CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217026Orig1s000

SUMMARY REVIEW

Summary Memorandum

<table>
<tr><td>Date</td><td>March 10, 2023</td></tr>
<tr><td>From</td><td>Laura Jawidzik, MD
Cross-Disciplinary Team Lead
Associate Director (Acting)
Division of Neurology 1 (DN1)

Teresa Buracchio, MD
Director, DN1
Director (Acting), Office of Neuroscience</td></tr>
<tr><td>Subject</td><td>Summary Memorandum</td></tr>
<tr><td>NDA/BLA # and Supplement#</td><td>NDA 217026</td></tr>
<tr><td>Applicant</td><td>Acadia Pharmaceuticals</td></tr>
<tr><td>Date of Submission</td><td>July 12, 2022</td></tr>
<tr><td>PDUFA Goal Date</td><td>March 12, 2023</td></tr>
<tr><td>Name</td><td>Daybue (trofinetide)</td></tr>
<tr><td>Dosage Form(s)/Strength</td><td>Solution 200 mg/ml</td></tr>
<tr><td>Applicant Proposed Indication(s)/Population(s)</td><td>treatment of Rett syndrome</td></tr>
<tr><td>Recommendation on Regulatory Action</td><td>Approval</td></tr>
<tr><td>Recommended Indication(s)/Population(s) (if applicable)</td><td>treatment of Rett syndrome in adults and pediatric patients 2 years of age and older</td></tr>
<tr><td>Recommended Dosing Regimen(s) (if applicable)</td><td>Twice daily dosing according to patient weight:

<table>
<tr><td>Patient Weight</td><td>Daybue Dose</td></tr>
<tr><td>9 kg to <12 kg</td><td>25 mL (5 g) twice daily</td></tr>
<tr><td>≥12 kg to <20 kg</td><td>30 mL (6 g) twice daily</td></tr>
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1. Benefit-Risk Assessment

Benefit-Risk Assessment Framework

Benefit-Risk Integrated Assessment

Trofinetide is a synthetic analog of the tripeptide glycine-proline-glutamate (GPE). GPE is a product of the naturally occurring cleavage of IGF-1 protein. The mechanism by which trofinetide exerts its effect in Rett syndrome is unclear. Trofinetide is supplied as a 200 mg/mL solution to be administered twice daily orally or by gastrostomy tube without regard to meals. The proposed dosage is a weight-band based dosing with fixed doses for five different weight bands from 9 kg to ≥ 50 kg.

Rett syndrome is a rare genetic disorder that occurs predominantly in females with an incidence of approximately 1 in 15,000 live births. Classical or typical Rett syndrome is caused by mutations in the methyl-CpG binding protein 2 (*MECP2*) gene on the X-chromosome. Approximately 95% of females with Rett syndrome have a mutation in the *MECP2* gene. Most cases are caused by spontaneous mutations in this gene. The severity of the disease depends on the location and type of mutation in the *MECP2* gene. X-inactivation also plays a role in the severity of the phenotype.

Rett syndrome is characterized by normal development up until 6 to 18 months of age, at which point patients begin to regress. Between one and four years of age, patients lose the ability to perform skills that they previously had attained. Loss of language, loss of motor control, diminished social interaction, and development of stereotypies occur. Patients may lose the ability to ambulate or develop ataxia. Later in the course of the disease, patients may develop muscles weakness, joint contractures, and scoliosis. Seizures may develop. Life expectancy is reduced to approximately 40 to 50 years of age.

There are no FDA-approved therapies for the treatment of Rett syndrome. Most therapies available for patients with Rett syndrome are supportive therapies for the various manifestations and complications of the disorder.

The Applicant has provided data from a single adequate and well-controlled clinical trial (Study 003) as the primary basis of support of the effectiveness of trofinetide for the treatment of Rett syndrome. The Applicant proposed the Rett Syndrome Behavioral Questionnaire (RSBQ) as the primary endpoint for this trial with which the Division did not agree. Given that questions on the RSBQ assess not just symptoms but also signs of Rett syndrome, it is not clear that small changes on this scale are clinically meaningful. The Division recommended to the Applicant to include a co-primary endpoint to support that changes on the scale are clinically meaningful. The Applicant agreed and included the Clinician's

Global Impression of Improvement as the co-primary endpoint in the study to support that a statistically significant change on the RSBQ is clinically meaningful.

Study 003 was a 3-month randomized, double-blind, placebo-controlled study of trofinetide in female patients aged 5 to 20 years with genetically confirmed Rett syndrome. Subjects were given trofinetide orally twice daily for three months. A total of 187 patients with Rett syndrome received placebo (N=94) or trofinetide (N=93) daily for 12 weeks. The co-primary endpoints for the study were the change from baseline (CFB) on the RSBQ at week 12, and the CGI-I. There was a statistically significant difference between trofinetide-treated patients and placebo-treated patients on both co-primary endpoints favoring trofinetide [(RSBQ CFB-3.2 points, p=0.018, and CGI-I -0.3, p=0.003)]. Findings on the co-primary endpoints were supported by statistically significant results on a multiplicity controlled secondary endpoint, the Communication and Symbolic Behavior Scales Developmental Profile-infant-toddler social composite score (CSBS-DP-IT-SCS).

Confirmatory evidence for this application is based on the analysis of clinical efficacy endpoints from Study 002, an exploratory dose-ranging study in females aged 5 to 15 years diagnosed with genetically confirmed Rett syndrome. For change from baseline (day 14) to day 54 in RSBQ total score, the highest dose arm (200 mg/kg) showed evidence of efficacy with 4.7-point difference ($p = 0.035$) compared to placebo. CGI-I at day 54 showed a -0.5-unit difference from placebo ($p = 0.029$) favoring 200 mg/kg of trofinetide.

Study 009, an open-label PK study was conducted to evaluate the pharmacokinetics (PK) and safety in patients with Rett syndrome between 2 and 4 years of age. The study was intended to support extrapolation of efficacy and to provide data for the safety of trofinetide patients 2 to 4 years of age.

Given the substantial unmet need with no approved treatments for Rett syndrome, some level of uncertainty is acceptable in this setting and consideration of these results in the context of regulatory flexibility is appropriate. The application meets the substantial evidence standard based on one adequate and well-controlled clinical investigation plus confirmatory evidence. The single adequate and well-controlled study with positive results on the co-primary endpoints, accompanied by confirmatory evidence from a Phase 2 dose-ranging study, are adequate to provide substantial evidence of effectiveness. The effectiveness of trofinetide in patients 2 to 4 years of age was established through extrapolation of the efficacy observed in the Study 003 in Rett syndrome patients 5 years of age and older, 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.

