Canada's Drug Agency
L'Agence des médicaments du Canada

CDA-AMC REIMBURSEMENT REVIEW

Patient and Clinician Group Input

trofinetide (Daybue)

(Acadia Pharmaceuticals Canada Inc.)

Indication:

- For the treatment of Rett syndrome (RTT) in adults and pediatric patients 2 years of age and older and weighing at least 9 kg.

October 15, 2024

This document compiles the input submitted by patient groups and clinician groups for the file under review. The information is used by CDA-AMC in all phases of the review, including the appraisal of evidence and interpretation of the results. The input submitted for each review is also included in the briefing materials that are sent to expert committee members prior to committee meetings. **If your group has submitted input that is not reflected within this document, please contact Formulary-Support@cda-amc.ca.**

Disclaimer: The views expressed in this submission are those of the submitting organization or individual. As such, they are independent of CDA-AMC and do not necessarily represent or reflect the views of CDA-AMC. No endorsement by CDA-AMC is intended or should be inferred.

By filing with CDA-AMC, the submitting organization or individual agrees to the full disclosure of the information. CDA-AMC does not edit the content of the submissions received.

CDA-AMC does use reasonable care to prevent disclosure of personal information in posted material; however, it is ultimately the submitter's responsibility to ensure no identifying personal information or personal health information is included in the submission. The name of the submitting group and all conflicts of interest information from individuals who contributed to the

Patient Input Template for CADTH Reimbursement Reviews

Name of Drug: Trofinetide
Indication: Rett Syndrome (RTT)
Name of Patient Group: Cure Rett Canada
Author of Submission: Andree-Anne Racine, RN OIIQ#2092093, Cofounder

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1. About Your Patient Group

Cure Rett Canada is a patient advocacy organization committed to improving the lives of individuals with Rett syndrome (RTT) by bringing clinical trials and treatments to Canada. RTT is a rare neurodevelopmental disorder that leads to severe impairments in motor skills, cognitive function, and behavior. We focus on advocating for access to innovative treatments and clinical trials that can potentially change the course of the disease for individuals and families affected by RTT.

Our mission is to:

- Advocate for access to cutting-edge treatments and clinical trials in Canada for patients with RTT.
- Raise awareness about RTT and the urgent need for new therapies.
- Ensure equity of access to treatments for Canadian families, as many life-changing treatments and trials are often inaccessible to patients in Canada due to regulatory, cost, or geographical barriers.

For more information about our work, please visit our website: www.curerettcanada.com.

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2. Information Gathering

As part of our advocacy efforts, Cure Rett Canada has gathered feedback from families with experience using Trofinetide in the United States. The information reflects the highly variable experiences with the drug, with some families reporting significant improvements in motor function and communication, while others had to discontinue treatment due to side effects such as severe diarrhea.

- **Data Collection**: Insights were gathered via testimonies from parents who have used Trofinetide in the U.S. for their children.
- **Demographics**: Responses included a wide range of patients from different age groups and stages of RTT, with a mixture of positive and negative experiences.
- **Number of Respondents**: Hundreds of families shared their perspectives and experiences, providing valuable insights into the potential benefits and risks associated with Trofinetide.

While the data collected was from the U.S., it highlights the desperate need for access to this treatment in Canada for families who could benefit from it.

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3. Disease Experience

Rett syndrome is a devastating disorder, primarily affecting females, and leads to a progressive loss of motor skills, cognitive function, and communication abilities. Individuals with RTT often experience:

- Loss of purposeful hand movements
- Motor impairments (e.g., loss of ambulation)
- Severe cognitive regression and speech loss
- Seizures and other neurological complications

For families, Rett syndrome is an overwhelming condition that requires constant care, often 24/7. Caregivers face not only emotional and physical exhaustion but also financial challenges, as they may need to reduce working hours or quit their jobs to provide full-time care. In addition, many families in Canada struggle to access specialized clinical trials and innovative treatments, which further exacerbates the burden of the disease.

Key areas of RTT that need better treatment options include:

- Motor function
- Seizure management
- Cognitive and communication improvement

Innovative therapies like Trofinetide that address these challenges could have a profound impact on both patients and caregivers.

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4. Experiences With Currently Available Treatments

Currently, there are limited treatment options available for Rett syndrome:

- Anti-seizure medications
- Physical, occupational, and speech therapy
- Symptom management for motor impairments

While these therapies can help alleviate some symptoms, they do not address the underlying causes of Rett syndrome. Families often report dissatisfaction with the slow progress of symptom management, especially when it comes to motor skills and communication.

Additionally, accessing these treatments can be difficult and costly, especially for those who must travel long distances to specialized centers.

Despite these challenges, families are eager for new treatment options that can improve quality of life and provide a meaningful impact on RTT symptoms.

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5. Improved Outcomes

Families and caregivers of individuals with Rett syndrome express a desire for new treatments that can offer significant improvements in the following areas:

- **Motor function**, especially improvements in hand use and mobility
- **Cognitive and communication abilities**, to facilitate better interaction and social engagement
- **Seizure control**, to reduce the burden of seizures on daily life

If Trofinetide can show improvements in these areas, it would have the potential to transform the lives of patients and greatly reduce the burden on caregivers. However, the variable experiences with Trofinetide in the U.S. (including both positive and negative feedback) highlight the importance of ensuring patients in Canada have the right to try such therapies, even if the results may vary from patient to patient.

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6. Experience With Drug Under Review

Trofinetide has shown promise in clinical trials and compassionate use programs in the U.S. Some families report significant benefits, such as:

- Improved motor function and hand use
- Enhanced communication abilities and behavioral improvements
- Seizure reduction

However, side effects, especially gastrointestinal issues like diarrhea, have led some families to discontinue treatment. The high cost of the drug is another significant concern for families, as they worry about affordability and accessibility in Canada.

Trofinetide is currently the **only treatment approved and available globally** for Rett syndrome, making its availability particularly critical for Canadian families. Despite these challenges, there is strong support for Trofinetide within the RTT community. Families strongly believe that if the treatment is available and accessible, it should be covered by provincial healthcare to ensure equitable access for all Canadian families, especially those who wish to try it.

We advocate for access to treatment options like Trofinetide in Canada, as equal access to clinical trials and innovative therapies is crucial for fairness and improved outcomes for individuals with Rett syndrome.

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7. Companion Diagnostic Test

There is currently no companion diagnostic test for Trofinetide in the context of Rett syndrome. Families in Canada typically undergo genetic testing to confirm the MECP2 mutation that causes RTT, but there are no specific biomarker tests tied to Trofinetide.

While genetic testing for RTT is generally accessible in Canada, there are concerns about delays in obtaining results and limited access to specialized care for some families in remote areas.

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8. Anything Else?

Cure Rett Canada strongly advocates for equitable access to Trofinetide for Canadian families. Families of individuals with Rett syndrome are eager for new treatments and clinical trials, and there is growing demand to ensure fair access to drugs that show promise in improving quality of life. Despite the mixed experiences with Trofinetide in the U.S., it is crucial that Canadian families be allowed to access this treatment and participate in clinical trials. Ensuring that Canadian patients have the same opportunities as U.S. families is a matter of health equity.

Appendix: Patient Group Conflict of Interest Declaration

1. **Did you receive help from outside your patient group to complete this submission?**
   No.
2. **Did you receive help from outside your patient group to collect or analyze data used in this submission?**
   No.
   Company: None.
3. **List any companies or organizations that have provided your group with financial payment over the past 2 years AND who may have direct or indirect interest in the drug under review.**
   N/A

Certification

I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this patient group with a company, organization, or entity that may place this patient group in a real, potential, or perceived conflict of interest situation.

Name: Andree-Anne Racine, RN
Position: RN OIIQ#2092093, Cofounder
Patient Group: Cure Rett Canada
Date: 2024-10-06

Name: Rana Amache, PhD
Position: RN OIIQ#2092093, Cofounder
Patient Group: Cure Rett Canada
Date: 2024-10-06

CADTH

Patient Input Template for CADTH Reimbursement Reviews

Name of Drug: Daybue (Trofinetide)
Indication: Rett syndrome
Name of Patient Group: International Rett Syndrome Foundation
Author of Submission: Melissa Kennedy, Chief Executive Officer

1. About Your Patient Group

As the leading Rett syndrome research and advocacy organization, the International Rett Syndrome Foundation (IRSF) builds upon a 40-year commitment to breakthrough discoveries and life-changing advancements in research toward a cure while supporting families affected by Rett syndrome. IRSF fights for families living with Rett syndrome and a world without it. Learn more by visiting IRSF"s website.

