New Drug Fact Blast

Clinical Services

Drug/Manufacturer:	**Daybue™ (trofinetide) [Acadia Pharmaceuticals Inc.]**
Dosage Formulations:	200 mg/mL pink to red, strawberry-flavored oral solution.
FDA Approval Date: FDB File Date:	FDA: March 10, 2023 FDB: March 19, 2023
Indication:	Treatment of Rett Syndrome (RTT) in adults and pediatric patients two years of age and older.
Mechanism of Action:	Daybue is a synthetic analog of glycine-proline-glutamate, the N-terminal tripeptide of insulin-like growth factor (IGF-1). The mechanism by which it treats RTT is unknown. • The proposed mechanism by which it treats RTT is reducing neuroinflammation, supporting synaptic function, stimulating synaptic maturation, and overcoming RTT's synaptic and neuronal immaturity characteristics. Daybue has been shown to inhibit the production of inflammatory cytokines, inhibit the overactivation of microglia and astrocytes, and increase the amount of available IGF-1 receptors.

Dose/ Administration:	• Daybue is administered orally or via a gastrostomy (G) tube twice daily (morning and evening) according to weight-based dosing. It can be given with or without food.
	  ○ Administration via gastrojejunal (GJ) tubes must be through the G-port.
	  ○ Doses:

Patient Weight	Daybue Dose	Daybue Volume
9 kg to < 12 kg	5,000 mg twice daily	25 mL twice daily
12 kg to < 20 kg	6,000 mg twice daily	30 mL twice daily
20 kg to < 35 kg	8,000 mg twice daily	40 mL twice daily
35 kg to < 50 kg	10,000 mg twice daily	50 mL twice daily
50 kg or more	12,000 mg twice daily	60 mL twice daily

• An oral dosing syringe or oral dosing cup should be obtained from the pharmacy.
• Discard unused Daybue after 14 days of first opening the bottle.
• Missed dose: next dose should be taken as scheduled. Doses should not be doubled.
• Vomiting after dose administration: the dose should not be replaced, and the next dose should be taken as scheduled.

Disease State Clinical Highlights:

• RTT is a rare genetic (X-linked) neurodevelopment disorder that occurs due to a pathogenic variant in the X chromosome on the methyl CpG binding protein 2 (*MECP2*) gene. It is a spectrum disorder with a wide range of severity. Symptoms appear around age 18 months, followed by clinical regression between ages 1 and 4 years.
• It is characterized by typical early growth and development followed by slowing of development, loss of function of the hand, unusual hand movement, slowed brain and head growth, problems with walking, seizures, and intellectual disability.
• RTT can be classical or atypical based on symptoms and type of gene variant. The majority of RTT patients have the classic form.

Classical RTT	Atypical RTT

• The classic form of RTT progresses in phases:
  ○ Early onset phase (6 - 18 months): development slows or stops completely.
  ○ Rapid destructive phase (1 - 4 years): loss of skills quickly.
  ○ Plateau phase (2 – 10 years): regression slows and may show improvement in some areas.
  ○ Late Motor deterioration phase (after age 10 years): body becomes stiff, or loss of muscle tone leads to immobility. Scoliosis may also occur.
	• Symptoms may start as a newborn.
	• The genetic variant can be in the X-linked *MECP2, NTNG1, CDKL5, SMC1A,* or *GABBR2* gene.
	• Forms of atypical RTT:
	  ○ Congenital Rett Syndrome (Rolando Variant).
	  ○ Early-Onset Rett Syndrome (Hanefeld Variant).
	  ○ Late-Childhood Rett Syndrome.
	  ○ Forme Fruste Rett Syndrome.
	  ○ Preserved-Speech Variant of Rett Syndrome (Zappella Variant).