The safety database for trofinetide was adequate for the intended population and proposed dosing regimen. There are no safety issues that preclude approval. Identified risks can be mitigated through product labeling. Warnings related to the risk of diarrhea and weight loss will be added to the product labeling. The overall benefit-risk profile is favorable as described in the benefit-risk framework below.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Rett syndrome is a rare genetic disorder that occurs predominantly in females with an incidence of approximately 1 in 15,000 live births. Classical or typical Rett syndrome is caused by mutations in the methyl-CpG binding protein 2 (*MECP2*) gene on the X-chromosome. Approximately 95% of females with Rett syndrome have a mutation in the *MECP2* gene. Most cases are caused by spontaneous mutations in this gene. The severity of the disease depends on the location and type of mutation in the *MECP2* gene. X-inactivation also plays a role in the severity of the phenotype. • Rett syndrome is characterized by normal development up until 6 to 18 months of age, at which point patients begin to regress. Between one and four years of age, patients lose the ability to perform skills that they previously had. Loss of language, loss of motor control, diminished social interaction, and development of stereotypies occur. Patients may lose the ability to ambulate or develop ataxia. Later in the course of the disease, patients may develop muscles weakness, joint contractures, and scoliosis. Seizures may develop. Life expectancy is reduced to approximately 40 to 50 years of age.	Rett syndrome is a serious and life-threatening pediatric disease causing significant neurological disability and early death in adults.
Current Treatment Options	• There are no FDA-approved treatments for Rett syndrome. • Current treatment focuses on management of complications of the disease such epilepsy, constipation, dysphagia, contractures, and scoliosis	There is significant unmet clinical need for effective treatments for Rett syndrome.
Benefit	• Trofinetide is a synthetic analog of glycine-proline-glutamate (GPE). GPE is a product of the naturally occurring cleavage of IGF-1 protein. • Trofinetide is supplied as a 200 mg/mL solution to be administered twice daily orally or by gastrostomy tube without regard to meals. The proposed dosage is a weight-band based dosing with fixed doses for five different weight bands from 9 kg to ≥ 50 kg. • The Applicant has provided data from Study 003; a 3-month, multicenter double-blind, placebo-controlled trial. This trial evaluated weight-based dosing in female patients aged 5 through 20	Study 003 provided reliable and statistically persuasive evidence that trofinetide can help patients with Rett syndrome achieve a clinically meaningful improvement in symptoms of their disease. Confirmatory evidence is provided from Study 002, a dose-ranging study in subjects with Rett syndrome.

<table>
<tr><th>Dimension</th><th>Evidence and Uncertainties</th><th>Conclusions and Reasons</th></tr>
<tr><td></td><td>
diagnosed with genetically confirmed Rett syndrome. The first co-primary efficacy analysis demonstrated a highly statistically significant treatment effect (p=0.018) on the RSBQ; an observer-reported outcome measure that assesses signs and symptoms of Rett syndrome. The second co-primary efficacy analysis also demonstrated a highly statistically significant treatment effect (p=0.003) in favor of trofinetide and corroborated that the measured change on the RSBQ is clinically meaningful.

Study 003: Co-Primary Efficacy Endpoints
<table>
<tr><th colspan="2"></th><th>Mean Baseline Score (SE)</th><th>Mean Week 12 Score (SE)</th><th>LS Mean Change from Baseline to Week 12 (SE)</th><th>p-value</th></tr>
<tr><td rowspan="2">RSBQ</td><td>DAYBUE</td><td>43.7 (1.21)</td><td>39.9 (1.38)</td><td>-4.9 (0.94)</td><td rowspan="2">0.018</td></tr>
<tr><td>Placebo</td><td>44.5 (1.26)</td><td>42.8 (1.42)</td><td>-1.7 (0.90)</td></tr>
<tr><td>CGI-I</td><td>DAYBUE</td><td>--</td><td>3.5 (0.08)</td><td></td><td>0.003</td></tr>
<tr><td></td><td>Placebo</td><td></td><td>3.8 (0.06)</td><td></td><td></td></tr>
</table>

• Confirmatory evidence for this application is based on the analysis of clinical efficacy endpoints from Study 002, an exploratory dose-ranging study in females aged 5 to 15 years diagnosed with genetically confirmed Rett syndrome. For change from baseline (day 14) to day 54 in RSBQ total score, the highest dose arm (200 mg/kg) showed evidence of efficacy with 4.7-point difference (p = 0.035) compared to placebo. CGI-I at day 54 showed a -0.5-unit difference from placebo (p = 0.029) favoring 200 mg/kg of trofinetide. The 50 mg/kg and 100 mg/kg doses of trofinetide did not show any improvement compared
</td><td>Study 009 supports the approval of trofinetide in pediatric patients aged 2 through 4 with Rett syndrome.</td></tr>
</table>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	to placebo. • Study 009: The effectiveness of trofinetide in patients 2 to 4 years of age was established through extrapolation of the efficacy observed in the Study 003 in Rett syndrome patients 5 years of age and older, 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. Study 009, an open-label PK study was conducted to evaluate the pharmacokinetics (PK) and safety in Rett syndrome patients between 2 and 4 years of age. The interim PK analysis based on the data from 13 pediatric patients 2 to 4 years of age treated with trofinetide for 12 weeks demonstrated similar PK exposure of trofinetide and similar safety profiles to those in the pediatric patients ≥5 years of age and adults.	
Risk and Risk Management	• At the time of the 120-day safety update, 100 patients had ≥6 months of exposure, 86 had ≥9 months, and 69 had ≥ 12 months to trofinetide. • The most common adverse reactions reported in at least 5% of trofinetide-treated subjects (and ≥2% more frequently than in placebo-treated patients) were diarrhea, vomiting, fever, seizure, anxiety, decreased appetite, fatigue, and nasopharyngitis. • Diarrhea occurred in nearly 85% of subjects on long-term treatment with trofinetide. Approximately 25% withdrew due to this adverse event. Of those who did not withdraw from treatment, 50% required concomitant therapy to treat the diarrhea. • During the blinded portion of Study 003, 12% of trofinetide-treated subjects (compared to 4% of placebo-treated subjects) experienced a loss of greater than 7% of body weight. 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.	The safety database was adequate in terms of size and duration given that Rett syndrome is a rare disease. The risks associated with the treatment of trofinetide are acceptable for the indicated population. Risk will be managed through product labeling. Warnings and precautions will include diarrhea and weight loss. Because pregnancy is expected to be extremely rare in this population, a pregnancy outcomes study will not be a postmarketing requirement.

2. Background

This review discusses the data submitted by Acadia Pharmaceuticals in support of a new drug application (NDA) for trofinetide for the treatment of the Rett syndrome in adults and pediatric patients 2 years of age and older. Trofinetide is a new molecular entity (NME) that has not been approved for any indication and has not been the subject of a prior marketing application.

Rett syndrome is a rare genetic disorder that occurs predominantly in females with an incidence of approximately 1 in 15,000 live births. Classical or typical Rett syndrome is caused by mutations in the methyl-CpG binding protein 2 (*MECP2*) gene on the X-chromosome. Approximately 95% of females with Rett syndrome have a mutation in the *MECP2* gene. Most cases are caused by spontaneous mutations in this gene. The severity of the disease depends on the location and type of mutation in the *MECP2* gene. X-inactivation also plays a role in the severity of the phenotype.

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Trofinetide is a synthetic analog of glycine-proline-glutamate (GPE). GPE is a product of the naturally occurring cleavage of IGF-1 protein. The mechanism by which trofinetide exerts its effect in Rett syndrome is unclear. Trofinetide is supplied as a 200 mg/mL solution to be administered twice daily orally or by gastrostomy tube without regard to meals. The proposed dosage is a weight-band based dosing with fixed doses for five different weight bands from 9 kg to $\geq$ 50 kg.

There are no FDA-approved therapies for the treatment of Rett syndrome. Most therapies available for patients with Rett syndrome are supportive therapies for the various manifestations and complications of the disorder.

