7 (26.9)	3 (42.9)
Breathing problems	9 (34.6)	0
Limited ability to use hands	6 (23.1)	3 (42.9)
Unable to crawl	6 (23.1)	2 (28.6)
Scoliosis	7 (26.9)	0
Difficulty swallowing	7 (26.9)	0
Requires feeding tube	7 (26.9)	0
Unable to walk unassisted	4 (15.4)	1 (14.3)
Unable to toilet independently	4 (15.4)	1 (14.3)
Unable to sit independently	3 (11.5)	2 (28.6)
Disrupted sleep	3 (11.5)	2 (28.6)
Impaired gait	3 (11.5)	1 (14.3)
Impaired balance	0	4 (57.1)
Impaired motor planning	3 (11.5)	1 (14.3)
Teeth grinding	3 (11.5)	1 (14.3)
Slow response time	3 (11.5)	1 (14.3)
Rett spells	3 (11.5)	0
Dystonia/uncontrolled muscle contraction	3 (11.5)	0
Poor eye contact	1 (3.8)	2 (28.6)
Delayed development of walking ability	0	2 (28.6)
Unable to stand unassisted	2 (7.7)	0
Abdominal pain	2 (7.7)	0
Tight muscles	2 (7.7)	0
Unable to roll over	2 (7.7)	0
Biting	2 (7.7)	0
Acid reflux	1 (3.8)	1 (14.3)
Low muscle tone	1 (3.8)	1 (14.3)

RTT = Rett syndrome.  
\* The included RTT effects were reported by a total of 2 or more caregivers across the trials.

Effects of RTT Reported by Caregivers

When asked about their child’s experiences with RTT before the beginning of any clinical trial, caregivers spontaneously reported a wide array of behaviors, somatic symptoms, and functional impairments, referred to as effects of RTT (Table 2). These caregiver-reported RTT effects included lack of verbal communication; lack of purposeful hand use or very limited hand use; repetitive hand movements; lack of independent mobility (ie, no walking or crawling); inability to perform self-care tasks; unhappy, irritable, or anxious mood; constipation; and impaired social engagement. Several effects of RTT were reported only by caregivers of participants from LILAC/LILAC-2, most notably seizures, breathing problems, scoliosis, and need for a feeding tube. Impaired balance was reported by 4 caregivers from DAFFODIL and none from LILAC/LILAC-2.

The RTT effect with the most impact on participants from LILAC/LILAC2 and DAFFODIL as perceived by caregivers was the inability of the participant to communicate (reported as the most impactful by 14/26 [54%] and 3/7 [43%] of the caregivers, respectively). Caregivers noted being worried because their child often seemed distressed but could not communicate if they were in pain or needed something. Furthermore, they believed that inability to communicate prevented their child from engaging or forming relationships with others. The following quotations illustrate the perspective of these caregivers in their own words:

■ “I’d say communication [has the most impact] because a lot of it is just figuring out how we can best help her or what she’s needing or

wanting. I think for any person in a caregiver role or any parent, being able to communicate with a child is one of the biggest, and it's one of the most rewarding things—when she can tell us what she wants, or she can say, 'I love you,' or whatever it is that she's trying to get across." [DAFFODIL]

■ “Definitely the big thing was the communication piece. Obviously, verbally is the biggest thing, but even nonverbal communication and just purposeful [communication] and initiation was definitely a big thing—just her willingness or ability to interact with others.” [DAFFODIL]

■ “She’s actually never communicated.” [LILAC/LILAC-2]

■ “I would say communication [has the most impact], because she’s always trying to verbalize things, and it’s hard for her, and I think it’s frustrating. So to me, that would be the number one thing that is the hardest.” [LILAC/LILAC-2]

■ “Definitely the communication [has the most impact]. I feel like even—having a child that is nonmobile, completely nonambulatory—being able to communicate would have made it easier, being able to communicate any sort of need or discomfort.” [LILAC/LILAC-2]

Lack of or limited ability to use their hands was reported by some caregivers in LILAC/LILAC-2 and DAFFODIL as having the most significant impact on participants (4/26 [17%] and 1/7 [14%], respectively) because it interfered with participants’ performance of self-care activities and independent use of mobility aids (eg, wheelchair or walker), and limited the options for nonverbal communication (eg, through signing or meaningful hand gestures). The following quotations convey the perspective of these caregivers:

