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New Drug Evaluation: Trofinetide 200 mg/mL, oral solution

Date of Review: August 2023
Generic Name: Trofinetide

End Date of Literature Search: 05/05/2023
Brand Name (Manufacturer): DAYBUE (Acadia Pharmaceuticals, Inc.)
Dossier Received: yes

Plain Language Summary:

- Trofinetide is the first medicine that the United States Food and Drug Administration has approved to treat Rett syndrome in patients aged 2 years and older.
- Rett syndrome is a rare, inherited disorder that affects the way the brain develops. It is most common in females and rarely affects males.
- Most babies with Rett syndrome lose skills, such as the ability to crawl, walk, communicate, or use their hands between 6 and 30 months of age. Rett syndrome affects nearly every aspect of life including the ability to speak, walk and eat. Most people with Rett syndrome:
    - are dependent on a caregiver to complete activities of daily living,
    - have limited mobility resulting in the use of a wheelchair, and
    - have a reduced life expectancy of around 40 to 50 years of age.
- A 12-week study showed trofinetide improved Rett syndrome symptoms by a modest amount compared with placebo. More data is needed to understand the long-term safety and effectiveness of trofinetide.
- The most common side effect of trofinetide is mild to moderate diarrhea, which was reported in 81% of people treated with trofenitide compared with 19% of patients who received placebo in the largest clinical trial.
- For people enrolled in the Oregon Health Plan, providers must explain to the Oregon Health Authority why someone needs trofinetide before Medicaid will pay for it. This process is called prior authorization. We recommend continuing this policy.

Research Questions:

1. What is the evidence for the efficacy of trofinetide for treatment of Rett syndrome?
2. What are the harms associated with the use of trofinetide?
3. Are there specific populations or communities, based on demographic characteristics, who would be more likely to benefit or be harmed from the use of trofinetide?

Conclusions:

- Trofinetide (DAYBUE) is indicated for the treatment of Rett syndrome in adults and pediatric patients aged 2 years and older.[1] The mechanism of trofinetide in treating Rett syndrome is not clear.[2]

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- The efficacy and safety of trofinetide were evaluated in the LAVENDER trial, a double-blind, placebo-controlled, phase 3, randomized clinical trial (RCT) of 187 female patients aged 5 to 20 years with genetically confirmed Rett syndrome.[3] Patients were randomized 1:1 to receive trofinetide 200 mg/kg or matching placebo twice daily for 12 weeks.[3] The co-primary efficacy measures were changes from baseline in the caregiver-reported 90-point Rett Syndrome Behavior Questionnaire (RSBQ) score and the clinician-administered 7-point Clinical Global Impression-Improvement (CGI-I) score at week 12.[3] For the RSBQ score, the least squares mean (LSM) change from baseline to week 12 was −4.9 for trofinetide versus −1.7 for placebo (difference: −3.2; 95% confidence interval [CI] −5.7 to −0.6; P=0.018; low-quality evidence).[2,3] The mean CGI-I score at Week 12 was 3.5 for trofinetide versus 3.8 for placebo (difference: −0.3; 95% CI −0.5 to −0.1; P=0.003; low-quality evidence).[2,3] Efficacy results from a dose-finding phase 2 RCT were considered confirmatory evidence by the FDA to support results from the phase 3 RCT.[4] There is insufficient efficacy data of trofinetide beyond 12 weeks.
- To assess safety in patients 2 to 4 years of age, an open-label pharmacokinetic (PK) bridging study was conducted in 13 children with Rett syndrome.[2] The effectiveness of trofinetide in patients in this age group was hypothesized through extrapolation of the results observed in the LAVENDER study population, based on the similarity of the disease pathophysiology as well as the assumption of similar exposure response relationship between patients aged 2 to 4 years and patients 5 years of age and older.[2]
- The most common adverse effect leading to discontinuation of trofinetide treatment in clinical trials was diarrhea.[1] In the LAVENDER trial, 81% of trofinetide-treated patients reported mild to moderate diarrhea compared with 19% of placebo treated patients.[3] In an open-label, extension trial, diarrhea occurred in 84% of subjects on long-term (greater than 1 year) treatment with trofinetide.[2] Approximately 40% of patients withdrew from both the placebo and active compartor arms due to this adverse event.[2] Of those who did not withdraw from treatment, 50% required concomitant therapy with loperamide to treat the diarrhea.[2] In addition, weight loss greater than 7% from baseline was observed in 12% of patients treated with trofinetide compared with 4% of patients treated with placebo.[1] There is insufficient data for the long-term safety of trofinetide in people with Rett syndrome beyond 1 year.
- According to the FDA reviewers, limitations of the trofinetide evidence include:
    - reliance on one single adequate and controlled study with confirmatory evidence,
    - the limitations of the RSBQ as a tool to measure functional improvement in Rett syndrome,
    - the disproportionate study withdrawal rate (23 trofinetide-treated patients versus 9 placebo-treated patients), and
    - the disproportionate and rapid onset of diarrhea in the trofinetide arm along with the disproportionate use of loperamide in the trofinetide arm, with a risk for functional unblinding (**Table 4**).[4]
- The wholesale acquisition cost of trofinetide is $9,495 for a 450 ml bottle. A patient weighing 50 kg or more would require 60 ml twice daily; or 8 bottles per month which would cost approximately $76,000.
- No specific populations were identified that would be more likely to benefit or be harmed from the use trofinetide. All patients enrolled in the phase 3 RCT had genetically confirmed Rett syndrome and were 5 to 20 years of age.[2] The efficacy of trofinetide in patients that do not have genetically confirmed Rett syndrome and are older than 20 years of age is unknown. The effects of trofinetide in pregnancy and lactation were not evaluated in clinical trials, as pregnant individuals were excluded from study enrollment.[1] Although trofinetide is primarily renally eliminated, no clinical study was conducted to evaluated pharmacokinetic (PK) parameters in renal impairment. Administration of trofinetide to patients with moderate or severe renal impairment is not recommended.[1]

Recommendations:

- Maintain trofinetide as non-preferred on the PMPDP.
- Implement clinical prior authorization (PA) criteria for trofinetide to ensure medically appropriate use.

