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COMMENTARY

Managing Gastrointestinal Symptoms Resulting from Treatment with Trofinetide for Rett Syndrome: Caregiver and Nurse Perspectives

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ABSTRACT

Rett syndrome (RTT) is a rare genetic neurodevelopmental disorder mainly affecting female individuals. Trofinetide was recently approved as the first treatment for RTT, largely on the basis of results from the phase 3 LAVENDER trial, in which trofinetide showed improvements in core symptoms of RTT compared with placebo. However, gastrointestinal (GI) symptoms such as diarrhea and vomiting were commonly reported side effects, and taste was also a reported issue. The objective of this article is to describe the perspectives of five caregivers of girls in trofinetide clinical trials as well as those of three nurse trial coordinators, with a focus on management of GI symptoms of trofinetide treatment.
Audio Abstract available for this article.

Keywords: Diarrhea; Rett syndrome; Taste; Trofinetide; Vomiting

Key Summary Points

Rett syndrome (RTT) is a rare genetic neurodevelopmental disorder that mainly affects female individuals.

Trofinetide is the first approved treatment for RTT.

Gastrointestinal (GI) symptoms, including diarrhea and vomiting, were common side effects in the LAVENDER, LILAC, and DAFFODIL trials of trofinetide treatment of RTT.

We present the experiences and perspectives on management of GI symptoms of five caregivers whose daughters with RTT participated in the trials and those of nurses who served as a research nurse manager or coordinator and managed participants in the trials.

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DIGITAL FEATURES

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INTRODUCTION

Rett syndrome (RTT) is a rare genetic disorder [1] that most often occurs in female individuals, with a worldwide prevalence of about 5–10 per 100,000 in the female sex [2]. Those with RTT appear to develop normally until about 6 months of age, when developmental stagnation begins followed by regression that results in losses of motor and communication skills and development of stereotypic hand movements [3]. RTT is characterized by several neurological comorbidities including behavioral disturbances, sleep dysfunction, irregular breathing patterns, epilepsy, and movement disorders [4]. Gastrointestinal (GI) problems are also common, with constipation reported in 80% and gastroesophageal reflux in 39% of girls and women with RTT [5]. Feeding problems (present in 81%), including difficulty swallowing (43%) and choking or gagging with feedings (27%), nutritional problems (47%), and poor growth with age are also prevalent in those with RTT [5, 6].

Trofinetide (glycyl-L-2-methylprolyl-L-glutamic acid) is a synthetic version of a naturally occurring peptide in the brain [7]. It was recently approved by the US Food & Drug Administration (FDA) for the treatment of RTT in adult and pediatric patients aged 2 years or older. It is the first and currently only approved treatment for RTT.

The FDA approval of trofinetide was based in part on the results from the phase 3 LAVENDER trial (ClinicalTrials.gov identifier NCT04181723), which was a randomized, double-blind, placebo-controlled study of trofinetide in girls aged 5–20 years with RTT [8]. Trofinetide was administered twice daily via weight-based dosing either orally or by gastrostomy tube (g-tube). After 12 weeks of treatment, changes favoring trofinetide over placebo were seen by both caregivers and physicians, as reflected in the coprimary endpoints of the Rett Syndrome Behaviour Questionnaire and Clinical Global Impression-Improvement. Diarrhea was the most common adverse event (AE), experienced by 80.6% in the trofinetide group and 19.1% in the placebo group; most cases were mild or moderate [8]. Diarrhea rates did not largely differ by route of administration or by age group [9]. Vomiting was the second-most common AE, with rates of 26.9% and 9.6% in the trofinetide and placebo groups, respectively [8]. Although not an AE, there were reports of a very sweet and sometimes strong taste of trofinetide from caregivers whose children were enrolled in LAVENDER.

Participants in LAVENDER had the option to continue with open-label trofinetide treatment in the 40-week LILAC extension study (ClinicalTrials.gov identifier NCT04279314). Although symptoms of RTT continued to improve with open-label treatment with trofinetide, diarrhea and vomiting were the most common AEs, with rates of 74.7% and 28.6%, respectively [10].

Younger girls (aged 2–5 years) with RTT were eligible to enroll in the open-label DAFFODIL trial (ClinicalTrials.gov identifier NCT04988867). Interim analysis of the 12-week treatment period A found rates of diarrhea and vomiting of 64.3% and 35.7%, respectively [11].