The Applicant has provided data from a single adequate and well-controlled clinical trial (Study 003) as the primary basis of support of the effectiveness of trofinetide for the treatment Rett syndrome. In addition, the Applicant submitted data from Study 002, an exploratory dose-finding study as confirmatory evidence in support of the application. Study 003 was a Phase 3, randomized, double-blind, placebo-controlled trial of patients aged 5 to 20 years diagnosed with Rett syndrome. The choice of endpoints for this trial was discussed with the Applicant at the end-of-phase 2 (EOP2) meeting (October 24, 2017). The Division did not agree with the Applicant's proposal to use the Rett Syndrome Behavior questionnaire (RSBQ) as the primary endpoint for the planned Phase 3 study. The Division noted that many of the items in the scale reflected signs of the disease and not necessarily directly reflect how patients feel or function. The Division recommended that the Applicant analyze the Clinician's Global Impression of

Improvement (CGI-I) as a co-primary endpoint to contextualize whether a statistically significant change on the RSBQ was clinically meaningful. Study 002 studied a range of doses of trofinetide in a similar population of subjects and incorporated the same endpoints as Study 003, including the RSBQ and CGI-I.

3. Product Quality

The Office of Pharmaceutical Quality (OPQ) review team recommends approval. From a quality perspective, the review team finds that the application provides for adequate assurance that the product will be suitable for use by the intended patient population. From a quality perspective, the application meets all applicable standards to support identity, strength, quality, and purity of the product. OPQ recommends approval of the application.

The technical lead on the Office of Product Quality (OPQ) review was Dr. Martha Heimann. The OPQ integrated review lists the entire OPQ team that was involved with the review of this application. Please refer to the integrated OPQ review for details of the product quality assessment.

Drug Substance
According to the OPQ review, the drug substance is produced with adequate quality for use in the intended patient population. No deficiencies were identified by the drug substance reviewers.

Drug Product
The drug product is provided in a single strength of 200 mg/mL. The proposed maximum daily dose is 120 mL which equates to 24 g of trofinetide. The final drug product is stored in a 500 mL bottle. The excipients in the formulation include malitol, methylparaben sodium, propylparaben sodium, FD&C Red No. 40, strawberry flavor, sucralose, and purified water. The drug product is a pink to red solution with a strawberry flavor. The product has a shelf-life of 18 months and is to be stored at 5 ºC.

The Applicant evaluated gastrostomy tube compatibility with trofinetide. The drug product reviewers found the compatibility study with g-tubes to be adequate.

No outstanding deficiencies were identified by the drug product reviewers.

Manufacturing and Facilities
OPQ determined the proposed commercial manufacturing process and in process controls are adequate to ensure product quality and patient safety. All facilities that will be used for commercial manufacture and testing of trofinetitde were evaluated and deemed acceptable.

Drug product manufacturers (b) (4) and drug substance manufacturers (b) (4) as well as analytical laboratories for drug substance/drug product microbial testing

and impurities testing were found to be acceptable based on compliance status and manufacturing or testing experience.

There were no outstanding issues identified in the integrated OPQ review.

4. Nonclinical Pharmacology/Toxicology

The primary nonclinical reviewer for the application was Dr. Richard Siarey and Dr. Lois Freed performed the secondary review. The Division of Pharmacology-Toxicology for Neuroscience (DPT-N) concludes that the nonclinical data support approval of trofinetide.

The following are the key findings from the nonclinical review:

- No clear mechanism of action has been determined for trofinetide with no significant binding at any target in binding assays or inhibitory effect on the function of any kinase in functional assays. The Applicant hypothesized that trofinetide enhances neuronal synaptic function and morphology due to data from a mouse model of Rett syndrome. However, although hippocampal synaptic plasticity increased, only a trend for increased dendritic complexity and spine length was observed and there was no change in motor or respiratory functions.
- Safety pharmacology studies were conducted using IV administration of trofinetide. In rats, no adverse effects on the CNS (up to 350 mg/kg) or respiratory system (up to 700 mg/kg) were observed after IV trofinetide dosing. In dogs, IV infusion of trofinetide (800 mg/kg) had no effects on heart rate or arterial blood pressure; however, the QTcV interval was slightly prolonged
- Tmax in animals after oral administration was approximately two hours. In rats, plasma exposure to trofinetide was similar between the sexes with no accumulation observed. [^{14}C]-Trofinetide distributed to most tissues in rats, including the brain. No metabolites were detected in rat bile, feces, urine, plasma, or brain samples after oral administration of [^{14}C]-trofinetide with [^{14}C]-trofinetide excreted equally in the urine and feces, but with minimal levels detected in the bile.
- In toxicology studies, oral trofinetide was well tolerated up to the high dose, 1000 mg/kg BID and 500 mg/kg/day BID in 26- and 39-week studies in rat and dog, respectively, with no trofinetide-related deaths, minimal clinical signs, no adverse change in body weight, and few microscopic findings noted. In dog, only a decrease in uterine weight, likely due to a tendency for females to be in anestrus, and a stress-related effect on the estrus cycle were noted and considered adverse at the HD (1000 mg/kg/day). These data resulted in NOAELs of 2000 mg/kg/day (1000 mg/kg BID) in juvenile rats, 1000 mg/kg/day (500 mg/kg BID) in M dogs, and 300 mg/kg/day (150 mg/kg BID) in F dogs.
- In genetic toxicology studies, trofinetide did not demonstrate mutagenic potential in the Ames assay, structural chromosomal abnormalities in the chromosomal aberration assay, or clastogenic potential up to oral administration of 2000 mg/kg/day in the *in vivo* mouse micronucleus assay.
- Fertility was not affected in female or male rats. Trofinetide was tolerated up to 2000 mg/kg/day. In the rat embryo-fetal development study (150, 450, and 1000 mg/kg BID), trofinetide was well tolerated, with no unscheduled deaths, adverse clinical signs,

changes in body weight and food consumption, or adverse findings in ovarian, uterine, or litter parameters, and no adverse increase in malformations. The fetal NOAEL was established at 2000 mg/kg/day. In the rabbit embryo-fetal development study (0, 75, 150, and 300 mg/kg BID), abortions occurred in 1 control and 2 HD dams and were associated with severe reductions in food consumption and body weight loss. In dams, slight increases in early resorptions and post-implantation loss were noted at the HD, but with minimal decrease in live births, no dead fetuses, and similar incidences of malformations, suggesting no adverse findings were observed in ovarian, uterine, or litter parameters resulting in a fetal NOAEL at 600 mg/kg/day. In the rat pre- and postnatal developmental study (0, 150, 450, and 1000 mg/kg BID), no trofinetide-related deaths, adverse clinical signs, or changes in body weight were observed and reproductive parameters were comparable between all the groups. In F_1 animals, all endpoints post-weaning were comparable between the groups. Therefore, trofinetide was well tolerated and the NOAEL for postnatal development of offspring and reproductive performance was 2000 mg/kg/day.

- In two 13-week toxicity studies to qualify impurities, there were no substantial differences between the groups dosed with trofinetide with or without impurities suggesting that the impurities at the levels dosed did not cause toxicity. However, the following impurities, (b) (4) , were not qualified at the Applicant's proposed acceptance levels. Subsequently in a later submission (January 29, 2023) the Applicant reduced the acceptance criteria to acceptable levels. Four extractable/leachable compounds have limits of detection above the analytical evaluation thresholds which could result in a dose higher than the threshold for an impurity with genotoxic concern. The Applicant demonstrated these compounds were negative for mutagenicity based on citations and (Q)SAR analyses, which was confirmed by the Agency's Computational Toxicology Consultation Service.
- Per prior agreement, carcinogenicity studies of trofinetide in two species are to be conducted as postmarketing requirements.