- “She lost the ability to finger feed, lost the ability to use her hands to play with toys or do anything, drink from a cup, or hold anything.” [LILAC/LILAC-2]
- “The hand wringing [has the most impact] because she’s unable to use her hands daily. She has no functional use of her hands. She can’t care for herself at all.” [LILAC/LILAC-2]
- “Yeah, so the hand function was the biggest thing for her as far as affecting her. She had ended up losing the ability to feed herself, the ability to play with a lot of her toys, holding a toothbrush to brush her teeth.” [DAFFODIL]
- “The loss of purposeful hand use [has the most impact]. Right? Because now she has, like, she’s completely reliant on somebody to feed and water her. Or help her get up, or help her get dressed, or any little tiny thing that you use your hands for. She just can’t do it, so.” [DAFFODIL]

Caregivers were also asked about the RTT effect that had the most impact on them. Nine (35%) LILAC/LILAC-2 caregivers said the inability of the participant to communicate had the most impact on them. Five caregivers (19%) from LILAC/LILAC-2 reported that meeting the physical demands of care provision had the most significant impact on them, and related to that, the child’s inability to walk was reported by 4 LILAC/LILAC-2 caregivers (15%) as most impactful on them because of its contribution to the physical burden of caregiving.

Caregivers from DAFFODIL most frequently reported being affected by their child’s inability to communicate (3/7 [43%]) and use their hands (2/7 [29%]). One caregiver from DAFFODIL noted that their child’s RTT affected “everything” in their lives: “It changes everything in our lives.... We need to give attention to her every single minute of the day. So that’s the biggest impact in our family, that we cannot leave her in her room playing like a normal kid, because we don’t know what she will do. She can eat something, she can eat a toy, or she can just fall down and then hit her head.”

Caregivers were asked which RTT effects they most wanted to improve. Across both trials, they most frequently desired improvement in their child’s ability to communicate (Table 3).

**Table 3**  
Number of caregivers reporting specific desired treatment effects before the trial began.

Treatment Effect,* n (%)	LILAC/LILAC-2 (n = 26)	DAFFODIL (n = 7)
Improved communication	15 (57.7)	5 (71.4)
Improved hand use	10 (38.5)	2 (28.6)
Improved walking	6 (23.1)	1 (14.3)
Improvement in seizures	6 (23.1)	0
Reduced repetitive hand movements	2 (7.7)	2 (28.6)
Increased physical/muscle strength	1 (3.8)	2 (28.6)
Improved sleep	2 (7.7)	1 (14.3)
Gross motor skills	3 (11.5)	0
Improved mood/reduced irritability	1 (3.8)	1 (14.3)
Improved self-feeding	2 (7.7)	0
Attention/concentration/focus	2 (7.7)	0
Any Rett syndrome symptom or effect	2 (7.7)	0

\* The included desired treatment effects were reported by a total of 2 or more caregivers across the trials. Caregivers could report more than 1 desired treatment effect.

Types of Improvement in RTT Effects During Clinical Trials

Caregivers from LILAC/LILAC-2 and DAFFODIL were asked to describe any changes or improvements they observed in their child with RTT during the clinical trials. Those from LILAC/LILAC-2 were asked first about the experiences of their child in the double-blind, phase 3 trial (LAVENDER) and then in the open-label extensions (LILAC and LILAC-2). Although caregivers recalling their child’s experiences from LAVENDER were referring to events that occurred, on average, approximately 2 years before the time of the interview, most noted that changes (or lack of change) during LAVENDER were particularly memorable. Caregivers uniformly perceived the 2 open-label extensions to be a single trial. Therefore, improvements of participants in the LILAC/LILAC-2 cohort are described relative to LAVENDER or LILAC/LILAC-2.