To further understand how caregivers handled the gastrointestinal (GI) events of trofinetide treatment for RTT, a caregiver roundtable was held virtually on February 15, 2023. This article is coauthored by caregivers of those with RTT who were treated with trofinetide and describes their experiences with these GI symptoms and perspectives on management. In addition, nurses who managed patients in the LAVENDER, LILAC, and DAFFODIL trials shared their insights. A goal is to share information on the management of GI symptoms with healthcare providers (HCPs) so they can discuss these aspects with parents or other caregivers who may be considering initiating trofinetide treatment for their child with RTT.

Author Biographies

Rebecca Moore (RM) (caregiver coauthor) lives in central Oregon. Her daughter with RTT is 12.5 years old and participated in the LAVENDER and LILAC trials until withdrawal due to GI side effects.

Joshua Poulsen (JP) (caregiver coauthor) lives in Albuquerque, NM. His daughter with RTT is 15 years old and is continuing trofinetide treatment.

Lindsay Reardon (LR) (caregiver coauthor) lives in Darien, CT. Her daughter with RTT is 4 years old and is continuing trofinetide treatment.

Candice Samples-Morris (CS-M) (caregiver coauthor) lives in Jacksonville, FL. Her daughter with RTT is 12.5 years old and is continuing trofinetide treatment.

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The Caregiver Perspective

Identification of and Background on Caregiver Authors

Caregiver authors were identified from parents whose daughters had been enrolled in LAVENDER and continued in the LILAC study or were enrolled in the DAFFODIL study. These authors have also participated in other caregiver- and patient-focused activities. All five of the caregivers' daughters had constipation before the clinical trials and experienced diarrhea while on trofinetide. One of the caregivers' daughters experienced vomiting, and none had issues with taste. However, all five of these individuals with RTT were administered the medication via feeding tube, making it less likely that they would taste the medication.

These five caregivers were invited by Acadia Pharmaceuticals Inc. to participate in a virtual roundtable meeting to describe their experiences with the GI symptoms of trofinetide treatment of RTT. Four of the five caregivers' daughters were still being treated with trofinetide at the time of the roundtable. This roundtable was moderated by an external agency (Interactive Forums, Inc., Conshohocken, PA) to encourage candid and open discussion with the caregivers and nurses. The perspectives and experiences presented in this manuscript are individual to the authors and may not be representative of all caregivers of those with RTT. This article is based upon caregiver interviews and not on new clinical data with human participants or animals, so it did not require ethics committee approval.

Interview Questions and Answers

How Did Your HCP Prepare You for the Potential Symptom of Diarrhea?

HS: I think her father and I were pretty prepared because she's had GI issues with either constipation or diarrhea since she was diagnosed [with RTT] at 12 months. So, it wasn't too much of a change of lifestyle for us since we had been dealing with it.

LR: I feel like [our clinical site] did a good job warning us that there was going to be a high likelihood that [my child] would have diarrhea and that it might be pretty severe. I think our expectations were that it's something that we would be dealing with. Similarly to others, we've been dealing with constipation, very badly, before that and sometimes alternating with diarrhea. What we weren't informed about was any way to combat the diarrhea. While we were given the warning that it would be coming, we didn't really know or have any tools handy for how to manage it right off the bat.

JP: [Our doctor] really tried to explain everything to us, but I think sometimes you don't really know what you don't know until you go through it…. When we first started, we were having really, really bad blowouts to the extent to where we had to change clothes… it would go everywhere. It was just really watery and leaky.

RM: Our doctor and nurse did say that quite a few patients were experiencing some diarrhea. We did kick around the idea of using Metamucil, potentially to curb any side effects, and maybe some Imodium if it got really bad. We were not prepared for the fact that it was going to be as intense as it was: from head to toe, all over the bed. We were doing some pretty intensive laundry. Traveling for up to 12 hours just to get home [from the trial site] was a nightmare; all over the car seat, all over the seats. It was pretty much everywhere it could be. We weren't prepared for that, and it took us a while to dial it in and get it figured out.

CS-M: I had never dealt with diarrhea. I thought [that] if she gets diarrhea, then it's just going to make the constipation go away and she'll have a normal poop. That was not the case.

