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

Reimbursement Recommendation

Reimbursement Recommendation

(Draft)

Trofinetide (Daybue)

Indication: For the treatment of Rett syndrome in adults and pediatric patients 2 years of age and older and weighing at least 9 kg.

Sponsor: Acadia Pharmaceuticals Canada Inc.

Recommendation: Do Not Reimburse

Publication Date: April 2025

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Recommendation

The CDA-AMC Canadian Drug Expert Committee (CDEC) recommends that trofinetide not be reimbursed for the treatment of Rett syndrome in adults and pediatric patients 2 years of age and older and weighing at least 9 kg.

Rationale for the Recommendation

Rett syndrome is a rare, incurable, neurodevelopmental disorder with substantial morbidity and a lack of effective disease-modifying treatments available. Furthermore, current supportive therapies do not sufficiently manage the disease. CDEC acknowledged that there is considerable disease heterogeneity and the absence of standardized outcomes used in clinical practice that contribute to the uncertainty in the clinical evidence available to assess the effects of trofinetide. Patients, caregivers, and clinicians identified a need for safe and effective treatments that improve communication skills, motor skills, HRQoL, caregiver burden, and comorbidities of Rett syndrome; however, based on the available evidence, CDEC could not conclude that trofinetide meets this need.

Evidence from 1 double-blind, randomized controlled trial (LAVENDER, N = 187) in female patients aged 5 to 20 years weighing at least 12 kg diagnosed with classic or typical Rett syndrome and a documented *MECP2* variant demonstrated that, compared with placebo, 12 weeks of treatment with trofinetide resulted in improvements in neurobehavioural symptoms associated with Rett syndrome as measured by the Rett Syndrome Behaviour Questionnaire (RSBQ) (–3.1 points; 95% confidence interval [CI], –5.7 to –0.6 points) and overall clinical improvement as measured by the Clinical Global Impression – Improvement (CGI-I) score (–0.3 points; 95% CI, –0.5 to –0.1 points). Although the results for the RSBQ and CGI-I were statistically significant in favour of trofinetide over placebo, it was uncertain whether the results were clinically meaningful as no minimally important differences (MIDs) have been established. Additionally, 24.7% of patients who received trofinetide, and 9.6% of patients who received placebo discontinued from the LAVENDER trial, and up to 16% of patients in the trofinetide group and 9% of patients in the placebo group had missing data for the coprimary end points. There is also limited evidence supporting the use of the RSBQ in measuring treatment effects and the instrument is not commonly used in clinical practice. Results for other outcomes of importance to patients, caregivers, and clinicians, including communication, motor skills, and caregiver burden, were uncertain due to the lack of standardized measures and a validated MID. Because of these limitations, the committee could not determine if trofinetide addressed these unmet needs or if the results from the trial translate to meaningful benefits in a real-world setting. There was also no comprehensive measure of HRQoL in the LAVENDER trial, which is a primary goal of treatment for patients with Rett syndrome, and the impact trofinetide has on this outcome for either patients or caregivers remains unknown.

Discussion Points

- **Criteria for Significant Unmet Need:** CDEC noted that there was uncertainty with the clinical evidence; therefore, the committee deliberated on trofinetide considering the criteria for significant unmet need described in the Procedures for CDA-AMC Reimbursement Reviews. CDEC acknowledged the rarity of this condition and concluded that the criteria allowing for additional uncertainty in the evidence were met. However, CDEC concluded that the submitted evidence was insufficient to determine the value of trofinetide as a treatment option for patients with Rett syndrome in Canada.
- **Unmet Needs:** CDEC considered the patient population, severity of the condition, and the lack of disease-modifying treatments indicated for Rett syndrome, all of which represent a significant unmet need for this population. CDEC noted that currently available therapies are only supportive in nature and only partially manage the multisystem symptoms of the disease. Beyond the lack of a disease-modifying treatment options, the committee also acknowledged that nonpharmacologic supportive care (e.g., speech therapy, physiotherapy) may not currently be insured for Rett syndrome through public health plans. As such, they discussed how accessing supportive care can add additional financial strain for families unable to access public coverage through alternative diagnoses (e.g., autism spectrum disorder) or without a private insurance plan. While this may create significant inequities in accessing care for all patients with Rett syndrome, the committee noted how this was likely exacerbated for people living in rural or remote locations where specialized supportive care may not be readily available even if funding exists.
- **Relevance of Trial Outcomes and Trial Duration:** CDEC deliberated on the appropriateness of the trial outcomes. The committee noted that none of the outcomes used in the trial are standard in clinical practice in Canada, challenging the interpretation on the effect of trofinetide on patients with Rett syndrome. Furthermore, there was a lack of evidence on the impact of trofinetide on HRQoL (one of the main goals of treatment for this patient population) or if the drug provides relief

of the comorbidities related to Rett syndrome. CDEC also noted that Rett syndrome is a lifelong disease and emphasized that the 12-week duration of the LAVENDER trial is not adequate to determine meaningful, long-term changes in important outcomes such as motor skills, communication, and potential harms. Though there was evidence from the open-label extension (OLE) studies which provided data for up to 104 weeks, the open-label design, lack of comparator, and potential attrition bias contributed to the uncertainty of the evidence.

- **Certainty of Evidence:** CDEC discussed the pivotal evidence submitted for this review which consisted of 1 phase III, randomized controlled trial (LAVENDER). The results for the coprimary end points of change from baseline in RBSQ and CGI-I were statistically significant in favour of trofinetide over placebo at 12 weeks (LSM difference, –3.1 points [95% CI, –5.7 to –0.6 points] for the RSBQ and –0.3 points [95% CI, –0.5 to –0.1 points] for the CGI-I). CDEC highlighted that the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) assessment of the evidence suggested that the certainty of these results was very low, primarily due to missing data, differences between the trial population and reimbursement request, and lack of established MIDs. The committee noted that there are no established or validated MIDs for the coprimary end points, but recognized the thresholds suggested by the clinical experts of 3 points for change from baseline in RBSQ and 1 point change for CGI-I. CDEC questioned whether a 3-point change in the 90-point RSBQ scale is meaningful and relevant. CDEC noted that while the threshold for the RSBQ was reached, the threshold for the CGI-I was not achieved. The 95% CI for the RSBQ included the possibility of benefit and no benefit, and for the CGI-I there was no benefit. This, in addition to the reasons for the very low certainty of evidence rating, precluded CDEC from making firm conclusions on the effectiveness of trofinetide in patients with Rett syndrome.
- **Harms and Treatment Withdrawal:** CDEC discussed the adverse events (AEs) profile of trofinetide from the LAVENDER study, emphasizing the high incidence of diarrhea and vomiting which occurred in 80.6% and 26.9% of patients in the trofinetide group compared to 19.1% and 9.6% in the placebo group, respectively. Additionally, CDEC noted the high rate of discontinuation due to AEs in the trofinetide group compared to placebo (17.2% vs. 2.1%). Elevated rates of diarrhea and vomiting were also observed in the long-term LILAC and LILAC-2 extension studies, as well as the supportive DAFFODIL and LOTUS studies, with AEs being the primary reason for discontinuation.
- **Supportive Studies:** CDEC discussed the results of 2 OLE studies (LILAC and LILAC-2) and 2 studies addressing gaps in the evidence (DAFFODIL and LOTUS). Results of the additional supportive studies were generally consistent with the LAVENDER trial. However, CDEC noted limitations of the OLE studies, including the lack of comparator, likelihood of selection bias (the population consisted of patients who completed LAVENDER – i.e., responders and patients who tolerated the treatment), and high discontinuation rate, which limits the interpretation and generalizability of the results. CDEC noted the evidence from DAFFODIL (N = 15), a phase II/III study of female patients aged 2 to 5 years with Rett syndrome and a documented disease-causing *MECP2* variant; and LOTUS (N = 154) an ongoing, real-world study of patients with Rett syndrome prescribed trofinetide under routine clinical care in the United States, may provide information on patients outside of the LAVENDER population. However, the open-label designs, lack of blinding, lack of comparator group, and small sample sizes (DAFFODIL) prevented CDEC from making firm conclusions on the treatment effect of trofinetide on patients outside of the LAVENDER trial population.