5. Clinical Pharmacology

An integrated Office of Clinical Pharmacology (OCP) review was conducted by Min Li, PhD (primary reviewer); Jie Liu, Ph.D.; Ying-Hong Wang, PhD; Atul Bhattaram, PhD; Yuching Yang, PhD; and Bilal AbuAsal, PhD (team lead). The signatory for the OCP review was Mehul Mehta, PhD. OCP recommends approval of this application.

Table 1 summarizes the conclusion of the OCP review with respect to the pharmacologic and clinical pharmacokinetic properties of trofinetide.

Table 1: Summary of OCP Findings

Mechanism of Action	The mechanism of action in the treatment of Rett syndrome is unclear.
General pharmacokinetics (PK)	In subjects with Rett syndrome, trofinetide exposure increased in a dose-proportional manner over the therapeutic dose range (up to 12 g). Increase in exposure appeared to be less than dose proportional at supratherapeutic doses (18 g and 24 g). No drug accumulation was observed following recommended dosing regimen. PopPK model

	predicted steady-state C_{max} and AUC of trofinetide were 139.5-215.8 μg/mL and 839.6-1109.2 h*ng/mL, respectively, in subjects with Rett syndrome at the recommended dosage (12 g BID). Tmax is approximately 2-3 hours.
Absorption	Trofinetide is rapidly absorbed after oral administration with time to maximum drug concentration (T_{max}) of 2 to 3 hours under both fasted and fed state. Based on the mass balance study, at least 83.8% of the administered dose was absorbed following oral administration of 12 g trofinetide. Exposure parameters for trofinetide (maximum observed drug concentration [C_{max}] and area under the concentration-time curve [AUC]) after administration of trofinetide solution through G-tube were similar to those after oral administration.
Distribution	The apparent volume of distribution of trofinetide in adult healthy subjects was approximately 80 L. Trofinetide exhibits low protein binding in human plasma (less than 6%). The blood-to-plasma ratio (R_{bp}) was consistent ranging between 0.529 and 0.592 over the studied concentration range, indicating that trofinetide is not preferentially distributed into red blood cells.
Metabolism	Trofinetide is not significantly metabolized by CYP450 enzymes. Hepatic metabolism is not a significant route of disposition for trofinetide.
Elimination	Trofinetide is primarily excreted unchanged (approximately 80% of the dose) in urine, with minor excretion in feces (15.3%). The elimination is characterized by an initial rapid elimination phase ($t_{½,\alpha}$ 1.5 hours) followed by a relatively slow elimination phase ($t_{½,\beta}$ 30 hours). The initial elimination half-life is considered the effective half-life. Based on population PK analysis, the trofinetide CL/F is estimated to be 11.8 L/h at steady state.
QT prolongation	The effect of trofinetide was evaluated in a thorough QT study (ACP-2566-008). Study 008 evaluated the potential for trofinetide to prolong QTcF at a single dose of 24g in healthy subjects. There was no clinically significant effect of trofinetide on the ECG at the resulting exposure level. The QT-IRT review concludes that the totality of evidence from the TQT study suggests an absence of QTc prolongation at the clinical exposure; however, the data does not permit excluding QTc prolongation at the high clinical exposure scenario (i.e., renal impairment).
Drug-drug interactions	Trofinetide is not a substrate of CYP450 enzymes, uridine diphosphate glucuronosyltransferase (UGT), or major drug transporters. Therefore, coadministration of drugs that are inducers or inhibitors of CYP450, or major drug transporters will not significantly affect the systemic exposure of trofinetide. Coadministration of trofinetide with orally administered midazolam (a sensitive CYP3A4 substrate) was predicted to increase the AUC of midazolam by approximately 1.33-fold,

	indicating trofinetide is a weak inhibitor of CYP3A4. Trofinetide inhibits OATP1B1 and OATP1B3 in vitro. Per the OCP review, safety should be monitored closely when trofinetide is used in combination with CYP3A4 sensitive substrates administered orally. Use of OAT1B1 and OAT1B3 sensitive substrates, for which a small change in substrate plasma concentration may lead to serious toxicities, should be avoided.
Intrinsic/Extrinsic	No dedicated clinical studies were conducted to evaluate the PK of trofinetide in patients with renal impairment. Based on popPK data, no impact on the exposure of trofinetide in patients with mild renal impairment is expected. Trofinetide should be avoided in patients with moderate or severe renal impairment until results of an ongoing PK study in patients with moderate renal impairment is completed. No dose adjustment is needed for the following intrinsic factors: mild renal impairment; mild, moderate, or severe hepatic impairment. No dedicated clinical studies were conducted to evaluate the PK of trofinetide in patients with hepatic impairment. The in vitro studies and the mass balance study indicate that trofinetide is not significantly metabolized by hepatic enzymes and hepatic clearance is not a primary route of trofinetide elimination. Hepatic impairment is not expected to have a clinically meaningful effect on the exposure of trofinetide.
Food effects	The rate of absorption of trofinetide was affected to a small extent by oral administration with a high-fat meal, with the C_{max} being reduced by approximately 20% and a 0.5-hour delay in T_{max} (from 2 hours [fasted] to 2.5 hours [with a high-fat meal]) when compared with administration after fasting. The extent of absorption, expressed as AUC, was unaffected by administration with food. The time of day of administration (morning versus evening dose) showed no impact on trofinetide PK.

Source: Adapted from the integrated clinical pharmacology review

OCP agrees with the Applicant's proposed dosing regimen. The recommended dosage is weight-banded dosing (Table 2) via oral or via gastrostomy tube. The drug is taken twice daily without regard to food.

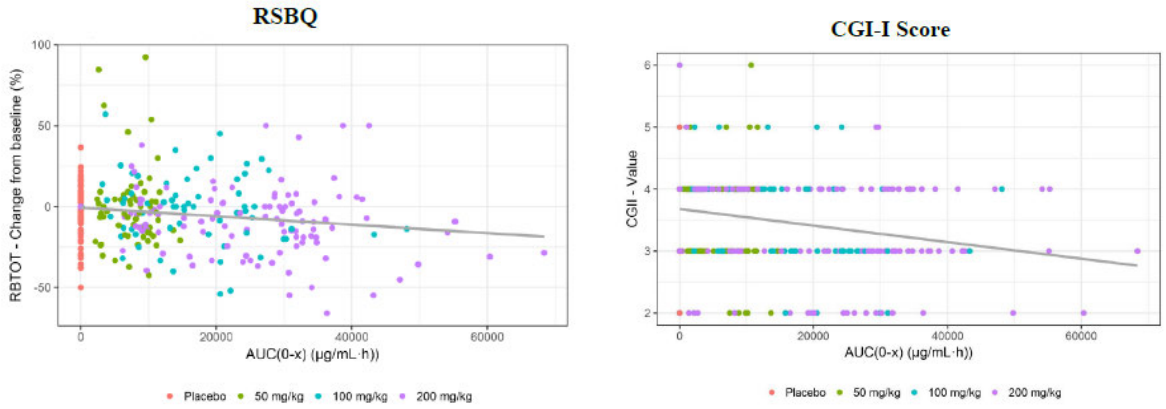
Table 2: Weight-based Dosing for Trofinetide

Patient Weight	Dose
9 kg to <12 kg	25 mL (5 g) twice daily
≥12 kg to <20 kg	30 mL (6 g) twice daily
≥20 kg to <35 kg	40 mL (8 g) twice daily
≥35 kg to <50 kg	50 mL (10 g) twice daily
≥50 kg	60 mL (12 g) twice daily

Study 002

In Study 002 subjects with Rett syndrome were given the following doses of trofinetide (50 mg/kg, 100 mg/kg, and 200 mg/kg) for 6 weeks. Evidence of efficacy was found only at the 200 mg/kg BID dose as measured by the RSBQ and CGI-I. An exploratory PK/PD analysis of the drug exposure and efficacy data suggested a correlation between trofinetide exposure ($AUC_{0\text{-}12h}$ and cumulative AUC [over 42 days]) and the magnitude of response for these two measures (Figure 1).

