Expert Consensus on Real-World Use of Trofinetide for Rett Syndrome Using a Modified Delphi Method

Erin Prange,[1] Art Beisang,[2] Davut Pehlivan,[3] Bernhard Suter,[4] Paula Schleifer[5]

[1]Division of Neurology, Children's Hospital of Philadelphia, Philadelphia, PA, USA; [2]Department of Pediatrics, Gillette Children's Hospital, Saint Paul, MN, USA; [3]Department of Pediatrics and Neurology, Baylor College of Medicine, Texas Children's Hospital, Houston, Houston, Texas, USA; [4]Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, TX, USA, Texas Children's Hospital, Houston, TX, USA; Section of Pediatric Neurology and Developmental Neuroscience, Department of Pediatrics, Baylor College of Medicine, Houston, TX, USA; [5]Department of Neurology, Nicklaus Children's Hospital, Miami, FL, USA

BACKGROUND

- Rett syndrome (RTT) is a rare neurodevelopmental disorder characterized by core symptoms of loss of purposeful hand skills and verbal communication, gait abnormalities, and hand stereotypies[1,2]
- Trofinetide is the first and only FDA-approved treatment for RTT in adults and pediatric patients aged ≥2 years[3]
- Clinical trial data demonstrate trofinetide led to sustained improvements in RTT core symptoms, as measured by caregivers and clinicians[4-6]
- Real-world evidence supports these findings, with caregivers reporting meaningful improvements in nonverbal communication, alertness, social engagement, and overall quality of life[7]
- A Delphi method was initiated to establish best practices for trofinetide from US RTT experts practicing at an International RTT Syndrome Foundation (IRSF)-designated Center of Excellence (COE)

OBJECTIVE

- To establish consensus on trofinetide use in RTT across key domains of clinical practice

METHODS

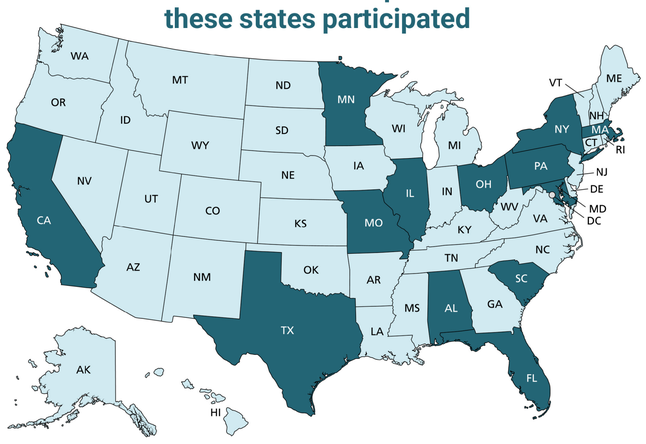
- A modified Delphi method convened a virtual steering committee of five US RTT experts, defined as individuals practicing at one of the 21 US COEs
- The steering committee generated 72 consensus statements across 6 key domains:
  - **A. Trofinetide as a first-line treatment for RTT**
  - **B. Pre-trofinetide assessments and counseling**
  - **C. Initiating trofinetide**
  - **D. Assessing trofinetide benefits**
  - **E. Assessing and managing trofinetide tolerability**
  - **F. Discontinuing or pausing trofinetide**
- An electronic survey containing these statements was developed and distributed to all US RTT experts with experience prescribing trofinetide as Round 1
- Respondents rated their level of agreement with each statement using a four-point Likert scale
- Results were analyzed to determine level of agreement for each statement and need for revision and retesting
- The panel developed an additional 10 statements for re-testing, which was again sent to all US RTT experts as Round 2 and followed the same process as Round 1
- The consensus threshold was set *a priori* at ≥75% agreement (i.e., strongly agree and tend to agree)

RESULTS

Figures. RTT Expert Delphi Participation by (A) State; (B) Proportion of US RTT COEs; and (C) Proportion of US RTT Experts