Background

Rett syndrome is a rare, neurodevelopmental disorder characterized by normal early development followed by a progressive loss of speech, purposeful hand use, and motor skills. Rett syndrome is most often caused by genetic variants in *MECP2* located on the X chromosome, primarily affecting females, though it can occur in males in rare cases. The disorder progresses through 4 stages categorized based on speed of development, regression of learned skills, appearance of symptom stabilization, and late motor deterioration. Patients living with Rett syndrome require lifelong care and assistance with daily activities, significantly impacting both the patient and their caregivers. Rett syndrome is clinically diagnosed based on criteria that differentiate between classic and atypical disease. Although mutations in *MECP2* are neither necessary nor sufficient for the diagnosis of Rett syndrome, the majority of individuals with Rett syndrome have a *MECP2* variant. Detection of pathogenic *MECP2* variants confirms the diagnosis; however, *MECP2* variants may not be detected in up to 5% of typical Rett syndrome cases and approximately 25% of atypical cases. A one-time genetic test for *MECP2* mutations is recommended by Rett syndrome specialists for establishing or confirming a molecular diagnosis in patients with suspected Rett syndrome. The availability and reimbursement status of *MECP2* testing vary across jurisdictions in Canada, and this information was not readily available for all provinces and territories. Rett syndrome is estimated to affect 1 in 10,000 females aged 12 years and younger, with a worldwide prevalence of 1 in 20,000 to 1 in 40,000. According to the sponsor, the estimated prevalence is between 600 and 900 cases in Canada based on extrapolation of US epidemiological data.

The panel of experts consulted for this review stated that improving HRQoL is 1 of the main goals when treating Rett syndrome. Currently there are no Health Canada–approved therapies or disease-modifying treatments indicated for this disease. Available therapies are supportive in nature and only partially manage the multisystem symptoms of the disease. Pharmacological treatments for symptom management can include drugs for seizures, bone health, contractures, gastrointestinal disturbances, sleep, anxiety, and pain. Nonpharmacological treatments are used to optimize developmental potential, promote communication, and treat musculoskeletal complications and can include physical and occupational therapy, speech therapy, and surgery.

Trofinetide has been approved by Health Canada for the treatment of Rett syndrome in adults and pediatric patients aged 2 years and older and weighing at least 9 kg. Trofinetide is a synthetic analogue of the N-terminal tripeptide of insulin-like growth factor 1. It is available as a 200 mg/mL solution for oral or gastrostomy tube administration twice a day and the dosage recommended in the product monograph is based on body mass. The twice daily recommended dose for patients weighing 9 kg to less than 12 kg is 4 g, 12 kg to less than 20 kg is 6 g, 20 kg to less than 35 kg is 8 g, 35 kg to less than 50 kg is 10 g, and 50 kg or greater is 12 g.

Sources of Information Used by the Committee

To make its recommendation, the committee considered the following information:

- a review of 1 phase III, double-blind, placebo-controlled clinical trial in patients aged 5 to 20 years with classic or typical Rett syndrome and a documented disease-causing *MECP2* variant (LAVENDER); 2 long-term extension studies (LILAC and LILAC-2); and 2 open-label studies included in the Studies Addressing Gaps in Systematic Review Evidence section (DAFFODIL and LOTUS)
- patients' perspectives gathered by 3 patient groups, including Ontario Rett Syndrome Association, Cure Rett Canada, and the International Rett Syndrome Foundation
- input from public drug plans that participate in the reimbursement review process
- 3 clinical specialists with expertise diagnosing and treating patients with Rett syndrome
- input from 1 clinician group, Canadian Rett Syndrome Consortium (including Acadia Pharmaceuticals Inc. advisory board members for trofinetide)
- a review of the pharmacoeconomic model and report submitted by the sponsor
- a review of relevant ethical issues related to trofinetide.

Perspectives of Patients, Clinicians, and Drug Programs

Patient Input

CDA-AMC received patient group input from 3 organizations. The Ontario Rett Syndrome Association provided an overview of the challenges experienced by patients living with Rett syndrome in Canada and their caregivers with data gathered from a series of surveys for caregivers' to provide their unique experience caring for an individual living with Rett syndrome in Canada. Input received from Cure Rett Canada and the International Rett Syndrome Foundation included information from families and caregivers of patients with Rett syndrome about their experience with trofinetide.

The groups stated that 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 breathe, with about 80% to 90% of patients experiencing epilepsy. Patients often have severe physical and cognitive impairments, communication difficulties, sensory sensitivities, behavioural issues (such as anxiety, agitation, and mood disorders), as well as respiratory problems, gastrointestinal issues, cardiac abnormalities, and osteoporosis. Caregivers not only face 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. Rett syndrome can disrupt family dynamics, put strain on relationships, and affect the well-being of siblings and other family members.

The input received from caregivers described how current treatments for Rett syndrome in Canada focus on symptom management with the use of antiseizure medications, surgical interventions, as well as physical, occupational, and speech therapies. Caregivers

reported dissatisfaction with the slow progress of symptom management, particularly with respect to motor skills and communication.

The patient groups stated that any new therapies that result in minor improvements in motor function would result in HRQoL benefits for patients living with Rett syndrome. There is also a need for better treatment options that could lead to improvements in communication abilities, behavioural and emotional stability, as well as a reduction in seizures, gastrointestinal issues, and respiratory problems. According to the groups, 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. Among patients who have had experience with trofinetide, there were reported improvements in patient motor function and hand use, communication abilities, behaviour, HRQoL, as well as a reduction in seizures. Common side effects included gastrointestinal disturbances, fatigue, and irritability, which may have impacted drug tolerability and adherence to treatment.

Clinician Input

Input from Clinical Experts Consulted for this Review

According to the panel of experts consulted for this review, 1 of the main unmet need of patients with Rett syndrome is that there are no approved disease-modifying treatments in Canada and current supportive therapies do not sufficiently manage the disease. In general, there is a need for treatment that promotes better HRQoL and addresses the individualized needs of a patient (may include treatment for seizures and issues with communication, motor skills, cognition, behaviour, feeding, and sleep). Therapies that better support families as well as patient and caregiver daily activities are also important.

The experts stated that patients would not have to exhaust supportive therapies before accessing trofinetide. Once a diagnosis of Rett syndrome is confirmed, trofinetide would be used as a first-line therapy along with other drugs and nonpharmacological supportive therapies to manage symptoms as outlined in the care management guidelines.

The clinical experts stated that at this time, there are no specific characteristics or markers that would identify a group of patients who would benefit more from trofinetide. Despite the available evidence from LAVENDER, the experts indicated that patients aged 2 years and older with a confirmed clinical diagnosis of classic Rett syndrome (with or without a disease-causing *MECP2* variant) or atypical Rett syndrome (with a disease-causing *MECP2* variant) would be suitable candidates for receiving trofinetide. The clinicians also noted that there is a small part of the population that is clinically diagnosed with Rett syndrome but does not have a *MECP2* variant, and if these patients are diagnosed by Rett syndrome experts, they may also be candidates for trofinetide. However, the experts agreed they would not treat patients with atypical Rett syndrome without a confirmed *MECP2* variant. The experts explained that Rett syndrome may be suspected clinically as early as 2 years of age and once a patient has a confirmed diagnosis, it would be reasonable to start treatment at that time. One expert also highlighted they would not treat patients with trofinetide who weigh less than 9 kg as there are added concerns with diarrhea, hydration, and nutrition.