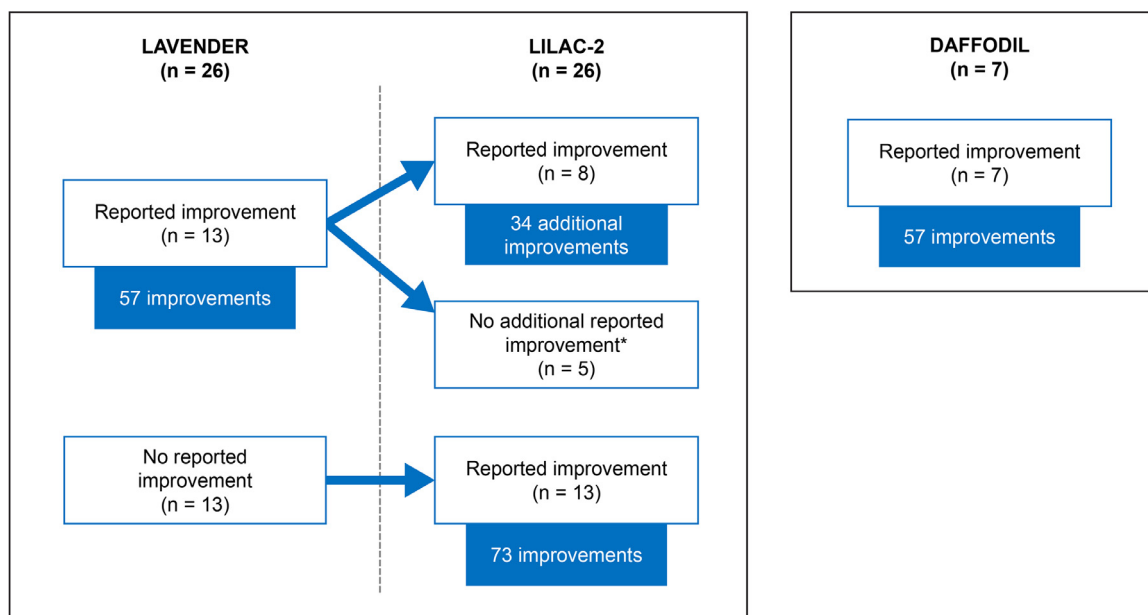
Caregivers from both trials described a range of improvements, including increased engagement and interaction with others through verbal (eg, new sounds and words) and nonverbal (eg, improved eye contact) means; improvements in hand use, mobility, and motor skills that affected functional capabilities; and improvements in mood and ability to focus (Table 4).

The most frequently observed improvements in LAVENDER/LILAC/LILAC-2 were increased ability to engage with others (n = 12; 46%), improved hand use (n = 11; 42%), improved eye gaze (n = 8; 31%), improved focus and use of the Tobii eye tracking device (each n = 7; 27%), and happier mood and improved ability to make sounds (each n = 6; 23%). The most frequently observed improvements in DAFFODIL were the ability to say new words, reported for 5 participants (71%), followed by improved hand use and eye contact (each n = 4; 57%). Improvement in eye gaze, focus, balance, and gross motor skills were each reported by 3 caregivers (43%).

Number of Improvements in RTT Effects During Clinical Trials

Counts of instances of improvement also were gathered per trial. The interviewers were not aware of participants’ LAVENDER treatment assignment, and these results were compiled with blinding in place. During the 12-week LAVENDER trial, 13 of the 26 participants experienced improvement based on caregiver reports (Figure 2). Caregivers of these 13 participants noted a total of 57 instances of improvement during LAVENDER, a mean (SD) of 4.4 (2.8) improvements per participant. During the open-label extensions LILAC/LILAC-2, 8 of these 13 participants experienced 34 additional instances of improvement. Five of these participants did not experience new improvements during LILAC/LILAC-2; however, their caregivers noted that the 18 total improvements they experienced during LAVENDER were maintained during LILAC/LILAC-2, with the exception of 1 participant who was able





**Figure 2.** Reported improvements in Rett syndrome effects during clinical trials. \*Caregivers reported that 18 improvements experienced during LAVENDER were maintained.