Background:
Rett syndrome is a rare, progressive, neurodevelopmental disorder which affects approximately 1 in 15,000 live female births worldwide and is even rarer in boys.[2,5] Rett syndrome occurs in all ethnic and racial groups, and at similar rates.[6] This condition is often caused by spontaneous mutations in the methyl-CPG-binding protein 2 (MECP2) gene on the X chromosome.[5,7] Although MECP2 is expressed in all tissues, it is most abundant in the brain, which may be more sensitive to abnormal MECP2 protein than other tissues.[8] Methyl-CPG-binding protein 2 is known to play a role in chromatin organization and transcriptional regulation and is essential for normal brain function.[9] These mutations are almost exclusively inherited from the paternally derived X chromosome, which may explain the high female to male ratio.[10] Most individuals with Rett syndrome have random X-inactivation so that the normal MECP2 allele is expressed in some cells.[8] The normal allele appears to enable affected females to survive but does not protect them from neurodevelopmental abnormalities.[8] Similar pathogenic variants in brothers of affected females most often result in severe neonatal encephalopathy and are lethal to the boys, because all their cells express mutated MECP2 protein.[8] Random inactivation also contributes to the spectrum of phenotypes in Rett syndrome.[8] There are more than 250 known pathogenic variants in MECP2 associated with Rett syndrome.[11] The severity of the Rett syndrome depends on the location and type of mutation on the MECP2 gene.[2] Eight of the most frequently identified mutations account for more than 60% of typical Rett syndrome cases.[12] There is a broad range of clinical and genotypic heterogeneity in Rett syndrome, which has posed a challenge to the study of the condition.[13]

The onset of Rett syndrome occurs most commonly between 6 and 18 months of age, first with a plateau in development and then regression of motor and communication skills.[11] Patients with Rett syndrome develop progressive loss of purposeful hand skills, speech and language regression, gait abnormalities, and development of stereotypical hand movements. (i.e., hand wringing, clapping, tapping, washing, rubbing).[13] Abnormal head growth deceleration, markedly altered height and weight, and epilepsy occur in most patients.[11] Between one and 4 years of age, patients lose the ability to perform skills they previously had mastered.[2] The average age of diagnosis is 2.5 years, but has been trending downwards due to increasing availability of genetic testing.[14] After initial regression, the condition stabilizes and patients usually survive into adulthood.[8] Life expectancy is reduced to approximately 40 to 50 years of age.[2] In the Oregon Health Plan, claims data from 2022 indicated that approximately 114 people have Rett syndrome; 76 people are enrolled in a Coordinated Care Organization, and 31 are enrolled in Fee-for-Service.

The diagnosis of Rett syndrome is based upon clinical and genetic characteristics. Rett syndrome is suspected in individuals who have apparently normal development in the first 6 to 18 months of life followed by regression of purposeful hand skills and spoken language along with the onset of gait abnormalities and stereotypic hand movements.[5] **Table 1** summarizes diagnostic criteria for the 2 types of Rett syndrome: typical (classic) and atypical (variant) Rett syndrome. Postnatal deceleration of head growth also raises suspicion for Rett syndrome, although it does not occur in all individuals with typical Rett syndrome.[5] Rett syndrome accounts for 10% of cases of profound intellectual disability of genetic origin in females.[4] In typical Rett syndrome, 90% of reported cases have the MECP2 mutation, which is a spontaneous mutation in almost all cases.[5] Atypical Rett syndrome may be suspected in individuals who have many but not all of the clinical features of typical Rett syndrome.[4] Atypical Rett syndrome cases generally have a limited phenotype, and only about 75% of patients with Rett syndrome are found to have MECP2 genetic mutations.[4]

Table 1. Required Criteria for Diagnosis of Rett Syndrome[5]

Required Criteria for Typical Rett Syndrome	Required Criteria for Atypical Rett Syndrome
1. A period of regression followed by recovery or stabilization. 2. All main criteria and all exclusion criteria.	1. A period of regression followed by recovery or stabilization. 2. At least 2 out of the 4 main criteria and 5 out of 11 supportive criteria.

3. Supportive criteria are not required, although often present in typical Rett syndrome.	
Main Criteria	
• Partial or complete loss of acquired purposeful hand skills • Partial or complete loss of acquired spoken language • Gait abnormalities: impaired or absence of ability • Stereotypic hand movements such as hand wringing/squeezing, clapping/tapping, mouthing and washing/rubbing automatisms	
Supportive Criteria	
• Breathing disturbances when awake • Bruxism when awake • Impaired sleep pattern • Abnormal muscle tone • Peripheral vasomotor disturbances • Scoliosis/kyphosis • Growth retardation • Small cold hands and feet • Inappropriate laughing/screaming spells • Diminished response to pain • Intense eye communication	
Exclusion Criteria	
• Brain injury secondary to trauma (peri- or post-natal), neurometabolic disease, or severe infection that causes neurological problems. • Grossly abnormal psychomotor development in first 6 months of life.	

