Nature Medicine Publishes Results from Pivotal Phase 3 LAVENDER™ Study Evaluating DAYBUE™ (trofinetide) Efficacy and Safety in Patients with Rett Syndrome

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-- Statistically significant differences demonstrated between DAYBUE ™ and placebo on efficacy endpoints relevant to Rett syndrome suggest treatment potentially capable of modifying core symptoms consistent with underlying pathophysiology of disease

-- Study results provided basis for first FDA-approved treatment for Rett syndrome

SAN DIEGO--(BUSINESS WIRE)--Jun. 8, 2023-- Acadia Pharmaceuticals Inc. (Nasdaq: ACAD) today announced that *Nature Medicine* published results from the pivotal Phase 3 LAVENDER™ trial, a 12-week randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of DAYBUE ™ in patients with Rett syndrome five to 20 years of age.

"The LAVENDER study was designed to measure the effect of DAYBUE treatment on the range of behavioral, communication, and physical Rett syndrome symptoms that significantly impact the quality of life for patients and their loved ones," said Jeffrey L. Neul, M.D., Ph.D., Annette Schaffer Eskind Chair and Director, Vanderbilt Kennedy Center, Professor of Pediatrics, Division of Neurology, Pharmacology, and Special Education, Vanderbilt University Medical Center and LAVENDER study lead author. "The publication of the efficacy and safety results for DAYBUE reinforces the significance of this study as a critical advancement in Rett syndrome research, furthering our ability to treat this devastating disease."

In the study, treatment with DAYBUE (n=93) demonstrated statistically significant improvement compared to placebo (n=94) on both co-primary efficacy endpoints, with the following key findings:

- The mean change from baseline to week 12 in the Rett Syndrome Behaviour Questionnaire (RSBQ) total score was −5.1 and −1.7 in the DAYBUE and placebo groups, respectively. Based on the mixed-effects model for repeated measures (MMRM) analysis, the least squares mean (LSM) [SE] change from baseline to week 12 in the RSBQ total score was statistically significantly greater with DAYBUE (−4.9 [0.94]) than with placebo (−1.7 [0.90]), with an LSM placebo-subtracted difference of −3.1 [1.30], a 95% confidence interval (CI) of −5.7 to −0.6, a p-value of 0.0175, and a Cohen's d effect size of 0.37.
- Change from baseline for all RSBQ domain subscores were numerically in favor of DAYBUE.
- At week 12 in the DAYBUE and placebo groups, respectively, the mean [SE] Clinical Global Impression–Improvement (CGI-I) scores were 3.5 [0.08] and 3.8 [0.06]. MMRM analysis showed a statistically significant improvement with DAYBUE compared with placebo at week 12, with a LSM [SE] difference of −0.3 [0.10], a 95% CI of −0.5 to −0.1, a p-value of 0.0030 and a Cohen's d effect size of 0.47.
- A subgroup analysis showed a similar benefit with DAYBUE over placebo irrespective of age, baseline RSBQ severity, and category of documented disease-causing *MECP2* mutation severity.

"We are pleased that *Nature Medicine* has published these important results from the pivotal LAVENDER trial," said Kathie Bishop, Acadia's Senior Vice President, Chief Scientific Officer and Head of Rare Disease. "The positive findings from this study were integral to the FDA's approval of DAYBUE for Rett syndrome, ushering in the first available treatment option approved by the agency to address a multitude of challenging symptoms in those living with Rett syndrome with the potential to create significant impact for patients and their families."

About LAVENDER ™

The LAVENDER study was a Phase 3, 12-week, double-blind, randomized, placebo-controlled study of DAYBUE in 187 girls and young women aged 5-20 years with Rett syndrome, designed to evaluate its efficacy and safety. Patients were randomized to receive DAYBUE (n=93) or matching placebo (n=94) for 12 weeks. The co-primary endpoints of LAVENDER included both a caregiver (Rett Syndrome Behaviour Questionnaire [RSBQ]) and physician (Clinical Global Impression–Improvement [CGI-I]) assessment. The RSBQ is a caregiver assessment that evaluates a range of symptoms of Rett syndrome including vocalizations, facial expressions, eye gaze, hand movements (or stereotypies), repetitive behaviors, breathing, night-time behaviors and mood. The CGI-I is a global physician assessment of whether a patient has improved or worsened.