**Table 4**  
Caregiver-reported improvements in RTT effects.

RTT Effect,* n (%)	LILAC/LILAC-2 (n = 26)	DAFFODIL (n = 7)
Hand use	11 (42.3)	4 (57.1)
Engagement with others	12 (46.2)	2 (28.6)
Eye gaze	8 (30.8)	3 (42.9)
New words	5 (19.2)	5 (71.4)
Tobii use	7 (26.9)	2 (28.6)
Attention/focus/concentration	7 (26.9)	2 (28.6)
Happier mood or disposition	6 (23.1)	2 (28.6)
Ability to walk	5 (19.2)	2 (28.6)
Ability to make sounds	6 (23.1)	0
Aware of environment	4 (15.4)	2 (28.6)
Alertness	5 (19.2)	0
Repetitive hand movement	4 (15.4)	1 (14.3)
Seizures	4 (15.4)	0
Eye contact	0	4 (57.1)
Quicker response time	2 (7.7)	2 (28.6)
Motor skills	1 (3.8)	3 (42.9)
Balance	1 (3.8)	3 (42.9)
Constipation	2 (7.7)	1 (14.3)
Following directions	1 (3.8)	2 (28.6)
Nods head to answer question	1 (3.8)	1 (14.3)
Gait	1 (3.8)	1 (14.3)
Connecting words and actions	1 (3.8)	1 (14.3)
Fine motor skills	0	2 (28.6)

RTT = Rett syndrome.

\* The included improvements were reported by a total of at least 2 caregivers across the trials.

to walk independently during LAVENDER but had lost the ability over time.

Caregivers of 13 of 26 participants reported no improvement in RTT effects during LAVENDER. All of these participants experienced improvement during the open-label extensions LILAC/LILAC-2, with a total of 73 reported instances of improvement, or a mean (SD) of 5.6 (3.0) improvements per participant. Across LAVENDER and LILAC/LILAC-2, 26 participants experienced a total of 164 improvements, for a mean (SD) of 6.3 (3.0) improvements per participant. Caregivers of the 7 participants in DAFFODIL reported a total of 57 improvements, a mean of 8 per participant during the 24-month open-label trial.

#### Meaningfulness of Improvements in RTT Effects

Among the caregivers from LILAC/LILAC-2, 25 of 26 (96%) reported that the improvements their child experienced during the trofinetide trials were meaningful. All 7 caregivers from DAFFODIL reported that the trofinetide-related improvements their child experienced were meaningful. Selected quotations in Table 5 from caregivers from LILAC/LILAC-2 and DAFFODIL illustrate how improvements were meaningful to participants and caregivers.

Caregivers were also asked about the meaningfulness of stabilizing RTT effects. They regarded stabilization as an important and worthwhile treatment effect:

- “Oh, it’s very important. I’m happy with stabilizing. Yes, I think that if she’s stable, at least if not in my mind, it’s not getting any worse and at least she is doing something.” [LILAC/LILAC-2]
- “I don’t want anything to get worse. We already have the front end of the deal. [name deleted] has all these things that Rett can cause, and she has all of them. But for them to get worse is not—I don’t want that. If they can just be stable, if we can just have a set thing, that it’s not going to get worse, I would be okay with that, yes.” [LILAC/LILAC-2]
- “So as of now, I value it, and I think it’s important, just because, you wonder, well, if you came off of that medication, are you going to just lose all of that? I think that even a small, even if it’s small, improvements and then it being stabilized, I think that that’s still important.” [DAFFODIL]
- “... at this point, anything that’s not a regression, anything that’s not her losing a skill, is a success in our eyes. If we can, even if we’re in, like, a maintenance phase, if we’re in a stabilization phase that lasts for a couple months, and then she finally has a breakthrough, it’s worth it for us.” [DAFFODIL]

#### Satisfaction With Trofinetide

Caregivers were asked to rate their level of satisfaction with the effectiveness of the study medication and to provide their perception of the level of satisfaction of the participant (ie, to proxy-report on their child’s behalf; Table 6). All DAFFODIL caregivers reported being either “satisfied” (4/7 [57%]) or “very satisfied” (3/7 [43%]), and