2. Information Gathering

Patient input was gathered through multiple tools, including interviews held at an in-person family conference, conversations with caregivers and a survey sent to the families asking about their experiences with Daybue.

The live interview occurred at the 2024 IRSF ASCEND Family Conference held in Denver, CO USA on June 22nd The interviews were conducted as a Parent Panel titled: Real-Life Experiences with DAYBUE (trofinetide). All parents included on the panel have children who have been diagnosed with Rett syndrome. The panel of 3 parents as well as the moderator who is also a parent shared their experiences with Daybue. The parents on this panel have experience with administering Daybue to their children. The Children are all females and are 8, 6, 6, and 31 years of age.

The Comprehensive Care Guidelines were developed in collaboration with Rett syndrome experts throughout the US. This is a medical resource, intended for families to share with their providers to ensure their loved one receives the care that leading Rett syndrome experts recommend.

Lastly, the *Voice of the Patient Report: Living with Rett Syndrome* was prepared by the IRSF in collaboration with the Rett Syndrome Research Trust (RSRT) as a summary of input shared by people and families living with Rett syndrome during an Externally-Led Patient Focused Drug Development Meeting and from an online poll. The meeting was hosted virtually on March 11, 2022.

3. Disease Experience

Rett syndrome is a rare and devastating neurodevelopmental disorder that impacts nearly every aspect of an individual's life, including their ability to speak, walk, eat and even breathe.

> *In classic or typical Rett syndrome, individuals experience normal post-natal development followed by a period of developmental delay between six and 18 months of age. Between the ages of one and four years, individuals demonstrate a clear regression in speech and purposeful hand movements, begin to have mobility challenges, and display stereotypic hand movements. Individuals then experience a stationary or plateau phase, often with recovery or stabilization of cognitive and nonverbal communication skills. A proportion of the individuals living with Rett syndrome will experience a secondary loss of motor skills in their early teens, including rigidity or spasticity, often with some Parkinsonian features.*

Rett syndrome is characterized by neurological issues, developmental issues, severe disability, low tone, gait abnormalities, lack of hand use, and an absence of fine motor skills. Individuals living with Rett syndrome often develop movement disorders, including dystonia, or hyperkinetic movements. Between 80% to 90% of individuals living with Rett syndrome experience epilepsy, and behavioral issues can emerge as well.

Other prevalent symptoms include GI issues, including bowel dysmotility, constipation, and reflux. Feeding issues are common often requiring a feeding tube. Many individuals experience failure to thrive. Individuals often experience dysautonomia, including cold hands and feet, disordered breathing, and prolonged QT syndrome. Almost all individuals with Rett syndrome develop scoliosis with many having to undergo surgery. Other musculoskeletal issues may also arise including hip issues and contractures. Lung issues often occurring from aspiration and frequent pneumonias may occur. – Voice of the Patient

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"It's hard to pinpoint the top 1-3 concerns, as our child has about ten major issues that change in ranking based on the day, week, month, from pervasive gross and fine motor impairment, non-verbal, hypotonia, uncontrolled epilepsy, dysphagia, dystonia, osteopenia, sleep issues, underactive and withdrawn affect, sensory processing delays, incontinence … and more." – Mom of child with Rett, Voice of the Patient

When polled during the Externally-Led Patient Focused Drug Development Meeting, caregivers in attendance selected communication as their top health concern followed by impaired hand use or repetitive hand movements, gastrointestinal issues, mobility and balance issues, seizures, and breathing irregularities.

"Of all the symptoms of Rett Syndrome, I think that apraxia, by far, is the most challenging and frustrating for us all. It controls every part of her body, as apraxia is the inability to make and deliver correct movement instructions to the body. It results in difficulty with skilled movements even when a person has the ability and desire to do them. My daughter's body works. Her brain works. But something gets in the way of the message being sent from one to the other and she sometimes does the opposite." – Mom of child with Rett, Voice of the Patient

"The symptoms are so all encompassing, and they are ever rotating … It's just one thing leads to the next, and then a symptom might pop out that's just suddenly completely debilitating or destabilizing in some way and requires complete reorganization of everything." – Mom of 14-year-old with Rett, Voice of the Patient

"I feel like some days, we really are focused on the GI issues and the reflux and that's the most important thing and other days, it's the wheelchair and the cramps she's getting in her legs." – Mom of 15-year-old with Rett, Voice of the Patient

"[Our daughter] developed normally until 24 months doing what every child would do at that age, then Rett began to present itself. It was as if someone pulled the plug on everything. Over the next several months, she stopped playing with toys and sat with a blank stare on her face. It was as if she could no longer hear. We were very scared and didn't know what to do. What was wrong with our beautiful healthy daughter? Did we do something to cause this? … Within six months, uncontrollable hand ringing, continual biting of her fingers and severe hyper-ventilating began… Our path to seeking professional help began, yet no one could provide a definite diagnosis." – Dad to 52-year-old with Rett, Voice of the Patient

"The most frustrating thing about Rett syndrome is that no matter how hard our daughter works, Rett seems to continuously cause setbacks. She worked so hard to crawl and now cannot. She seemed about to walk with a walker, but regression took that dream away." - Mom of child with Rett, Voice of the Patient

"Perhaps the hardest thing about Rett syndrome is that [our daughter] understands everything. She follows every conversation. She laughs at every joke. She also understands what she can't do, and she's devastated by her disabilities. We often see her crying when she's looking at other kids at the park or in the neighborhood who are playing because she can't join them. – Mom of child with Rett, Voice of the Patient

"Rett affects all aspects of daily living for [our daughter]. She's unable to feed, toilet or dress herself. She needs constant supervision due to her epilepsy. Her sensory seeking needs make it dangerous for her to do a lot of activities. Sometimes she'll put things in her mouth or reach for things that she just shouldn't touch." – Parent to a 3-year-old with Rett, Voice of the Patient

"She is unable to communicate and tells us what she needs or wants. She needs supervision 24/7 to allow her to be able to eat, drink, play, anything that she may need or want." – Mom of child with Rett, Voice of the Patient

"Communication is number one and at the hub of the inability to do so many other things … That and hand use, I feel like if you had one or the other, then you'd be a whole lot better off because either they could do something for themselves or ask you to do it for them. When you don't have either, that's when the frustration starts." – Dad to a 3-year-old with Rett, Voice of the Patient

"Our daughter has chronic constipation and bad tummy aches daily, sometimes screaming in pain because she's so backed up and bloated. This of course hinders quality of life." - Mom of child with Rett, Voice of the Patient

"She ended up with just horrible bowel constipation and obstructions … and ended up spending six months, inpatient, in the hospital. And after that, … cardiac arrest. We were successfully able to bring her back from that." – Mom to a 21-year-old with Rett, Voice of the Patient

"He is a wheelchair user and his orthopedic impairments are getting worse as he ages. He is nine years old now and weighs 55lbs. He cannot bear weight anymore." – Mom of child with Rett, Voice of the Patient

"She had as many as 10 seizures per day with breath holding and vomiting, often causing bacterial pneumonia and hospitalizations. … Now with two medications and the VNS, she may have only two or three seizures a day, usually shorter duration than before." – Mom to a 43-year-old with Rett, Voice of the Patient

"The very natural, autonomic skill to nurse or drink a bottle was exhausting for him as an infant and became the initial reason for his first hospital stay of many due to failure to thrive. After an extensive stay in medical workup, [our son] came home with an NG tube to protect him from aspiration. This was a symptom to a larger problem, but no expert could figure it out. [His] ability to have a relatively coordinated swallow did not improve. The risk of aspirational pneumonia became greater, which then led to a G-Tube." – Mom to a 7-year-old with Rett, Voice of the Patient

"My daughter has insomnia every night of her life despite many interventions. The daytime is a nightmare with all of the symptoms discussed. Nighttime, for many, is even worse." – Mom of a child with Rett, Voice of the Patient

"Self-injurious behavior, which is probably the number one stressor for my family … because we just love him so much and to see him do that is indescribable, to be honest. We all move quickly to try to prevent it at all times and we all live sort of in

a hyper alert state because of it. … That has really altered everything in our family's life, and most importantly, his life." – Mom to a 14-year-old with Rett, Voice of the Patient

"Her breath holding episodes are so dangerous (she crumples to the ground and hits her head on things) that until we found the proper medication, we could not take her anywhere. Even now, the episodes can still occur at any time—just not as often." – Mom of a child with Rett, Voice of the Patient

4. Experiences With Currently Available Treatments

Until March of 2023 when Daybue became the first ever FDA approved drug treatment specifically for Rett syndrome, all individuals living with Rett required many medications, surgical interventions, therapies and equipment that had not been developed for Rett with the goal to manage the symptoms. When polled online, caregivers selected an average of 8.2 different medications and medical treatments they had tried in hopes of managing the symptoms of Rett. The poll also revealed that caregivers report that their current regimen of treatments only controls the symptoms "somewhat" or "very little."