	• No risk factors for RTT have been identified. Although it can occur randomly, one percent of recorded cases are inherited. • It has no racial preference but is more prevalent among females than males. It affects one in each 10,000 to 15,000 live female births. • Limited treatment guidelines are available. Available management advisories/guidelines recommend symptom-based supportive therapy.
Drug Clinical Highlights:	• Daybue is the first FDA-approved therapy for the treatment of RTT. It received Fast Track, Orphan Drug, and Rare Pediatric Disease designations. Contraindications: None Warnings/precautions: • Diarrhea: o In the clinical studies, diarrhea occurred in 85% of the patients treated with Daybue, with 96% being mild to moderate in severity. It is recommended that patients discontinue the use of laxatives prior to starting treatment with Daybue. o Some diarrhea can persist during treatment. Of the Daybue-treated participants in the clinical studies, 15% discontinued treatment due to diarrhea and 51% used antidiarrheal medication. o Therefore, the any laxatives used prior to the start of Daybue should be discontinued before starting Daybue. • Vomiting: o Occurred in 29% of the patients taking Daybue vs. 12% of patients taking placebo in the clinical studies. Caregiver should be advised not to replace a dose due to vomiting and the next dose should be taken as scheduled. • Weight loss: o 12% of the patients treated with Daybue reported weight loss of ≥ 7% from baseline, compared to 4% in patients taking placebo. o In long-term studies, 2.2% of patients discontinued Daybue treatment due to weight loss. • Other reported adverse events: o Fever, seizure, anxiety, decreased appetite, fatigue, and nasopharyngitis. Pregnancy and lactation: • No adverse effects were observed following Daybue administration in pregnant animals at a dose associated with plasma exposures below those used clinically. • No information regarding Daybue's presence in human milk, the effect on the breastfed infant, or the effect on milk production is available. Pediatric use: • The effectiveness and safety of Daybue treatment of RTT has been established in pediatric patients aged ≥ 2 years through clinical studies. However, no safety and efficacy data exist in patients under 2 years. Use in geriatric and renal impaired population**:** • No data is available. • Not recommended in patients with moderate or severe renal impairment. Use in hepatic impaired population: • No safety data is available, but hepatic metabolism is not expected to impact the therapeutic level of Daybue as the liver does not significantly eliminate Daybue. Clinical Studies: LAVENDER (NCT04181723): • A 12-week, randomized, double-blind, placebo-controlled study that evaluated the efficacy and safety of Daybue in patients with RTT aged 5 to 20 years. • Open-label extension study of 40 weeks was conducted to follow LAVENDER to evaluate the long-term effect of Daybue. Most LAVENDER participants participated in the extension study. • Method: o The study enrolled 187 females aged 5 to 20 years with RTT, randomized 1:1 ratio to an intervention group and placebo group. o The co-primary endpoints of LAVENDER were the Rett Syndrome Behavior Questionnaire (RSBQ), and clinical Global Impression-Improvement (CGI-I) assessments.

- RSBQ is a 45-item rating scale assessing mood disruption, maladaptive behaviors, fear/anxiety, repetitive movements, hand behaviors, breathing abnormalities, and gross motor skills (waking/standing). It is conducted by the caregiver. The maximum possible score is 90 points, with lower scores indicating lesser severity of RTT symptoms and signs.
- CGI-I clinical domains are communication, ambulation, hand use, seizures, attentiveness, and social (eye contact) and autonomic (breathing) aspects. It is a clinical tool assessing whether the patient has improved or worsened based on a 7-point scale. A low number indicates improvement, and a higher number suggests worsening (1 = Normal; 2 = Borderline ill; 3 = Mildly ill; 4 = Moderately ill; 5 = Markedly ill; 6 = Severely ill; and 7 = extremely ill).

- The secondary endpoints were a novel RTT-specific clinician rating (derived from the RTT-DSC-VAS) of hand function, ambulation, ability to communicate, and verbal communication, along with existing scales, which evaluates other core symptoms of RTT, quality of life, and caregiver burden.

Inclusion criteria	Exclusion criteria
• Female aged 5 to 20 years. • Weight ≥ 12 kg. • Classic/typical RTT. • Documented disease-causing mutation in the *MECP2* gene. • At least 6 months post regression at screening (i.e., no loss or degradation in ambulation, hand function, speech, nonverbal communication, or social skills within 6 months of screening). • Rett Syndrome Clinical Severity Scale rating of 10 to 36. • CGI-I score of ≥ 4. • A stable pattern of seizures or has had no seizures within eight weeks of screening.	• Current clinically significant cardiovascular, endocrine (hypo- or hyperthyroidism, type 1 diabetes, or uncontrolled type 2 diabetes), renal, hepatic, respiratory, or gastrointestinal disease (such as celiac disease or inflammatory bowel disease), or significant surgery planned during the study. • Known history or symptoms of long QT syndrome. • Corrected QT interval using Fridericia method (QTcF) interval > 450 ms (history of risk factor for Torsades de Pointes or clinically significant QT prolongation considered increased risk). • Treatment with insulin, IGF-1, or growth hormone within 12 weeks of baseline.