Rett syndrome is divided into 4 progressive stages.[15] Patients initially display seemingly normal early development. Between 6 and 18 months of age, patients experience a period of developmental stagnation (Stage I) and no longer meet their mental, cognitive or motor milestones.[15] Head circumference growth slows and this period lasts for weeks to months.[15] Stage II is defined by rapid developmental regression around the age of 1 to 4 years, in which acquired purposeful hand movements and verbal skills are lost.[15] Microcephaly worsens and breathing irregularities and seizures may arise.[15] Stage III is a pseudo-stationary plateau period in which patients may show mild recovery in cognitive interests, but purposeful hand and body movements remain severely diminished.[15] Stage IV is defined by motor deterioration, dystonia, bradykinesia, and scoliosis, and may last for decades.[15] Many patients are wheelchair and/or gastrostomy-tube dependent.[15] However, not all patients progress to this severe stage.[15]

Treatment options for Rett syndrome are currently limited to supportive care, symptom relief, and managing complications such as epilepsy, dysphagia, scoliosis, spasticity, and constipation.[15] Managing the various symptoms over the lifetime of an individual with Rett syndrome is challenging and often requires the collaboration of numerous providers.[15] Trofinetide is the first FDA-approved treatment for Rett syndrome. As of January 2021, there are 18 Rett syndrome clinics across the United States that are available to consult and/or manage the individual with Rett syndrome.[15] None of the clinics are based in Oregon, the 2

clinics closest to Oregon are located in Oakland, California and Aurora, Colorado.[16] The medical teams that are part of a Rett Syndrome Consortium have prepared a guideline, to help with the evolving management of a person with Rett syndrome across their lifespan.[14]

Three instruments were used to assess trofinetide efficacy in clinical trials. The RSBQ was developed as a diagnostic tool to clinically differentiate people with Rett syndrome from those with other severe intellectual disabilities.[17] The RSBQ is a 45-item rating scale completed by the caregiver and assesses a range of 8 individually assessed symptoms of Rett syndrome (general mood, breathing problems, hand behavior, face movements, body rocking/expressionless face, night-time behaviors, fear/anxiety, and walking/standing).[18] As the questions in the RSBQ include questions regarding the signs of Rett syndrome and not just the symptoms, the RSBQ may detect changes in some of its components that may not clearly be clinically meaningful.[2] Each item is scored as 0 (not true), 1 (somewhat or sometimes true), or 2 (very true or often true), with a maximum possible score of 90 points.[2] Lower RSBQ scores reflect less severity in signs and symptoms of Rett syndrome.[2] A decrease in total score over time may indicate improvement in neurobehavioral features assessed by the questionnaire.[2] A minimal clinically important difference (MCID) has not been determined nor validated for this tool. Although it was not designed to measure symptom improvement in a clinical trial and has not been validated for this purpose, in the absence of any other Rett syndrome-specific instruments, the RSBQ has been used as an outcome measure in clinical trials.[17]

Three ordinal Clinical Global Impression (CGI) scales (Severity, Improvement, and Efficacy) have been used as an outcome measures in psychopharmacology (depression, social anxiety disorder, panic disorder, schizophrenia, and bi-polar disorder) clinical trials.[17,19,20] The CGI scales were designed to provide a basis, independent of ratings on a questionnaire, for the study clinician to make a global assessment of a study patient's condition before and after the initiation of a study medication.[19] This provides a means of determining whether in the view of an experienced clinician the condition under study had improved, worsened, or stayed the same.[19] The CGI-Improvement (CGI-I) score is rated by clinicians to assess whether a patient has improved or worsened relative to baseline on a 7-point scale ranging from 1 (very much improved) to 7 (very much worse) in which a 1 point decrease in score from baseline indicates improvement.[20] A CGI-I score of 2 (much improved) is appropriate for definite, unequivocal improvement of a magnitude that makes the clinician confident that the treatment is helping.[19] A score of 3 or 5 (minimally improved or minimally worse) is appropriate if variations in ratings and other criteria appear to represent more than random chance or rating error, but are not definite and unequivocal.[19] A score of 4 (no change) is appropriate for slight variation in either direction of a magnitude that is likely due to chance, natural history, external events, or rating error.[19] Higher scores signify greater severity and/or worse outcomes.[20] The CGI-I scale was recently adapted to assess changes in patients with Rett syndrome.[21] The use of the CGI-I scale in Rett syndrome requires familiarity with the condition that limits its use to major clinical centers and may be difficult to translate into wider use.[17]

The Communication and Symbolic Behavior Scales Developmental Profile-Infant-Toddler Social Composite Score (CSBS-DP-IT-SCS) was used as a secondary outcome in the trofinetide phase 3 RCT. The CSBS-DP-IT-SCS is a 24-item caregiver screening assessment of pre-verbal healthy infants and toddlers aged 6 through 24 months.[22] The instrument was designed to screen healthy children for potential communication deficits.[2] The scale asks parent impressions regarding infant development in 7 domains: emotion and eye gaze, communication, gestures, sounds, words, understanding, and object use.[4] Each item is scored using a three-level rating of frequency: “not yet”, “sometimes”, and “often.”[4] The tool is intended to be a screener in healthy children and was not designed to detect improvement or worsening in communication in the setting of a clinical trial.[4] There is concern that parents may not always be able to objectively assess a neurologically impaired child’s non-verbal cues.[4]