Clinicians routinely record developmental and functional history to track changes in a patient and to help determine if there are clinical responses to treatment. The family's perspective, caregiver reports (including the primary care physician, specialists, therapists, and educational assistants in the school), and physician symptom assessments were highlighted as being valuable for providing detailed insight into a patient's day-to-day wellness and needs that lead to changes in care management. The experts stated that they would assess whether a drug was beneficial in a meaningful way to the patient and caregivers and if HRQoL improved while being balanced with the adverse effects patients can experience. The clinical experts confirmed that there are currently no standard outcomes used in clinics across Canada for measuring response to treatment, and that the outcomes used in LAVENDER are not used in clinical practice.

When deciding to discontinue treatment, the experts stated that adverse effects (specifically vomiting, diarrhea, dehydration, and weight loss), hospitalization due to adverse effects, and the impact on the patient's HRQoL are factors to consider and discuss with the caregivers. There were different perspectives on deciding when to discontinue treatment with 1 expert suggesting an adequate trial of trofinetide at the target dose for 3 months (based on the duration of LAVENDER) and others suggesting 6 to 12 months at the target dose to avoid premature discontinuation should benefits only be observed after at least 3 months of use. The experts also suggested that if there was no improvement or clinical change despite an adequate trial of trofinetide at the target dose, it would be reasonable to trial off the medication and evaluate if there is a difference. If there was an abrupt decline in the patient's health during

the trial off the medication, the experts suggested restarting treatment. The clinical experts noted that this approach would also be taken for patients outside of the LAVENDER population (i.e., males, patients older than 20 years). Overall, they agreed that most families would not continue treatment with trofinetide if they believed that the patient was not benefiting from the treatment.

The experts noted that they may follow-up with patients more often when starting a new treatment or if the disease is not stable. Additionally, they stated that consultation with the patient's primary care team, who the patient and caregivers have more regular interactions with (particularly for monitoring and treating adverse effects), is important. They suggested that patients starting trofinetide may see Rett syndrome specialists at 1 month after initiation, at 3 months, and less frequently if they are stable.

The experts indicated that Rett syndrome specialists as well as pediatricians and neurologists with expertise in Rett syndrome would prescribe trofinetide at first because it is a new medication. However, it was noted that as experience with the drug increases, it may be possible for other physicians to prescribe the drug to improve access to patients in remote areas and outside major cities where specialists practice.

Clinician Group Input

The Canadian Rett Syndrome Consortium (including Acadia Pharmaceuticals Inc. advisory board members for trofinetide) provided input for this review. The input included 6 clinicians consisting of pediatric neurologists, developmental pediatricians, and medical geneticists in Canada.

The clinician group stated that, in Canada, there is currently no approved treatment for Rett syndrome (aside from trofinetide) and that existing medications focus on managing disease symptoms only. The group stated that no medications to date have targeted the underlying biology or the course of the disease and the deteriorating developmental trajectory characteristic of Rett syndrome. According to the group input, trofinetide is unique in this space and first in class, although its exact mechanism of action is unknown. The clinician group input was consistent with the clinical experts consulted for this review, noting that trofinetide would be used as a first-line treatment and other medications may be added to address associated symptoms tailored to an individual patient's needs.

Outcomes used to determine whether a patient is responding to trofinetide would rely on caregiver reports. A clinically meaningful response to treatment would include improvements in communication, alertness, engagement, and respiratory symptoms; the ability to move independently; as well as decreases in repetitive movements or stereotypies. The clinician group anticipates that trofinetide would initially be prescribed in specialized medical centres on an outpatient basis, and over time with education and experience, by community physicians, such as pediatricians or internists. Considerations for discontinuing trofinetide include no improvement in symptoms after 6 to 12 months of therapy, persistent moderate to severe diarrhea or vomiting with weight loss that are not controlled with appropriate medications or lowering the dose of trofinetide.

Drug Program Input

Input was obtained from the drug programs that participate in the reimbursement review process. The following were identified as key factors that could potentially impact the implementation of a recommendation for trofinetide:

- considerations for initiation of therapy
- considerations for continuation or renewal of therapy
- considerations for discontinuation of therapy
- considerations for prescribing of therapy
- generalizability of trial populations to the broader populations in the jurisdictions
- care provision issues
- system and economic issues

The clinical experts consulted for the review provided advice on the potential implementation issues raised by the drug programs.

Clinical Evidence

Systematic Review

Description of Studies

One phase III, double-blind, randomized controlled trial (LAVENDER; N = 187) of female patients aged 5 to 20 years weighing at least 12 kg diagnosed with classic or typical Rett syndrome with a documented disease-causing *MECP2* variant assessed the efficacy and safety of trofinetide 200 mg/mL (n = 93), twice a day, compared to placebo (n = 94) at 12 weeks. Efficacy was measured through coprimary end points of RSBQ total score and CGI-I score, while other clinically relevant outcomes included communication (through nonverbal means and symbolic behaviours). Outcomes relating to physical function, HRQoL, and caregiver burden were noted as being important to patient and clinician groups and were included as supportive evidence (GRADE was not applied), where data were available from the sponsor's submission.

LAVENDER included only females with Rett syndrome, and the mean age of patients was 11.0 (standard deviation [SD] = 4.7) years and 10.9 (SD = 4.6) years in the trofinetide and placebo groups, respectively. Clinical characteristics were generally balanced between the groups and the mean Clinical Global Impression–severity (CGI-S) score was 4.9 (SD = 0.8) points for both groups indicating patients were moderately or markedly ill. Disease history was generally similar between the groups.

Efficacy Results

Rett Syndrome Behaviour Questionnaire (RSBQ)

The RSBQ is a 45-item, caregiver-completed assessment with 8 subscales evaluating various neurobehavioural symptoms known to be impaired in patients with Rett syndrome, rated as 0 (not true), 1 (somewhat or sometimes true), or 2 (very true). A total score is calculated as the sum of the scores for all 45 items and ranges from 0 to 90, where higher scores indicate symptoms are more frequent. No MID was identified from the literature and clinical expert opinion indicated that a between-group difference of 3 would be meaningful.

The mean change from baseline in RSBQ score was –4.9 (standard error [SE] = 0.9) points and –1.7 (SE = 0.9) points in the trofinetide and placebo groups, respectively, resulting in a between-group difference of –3.1 (95% confidence interval [CI], –5.7 to –0.6; P = 0.0175) points.

Clinical Global Impression–Improvement (CGI-I)

The CGI-I is a clinician-rated scale ranging from 1 (very much improved) to 7 (very much worse) used to assess improvement or worsening compared to baseline. Disease-specific anchors were used to guide the assessor and anchor descriptions included characterization of impairment levels across core Rett syndrome signs and symptoms. No MID was identified from the literature and clinical expert opinion indicated that a between-group difference of 1 would be meaningful.

The mean CGI-I score at week 12 was 3.5 (SE = 0.1) points and 3.8 (SE = 0.1) points for the trofinetide and placebo groups, respectively, resulting in a between-group difference of –0.3 (95% CI, –0.5 to –0.1; P = 0.0030) points.

Rett Syndrome Clinician Rating of Ability to Communicate Choices (RTT-COMC)

The RTT-COMC is a clinician-completed instrument that assess a patient's ability to communicate choices (including nonverbal means) using a Likert scale ranging from 0 (normal functioning) to 7 (most severe impairment). No MID was identified from the literature and there was no suggested meaningful threshold based on clinical expert opinion.

The mean change from baseline in RTT-COMC score was –0.4 (SE = 0.1) points and 0.0 (SE = 0.1) points in the trofinetide and placebo groups, respectively, resulting in a between-group difference of –0.3 (95% CI, –0.6 to 0.0) points.

