Clinical Data from Open-Label Extension LILAC-1™ and LILAC-2™ Studies Evaluating Long-Term Safety and Efficacy of DAYBUE™ (trofinetide) in Patients with Rett Syndrome Published in Med

July 18, 2024

-- Continued Improvements in RSBQ and CGI-I scores seen with long-term DAYBUE treatment in Phase 3 LAVENDER™ and LILAC studies

-- DAYBUE safety profile was consistent with findings from the LAVENDER trial

SAN DIEGO--(BUSINESS WIRE)--Jul. 18, 2024-- Acadia Pharmaceuticals Inc. (Nasdaq: ACAD) today announced that the journal *Med* published results from two open-label extension studies, LILAC-1™ and LILAC-2™, which showed that patients treated with DAYBUE™ who completed these studies experienced improvement in Rett symptoms as measured by the Rett Syndrome Behaviour Questionnaire (RSBQ). LILAC-1 was a 40-week, open-label extension study of the 12-week Phase 3 LAVENDER™ trial, evaluating the long-term safety and efficacy of DAYBUE in patients with Rett syndrome five to 21 years of age. LILAC-2 was a 32-month open-label extension study, evaluating the long-term safety and efficacy of DAYBUE in females aged five to 22 years who completed LILAC-1. The most common side effects reported in these studies were diarrhea and vomiting. Results from both studies also showed DAYBUE's safety profile was consistent with results from the LAVENDER trial.

"These data from the open-label extension LILAC studies provide deeper insight into the long-term safety and potential benefit of DAYBUE for patients with Rett syndrome," said Alan Percy, M.D., Professor of Pediatrics, Neurology, Neurobiology, Genetics, and Psychology at University of Alabama, Birmingham and lead author for the LILAC-1 and LILAC-2 studies. "These publications add to the growing body of research on clinical experience with DAYBUE and its potential ongoing impact for those living with this condition."

"These findings from LILAC-1 and LILAC-2 add to the results from the pivotal Phase 3 LAVENDER trial and the ongoing LOTUS real-world evidence study and include patients who have been on treatment for over two years, contributing to a robust and growing portfolio of impactful data furthering our understanding of DAYBUE for the treatment of Rett syndrome," said Ponni Subbiah, M.D., M.P.H., Acadia's Senior Vice President, Global Head of Medical Affairs and Chief Medical Officer.

About the data:

- In LILAC-1, 154 females with Rett syndrome five to 21 years of age received open-label treatment with DAYBUE for 40 weeks following double-blind treatment with DAYBUE (n = 69) or placebo (n = 85) in the 12-week LAVENDER study. The RSBQ mean (SE) change from LAVENDER baseline to week 40 in LILAC-1 was −7.3 (1.62) for participants who had been treated with DAYBUE in LAVENDER and completed the LILAC-1 study (N=44) and −7.0 (1.61) for participants who had been treated with placebo in LAVENDER and then were switched to DAYBUE in LILAC-1 and completed LILAC-1 (N=44). Changes from LAVENDER baseline to LILAC-1 week 40 for all RSBQ domain subscores were directionally in favor of DAYBUE regardless of treatment during LAVENDER, irrespective of age, baseline RSBQ severity or underlying *MECP2* mutation severity. Mean (SE) Clinical Global Impression–Improvement (CGI-I) scores at week 40 compared to LILAC-1 baseline were 3.1 (0.11) and 3.2 (0.14) for participants who had been treated with DAYBUE or placebo in LAVENDER and completed the LILAC-1 study, respectively.

- In the 32-month LILAC-2 study, 77 participants who completed LILAC-1 continued to receive open-label treatment with DAYBUE for up to an additional 104 weeks. Improvements in RSBQ scores were reported for participants treated with DAYBUE with a score decrease of ≥ 10% reported in 81.8% of participants at week 104. The mean (SE) change in RSBQ score from LAVENDER baseline to week 104 of LILAC-2 was −9.8 (3.38) for participants who had been treated with DAYBUE in LAVENDER and completed the LILAC-2 study (N=11), and −13.8 (3.61) for participants who received placebo in LAVENDER and completed the LILAC-2 study (N=11). The mean CGI-I from LILAC-1 baseline to Week 12 of LILAC-2 was 3.1 (0.10) for the overall population. 20.8% of patients had discontinued the study.

- 27 caregivers of 26 study participants took part in optional exit interviews to explore the patients' experiences with Rett syndrome and DAYBUE during the trials. The most frequently reported improvements observed by caregivers to participants treated with DAYBUE in the studies were engagement with others (46.2%), hand use (42.3%), and eye gaze (30.8%). Caregivers also reported that some participants acquired new sounds (23.1%) or words (19.2%).

- The safety profile of DAYBUE in LILAC-1 and LILAC-2 was consistent with the safety profile demonstrated in LAVENDER. The most common adverse events in LILAC-1 were diarrhea (74.7%) and vomiting (28.6%) with most reports of diarrhea as mild or moderate in severity and all reports of vomiting as mild or moderate in severity. In LILAC-2, the most common adverse events were diarrhea (53.2%), COVID-19 (27.3%), and vomiting (19.5%). The studies were conducted during the COVID pandemic. All reports of diarrhea were of mild or moderate severity and most reports of vomiting (93.3%) were mild or moderate in severity.