**Table 5**  
Caregiver descriptions of improvements in RTT effects and their meaningfulness.

Communication
<p>“Her communication is so much better. So, she actually is able to let me know good things, bad things, anything. She’s just able to communicate, finally. She’s got so much to say.” [LILAC/LILAC-2]</p> <p>“Just because I know she’s trying to communicate, and she knows what she wants to say. She knows what she wants. She can tell me some things.” [LILAC/LILAC-2]</p> <p>“Some parents may get tired of their kid’s babbling, but I love hearing her babble and laugh more and vocalize. And I love seeing her try to try out new words, even if she didn’t make it. You can watch her. She’ll stare at your mouth and watch how you’re saying something, and she’ll try to mimic it, and you can see her trying to work it out. I’ve seen her try to say, ‘I love you.’” [LILAC/LILAC-2]</p> <p>“For her I’m sure it was [meaningful]. Finally, it came out—this is what I’m trying to say! And for us it was just, my gosh, this is what her voice sounds like. We’d never heard her voice before. It’s totally different than what sounds sound like than when you actually [hear] a word.” [LILAC/LILAC-2]</p> <p>“It helps her a lot because sometimes when she gets so frustrated—we don’t know, and we’ll just show her options and then just her having that knowledge of even choosing or picking, it helps her a lot because if we would have never taught her that, she would be more frustrated and crying.” [LILAC/LILAC-2]</p> <p>“So I think this is the most important for us, this ability, this type of communication that we can have with her now that...it’s just a small thing, but it’s so important.” [DAFFODIL]</p> <p>“I would say from her perspective, it’s a communication piece. Being able to tell us easier what she wants or needs.” [DAFFODIL]</p> <p>“That communication. She’s less frustrated because she has more success communicating.” [DAFFODIL]</p>
Hand use
<p>“I would say it’s meaningful. Probably because she doesn’t have to depend on me all the time. She doesn’t have to wait for me to just give her things. She could just go and grab it herself now.” [LILAC/LILAC-2]</p> <p>“To give her some independence. And feeding herself is a big independent skill. And anything she can be doing to increase her independence, to increase her competence, to increase her functioning? That’s all victory, so.” [LILAC/LILAC-2]</p> <p>“Just again, anything that gives her some control over her own body and her own life and gives her a bit of independence. That means a lot to all of us.” [LILAC/LILAC-2]</p> <p>“Improved hand use is a huge thing in my opinion...her being able to reach and do things intentionally is a good thing.” [LILAC/LILAC-2]</p> <p>“Just because she used to have good, purposeful hand movement. And then I feel like she lost a lot of that. So seeing her get that back was really good. Well, she used to be able to get drinks to her mouth by herself, and then she lost that for a while. So she’ll be getting some independence back.” [LILAC/LILAC-2]</p> <p>“So it’s cool to see her do these things, like go over to the snack cabinet and open it herself. She loves being able to do that kind of stuff on her own, and she’ll kind of light up, so you know that she’s pretty excited about what she can do.” [DAFFODIL]</p> <p>“And it’s gotten better for sure, and her hands are less active. When she needs to use them—she can’t like do pencil or grab and pick up small things, but like she can pick up a loaded fork and with help get it to her mouth, or hit a toy to activate it, like if it has a big button. I know that, like, when she successfully picks up a loaded fork or picks something up like that, I know that part of it is meaningful to her, or when she can hit her toys and make them activate, I know that that’s meaningful.” [DAFFODIL]</p>
Ability to walk or move
<p>“Yeah, because she doesn’t have to wait on me. I always say that she gets sick and tired of us down here, so when she’s sick and tired of us, she’ll just start walking upstairs, and she knows where her room is too, so she’ll just walk right up the stairs now and into her room. I love it.” [LILAC/LILAC-2]</p> <p>“She’s starting to see the connection between walking, how she can use her hands to reach for the grab bars or the gate trainer.... So, from a sitting position in a chair, just a few weeks ago, she went from a sitting position and she stood up all on her own for the first time since she was 2 years old. With no help. She wasn’t holding on to anything, she just stood up.” [LILAC/LILAC-2]</p> <p>“I mean, certain things have gotten easier, [the patient] standing for longer periods of time makes it easier to help her...put her clothes on or help her in the bathroom or transfer from one thing to another...” [LILAC/LILAC-2]</p> <p>“When it comes to like, gross motor, for example, I think it helps us because we feel safer. She’s falling less, and when she does fall, it’s safer. For a point in time when she would fall, she would just kind of fall with her entire body straight. She would like hit her head. Where now, it’s more of a controlled, she’ll bend, she’ll put her hands out, she’s not falling like right on her head. So that safety piece of course is huge.” [DAFFODIL]</p> <p>“Yes, it was meaningful improvement to us, because when she falls down, she hurts herself, and we don’t want her to be hurt.” [DAFFODIL]</p>
Engagement with others
<p>“I mean, just her being like, ‘Hey mom, I’m here. I’m present. I understand what’s going on, and I’m here laughing with you.’ Just being a part of it.... It’s a beautiful thing because then when I have my aunt, my uncle over, or my brother, or her cousin, she’s staring at them, she’s looking at them, she’s smiling at them, she’s reaching out to them. She wants them to have a conversation with her, and I love that.” [LILAC/LILAC-2]</p> <p>“Because she seemed like she was enjoying her day more. She seemed more present in our life, I guess you could say, like she was wanting to engage with her family.” [LILAC/LILAC-2]</p> <p>“Yeah, so by her engaging, it just made her feel like she was just like everybody else, and I’m sure that she felt that by looking at us she was saying so much more even though...it wasn’t coming out of her mouth. It was, she was, involved and engaged with us. I don’t know how else to describe it.” [LILAC/LILAC-2]</p> <p>“I think the most important one is just her being more awake and alert and just participating in life and what’s going on around her.” [LILAC/LILAC-2]</p> <p>“Oh, yeah. It was [meaningful] to say her name and then have her at least respond where she would either look at you or turn, and then, if she hears, like, me or her dad or her grandma say something, like, to turn and look, like that was a big deal because she hadn’t done that before, right? Like to the point where we thought she was completely deaf. So it really did mean a lot. Like, I don’t even, I can’t explain it.” [DAFFODIL]</p> <p>“It’s meaningful when somebody is in tune to what you’re doing. Others have always been in tune to what she’s doing. But for her to be in tune with what others are doing around her, in her surroundings.” [DAFFODIL]</p> <p>“She’s more engaged definitely. You can tell when you say, ‘Okay, we’re going to go to school,’ or ‘Time to go to the gym,’ which is her therapy office, she smiles. She knows who she is going to see every day after school, because she’s in class with a bunch of boys right now. So she’ll come home from school, and I would be like, ‘How was your day? Did you get stuck with the boys again?’ And she looked at me, and she just kind of rolled her eyes and smiled like, ‘Duh.’ So, it’s almost like you can have a conversation with her.” [DAFFODIL]</p> <p>“Seeing her smile and then lose the smile and then get the smile back was everything for us. She’s very interactive and very social. So the, being, just in a good mood, I really think just makes her happy.” [DAFFODIL]</p>
RTT effects overall or generally
<p>“Unexplainably meaningful. That really changed the course of everything, really, as far as what [name deleted] was able to do, where she went. Her social skills blossomed, really everything. It changed her attitude, I think, because she wasn’t in pain [from movement problems].” [LILAC/LILAC-2]</p> <p>“I just love seeing her just learning new things. It’s meaningful, like, I don’t have to constantly help her walk up the stairs, and then she also, I feel, herself, she gets happy because she’s doing it on her own.” [LILAC/LILAC-2]</p> <p>“It [treatment-related improvements] made things easier. It, it took a little stress off of me, to be honest, in like a really selfish way.... It took just weights off of me to have her be able to go to a therapy or to school even with her friends and participate in the activities and pay attention.... And so it really opened up things to where, like I said, I was able to go into a full-time job, and we didn’t have to worry that everything was going to send her into a spiral. We could go places and do things, and if she was going to be upset, it would be manageable. Where before it had not been.” [DAFFODIL]</p>

