DAYBUE™ treatment management guide for healthcare professionals

Daybue™ (trofinetide)

The first and only FDA-approved treatment for Rett syndrome (RTT) in adults and pediatric patients 2 years and older.[1,2]

Indication

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

Important Safety Information

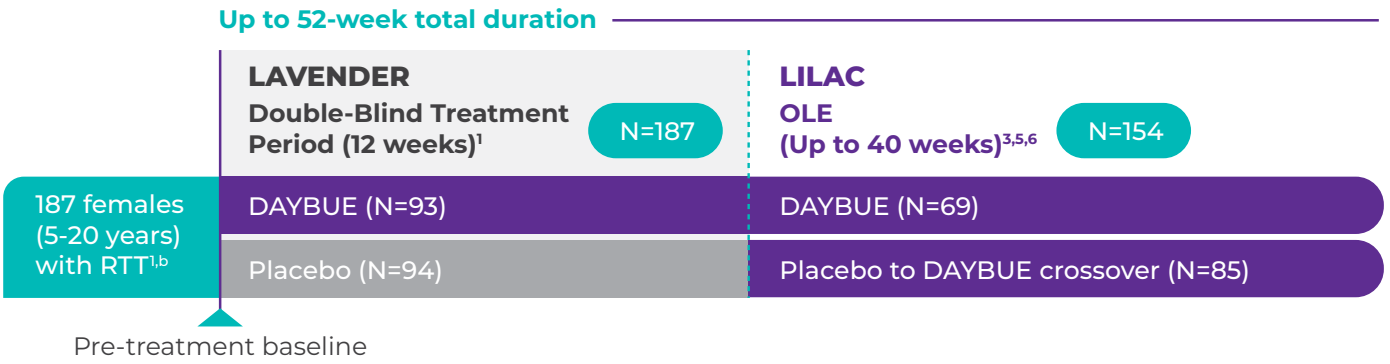
- **Warnings and Precautions**
  - **Diarrhea:** In a 12-week study and in long-term studies, 85% of patients treated with DAYBUE experienced diarrhea. In those treated with DAYBUE, 49% either had persistent diarrhea or recurrence after resolution despite dose interruptions, reductions, or concomitant 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 located throughout.
Please read the full Prescribing Information, also available at DAYBUEhcp.com.

DAYBUE was evaluated in a pivotal Phase 3 trial of 187 patients (aged 5 to 20 years) with 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.[1,5,a] Following LAVENDER, patients could enter LILAC™ (NCT04279314), an open-label extension (OLE) study for up to an additional 40 weeks.[5]

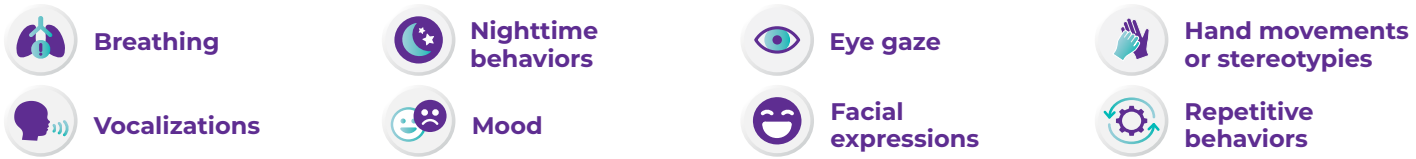


In LAVENDER, two co-primary endpoints evaluated changes in signs and symptoms of RTT, as assessed by caregivers and clinicians.[1]

Caregiver completed scale: Caregivers assessed RTT symptoms with the Rett Syndrome Behaviour Questionnaire (RSBQ) measuring change from Baseline to Week 12.[1,7]

RSBQ measures severity using a 0- to 2-point scale

- RSBQ is a 45-item rating scale of common symptoms of RTT. An RSBQ total score is a sum of all scores (max 90)[1,7]
- Lower score indicates lesser severity of signs and symptoms of RTT. Items in the RSBQ include a range of symptoms, such as[1,7]:



Clinician completed scale: Clinical Global Impression-Improvement (CGI-I) score at Week 12. The scale assesses improvement or worsening of patient's illness as a whole, with a decrease in score indicating improvement.[1]

The CGI-I measures improvement using a 7-point scale[1,8]

1	2	3	4	5	6	7
Very much improved	Much improved	Minimally improved	No change	Minimally worse	Much worse	Very much worse

