Daybue™ (trofinetide)

DAYBUE™ provides an opportunity to help spark meaningful improvements in the signs and symptoms of Rett syndrome

Indication

DAYBUE is indicated for the treatment of Rett syndrome in adults and pediatric patients 2 years of age and older.

Important Safety Information

- **Warnings and Precautions**
  - **Diarrhea:** In a 12-week study and in long-term studies, 85% of patients treated with DAYBUE experienced diarrhea. In those treated with DAYBUE, 49% either had persistent diarrhea or recurrence after resolution despite dose interruptions, reductions, or concomitant antidiarrheal therapy. Diarrhea severity was of mild or moderate severity in 96% of cases. In the 12-week study, antidiarrheal medication was used in 51% of patients treated with DAYBUE.

    Patients should stop taking laxatives before starting DAYBUE. If diarrhea occurs, patients should notify their healthcare provider, consider starting antidiarrheal treatment, and monitor hydration status and increase oral fluids, if needed. Interrupt, reduce dose, or discontinue DAYBUE if severe diarrhea occurs or if dehydration is suspected.

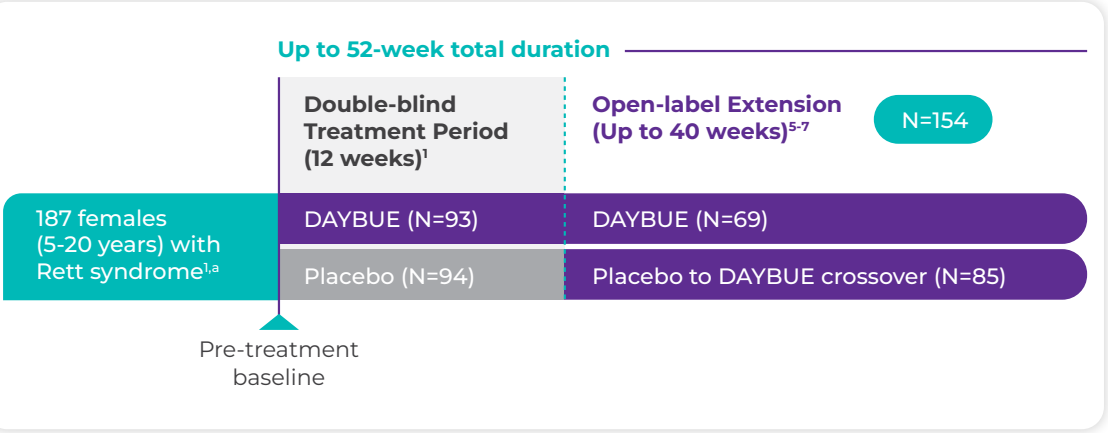
See additional Important Safety Information on page 12.

Please read the full Prescribing Information, also available at DAYBUEhcp.com.

DAYBUE was evaluated in a pivotal Phase 3 trial of 187 patients with Rett syndrome (RTT)[1,3]

LAVENDER™ (NCT04181723)[4] was a 12-week, randomized, double-blind, placebo-controlled trial designed to evaluate the efficacy and safety of DAYBUE[1,3]

Following LAVENDER, patients could enter an open-label extension study for up to 40 weeks.[3]



Select inclusion criteria[5]

- Female patients 5 to 20 years of age
- Body weight ≥12 kg at screening
- Could swallow the study medication provided as an oral solution or could take it by gastrostomy tube
- Had classic/typical RTT
- Had a documented disease-causing mutation in the *MECP2* gene
- Had a stable pattern of seizures, or has had no seizures, within 8 weeks of screening

At baseline, patients exhibited a range of clinical characteristics, disease severity and comorbidities.[5]

In an open-label study in pediatric patients 2 to 4 years of age with RTT, a total of 13 patients received DAYBUE for at least 12 weeks and 9 patients received DAYBUE for at least 6 months.[1]

[a]Patients were stratified by age (5-10, 11-15, and 16-20 years) and baseline RSBQ severity (total score of <35 and ≥35) and randomized 1:1 to trofinetide or placebo groups.[5]

RSBQ=Rett Syndrome Behaviour Questionnaire.