RTT = Rett syndrome.

**Table 6**  
Caregiver-reported ratings of satisfaction with effectiveness of trofinetide.

Rating, n (%)	LILAC/LILAC-2 (n = 25)*		DAFFODIL (n = 7)	
	Caregiver	Patient (Proxy)	Caregiver	Patient (Proxy)
Very satisfied	10 (40)	9 (36)	3 (43)	2 (29)
Satisfied	14 (56)	9 (36)	4 (57)	3 (43)
Neither satisfied nor dissatisfied	1 (4)	2 (8)	0	1 (14)
Dissatisfied	0	0	0	1 (14)
Very dissatisfied	0	1 (4)	0	0

\* One caregiver was not asked about treatment satisfaction because they left the interview early; 4 caregivers said they could not provide a proxy report for their child.

almost all LILAC/LILAC-2 caregivers reported being either “satisfied” (15/26 [56%]) or “very satisfied” (10/26 [40%]). Related to their child’s perceived satisfaction, 19/26 (72%) of LILAC/LILAC-2 and 5/7 (71%) of DAFFODIL caregivers reported that their child was either “satisfied” or “very satisfied” with trofinetide. Reasons provided by the 2 LILAC/LILAC-2 caregivers who reported a less-than-satisfied rating for their child included improvement not perceived as significant, child disliking taking medication due to the taste, and unspecified side effects of trofinetide. Two DAFFODIL caregivers reporting a less-than-satisfied rating for their child stated that the rating was related to the taste of the medication and related difficulty in taking it.