JP: I think an easy way to explain it to other people who maybe haven't experienced diarrhea yet with the trofinetide: think of amoxicillin when you had to take [it] and the diarrhea you get.

Did the Frequency and the Severity of the Diarrhea Fluctuate or Was It at a Consistent Level?

LR: We have not seen a decrease over time, and she's been on it for over a year…. Some days, it's really severe, upwards of 8 to 10 times that she has diarrhea, and some days, it's only once or twice.

JP: We've been on it almost 2 years now, and I think it started decreasing after about 8 months. It seemed like her body got used to it, but they [clinical trial team] also decreased the dosage of her medication, so that might be another reason why it went down, too.

RM: I think from our end our situation might have been a little bit different just because of our daughter needing to be on [tube] feeds 24/7. We had a lot of really intense experiences, and it didn't really get better until we started dialing it in with the Imodium AD. We did try the Metamucil, and it swung the pendulum back the other direction to where she got so constipated, it was like powder when she pooped. We had to get it dialed in quickly as well because she got a UTI from the diarrhea effect and it was 5 days in the PICU.

HS: I would say for us that it was pretty consistent for that 1 month when she had diarrhea until it did subside.

CS-M: We had that initial period for about a month, month and a half… once we got the Metamucil sorted out… it's leveled off, so now [bowel movements are] pretty consistent.

How Would You Characterize the Burden of Diarrhea?

CS-M: It wasn't insurmountable. That was my experience. We stuck it out. We found what worked, and we just made the adjustments as we could.

HS: We would describe the diarrhea as time-consuming.

LR: I just characterize the burden of it as something that we have to deal with for the benefits of the of the treatment, right? It's not insurmountable.

RM: In our world, it was life-changing.

JP: I think it was overwhelming, but worth it.

Did You Have Input from the Study Nurse or from Your Physician on Managing the Diarrhea? What Did "Managing the Diarrhea" Mean to You?

HS: [Our nurse] was very proactive with [my child]. He really was very invested in her GI issues. He was really involved in the constipation and the diarrhea, with the Metamucil and the water and the fiber, and he really did keep her on track with that. He would advise either with the Metamucil or with the Imodium, so we were in that first month using both consistently until her diarrhea subsided. When [the diarrhea] did subside, what a manageable day looks like is semi-solid BMs [bowel movements] once a day.

CS-M: We spoke with the clinical trial nurses and the aides… anything dealing with [diarrhea] went directly to them, and they did great. We wanted at least one good bowel movement a day, and consistency would be along the lines of thick, soft mashed potatoes. It wasn't coming out of the diaper.

JP: Yes, we had a lot of input from the study nurse and doctor about the diarrhea. They asked many questions about consistency and frequencies of diaper changes. They also gave us ideas of how to handle the diarrhea, and reduced the dose to a level that made her poop [consistency] more like soft-serve ice cream.

LR: For us, management's a little bit different in the sense that [her] stomach is just terrible. It always has been, it's been a massive source of challenges for us and everything seems to irritate it: food, medication. Management has been more in terms of prevention and lifestyle management as opposed to actually stopping the diarrhea… remembering to bring extra clothes, put down towels if we need to… as opposed to giving her more medication, which seems to cause her more discomfort, more fussiness, and a lot more screaming. She used to scream so much because of her stomach issues, constipation, gas, and abdominal pain. And she doesn't as much anymore with the diarrhea… she's more comfortable, so we're just dealing with managing the mess as much as possible.

Did You Try Dietary Changes to Manage the Diarrhea and Were They Successful?

CS-M: We tried to increase fiber [with] avocados, a bit more Benefiber, raspberries. I was looking up everything [that was] high fiber. [She's] purely g-tube [fed]. I know how to get everything pulsed and pureed down fine enough to go through her button. This didn't last very long because it was way too tedious to try to manage. So that's why we just tried the Metamucil.

JP: For us, fiber worked. We increased fiber, we increased oatmeal. We had chia seeds. That seemed to help her. It seemed like after a while it made a difference; it just took a long time to get to that point.

HS: We didn't really increase dietary [fiber] so much. I know her GI doctor did increase the Miralax a bit, but not so much specifically foods.

LR: We didn't change food. She's g-tube-fed and she's predominantly formula-fed. She's really struggled with food in general and creates a lot of gassiness. So, we haven't even adjusted fiber because that tends to increase gas.