See **Appendix 1** for **Highlights of Prescribing Information** from the manufacturer including, indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:
Trofinetide is indicated for the treatment of Rett syndrome in adults and pediatric patients aged 2 years and older.[1] Trofinetide is supplied as a 200 mg/mL oral solution administered twice daily as a weight-based dose either orally or via gastrostomy tube.[2] The wholesale acquisition cost (WAC) of trofinetide is $9,495 for a 450 ml bottle. A patient weighing 50 kg or more would require 60 ml twice daily, or 8 bottles per month which would cost approximately $76,000. Trofinetide oral solution received FDA approval in March 2023 with fast tracked, priority review under orphan drug and rare pediatric disease designations.[4] Trofinetide is a synthetic analog of the N-terminal tripeptide of insulin like growth factor 1, glycine-proline-glutamate.[4] Based on data from mouse models, it is hypothesized that trofinetide may decrease neuroinflammation potentially leading to normalized synaptic function.[2]

An exploratory dose-ranging phase 2 study was conducted in females aged 5 to 15 years diagnosed with genetically confirmed typical Rett syndrome (**Table 4**).[23] The study had a two-week placebo run-in after which time baseline assessments for the randomized phase were assessed.[23] Patients were given the following trofinetide doses (50mg/kg, 100 mg/kg, and 200 mg/kg) twice daily for 40 days after being up-titrated to their respective dose.[23] The primary outcome was an assessment of adverse effects and serious adverse effects (n=62).[23] Only one participant (200 mg/kg group) was withdrawn from the study because of increased gastroesophageal reflux, moderate diarrhea, and mild vomiting, which resolved uneventfully after discontinuation.[23] Four serious adverse effects occurred in 3 participants: 1 participant receiving placebo, 1 participant receiving 100 mg/kg, and 1 participant receiving 200 mg/kg.[23] Following a review of safety data, an additional 20 patients were randomized 1:1 to placebo or the 200 mg/kg dosing regimen for a total enrollment of 82 patients in the modified intention to treat (mITT) population.[23] The purpose of enriching these groups was to maximize detection of clinical benefit.[23] Secondary outcomes include evidence of efficacy as measured by the RSBQ and CGI-I. Only the 200 mg/kg twice daily dosing regimen showed improvement compared placebo.[23] For change from baseline on day 14 to day 54 in RSBQ total score, trofinetide 200 mg/kg showed evidence of efficacy with 4.4-point difference ($p = 0.042$) compared to placebo.[23] The CGI-I score at day 54 showed a -0.5 unit difference from placebo ($p = 0.029$) favoring 200 mg/kg of trofinetide.[23] These results were considered confirmatory evidence by the FDA to support results from the phase 3 RCT.[4]

The efficacy and safety of trofinetide were evaluated in single double-blind, placebo-controlled, phase 3, RCT (LAVENDER) of 187 female patients aged 5 to 20 years with genetically confirmed typical Rett syndrome.[3] Patients were randomized 1:1 to receive trofinetide 200 mg/kg oral solution (n=93) or matching placebo oral solution (n=94) twice daily for 12 weeks.[3] In the respective trofinetide and placebo groups, 41% and 42% of patients recived the study medication via gastrostomy tube.[3] The dose of trofinetide was based on patient weight to achieve similar exposure in all patients.[3] Patients were stratified into 3 age groups (5 to 10 years, 11 to 15 years, 16 to 20 years) and by baseline RSBQ score (<35 or ≥ 35).[4] The results of this RCT were not published until May 2023, therefore, the trofinetide FDA summary and review were the primary sources for study details prior to publication.[2,4] The mean age of enrolled participants in this trial was 11 years.[2] Most of the patients were White (92%), 6% were Asian, and 2% were Black.[2] Patients with celiac disease, irritable bowel syndrome, and diabetes were excluded from trial enrollment.

The co-primary efficacy measures were changes from baseline in the caregiver administered RSBQ total score and the CGI-I score at week 12.[3] Scores on the RSBQ can range from 0 to 90 with higher scores indicating higher severity of the signs and symptoms of Rett syndrome.[2] The manufacturer proposed the RSBQ as the primary endpoint for the LAVENDER trial, but the FDA did not agree, as it is not clear that small changes on this scale are clinically meaningful.[2] The FDA also noted that many of the items in the scale reflected signs of the disease and not necessarily directly reflect how patients feel or function.[2] Based on FDA recommendations, the CGI-I score was added as a co-primary endpoint to support a statistically significant change in the RSBQ as clinically meaningful.[2] The CGI-I is a 7-point scale rated by clinicians to assess how much a patient's illness has improved or worsened.[21] In general, a one-point change will signify improvement or worsening of the symptoms. For the RSBQ score, the LSM change from baseline to week 12 was −4.9 for trofinetide versus −1.7 for placebo (difference: −3.1; 95% CI −5.7 to −0.6; P=0.0175; low-quality evidence).[2] Although the study was not designed or powered to show a statistically significant difference from

placebo on each RSBQ subscale, change from baseline was directionally in favor of trofinetide.[4] The mean CGI-I score at Week 12 was 3.5 for trofinetide versus 3.8 for placebo (difference: −0.3; 95% CI −0.5 to −0.1; P=0.003; low-quality evidence).[2] According to the FDA, the modest finding of a benefit on these endpoints supports the effectiveness of trofinetide in symptom improvement over 12 weeks in people with Rett syndrome.[4]

A secondary endpoint was the effect of trofinetide on the individual's ability to communicate as assessed by the caregiver using the Communication and Symbolic Behavior Scales Developmental Profile-Infant-Toddler Social Composite Score (CSBS-DP-IT-SCS).[2] On the CSBS-DP-IT score the LSM change was −0.1 for trofinetide and −1.1 for placebo from baseline to Week 12 (difference: 1.0; 95% CI 0.3 to 1.7; p=0.0064).[2] This data seems to indicate that placebo-treated patients worsened in their ability to communicate while trofinetide-treated patients maintained their ability to communicate as assessed by the CSBS-DP-IT-SCS.[4] According to the FDA reviewers, insufficient evidence was provided to justify the administration, scoring, and interpretation of the CSBS-DP-IT-SCS for people with Rett syndrome, as this tool has not been validated for use in this population.[2]