Daybue™ (trofinetide)

Both caregivers and clinicians evaluated the efficacy of DAYBUE[1]

2 co-primary endpoints

Assessment of changes in signs and symptoms of RTT[1]

Caregiver completed

Rett Syndrome Behaviour Questionnaire (RSBQ) total score

Change from baseline to Week 12[1]

- 45-item rating scale[1,8]
- Assesses range of symptoms of RTT[1,8]

Decrease in **total score** reflects lesser severity in signs and symptoms of RTT[1]

Clinician completed

Clinical Global Impression-Improvement (CGI-I)

Score at Week 12[1]

- Assesses improvements or worsening of patient's illness as a whole[1,9]
- 7-point scale relative to baseline[1,9]

Decrease in **score** indicates improvement[1]

In LAVENDER, caregivers assessed a range of RTT symptoms using the RSBQ, such as[1,8]:

- Breathing
- Nighttime behaviors
- Eye gaze
- Hand movements or stereotypies
- Vocalizations
- Mood
- Repetitive behaviors
- Facial expressions

Important Safety Information (continued)

- **Warnings and Precautions: Weight Loss**
  - In the 12-week study, 12% of patients treated with DAYBUE experienced weight loss of greater than 7% from baseline, compared to 4% of patients who received placebo. In long-term studies, 2.2% of patients discontinued treatment with DAYBUE due to weight loss. Monitor weight and interrupt, reduce dose, or discontinue DAYBUE if significant weight loss occurs.

See additional Important Safety Information on page 12.

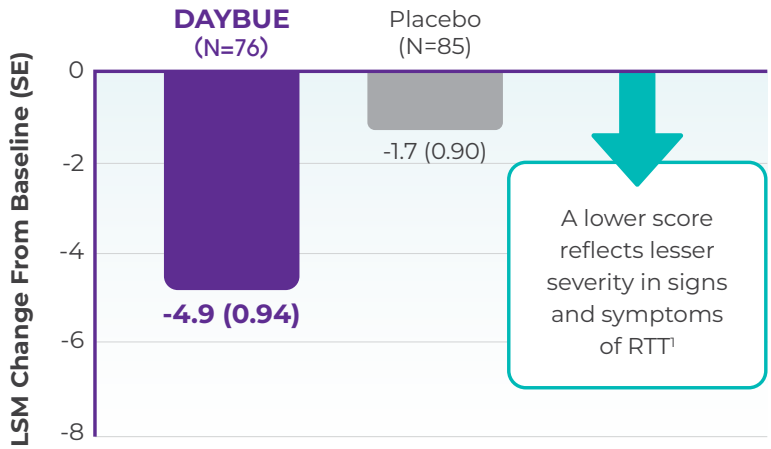
Daybue™ (trofinetide)

Demonstrated improvements with DAYBUE in as little as 12 weeks, as assessed by caregivers[1]

At Week 12, significant improvements in signs and symptoms of RTT were achieved with DAYBUE compared with placebo as assessed by the RSBQ scale[1]

The LSM change from baseline (SE) to Week 12 was -4.9 (0.94) for DAYBUE and -1.7 (0.90) for placebo, with an LSM placebo-subtracted treatment difference (drug minus placebo) of -3.2 (95% CI: -5.7, -0.6; *P*=0.018).[1]

Change From Baseline in RSBQ Total Score at Week 12[1]



3x

Almost 3x greater mean score reduction from baseline vs placebo[1]

Mean RSBQ score (SE)	DAYBUE	Placebo
Baseline	**43.7 (1.21)**	44.5 (1.26)
Week 12	**39.9 (1.38)**	42.8 (1.42)

Learn about Kate's experience with DAYBUE.
Visit **DAYBUEhcp.com/caregiver-perspectives**

Kate**, age 9, living with **Rett syndrome

CI=confidence interval; LSM=least squares mean; SE=standard error.

Important Safety Information (continued)

- **Adverse Reactions:** The common adverse reactions (≥5% for DAYBUE-treated patients and at least 2% greater than in placebo) reported in the 12-week study were diarrhea (82% vs 20%), vomiting (29% vs 12%), fever (9% vs 4%), seizure (9% vs 6%), anxiety (8% vs 1%), decreased appetite (8% vs 2%), fatigue (8% vs 2%), and nasopharyngitis (5% vs 1%).

Daybue™ (trofinetide)

See additional Important Safety Information on page 12.