Figure 1 Study 002: Relationship Between RSBQ and CGI-I and Cumulative Exposure (AUC) During Active Dosing Period



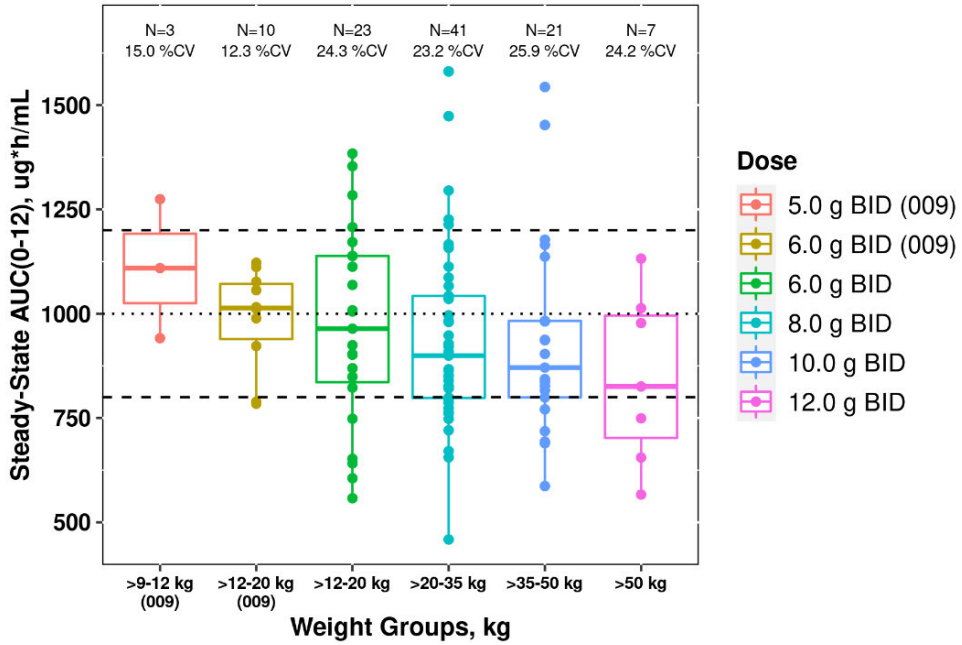
Source: Figure 1, clinical pharmacology review

Study 009

Study 009 is an ongoing open-label study that evaluates the safety and tolerability, PK, and efficacy of trofinetide in female subjects aged 2 to 4 years. The study consisted of two treatment periods: Treatment Period A (12 weeks) and Treatment Period B (up to approximately 21 months for long-term safety). The clinical study dose levels in this younger patient population have been selected based on popPK simulation targeting similar PK exposure as seen in the older patient population (≥5 years old). While this study is ongoing, as of the interim cut-off date of 14 March 2022, a total of 15 subjects were enrolled, of which 14 subjects were dosed. After administration of trofinetide using the proposed weight-band based dosing, interim evaluation of PK from 13 subjects who completed 12 weeks of treatment with trofinetide in Study 009 indicated that the median $AUC_{0\text{-}12h,ss}$ values at steady state in the younger children

(based on popPK analysis) were largely contained within the target exposure range, and similar to the exposure levels seen in the 5 to 20-year-old subjects enrolled in Study 003 (Figure 2).

Figure 2: Boxplot of Population Pharmacokinetic Model-Predicted $AUC_{0\text{-}12,ss}$ Values in Studies 003 and 009 Subjects by Body Weight-Based Banded Dosing Regimen



Source: Figure 2, clinical pharmacology review

Conclusions from OCP

OCP concludes that the exposure-response models from Study 003 demonstrated a significant exposure-related effect of trofinetide on RSBQ total scores, and the CSBS-DP-IT-SCS, with no relationship found for CGI-I scores.

OCP concludes that Study 002, dose-ranging study provides supportive evidence of effectiveness. Significant evidence of efficacy was found only at the 200 mg/kg BID dose while exploratory pharmacokinetics/pharmacodynamics (PK/PD) analyses suggested a correlation between trofinetide exposure and the magnitude of clinical response for core clinical measures.

OCP concludes that the interim PK analysis from Study 009 supports those subjects 2 to 4 years of age treated with trofinetide demonstrated similar PK exposure with trofinetide.

6. Clinical/Statistical- Efficacy

Dr. Michael Dimyan was the clinical reviewer for this application. Dr. Andrew Potter and Hye Soo Cho, MS were the biometrics reviewers. Dr. John Lawrence and Dr. James Hung performed the secondary review.

ACP-2566-003 (Study 003)

The primary evidence of effectiveness for this application is based on the analysis of clinical efficacy endpoints from Study 003. Study 003 was a multicenter, parallel group, double-blind, placebo-controlled study that enrolled female patients aged 5 through 20 years who were diagnosed with Rett syndrome. The co-primary efficacy endpoints were change from baseline on the Rett Syndrome Behavior Questionnaire (RSBQ) and the Clinical Global Impression of Improvement (CGI-I) measured after 12 weeks treatment with trofinetide or placebo.

Study 003 was conducted in the United States at 21 different clinical sites across the country. A total of 187 subjects were randomized 1:1 to receive either trofinetide (weight-based dosing) or placebo twice daily. Randomization was stratified by age (5 to 10 years old, 11 to 15 years old, and 16 to 20 years old) and baseline RSBQ severity score (<35 total and ≥ 35 total score).

Subjects were required to be females between 5 and 20 years of age (inclusive) and have a diagnosis of genetically confirmed Rett syndrome. Documentation of a known disease-causing mutation in the *MECP2* gene was required for enrollment. Subjects were also required to have a baseline weight of ≥ 12 kg.

The first co-primary efficacy endpoint was the change from baseline to week 12 on the RSBQ total score as compared to placebo, analyzed using a mixed effects model for repeated measures (MMRM). Scores on the RSBQ can range from 0 to 90 with higher scores indicating higher severity of the signs and symptoms of Rett syndrome.

The RSBQ is an observer-reported outcome measure that asks parents and caregivers about certain aspects of the disease such as general mood, breathing problems, hand behaviors, repetitive movements, night-time behaviors, anxiety, and eye movements 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. For this reason, the Division has required the Applicant to include additional measures to support the clinical meaningfulness of the RSBQ. Study 003 included a clinician global impression of improvement to support the clinical meaningfulness of the RSBQ.