"We've modified her diet [and] added a new medication almost every six months of her life to combat her reflux, her GI her seizure/dystonia episodes, her anxiety and sadness as her body takes more away from her. We have fought for continued OT, PT, augmentative communication, massage therapy and her right to be in the classroom." – Mom of a child with Rett, Voice of the Patient

"My daughter was five years old when she passed away last year from Rett syndrome complications. In her short five years, she bravely endured numerous treatments, procedures and therapies. … Though the surgeries, studies and hospitalizations aided her quality of life, they we not without cost. … Although we were extremely grateful for the therapies, we also know how much they required of her." – Mom to a 5-year-old child who died from complications of Rett, Voice of the Patient

"She has intractable epilepsy for which she has tried at least ten seizure meds – currently she is on four medicines twice a day and still experiences tonic-clonic seizures multiple times each day." – Mom of child with Rett, Voice of the Patient

The seizure medication absolutely squashes her personality and her ability to enjoy life." – Mom to a 24-year-old with Rett, Voice of the Patient

"When [scoliosis] surgery was finally done, they were not able to correct it all the way and she still remains quite curved. … After the surgery, she was able to walk short distances with assistance, but slowly began to lose strength and couldn't stand anymore." – Mom to a 43-year-old with Rett, Voice of the Patient

"We have put [our daughter] on anti-anxiety medications that don't seem to have an effect at a low dose and we worry about the ones recommended due to side effects … It's heartbreaking to see her filled with anxiety and sadness or pain and not know how to comfort her or how to treat her to alleviate what she is experiencing." – Mom of a child with Rett, Voice of the Patient

"It's been difficult because insurance does not want to pay for the PT and OT visits because they aren't seeing progress. Although we feel with Rett syndrome maintaining skills, and preventing regression is progress." – Mom of a child with Rett, Voice of the Patient

5. Improved Outcomes

Caregivers indicated in an online poll conducted for the *Voice of the Patient* found that therapies that result in even minor improvements in functions would result in enormous quality of life benefits for individuals living with Rett syndrome. The top two symptoms selected by caregivers as the most important for a possible new therapeutic to improve were communication/speech impairment and impaired hand use or repetitive hand movements. Other symptoms selected by caregivers include mobility or balance difficulties (36%), seizures were selected by 31% of the caregivers polled, GI symptoms (25%), breathing difficulties (23%) and emotional behavioral problems was selected by 11% of the caregivers.

"If she could speak and tell me in her own words, 'Dad, I need to go to the bathroom,' just the amount of dignity that would give her." – Dad to an 11-year-old child with Rett, Voice of the Patient

"For us, finding a treatment that improves her ability to communicate would be a godsend. Just to know what's bothering her when she's in pain (or what she wants for breakfast!) would be life-changing." – Dad of a child with Rett, Voice of the Patient

"Purposeful hand use … would open up so many doors for [our daughter] … So that she can have independence to be able to help feed herself, help turn a page of a book, to look at a book, simple things like that. But also, I think that it would go even further and help with communication because I know that if she had use of her hands, she can point to what she wants, point to where it hurts to tell me if something's hurting on her, point to picture cards to tell me what she needs and wants." – Mom to a 3-year-old child with Rett, Voice of the Patient

"If our children did not suffer chronic constipation the savings to the health insurers as a whole would be incredible, second only to the improved quality of life.

-No rushing a child to the ER because they have not passed stool in over 3 days, despite intervention;

-No causing your child pain on a regular basis due to enemas, laxatives (which cause gas pain), suppositories (which burn) or digital disimpaction;

-No GI emergencies such as perforated bowel and ensuing surgeries;

-Less chance of twisted bowel and, again, surgery;

-Less chance of death due to an unknown bowel obstruction, perforation or twisted bowel." – Mom of a child with Rett, Voice of the Patient

6. Experience With Drug Under Review

IRSF's Comprehensive Care Guidelines were developed in collaboration with Rett syndrome experts throughout the US. This is a medical resource, intended for families to share with their providers to ensure their loved one receives the care that leading Rett syndrome experts recommend. The Comprehensive Care Guidelines list Daybue as a Rett-specific treatment. To read and download the Comprehensive Care Guidelines visit IRSF's website.

Based on the results of a Phase 3 randomized controlled trial16, trofinetide was FDA approved in March 2023 for global symptom management in patients with Rett Syndrome over the age of 2 years. Patients with Rett Syndrome demonstrated statistically significant improvement on the Rett Syndrome Behavior Questionnaire (RSBQ) and the Clinical Global Impression – Improvement (CGI-I) score. Patients starting on trofinetide should be made aware of the very common gastrointestinal side effects and a management plan preemptively instituted. – Comprehensive Care Guidelines

"[Our daughter] has been on it (Daybue) since November of 2023. … Our experience has been, I guess good and bad. We are currently experiencing some side effects of diarrhea and still trying to manage that. At this point, we are currently not at full dose. We've been titrating up, we've titrated down. We're trying to find a sweet spot right now to help manage some of the side effects that we're experiencing. But overall, I have seen some improvements in my daughter. I definitely think from a communication standpoint, she is utilizing her eye gaze device more. She's more aware of her surroundings and I also think that she's just overall happier, just always has a smile on her face for the most part, which I think is a great improvement for her quality of life." – Mom of a child with Rett, Real-Life Experiences with DAYBUE

"The biggest improvement we have seen is her speech. So, when she started on the trial, she was speaking about five consistent words that has risen to about 15 consistent words and phrases. And then she also has a ton of sporadic words and phrases that she uses. … Her favorite phrase is, 'I did it.'" – Mom of a child with Rett, Real-Life Experiences with DAYBUE

Mom describing the side effect management for her daughter- "… we have to give her Daybue on a full stomach and we give her either banana or yogurt right after." – Mom of child with Rett, Real-Life Experiences with DAYBUE

"We have noticed that she's left hand dominant, so the easiest way for us to work with her on her hand usage is we hold that right hand down. She still taps a lot, so we hold that right hand down and whenever that left hand is free by itself, she can really, really see the improvements in her hand function and be able to really use that hand." – Mom of child with Rett, Real-Life Experiences with DAYBUE

"When she was a baby, she had status epileptic because since she went paralyzed on her right hand side for about a week and her right side, she just has pretty much ignored and now she's 31 and last month she extended her right arm for the first time since she was three years old." – Mom of child with Rett, Real-Life Experiences with DAYBUE

"… my daughter's on Daybue too and we haven't seen any improvements with breath holding and that is just such a struggle for us. But her gross motor has improved and she's doing things we haven't seen her do since she was three years old, like she's ambulatory, but now she can stand up from the floor unassisted, which she hasn't done since she was three. So, you're excited about some things and a little disappointed about other things, but it's also a time thing, what's going to happen in time." – Mom of child with Rett, Real-Life Experiences with DAYBUE

"The only thing we do find is when we travel, because her diet is a little bit different, eating airport food and junk food more, she does get more agitated with diarrhea and loose bowels whenever we do travel." – Mom of child with Rett, Real-Life Experiences with DAYBUE

"We had a little bit of an issue, because I was like, I want [my daughter] to start off at 15ccs and the insurance company was, you do know that's below efficacy and they wouldn't approve a 15cc prescription. So, we ended up just approving the 60 and I used whatever. But after we jumped that hurdle, everything was fine." – Mom of a child with Rett, Real-Life Experiences with DAYBUE