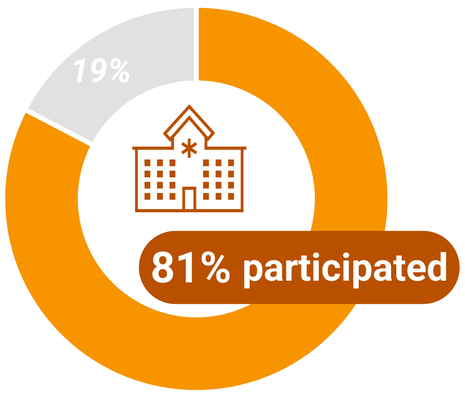
A

At least 1 RTT expert in these states participated



B

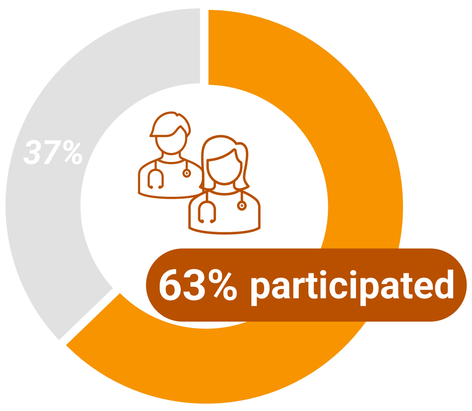
Four in five RTT COEs participated



17 of 21 US RTT COEs were represented across the 25 responses received in each round

C

Nearly two thirds of RTT experts participated



27 of 43 US RTT experts participated with a representative mix of MDs, DOs, and NPs spanning <5 to 20+ years in their RTT-related practice

Table 1. Consensus Agreement for Key Statements After 2 Survey Rounds *(all numbers rounded to the nearest whole number)*

No.	Key statements	Agree	Disagree
Domain A: Trofinetide as a first-line treatment for Rett syndrome (RTT)			
1	Trofinetide is the first FDA-approved treatment to demonstrate improvement in several core symptoms of RTT, in contrast to other therapies which primarily target one symptom of RTT	**88%**	12%
2	Trofinetide should be part of standard of care for RTT individuals at least 2 years of age, as indicated	**88%**	12%
4	The side effects of trofinetide can be successfully managed in most cases	**96%**	4%
7	Trofinetide can be given at any time throughout the patient's lifetime as indicated	**100%**	0%
8	Trofinetide may improve patient's attention and (non-verbal and verbal) communication within a month of initiation	**92%**	8%
9	Trofinetide may improve patient's (fine and gross) motor skills, hand use, hyperventilation, altered breathing patterns, bruxism, sleep patterns, anxiety and irritability, as early as three months after initiation	**84%**	16%
Domain B: Pre-trofinetide assessments and counseling			
14	Functional status (daily living activities, communication and motor function) should ideally be documented prior to initiating trofinetide, to help assess any improvements while on trofinetide	**92%**	8%
22	Counsel patients and/or caregivers that improvements may be subtle, incremental, and variable depending on the patient	**100%**	0%
23	Counsel patients and/or caregivers that the results of treatment may appear in different symptom domains based on the individual patient	**100%**	0%
24	Counsel patients and/or caregivers that potential side effects may occur (diarrhea and vomiting) and guidance for managing them	**100%**	0%
27	Encourage patients to start, or restart, supportive therapies (e.g., physical therapy, occupational therapy, speech therapy) to maximize the benefits of trofinetide after initiation	**100%**	0%
Domain C: Initiating trofinetide			
29	A dose titration schedule should be created prior to initiation, with flexibility to adapt as needed based on tolerability	**100%**	0%
32	Particularly if there are tolerability concerns (e.g., GI comorbidities), most physicians initiate trofinetide at either 5-10 mL (1,000-2,000 mg) BID or 25-50% of the recommended weight-banded dose BID and titrate thereafter; however, the starting dose should be individualized, taking into account factors such as the ability to consume liquids	**84%**	16%
35	For patients unable to tolerate titration of 5-10 mL (1,000-2,000 mg) per dose every 1-2 weeks, slower titrations should be considered	**92%**	8%
36	Most patients achieve their full recommended weight-banded dose, but those who do not may still achieve significant benefits from trofinetide treatment on a lower dose	**88%**	12%
Domain D: Assessment of trofinetide benefits			
41	Patients should receive trofinetide for six months after titrating to their weight-banded, or highest tolerable, dose to properly assess the efficacy of the treatment	**96%**	4%
43	Documentation of improvements on trofinetide should be mainly based on caregiver and/or clinician observations, rather than the exclusive use of CGI-I or RSBQ assessments, as not all improvements can be captured by these assessments	**96%**	4%
Domain E: Assessing and managing trofinetide tolerability			
46	Reducing a patient's trofinetide dose to a level at which side effects can be managed, or pausing and restarting on a lower dose with the intention to increase as tolerated, is preferable to stopping the dose entirely	**100%**	0%
51	Fibrous foods such as bananas, peanut butter, avocado or fiber bars may be used to manage diarrhea	**96%**	4%
52	For those receiving nutrition through gastrostomy, consider switching to an alternative brand of formula or a blenderized diet to improve digestive tolerance and manage diarrhea	**76%**	24%
54	Imodium may be considered short-term (i.e., a few days) to manage severe diarrhea, but only if other options are unsuitable or ineffective, and should be discontinued as soon as clinically appropriate	**80%**	20%
56	Despite trofinetide's risk of diarrhea, maintaining adequate hydration and routinely monitoring bowel activity are important to prevent or minimize development or redevelopment of constipation as their body adjusts to trofinetide	**100%**	0%
65	Based on limited data, trofinetide is generally accepted as "seizure neutral"	**100%**	0%
Domain F: Discontinuing or pausing trofinetide			
69	Pausing the dose is an option if a patient is traveling, hospitalized, or experiencing acute, severe side effects	**100%**	0%
71	Trofinetide can be safely discontinued without tapering	**94%**	4%
72	Stopping trofinetide may lead to the loss of improvements acquired during treatment, although further observation and research is required	**88%**	12%