A secondary endpoint for Study 003 was the Communication and Symbolic Behavior Scales Developmental Profile-infant-toddler social composite score (CSBS-DP-IT-SCS). The CSBS-DP-IT-SCS is a screening assessment of healthy infants and toddlers aged 6 through 24 months. The instrument was designed to screen healthy children for potential communication deficits.

The Applicant controlled for multiple comparisons by requiring both co-primary endpoints to have a p-value <0.05 to declare the study a success. The CSBS-DP-IT-SCS was only to be tested if both co-primary endpoints were significant at alpha=0.05.

Results

Study 003 randomized 187 subjects (93 trofinetide-treated, and 94 placebo-treated). The mean age of the subjects was 11.0 (range 5 to 20). All patients enrolled were female, 92% were white, 6% were Asian, and 2% were black.

Baseline characteristics for the randomized analysis set between the trofinetide-treated group and the placebo group were well-balanced (Table 3).

Table 3: Study 003: Baseline Demographic Values

Demographic	Placebo (N=94)	Trofinetide (N=93)
Age (median) (min, max)	10.0 (5, 20)	10.0 (5, 20)
5 to <12 years n (%)	55 (58.5)	53 (57.0)
12 to <17 years n (%)	24 (25.5)	23 (24.7)
≥17 years n (%)	15 (16.0)	17 (18.3)
Sex (% female)	100	100
Mean weight (kg)	29.2	30.5
Mean baseline RSBQ	44.5	43.7

Source: statistical review Table 5 and Table 6

Of the 187 randomized subjects, 32 (17.1%) discontinued the study early. The majority (18/32) discontinued due to an adverse event.

The full analysis set for the primary endpoints consisted of subjects who were randomized, received at least one dose of study drug, and had a baseline and at least one post-baseline value for the RSBQ or CGI-I.

The results of the primary efficacy analysis at week 12 for the RSBQ were statistically significant in favor of trofinetide. At week 12, the trofinetide-treated subjects had greater decrease in the RSBQ total score as compared to placebo-treated patients (Table 4).

Table 4: Study 003 Co-Primary Analysis: RSBQ Change from Baseline at Week 12

	Placebo (N=93)	Trofinetide (N=91)
Mean baseline value (SD)	44.5 (12.2)	43.7 (11.5)
Week 12 observed mean (SD)	42.8 (13.1)	39.9 (12.0)
Change from baseline to Week 12*	-1.7	-5.1
MMRM analysis LS mean (SE)	-1.7 (0.9)	-4.9 (0.94)
LS Mean Difference (SE) (trofinetide-placebo)		**-3.2 (1.30)**
95% CI		(-5.7, -0.6)
p-value		0.016

Source: statistical review table 6
*includes only subjects with both baseline and week 12 measurement

The results of the analysis of the CGI-I were also statistically significant in favor of trofinetide (Table 5).

Table 5 Study 003 Co-Primary Analysis: CGI-I at Week 12

	Placebo (N=90)	Trofinetide (N=90)
Week 12		
Mean (SD)	3.8 (0.55)	3.8 (0.08)
MMRM analysis LS mean (SE) 95% CI	 3.8 (0.07) (3.7, 4.0)	 3.5 (0.07) (3.4, 3.7)
LS Mean Difference (SE) (trofinetide-placebo)		**-0.3 (0.10)**
95% CI		(-0.5, -0.1)
p-value		0.002

Source: statistical review table 7

The trial also evaluated the CSBS-DP-IT-SCS in the testing hierarchy (Table 6). Although the results of the CSBS-DP-IT-SCS support the efficacy conclusion, (b) (4) . Per Dr. Michelle Campbell, associate director for stakeholder engagement and clinical outcomes, there is insufficient evidence to support the use of the scale in this population. Insufficient evidence was provided to justify the administration, scoring, and interpretation of the CSBS-DP-IT-SCS for the population of subjects with Rett syndrome studied. 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. It is not clear how to interpret the observed difference between treatment and placebo detected by the instrument.

Table 6 Study 003: CSBS-DP-IT-SCS at Week 12

	Placebo (N=93)	Trofinetide (N=91)
Mean baseline value (SD)	8.8 (3.24)	8.7 (0.35)
Week 12 observed mean (SD)	7.5 (2.99)	8.9 (3.74)
MMRM analysis **LS mean (SE)**	-1.1 (0.25)	-0.1 (0.26)
LS Mean Difference (SE) (trofinetide-placebo)		1.0 (0.37)
95% CI		(0.3, 1.7)
p-value		0.006

Source: statistical review table 8

Key Review Issues
Key review issues for this study were whether the imbalance in the adverse events of diarrhea with associated dropouts in Study 003 and higher use of loperamide in trofinetide-treated patients led to functional unblinding that could have impacted the efficacy results. The Applicant did not query caregivers as to whether they were aware of which treatment the subject was receiving (trofinetide versus placebo). The review team instead explored the impact of loperamide use on the efficacy analyses as a proxy for the impact of diarrhea on functional unblinding.
Dr. Potter explored the impact of loperamide use through descriptive plots and post hoc mediation analysis of the co-primary endpoints. He concludes that the use of loperamide does not completely explain the observed effects of trofinetide on the co-primary endpoints.

Dr. Potter also conducted sensitivity analyses of the co-primary endpoint to assess the impact of missing data and the impact of dropouts on the primary analyses. He concludes that for Study 003, the small percentage of dropouts limits the impact of missing data.

Dr. Potter concludes that Study 003 provides statistical evidence that there was a treatment-effect in favor of trofinetide on both co-primary endpoints (RSBQ and CGI-I) as well as on the CSBS-DP-IT-SCS. He also concludes that there was a similar effect of trofinetide on important subgroups such as age, baseline disease severity, and *MECP2* mutation severity.

Study Neu-2566-RETT-002 (Study 002)
Confirmatory evidence for this application is based on the analysis of clinical efficacy endpoints from Study 002. Study 002 was a single-blind, placebo run-in, followed by a randomized double-blind placebo-controlled, dose-ranging clinical trial of trofinetide treatment in females with Rett syndrome ages 5 to 15 years. Documentation of a known disease-causing mutation in the *MECP2* gene was required for enrollment. The study had a two-week placebo run-in after which time baseline assessments for the randomized phase were assessed. Subjects were then randomized 1:1:1:1: to placebo or trofinetide and treated for 40 days. As this was an exploratory, dose-finding study, the primary objective of the study was safety, tolerability, and measurement of PK.

Subjects were required to be females between 5 and 25 years of age (inclusive) and have a diagnosis of genetically confirmed Rett syndrome. Documentation of a known disease-causing mutation in the *MECP2* gene was required for enrollment.

Study 002 was conducted in the United States at 12 different clinical sites across the country. There were 64 subjects randomized 1:1:1:1 to trofinetide in the first phase of the study. An additional 28 subjects were randomized to either trofinetide 200 mg/kg or placebo.

Because this was an exploratory study, there was no single prespecified analysis method or control for multiplicity. Study 002 included eight clinician and caregiver reported efficacy outcomes. To use this study as confirmatory evidence and make comparisons to Study 003, our statistician applied the same statistical methods to Study 002 that were utilized to analyze Study 003.