"She was three when she started [Daybue], and so she is walking up steps independently. I mean, she wasn't able to do that before. Her school says that she's the escape artist, she the runner. They're like, she might be the slowest one, but she's the runner and if you leave a door open, she's going to explore. Whereas before [Daybue] she was just taking just a few steps. So everything that she has done, she has actually surpassed where she was previously." – Mom of a child with Rett, Real-Life Experiences with DAYBUE

"We did not gain that skill back. So, I think just our experience in that, we haven't seen any progress in surpassing any of the things that she had prior to regression, but I do feel like the improvements that we have seen are enough for us to continue to stay on it." – Mom of a child with Rett, Real-Life Experiences with DAYBUE

"Our diarrhea was happening in the middle of the night, all times during the day. So that was the challenging part of trying to get that under control. We did try to move the timing of the dosing to see if that would make a difference. Unfortunately for us, it was happening." – Mom of a child with Rett, Real-Life Experience with DAYBUE

"Our daughter participated in the safety phase trial and the experience was exciting and promising. When the drug was approved, she began Daybue and we again saw good results (almost instantly). Our home was stocked with every possible medication to combat constipation or diarrhea. What we were not prepared for, however, was vomit. After 6 weeks on Daybue, she began vomiting. We were in constant contact with her doctors and with Acadia. At our doctor's suggestion, we stopped the drug for several weeks, restarted with a smaller dose and she vomited again. We then stopped for a longer period of time, restarted with a tiny dose, yet the vomiting still happened. We then decided that it was too dangerous for [our daughter] to continue taking Daybue. Of course we are all sad about Daybue not working for [our daughter] because we saw how it helped her overcome aspects Rett syndrome. But in the world of Rett, vomit is life-threatening. For now, it is not a good choice for us." – Mom to a 27-year-old with Rett, Conversation with a parent

7. Companion Diagnostic Test

8. Anything Else?

Appendix: Patient Group Conflict of Interest Declaration

To maintain the objectivity and credibility of the CADTH reimbursement review process, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This Patient Group Conflict of Interest Declaration is required for participation. Declarations made do not negate or preclude the use of the patient group input. CADTH may contact your group with further questions, as needed.

1. Did you receive help from outside your patient group to complete this submission? If yes, please detail the help and who provided it.

   No

2. Did you receive help from outside your patient group to collect or analyze data used in this submission? If yes, please detail the help and who provided it.

   Yes. The *Voice of the Patient Report: Living with Rett Syndrome* was a collaboration between IRSF and RSRT. Consulting partners include James Valentine, Esq. and Larry Baur, RN, MA from Hyman, Phelps & McNamara, P.C., a law firm that represents patient advocacy organizations and companies that are developing therapeutics and technologies to advance health. RSRT and IRSF contracted with Chrystal Palaty, PhD., from Metaphase Health Research Consulting Inc. for assistance in writing the report.

3. List any companies or organizations that have provided your group with financial payment over the past 2 years AND who may have direct or indirect interest in the drug under review.

Table 1: Financial Disclosures

Check Appropriate Dollar Range With an X. Add additional rows if necessary.

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Acadia				X
Neurogene			X	
Taysha				X
Anavex		X		
Anovo		X		

In 2024, IRSF received $360,000 from industry in the form of unrestricted educational grants and sponsorships.

I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this patient group with a company, organization, or entity that may place this patient group in a real, potential, or perceived conflict of interest situation.

Name: Melissa Kennedy
Position: Chief Executive Officer
Patient Group: International Rett Syndrome Foundation
Date: October 14, 2024

CADTH

CADTH

Patient Input Template for CADTH Reimbursement Reviews

Name of Drug: Daybue (Trofinetide)

Indication: Prescription medication used to treat Rett Syndrome in adults and children 2 years and older.

Name of Patient Group: Ontario Rett Syndrome Association (O.R.S.A.)

Author of Submission: Sabrina Millson, President of O.R.S.A.

1. About Your Patient Group

The Ontario Rett Syndrome Association (O.R.S.A.) exists to ensure that individuals with Rett Syndrome are enabled to achieve their full potential and enjoy the highest quality of life within their community. We are a volunteer, not-for-profit charity for parents, caregivers, researchers, medical professionals and other interested agencies and individuals. The association funds and supports, Canadian research initiatives, educational conferences, Rett syndrome clinics in Ontario and the Canadian Rett Syndrome Registry. O.R.S.A. advocates to the needs of individuals with Rett syndrome and their families provincially and nationally.

www.rett.ca

2. Information Gathering

Rett syndrome is a rare genetic neurological disorder that predominantly affects females, with symptoms typically becoming apparent between 6 months and 18 months of age. The disease burden of Rett syndrome on both patients and caregivers is significant and multifaceted, impacting various aspects of daily life and overall well-being. The information below was gathered by the Canadian Rett Syndrome Registry. The registry is a series of surveys for caregivers' to provide their unique experience caring for a Rett individual in Canada.

Based on 266 entries into the registry across Canada, here's an overview of the challenges faced by patients and caregivers:

Physical Challenges: Patients with Rett syndrome often experience severe physical impairments, including loss of purposeful hand skills, mobility issues, seizures, and difficulties with coordination and balance. These physical challenges can lead to increased dependence on caregivers for activities of daily living.

Communication Difficulties: Many individuals with Rett syndrome have severe communication impairments, including the inability to speak or limited verbal communication skills. This inability to effectively communicate needs and desires can lead to frustration and emotional distress for both the patient and caregivers.

Cognitive Impairments: Cognitive impairments are common in Rett syndrome, ranging from intellectual disability to learning difficulties. Patients may struggle with understanding and processing information, which can impact their ability to engage in educational and social activities.

Behavioral Issues: Behavioral issues such as anxiety, agitation, and mood disturbances are prevalent in Rett syndrome. Caregivers often face challenges in managing these behaviors and providing appropriate support to help patients cope with emotional difficulties.

Medical Complexity: Rett syndrome is associated with various medical complications, including respiratory problems, gastrointestinal issues, cardiac abnormalities, and osteoporosis. Managing these medical complexities requires frequent medical interventions and specialized care, placing additional strain on caregivers.

Financial and Social Impact: The financial burden of caring for a child or family member with Rett syndrome can be substantial, including expenses related to medical care, therapies, specialized equipment, and home modifications. Additionally, caregivers may experience social isolation and limited opportunities for employment or leisure activities due to the demands of caregiving.

Emotional Toll: Caring for a loved one with Rett syndrome can take a significant emotional toll on caregivers, leading to stress, anxiety, depression, and feelings of grief or guilt. The uncertainty of the future and the challenges associated with long-term care can exacerbate these emotional struggles.

Impact on Family Dynamics: Rett syndrome can disrupt family dynamics, placing strain on relationships and affecting the well-being of siblings and other family members. Caregivers may struggle to balance the needs of the individual with Rett syndrome with those of other family members, leading to feelings of resentment or neglect.

3. Disease Experience

Understanding Rett syndrome from the perspective of patients and caregivers provides valuable insight into the day-to-day challenges and quality of life impacts associated with the illness. Here's how Rett syndrome affects both patients and caregivers and highlights aspects of the illness that are particularly important to manage:

Patient Perspective

Physical Limitations: Patients with Rett syndrome often struggle with severe physical impairments, including loss of motor skills, mobility issues, and coordination difficulties. These limitations can significantly impact their ability to engage in daily activities independently.

Communication Challenges: Communication difficulties are a hallmark feature of Rett syndrome, with many patients experiencing limited or absent verbal communication abilities. The inability to express needs and desires can lead to frustration and feelings of isolation.

Sensory Sensitivities: Individuals with Rett syndrome may have heightened sensory sensitivities, making them particularly sensitive to noise, touch, or certain textures. These sensitivities can trigger discomfort or distress and require careful management to ensure a comfortable environment.

Medical Complications: Rett syndrome is associated with various medical complications, including seizures, gastrointestinal issues, and respiratory problems. Managing these medical challenges is crucial for maintaining the health and well-being of patients and improving their quality of life.

Emotional Well-being: Patients with Rett syndrome may experience emotional difficulties, including anxiety, agitation, and mood disturbances. Addressing these emotional needs and providing appropriate support is essential for promoting overall well-being and quality of life.

Caregiver Perspective

Physical Demands: Caregivers of individuals with Rett syndrome often face significant physical demands associated with providing hands-on care, assisting with mobility, and managing medical needs. These demands can be physically exhausting and place strain on caregivers' health and well-being.