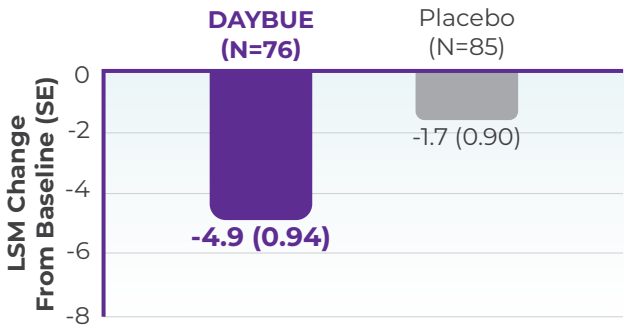
- At baseline, patients exhibited a range of clinical characteristics, disease severity, and comorbidities[3]

[a]Patients had a diagnosis of typical RTT with a documented disease-causing mutation in the *MECP2* gene. Patients were randomized to receive DAYBUE (N=93) or matching placebo (N=94) for 12 weeks.[1]
[b]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 DAYBUE or placebo groups.[3]

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

Caregivers observed an almost 3x greater mean RSBQ score reduction from baseline with DAYBUE versus placebo.
At Week 12, 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[1,3]

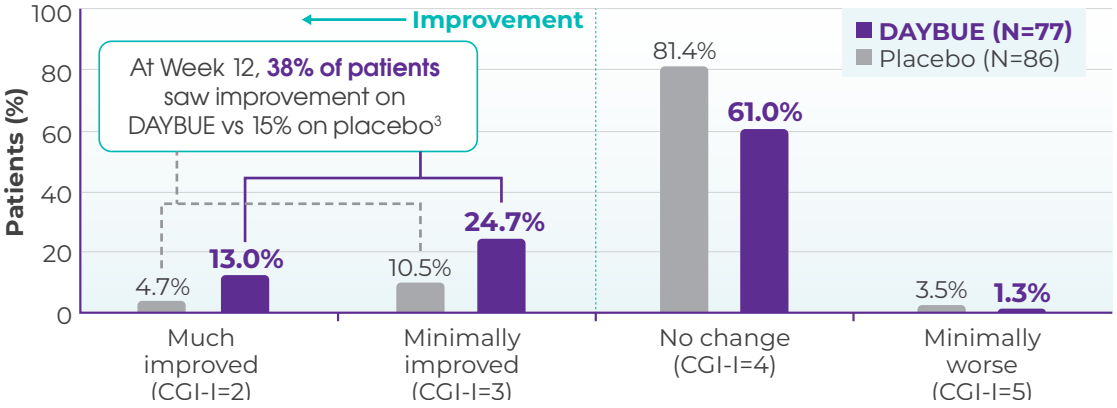


Almost 3x greater mean score reduction from baseline vs placebo[3]

The mean (SE) baseline RSBQ score was 43.7 (1.21) for the DAYBUE group. For the placebo group, it was 44.5 (1.26). At Week 12, the mean (SE) scores for the DAYBUE and placebo groups were 39.9 (1.38) and 42.8 (1.42), respectively.[1]

Statistically significant improvement vs placebo in CGI-I was seen at Week 12, as assessed by clinicians.
At Week 12, the mean score (SE) was 3.5 (0.08) for DAYBUE 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).[1,3]

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



[c]"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]

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

Important Safety Information (cont'd)

- **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%).

See additional Important Safety Information located throughout.

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Demonstrated safety and tolerability profile of DAYBUE in LAVENDER[1]

Adverse reactions 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 treatment with DAYBUE was diarrhea (15%)[1]
- 35.5% of patients in LAVENDER had their DAYBUE dose reduced versus 5.3% for placebo[9]

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]

If severe diarrhea or significant weight loss occurs, or dehydration is suspected
Interrupt, reduce the dosage, or discontinue DAYBUE.[1]

Eligible patients who completed LAVENDER were enrolled in LILAC[3,10]

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 the end of the study. Patients in both the DAYBUE and the placebo arms of LAVENDER received DAYBUE for up to 40 additional weeks in the LILAC trial (N=154).[10]

Safety Data From LILAC[6,a]

Adverse Events	DAYBUE (N=154)
Diarrhea	**74.7%**
Vomiting	**28.6%**
COVID-19	**11.0%**
Seizure	**9.1%**
Upper respiratory tract infection	**8.4%**
Pyrexia	**7.8%**
Decreased appetite	**7.1%**
Urinary tract infection	**6.5%**
Irritability	**6.5%**
Weight decrease	**5.8%**

[a]Table includes both treatment-emergent adverse events and adverse events ≥5% based on MedDRA preferred terms.[6]

Of the 154 patients who enrolled in LILAC, 84 (54.5%) completed the study[6]

- 35.7% of patients discontinued due to an adverse event[6]
- 3.2% of patients discontinued due to lack of efficacy[6]
- 51.3% of patients in LILAC had their DAYBUE dose reduced[11]

Types of adverse events reported in the OLE study were comparable to those observed in LAVENDER.[1]

Important Safety Information (cont'd)

- **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 located throughout.