Results
The mean age of the subjects was 9.7 (range 5 to 16). All patients enrolled were female, 94% were white, 4% were Asian, and 1% were black.

In Study 002, 82 subjects were randomized as follows: 24 subjects in the placebo arm, 15 subjects 50 mg/kg, 16 subjects in 100 mg/kg, and 27 subjects in 200 mg/kg. One subject dropped out of the 200 mg/kg arm.

For change from baseline (day 14) to day 54 in RSBQ total score, the 200 mg/kg trofinetide arm showed evidence of efficacy with 4.7-point greater improvement (p = 0.035) compared to placebo (Table 7). CGI-I at day 54 showed a -0.5-unit difference from placebo (p = 0.029) favoring 200 mg/kg of trofinetide. The 50 mg/kg and 100 mg/kg doses of trofinetide did not show any improvement compared to placebo. Per Dr. Dimyan, the Applicant analyzed 8 subscales of the RSBQ and demonstrated numerical trend in favor of trofinetide for 7 out of 8 of the subscales at the high dose of 200 mg/kg BID. Trofinetide performed worse than placebo in the walking/standing subdomain.

Table 7: Study 002: RSBQ and CGI-I after 40 Days of Treatment

	Placebo (N=24)	50 mg/kg (N=15)	100 mg/kg (N=16)	200 mg/kg (N=27)
RSBQ D14 baseline	39.5	44.7	40.3	42.2
Change D14 to D54 (LSMean)	**-2.0**	**-3.0**	**-1.5**	**-6.7**
Difference from PBO		-1.0	0.5	-4.7
p-value vs placebo		0.680	0.841	0.035
CGI-I D14 baseline	3.8	3.8	3.9	3.9
D54 treatment	3.5	3.3	3.4	3.0
p-value vs placebo		0.391	0.703	0.029

Source: statistical review table 12

Study ACP-2566-009 (Study 009)
The effectiveness of trofinetide in patients 2 to 4 years of age was established through extrapolation of the efficacy observed in the Study 003 in Rett syndrome patients 5 years of age and older, 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. Study 009, an open-label PK study was conducted to evaluate the pharmacokinetics (PK) and safety in Rett syndrome patients between 2 and 4 years of age. The interim PK analysis based on the data from 13 pediatric patients 2 to 4 years of age treated with trofinetide for 12 weeks demonstrated similar PK exposure of trofinetide and similar safety profiles to those in the pediatric patients ≥5 years of age and adults.

Efficacy Conclusions

Per the 2019 FDA draft guidance, *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products*, "In all cases, FDA must reach the conclusion that there is substantial evidence of effectiveness to approve a drug; however, the degree of certainty supporting such a conclusion may differ, depending on clinical circumstances (e.g., severity and rarity of the disease and unmet medical need)." The guidance also outlines the general requirements for determination of substantial evidence of effectiveness, the situations in which a single adequate and well-controlled study could establish effectiveness and cites the ability of the Agency to consider "data from one adequate and well-controlled clinical investigation and confirmatory evidence" to constitute substantial evidence of effectiveness. The guidance states that the FDA can consider numerous factors when determining whether reliance on a single adequate and well-controlled study plus confirmatory evidence is appropriate. These factors include but are not limited to the persuasiveness of the single trial, the seriousness of the disease, and the presence of unmet medical need.

The application for trofinetide includes data from one adequate and well-controlled clinical investigation (Study 003) plus confirmatory evidence (Study 002). Study 003 was an adequate and well-controlled clinical investigation that showed a statistically significant difference between treatment and placebo on the co-primary endpoint, CFB on the RSBQ. The clinical meaningfulness of the change in the RSBQ was supported by a statistically significant change on the CGI-I. Additionally, the treatment effect for trofinetide was supported by an effect on the secondary endpoint CSBS-DP-IT-SCS and was controlled for type I error. Given the size of the patient population, the study was large and multicenter. No single clinical site contributed disproportionately to the observed treatment effect. Results were generalizable across important demographic subgroups. Despite the limitations described in the review, the results of the study were persuasive with low p-values and robust to sensitivity analyses. The consistent results on the CGI-I and CSBS-DP-IT-SCS support the clinical meaningfulness of the changes on the RSBQ.

Finally, confirmatory evidence is provided by data from an exploratory dose-finding study (Study 002) in Rett syndrome patients in which the highest dose also demonstrated a treatment effect on the RSBQ and CGI-I. Although the study was exploratory and did not have a pre-specified analysis plan for efficacy, the statistical review team applied that same statistical analysis from Study 003 to the Study 002 and obtained nominally significant results on the RSBQ and CGI-I at the 200 mg/kg BID dose, which has similar exposures that the proposed recommended dosage regimen. The exposure response analyses for Study 002 and 003 conducted by clinical pharmacology also provide supportive evidence of effectiveness. Section IV.B. of the above referenced 2019 draft FDA effectiveness guidance does not define what can be considered confirmatory evidence but does provide examples of types of data or information that could potentially be considered confirmatory evidence. The character and strength of confirmatory evidence can vary and depends on the strength and robustness of the single adequate and well-controlled study and factors such as seriousness of the disease and unmet medical. Given the persuasiveness and robustness of Study 003 and the unmet need in Rett syndrome, the data from Study 002 appear adequate to provide confirmatory evidence.

The evidence for effectiveness in patients with Rett syndrome aged 2 to 4 was provided by the bridging PK study, ACP-2566-009 in which 10 patients completed 12 weeks of treatment with trofinetide at banded-weight-based-dosing. The study achieved exposure comparable to that required to achieve response in ACP-2566-003. Study 009 was an open-label study not designed to assess effectiveness; however, CGI-I mean score at the end of 12 weeks was 3.3 (SE 0.24) indicating clinician impression of improvement.

The application meets the substantial evidence effectiveness based on one adequate and well-controlled clinical investigation plus confirmatory evidence. Rett syndrome is clearly a severely debilitating and life-threatening disease with substantial unmet need, and the exercise of regulatory flexibility in applying our statutory standards is appropriate. Although the studies were conducted in female subjects with Rett syndrome, the product will be approved for both males and females as there is no scientific reason to expect the product will perform differently in males than females.

7. Clinical/Safety

Dr. Dimyan conducted the safety review of this application with support from clinical data analyst, Dr. Rui Li.

Dr. Dimyan's safety review focused on the blinded data from Study 003 and supplemented by pooled data from the blinded portions of Study 001, 002, and 003. Open-label pooled safety data from Studies 004, and 005 were also reviewed for long-term exposure to trofinetide.

Dr. Dimyan's review indicates that a total of 178 patients diagnosed with Rett syndrome have been exposed to trofinetide. In addition, 183 healthy volunteers were exposed in Phase 1 studies with the highest single doses up to 24 g. At the initial filing, a total of 92 subjects with Rett syndrome received trofinetide for ≥6 months, 61 for ≥9 months, and 40 for ≥ 12 months. At the time of the 120-day safety update, 100 subjects had ≥6 months of exposure, 86 had ≥9 months, and 69 had ≥ 12 months. Dr. Dimyan concludes that the safety database is adequate and is consistent with what the Agency agreed to at the pre-NDA meeting.