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 5,000 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 is thought 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)

Trofinetide is a synthetic analog of the N-terminal tripeptide of insulin-like growth factor 1. The mechanism by which trofinetide exerts therapeutic effects in patients with Rett syndrome is unknown. In animal studies, trofinetide has been shown to increase branching of dendrites and synaptic plasticity signals.[10]

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 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 FDA-approved drug to treat hallucinations and delusions associated with Parkinson's disease psychosis and the first and only FDA-approved drug for the treatment of Rett syndrome. Our clinical-stage development efforts are focused on Prader-Willi syndrome, Alzheimer's disease psychosis and multiple other programs targeting neuropsychiatric symptoms in central nervous system disorders. For more information, visit us at Acadia.com and follow us on LinkedIn and Twitter.

Forward-Looking Statements

This press release contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995. Forward-looking statements include all statements other than statements of historical fact and can be identified by terms such as "intends," "may," "will," "should," "could," "would," "expects," "plans," "anticipates," "believes," "estimates," "projects," "predicts," "potential" and similar expressions (including the negative thereof) intended to identify forward-looking statements. Forward-looking statements contained in this press release, include, but are not

limited to, statements about: (i) the clinical benefits of DAYBUE and continued statistically significant efficacy observed in the DAYBUE Phase 3 clinical trial program and LILAC-1 and LILAC-2 open label extension studies, (ii) the safety and tolerability profile of DAYBUE and anticipated Rett syndrome symptom improvements, and (iii) the timing and outcome of future results from, and continued enrollment and possible participation extensions in, the real world, observational LOTUS study. Forward-looking statements are subject to known and unknown risks, uncertainties, assumptions and other factors that may cause our actual results, performance or achievements to differ materially and adversely from those anticipated or implied by our forward-looking statements. Such risks, uncertainties, assumptions and other factors include, but are not limited to: our ability to continue to successfully commercialize DAYBUE, the timing, enrollment and results of ongoing and future clinical trials and our ability to continue to stay in compliance with applicable laws and regulations. Given the risks and uncertainties, you should not place undue reliance on these forward-looking statements. For a discussion of these and other risks, uncertainties, assumptions and other factors that may cause our actual results, performance or achievements to differ, please refer to our quarterly report on Form 10-Q for the period ended March 31, 2024 filed with the Securities and Exchange Commission on May 9, 2024, as well as our subsequent filings with the Securities and Exchange Commission from time to time. The forward-looking statements contained herein are made as of the date hereof, and we undertake no obligation to update them after this date, except as required by law.

References

[1] Acadia Pharmaceuticals Inc., Data on file. RTT US Prevalence. March 2022.

[2] Fu C, Armstrong D, Marsh E, et al. Consensus guidelines on managing Rett syndrome across the lifespan. *BMJ Paediatrics Open*. 2020; 4: 1-14.

[3] Kyle SM, Vashi N, Justice MJ. Rett syndrome: a neurological disorder with metabolic components. *Open Biol*. 2018; 8: 170216.

[4] Acadia Pharmaceuticals Inc., Data on file.

[5] Amir RE, Van den Veyver IB, Wan M, et al. Rett syndrome is caused by mutations in X-linked MECP2, encoding methyl-CpG-binding protein 2. *Nat Genet.* 1999; 23(2): 185-188.

[6] Fukuda T, Itoh M, Ichikawa T, et al. Delayed maturation of neuronal architecture and synaptogenesis in cerebral cortex of Mecp2-deficient mice. *J Neuropathol Exp Neurol.* 2005; 64(6): 537-544.

[7] Asaka Y, Jugloff DG, Zhang L, et al. Hippocampal synaptic plasticity is impaired in the Mecp2-null mouse model of Rett syndrome. *Neurobiol Dis*. 2006; 21(1): 217-227.

[8] Neul JL, Kaufmann WE, Glaze DG, et al. Rett syndrome: revised diagnostic criteria and nomenclature. *Ann Neurol*. 2010; 68(6): 944-950.

[9] Daniel C, Tarquinio DO, Hou W, et al. The changing face of survival in Rett syndrome and MECP2-related disorders. *Pediatr Neurol*. 2015; 53(5): 402-411.

[10] Acadia Pharmaceuticals Inc., Data on file.

View source version on businesswire.com: https://www.businesswire.com/news/home/20240718277446/en/

Investor Contact:
Acadia Pharmaceuticals Inc.
Al Kildani
(858) 261-2872
ir@acadia-pharm.com

Acadia Pharmaceuticals Inc.
Jessica Tieszen
(858) 261-2950
ir@acadia-pharm.com

Media Contact:
Acadia Pharmaceuticals Inc.
Deb Kazenelson
(818) 395-3043
media@acadia-pharm.com

Source: Acadia Pharmaceuticals Inc.