Of the randomized patients, 23 (25%) in the trofinetide arm discontinued the study early compared with 9 patients (10%) in the placebo arm who prematurely withdrew from the study.[3] The majority of trofinetide patients (70%) discontinued the study due to an adverse event (diarrhea or vomiting); while the majority fo placebo-treated patients (56%) withdrew due to COVID-19 quarantine measures.[3] Thirty-eight patients (41%) in the trofinetide arm used loperamide during the study compared with 1 patient (1%) in the placebo arm.[4] Twelve percent of trofinetide-treated subjects (compared to 4% of placebo-treated subjects) experienced a loss of greater than 7% of body weight.[2] This is clinically significant as this is a primarily pediatric population who would be expected to gain weight over time rather than lose a significant amount of weight in a short period of time.[2]

The effectiveness of trofinetide in patients 2 to 4 years of age was hypothesized through extrapolation of the results observed in the LAVENDER study population, based on the similarity of the disease pathophysiology as well as the assumption of similar exposure response relationship between patients aged 2 to 4 and patients 5 years of age and older.[2] An open-label PK study was conducted in 2 treatment periods; 12 weeks to evaluate the drug PK characteristics and 21 months to evaluate long-term safety. Thirteen patients with Rett syndrome between 2 and 4 years of age completed 12 weeks of treatment.[2] The PK analysis demonstrated similar PK exposure of trofinetide and similar safety profiles in the younger pediatric population compared with pediatric patients 5 years of age and older.[2]

Specific details for the Phase 2 and Phase 3 clinical trial (LAVENDER), which contribute to the safety and efficacy data for the use of trofinetide in people with Rett syndrome are described and evaluated below in **Table 4.**

Study Limitations:
According to the FDA reviewers, limitations of the trofinetide evidence are the: 1) reliance on one single adequate and well controlled study with confirmatory evidence, 2) the limitations of the RSBQ as a tool to measure functional improvement, 3) the disproportionate study withdrawal rate (23 trofinetide-treated patients versus 9 placebo-treated patients), and 4) the disproportionate and rapid onset of diarrhea in the trofinetide arm along with the disproportionate use of loperamide in the trofinetide arm, with a risk for functional unblinding (see **Table 4**).[4] There was little racial or ethnic diversity among the enrolled subjects (92% of patients were White and 91% were not Hispanic or Latino).[4] Patients younger than 5 years of age were not enrolled, despite the mean age of symptom onset between 6 and 30 months and diagnosis around 3 years of age. There is insufficient evidence to support the use of the CSBS-DP-IT as an assessment tool in patients with Rett syndrome.[2] This tool is intended to be a screener for healthy children and was not designed to detect improvement or worsening in communication in the setting of a clinical trial.[2] In addition, 12 weeks is relatively short time period to assess functional improvement in a life-long, progressive disease.

A 40-week, open-label extension of LAVENDER (LILAC-1) was conducted to evaluate long term safety and tolerability of trofinetide in 154 patients.[4] Results are not yet published. Information about this trial was obtained from the FDA review of trofinetide.[2] Another open-label extension of LILAC-1 (LILAC-2) is currently ongoing to evaluate long-term safety in 47 patients.[4] Finally, a phase 2/3 RCT (DAFFODIL) is being conducted in 13 patients aged 2 to 4 years of age with Rett syndrome to evaluate safety, tolerability, and PK of trofinetide in this population.[4]

Clinical Safety:
Diarrhea was reported in 81% of trofinetide-treated patients compared with 19% of placebo-treated patients in the phase 3 LAVENDER trial.[3] In this trial vomiting was also reported more frequently in the trofinetide-treated patients compared with placebo-treated patients (27% vs. 10%, respectively).[3] Approximately 17% of trofinetide-treated patients withdrew from therapy due diarrhea or vomiting.[3] In the open-label extension trial, diarrhea occurred in 84% of subjects on long-term (greater than 1 year) treatment with trofinetide.[2] Of those who did not withdraw from treatment, 40% required concomitant therapy with loperamide to treat the diarrhea and prevent dehydration.[2] The manufacturer recommends if patients are taking a laxative prior to starting trofinetide, it should be discontinued before starting therapy.[1]

Weight loss is possible during trofinetide treatment.[1] Weight loss greater than 7% from baseline was observed in 12% of trofinetide-treated patients compared with 4% of placebo-treated patients.[1] This is clinically significant as this is a primarily pediatric population who would be expected to gain weight over time rather than lose a significant amount of weight in a short period of time.[2] Patient weight should be monitored and if significant weight loss occurs, the manufacturer recommends interrupting therapy, reducing trofinetide dose or discontinuing the drug.[1]

Rates of adverse effects observed with trofinetide compared with placebo are presented in **Table 2**.[4] Serious adverse events included 2 events of seizure that were possibly be related to trofinetide; one case of urosepsis from urinary tract infection that occurred in the setting of diarrhea was deemed possibly related by the investigator; and a number of infections and respiratory conditions that occur frequently in the Rett syndrome and cannot be clearly attributed to trofinetide.[4]

Table 2. Adverse Reactions in at least 5% of Patients Treated with Trofinetide Compared with Placebo in the Phase 3 RCT[1]