In both rounds of survey, completed questionnaires were received from 25 respondents. Following Round 1, 10 statements failed to meet the 75% consensus threshold. These were reviewed by the steering group, amended, and reissued in Round 2. At the end of Round 2, consensus threshold was achieved for all remaining statements.

Based on the final statement set the following recommendations have been developed:

1. **Enlist trofinetide as part of standard of care for eligible patients with RTT**
2. **Conduct baseline functional assessments and provide education on potential improvements and side effects**
3. **Initiate trofinetide early, monitor broadly for improvements, and personalize care**
4. **Start trofinetide at a low dose, titrate slow, and tailor the dose to patient needs**
5. **Customize administration strategies to fit each patient's unique need**
6. **Allow adequate time, at least 6 months, to fully assess trofinetide benefits**
7. **Manage side effects with dose adjustments, pauses, & other interventions prior to discontinuation**

CONCLUSIONS

- **This Delphi consensus recommends trofinetide as part of RTT standard of care and supports a flexible, patient-centered approach to individualized dosing and titration, real-world benefit assessment, and side effect management**
- **These recommendations aim to guide best practice across care settings and improve patient and caregiver outcomes**

Scan code to view poster and supplemental material

REFERENCES

1. Neul JL, et al. *Ann Neurol*. 2010;68(6):944–950. **2.** Motil KJ, et al. *J Pediatr Gastroenterol Nutr*. 2012;55(3):292–298. **3.** DAYBUE (trofinetide) [package insert]. San Diego, CA: Acadia Pharmaceuticals; 2024. **4.** Neul JL, et al. *Nat Med*. 2023;29(6):1468–1475. **5.** Percy AK, et al. *Med*. 2024;5(9):1178–1189.e3. **6.** Percy AK, et al. *Med*. 2024:5(10):1275–1281.e2. **7.** Cosand L, et al. Poster presented at IRSF, June 18–19, 2024, Denver, CO, USA; Cosand L, et al. Poster presented at CNS, November 11–14, 2024, San Diego, CA, USA.

ACKNOWLEDGMENTS

The study was supported by Acadia Pharmaceuticals Inc. ("Acadia", San Diego, CA, USA). Medical writing and project facilitation were provided by Emily Lassman and Ian Walker of Triducive Partners Limited ("Triducive").

DISCLOSURES

All authors served as consultants to Acadia during this Delphi consensus project. Financial compensation was provided for their steering committee activities. Triducive was commissioned by Acadia to facilitate the Delphi process and analyze responses.