Daybue™ (trofinetide)

Gastrointestinal (GI) issues are experienced in the vast majority of people with RTT

According to a survey of caregivers of 983 patients with RTT:

of patients with RTT experience GI issues.[12,a]

It is important to be vigilant and proactive about managing these issues.

Abnormalities in swallowing and reduced oropharyngeal clearance in patients with RTT may increase the risk of aspiration.[13,b]

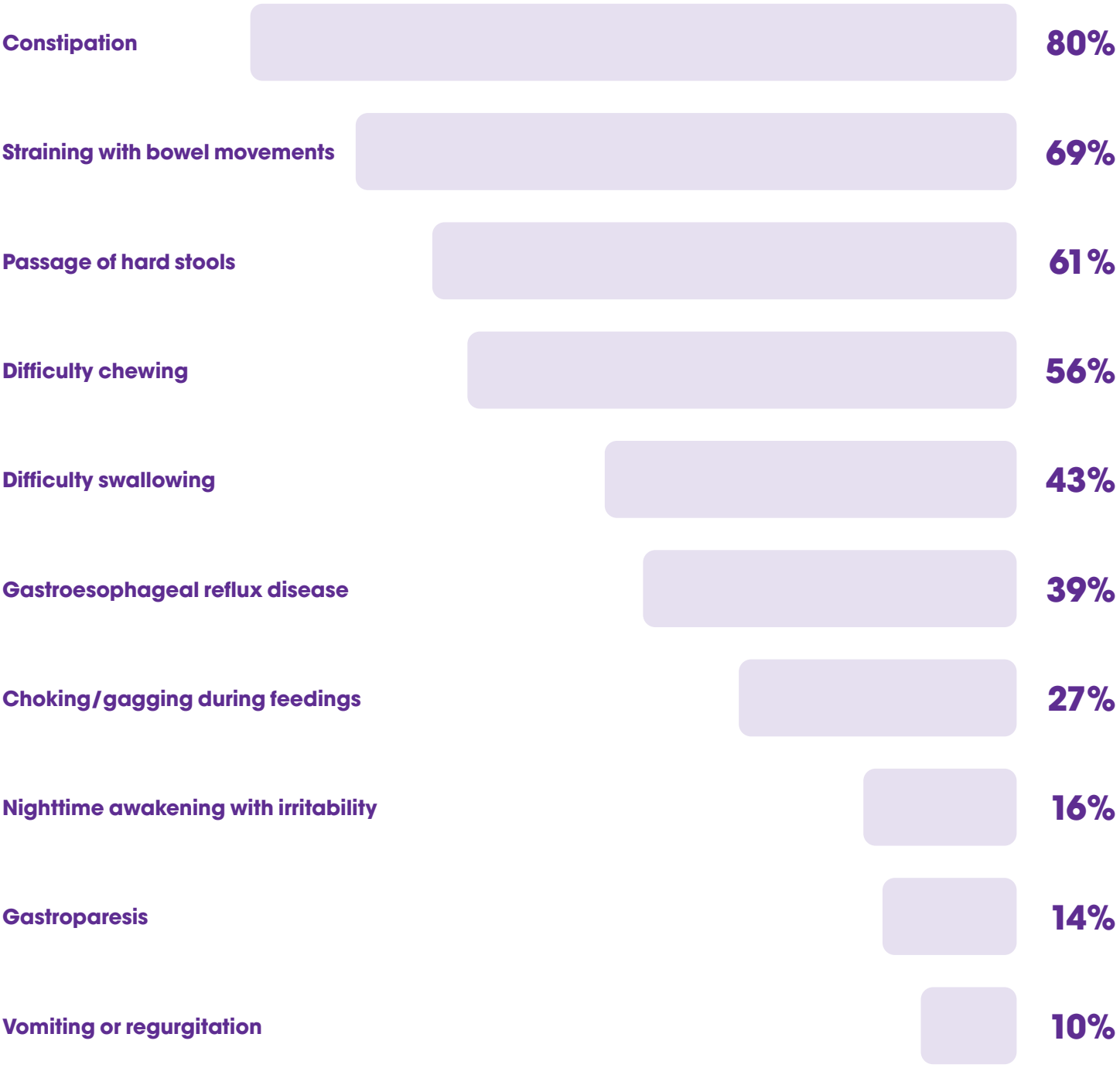
"Gastrointestinal and nutritional problems occur frequently throughout life in girls and women with RTT and pose a significant medical burden to their caregivers."