Communication and Symbolic Behaviour Scales Developmental Profile Infant-Toddler (CSBS-DP-IT) Checklist

The CSBS-DP-IT checklist is a caregiver-completed assessment for communication and prelinguistic skills in young children and older children with developmental delay. Each item is rated on a scale from 0 (not yet), 1 (sometimes), or 2 (often). The social composite (emotion and eye gaze, communication rate and function, and gestures) consists of items 1 to 13 and scores range from 0 to 26, where higher scores indicate better social communication development. No MID was identified from the literature and there was no suggested meaningful threshold based on clinical expert opinion.

The mean change from baseline in CSBS-DP-IT checklist social composite score was –0.1 (SE = 0.3) points and –1.1 (SE = 0.3) points in the trofinetide and placebo groups, respectively, resulting in a between-group difference of 1.0 (95% CI, 0.3 to 1.7; P = 0.0064) points.

Health-related Quality of Life

There was no information on HRQoL in LAVENDER.

Other Efficacy Results Related to Patient-, Caregiver-, and Clinician-important Outcomes

The RTT-HF (ability to use hands for functional purposes), RTT-AMB (ability to sit, stand, and ambulate), and RTT-VCOM (ability to communicate verbally) are clinician-completed, disease-specific instruments that rate a patient's abilities from 0 (normal functioning) to 7 (most severe impairment). The between-group difference for the RTT-HF score was –0.1 (95% CI, –0.3 to 0.1) points, for the RTT-AMB score was –0.1 (95% CI, –0.3 to 0.1) points, and for the RTT-VCOM score was 0.0 (95% CI, –0.2 to 0.2) points.

The patient's overall quality of life was rated from 1 (poor) to 6 (excellent). The between-group difference for the overall quality of life rating was 0.1 (95% CI, –0.1 to 0.4) points.

The RTT-CBI is completed by the caregiver to assess the burden of caring for the patient on their daily life in 4 areas (physical, emotional, and social burden, and time dependence). Caregivers rate how often a statement describes their feelings or experiences with frequency rated on a Likert scale from 0 (never) to 4 (nearly always). Items 1 to 24 yield a total burden score from 0 to 96 and items 25 and 26 make up the optimism index (which were not used in the analyses). Higher scores indicate greater burden on the caregiver. The between-group difference for the RTT-CBI total score was –0.8 (95% CI, –3.5 to 2.0) points.

Harms Results

In LAVENDER, 92.5% of patients in the trofinetide group and 54.3% of patients in the placebo group experienced at least 1 treatment-emergent adverse event (TEAE). Diarrhea and vomiting were the most common TEAEs and were imbalanced between the treatment groups: 80.6% of patients in trofinetide group and 19.1% of patients in the placebo group reported diarrhea while 26.9% of patients in the trofinetide group and 9.6% of patients in the placebo group reported vomiting. In the trofinetide group, 2.2%, 36.6%, and 41.9% of patients experienced severe, moderate, and mild diarrhea, respectively, while 1.1%, 6.5%, and 19.4% of patients experienced severe, moderate, and mild vomiting, respectively. In the trofinetide group, 3 (3.2%) patients reported 5 serious adverse events (SAEs) and in the placebo group, 3 (3.2%) patients reported 3 SAEs. During the study, 17.2% of patients in the trofinetide group and 2.1% of patients in the placebo group stopped treatment due to TEAEs; the most frequently reported TEAE leading to treatment discontinuation was diarrhea (12.9% in the trofinetide group and 0% in the placebo group). There were no deaths in the study.

TEAEs considered clinically important by the clinical experts and noted in the product monograph included diarrhea and vomiting, which have been described.

Critical Appraisal

Reports of TEAEs were imbalanced between the treatment groups, particularly for diarrhea and vomiting. This most likely resulted in functional unblinding and may impact the ratings of assessors who were aware of a patient's TEAEs (e.g., caregivers, clinicians). Furthermore, efficacy outcomes were subjective in nature and there is the potential for overestimation of the treatment effect if the suspected treatment assignment was revealed to the assessors. The RSBQ was originally developed as a diagnostic tool rather than for measuring treatment effect. The RTT-COMC and CSBS-DP-IT checklist social composite have not been validated in

patients with Rett syndrome and both Health Canada and the FDA indicated the latter was not adequate for establishing efficacy for trofinetide. No MIDs were identified from the literature for any of the trial outcomes. Moreover, the clinical experts consulted on this review stated that the trial outcomes are not commonly used in practice nor are there standardized measures used across clinics in Canada. The greatest number of patients who discontinued study treatment was from the trofinetide group and the difference between groups is large. This introduces the potential for bias against the null as the data driving the model are largely from those who stayed in the study and were likely better responders and had fewer TEAEs. The investigators assumed data were MAR, which is not supported by the differential losses to follow-up and reasons for discontinuations.

The Health Canada indication is broader than the trial population. LAVENDER did not enrol patients who were male, aged younger than 5 years or older than 20 years, did not have classic or typical Rett syndrome, did not have a confirmed disease-causing *MECP2* variant, were not at least 6 months postregression, did not have a CGI-S of at least 4, and did not have stable standard therapies or a stable pattern of seizures. The panel of experts consulted for this review indicated that patients would be treated with trofinetide if there was a confirmed clinical diagnosis of classic Rett syndrome (with or without a disease-causing *MECP2* variant) or atypical Rett syndrome (with a disease-causing *MECP2* variant). Patients without a *MECP2* variant would have to have a confirmed clinical diagnosis of classic Rett syndrome in order to receive trofinetide, but those without a *MECP2* variant and with an atypical Rett syndrome diagnosis would not receive trofinetide due to lack of evidence in this population. Because none of the LAVENDER outcomes are used in clinical practice, it is challenging to apply the results to a real-world setting. There was no comprehensive measure of HRQoL and it is uncertain how trofinetide impacts this outcome, which is an important treatment goal in managing Rett syndrome. LAVENDER was 12 weeks long which is not long enough to assess meaningful, long-term changes in motor skills, communication, and harms in patients with Rett syndrome.

GRADE Summary of Findings and Certainty of the Evidence

For pivotal studies and randomized controlled trials identified in the sponsor's systematic review, Grading of Recommendations Assessment, Development and Evaluation was used to assess the certainty of the evidence for outcomes considered most relevant to inform expert committee deliberations, and a final certainty rating was determined as outlined by the GRADE Working Group.

Following the GRADE approach, evidence from randomized controlled trials started as high-certainty evidence and could be rated down for concerns related to study limitations (which refers to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias.

When possible, certainty was rated in the context of the presence of an important (nontrivial) treatment effect; if this was not possible, certainty was rated in the context of the presence of any treatment effect (i.e., the clinical importance is unclear). In all cases, the target of the certainty of evidence assessment was based on the point estimate and where it was located relative to the threshold for a clinically important effect (when a threshold was available) or to the null.

The selection of outcomes for GRADE assessment was based on the sponsor's Summary of Clinical Evidence, consultation with clinical experts, and input received from patient and clinician groups and public drug plans. The following list of outcomes was finalized in consultation with expert committee members:

- RSBQ total score
- CGI-I score
- RTT-COMC score
- CSBS-DP-IT checklist social composite score

Table 1: Summary of Findings for Trofinetide versus Placebo for Patients with Rett Syndrome

Outcome and follow-up	Patients (studies), N	Absolute effects			Certainty	What happens
		Placebo	Trofinetide	Difference (95% CI)		
RSBQ total score						
RSBQ total score (0 [best] to 90 [worst]) Follow-up: 12 weeks	184 (1 RCT)	–1.7	–4.9 (SE = 0.9)	–3.1 (–5.7 to –0.6)	Very low[a]	The evidence is very uncertain about the effect of trofinetide on RSBQ total score when compared with placebo.
CGI-I score						
CGI-I score (0 [best] to 7 [worst]) Follow-up: 12 weeks	184 (1 RCT)	3.8	3.5 (SE = 0.1)	–0.3 (–0.5 to –0.1)	Very low[b]	The evidence is very uncertain about the effect of trofinetide on CGI-I score when compared with placebo.
RTT-COMC score						
RTT-COMC score (0 [best] to 7 [worst]) Follow-up: 12 weeks	184 (1 RCT)	0.0	–0.4 (SE = 0.1)	–0.3 (–0.6 to 0.0)	Very low[c,d]	The evidence is very uncertain about the effect of trofinetide on RTT-COMC score when compared with placebo.
CSBS-DP-IT checklist social composite score						
CSBS-DP-IT checklist social composite score (0 [worst] to 26 [best]) Follow-up: 12 weeks	184 (1 RCT)	–1.1	–0.1 (SE = 0.3)	1.0 (0.3 to 1.7)	Low[e]	Trofinetide may result in an increase in prelinguistic communication skills when compared with placebo. The clinical importance of the increase is unclear.
HRQoL						
NR	NA	NA	NA	NA	NA	There is no evidence for the effect of trofinetide on HRQoL.