Presented at the 54th Annual Meeting of the Child Neurology Society (CNS) | October 8-11, 2025 | Charlotte, NC, USA

ACADIA®

Expert Consensus on Real-world Use of Trofinetide for Rett Syndrome Using a Modified Delphi Method

Erin Prange,[1] Art Beisang,[2] Davut Pehlivan,[3] Bernhard Suter,[4] Paula Schleifer[5]

[1]Division of Neurology, Children's Hospital of Philadelphia, Philadelphia, PA, USA; [2]Department of Pediatrics, Gillette Children's Hospital, Saint Paul, MN, USA; [3]Department of Pediatrics and Neurology, Baylor College of Medicine, Texas Children's Hospital, Houston, Houston, Texas, USA; [4]Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, TX, USA, Texas Children's Hospital, Houston, TX, USA; Section of Pediatric Neurology and Developmental Neuroscience, Department of Pediatrics, Baylor College of Medicine, Houston, TX, USA; [5]Department of Neurology, Nicklaus Children's Hospital, Miami, FL, USA

SUPPLEMENT

Table S1. Consensus agreement for all statements after 2 rounds *(all numbers rounded to the nearest whole number)*

No.	Statement	Strongly Agree	Tend to Agree	Tend to Disagree	Strongly Disagree	Overall Agree
Domain A: Trofinetide as a first-line treatment for Rett syndrome (RTT)						
1	Trofinetide is the first FDA-approved treatment to demonstrate improvement in several core symptoms of RTT, in contrast to other therapies which primarily target one symptom of RTT	64%	24%	12%	0%	**88%**
2	Trofinetide should be part of standard of care for RTT individuals at least 2 years of age, as indicated	56%	32%	12%	0%	**88%**
3	Trofinetide is generally well-tolerated	20%	56%	24%	0%	**76%**
4	The side effects of trofinetide can be successfully managed in most cases	36%	60%	4%	0%	**96%**
5	Trofinetide can be prescribed by any eligible member of the patient's healthcare team who is involved in the management of RTT	56%	44%	0%	0%	**100%**
6	Trofinetide may be used as chronic therapy	60%	36%	4%	0%	**96%**
7	Trofinetide can be given at any time throughout the patient's lifetime as indicated	68%	32%	0%	0%	**100%**
8	Trofinetide may improve patient's attention and (non-verbal and verbal) communication within a month of initiation	44%	48%	8%	0%	**92%**
9	Trofinetide may improve patient's (fine and gross) motor skills, hand use, hyperventilation, altered breathing patterns, bruxism, sleep patterns, anxiety and irritability, as early as three months after initiation	32%	52%	12%	4%	**84%**
10	Chronic use of trofinetide that results in improved (non-verbal and verbal) communication may help patients better express their needs	40%	48%	12%	0%	**88%**
11	Chronic use of trofinetide may improve quality of life of both the caregiver and the patient	32%	56%	12%	0%	**88%**
Domain B: Pre-trofinetide assessments and counseling						
12	Clinical function and RTT severity should be documented prior to initiating trofinetide, if possible	64%	24%	8%	4%	**88%**
13	All core symptoms of RTT (communication, motor function, altered breathing patterns, bruxism and repetitive hand movements/stereotypies) should ideally be fully documented prior to initiating trofinetide, to help assess any improvements while on trofinetide	80%	12%	8%	0%	**92%**
14	Functional status (daily living activities, communication and motor function) should ideally be documented prior to initiating trofinetide, to help assess any improvements while on trofinetide	80%	12%	8%	0%	**92%**
15	Patient history of seizures should be taken prior to initiating trofinetide, if possible	76%	16%	8%	0%	**92%**
16	Caregivers should be encouraged to keep a detailed diary of a patient's symptoms prior to and in the months after initiating trofinetide	56%	32%	12%	0%	**88%**
17	Patient history of bowel activity, vomiting and nutritional status should be obtained prior to initiating trofinetide, to help individualize bowel management	80%	20%	0%	0%	**100%**
18	Consider discontinuing all constipation medications prior to initiating trofinetide	48%	36%	16%	0%	**84%**
19	Consider decreasing the dose of all constipation medications prior to initiating trofinetide, as deemed appropriate based on the individual patient	48%	44%	8%	0%	**92%**
20	Consulting with specialists should be considered before offering trofinetide to a patient who is severely underweight or malnourished, or has significant GI comorbidities or renal disease	72%	20%	4%	4%	**92%**
21	Counsel patients and/or caregivers that they may not experience immediate benefits	88%	8%	4%	0%	**96%**
22	Counsel patients and/or caregivers that improvements may be subtle, incremental, and variable depending on the patient	92%	8%	0%	0%	**100%**