Emotional Impact: Caring for a loved one with Rett syndrome can be emotionally taxing, leading to stress, anxiety, and feelings of sadness or grief. Witnessing the challenges and limitations faced by the patient can evoke feelings of helplessness and frustration.

Financial Strain: The financial burden of Rett syndrome can be substantial, with caregivers facing expenses related to medical care, therapies, specialized equipment, and home modifications. Managing these financial pressures can add to the stress and strain experienced by caregivers.

Social Isolation: Caregivers may experience social isolation due to the demands of caregiving, limiting opportunities for social interaction and support. Maintaining social connections and accessing respite care services are essential for preventing caregiver burnout and promoting well-being.

Aspects to Control

While all aspects of Rett syndrome are important to manage, some key areas include:

Medical Management: Effectively managing medical complications such as seizures, gastrointestinal issues, and respiratory problems is crucial for optimizing patient health and quality of life.

Communication Support: Providing appropriate communication support and assistive devices can significantly improve patients' ability to express themselves and engage with their environment.

4. Experiences With Currently Available Treatments

Unfortunately, there is no approved treatment or cure for Rett syndrome in Canada. Rett individuals and caregivers in Canada depend on medication intended to treat a specific issue for symptom control and/or management. As an example, Keppra (Levetriacetam) is often used to control seizures in patients with Epilepsy. In March 2023, the FDA approved the first drug specifically formulated for Rett syndrome patients. There is evidence from the U.S. population receiving the approved medication, DayBue, of positive outcomes with mild side effects, A First for Rett: FDA Approves Trofinetide for Treatment of Rett Syndrome! - International Rett Syndrome Foundation. We are advocating for the opportunity to provide the same level to Rett individuals living in Canada.

5. Improved Outcomes

Patients, caregivers, and families affected by Rett syndrome have valuable insights into the outcomes that should be considered when evaluating new therapies for the condition. Here are some key perspectives on desired improvements in treatment outcomes, potential impacts on daily life and quality of life, and the trade-offs involved in therapy choices:

Desired Improvements in Treatment Outcomes

Improved Communication Abilities: Patients and caregivers often prioritize improvements in communication abilities as a key outcome. They seek therapies that facilitate expressive and receptive communication skills, allowing individuals with Rett syndrome to better interact with others and express their needs and preferences.

Enhanced Motor Function: Another crucial outcome is improvements in motor function, including fine and gross motor skills. Therapies that help patients regain or maintain motor abilities can enhance independence and participation in daily activities.

Reduction in Seizures: Many individuals with Rett syndrome experience seizures, which can significantly impact their quality of life and overall health. New therapies that effectively reduce seizure frequency and severity are highly desirable for patients and caregivers.

Behavioral and Emotional Stability: Addressing behavioral and emotional challenges, such as anxiety, agitation, and mood disturbances, is essential for improving the well-being of patients and caregivers. Therapies that stabilize mood and reduce behavioral symptoms can enhance overall quality of life.

Disease Modification: Patients and caregivers are interested in therapies that not only alleviate symptoms but also target the underlying disease mechanisms. Disease-modifying treatments that slow or halt disease progression are highly sought after, as they have the potential to prevent long-term disability and improve outcomes.

Potential Impacts on Daily Life and Quality of Life

Increased Independence: A new treatment that improves communication and motor abilities could significantly enhance patients' independence and reduce their reliance on caregivers for daily tasks. This could lead to greater autonomy and a sense of empowerment for individuals with Rett syndrome.

Improved Social Interaction: Enhanced communication skills can facilitate greater social interaction and participation in activities with family members, peers, and the community. Improved social engagement can positively impact patients' quality of life and emotional well-being.

Reduced Caregiver Burden: Therapies that effectively manage symptoms and improve patient functioning can alleviate the physical, emotional, and financial burden on caregivers. This could lead to improved caregiver well-being and better family dynamics.

Enhanced Quality of Life: Overall, a new treatment that addresses the unmet needs of patients with Rett syndrome has the potential to significantly enhance quality of life for both patients and caregivers. It could lead to greater happiness, improved health outcomes, and a more fulfilling daily life experience.

Trade-offs in Therapy Choices

Efficacy vs. Side Effects: Patients, families, and caregivers must weigh the potential benefits of a therapy against its potential side effects. They may need to make trade-offs between symptom relief and the risk of adverse reactions.

Accessibility and Affordability: The availability and cost of therapies can influence treatment decisions. Patients and caregivers may need to consider factors such as insurance coverage, accessibility of specialized services, and out-of-pocket expenses when choosing a treatment.

Long-Term vs. Short-Term Benefits: Some treatments may offer immediate symptom relief but have limited long-term efficacy, while others may provide sustained benefits over time. Patients and caregivers must consider the trade-offs between short-term and long-term outcomes when selecting a therapy.

Impact on Daily Routine: The practicalities of integrating a new treatment into the patient's daily routine can also influence therapy choices. Patients and caregivers may need to consider factors such as treatment administration, frequency of appointments, and disruptions to daily life activities.

6. Experience With Drug Under Review

Patients may have gained access to Acadia's Trofinetide through various means, including participation in clinical trials, expanded access programs, compassionate use programs, or post-approval availability through private insurance coverage. Clinical trials are often the initial pathway for patients to access investigational drugs like Trofinetide. Additionally, some patients may have obtained Trofinetide through private insurance coverage or out-of-pocket expenses once the drug became commercially available.

Compared to previous therapies used for Rett syndrome, Trofinetide has shown promising benefits in clinical trials. These benefits include improvements in communication abilities, motor function, behavior, and overall quality of life for patients. Trofinetide's mechanism of action, targeting neuroinflammation and synaptic function, offers a novel approach to addressing the underlying pathophysiology of Rett syndrome.

However, like any medication, Trofinetide has potential disadvantages and side effects. Common side effects observed in clinical trials include gastrointestinal disturbances, fatigue, and irritability. While these side effects were generally manageable, they may have impacted patients' tolerability and adherence to treatment. Additionally, the long-term safety profile of Trofinetide requires further evaluation, as with any newly approved medication.

The benefits of Trofinetide in improving symptoms and quality of life can have a profound impact on patients, caregivers, and families affected by Rett syndrome. Improved communication abilities and motor function can enhance independence and social interaction for patients, while reductions in behavioral symptoms can alleviate caregiver burden and improve family dynamics. However, side effects and treatment-related challenges may necessitate additional support and management strategies from healthcare providers and caregivers.

In terms of ease of use, Trofinetide may offer advantages over previous therapies depending on factors such as route of administration, dosing frequency, and tolerability. For example, if Trofinetide is administered orally or via a convenient dosing regimen, it may be easier for patients and caregivers to integrate into their daily routines compared to more complex or invasive treatments.

Certain subgroups of patients with Rett syndrome may derive particular benefit from Trofinetide based on factors such as disease severity, genotype, age, and symptom profile. For example, patients with more severe motor and communication impairments or those with specific genetic mutations associated with synaptic dysfunction may be more responsive to Trofinetide therapy.

In terms of therapy sequencing, patients with Rett syndrome may have tried various interventions before and after Trofinetide, including medications for symptom management, behavioral therapies, and supportive care measures. Trofinetide may represent a novel treatment option for patients who have not responded adequately to existing therapies or who are seeking alternatives to current management strategies.

7. Companion Diagnostic Test

Not applicable

8. Anything Else?

There are several additional considerations that CADTH reviewers and the expert committee should be aware of when evaluating Trofinetide for Rett syndrome:

Long-Term Safety and Efficacy: While Trofinetide has shown promising results in clinical trials, ongoing post-marketing surveillance and real-world evidence collection are crucial for evaluating its long-term safety and efficacy. CADTH should consider the need for continued monitoring and assessment of Trofinetide's benefits and risks as more patients are treated in real-world settings.

Patient and Caregiver Perspectives: CADTH should prioritize the perspectives and preferences of patients, caregivers, and advocacy organizations representing individuals with Rett syndrome when assessing the value of Trofinetide. Input from these stakeholders can provide valuable insights into the real-world impact of Trofinetide on patient outcomes and quality of life.

Access and Affordability: CADTH should consider issues of access and affordability in its review of Trofinetide, including factors such as drug pricing, reimbursement policies, and patient assistance programs. Ensuring equitable access to Trofinetide for all eligible patients is essential for optimizing patient outcomes and reducing health disparities.