RM: Our girl is on KetoVie; she's j-tube [jejunostomy tube]-fed. When they suggested that we try Metamucil, we did so and that caused so much pain and so much gas for our kiddo. And like I said, it turned to powder by the time it got to the end of her body. So, we cut out the Metamucil, very, very quickly. Not only that, there can be issues with throwing the keto diet off, depending on what type of fiber you're adding. So, we went straight to the Imodium that has the simethicone.

Were Dose Adjustments Made to Manage the Diarrhea? Were Further Interventions Needed?

JP: We did reduce the dose; I think it's down to 30 [mL] twice a day, and it still is helping her. I think that was one of their ways to help us with the diarrhea…. They reduced it from 60 to 50 to 40 to 30…. We still give her fiber. We still give her a lot of oatmeal every morning, but I think the dose adjustment helped. We've been on that same dose for a long time. I don't see as many accidents as before. We still have some accidents every once in a while, but most of the time, her poop's improved.

CS-M: No dose adjustments; we never did one.

RM: We went through dose adjustments, but if I'm recalling correctly, those were mainly around when we had hospital stays and other illnesses where she just would not tolerate the quantity of fluid that needed to go into her stomach. We always tried to get back up to our optimal dose as quickly as we could.

LR: We also had dose adjustments early on just to get to the optimal dose. We haven't adjusted for purposes of diarrhea.

HS: We also had a dose change at least a year ago, if not longer, but it wasn't because of diarrhea. She actually had started grinding her teeth a lot, so they increased her from 30 BID [twice-daily] to 35 BID.

What Would You Recommend to Other Parent Caregivers for Managing Diarrhea?

CS-M: Learn how to accurately describe it. If you're trying to manage this with a doctor that may not be available in-house or [are] doing this over the phone or email, learn how to properly describe it in a medical sense so they have a better understanding of what it is, because they can't see it. We have the chart [Bristol stool scale]; they mailed us a printout and I laminated it and set it up for all of the nurses and everybody to see. [Also,] don't hesitate to try what they're recommending first because at the end of the day, what they were suggesting for us worked instead of what I thought was going to be better.

HS: Try to put a plan in place as best as you can. Definitely utilize others such as support groups, healthcare providers, other families that have Rett girls.

LR: Upon starting the medication, have a plan in place with your physician on what to try and how to try it to manage it up front.

RM: Not only should you have a plan but you should have a plan A, B, C, and D…. Always know that you have resources and avenues and choices that you can be making, and be prepared. Always be prepared.

Practical tips from the caregivers on managing diarrhea from trofinetide treatment are shown in Table 1. Caregivers also mentioned that several Rett-related organizations and groups could aid in alerting caregivers to the potential side effects of trofinetide treatment, such as the Rett Syndrome Research Trust, International Rett Syndrome Foundation, RettEd, and Facebook support groups. Programs focused on informative training for parents on Zoom meetings or in-person at a Rett conference could help. Several caregivers mentioned the importance of not only a treatment team of experienced HCPs but also family members and other parents who have a child with RTT, the latter of whom might serve as parent ambassadors for feedback and support.

What Was Your Motivation to Manage the Diarrhea So Your Child Could Stay on Study Treatment?

RM: For us, it was a really emotional thing. We had waited for trofinetide for 9-plus years. Trofinetide, for the time, was supposed to be the thing that could make a huge difference for our girl…. We were willing to do just about anything to make sure she could be in this study…. And we were in it until the juice was no longer worth the squeeze…. When our daughter vomited, there was trofinetide in that vomit. She got aspiration pneumonia and then Covid on top of it, and we were life-flighted to the hospital. That was really the time that my husband and I had to sit back and go, "Okay, let's really evaluate this. Is this worth it? We've given it our all. And is it worth it to continue doing what we were doing for the results that were getting? And also knowing that our daughter had multiple surgeries coming up, is it okay for poop to be out of control and for vomit to rule our lives?" And that's the point at which we said, "no, not worth it."