23	Counsel patients and/or caregivers that the results of treatment may appear in different symptom domains based on the individual patient	88%	12%	0%	0%	**100%**
24	Counsel patients and/or caregivers that potential side effects may occur (diarrhea and vomiting) and guidance for managing them	96%	4%	0%	0%	**100%**
25	Counsel patients and/or caregivers that if a patient experiences vomiting, they should contact their healthcare provider, particularly for patients at risk of aspiration	88%	12%	0%	0%	**100%**
26	Plan to remain in close communication with the patient and/or caregiver for the first three months to evaluate dose, improvements, and side effects until either a stable or target dose is reached	88%	8%	0%	4%	**96%**
27	Encourage patients to start, or restart, supportive therapies (e.g., physical therapy, occupational therapy, speech therapy) to maximize the benefits of trofinetide after initiation	88%	12%	0%	0%	**100%**
Domain C: Initiating trofinetide						
28	Trofinetide is not typically initiated at the full weight-banded dose	80%	16%	4%	0%	**96%**
29	A dose titration schedule should be created prior to initiation, with flexibility to adapt as needed based on tolerability	84%	16%	0%	0%	**100%**
30	Titration should be adapted based on the patient's individual tolerance of the dose	92%	8%	0%	0%	**100%**
31	Particularly if there are tolerability concerns (e.g., GI comorbidities), most physicians initiate trofinetide at either 5 mL BID or 25% of the recommended weight-banded dose BID and titrate thereafter; however, the starting dose should be individualized, taking into account factors such as the ability to consume liquids	48%	36%	16%	0%	**84%**
32	Particularly if there are tolerability concerns (e.g., GI comorbidities), most physicians initiate trofinetide at either 5-10 mL BID or 25-50% of the recommended weight-banded dose BID and titrate thereafter; however, the starting dose should be individualized, taking into account factors such as the ability to consume liquids	56%	28%	16%	0%	**84%**
33	Flexibility in physician management approaches is essential to accommodate individual patient history, tolerability, and clinical needs when initiating and titrating trofinetide	80%	20%	0%	0%	**100%**
34	Patients should be titrated at a rate of 5 mL per dose every 1-2 weeks, if they are tolerating trofinetide well	32%	44%	20%	4%	**76%**
35	For patients unable to tolerate titration of 5-10 mL per dose every 1-2 weeks, slower titrations should be considered	60%	32%	4%	4%	**92%**
36	Most patients achieve their full recommended weight-banded dose, but those who do not may still achieve significant benefits from trofinetide treatment on a lower dose	44%	44%	8%	4%	**88%**
37	Dosage should be reassessed at every visit and ideally, every six months, until reaching target dose	68%	28%	0%	4%	**96%**
38	Dosage should be reassessed once the patient progresses to the next weight band	72%	24%	4%	0%	**96%**
39	Periodic dose re-challenges to achieve recommended weight-banded dose is encouraged, particularly if patients have been tolerating their current dose	52%	40%	8%	0%	**92%**
Domain D: Assessing trofinetide benefits						
40	While there may be evidence of improvement during acute periods of intolerability, proper assessment of improvement should take place after tolerability has been properly managed	48%	44%	8%	0%	**92%**
41	Patients should receive trofinetide for six months after titrating to their weight-banded, or highest tolerable, dose to properly assess the efficacy of the treatment	56%	40%	4%	0%	**96%**
42	The decision to continue a patient on trofinetide should be guided by improvements in the patient's function and/or quality of life	88%	12%	0%	0%	**100%**
43	Documentation of improvements on trofinetide should be mainly based on caregiver and/or clinician observations, rather than the exclusive use of CGI-I or RSBQ assessments, as not all improvements can be captured by these assessments	80%	16%	4%	0%	**96%**
44	CGI-I and RSBQ assessments are primarily used as research instruments and not routinely used in clinical practice	72%	20%	8%	0%	**92%**
45	Improvements that may be meaningful to patients and caregivers are not always captured by CGI-I or RSBQ	64%	28%	8%	0%	**92%**
Domain E: Assessing and managing trofinetide tolerability						
46	Reducing a patient's trofinetide dose to a level at which side effects can be managed, or pausing and restarting on a lower dose with the intention to increase as tolerated, is preferable to stopping the dose entirely	72%	28%	0%	0%	**100%**