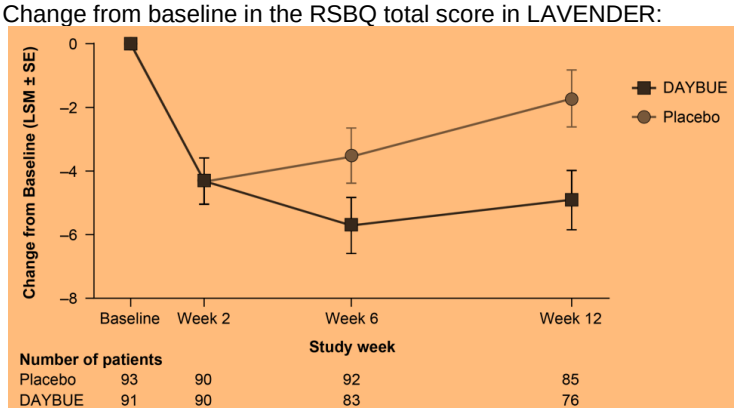
- Intervention:
  - Daybue oral solution (1 g/5 mL strawberry-flavored solution) twice daily.
  - Matching placebo twice daily.
- Results:
  - Efficacy results of LAVENDER:

		Mean baseline score (SE)	Mean Week 12 score (SE)	LS mean change from baseline to week 12 (SE)	Daybue-Placebo treatment difference LS Mean (95% CI)	P-Value
RSBQ	Daybue	43.7 (1.21)	39.9 (1.38)	- 4.9 (0.94)	- 3.2 (-5.7, - 0.6)	0.018
	Placebo	44.5 (1.26)	42.8 (1.42)	-1.7 (0.90)		
CGI-I	Daybue	--	3.5 (0.08)	--	- 0.3 (- 0.5, -0.1)	0.003
	Placebo	--	3.8 (0.06)			

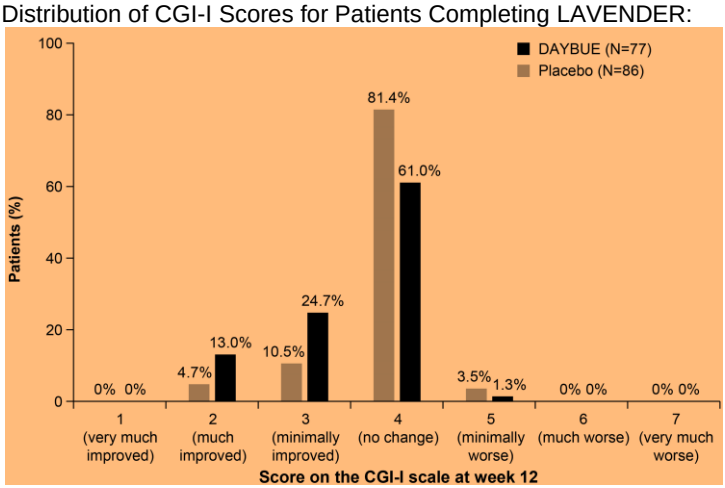
CI: confidence interval; LS mean: Least-squares mean; SE: standard error; the difference in LS means from the mixed-effect model for repeated measure analysis. Alpha set at 0.05.

- RSBQ result indicates statistical significance with a P-Value of 0.018. It may be considered clinically significant because there is a decrease from baseline by around 3 points following 12 weeks of treatment with Daybue.
- CGI-I result indicates statistical significance with a P-Value of 0.003.

  - Change from baseline in the RSBQ total score in LAVENDER:



- Distribution of CGI-I Scores for Patients Completing LAVENDER:



- Safety summary of LAVENDER:

Adverse reaction	Daybue (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	2
Nasopharyngitis	5	1

  - Adverse reactions occurring in at least 5% of Daybue-treated patients and 2% greater than the placebo group.

DAFFODIL (NCT04988867):

- This trial provided safety and pharmacokinetic data for treatment with Daybue in patients with RTT age 2 to 4 years. The findings of this study indicated the safety of Daybue in younger patients (2 to 4 years of age).

Price Per Unit (WAC):

- $21.10 per mL.
- $9,495 per bottle containing 450 mL.
- Dosing is weight-based: A dose of 40 mL twice daily costs $1,688 per day or $50,640 per month (using average patient weight of 27 kg).

Therapeutic Alternatives:

- There is no FDA-approved alternative therapy, and Daybue is the only approved drug for managing RTT.
- Before Daybue's approval, treatment for patients with RTT was mainly supportive symptoms-based therapy.
- Example of supportive therapies:

Symptoms	Supportive Therapy
Constipation	Laxatives (polyethylene glycol, magnesium hydroxide, glycerin, and bisacodyl suppository).
Reflux	Proton pump inhibitors or H2 blockers are used empirically.
Poor weight gain	Energy-dense foods (oils, syrups, avocado).
Calcium/vitamin D	Vitamin D 600 to 1000IU or more daily.
Prolonged feeding times	A gastrostomy button is needed.
Chewing/swallowing difficulties and aspiration concern	Thickeners for liquids may help prevent aspiration.
Sleep disruption	Melatonin, trazodone, or clonidine.
Anxiety and depression	Selective serotonin reuptake inhibitor.
Seizure	Antiseizure medications.