LR: [Prior to the trial], we were just witnessing our child lose every skill that she had, which wasn't much to begin with, and she was screaming sometimes 6 h a day; she was miserable. She was in agony. Her stomach was a big, big driver in that. The regression was also a factor…. We weren't able to give [our other two kids] the attention that they deserved. So, we were desperate. It seemed like there were limited minimal risks, diarrhea being the biggest one, which to me in the grand scheme of things is not a reason to not try something. And so for us, there was only upside potentially, right? We're still in the trial. [Note: all three trials have ended by the time of publication.] We're still on the drug. She's a different kid than she was when we started. I think part of that is definitely the drug. I think part of it is her coming out of regression as well. But our family is in a far, far better place than we were when we started a year ago.

CS-M: We weren't seeing any of the major side effects that we have seen with other trials or have had with other drugs for other issues. The worst thing we had was diarrhea. As long as we didn't see anything adverse happening to

Table 1 Practical tips for managing trofinetide-induced diarrhea

Preventing dehydration
Powdered packets of Pedialyte allow for as-needed use (premixed bottles of Pedialyte are large and must be discarded 24 h after opening)
Protein water
Packing supplies for trips
Extra clothes
Chuck pads[a]
Diapers
Wipes (larger ones preferred)
Cleaning supplies
Gloves
Trash bags
Scissors
For those with a feeding tube: supplies for bolus administration of water, Pedialyte, Imodium
"*If you think you have enough supplies, grab more*"
Preparing areas for cleanup, diaper changes
Laying towels over the car seat
Bedding: make several layers of full bed-sized chucks with a sheet on top; this allows for removal of the top sheet/chuck if soiled, with a clean layer underneath
Van: something to lay down in the back for changing, such as a folding tumbling mat, folding massage table; curtain for privacy[b]
Clearing/preventing diaper rash
After cleaning up diarrhea, use a hair dryer to dry the area and then apply Aquaphor, Desitin, or Butt Paste (any or all combined)
Expert recommendations on diarrhea management are available for clinicians [9] and in a plain-language version [14]

[a]Disposable underpads named because they are "chucked" after use
[b]Several caregivers noted that public changing stations, especially ones for larger children/adolescents, are difficult to find. Those that do exist are often in women's restrooms, making it difficult for male caregivers to access

her, I felt it was worth staying in it and as long as I could manage the diarrhea, that was a reasonable accommodation. Then the longer we were in it, the more information they would have and the more potential for families to be prepared or for them to actually be able to go to the FDA and say, "we've gathered good information, good data." There wasn't anything adverse that we saw. We didn't develop long QT or anything like that. And what we did get was benefits. We saw benefits.

JP: We stayed in it because we wanted to; we thought it would benefit other people…. We knew it was going to help her, and I think we've seen a lot of benefits from it, especially with her eye gaze and her attention and more

focusing…. It motivated us to try to contribute as much as we can to the study with trofinetide…. We knew it wasn't going to fully take away all the symptoms of Rett syndrome, but it was good enough for us to be able to keep going through it. So, we're still in the study now, we're still doing the work, still giving her the trofinetide. So, we're just glad to be in it.

HS: For us with [my child], we were looking to give her possibly a better quality of life, and not just for her; for us, too. So, we also were looking to possibly minimize the symptoms of Rett syndrome and like Josh said, certainly not eliminate them because that I don't think would have been realistic. But yes, a lot of her behaviors have decreased. Her teeth grinding was non-stop: all the time, every day; that barely happens now. She would scream all the time…. So, I would say that her emotions now are much more appropriate and she's much more focused when she sees people… she's nonverbal, but when she interacts with them, she's much more alert.

CS-M: [My child's] grinding has reduced to a minimum, and I hadn't even connected that it could be due to the trial drug.

Moving on to Vomiting: How Prepared Were You for the Potential of Vomiting, and Who Prepared You?

LR: Our experience with vomiting was not related to the medication. [My child] vomited prior to the start of the medication a decent amount, usually after feedings. It took us a while to figure out it was reflux-driven, and in that time she had started the medication. There was about a 5-month period where she was on the medication and also vomiting, but the minute we got her on a PPI [proton pump inhibitor] her vomiting stopped. She has not vomited really at all since with the exception of when she gets really sick.

RM: We hadn't really done a whole lot of talking [with the trial team] about vomiting being a big issue…. [My child] has one of her types of seizures that presents as very large-scale grand mal-type and then she generally vomits immediately after that seizure… so vomiting is something that we too were accustomed to. She also had a GJ-tube [gastrostomy-jejunostomy tube] placed because vomiting was an issue. She's had a fundoplication. She's also been on PPIs for a really long time, so vomiting is not something that was uncommon. However, we did start to experience quite a bit of vomiting with this medication, and the crazy thing was it could be hours after the medication had been administered and she would still throw up strawberry-scented, colorful vomit.