CI = confidence interval; CGI-I = Clinical Global Impression–improvement; CSBS-DP-IT = Communication and Symbolic Behaviour Scales Developmental Profile Infant-Toddler; HRQoL = health-related quality of life; MID = minimal important difference; NA = not applicable; NR = not reported; RCT = randomized controlled trial; RSBQ = Rett Syndrome Behaviour Questionnaire; RTT-COMC = Rett Syndrome Clinician Rating of Ability to Communicate Choices; SE = standard error.

Note: Study limitations (which refer to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias were considered when assessing the certainty of the evidence. All serious concerns in these domains that led to the rating down of the level of certainty are documented in the table footnotes.

[a] -1 level for serious study limitations (risk of bias due to missing data [results missing for 16% and 9% of trofinetide and placebo groups, respectively], potential for functional unblinding due to differences in harms, and instrument not being widely used in clinical practice for measuring treatment effect). -1 level for serious indirectness (trial population is narrower than the Health Canada indication and requested reimbursement population; results based on the trial population may not be generalizable to the Health Canada–indicated population). -1 level for serious imprecision (based on a clinical expert-suggested meaningful threshold of 3; CI for difference between groups includes possibility of a difference that is not clinically meaningful).

[b] -1 level for serious study limitations (risk of bias due to missing data [results missing for 15% and 8% of trofinetide and placebo groups, respectively] and instrument not being widely used in clinical practice for measuring treatment effect). -1 level for serious indirectness (trial population is narrower than the Health Canada indication and requested reimbursement population; results based on the trial population may not be generalizable to the Health Canada–indicated population). -2 levels for very serious imprecision (based on a clinical expert-suggested meaningful threshold of 1; CI for difference between groups suggests no difference).

[c] -1 level for serious study limitations (risk of bias due to missing data [results missing for 16% and 12% of trofinetide and placebo groups, respectively]; potential for functional unblinding due to differences in harms; lack of evidence supporting the instrument's validity, reliability, or responsiveness; and instrument not being widely used in clinical practice for measuring treatment effect). -1 level for serious indirectness (trial population is narrower than the Health Canada indication and requested reimbursement population; results based on the trial population may not be generalizable to the Health Canada–indicated population). -2 levels for very serious imprecision (no known MID so the target of certainty appraisal was any effect; CI for difference between groups includes the possibility of no difference).

[d] Statistical testing for this outcome was not adjusted for multiplicity. The results are considered as supportive evidence.

[e] -1 level for serious study limitations (risk of bias due to missing data [results missing for 20% and 13% of trofinetide and placebo groups, respectively]; potential for functional unblinding due to differences in harms; lack of evidence supporting the instrument's validity, reliability, or responsiveness; and instrument not being widely used in clinical practice for measuring treatment effect). -1 level for serious indirectness (trial population is narrower than the Health Canada indication and requested reimbursement population; results based on the trial population may not be generalizable to the Health Canada–indicated population). No known MID, so the target of certainty appraisal was any effect.

Source: LAVENDER clinical study report and sponsor's Summary of Clinical Evidence. Details included in the table are from the sponsor's Summary of Clinical Evidence.

Long-Term Extension Studies

Description of Studies

Two open-label extension (OLE) studies, LILAC (N = 154) and LILAC-2 (N = 77) have been summarized to provide evidence regarding the long-term safety and tolerability of trofinetide in females with Rett syndrome. Patients who completed LAVENDER could enrol in LILAC, a 40-week OLE study and upon completion, could continue in LILAC-2, an OLE study of up to 32 months additional treatment time. Inclusion and exclusion criteria were consistent with those of LAVENDER. All patients received trofinetide in these studies. Seventy (45.5%) patients withdrew early from LILAC, primarily due to TEAEs with 84 (54.5%) patients completing the study. In LILAC-2, most patients (79.2%) discontinued due to the study's termination following market approval, while 5 (6.5%) patients discontinued due to TEAEs and 4 (5.2%) patients died.

Demographic characteristics in LILAC and LILAC-2 were similar to those in LAVENDER. The mean age of patients was 11.0 (SD = 4.6) years in LILAC and 12.0 (SD = 4.4) years in LILAC-2. The mean baseline CGI-S score was 4.8 (SD = 0.8) and 4.8 (SD = 0.9) in LILAC and LILAC-2, respectively, and most patients were moderately ill (36.4% and 41.6%) or markedly ill (41.6% and 31.2%) in the 2 studies, respectively. Dosing in the OLE studies was weight-based using the same weight bands as in LAVENDER.

Outcomes

The primary outcomes in both LILAC and LILAC-2 focused on safety including TEAEs, SAEs, withdrawals due to TEAEs, and potentially clinically important changes in other safety assessments. Relevant secondary and exploratory efficacy outcomes included the RSBQ, CGI-I, RTT-COMC, CSBS-DP-IT checklist social composite score, RTT-HF, RTT-AMB, RTT-VCOM, overall quality of life rating, and RTT-CBI at various time points across both studies. For both OLE studies, all results were summarized using descriptive statistics, performed using the Safety Analysis Set unless otherwise noted.

Efficacy Results

Patients who received trofinetide in LAVENDER showed a decrease in RSBQ total scores from LAVENDER baseline with a mean change of –7.3 (SD = 10.7) at week 40 in LILAC (N = 44) and –9.8 (SD = 11.2) at week 104 in LILAC-2 (N = 10). Patients who received placebo in LAVENDER also experienced decreases from LAVENDER baseline after switching to trofinetide in LILAC, with mean changes of –7.0 (SD = 10.7) at week 40 in LILAC (N = 44) and –13.8 (SD = 11.2) at week 104 in LILAC-2 (N = 11). Overall, patients who tolerated trofinetide showed at least a 5-point decrease in the RSBQ total score, which persisted throughout the extension studies.

For both OLE studies, changes in the CGI-I score were assessed relative to the patient’s baseline state of illness in LILAC. As such, there were no CGI-I scores assessed for the baseline visit in LILAC. Overall, mean CGI-I scores remained stable over time among patients in the OLE studies.

Other efficacy outcomes, including the RTT-COMC, CSBS-DP-IT checklist social composite score, RTT-HF, RTT-AMB, RTT-VCOM, overall quality of life rating, and RTT-CBI, generally remained stable over time among patients who continued in the OLE studies.

Harms Results

In LILAC, 132 patients (85.7%) reported at least 1 TEAE, with diarrhea (59.1%), vomiting (25.3%), and COVID-19 (11.0%) being the most common. SAEs occurred in 19 patients (12.3%), and 48 patients (31.2%) had TEAEs leading to drug discontinuation, primarily due to diarrhea (19.5%) and vomiting (5.8%). In LILAC-2, 68 patients (88.3%) reported at least 1 TEAE, with COVID-19 (26.0%), diarrhea (16.9%), pyrexia (16.9%), and urinary tract infection (15.6%) being the most common. SAEs occurred in 23 (29.9%) patients and 6 (7.8%) patients discontinued the drug. The most common SAEs were seizures (6.5%), followed by vomiting, pneumonia, urinary tract infection, and acute respiratory failure (2.6% each). A total of 4 deaths were reported, of which 3 (3.9%) were reported as TEAEs (cardiac arrest, aspiration and vomiting, and sudden unexplained death in epilepsy in 1 patient each).