Adverse Reaction	Trofinetide (n=93)	Placebo (n=94)
Diarrhea	82%	20%
Vomiting	29%	12%
Fever	9%	4%
Seizure	9%	6%
Anxiety	8%	1%
Decreased Appetite	8%	2%
Fatigue	8%	1%
Nasopharyngitis	5%	1%

The effects of trofinetide in pregnancy and lactation were not evaluated in clinical trials, as pregnant individuals were excluded from study enrollment.[1] Although trofinetide is primarily renally eliminated, no clinical study was conducted to evaluated pharmacokinetic (PK) parameters in renal impairment. Administration of

trofinetide to patients with moderate or severe renal impairment is not recommended.[1] The FDA has stipulated to the manufacturer that trofinetide post-marketing trials are required to evaluate the effect of moderate renal impairment on trofinetide elimination and to evaluate potential drug interactions.[4]

Look-alike / Sound-alike Error Risk Potential: No results available

Comparative Endpoints:

Clinically Meaningful Endpoints:
1) Improved symptom scores
2) Improved ability to complete activities of daily living
3) Prolonged survival
4) Serious adverse events
5) Study withdrawal due to an adverse event

Primary Study Co-Endpoints:
1) Improved symptom scores as assessed by the caregiver-administered RSBQ and provider-administered CGI-I scoring tools from baseline to 12 weeks.

Table 3. Pharmacology and Pharmacokinetic Properties.[1]

Parameter	
Mechanism of Action	Unknown
Oral Bioavailability	84% of dose was absorbed following oral administration of a 12-gram dose
Distribution and Protein Binding	Volume of distribution: 80 Liters in adults. Protein binding is low (< 6%).
Elimination	Primarily excreted unchanged (approximately 80% of dose) in the urine.
Half-Life	Half-life is 1.5 hours
Metabolism	Hepatic metabolism is not a not a significant route of trofinetide elimination.

Table 4. Comparative Evidence Table.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1.Glaze, DG, et al[23] DB, MC, PC Phase 2 RCT	1.Trofenetide 50 mg/kg orally twice daily 2.Trofenetide 100 mg/kg orally twice daily 3.Trofenetide 200 mg/kg orally twice daily 4.Volume matched placebo orally twice daily	Demographics: 1. Median age: 9.7 yo 2. Female: 100% 3. Mean weight: 26 kg 4. Mean baseline RSBQ score: 44 points 5. Race -White: 94% -Asian: 4% -Black: 1% -Other: 1% Key Inclusion Criteria: -Aged 5 to 15 yo -Female with genetically confirmed typical RS	ITT (safety): 1. 15 2. 16 3. 17 4. 14 mITT (efficacy): 1. 15 2. 16 3. 27 4. 24 Attrition (ITT): 1. 0	Primary Endpoint: Number of patients with SAEs at 11 weeks (ITT population) 1. 0 2. 1 3. 1 4. 1 Secondary Endpoints: Change from baseline on the RSBQ and CGI-I scores over 40 days (day 14 - baseline to day 54) in mITT population	NA	Diarrhea 1. 4 (27%) 2. 2 (13%) 3. 15 (56%) 4. 1 (4%) Vomiting 1. 1 (7%) 2. 2 (13%) 3. 6 (22%) 4. 3 (13%) (p value and 95% CI NR)	NA NA	**Risk of Bias (low/high/unclear)**: Selection Bias: Low. Randomized 1:1:1:1 to trofinetide or placebo via IRTS for 54 days. After safety review, additional 20 patients randomized 1:1 to 200 mg/kg trofinetide or placebo. Stratified by age (≤ 10 yo and > 10 yo). Baseline characteristics were balanced between treatment groups. Performance Bias: Unclear. Placebo and trofinetide supplied in identical packaging and flavoring. Lack of consistency with titration/tapering dosing schedules may have led to variance in volumes of study drug being administered and may have led to unblinding. Adherence to treatment regimen was not assessed. Detection Bias: Unclear. Sponsor, participants, caregivers and clinicians all blinded to treatment assignment. Method of maintain blinding not described.