– Motil KL, et al. *J Pediatr Gastroenterol Nutr.* 2012.

[a]Data from a US survey conducted through International Rett Syndrome Foundation, of caregivers of 983 patients with RTT.[12]

[b]The clinical features of oropharyngeal and gastroesophageal dysfunction were characterized by an oral feeding assessment, swallowing function study, and upper GI series in patients with RTT (n=13).[13]

Select GI Issues in RTT[12,a]:



- Nutritional problems were reported by 47% of survey participants, and biliary tract disorders were reported by 3% of survey participants

Diarrhea management techniques

Severity of diarrhea that occurred in LAVENDER[3]

	DAYBUE (N=93)	Placebo (N=94)
Mild	39 (42%)	15 (16%)
Moderate	34 (37%)	3 (3%)
Severe	2 (2%)	0

Defining severity[14]:

Mild: Awareness of adverse event but easily tolerated, causing minimal discomfort, and not interfering with normal everyday activities

Moderate: Sufficiently discomforting to interfere with normal everyday activities

Severe: Incapacitating and/or preventing normal everyday activities

- None of the cases of diarrhea were associated with hospitalization[15]
  - Individual patient experience with DAYBUE will vary[1]

For patients with a history of constipation[3,9]:

70 of 93 DAYBUE-treated patients (75%) in the LAVENDER clinical trial experienced constipation before starting treatment.

Patients experienced diarrhea regardless of previous constipation history.

Preparation is key to help manage diarrhea

Before starting DAYBUE:

Consider keeping a stool log (consistency/frequency) 1 week prior to starting treatment to establish a baseline for bowel activity and fluid status

Stop use of laxatives[1]

If you are concerned about tolerability for your patient, you may consider titrating to the full recommended dose of DAYBUE based on your clinical judgment and experience[b]

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]

If severe diarrhea or significant weight loss occurs, or dehydration is suspected
Interrupt, reduce the dosage, or discontinue DAYBUE.[1]

[a]Consider fiber supplementation as needed at time of initiation of DAYBUE.
[b]The impact of titration of DAYBUE dosage during initiation of treatment on tolerability was not assessed in the LAVENDER study. Please see dosage and administration section within this brochure.

Practical recommendations for diarrhea management from a panel of advisors

Dietary considerations:

Monitor and reduce intake of sugar alcohols such as erythritol and xylitol, which are found in many processed foods and some liquid medications[16,17]

Provide food in smaller and more frequent volumes[16]

Mix fruit juice with equal parts water to reduce to half-strength[16]

Regularly consume milk, yogurt, and complex carbohydrates[16]

Avoid high-fat foods[16]

Add in fruits, vegetables, and lean meats[16]

Scan to read more about diarrhea management with DAYBUE

Important Safety Information (cont'd)

- **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.

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See additional Important Safety Information located throughout.

Daybue™ (trofinetide)

Considerations for helping caregivers manage vomiting[a]

Severity of vomiting cases that occurred in LAVENDER[3]

	DAYBUE (N=93)	Placebo (N=94)
Mild, n (%)	18 (19%)	8 (9%)
Moderate, n (%)	6 (7%)	1 (1%)
Severe, n (%)	1 (1%)	0

Defining severity[14]:

Mild: Awareness of adverse event but easily tolerated, causing minimal discomfort, and not interfering with normal everyday activities

Moderate: Sufficiently discomforting to interfere with normal everyday activities

Severe: Incapacitating and/or preventing normal everyday activities

Considerations to share with parents and caregivers about vomiting:

To prevent choking, caregivers should sit their child forward or turn their head to the side if vomiting occurs while lying down.[18,19]

When individuals vomit, they can lose water and important salts and become dehydrated. It is important for caregivers to monitor for dehydration.[20]

Signs suggestive of mild dehydration include:

- Dark yellow or brown urine
- Dizziness or light-headedness
- Dry mouth

Signs of severe dehydration include:

- Fewer wet diapers than usual or dark-colored urine
- Dry mouth
- No tears when crying
- Sunken eyes

[a]This guidance was developed by Acadia Pharmaceuticals Inc.

General tips to prevent vomiting

Eating in a calm environment. The digestive tract is sensitive to stress, so eating in a relaxed state may help reduce the risk of vomiting[21]

Keeping a meal journal to help find connections between certain foods and vomiting. Try removing one food at a time to see if symptoms improve[22]

Avoiding meals before sleeping or laying down

- To help prevent dental erosion after vomiting occurs, rinse patient's mouth with water, milk, or sodium bicarbonate rinse[23]

This is not a complete list. Consider outlining a personalized plan with patients and caregivers to help prevent and treat vomiting.