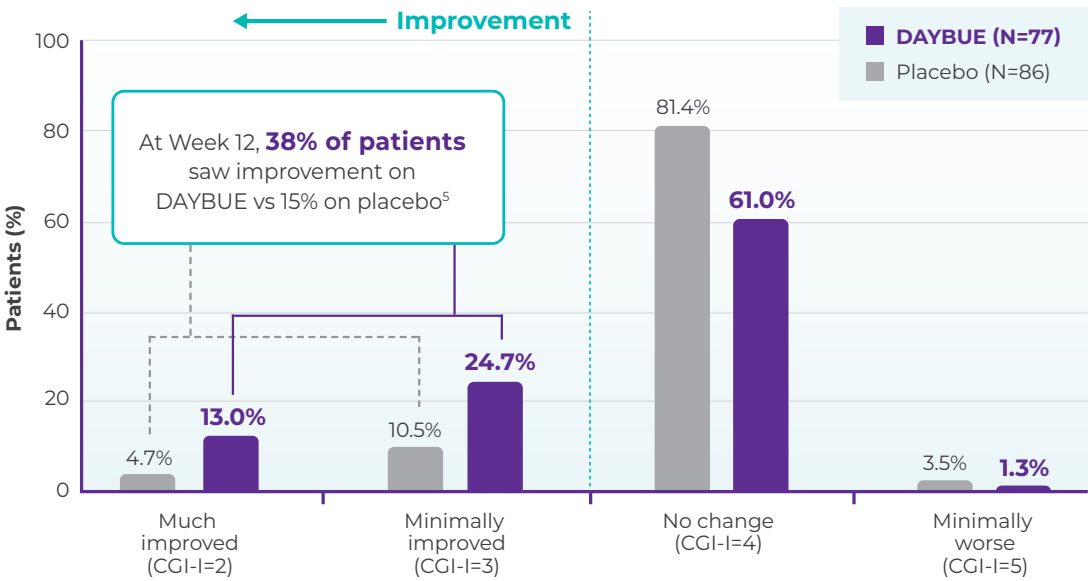
Clinician Assessment (CGI-I)

Demonstrated improvements with DAYBUE in as little as 12 weeks, as observed by clinicians[1]

Clinicians observed an improvement in illness as a whole as measured by the CGI-I, a co-primary endpoint of LAVENDER[1]

At Week 12, patients receiving DAYBUE demonstrated a statistically significant improvement vs placebo in CGI-I, with a mean score (SE) of 3.5 (0.08) compared with 3.8 (0.06) for placebo. The LSM placebo-subtracted treatment difference was -0.3 (95% CI: -0.5, -0.1; *P*=0.003).[1]

Score on the CGI-I Scale at Week 12[1,a]



[a] "Very much improved," "much worse," and "very much worse" are not included on this view of the scores of the CGI-I scale at Week 12 as no patients received these scores.[1]

Because each individual with Rett syndrome is unique—with a unique set of symptoms[10]—improvements in the signs and symptoms of Rett syndrome with DAYBUE may be different for everyone

CGI-I=Clinical Global Impression-Improvement.

Important Safety Information (continued)

- **Adverse Reactions:** The common adverse reactions (≥5% for DAYBUE-treated patients and at least 2% greater than in placebo) reported in the 12-week study were diarrhea (82% vs 20%), vomiting (29% vs 12%), fever (9% vs 4%), seizure (9% vs 6%), anxiety (8% vs 1%), decreased appetite (8% vs 2%), fatigue (8% vs 2%), and nasopharyngitis (5% vs 1%).

Daybue™ (trofinetide)

See additional Important Safety Information on page 12.

Demonstrated safety and tolerability profile of DAYBUE[1]

In controlled and uncontrolled trials in patients with RTT, 260 patients ages 2 to 40 years were treated with DAYBUE, including 109 patients treated for more than 6 months, 69 patients treated for more than 1 year, and 4 patients treated for more than 2 years.[1]

Adverse reactions seen in at least 5% of patients treated with DAYBUE and at least 2% greater than placebo in the 12-week LAVENDER study were[1]:

Adverse Reactions	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%

- 18 patients (19%) receiving DAYBUE had adverse reactions that led to withdrawal from the study[1]
- The most common adverse reaction leading to discontinuation of DAYBUE treatment was diarrhea (15%)[1]

In an open-label study in pediatric patients 2 to 4 years of age with RTT, a total of 13 patients received DAYBUE for at least 12 weeks and 9 patients received DAYBUE for at least 6 months. **Adverse reactions in pediatric patients 2 to 4 years of age treated with DAYBUE were similar to those reported in LAVENDER.[1]**

Warnings and Precautions

Weight loss

- In LAVENDER, 12% of patients treated with DAYBUE experienced weight loss of greater than 7% from baseline, compared to 4% of patients who received placebo
- In long-term studies, 2.2% of patients discontinued treatment with DAYBUE due to weight loss

Daybue™ (trofinetide)

See additional Important Safety Information on page 12.