DAYBUE also demonstrated statistically significant difference versus placebo on the key secondary endpoint, as measured by change from baseline to week 12 in the Communication and Symbolic Behavior Scales Developmental Profile™ Infant-Toddler Checklist (CSBS-DP-IT) Social Composite score. The CSBS-DP-IT Social Composite score was −0.1 (0.28) and −1.1 (0.28) in the DAYBUE and placebo groups, respectively. MMRM analysis showed a statistically significant difference between DAYBUE and placebo, with an LSM (SE) treatment difference of 1.0 (0.37), a 95% CI of 0.3 to 1.7, a p-value of 0.0064 and a Cohen's d effect size of 0.43. The CSBS-DP-IT is intended to be a screening tool to identify potential communication issues in otherwise healthy infants/toddlers. In the study, the most common side effects in the DAYBUE and placebo groups were diarrhea (80.6% and 19.1%, respectively) and vomiting (26.9% and 9.6%, respectively).

Of the 187 participants in the LAVENDER study, 154 elected to roll over to the open-label LILAC ™ extension study and may be eligible to enter the follow-up LILAC-2 ™ extension study.

About Rett Syndrome

Rett syndrome is a rare, complex, neurodevelopmental disorder that may occur over four stages and affects approximately 6,000 to 9,000 patients in the U.S., with approximately 4,500 patients currently diagnosed according to an analysis of healthcare claims data.[1-4] A child with Rett syndrome exhibits an early period of apparently normal development until six to 18 months, when their skills seem to slow down or stagnate. This is typically followed by a duration of regression when the child loses acquired communication skills and purposeful hand use. The child may then experience a plateau period in which they show mild recovery in cognitive interests, but body movements remain severely diminished. As they age, those living with Rett may continue to experience a stage of motor deterioration which can last the rest of the patient's life. [3] Rett syndrome is typically caused by a genetic mutation on the *MECP2* gene.[5] In preclinical studies, deficiency in MeCP2 function has been shown to lead to impairment in synaptic communication, and the deficits in synaptic function may be associated with Rett manifestations.[5-7]

Symptoms of Rett syndrome may also include development of hand stereotypies, such as hand wringing and clapping, and gait abnormalities.[8] Most Rett patients typically live into adulthood and require round-the-clock care.[2,9]

About DAYBUE ™ (trofinetide)

DAYBUE is a synthetic version of a naturally occurring molecule known as the tripeptide glycine-proline-glutamate (GPE). The mechanism by which DAYBUE exerts therapeutic effects in patients with Rett syndrome is unknown. In animal studies, DAYBUE has been shown to increase branching of dendrites and synaptic plasticity signals.[10,11]

Important Safety Information for DAYBUE ™ (trofinetide)

- **Warnings and Precautions**
  - **Diarrhea**: In a 12-week study and in long-term studies, an aggregate of 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 (200 mg/mL).

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

About Acadia Pharmaceuticals

Acadia is advancing breakthroughs in neuroscience to elevate life. For almost 30 years we have been working at the forefront of healthcare to bring vital solutions to people who need them most. We developed and commercialized the first and only approved therapies for hallucinations and delusions associated with Parkinson's disease psychosis and for the treatment of Rett syndrome. Our clinical-stage development efforts are focused on treating the negative symptoms of schizophrenia, Alzheimer's disease psychosis and neuropsychiatric symptoms in central nervous system disorders. For more information, visit us at www.acadia.com and follow us on LinkedIn and Twitter.

Forward-Looking Statements

Statements in this press release that are not strictly historical in nature are forward-looking statements. These statements include but are not limited to statements regarding the timing of future events. These statements are only predictions based on current information and expectations and involve a number of risks and uncertainties. Actual events or results may differ materially from those projected in any of such statements due to various factors, including the risks and uncertainties inherent in drug development, approval and commercialization. For a discussion of these and other factors, please refer to Acadia's annual report on Form 10-K for the year ended December 31, 2022, as well as Acadia's subsequent filings with the Securities and Exchange Commission. You are cautioned not to place undue reliance on these forward-looking statements, which speak only as of the date hereof. This caution is made under the safe harbor provisions of the Private Securities Litigation Reform Act of 1995. All forward-looking statements are qualified in their entirety by this cautionary statement and Acadia undertakes no obligation to revise or update this press release to reflect events or circumstances after the date hereof, except as required by law.

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