The Story of Trofinetide

ACADIA

For 30 years, Acadia has been elevating science to address unmet need for people with neurological conditions, including those that are notoriously hard diseases to research due to high clinical trial failure rates.

In 2018, Acadia entered into an exclusive licensing agreement with Neuren Pharmaceuticals Ltd. to develop and commercialize trofinetide in North America, a decision that was driven by the company mission and an appreciation that Rett syndrome is a rare disease therapeutic area of high unmet need.

Acadia leadership understood that by its nature, bringing a treatment option for such a complex, rare disease through FDA review and commercialization would not be easy. However, the development of trofinetide up until that point was encouraging to a patient community facing a devastating disorder with no FDA approved options to treat Rett syndrome.

Following positive Phase 2 results, trofinetide was Phase 3-ready as an investigational treatment for an orphan disease that would allow Acadia to expand its central nervous system (CNS) focus to include rare diseases.

Acadia's acquisition of trofinetide and success leading the therapy through FDA approval is a historic achievement. DAYBUE™ (trofinetide) is the first FDA-approved medicine indicated for the treatment of Rett syndrome for patients two years of age and older. The approval of a therapy for Rett syndrome can help increase awareness, drive further research investment and serve as a gateway to future development for Rett syndrome.

Trofinetide Development Timeline

2002
Patent filed for NNZ-2566 (later renamed "trofinetide")

2015
Positive data from the Phase 2, randomized, double-blind, placebo-controlled, dose-escalation study examining the safety and efficacy of trofinetide in adolescent and adult female Rett patients presented at the American Academy of Neurology Annual Meeting

Neuren receives Orphan Drug designation from FDA for trofinetide in Rett syndrome

2018
Acadia Pharmaceuticals enters into exclusive licensing agreement with Neuren to commercialize trofinetide in North America, initiates plans for Phase 3 and open-label studies, and works with the U.S. FDA to meet regulatory milestones to inform the New Drug Application

Acadia begins to engage directly with the Rett syndrome disease community and advocacy

2019
Positive data from a Phase 2, multicenter, double-blind, placebo-controlled, parallel-group study, examining the safety, tolerability, pharmacokinetics, and clinical response to trofinetide in adolescent and adult female Rett patients published in *Neurology*

Acadia initiates pivotal Phase 3 LAVENDER™ trial, a 12-week randomized, double-blind, placebo-controlled study in patients with Rett syndrome five to 20 years of age

2021
Acadia announces positive top-line results from the pivotal Phase 3 LAVENDER trial of trofinetide for the treatment of Rett syndrome

2022
Acadia submits NDA for trofinetide for the treatment of Rett syndrome and FDA accepts NDA for filing

2023
FDA grants approval of DAYBUE™ (trofinetide) for the treatment of Rett syndrome in adults and pediatric patients two years of age and older

See Important Safety Information on following page

Indication

DAYBUE™ (trofinetide) 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 accompanying full Prescribing Information, also available at DAYBUE.com.

ACADIA®