Critical Appraisal

The OLE studies provided longer-term efficacy and safety data of trofinetide for up to 104 weeks. The open-label design increases the potential for bias, particularly in subjective outcomes and adverse events reporting. Since completion of the pivotal trial was

required for enrolment, patients who discontinued LAVENDER were excluded, resulting in a patient population that was more tolerant and responsive to trofinetide and introducing selection bias. Additionally, with a high discontinuation rate in LILAC (45.5%) mainly due to TEAEs, the impact of patient dropout on outcomes is unclear, as analyses were not conducted to assess how discontinuation affected treatment results.

Indirect Comparisons

No ITCs were submitted for the review of trofinetide.

Studies Addressing Gaps in the Evidence from the Systematic Review

Description of Studies

Two studies have been summarized to provide additional evidence to the systematic review. DAFFODIL is a multicentre, open-label, long-term phase II/III study in the US that provides evidence regarding the efficacy and safety of trofinetide in females aged 2 to 5 years with Rett syndrome. LOTUS is an ongoing, phase IV, observational, real-world study of patients prescribed trofinetide under routine clinical care in the US for up to 24 months, with interim results at 6 months submitted by the sponsor.

DAFFODIL enrolled 15 female patients in the US living with Rett syndrome, a *MECP2* variant, and with a CGI-S score of 4 or greater at screening and baseline. Eligible patients were aged 2 to 4 years with a body mass ranging from 9 kg to less than 20 kg or aged 5 years with a body mass ranging from 9 kg to less than 12 kg. Aside from the age restriction, the inclusion and exclusion criteria were comparable to those used in the pivotal trial. The mean age at the time of diagnosis was 1.9 (SD = 0.1) years. Trofinetide was dosed by weight and administered orally or by gastrostomy tube.

In total, 154 patients were included in the interim analysis of the LOTUS study. Most patients had classic Rett syndrome (66.7%) and were female (96.1%) and the age of patients in the study ranged from 2 to 60 years. The mean age at the time of diagnosis was 5.2 (SD = 5.37) years and the mean age at the time of trofinetide initiation was 16.5 (SD = 11.16) years. There were no exclusion criteria in the study.

Outcomes

Relevant exploratory efficacy outcomes in DAFFODIL included the CGI-I score from baseline to week 104 and the overall quality of life rating. In both studies, safety assessments were based on the proportion of patients experiencing TEAEs, SAEs, and withdrawals due to TEAEs. Efficacy and safety data were summarized using descriptive statistics in both studies.

Efficacy Results

In DAFFODIL, the mean CGI-I score decreased from week 2 (n = 13) through to week 78 (n = 9) from 3.5 (SD = 0.66) to 2.2 (SD = 0.67). The mean change from baseline in overall quality of life rating at week 12 was 0.3 (SD = 0.72) and continued to increase through to week 78 with a mean change of 0.7 (SD = 0.95).

Harms Results

In DAFFODIL, safety outcomes were similar to those of the pivotal and OLE studies. In total, 14 (93.3%) patients experienced at least 1 TEAE, the most common of which were diarrhea (73.3%) and vomiting (46.7%). Four (26.7%) patients reported SAEs and 2 (13.3%) patients experienced TEAEs leading to drug and study discontinuation. As of the LOTUS interim analysis, 20 patients reported 43 TEAEs, with diarrhea, vomiting, and insomnia being the most common. Five SAEs occurred: 2 cases of recurrent constipation leading to hospitalization, 1 hospitalization due to severe dehydration from diarrhea, and 1 each for pneumonia and viral gastroenteritis. No deaths were reported in either study.

Critical Appraisal

The longer-term harms data from both DAFFODIL and LOTUS are generally consistent with those from the pivotal trial, with diarrhea and vomiting being the most common. While the 2 studies attempted to fill the evidence gaps for patients aged 2 to 5 years (DAFFODIL) or aged 20 years or older, diagnosed with atypical disease, or who are male (LOTUS), there remains uncertainty in the

study results due to various limitations with the data. Neither study was designed to assess the efficacy and safety of trofinetide in a statistically rigorous manner. Other limitations include potential selection bias, lack of blinding, small study population (DAFFODIL), and lack of comparator group, which may have affected the internal validity of the safety and efficacy results. In addition, the lack of blinding could have introduced bias in the reporting of subjective adverse events in favour of trofinetide if patients and/or caregivers believed the drug was beneficial.

Ethical Considerations

Patient group, clinician group, and drug plan input, as well as consultation with clinical experts were reviewed to identify ethical considerations specific to the use of trofinetide for the treatment of Rett syndrome in adults and pediatric patients 2 years of age and older weighing at least 9 kg.

Diagnosis, treatment, and experiences of people living with Rett Syndrome

- Diagnostic Complexity and Equity Concerns:
  Rett syndrome includes classic and atypical forms, which differ in patterns of regression and severity. While 95–97% of classic cases and 50–70% of atypical cases are associated with pathogenic MECP2 mutations, some individuals lack identifiable genetic variants, adding complexity to diagnosis and treatment planning. Though not required for the diagnosis of Rett syndrome, clinical experts indicated that genetic confirmation is commonly pursued and generally accessible in Canada. Patient group input noted that families in rural areas may face greater challenges in accessing genetic testing, raising concerns about equity. The phenotypic variability of Rett syndrome, even among those with MECP2 mutations, further complicates efforts to predict disease progression and develop equitable and broadly applicable treatment options. This variability also poses challenges for defining treatment eligibility, as relying solely on clinical diagnosis or genetic status may inadvertently exclude some individuals who could benefit.

- Challenges in Caregiving and Burden of Illness:
  Caring for individuals with Rett syndrome is challenging due to the condition's complexity and unpredictability. Patient group input highlighted acute concerns (e.g., seizures, respiratory distress, feeding difficulties, and mobility issues), which place a heavy emotional, physical, and financial burden on families. The regression following an initial period of typical development is especially distressing, with some caregivers describing it as if "someone pulled the plug on everything." Many caregivers reported reducing work hours or leaving employment entirely to provide care, further exacerbating financial strain. Patient group input also underscored a lack of societal resources to support families in managing these burdens, contributing to feelings of isolation and unmet need.

- Lack of Disease-Modifying Treatments and Barriers to Care:
  Currently, there are no disease-modifying treatments for Rett syndrome, and care is focused on symptom management to improve health-related quality of life. Interventions include pharmacological treatments for seizures, gastrointestinal disturbances, and sleep issues. It also includes nonpharmacological approaches like physical therapy for motor impairments, speech therapy to address communication challenges, and occupational therapy to support daily activities. This multidisciplinary care often requires coordination across multiple specialists. There are only five Rett specialty clinics in Canada – all located in urban centers – and families without access to these clinics are frequently left to organize and manage these complex care pathways themselves. Delays in accessing care, particularly for families in rural or remote areas, may limit opportunities to mitigate complications or improve outcomes. Symptom management approaches also fail to address the underlying disease mechanisms, leaving families without the hope of slowing disease progression. This may contribute to emotional distress and a sense of unmet need. Access to supportive services (e.g., speech therapy, physiotherapy) is further complicated by funding structures that often require alternative diagnoses (e.g., autism spectrum disorder) for coverage. This can lead to out-of-pocket costs and/or additional advocacy from families. These barriers highlight significant inequities in accessing timely, comprehensive care for a population already managing substantial burdens.