CS-M: This was not part of our experience with [my child].

JP: We never really experienced vomiting with [my child].

HS: I do believe that when we first started the trial, her treatment team did inform us about the possibility of the vomiting. The doctor and case manager and the nurse that made up her treatment team were really helpful with that.

Did the Frequency of Vomiting Decrease Over Time?

RM: In our situation, the amount of vomiting that occurred was significant and it would come on at any given time. You never knew when it was going to happen. We had lots of scary driving incidents where she would just out of nowhere, not seizure-related, begin throwing up. And it would get all over and it was staining and it was problematic in our case… independent of the PPI that was given and the fact that it was happening away from her seizures leads me to believe that it was the medication that was causing the problem…. I would even venture to say that it started to get worse towards the end…. The only thing that went into her stomach was medications or formulas and it didn't seem to matter if we coupled the medication with formula or if we didn't, but it would be a large quantity of regurgitation. Even several hours after the medication was given, we would experience these regurgitation sessions, so it was quite uncomfortable and unpleasant for her.

How Burdensome Was the Vomiting for You and Your Family?

RM: I would say it came in a close second to the diarrhea for our family. It was scary because [my child] is a very high aspiration risk and that is

eventually one of the episodes that took us out of the trial. It meant that I couldn't travel by myself. I either had to have one of my children go with us or someone else when we were traveling…. I couldn't leave the room because what if she vomited and aspirated. Our other kids were constantly grabbing towels and vomit bags and having to help me change her clothes and things like that. So, I would say it made a bit of a difference in our family life, fairly significant.

The Healthcare Provider Perspective

In addition to the parent caregivers, three nurses involved in the LAVENDER, LILAC, and DAFFODIL trials described their experiences with the GI side effects of trofinetide treatment.

Diarrhea

At the beginning of the LAVENDER trial, it was not known that diarrhea would be such a problem since diarrhea rates were lower in the phase 2, randomized, double-blind, placebo-controlled trials in female participants with RTT. In one of the phase 2 trials, diarrhea rates were 39%, 11%, and 15% in those who received twice-daily trofinetide 35 mg/kg, trofinetide 70 mg/kg, and placebo, respectively [12]. In the other phase 2 trial, rates of diarrhea were 27%, 13%, 56%, and 4% in those who received twice-daily trofinetide 50 mg/kg, trofinetide 100 mg/kg, trofinetide 200 mg/kg, and placebo, respectively [13]. For reference, trofinetide dosing was higher in the LAVENDER trial, at 200–500 mg/kg twice daily [8].

Partly because of these lower diarrhea rates in earlier trials and because of the significant constipation almost universally experienced in this population [5], the nurse authors noted that sites were not initially prepared for the diarrhea AE. In addition, those in the LAVENDER trial did not know whether they were receiving trofinetide or placebo. Thus, the nurses pointed out that they could not initially treat everyone in LAVENDER as though they were receiving trofinetide and recommend antidiarrheal measures such as stopping constipation medications. Once the pattern of diarrhea was recognized, and trial sites gained more experience with participants in the trial and received training from the trial sponsor, the nurses were able to assist with diarrhea management plans.

One nurse stated that open communication with the participants and caregivers was vital in managing the diarrhea. Their site instructed caregivers to call them immediately at the first signs of loose stools or more frequent stools compared to the participant's baseline. This enabled initiation of an antidiarrheal management plan as early as possible to prevent the diarrhea from becoming out of control. Many caregivers expressed that one or two "controllable" stools a day would be ideal for their child. Similar to the opinion of the caregiver authors here, "controllable" was mostly considered as stools that were contained within a diaper or brief instead of soiling clothes and wheelchairs. Diarrhea management was important in part because weight loss and decreased appetite were a concern for many families. In addition, some parents expressed the difficulty of sending their children to school with diarrhea, as diarrhea added stress on the school staff to provide multiple diaper changes throughout the day. One nurse noted that they had to provide notes to the school for two patients explaining that the diarrhea was secondary to the medication and not infectious in nature.