47	For patients experiencing severe side effects, their dosage should be reduced to a level at which they no longer experience side effects	88%	12%	0%	0%	**100%**
48	Should any side effect require dose reduction, the side effect should be carefully managed until it is safe to increase the dose again	80%	20%	0%	0%	**100%**
49	For patients experiencing severe and/or persistent side effects, healthcare providers should consider alternative underlying causes not related to trofinetide (e.g., diet, other medications)	36%	60%	0%	4%	**96%**
50	The healthcare provider should adapt the titration schedule first before introducing additional medications, such as Imodium, to manage diarrhea	52%	28%	20%	0%	**80%**
51	Fibrous foods such as bananas, peanut butter, avocado or fiber bars may be used to manage diarrhea	60%	36%	4%	0%	**96%**
52	For those receiving nutrition through gastrostomy, consider switching to an alternative brand of formula or a blenderized diet to improve digestive tolerance and manage diarrhea	32%	44%	20%	4%	**76%**
53	If a patient's stool becomes "peanut butter consistency", they should be encouraged to increase their fiber intake	32%	44%	24%	0%	**76%**
54	Imodium may be considered short-term (i.e., a few days) to manage severe diarrhea, but only if other options are unsuitable or ineffective, and should be discontinued as soon as clinically appropriate	48%	32%	12%	8%	**80%**
55	Ongoing monitoring and management of bowel activity is important, as patients may develop or redevelop constipation after their body adjusts to prolonged use of trofinetide	64%	36%	0%	0%	**100%**
56	Despite trofinetide's risk of diarrhea, maintaining adequate hydration and routinely monitoring bowel activity are important to prevent or minimize development or redevelopment of constipation as their body adjusts to trofinetide	80%	20%	0%	0%	**100%**
57	For patients experiencing severe side effects (i.e., incapacitating and/or preventing normal everyday activities), their dosage should be reduced to a level at which they no longer experience severe side effects	84%	12%	4%	0%	**96%**
58	Positioning the patient upright during trofinetide administration may be used to manage vomiting	28%	52%	16%	4%	**80%**
59	Smaller feeds, or slower rates of feed, may be used to manage vomiting	52%	44%	0%	4%	**96%**
60	A patient's trofinetide dose may be further divided into more doses (i.e., smaller volume) as needed to manage vomiting	40%	56%	0%	4%	**96%**
61	Proton pump inhibitors or H2 receptor antagonists may be used to suppress acid in an effort to reduce discomfort, the amount regurgitated, or feeding intolerance	56%	40%	4%	0%	**96%**
62	Prokinetic agents may be used in cases where impaired motility is suspected	40%	60%	0%	0%	**100%**
63	In the unlikely event that a patient experiences severe vomiting (i.e., incapacitating and/or preventing normal everyday activities) as a result of taking trofinetide, they should be referred to a GI specialist for further evaluation	40%	36%	12%	12%	**76%**
64	For patients with a history of medication refusal or administration difficulty, caregivers should avoid mixing trofinetide with the patient's main nutritional source, to reduce the risk of weight loss	48%	40%	8%	4%	**88%**
65	Based on limited data, trofinetide is generally accepted as "seizure neutral" (i.e., the majority will not experience changes in seizures, while the minority may experience improvement or worsening during treatment, depending on the individual patient)	64%	36%	0%	0%	**100%**
66	For patients experiencing administration difficulty, foods or liquids can be added to enhance taste	68%	28%	4%	0%	**96%**
67	For patients who have previously responded well to rewards or incentives, they can be used to facilitate medication adherence	56%	40%	4%	0%	**96%**
Domain F: Discontinuing or pausing trofinetide						
68	In general, trofinetide can be safely paused and restarted	84%	12%	4%	0%	**96%**
69	Pausing the dose is an option if a patient is traveling, hospitalized, or experiencing acute, severe side effects	76%	24%	0%	0%	**100%**
70	Discontinuing trofinetide should be a shared decision with the patient and/or caregiver(s)	84%	16%	0%	0%	**100%**
71	Trofinetide can be safely discontinued without tapering	60%	36%	4%	0%	**96%**
72	Stopping trofinetide may lead to the loss of improvements acquired during treatment, although further observation and research is required	44%	44%	8%	4%	**88%**

Presented at the 54th Annual Meeting of the Child Neurology Society (CNS) | 8-11 October 2025 | Charlotte, NC

ACADIA®