The following are the main conclusions from Dr. Dimyan's safety review of the application:

Deaths
There were two deaths in trofinetide-treated patients during open-label treatment. One subject died of complications due to aspiration of gastric contents (blood) following elective gastrostomy tube placement. The other death occurred after emergency gastric surgery for a perforated gastric ulcer secondary to chronic ibuprofen use. The subject was reported to have experienced three episodes of asystole following surgery. The final cause of the death was reported as complications from bleeding ulcer. Neither of the deaths had a clear relationship to the use of trofinetide.

Serious Adverse Events

Per Dr. Dimyan's review, the incidence of serious adverse events (SAEs) was 3.2% in the trofinetide arm, and 3.2% in the placebo arm of Study 003. In the double-blind period of pooled studies, this increased to 4.5% in the trofinetide arm and 3.0% in the placebo-treated arm. Seizure was the only serious adverse reaction that occurred in ≥ 1% of trofinetide-treated patients. In pooled studies, there were two (1.1%) trofinetide-treated subjects who experienced seizures (reported as an SAE) compared to none in the placebo group. In the long-term, open-label studies, eight (4.5%) additional subjects experienced seizures reported as SAEs.

Adverse Events Leading to Discontinuation
Dr. Dimyan notes that withdrawal from the study and from treatment were common. The most common adverse event leading to treatment withdrawal in the blinded period was diarrhea (15.1%). Additional 3.2% withdrew due to decreased appetite, 2.2% due to lethargy, and 2.2% due to seizure compared to none in the placebo group. During open-label treatment with trofinetide, 25% of subjects withdrew from the treatment secondary to diarrhea, 7% due to vomiting, and 4% due to seizures. Notably, subjects who remained in the study required additional concomitant medication to manage adverse events. In long-term treatment with trofinetide, the most common medications added for management of adverse effects of trofinetide were antipropulsives (61.2%) and intestinal adsorbents (34.3%), and anti-epileptic treatments (23.0%).

Treatment-Emergent Adverse Events
Table 8 reproduced from Dr. Dimyan's review, summarized the most common treatment-emergent adverse events that occurred during the blinded period of Study 003.

Table 8: Adverse Reactions from Study 003 that Occurred in at Least 5% of Trofinetide Treated Subjects and at least 2% Greater than Placebo

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

Source: clinical review

Notable Safety Issues
Diarrhea
Dr. Dimyan notes in his review that nearly 85% of patients on long-term treatment with trofinetide experienced diarrhea. Approximately 25% withdrew due to this adverse event. Of those who did not withdraw from treatment, 50% required concomitant therapy with

loperamide. The majority of cases were mild to moderate in severity with approximately 4% reported as severe.

Weight Loss/Inadequate Weight Gain

As noted by Dr. Dimyan, patients with Rett syndrome can have difficulty with oral intake, poor weight gain, and reduced growth in general as compared to unaffected children. The Applicant was asked to provide a dataset of subject weights referenced to where subjects would fall on the Rett syndrome adjusted growth curve for weight. Individual subjects' weight and the population mean weight from the long-term data was plotted over time as described by the Rett syndrome adjusted growth curve. Data from the analysis show a decrease in weight and inadequate weight gain over time in the treated population when compared to the Rett syndrome adjusted growth curve. In Study 003, 12% of trofinetide-treated subjects (compared to 4% of placebo-treated subjects) experienced a loss of greater than 7% of body weight. Four (2.2%) subjects withdrew from long-term treatment with trofinetide due to weight loss.

Per Dr. Dimyan's review, aside from weight loss, there were no clinically significant changes in for vital signs including blood pressure, heart rate, respiratory rate, and temperature.

There were no clinically significant differences between trofinetide-treated and placebo-treated subjects on hematological parameters, blood chemistry, renal function, liver function tests (LFTs), thyroid function, and coagulation parameters. There were no cases of Hy's Law.

Safety Conclusions

Overall, the risks associated with trofinetide are acceptable and do not preclude approval. The most common adverse events were primarily GI-related (e.g., diarrhea and vomiting). Warnings for clinically significant adverse events of diarrhea and weight loss will be added to the product labeling.

8. Advisory Committee Meeting

This application was not referred to an FDA advisory committee because the application did not raise significant efficacy or safety issues in the intended population.

9. Pediatrics

Because this product has an orphan indication, there are no requirements under the Pediatric Research Equity Act (PREA) to study pediatric patients. This product will be approved for pediatric and adult patients aged 2 and older.

10. Other Relevant Regulatory Issues

Financial disclosures

Dr. Dimyan concluded that the Applicant has adequately disclosed financial interests and arrangements with clinical investigators.

Good Clinical Practice (GCP) issues
No GCP issues were noted during the review.

Office of Scientific Investigations (OSI) audits
OSI investigated three clinical investigator sites and concluded that the data generated by these sites appears acceptable in support of the indication.

Controlled Substance Staff
A consult was placed to CSS who determined during the NDA review that trofinetide does not appear to present a potential for abuse and does not warrant scheduling under the Controlled Substances Act. Section 9 will not be included in the product labeling.

Division of Medication Error Prevention and Analysis
DMEPA2 has determined that the Applicant's proposed proprietary name Daybue is acceptable

11. Labeling

Please refer to the final negotiated product label. Labeling negotiations with the Applicant have been completed and the Applicant has accepted all recommended changes.

12. Postmarketing Recommendations

Risk Evaluation and Management Strategies (REMS)

The Division of Risk Management concluded that a risk evaluation and mitigation strategy (REMS) is not necessary for the safe use of trofinetide.

Postmarketing Requirements (PMRs) and Commitments (PMCs)

The following will be postmarketing requirements:

PMR 1: A carcinogenicity study of trofinetide in mouse.

Draft Protocol Submission:	06/2023
Final Protocol Submission:	08/2023
Study Completion:	08/2025
Final Report Submission:	08/2026

PMR 2: A 2-year carcinogenicity study of trofinetide in rat.

Draft Protocol Submission:	06/2023
Final Protocol Submission:	08/2023
Study Completion:	08/2025
Final Report Submission:	08/2026

PMR 3: In vitro drug interaction study to evaluate the time-dependent inhibition of CYP 2B6 enzyme by trofinetide based on the guidance for industry *In Vitro Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions*.[1]

Draft Protocol Submission:	04/2023
Final Protocol Submission:	08/2023
Study Completion:	02/2024
Final Report Submission:	05/2024

PMR 4: Conduct a clinical trial to evaluate the effect of moderate renal impairment on the exposure of trofinetide relative to that in subjects with normal renal function after oral administration of trofinetide. Please refer to the guidance for industry *Pharmacokinetics in Patients with Impaired Renal Function: Study Design, Data Analysis, and Impact on Dosing and Labeling*.[2]

Draft Protocol Submission:	04/2021
Final Protocol Submission:	10/2021
Study Completion:	12/2022
Final Report Submission:	09/2023

PMR 5: In vivo pharmacokinetic drug interaction study in healthy subjects to evaluate the effect of trofinetide on inhibiting OATP1B1 and OATP1B3 transporters using an appropriate probe substrate for each transporter. Please refer to the guidance for industry *Clinical Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions*.[3]

Draft Protocol Submission:	03/2024
Final Protocol Submission:	06/2024
Study Completion:	12/2025
Final Report Submission:	09/2026

13. Recommended Comments to the Applicant

None.

[1] https://www.fda.gov/media/134582/download
[2] https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM204959.pdf
[3] https://www.fda.gov/media/134581/download

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/s/

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