Strategies for diarrhea management were developed during the LAVENDER trial. One nurse noted that loperamide helped with the diarrhea, but that many families were reluctant to use it every day and/or did not want to add another medication to their daughter's regimen. Instead, they first tried adjusting the diet or using supplemental therapies. In retrospect, this nurse would promote using loperamide regularly at first and trying dietary changes alongside it, as she saw that many of the alternative therapies that were first attempted did not work. Some difficulty in taking liquid loperamide in addition to the liquid trofinetide was seen in some participants and so switching to a pill form of loperamide was recommended for those participants who were able to swallow pills. For one family, the diarrhea improved by giving a daily banana and rice, while fiber

gummies and psyllium fiber had varying results. Similarly, another nurse relayed that some of their antidiarrheal strategies worked well for some participants, some treatments worked well for a period of time for some participants, and some treatments did not work at all to decrease the diarrhea.

To prevent dehydration, the nurses noted that it was beneficial for caregivers and/or school employees to provide cups of Pedialyte consistently throughout the day to the participants who were able to drink oral fluids. For participants with a g-tube, dehydration could be prevented by administering water continuously through the tube overnight or between feedings.

One of the site nurses noted that they decreased the dosage of trofinetide in five of their ten LILAC trial participants. Reducing the dose by 30–40% helped reduce diarrhea in two of the participants. Of these two, one maintained this lower dose while the other patient was receiving 90% of her initial starting dose at the end of the trial. For the other three patients, reducing the trofinetide dose initially helped to reduce diarrhea but then the diarrhea returned.

One nurse noted that preparation for potential diarrhea and starting diarrhea management in the open-label extension LILAC trial was much easier than in the LAVENDER trial, as they were able to inform caregivers of learnings from LAVENDER before initiation of trofinetide treatment. Now that trofinetide is FDA-approved, diarrhea management can be pursued as soon as an individual initiates treatment with trofinetide. Expert recommendations on diarrhea management with trofinetide treatment for RTT are available for clinicians [9] and in a plain-language version [14].

Vomiting

Similar to diarrhea, the rates of vomiting were lower in the phase 2 trials of trofinetide for RTT than in LAVENDER, with rates of 0%, 11%, and 0% with twice-daily trofinetide 35 mg/kg, trofinetide 70 mg/kg, and placebo, respectively [12] and 7%, 13%, 22%, and 13% with twice-daily trofinetide 50 mg/kg, trofinetide 100 mg/kg, trofinetide 200 mg/kg, and placebo, respectively [13].

The nurses relayed that they also learned very quickly after the LAVENDER trial commenced that vomiting was a potential side effect of treatment with the study drug, and so it became a routine part of education of patients and caregivers, along with diarrhea, before initiating treatment in the trials. Some caregivers whose daughters were administered trofinetide orally attributed the vomiting to its taste. One of the nurses noted that ondansetron was helpful in reducing vomiting in one patient.

The original protocol for the LAVENDER trial mandated that the participants should not eat for 1 hour before and 1 hour after trofinetide administration. However, several caregivers found that administering trofinetide closer to breakfast and dinner helped reduce vomiting in their children. The trial protocol was later amended to eliminate the restrictions on eating before or after trofinetide administration. One nurse stated that she encouraged families to try different times for administration since individuals varied on whether trofinetide was more tolerable before or after a meal.

Taste

While taste was not an issue for the five parent-authors of this paper, all of whom had daughters whose trofinetide was administered via feeding tube, several caregivers of participants whose daughters took trofinetide orally relayed to the trial sites that the taste of trofinetide affected administration. Taste appeared to be less of an issue in smaller children who had a smaller dose of trofinetide, which is likely due to the weight-based dosing in LAVENDER. Similar to the issues with diarrhea and vomiting, the nurse coordinators learned to educate caregivers that the taste of trofinetide could be problematic and suggested ideas on ways to ensure the full dose was administered. It was frequently reported that the participants would hold the trofinetide in their mouths without swallowing, which sometimes prolonged the administration times up to an hour or more. This was problematic for the morning routines of caregivers who needed to get their children to school and themselves to work on time. Thus, the nurse coordinators recommend that caregivers allot extra time for administration, as

rushing usually resulted in less medication administered.