Demonstrated safety and tolerability profile of DAYBUE[1] (continued)

Warnings and Precautions (continued)

Diarrhea

- In LAVENDER and in long-term studies, 85% of patients treated with DAYBUE experienced diarrhea[1]
- In those treated with DAYBUE, 49% either had persistent diarrhea or recurrence after resolution despite dose interruptions, reductions, or concomitant antidiarrheal therapy[1]
- Diarrhea severity was of mild or moderate severity in 96% of cases[1]
- In LAVENDER, antidiarrheal medication was used in 51% of patients treated with DAYBUE[1]
- In LAVENDER and in long-term studies, none of the cases of diarrhea were associated with hospitalization[11]

Monitor weight and, if significant weight loss or severe diarrhea occurs, or dehydration is suspected, interrupt, reduce the dosage, or discontinue DAYBUE[1]

Education and support are key for helping caregivers manage side effects

The management techniques below may help caregivers further prepare for the possibility of diarrhea.

Before starting DAYBUE:

- Consider establishing a baseline for bowel activity and fluid status by keeping a log to track stool consistency/frequency for 1 week prior to starting treatment
- Stop use of laxatives[1]

If diarrhea occurs:

- Monitor hydration status and increase oral fluids, if needed[1]
- Dietary interventions such as administration of fiber supplements may be appropriate[a]
- Consider starting antidiarrheal medications such as loperamide (IMODIUM)[1]

Daybue™ (trofinetide)

[a]Consider fiber supplementation as needed at time of initiation of DAYBUE.

LILAC™ long-term open-label extension (OLE) study: safety and efficacy data[1]

Eligible patients who completed LAVENDER were enrolled in LILAC[5,6]

LILAC was a long-term OLE safety study that also evaluated efficacy (as measured by mean change from baseline in RSBQ total score and the CGI-I score at end of study). Patients in both the DAYBUE and placebo arms of LAVENDER received DAYBUE for up to 40 additional weeks in the LILAC trial (N=154).[6]

Adverse Events[7,a]	n=154
Diarrhea	74.7%
Vomiting	28.6%
COVID-19	11.0%
Seizure	9.1%
Upper respiratory infection	8.4%
Pyrexia	7.8%
Decreased appetite	7.1%
Urinary tract infection	6.5%
Irritability	6.5%
Weight decrease	5.8%

- Of the 154 patients who enrolled in LILAC, 84 (54.5%) completed the study[7]
  - 35.7% of patients discontinued due to an adverse event[7]
  - 3.2% of patients discontinued due to lack of efficacy[7]

Types of adverse events reported in the OLE study were comparable to those observed in LAVENDER.

[a]Table includes both TEAEs and AEs ≥5% based on MedDRA preferred terms.

AE=adverse event; MedDRA=Medical Dictionary for Regulatory Activities; TEAE=treatment-emergent adverse event.

Important Safety Information

- **Warnings and Precautions: Diarrhea**
  - In a 12-week study and in long-term studies, 85% of patients treated with DAYBUE experienced diarrhea. In those treated with DAYBUE, 49% either had persistent diarrhea or recurrence after resolution despite dose interruptions, reductions, or concomitant antidiarrheal therapy. Diarrhea severity was of mild or moderate severity in 96% of cases. In the 12-week study, antidiarrheal medication was used in 51% of patients treated with DAYBUE.