- Therapeutic Needs and Expectations:
  Both clinical experts and patient group input emphasized the urgent need for therapies that address ability to communicate, motor function, cognition, and seizure management. Caregivers consistently highlighted communication—whether through speech, gestures, or assistive technologies—as a top priority, as even small improvements could significantly enhance their ability to understand and respond to their child's needs. As such, they believed that these small improvements would improve their child's quality of life. Additionally, patient group input suggested it would also foster greater autonomy for individuals with Rett syndrome by enabling them to better express their needs and preferences.

Clinical evidence used in the evaluation of trofinetide

- Pivotal Trial Evidence and Limitations:
  The sponsor submitted evidence from the phase III, double-blind, randomized, placebo-controlled LAVENDER trial (N = 187), which evaluated trofinetide in female patients aged 5–20 years with typical Rett syndrome and an MECP2 variant. Co-primary outcomes, change from baseline to week 12 in Rett Syndrome Behaviour Questionnaire (RSBQ) and Clinical Global Impression – Improvement (CGI-I) scores at week 12, showed greater decreases (indicating improvement) compared to placebo. However, the absence of validated minimal important differences for these outcomes limits the ability to interpret what constitutes a clinically meaningful change. Similarly, missing data and concerns about the utility of RSBQ as an outcome assessment, further reduced confidence in the findings. Adverse events, particularly diarrhea and vomiting, were frequently reported and contributed to trial dropouts, raising the importance of balancing potential benefits against the burdens of treatment.

- Long-Term Safety, Efficacy, and Evidence Gaps:
  Long-term safety and efficacy of trofinetide were assessed in two open-label extension (OLE) studies, LILAC (N = 154) and LILAC-2 (N = 77), which intended to follow patients from LAVENDER for up to 3.5 years. The mean duration of exposure to trofinetide across the pivotal trial and two OLEs was approximately 2 years. While this follow-up period offers some insight into long-term use, Rett syndrome is a lifelong condition, thus uncertainty remains regarding long-term clinical benefit and safety. Both studies demonstrated continued decreases in RSBQ and CGI-I scores through week 104; however, improvements in CGI-I were modest at less than a 1-point change over the OLE period. Both studies were also limited by high dropout rates in LILAC due to adverse events and the early termination of LILAC-2 following U.S. market approval. As these studies included only patients who completed LAVENDER, they excluded individuals who dropped out of the pivotal trial. This potentially skewed results toward a more favorable representation of the clinical effectiveness of trofinetide by focusing on participants who are more likely to tolerate and benefit from the treatment.

- Representation and Generalizability:
  The pivotal trial and OLE studies excluded males, patients younger than 5 years or older than 20 years, individuals without an MECP2 variant, and those with atypical Rett syndrome. This creates uncertainty regarding the safety and efficacy of trofinetide in these populations. Additionally, clinical experts noted that the predominance of white participants in these studies does not reflect the diversity of patients seen in Canadian clinical practice, raising concerns about the generalizability of the findings. This is particularly important given that the proposed Health Canada indication includes all individuals aged 2 years and older with Rett syndrome, regardless of sex, clinical diagnosis (i.e., atypical or classic Rett syndrome), or genetic status. To address some of these gaps, the sponsor submitted data from two additional studies: DAFFODIL, an open-label study evaluating trofinetide in females aged 2 to 5 years, and LOTUS, an ongoing observational study assessing real-world use of trofinetide in individuals under routine care in the US. However, both studies have notable limitations, including the absence of control groups, potential for selection bias, and open-label designs, which introduce challenges in objectively interpreting results. These factors limit the reliability of the data and contribute to ongoing uncertainty about the safety and efficacy of trofinetide in populations not included in the pivotal trial. These gaps in evidence underscore the importance of robust informed consent processes to ensure patients and families are aware of uncertainties and potential risks, especially for those whose clinical profiles fall outside the trial population. Providers navigating these complexities will need to engage in shared decision-making and weigh potential benefits and harms on a case-by-case basis. Post-market data collection will be critical to address these gaps, ensuring equitable and evidence-based access to trofinetide across all populations living with Rett syndrome.

Clinical use of trofinetide

- Balancing Benefits and Risks:
  Trofinetide represents the first Health Canada-approved therapy targeting the underlying disease course of Rett syndrome. As such, clinical experts and clinician group input expect it to become the first-line treatment option for Rett syndrome if recommended for public reimbursement. Despite the clinical review report's very low certainty regarding improvements as assessed by the primary outcomes (RSBQ and CGI-I) in the LAVENDER and the OLE trials, clinical experts and clinician group input indicated a willingness to prescribe trofinetide to their eligible Rett patients. While diarrhea and vomiting were primary side effects leading to trial withdrawals, clinical experts believed that these could be managed more effectively in clinical practice than in the trial setting.

- Caregivers cited in patient group input emphasized that even modest improvements in their child's communication, cognition, or mobility could have a meaningful impact on their quality of life. However, the potential caregiving challenges posed by side effects like diarrhea underscore the need for providers to work closely with families to ensure that expectations are aligned with treatment realities. Given the trade-offs between potential benefits and caregiving burdens, clinical experts stressed the importance of robust shared decision-making processes. Additionally, there is limited data on

the long-term safety and effectiveness of trofinetide. Providers must prioritize patient and caregiver autonomy by presenting clear, comprehensive information about risks, benefits, and uncertainties to enable informed choices.

- Eligibility:
  The heterogeneity of Rett syndrome – including distinctions between classic and atypical forms and variability in MECP2 status – complicates questions of eligibility for trofinetide. Clinical evidence from the pivotal trial is limited to females aged 5-20 years with typical Rett syndrome and a confirmed MECP2 variant. As a result, there is uncertainty regarding the safety and efficacy of trofinetide for atypical patients, males, and those without MECP2 variants. While DAFFODIL and LOTUS provide some evidence on the use of trofinetide in a broader population, their design limitations leave residual uncertainty regarding populations excluded from the pivotal trial. Given these uncertainties, clinical experts suggested limiting eligibility to patients aligned with the trial population, classic Rett patients without a known MECP2 variant, and atypical patients with a confirmed MECP2 variant. In contrast, clinician group input supported the broader Health Canada indication, which includes all patients aged 2 and older with Rett syndrome, regardless of sex, clinical diagnosis (i.e., typical or atypical), or genetic status. Caregivers may also advocate for trofinetide access for patients who fall outside narrower eligibility criteria, creating ethical and emotional challenges for providers navigating these conversations. clinical experts emphasized the need for clear prescribing guidance beyond the parameters of the pivotal trial, alongside robust shared decision-making processes to facilitate informed decisions. Without such guidance, inconsistencies in prescribing practices may lead to inequitable access across providers and jurisdictions.

- Prioritization:
  Clinical experts suggested that individuals with lower disease burden, often younger patients, may be more likely to benefit from trofinetide. As a non-curative treatment, they expected trofinetide to have greater impact when introduced earlier in the course of disease, before significant progression occurs. However, there is no clinical evidence to support this claim. As such, the experts emphasized that eligibility criteria should not rely solely on age or disease burden, as some older patients or those with more advanced disease may still see meaningful improvements in communication, mobility, or overall quality of life. Overly rigid prioritization criteria could inadvertently exclude patients who fall outside the typical profile of trial participants but could still derive significant benefit from treatment.

- Geographic and Access Disparities:
  Clinician group input and clinical experts recommended that trofinetide initially be prescribed only by specialists with expertise in Rett syndrome, likely based in specialized medical centers. While this approach may help ensure appropriate use during early implementation, it could create geographic access barriers for patients living in rural or remote areas without access to Rett specialists or specialty clinics. Over time, broader familiarity with trofinetide may enable prescribing and management of treatment by a wider range of providers, potentially reducing these inequities. Families with fewer resources or limited access to specialized care may face greater challenges in managing treatment protocols. Addressing these barriers will be crucial to promoting equitable outcomes for all individuals with Rett syndrome.