	*Two-week placebo run in for all patients, baseline assessments recorded on day 14	-Baseline weight 15 to 100 kg -Documented mutation in MeCP2 gene -Able to swallow medication or have it administered via gastrostomy tube Key Exclusion Criteria: -History of long QT syndrome -Unstable seizure profile -Significant gastrointestinal disease -Treatment with insulin or anticonvulsants with liver enzyme inducing effects	2. 0 3. 1 4. 0	a. LSM change in RSBQ Score at 40 days from baseline 1. -3.0 2. -1.5 3. -6.7 4. -2.3 1 vs. 4: NS 2 vs. 4: NS 3 vs 4: p= 0.042 (95% CI NR) b. LSM change in CGI-I score at 40 days from baseline in mITT population. 1. 3.3 2. 3.4 3. 3.0 4. 3.5 1 vs. 4: NS 2 vs. 4: NS 3 vs. 4: p=0.029 (95% CI NR)	NA NA			Attrition Bias: Low. One patient in the 200mg/kg ITT group withdrew due to GI effects. Reporting Bias: Low. Protocol available on line. Other Bias: High. Manufacturer funded the study and contributed to study design and report writing. **Applicability**: Patient: There was little racial or ethnic diversity among the enrolled subjects (94% of patients were White). Patients younger than 5 yo not enrolled, despite mean age of diagnosis at 2.5 yo. All patients had genetically confirmed RS. Cannot extrapolate results to patients with atypical RS. Intervention: Phase 2 dose finding trial to assess safety. Comparator: As no other FDA-approved treatments are available, placebo was an appropriate comparator. Outcomes: Primary outcome was safety assessment. Secondary outcomes: change in symptoms assessed from baseline to 12 weeks in RSBQ and CGI-I scales. MCID not determined for either scale. CGI-I was not designed for RS assessment. Setting: 12 clinical sites in the United States
2. Neul JL, et al.[3] FDA review[2,4] LAVENDER trial DB, PC, PG Phase 3 RCT	1. Trofinetide 200 mg/kg orally or via gastrostomy tube twice daily 2. Placebo 25 ml to 60 mL orally or via tube twice daily	Demographics: 1. Median age: 10.9 yo 2. Female: 100% 3. Mean weight: 30 kg 4. Mean baseline RSBQ score: 44 points 5. Race -White: 92% -Asian: 6% -Black: 2% Key Inclusion Criteria: -Aged 5 to 20 yo -Female with genetically confirmed typical RS -Baseline weight ≥ 12 kg -Documented mutation in MeCP2 gene -CGI-S score ≥ 4 points -Able to swallow medication or have it	ITT: 1. 93 2. 94 Attrition: 1. 23 (25%) 2. 9 (10%)	Co-Primary Endpoints: Change from baseline on the RSBQ and CGI-I scores at week 12. a. LSM change in RSBQ Score at 12 weeks from baseline 1. -4.9 2. -1.7 LSM Difference: -3.1 95% CI: -5.7 to -0.6 P=0.0175 b. LSM change in CGI-I score at 12 weeks from baseline 1. 3.5 2. 3.8 Difference: -0.3 95% CI: -0.5 to -0.1 P=0.003	NA NA	Any TEAEs 1. 86 (93%) 2. 51 (54%) P<0.0001 Serious TEAE 1. 3 (3%) 2. 3 (3%) P=0.9894 Drug Withdrawal due to AE 1. 16 (17%) 2. 2 (2%) P=0.0005 Diarrhea 1. 75 (81%) 2. 18 (19%) P<0.001	NA NA NA NA NA	**Risk of Bias (low/high/unclear)**: Selection Bias: Low. Randomized 1:1 to trofinetide or placebo via IRTS. Stratified by age and baseline RSBQ severity score. Baseline characteristics were balanced between treatment groups. Performance Bias: High. Placebo and trofinetide supplied in identical packaging and flavoring. Side effects such as severe diarrhea requiring treatment could have led to unblinding of caregiver or investigators, who provided the co-primary endpoint scoring. Detection Bias: High. Sponsor, participants, caregivers and clinicians all blinded to treatment assignment. Method of maintain blinding was not described. Unblinding may have occurred due to adverse effects (diarrhea, vomiting) observed with trofinetide. Attrition Bias: High. Overall high attrition for short term study and with unbalanced overall attrition in the active treatment group compared with placebo (25% vs. 10%). Most withdrawals in the trofinetide group (70%) were due to AEs (diarrhea/vomiting). Most withdrawals in the

		administered via gastrostomy tube -Either no seizures or a stable pattern of seizures and medication within 8 weeks of study enrollment -Caregiver is English-speaking <u>Key Exclusion Criteria</u>: -History of long QT syndrome -Significant cardiovascular, gastrointestinal, or endocrine disease (e.g., thyroid disease or diabetes) -Treatment with insulin, insulin-like growth factor 1, or growth hormone within 12 weeks of study enrollment		<u>Secondary Endpoint</u>: LSM change from baseline on the CSBS-DP-IT-social composite score at 12 weeks 1. -0.1 2. -1.1 Difference: 1.0 95% CI: 0.3 to 1.7 P=0.006	NA	<u>Vomiting</u> 1. 25 (27%) 2. 9 (10%) P=0.0022		placebo group (56%) were due to COVID-19 quarantine measures. <u>Reporting Bias</u>: High. Protocol available on-line. For missing data, last observation carried forward was imputed by the last expected dosing date. Protocol amended during the study to add a plan for managing diarrhea, which may have compromised the blinding of the study. <u>Other Bias:</u> High. Manufacturer funded the study and contributed to study design and report writing. Several authors received personal compensation and research support from the manufacturer, which may resulted in a conflict of interest that could influenced the conduct or outcomes of the study. Four authors are employed by manufacturer. **Applicability**: <u>Patient</u>: There was little racial or ethnic diversity among the enrolled subjects (92% of patients were White and 91% were not Hispanic or Latino). Caregiver had to be English speaking, which excluded non-English speakers. Patients younger than 5 yo not enrolled, despite mean age of diagnos around 3 yo. All patients had genetically confirmed RS. Patients older than 20 yo also excluded, which limited applicability of results to older patients with RS. <u>Intervention</u>: Safe weight-based dosing determined in dose-finding phase 2 trials. Duration of trial was short for a life time condition. <u>Comparator</u>: As no other FDA-approved treatments are available, placebo was an appropriate comparator. <u>Outcomes</u>: Change in symptoms assessed from baseline to 12 weeks in RSBQ and CGI-I scales. MCID not determined for either scale. CGI-I was not designed for RS assessment. <u>Setting</u>: 21 clinical sites in the United States
<u>Abbreviations</u>: AE = adverse effect; ARR = absolute risk reduction; CGI-I = Clinician's Global Impression of Improvement; CSBS-DP-IT = Communication and Symbolic Behavior Scales Developmental Profile-Infant Toddler; CI = confidence interval; FDA = United States Food and Drug Administration; IRTS = interactive response technology system; ITT = intention to treat; kg = kilograms; LSM = least squares mean; MCID = minimal clinically important difference; MECP2 = methyl-CpG-binding protein 2; mITT – modified intention to treat; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NR = not reported; PG = parallel group; PP = per protocol; RS = Rett syndrome; RSBQ = Rett Syndrome Behavioral Questionnaire; SAEs = serious adverse events; TEAEs = treatment-emergent adverse effects; yo = years old							

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Appendix 1: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use DAYBUE safety and effectively. See full prescribing information for DAYBUE.