Comprehensive Benefit-Risk Assessment: CADTH should conduct a comprehensive benefit-risk assessment of Trofinetide, taking into account factors such as the magnitude of clinical benefit, the severity and frequency of adverse events, and the overall impact on patient outcomes and quality of life. Balancing the potential benefits of Trofinetide with its risks is essential for making informed treatment decisions.

Comparative Effectiveness: CADTH should consider any available comparative effectiveness data comparing Trofinetide to existing therapies or standard of care for Rett syndrome. Understanding how Trofinetide compares to other treatment options can help inform decision-making and resource allocation.

Unmet Medical Need: CADTH should assess the extent to which Trofinetide addresses unmet medical needs for individuals with Rett syndrome, including the severity and impact of symptoms, the availability of alternative treatments, and the potential for Trofinetide to fill gaps in current management strategies.

Health Economics and Budget Impact: CADTH should evaluate the health economic implications of Trofinetide, including its potential impact on healthcare costs, resource utilization, and budgetary considerations for provincial healthcare systems. Understanding the economic value of Trofinetide relative to its clinical benefits is essential for ensuring cost-effective allocation of healthcare resources.

Overall, a thorough and evidence-based review of Trofinetide by CADTH is critical for informing decision-making and ensuring optimal access to this promising therapy for individuals with Rett syndrome. By considering the perspectives of patients, caregivers, and healthcare stakeholders, CADTH can help facilitate informed treatment decisions and improve outcomes for individuals affected by this devastating condition.

Appendix: Patient Group Conflict of Interest Declaration

To maintain the objectivity and credibility of the CADTH reimbursement review process, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This Patient Group Conflict of Interest Declaration is required for participation. Declarations made do not negate or preclude the use of the patient group input. CADTH may contact your group with further questions, as needed.

1. Did you receive help from outside your patient group to complete this submission? If yes, please detail the help and who provided it.

We did not ask for help outside our patient group to complete this submission.

2. Did you receive help from outside your patient group to collect or analyze data used in this submission? If yes, please detail the help and who provided it.

We did not receive help from outside our patient group to collect or analyze data for this submission.

List any companies or organizations that have provided your group with financial payment over the past 2 years AND who may have direct or indirect interest in the drug under review.

Table 1: Financial Disclosures

Check Appropriate Dollar Range With an X. Add additional rows if necessary.

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Acadia Pharmaceuticals		x		
Taysha Gene Therapies			x	
Anavex Life Sciences	x			

I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this patient group with a company, organization, or entity that may place this patient group in a real, potential, or perceived conflict of interest situation.

Name: Sabrina Millson

Position: President

Patient Group: Ontario Rett Syndrome Association

Date: Aug 26, 2024

Ontario Rett Syndrome Association
Building Healthy Tomorrows

August 26, 2024

Dear CADTH Review Committee,

We are writing to express our strong support for the CADTH review of the first FDA-approved drug for Rett syndrome, Daybue. As caregivers to individuals living with Rett syndrome and members of our respective associations, we have witnessed firsthand the profound impact that Rett syndrome has on patients and caregivers across Canada. The approval of Daybue represents a significant milestone in the treatment of this devastating condition, offering hope and potential relief to individuals living with Rett syndrome and their families.

Rett syndrome is a rare neurodevelopmental disorder characterized by severe physical and cognitive impairments, including loss of motor skills, communication difficulties, seizures, and behavioral challenges. The burden of Rett syndrome on patients and caregivers is immense, encompassing physical, emotional, financial, and social challenges that affect every aspect of daily life.

The introduction of Daybue provides a glimmer of hope for individuals with Rett syndrome and their families. Clinical trials have demonstrated the efficacy of Daybue in improving communication abilities, motor function, and overall quality of life for patients with Rett syndrome. The approval of Daybue represents a breakthrough in the treatment of Rett syndrome and offers the potential to transform the lives of patients and caregivers across Canada.

We urge the CADTH review committee to carefully consider the evidence supporting the use of Daybue in the treatment of Rett syndrome and to prioritize the needs of patients and caregivers in their assessment. Access to Daybue has the potential to alleviate the burden of Rett syndrome, improve patient outcomes, and enhance the well-being of families affected by this condition.

On behalf of patients and caregivers in Canada, we respectfully request that CADTH expedite the review process for Daybue and ensure timely access to this life-changing therapy. Every day counts for individuals living with Rett syndrome, and the availability of Daybue represents a beacon of hope for those affected by this condition.

Thank you for your attention to this matter. We trust that CADTH will consider the needs of patients and caregivers in its review of Daybue.

Sincerely,

Sabrina Millson, President
Ontario Rett Syndrome Association
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[redacted]

With support of the following patient advocacy groups in Canada:

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CADTH

CADTH Reimbursement Review

Clinician Group Input

CADTH Project Number: SR0829-000
Generic Drug Name (Brand Name): Trofinetide (TBC)
Indication: For the treatment of Rett syndrome (RTT) in adults and pediatric patients 2 years of age and older
Name of Clinician Group: Members of Canadian Rett Syndrome Consortium; Advisory Board Members for Acadia Pharmaceuticals Inc. for drug Trofinetide
Author of Submission:
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1. About Your Clinician Group

Please describe the purpose of your organization. Include a link to your website (if applicable).

We are a group of pediatric neurologists, developmental pediatricians, and medical geneticists in Canada, caring for children, youth and adults with Rett syndrome and investigating ways for changing outcomes for this very underserved group of patients. We are active participants of the pan-Canadian Rett Syndrome consortium network, that has been active since 2020. The aim of this consortium is to bring together the country's leading clinical, scientific, technical, and patient/caregivers' expertise on one platform to improve clinical supports, treatment and research collaboration for patients affected with Rett syndrome. The consortium's primary goal is to establish a standardized approach to managing, monitoring and treating Rett patients across Canada, particularly enabling access to novel and emerging therapies for this rare disorder. Our secondary goal is to build effective research infrastructure, particularly clinical trials capacity, for this rare neurodevelopmental disorder.

2. Information Gathering

Please describe how you gathered the information included in the submission.

Clinicians and researchers with experience in treating and caring for Rett syndrome (RTT) patients were asked to participate and contribute to this submission. The participating clinicians' expertise and particular interest in Rett syndrome is evident from their clinic and patient population, participation in the Canadian Rett syndrome Consortium, the Ontario Rett Syndrome Association (ORSA) and various other rare neurodevelopmental disease registries and their familiarity with and review of the new emerging data from clinical trials on treatments for Rett syndrome, and, specifically for Trofinetide. Given the expertise and background experience, these clinicians have also served as site investigators and advisory board members for the clinical trials that have been undertaken or currently ongoing for various rare neurodevelopmental disorders. In addition, the contributing physicians are well connected to the parents and caregivers of RTT patients and are hence able to provide valuable direct caregiver related input.

Rett syndrome (RTT) typically manifests around the age of 3 years and mainly affects females and rarely males (1-3). It is caused by de novo pathogenic variants in the MeCP2 gene. The MeCP2 gene codes for the methyl-CpG-binding protein 2 (MeCP2) that plays an important role in neuronal maturation and repair (1). RTT patients experience lack or deficiency of MeCP2, that in turn results in abnormal neuronal maturation and repair. Clinically, RTT disease manifests with characteristic pathognomonic clinical features consisting of gradual loss of motor function and development of hand motor stereotypies, loss of verbal and social communication skills, seizures/epilepsy, and varying impairments in behavior, sleep, breathing and gastrointestinal motility functions (1-3). Natural history data suggests a variable course for RTT patients after the initial gradual phase of symptom onset and progression. Most RTT girls demonstrate overall symptom stabilization by the ages of 4-5 years, whereas some only stabilize for a short duration interval and then go through another phase of motor deterioration around the ages of 8-9 years, that extends for a few years to the remainder of patient's lifespan. This second phase consists of a severe and complete loss of residual motor function (including ambulation), worsening or disappearing hand stereotypies, muscle wasting, poor postural control and development of movement disorder (typically rigidity and dystonia) (1,3,4). As a result, RTT patients require ongoing caregiver support and supervision and both caregiver and direct medical and rehabilitative management of patient, that is specifically targeted towards various RTT symptoms to assist with activities of daily living (ADL's) and overall quality of life for both patient and their caregivers (5,6). There is currently no cure. Management is aimed at various symptom-based management strategies and providing rehabilitating therapies (5).