Health systems impact

- Impact on health system budgets and equitable resource allocation:
  Expensive drugs for rare diseases, such as trofinetide, raise ethical considerations regarding equity, distributive justice, and the sustainability of health care budgets. Although there is a significant unmet need for effective, targeted therapies for Rett syndrome, the uncertainty surrounding the clinical value of trofenitide as described above complicates decisions about resource allocation. The CDA-AMC pharmacoeconomic report's conclusion that trofinetide is not cost-effective intensifies these concerns. As a result, establishing equitable and sustainable eligibility criteria is crucial, ensuring that those who stand to benefit most have access while maintaining a fair distribution of health resources.

- Changes in Rett specialists' roles and workloads:
  The introduction of trofinetide would shift Rett specialists' roles and workloads. Currently, these specialists act primarily as consultants, guiding the treatment of Rett syndrome's diverse symptomatic presentations. With the approval of trofinetide, they would likely take on more direct care responsibilities, requiring additional follow-up visits for monitoring, and collaboration with primary care providers. This shift could strain specialist availability and increase administrative costs, potentially creating bottlenecks in care delivery. Implementing clear protocols and investing in education for non-specialist providers could help mitigate these challenges over time.

Economic Evidence

Cost and Cost-Effectiveness

Table 2: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis Markov Model
Target population	Rett syndrome in adults and pediatric patients 2 years of age and older and weighing more than 9 kg.
Treatment	Trofinetide plus best supportive care (BSC)
Dose regimen	Patients aged 2 years and older:[a] • 9 kg to < 12 kg: 4 g twice daily • 12 kg to < 20 kg: 6 g twice daily • 20 kg to < 35 kg: 8 g twice daily • 35 kg to < 50 kg: 10 g twice daily • ≥ 50 kg: 12 g twice daily
Submitted price	Trofinetide: $13,714.11 per 450 mL bottle of 200 mg/mL oral solution
Submitted treatment cost	Annual cost (year 1 and year 2 plus):[a] • 9 kg to < 12 kg: $427,331 to $445,250 • 12 kg to < 20 kg: $640,997 to $667,876 • 20 kg to < 35 kg: $854,662 to $890,502 • 35 kg to < 50 kg: $1,068,328 to $1,113,127 • ≥ 50 kg: $1,281,993 to $1,335,754
Comparator	• BSC, defined as concomitant medications[b] that were taken by at least 10% of subjects from the LAVENDER and LILAC CSR data.
Perspectives	Publicly funded health care payer Societal perspective
Outcomes	QALYs, LYs
Time horizon	Lifetime (79.1 years, until age of 90)
Key data sources	LAVENDER trial, and long-term extensions LILAC-1 and LILAC-2
Submitted results	ICER = $5,864,321 per QALY gained (incremental costs = $3,386,675 and incremental QALYs = 0.578) for both the publicly funded health care payer perspective and societal perspective
Key limitations	• The sponsor's economic model is based on RSBQ scores as the primary measurement of changes in health status. Based on clinical expert feedback obtained by CADTH, RSBQ is not typically used in current clinical practice in Canada. Instead, clinical experts noted that in practice, the health status and treatment outcomes of individuals with Rett syndrome are assessed via discussions with patients' family members, clinical observations, review of chart history, or biomedical markers, depending upon the presentation of the patient. The sponsor assumed trofinetide does not impact survival; as a result, the key impact of trofinetide is on quality of life. However, the sponsor's use of RSBQ to estimate health related quality of life in the model is uncertain. This uncertainty in the measurable impact of treatment, limits the ability to accurately reflect the impact of trofinetide on clinically important outcomes. • The sponsor assumed patients who discontinued trofinetide would remain in the same health state for the duration of the model, implying that any clinical improvement obtained from trofinetide would persist indefinitely even after treatment was stopped. Given the high proportion of missing RSBQ data in the extension trials, as well as the feedback from clinical expert consulted by CADTH, this assumption likely overestimates the benefit of trofinetide.

Component	Description
	• The sponsor assumed a discontinuation rate of 10% per year for years 2 and beyond for trofinetide (trial evidence was up to 2 years), resulting in [redacted] discontinuation at 10 years. Feedback from clinical experts expected that discontinuation due to AEs is likely to decrease over time, so the sponsor's approach may underestimate the long-term drug costs associated with trofinetide.
CADTH reanalysis results	• Given the limitations identified with the sponsor's clinical evidence and economic analysis, CADTH was not able to provide a reliable estimate of the cost-effectiveness of trofinetide. • Based on the sponsor's analysis, trofinetide plus BSC is associated with an ICER of approximately $6 million per QALY gained compared to BSC alone. A price reduction of more than 98% would be required for trofinetide plus BSC to be considered cost-effective at a willingness-to-pay threshold of $100,000 per QALY gained. • CADTH undertook scenario analyses altering the duration of treatment effect and rate of discontinuation which resulted in higher ICERs. Given the limitations in the submission that could not be addressed by CADTH, the estimate of cost-effectiveness is uncertain.

BSC = best supportive care; ICER = incremental cost-effectiveness ratio; LY = life-year; NOC = Notice of Compliance; QALY= quality-adjusted life-year; RSBQ = Rett Syndrome Behaviour Questionnaire.

[a] The Health Canada product monograph recommends that trofinetide be titrated starting with 50% of the recommended dose taken twice daily, then the dose be increased over 4 to 8 weeks until the recommended dose is reached.

[b] adrenergics, anti-depressants, anti-epileptics, anxiolytics, laxatives, anti-propulsives, drugs for peptic ulcer and GORD, muscle relaxants, other alimentary track and metabolism products, and psychostimulants.

Trofinetide is being reviewed by CDA-AMC through the complex review pathway; as such, CDA-AMC has appraised 2 cost-effectiveness analyses submitted by the sponsor, one adopting a publicly funded health care payer perspective and one adopting a societal perspective.

Budget Impact

CADTH identified the following key limitations with the sponsor's analysis: the number of patients with Rett syndrome in Canada is uncertain, the cost of treatment with trofinetide was not adequately derived, which likely underestimates the total costs associated with trofinetide as assumed by the sponsor, the proportion of patients eligible for public drug coverage was underestimated due to the assumption that patients with Rett syndrome would be eligible for public reimbursement at the same rate as the general population, the assumption that the use of trofinetide alters the cost of BSC was inappropriate, the relative dose intensity for trofinetide is uncertain, long term discontinuation rates and timepoints for trofinetide are uncertain, and the estimated uptake of trofinetide is uncertain and may be underestimated.

CADTH reanalyses revised the sponsor's submitted analysis by assuming dosing consistent with the distribution of patient weights of modelled patients, by increasing the proportion of patients who will be eligible for public funding, and by assuming that BSC does not change due to the addition of trofinetide therapy.

Results of the CADTH reanalyses suggest that the reimbursement of trofinetide for the treatment of Rett syndrome in patients 2 years of age and older, weighing at least 12 kg, and with a confirmed Rett syndrome diagnosis as described in Table 1 may be associated with a 3-year incremental budgetary cost of $166,461,725 (year 1: $53,775,386; year 2: $53,706,466; year 3: $58,979,873). As the size of the population with Rett syndrome as well as the uptake of trofinetide within that population remain uncertain, the estimated budget impact of trofinetide is uncertain. Scenario analyses resulted in budget impacts of up to $333 million.

CDEC Information

Members of the Committee:

Dr. Peter Jamieson (Chair), Dr. Sally Bean, Daryl Bell, Dan Dunsky, Dr. Trudy Huyghebaert, Morris Joseph, Dr. Dennis Ko, Dr. Christine Leong, Dr. Kerry Mansell, Dr. Alicia McCallum, Dr. Srinivas Murthy, Dr. Nicholas Myers, Dr. Krishnan Ramanathan, Dr. Marco Solmi, Dr. Edward Xie, and Dr. Peter Zed.

Meeting date: March 27, 2025

Regrets:

Three expert committee members did not attend.

Conflicts of interest:

None.