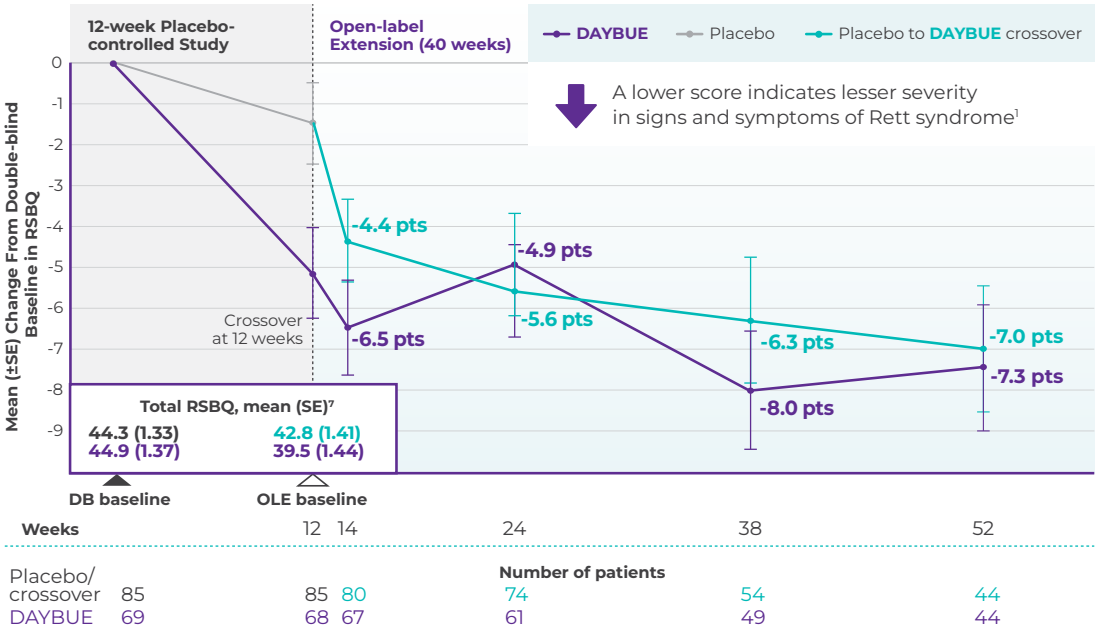
    Patients should stop taking laxatives before starting DAYBUE. If diarrhea occurs, patients should notify their healthcare provider, consider starting antidiarrheal treatment, and monitor hydration status and increase oral fluids, if needed. Interrupt, reduce dose, or discontinue DAYBUE if severe diarrhea occurs or if dehydration is suspected.

See additional Important Safety Information on page 12.

Daybue™ (trofinetide)

LILAC long-term open-label extension (OLE) study: safety and efficacy data (continued)

Mean change from double-blind baseline in RSBQ total score through Week 52[7]



- The mean (SE) change from OLE baseline to OLE Week 40 for those who completed the OLE study was -5.3 (1.86) and -0.4 (1.33) in the crossover and DAYBUE arms, respectively[7,a]

CGI-I was administered throughout the open-label study

Mean (SE) CGI-I scores for those who completed the OLE study were 3.2 (0.14) and 3.1 (0.11), respectively, for subjects previously randomized in LAVENDER to placebo (n=44) and DAYBUE (n=47).[7,a]

[a]Improvement was assessed from the start of the open-label baseline. Mean values are reported for patients who completed 40 weeks of treatment.

Important Note

These RSBQ and CGI-I descriptive data should be interpreted cautiously and may represent chance findings given the limitations of the open-label study design and lack of control arm.

Individual patient results may vary.

Important Safety Information (continued)

- **Warnings and Precautions: Weight Loss**
  - In the 12-week study, 12% of patients treated with DAYBUE experienced weight loss of greater than 7% from baseline, compared to 4% of patients who received placebo. In long-term studies, 2.2% of patients discontinued treatment with DAYBUE due to weight loss. Monitor weight and interrupt, reduce dose, or discontinue DAYBUE if significant weight loss occurs.

See additional Important Safety Information on page 12.

Daybue™ (trofinetide)

DAYBUE is a twice-daily oral treatment for RTT[1]

DAYBUE is an oral solution (200 mg/mL) that is:

Given in the morning and evening, with or without food[1]

Strawberry flavored[1]

For oral administration or via G-tube or G-port of GJ-tube[1]

Recommended dosage for DAYBUE[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

If a dose of DAYBUE is missed, the next dose should be taken as scheduled. Doses should not be doubled. If vomiting occurs after DAYBUE administration, an additional dose should not be taken. Instead, continue with the next scheduled dose.[1]

G-port=gastrostomy port; G-tube=gastrostomy tube; GJ=gastrojejunal.