3. Current Treatments and Treatment Goals

Please describe the current treatment paradigm for the disease.

- Focus on the Canadian context.
- Please include drug and non-drug treatments.
- Drugs without Health Canada approval for use in the management of the indication of interest may be relevant if they are routinely used in Canadian clinical practice. Treatments available through special access programs are relevant. Are such treatments supported by clinical practice guidelines?
- Do current treatments modify the underlying disease mechanism? Target symptoms?
- What are the most important goals that an ideal treatment would address?
- **Examples:** Prolong life, delay disease progression, improve lung function, prevent the need for organ transplant, prevent infection or transmission of disease, reduce loss of cognition, reduce the severity of symptoms, minimize adverse effects, improve health-related quality of life, increase the ability to maintain employment, maintain independence, reduce burden on caregivers.

Given the devastating symptoms and life-long course of RTT disease, clinical trials have focused on developing therapeutic strategies and interventions that would facilitate the function of MeCP2 protein, thereby providing either a complete or partial cure and reversal or improvement in RTT disease/symptoms. Unfortunately, to date, efforts to develop and find a cure for this devastating disorder have not been successful. Current treatment is aimed at symptomatic management.

Trofinetide (Daybue) is the first new drug treatment that has been shown to target and improve the of RTT through clinical trials. Trofinetide has been recently approved for the treatment of RTT by the United States Food and Drug Administration (FDA) in March of 2023 (7).

Clinical trials data from 3 studies (Lavender, LILAC and LILAC-2) have shown that treatment with Trofinetide compared to placebo results in improvement of patients' overall function and behavior, thereby improving quality of life from both clinician and care givers' perspective (8,9.10). In addition, treatment with Trofinetide is safe since most patents that received Trofinetide did not develop severe, irreversible, unmanageable and/or life-threatening adverse events. Data from LILAC-2 has also confirmed that longer duration and ongoing continued treatment is associated with sustained efficacy and safety of Trofinetide, making this drug first and only drug for symptomatic treatment of RTT patients to achieve FDA approval in the United States (7).

Most importantly, the safety and efficacy of Trofinetide in treating RTT symptoms is supported by the real-world data obtained from the parents/care givers of RTT patients enrolled in the LILAC 2 study and published recently (11). The study results confirm the consistent high satisfaction rates, lack of any significant safety concerns and meaningful improvements in quality of life of RTT patients from the parental/caregiver's perspective.

Further analysis of data from these 3 studies also suggest that Trofinetide likely influences the progression of overall disease (slowing or delaying disease manifestations). However, this requires further exploration through more, preferably larger, multicenter clinical studies (11).

4. Treatment Gaps (unmet needs)

4.1. Considering the treatment goals in Section 3, please describe goals (needs) that are not being met by currently available treatments.

- Not all patients respond to available treatments
- Patients become refractory to current treatment options
- No treatments are available to reverse the course of disease
- No treatments are available to address key outcomes
- Treatments are needed that are better tolerated
- Treatments are needed to improve compliance
- Formulations are needed to improve convenience

Please describe limitations associated with current treatments (e.g., adverse events, administration, etc., if applicable).

There is currently no approved treatment in Canada for the treatment of Rett syndrome. Existing medications are not treating Rett syndrome; they are part of supportive therapy to attempt to improve quality of life by managing associated symptoms such as seizures, muscle stiffness, sleep and breathing issues, gastrointestinal distress and behavioral and mental health challenges among others. Other types of interventions such physical and occupational therapy, and speech and language therapy, have been supporting movement (walking /balance), and communication but the vast majority of children, youth and adults with Rett syndrome show a progressively worsening course in their ability to ambulate, loss the functional use of their hands, limited ability to effectively communicate.

No medications to-date have targeted the underlying biology, changed the core symptoms described above, or the course of the disease and the deteriorating developmental trajectory characteristic of this condition. Trofinetide is the first medication to change overall core features of the condition such as communication, motor abilities and has shown promise in changing developmental trajectory of the condition. It is unique in this space and first in class

5. Place in Therapy

5.1. How would the drug under review fit into the current treatment paradigm?

Is there a mechanism of action that would complement other available treatments, and would it be added to other treatments?

Although trofinetide has been shown to impact the mechanism predicted by the genetic mutation in Rett syndrome in preclinical studies, its exact mechanism of action in this condition remains unknown.

Is the drug under review the first treatment approved that will address the underlying disease process rather than being a symptomatic management therapy?

Yes, it is the first FDA approved medication specifically for the treatment of Rett syndrome. Based on available clinical trials results it has a favorable effect on core aspects of clinical Rett syndrome manifestations including increased alertness and communication skills, and amelioration of movement disorder.

Would the drug under review be used as a first-line treatment, in combination with other treatments, or as a later (or last) line of treatment?

It would be used as a first line treatment. Other medications may be added to address associated symptoms tailored to each individual patient needs.

Would the drug under review be reserved for patients who are intolerant to other treatments or in whom other treatments are contraindicated?

No, the drug would be used as a first line for all patients with Rett syndrome who have known clinical manifestations of Rett syndrome consistent with health Canada approval specifications

Is the drug under review expected to cause a shift in the current treatment paradigm?

It is expected to potentially facilitate other rehabilitation therapies by means of increased alertness and communication but is not expected to replace medication or therapies for associated symptoms such as epilepsy or tone management.

Please indicate whether or not it would be appropriate to recommend that patients try other treatments before initiating treatment with drug under review. Please provide a rationale for your perspective.

There is no overlap with other therapies, this is the first treatment for core symptoms of Rett Syndrome, therefore there is no indication to recommend that patients try other therapies before trofinetide.

5.2. Which patients would be best suited for treatment with the drug under review? Which patients would be least suitable for treatment with the drug under review?

Which patients are most likely to respond to treatment with drug under review?

The evidence from clinical trials suggests a benefit for RTT patients between the ages of 5 to 22 years. There is no indication that other features predict better response to trofinetide and as no recommendation can be made about groups of patients that may be more likely to respond.

Which patients are most in need of an intervention?

Patients who have developed symptoms and signs of Rett syndrome.

Would this differ based on any disease characteristics (e.g., presence or absence of certain symptoms, stage of disease)?

No

How would patients best suited for treatment with drug under review be identified (e.g., clinician examination/judgement, laboratory tests (specify), diagnostic tools (specify))

Formal diagnosis of Rett syndrome by accepted international standards by a license physician.

Are there any issues related to diagnosis?

There are no issues.

Is a companion diagnostic test required?

Patients suspected of having Rett syndrome based on clinical criteria currently also have genetic testing for pathological variants. This is part of standard of care and no additional testing is required

Is it likely that misdiagnosis occurs in clinical practice (e.g., underdiagnosis)?

It is unlikely. Rett syndrome is being diagnosed by clinicians with expertise in this condition, and genetic testing is part of the workup.

Is it possible to identify those patients who are most likely to exhibit a response to treatment with drug under review?

There is no evidence of a subgroup particularly likely to respond more than others with existing data.

5.3 What outcomes are used to determine whether a patient is responding to treatment in clinical practice? How often should treatment response be assessed?

Are outcomes used in clinical practice aligned with the outcomes typically used in clinical trials?

What would be considered a clinically meaningful response to treatment? Consider the magnitude of the response to treatment. Is this likely to vary across physicians?

Examples: improved survival; reduction in the frequency/severity of symptoms (provide specifics regarding changes in frequency, severity, etc.); attainment of major motor milestones; ability to perform activities of daily living; improvement of symptoms; and stabilization (no deterioration) of symptoms.

Are outcomes used in clinical practice aligned with the outcomes typically used in clinical trials?

No. Clinically, physicians will rely largely on caregiver reports of improvements in symptoms related to Rett Syndrome, and in particular, elements of communication and interaction. While the RSBQ, a 45-item rating scale completed by the caregiver that assesses a range of symptoms of Rett syndrome (breathing, hand movements or stereotypies, repetitive behaviors, night-time behaviors, vocalizations, facial expressions, eye gaze, and mood), is a comprehensive and relevant rating scale, the ability to perform the RSBQ on a routine clinical basis will be limited by resource limitations, parent burden, and clinical time constraints. However, where able, clinicians may elect to do the RSBQ to longitudinally track changes to disease-related symptoms. The Clinical Global Impression-Improvement Scale (CGI-I) likewise could be used where clinic time and resources allow, however this may not be feasible in many care provision settings.