Prior Authorization Approval Criteria:

Must meet the following criteria:

Initial Therapy:

- Participant is aged ≥ 2 years **AND**
- Documented participant weight at baseline **AND**
- Documented diagnosis of RTT (ICD-10 F84.2) **AND**
- Diagnosis of classic or typical RTT **AND**
  - Diagnostic criteria may be required to confirm the diagnosis of typical RTT (see table below)

RTT diagnostic criteria table:	
A period of regression followed by recovery or stabilization. All main criteria and exclusion criteria must be met.	
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
Exclusion criteria	• Brain injury secondary to trauma (peri – or postnatally), neurometabolic disease, or severe infection that causes neurological problems. • Grossly abnormal psychomotor development in the first six months of life.

- Documented pathogenic variant in the *MECP2* gene **AND**
- RTT Clinical Severity Scale rating (RSBQ can be used) of 10 to 36 **AND**
- CGI-I score of ≥ 4 (moderately ill or worse) **AND**
- Prescribed by or in consultation with a neurologist experienced in managing RTT.
- Initial approval for 3 months.

Continuation of Therapy:

- Documented improved clinical measurable symptoms:
  - Decreased RSBQ and CGI-I score by 1 to 4 points after 12 weeks of treatment **OR**
  - Documented clinical benefit by the prescribing provider.
- Lack of severe weight loss, < 5%, from baseline.
- Documented follow-up and assessment of the disease status by a neurologist (or in consultation with a neurologist) experienced in managing RTT.
- Continued approval for 1 year.

Additional Provider Diagnostic/Monitoring Criteria:

- There are no concerns regarding use of Daybue in male patients with RTT. Male patients were not included in the LAVENDER trial due to the small number of male patients with RTT.
- Daybue is intended for outpatient clinical setting use.
- Regular monitoring of weight and clinical improvement is recommended.
- Current clinically significant cardiovascular, endocrine (hypo- or hyperthyroidism, type 1 diabetes, or uncontrolled type 2 diabetes), respiratory, or gastrointestinal disease (such as celiac disease or inflammatory bowel disease) may affect the response and the efficacy of Daybue.
  - Gastrointestinal diseases may increase the severity of Daybue's side effects (diarrhea).
- Recommended baseline examinations are vital signs, electrolytes studies, physical examination, and ECG. Keeping in mind there is no data to suggest Daybue would prolong QTc. Those recommendations are to evaluate the overall health of the patient.

Implication to State Medicaid Program:

LOE: 2035

Pipeline drugs:

- ANAVEX2-73:
  - AVATAR clinical study (NCT03941444) is a phase 3 randomized, double-blind, placebo-controlled trial in 33 adult female patients. Conducted by ANAVEX Life Sciences, which examined ANAVEX2-73 efficacy in treating RTT.
    - ANAVEX2-73 works by restoring cellular homeostasis by targeting sigma-1 muscarinic receptors.
    - The intervention was administering ANAVEX2-73, an oral solution once daily at a dose of up to 30 mg/day for seven weeks, and matching placebo.

- The primary endpoint was RSBQ total score. The ANAVEX2-73 group improved symptoms in 72.2% of patients compared to 38.5% on placebo (P = 0.037). Secondary efficacy endpoints were also statistically significant.
  - EXCELLENCE is a placebo-controlled phase 2/3 pediatric study (NCT04304482). It is evaluating ANAVEX2-73 in patients aged 5 to 17 years. The result of this study is expected during 2023, and if the results are positive, an FDA approval is expected in late 2024.
  - The estimated price for ANAVEX2-73 is $300,000 to $500,000 annually.
- Epidiolex (cannabidiol):
  - ARCH (NCT03848832) is a phase 3 placebo-controlled trial evaluating the efficacy and safety of Epidiolex (cannabidiol) in treating RTT. Participants were randomized into 3 groups: placebo, 5 mg/kg/day Epidiolex, and 15 mg/kg/day Epidiolex.
  - The estimated price of Epidiolex is $10,000 to $20,000 annually.

Additional information:

- LILAC is an extension study of the LAVENDER trial. It is evaluating the long-term effect of Daybue from baseline after 40 weeks of treatment. It included 154 participants of the LAVENDER trial. Primary endpoint outcomes were treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and withdrawals due to AEs.
- Currently, MO HealthNet has 117 documented participants with diagnosed RTT for the calendar year 2022.
- Daybue is exclusively distributed/dispensed through AnovoRx Specialty Pharmacy.

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