Important Safety Information (continued)

- **Drug Interactions: Effect of DAYBUE on other Drugs**
  - DAYBUE is a weak CYP3A4 inhibitor; therefore, plasma concentrations of CYP3A4 substrates may be increased if given concomitantly with DAYBUE. Closely monitor when DAYBUE is used in combination with orally administered CYP3A4 sensitive substrates for which a small change in substrate plasma concentration may lead to serious toxicities.
  - Plasma concentrations of OATP1B1 and OATP1B3 substrates may be increased if given concomitantly with DAYBUE. Avoid the concomitant use of DAYBUE with OATP1B1 and OATP1B3 substrates for which a small change in substrate plasma concentration may lead to serious toxicities.
- **Use in Specific Population: Renal Impairment**
  - DAYBUE is not recommended for patients with moderate or severe renal impairment.

See additional Important Safety Information on page 12.

Daybue™ (trofinetide)

Support by your patient's side

acadia connect®

Acadia Connect® is a patient and family support program that connects you, your patients, and their family members with dedicated tools and resources in the treatment journey after patients have been prescribed DAYBUE.

For providers:

- Access and coverage support services, including benefits investigations and information to assist with prior authorizations and appeals processes
- Information on appropriate financial assistance options for eligible patients
- Coordination of medication delivery to patients through AnovoRx Specialty Pharmacy
- Support and education throughout the DAYBUE treatment journey

For patients and caregivers:

- Help to understand and verify insurance coverage
- Information on appropriate financial assistance options
- Support and education throughout the DAYBUE treatment journey
- Coordination with AnovoRx Specialty Pharmacy for timely delivery of DAYBUE
- Ongoing engagement with educational tools and resources

Copay program

Eligible patients with commercial insurance may pay as little as $0 per month for DAYBUE after being automatically enrolled in the Acadia Connect Commercial Copay Program[a]

Visit AcadiaConnect.com to learn more about our personalized support program, designed to help meet the needs of your patients taking DAYBUE

[a]Terms, conditions, and program maximums apply. This program is not open to patients receiving prescription reimbursement under any federal, state, or government-funded healthcare program. Not valid where prohibited by law.

Daybue™ (trofinetide)

Indication and Important Safety Information

Indication

DAYBUE is indicated for the treatment of Rett syndrome in adults and pediatric patients 2 years of age and older.

Important Safety Information

- **Warnings and Precautions**
  - **Diarrhea:** In a 12-week study and in long-term studies, 85% of patients treated with DAYBUE experienced diarrhea. In those treated with DAYBUE, 49% either had persistent diarrhea or recurrence after resolution despite dose interruptions, reductions, or concomitant antidiarrheal therapy. Diarrhea severity was of mild or moderate severity in 96% of cases. In the 12-week study, antidiarrheal medication was used in 51% of patients treated with DAYBUE.

    Patients should stop taking laxatives before starting DAYBUE. If diarrhea occurs, patients should notify their healthcare provider, consider starting antidiarrheal treatment, and monitor hydration status and increase oral fluids, if needed. Interrupt, reduce dose, or discontinue DAYBUE if severe diarrhea occurs or if dehydration is suspected.
  - **Weight Loss:** In the 12-week study, 12% of patients treated with DAYBUE experienced weight loss of greater than 7% from baseline, compared to 4% of patients who received placebo. In long-term studies, 2.2% of patients discontinued treatment with DAYBUE due to weight loss. Monitor weight and interrupt, reduce dose, or discontinue DAYBUE if significant weight loss occurs.
- **Adverse Reactions:** The common adverse reactions (≥5% for DAYBUE-treated patients and at least 2% greater than in placebo) reported in the 12-week study were diarrhea (82% vs 20%), vomiting (29% vs 12%), fever (9% vs 4%), seizure (9% vs 6%), anxiety (8% vs 1%), decreased appetite (8% vs 2%), fatigue (8% vs 2%), and nasopharyngitis (5% vs 1%).
- **Drug Interactions: Effect of DAYBUE on other Drugs**
  - DAYBUE is a weak CYP3A4 inhibitor; therefore, plasma concentrations of CYP3A4 substrates may be increased if given concomitantly with DAYBUE. Closely monitor when DAYBUE is used in combination with orally administered CYP3A4 sensitive substrates for which a small change in substrate plasma concentration may lead to serious toxicities.
  - Plasma concentrations of OATP1B1 and OATP1B3 substrates may be increased if given concomitantly with DAYBUE. Avoid the concomitant use of DAYBUE with OATP1B1 and OATP1B3 substrates for which a small change in substrate plasma concentration may lead to serious toxicities.
- **Use in Specific Population: Renal Impairment**
  - DAYBUE is not recommended for patients with moderate or severe renal impairment.