Discussion

Understanding the patient experience is an increasingly important aspect of drug development, with recommended approaches and methodology described in recent FDA guidance documents on patient-focused drug development.<sup>11,12</sup> RTT causes a wide array of neurologic and developmental effects. Exploring the patient experience through caregiver interviews in the RTT treatment setting provides critical insight into RTT effects and treatment benefits that are important and meaningful to patients and caregivers but that may be difficult to comprehensively assess with existing clinical outcomes assessments. Furthermore, some of the changes that caregivers observed in their children during trofinetide trials seemed to subtly manifest and could potentially be overlooked or underestimated by clinician observers, such as increased efforts to engage and interact with family members and others, through verbal and nonverbal means, and increased alertness and awareness of their surroundings. Some changes in their children with RTT that might not be noticeable to others were reported by caregivers to be highly important and meaningful. Caregivers’ daily lives were positively affected by treatment-related benefits in their child’s communication abilities, engagement, ability to move or stand independently, and assistance in their own care. These caregivers noted that their families were able to have outings and attend social gatherings because their child with RTT was calmer, happier, and more able to focus. Additionally, caregivers’ emotional lives were positively affected by being able to interact with their child and have their child respond to them and others. However, most caregivers reported that the physical burden of caring for their child was not significantly different, even when these improvements were experienced.

The most frequently reported effects of RTT in this study (no verbal communication, unable to use hands, repetitive hand movements, unable to walk, and seizures) are consistent with those reported by caregivers in prior studies. Caregivers in one of the phase 2 trials of trofinetide in individuals with RTT identified communication, hand movements, seizures, mobility or range of motion, and dystonia as their RTT symptoms of most concern.<sup>14</sup> Similarly, the top concerns of caregivers of individuals with RTT who were participants in the US Natural History Study (N = 925) were lack of effective communication, seizures, lack of hand use, abnormal walking/balance, and constipation.<sup>15</sup> A key difference between that study and the present one is that the caregivers

in the Natural History Study chose their top concerns from a clinician-developed list of 21 concerns, whereas those in the present study gave their answers spontaneously during interviews.

Another study asked how 40 caregivers of individuals with RTT viewed meaningful changes in the RSBQ.<sup>16</sup> The most frequently reported RTT symptoms were difficulty stopping hand stereotypies; teeth grinding; restricted repertoire of hand movement; use of eye gaze to convey feelings, needs, and wishes; and not using hands for purposeful grasping. Caregivers’ most desired improvements from a treatment for RTT were related to communication ability, mobility, and hand use. They also noted that meaningful improvements in RTT symptoms would affect the health and well-being; psychological, social, and physical functioning; and functional independence of the individual with RTT.<sup>16</sup>

Although most caregivers were willing and frequently eager to describe their child’s experiences during the trofinetide clinical trials, this qualitative interview substudy has some limitations. In total, the caregivers of 26 participants of LILAC/LILAC-2 and 7 participants of DAFFODIL were interviewed, accounting for 34% and 47%, respectively, of the study populations. Although this sample is not large, the demographic and clinical characteristics of the LAVENDER/LILAC/LILAC-2 and DAFFODIL participants included in the interviews were similar to those of the overall population of the studies. Furthermore, RSBQ and CGI-I scores in LILAC-2 were similar for participants whose caregivers participated and did not participate in the exit interviews, providing additional evidence of the representativeness of the sample.<sup>9</sup> Caregivers who agreed to be interviewed may have had a more positive view of trofinetide treatment than those who did not participate. Bias in caregiver reporting could also have been introduced by the open-label nature of the clinical studies. Finally, caregivers of participants who discontinued treatment in the clinical studies before the qualitative exit interviews were implemented could not be included in the interviews; hence, the experiences of these participants were not included in the present study. Caregivers whose children participated in the phase 3 trial (LAVENDER) and 2 open-label extensions (LILAC and LILAC-2) were asked to describe their child’s experiences during all 3 trials. Experiences during LAVENDER would have been from approximately 2 years before the interview; hence, recall may have been negatively affected. Caregivers stated that their child’s experiences in LAVENDER were for the most part memorable, but some were not certain whether a specific treatment effect began during LAVENDER or LILAC/LILAC-2. However, the focus of the study was to elicit from caregivers a comprehensive list of potential treatment effects rather than to pinpoint the timing of improvements.