DAYBUE™ (trofinetide) oral solution
Initial U.S. Approval: 2023

----------INDICATIONS AND USAGE----------
DAYBUE is indicated for the treatment of Rett syndrome in adults and pediatric patients 2 years of age and older. (1)

----------DOSAGE AND ADMINISTRATION----------
- Recommended dosage is twice daily, morning and evening, according to patient weight. DAYBUE can be given with or without food. (2.1)

Patient Weight	DAYBUE Dosage	DAYBUE Volume
9 kg to less than 12 kg	5,000 mg twice daily	25 mL twice daily
12 kg to less than 20 kg	6,000 mg twice daily	30 mL twice daily
20 kg to less than 35 kg	8,000 mg twice daily	40 mL twice daily
35 kg to less than 50 kg	10,000 mg twice daily	50 mL twice daily
50 kg or more	12,000 mg twice daily	60 mL twice daily

- Can be given orally or via gastrostomy (G) tube; doses administered via gastrojejunal (GJ) tubes must be administered through the G-port. (2.2)

----------DOSAGE FORMS AND STRENGTHS----------
- Oral solution: 200 mg/mL (3)

----------WARNINGS AND PRECUATIONS----------
- Diarrhea: Most patients experience diarrhea during treatment with DAYBUE. Advise patients to stop laxatives before starting DAYBUE. If diarrhea occurs, patients should start antidiarrheal treatment, increase oral fluids, and notify their healthcare provider. Interrupt, reduce dose, or discontinue DAYBUE if severe diarrhea occurs or if dehydration is suspected. (2.4, 5.1)
- Weight Loss: Weight loss may occur in patients treated with DAYBUE. Monitor weight and interrupt, reduce dose, or discontinue DAYBUE if significant weight loss occurs. (5.2)

----------CONTRAINDICATIONS----------
None. (4)

----------ADVERSE REACTIONS----------
The most common adverse reactions (that occurred in at least 10% of DAYBUE-treated patients and at least 2% greater than in placebo) were diarrhea and vomiting. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Acadia Pharmaceuticals Inc. at 1-844-422-2342 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- Orally administered CYP3A4 sensitive substrates for which a small change in substrate plasma concentration may lead to serious toxicities: closely monitor for adverse reactions with concomitant use. (7.1)
- OATP1B1 and OATP1B3 substrates for which a small change in substrate plasma concentration may lead to serious toxicities: avoid concomitant use. (7.1)

----------USE IN SPECIFIC POPULATIONS----------
Moderate to severe renal impairment: DAYBUE is not recommended. (8.6)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 3/2023

Trofinetide (DAYBUE)

Goal(s):

- Promote use that is consistent with medical evidence and product labeling in patients with Rett syndrome.

Length of Authorization:

- Up to 12 months

Requires PA:

- Trofinetide oral solution

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Table 1. Recommended Weight-Based Trofinetide Oral Solution 200 mg/mL Dosing

Patient Weight	Trofinetide Dosage	Trofinetide Volume
9 kg to less than 12kg	5,000 mg twice daily	25 mL twice daily
12 kg to less than 20 kg	6000 mg twice daily	30 mL twice daily
20 kg to less than 35 kg	8,000 mg twice daily	40 mL twice daily
35 kg to less than 50 kg	10,000 mg twice daily	50 mL twice daily
50 kg or more	12,000 mg twice daily	60 mL twice daily
Abbreviations: kg = kilograms; mg = milligrams; mL = millilters		

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the request for continuation of therapy previously approved by the FFS program?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #3
3. Does the patient have a diagnosis of Rett syndrome?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
4. Is there documentation of genetic testing to confirm Rett syndrome diagnosis?	**Yes:** Go to #5	**No:** Pass to RPh. Refer to Medical Director for review.
5. Is the requested medication prescribed by a neurologist or a provider with experience in treating Rett syndrome?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness.
6. Is the request for an FDA approved age (e.g., 2 years of age and older)?	**Yes**: Go to #7	**No:** Pass to RPh. Deny; medical appropriateness
7. Is the request for an approved weight-based dosing regimen (see **Table 1**)?	**Yes:** Go to #8	**No:** Pass to RPh. Deny; medical appropriateness
8. Has the provider documented specific and measurable goals of therapy? Note: Documentation should include what will be assessed, how progress will be measured, and timeline for assessment. Goals should be attainable within 6 months and relevant to the condition or health of the patient. Documentation of progress toward or achievement of therapeutic goals will be required for renewal.	**Yes:** Document Assessment and Date:_____ Approve for 6 months. Note: The first 2 pharmacy fills are limited to 14 days each to assess tolerance to therapy. Initial fills can overlap to ensure adequate time for delivery. 1.Approve Initial Request for enough units up to 14 days. 2. Approve enough units to cover subsequent 14-28 days. 3. Approve enough units for up to 6 months (5 to 24 weeks).	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1. Is there evidence of adherence and tolerance to therapy through pharmacy claims/refill history and/or provider assessment?	**Yes:** Go to #2	**No:** Pass to RPh; Deny; medical appropriateness.
2. Has the patient met the goals of therapy described in the initial authorization by the prescribing provider and provider attests to patient's stabilization on therapy?	**Yes:** Approve for 12 months. Document assessment and provider attestation received.	**No:** Pass to RPh; Deny; medical appropriateness.

P&T/DUR Review: 8/23 (DM)
Implementation: 9/1/23