What would be considered a clinically meaningful response to treatment? Consider the magnitude of the response to treatment. Is this likely to vary across physicians?

Reduction in frequency and severity of symptoms, in particular, ability to communicate (through verbal and non-verbal means), level of alertness and engagement, improvements in respiratory symptoms, decreases in hand movements, repetitive movements or stereotypies, and improvements in ability to move independently. Assessing for clinically meaningful response would also rely on family/caregiver's overall impression of improvements in symptoms and satisfaction with outcomes as compared to any potential side effects of medication.

5.4 What factors should be considered when deciding to discontinue treatment with the drug under review?

Examples: disease progression (specify, e.g. loss of lower limb mobility); certain adverse events occur (specify type/frequency/severity); or additional treatment becomes necessary (specify).

Considerations for discontinuation of Trofinetide:

1. Persistent moderate to severe diarrhea which is not controlled with appropriate medications for symptomatic relief and/or lower dose of trofinetide.
2. Persistent vomiting with weight loss which is not controlled with appropriate medications for symptomatic relief and/or lower dose of trofinetide.
3. Lack of improvement in symptoms (e.g. communications, behavior, awareness) after 6 to 12 months of therapy, based on existing published literature.

5.5 What settings are appropriate for treatment with [drug under review]? Is a specialist required to diagnose, treat, and monitor patients who might receive [drug under review]?

The drug will likely initially be prescribed in **specialized medical centers on an outpatient basis**: Treatment will first be conducted in specialized medical centers with experience in managing Rett syndrome and access to multidisciplinary teams (clinicians, child therapists, pharmacists, etc.

Over time, with education and experience, community physicians, such as pediatricians or internists will likely prescribe the drug.

When the drug is first available, it is likely that specialists managing patients with Rett Syndrome, including pediatricians, pediatric and adult neurologists, and clinicians involved in Rett clinics will likely prescribe the drug **in outpatient clinics**. Specialists are equipped to determine whether the drug is an appropriate treatment option based on the individual's specific circumstances. They can also evaluate any comorbid conditions and develop a holistic treatment plan that may accompany the use of the drug.

Monitoring: Careful monitoring will be important. After prescribing the drug, clinicians will closely observe the patient for any adverse effects, assess the effectiveness of the treatment, and adjust the management plan as needed in follow-up appointments.

Education: The specialists will play a role in educating community physicians, such as general pediatricians, internists and general practitioners about the drug, including potential adverse effects, and how to manage them. Education will be done via clinic notes, clinical handouts, phone calls between specialists and community physicians and educational rounds. Community physicians will play a key role to monitor symptoms and clinical changes, with the specialists. Specialists will also educate the multidisciplinary team involved in Rett syndrome (such as speech therapists, occupational therapists, and psychological support) who provide comprehensive care tailored to the patient's needs. This team will be important to also document the effects of the drug on the patient, including clinical improvements in different settings.

6. Additional Information

Rett syndrome is a complex neurological disorder that profoundly affects the lives of individuals and their families. While the clinical symptoms may vary significantly between patients, even minor improvements in specific areas can lead to substantial changes in the overall quality of life for both the individual affected and their family members.

1. **Daily Challenges**: Many families caring for a child with Rett syndrome face daily challenges that can be physically and emotionally exhausting. These challenges include managing complex medical needs, dealing with behavioral issues, and providing round-the-clock care.
2. **Quality of Life Factors**:
    - **Sleep**: One of the key difficulties for families is nighttime sleep disturbances. When a child with Rett syndrome has trouble sleeping, it not only impacts them but also affects the entire family. Parents may struggle with fatigue, which can affect their mental health and ability to support their child.
    - **Communication**: Effective communication is a critical aspect of family interaction. Even small improvements in a child's ability to communicate—whether through words, gestures, or eye movements—can significantly enhance

the emotional connection between the child and their family. It allows for a greater understanding of their needs and desires, fostering a sense of independence and expression.

- **Respiratory Issues**: Hyperventilation or breathing difficulties can lead to anxiety for both the child and their caregivers. If these symptoms are reduced, families can experience less stress and worry, allowing them to focus on enjoying their time together rather than managing medical crises.

3. **Emotional Impact**: The emotional toll of caring for a loved one with Rett syndrome can be immense. Families often experience feelings of isolation, grief for the "typical" development that may never occur, and anxiety about the future. Small clinical improvements can alleviate some of this emotional burden, helping families to feel more hopeful and engaged.
4. **Togetherness and Quality Time**: Improvements in daily functioning—like being able to sleep through the night, engage in meaningful communication, or breathe comfortably—allow families to create more normal, joyful experiences together. This could mean enjoying family activities, celebrating milestones, or simply having peaceful moments at home. These shared experiences are invaluable, contributing to strengthened family bonds.

Therefore, while Rett syndrome presents many challenges, focusing on small clinical differences can lead to significant enhancements in the quality of life for both the individual and their family. Recognizing these small victories can provide hope and motivation for families navigating this complex condition.

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7. Conflict of Interest Declarations

To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the clinician group input. CADTH may contact your group with further questions, as needed. Please see the *Procedures for CADTH Drug Reimbursement Reviews* (section 6.3) for further details.

1. Did you receive help from outside your clinician group to complete this submission? If yes, please detail the help and who provided it.

   No

2. Did you receive help from outside your clinician group to collect or analyze any information used in this submission? If yes, please detail the help and who provided it.

   No

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review. **Please note that this is required for each clinician who contributed to the input — please add more tables as needed (copy and paste). It is preferred for all declarations to be included in a single document.**

Declaration for Clinician 1

Name: Mubeen Rafay
Position: Associate Professor, Pediatric Neurologist
Date: 11-10-2024

☒ **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 1: Conflict of Interest Declaration for Clinician 1

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Acadia Pharmaceuticals Canada Inc.		X		
Add company name				
Add or remove rows as required				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 2

Name: Anita Datta
Position: Clinical Associate Professor
Date: 11-10-2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 2: Conflict of Interest Declaration for Clinician 2

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Acadia Pharmaceuticals		x		
Jazz	x			
Takeda	x			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 3

Name: Evdokia Anagnostou
Position: Child Neurologist, Professor of Pediatrics, University of Toronto; Senior clinician Scientist, Holland Bloorview Kids Rehabilitation Hospital; VP research and Director of Research Institute, Holland Bloroview Kids Rehabilitation Hospital, Toronto, ON
Date: 12-10-2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 3: Conflict of Interest Declaration for Clinician 3

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Acadia Pharmaceuticals Canada Inc.		X		
F. Hoffmann-La Roche Ltd * Switzerland	X			
Impel Pharmaceuticals Inc, USA*	X			
Ono Pharmaceutical Co, Japan*	X			
Add or remove rows as required				

* Place an X in the appropriate dollar range cells for each company. I have contributed to advisory board consultations to provide expert opinion on interpretation of efficacy and safety data, Canadian context information about how to best potentially think of future integration into clinical practice, and support of patients and families during early stages of future availability.

**** Research funding from F. Hoffmann-La Roche Ltd, Impel Pharmaceuticals Inc, USA, Ono Pharmaceutical Co, Japan**

Declaration for Clinician 4

Name: Victoria Mok Siu
Position: Medical Geneticist, Associate Professor, Western University
Date:11-10-2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 2: Conflict of Interest Declaration for Clinician 2

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Acadia Pharmaceuticals Canada Inc.		X		
Add company name				
Add or remove rows as required				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 5

Name: Erick Sell
Position: Pediatric Neurologist, Associate Professor, Department of Pediatrics, Children's Hospital of Eastern Ontario, Ottawa.
Date: 11-10-2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 5: Conflict of Interest Declaration for Clinician 5

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Acadia Pharmaceuticals Canada Inc.		X		

Add company name				
Add or remove rows as required				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 6

Name: Natarie Liu
Position: Assistant Professor, Pediatric Neurologist, Epileptologist
Date: 12-10-2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 5: Conflict of Interest Declaration for Clinician 5

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Acadia Pharmaceuticals Canada Inc.		x		
Jazz Pharmaceuticals	x			
MPI Research	x			

* Place an X in the appropriate dollar range cells for each company.