Additionally, concept elicitation focused on gathering the spontaneous reports of caregivers. Follow-up probe questions, such as whether the participant experienced a potential symptom or treatment effect that the caregiver did not initially mention, were not included in the semistructured interview guide. As a result of this focus on spontaneous reporting, it was not possible to determine conclusively through analysis whether a caregiver neglected to mention an effect of RTT or an improvement or it was not relevant for their child. Relatedly, robust comparisons regarding the abilities and symptoms of each participant

before and after the trials were not captured. Finally, although qualitative research results are not intended to be generalizable to the larger RTT population, exit interviews conducted as an embedded substudy in a clinical trial may be particularly limited in this respect.

## Conclusions

Caregivers of participants in the DAFFODIL and LILAC/LILAC-2 clinical trials reported sustained and meaningful improvements with trofinetide treatment, giving insight into the effect of trofinetide in individuals experiencing different stages of the course of RTT. The improvements had significant impact on the social and physical function of participants, including better ability to communicate and interact with others and be included in family activities.

The results of these qualitative interviews provide a detailed description of the wide-ranging and profound effects of RTT as well as insight into the range and meaningfulness of improvements that patients receiving trofinetide experienced as observed by caregivers. The results and direct quotations from caregivers provide depth and detail regarding the treatment effects of trofinetide that were initially reported in the phase 3 LAVENDER trial and that continued to improve over the long-term in the LILAC/LILAC-2 extension studies as well as in the DAFFODIL trial of younger girls with RTT. These patient-experience data, although proxy-reported by caregivers, address the consistent requests of the FDA for data supporting the relevance and meaningfulness of treatment benefit and provide valuable insight for regulators, patient communities, health care providers, and payers. To our knowledge, this is the first caregiver-focused report of treatment effects for RTT.

## Declaration of competing interest

Amy M. Barrett, Oyebimpe Olayinka-Amao, and Susan Martin are employees of RTI Health Solutions, which was contracted by Acadia Pharmaceuticals Inc. to conduct the interviews and perform the analyses. Dilesh Doshi and James M. Youakim are employees of Acadia Pharmaceuticals Inc. and hold stock in Acadia Pharmaceuticals Inc. Kathie M. Bishop is a former employee of Acadia Pharmaceuticals Inc.

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## Author Contributions

Amy M. Barrett designed the study, conducted interviews, analyzed the data, interpreted the results, wrote the first draft of the manuscript, reviewed manuscript drafts, and approved the final draft of the manuscript for submission. Oyebimpe Olayinka-Amao designed the study, conducted interviews, analyzed the data, interpreted the results, reviewed manuscript drafts, and approved the final draft of the manuscript for submission. Susan Martin designed the study, conducted interviews, analyzed the data, interpreted the results, reviewed manuscript drafts, and approved the final draft of the manuscript for submission. Dilesh Doshi designed the study, interpreted the results, reviewed manuscript drafts, and approved the final draft of the manuscript for submission. Kathie M. Bishop designed the study, interpreted the results, reviewed manuscript drafts, and approved the final draft of the manuscript for submission. James M. Youakim designed the study, interpreted the results, reviewed manuscript drafts, and approved the final draft of the manuscript for submission.

## Ethics Approval and Consent to Participate

Interview study approval was obtained from relevant institutional review boards for all participating study sites. Caregivers who volunteered to be interviewed provided written informed consent.

## Consent for Publication

Not applicable.

## Availability of Data and Material

The datasets generated and/or analyzed during the current study are not publicly available due to the proprietary nature of the information and for protection of intellectual property but are available from the corresponding author on reasonable request.

## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.clinthera.2024.12.012](https://doi.org/10.1016/j.clinthera.2024.12.012).

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