Important Safety Information (cont'd)

- **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 located throughout.

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 Dose 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

Missed dose

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

Dose modification

Advise patients to stop laxatives before starting DAYBUE. Interrupt, reduce the dosage, or discontinue DAYBUE if severe diarrhea occurs, if dehydration is suspected, or if significant weight loss occurs.[1]

Storage and handling of DAYBUE

Inform caregivers that DAYBUE should be stored in an upright position and refrigerated at 2°C to 8°C (36°F to 46°F). DAYBUE should not be frozen and must be returned to refrigeration after each dose. **Discard any unused DAYBUE after 14 days of first opening the bottle.** Keep child-resistant cap tightly closed.[1]

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

Frequently asked questions (FAQs)

How long did it take for patients to see improvement in the symptoms of RTT in the clinical trial?
Improvements in the signs and symptoms of RTT in patients taking DAYBUE were seen at Week 12. Treatment with DAYBUE demonstrated a statistically significant difference in favor of DAYBUE as compared to placebo on the co-primary efficacy endpoints, the change from baseline in RSBQ total score, and the CGI-I score at Week 12.[1]

Will every patient experience diarrhea?
Every patient with RTT has a unique set of evolving symptoms, needs, and goals, which means each patient's experience with DAYBUE will also be unique. In LAVENDER and in long-term studies, 85% of patients treated with DAYBUE experienced diarrhea.[1,24]

Does diarrhea abate over time?
Diarrhea resulting from treatment with DAYBUE may change over time. The implementation of management strategies can help address GI issues, but it is important to note that in those treated with DAYBUE, 49% either had persistent diarrhea or recurrence after resolution despite dose interruptions, reductions, or concomitant antidiarrheal therapy.[1]

Is loperamide the only way to manage diarrhea?
Dietary modifications such as administering fiber supplements may also be appropriate. If severe diarrhea or significant weight loss occurs, or if dehydration is suspected, interrupt, reduce the dosage, or discontinue DAYBUE.[1]

Is it possible to experience both vomiting and diarrhea?
In the pivotal trial, 21 of 75 (28%) DAYBUE-treated patients who experienced diarrhea also experienced vomiting.[9]

What if the patient vomits up DAYBUE?
If the patient vomits after taking DAYBUE, instruct the caregiver to not give another dose. Instead, they should wait until the next scheduled time to administer DAYBUE.[1]

Important Safety Information (cont'd)

- **Warnings and Precautions:**
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See additional Important Safety Information located throughout.

Daybue™ (trofinetide)

Getting your patients started with DAYBUE

Consider the following when onboarding your patients

Set your patients up for success before starting DAYBUE

- Stop use of laxatives[1]
- Establish a baseline for bowel activity by tracking stool activity for 1 week prior to initiating treatment
- Review dosing and possible side effects of DAYBUE with caregivers and patients[1]
- Enroll patients in the Acadia Connect® patient and family support program. Call **1-844-737-2223** for more information

Establish a plan for managing diarrhea and vomiting

- Work with caregivers and patients to establish a personalized management plan should diarrhea or vomiting occur. See pages 8-11 for specific tips on managing diarrhea and vomiting

Monitor progress with DAYBUE

- Discuss symptoms with patients and/or caregivers regularly to track progress, improvements, and any possible adverse events
- Consider partnering with patients' allied healthcare team (speech therapists, physical therapists, etc.) to track progress and symptoms

For children with RTT, set expectations with their schools

Consider providing written communication to patient's school that mentions the following:

- Patient is taking DAYBUE and may experience diarrhea or vomiting
- Occurrence of diarrhea is likely not related to anything infectious

Learn more about the safety and tolerability of DAYBUE at DAYBUEhcp.com.

Important Safety Information (cont'd)

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See additional Important Safety Information located throughout.

Kate, age 9, living with **RTT** and her father

Scan to access the DAYBUE Daily Treatment Journal

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

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- **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.

References

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Daybue™ (trofinetide)

Help your patients with Rett syndrome (RTT) **get the most out of treatment** with DAYBUE

This treatment management guide will help you learn more about:

- Proven efficacy data[1]
- Long-term, open-label safety data[6]
- GI side effect management techniques
- Helping patients get started

Important Safety Information (cont'd)

- **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%).

See additional Important Safety Information located throughout.
Please read the full Prescribing Information, also available at DAYBUEhcp.com.

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