The nurses stated that caregivers tried various strategies to mitigate the taste issue. One mother said she would feed her daughter before giving her trofinetide because the taste of the medication would affect the participant's taste and she would eat less. Some caregivers found that alternating sips of trofinetide with a beverage, such as a favorite drink, to mask the taste of trofinetide was most helpful. One family tried multiple types of juices, reporting that they could get their daughter to take the medication with one flavor for a week or so but then would have to change to another flavor. Rotating flavors of juices became their method to getting her to take the full dose throughout the trial. Several caregivers said that after their daughters had been on treatment for a while, they recognized the syringe and would automatically refuse to open their mouths for trofinetide. They had a better experience of administering the total prescribed dose if the caregivers put the trofinetide in a sippy cup. Another parent successfully used medical-grade plastic tubing connected to the syringe for her daughter to use as a straw to drink the trofinetide. However, there were a few caregivers who tried a number of tricks and techniques to get their child to take the full dose but eventually realized all they could do was administer as much as the child would take for each dose.

Patient/Caregiver Education and Preparation

Prescription of a new medicine is accompanied by quite a bit of teaching on the part of HCPs, including presenting the pros and cons to patients and their caregivers. As noted previously, the nurses who managed patients in the LAVENDER trial adjusted their education of caregivers in response to the GI symptoms that emerged during the trial. One nurse noted that "the physicians that we work with are known to say, "this is not a dictatorship, this is a partnership." In addition, many families of children with RTT get information from other RTT families, which can be helpful when the information is accurate. However, sometimes this information is not applicable or accurate, so it is important for families to seek information from their HCPs as well. HCPs should also realize the need for individualized plans for management of the side effects of trofinetide because not everyone responded in the same way, which was also highlighted above in the parental experiences.

CONCLUSIONS

Trofinetide is the first drug approved for the treatment of RTT, but many experience GI side effects with treatment. In this group, all five caregivers' daughters had diarrhea with trofinetide treatment. One also experienced vomiting, which ultimately led to her withdrawal from the trial. Most of the caregivers who participated in this roundtable feel that the diarrhea is not insurmountable and are willing to manage it for the improvements in core RTT symptoms that they observe in their daughters. While they were informed of the possibility of diarrhea before the trial, some were still surprised at the intensity of the diarrhea. The caregivers gave several tips for managing the diarrhea, including increasing fiber, adjusting the dose, and being prepared for cleanup. Other published recommendations on diarrhea management are available [9, 14]. These caregiver authors also embrace the importance of clinical trials, not only for benefiting their own children but also for advancing science and helping others.

The nurse coordinators emphasized the importance of participant/caregiver education when introducing a new drug, and their experiences with the GI side effects of trofinetide in the LAVENDER trial informed their communications with the caregivers. A common theme is that, although there are some strategies for managing GI side effects that should be recommended initially (e.g., loperamide for diarrhea), each individual with RTT is unique and different methods may work better in some than others. This roundtable provided valuable insights that could benefit HCPs in their clinical practice when aiding both people with RTT and their caregivers in the management of GI side effects.

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Declarations

Conflict of Interest. The authors thank all participants in the LAVENDER, LILAC, and DAFFODIL trials and their caregivers. Rebecca Moore, Joshua Poulsen, and Holly Simmons are parents of children who participated in the LAVENDER and LILAC trials and have participated in advisory board meetings sponsored by Acadia Pharmaceuticals Inc. Lindsay Reardon is a parent of a child who participated in the DAFFODIL trial and has participated in advisory board meetings sponsored by Acadia Pharmaceuticals Inc. Candice Samples-Morris is a parent of a child who participated in the LAVENDER and LILAC trials, has participated in advisory board meetings sponsored by Acadia Pharmaceuticals Inc., and has spoken on behalf of Acadia Pharmaceuticals Inc. Keri M. Ramsey and Meagan L. Whatley participated in the LAVENDER, LILAC, and DAFFODIL trials as research nurse coordinators for their study site. Jane B. Lane participated in the LAVENDER, LILAC, and DAFFODIL trials as a research nurse manager for the study site and is a consultant for Acadia Pharmaceuticals Inc.

Ethical Approval. This article is based upon caregiver interviews and not on new clinical data with human participants or animals, so it did not require ethics committee approval. All authors met the criteria of the International Committee of Medical Journal Editors for this manuscript, take responsibility for the integrity of the work, and gave their final approval of the final draft.

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