DAYBUE is available as an oral solution (200mg/mL).

Please read the full Prescribing Information, also available at DAYBUEhcp.com.

Daybue™ (trofinetide)

References

1. Acadia Pharmaceuticals Inc. DAYBUE [Package Insert]. San Diego, CA, 2023. **2.** Acadia Pharmaceuticals announces U.S. FDA approval of DAYBUE™ (trofinetide) for the treatment of Rett syndrome in adult and pediatric patients two years of age and older. [press release]. Acadia Pharmaceuticals Inc. March 10, 2023. **3.** Neul JL, Percy AK, Benke TA, et al. Design and outcome measures of LAVENDER, a phase 3 study of trofinetide for Rett syndrome. *Contemp Clin Trials*. 2022;114:106704. **4.** Study of trofinetide for the treatment of girls and women with Rett syndrome (LAVENDER™). ClinicalTrials.gov identifier: NCT04181723. Accessed June 15, 2023. https://clinicaltrials.gov/ct2/show/NCT04181723. **5.** Neul JL, Percy AK, Benke TA, et al. Trofinetide for the treatment of Rett syndrome: a randomized phase 3 study. *Nat Med*. 2023;29(6):1468-1475. **6.** Open-label extension study of trofinetide for the treatment of girls and women with Rett syndrome (LILAC™). ClinicalTrials.gov identifier: NCT04279314. Accessed July 12, 2023. https://clinicaltrials.gov/ct2/show/NCT04279314. **7.** Acadia Pharmaceuticals Inc. Data on file. ACP- 2566-004. September 2022. **8.** Mount RH, Charman T, Hastings RP, et al. The Rett Syndrome Behaviour Questionnaire (RSBQ): refining the behavioural phenotype of Rett syndrome. *J Child Psychol Psyc*. 2002;43(8):1099-1110. **9.** Guy W. ECDEU Assessment Manual for Psychopharmacology, Revised, 1976. US Department of Health, Education, and Welfare. DHEW Publication No. (ADM) 76-338. Accessed Accessed July 12, 2023. https://archive.org/details/ecdeuassessmentm1933guyw/mode/1up?ref=ol&view=theater. **10.** Fu C, Armstrong D, Marsh E, et al. Consensus guidelines on managing Rett syndrome across the lifespan. *BMJ Paediatr Open*. 2020;4(1):e000717. **11.** Acadia Pharmaceuticals Inc. Data on file. ACP-2566-003, -004, -005. Post hoc analyses. 2022.

Discover an opportunity to help spark meaningful improvements in the signs and symptoms of RTT with DAYBUE

Proven efficacy[1]
DAYBUE demonstrated statistically significant improvements in the signs and symptoms of RTT vs placebo, as measured by the mean change from baseline in RSBQ total score and the CGI-I score at Week 12

Safety and tolerability[1]
The most common adverse reactions with DAYBUE were diarrhea and vomiting. Tips and strategies are available to help caregivers manage adverse events

Twice-daily dosing[1]
DAYBUE is a strawberry flavored oral solution given in the morning and evening, with or without food

Dedicated support
Acadia Connect provides support for patients and their caregivers, with access, insurance, affordability, and prescription assistance

See what DAYBUE may help illuminate in your patients. Learn more at **DAYBUEhcp.com**.

Important Safety Information

- **Warnings and Precautions**
  - **Diarrhea:** In a 12-week study and in long-term studies, 85% of patients treated with DAYBUE experienced diarrhea. In those treated with DAYBUE, 49% either had persistent diarrhea or recurrence after resolution despite dose interruptions, reductions, or concomitant antidiarrheal therapy. Diarrhea severity was of mild or moderate severity in 96% of cases. In the 12-week study, antidiarrheal medication was used in 51% of patients treated with DAYBUE.

    Patients should stop taking laxatives before starting DAYBUE. If diarrhea occurs, patients should notify their healthcare provider, consider starting antidiarrheal treatment, and monitor hydration status and increase oral fluids, if needed. Interrupt, reduce dose, or discontinue DAYBUE if severe diarrhea occurs or if dehydration is suspected.

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Daybue™ (trofinetide)

ACADIA