Acadia Pharmaceuticals Acquires Ex-North American Rights to Trofinetide and Global Rights to Neuren's NNZ-2591 in Rett Syndrome and Fragile X Syndrome

July 13, 2023

-- Expanded agreement follows Acadia's April 2023 U.S. launch of DAYBUE™ (trofinetide) as the first and only drug approved for the treatment of Rett syndrome

-- Acadia provides DAYBUE launch update and announces second quarter preliminary net sales and guidance for third quarter

-- Company to host conference call and webcast today at 4:30 p.m. Eastern Time

SAN DIEGO--(BUSINESS WIRE)--Jul. 13, 2023-- Acadia Pharmaceuticals Inc. (NASDAQ: ACAD) today announced that it has expanded its current licensing agreement for trofinetide with Neuren Pharmaceuticals to acquire ex-North American rights to the drug as well as global rights in Rett syndrome and Fragile X syndrome to Neuren's development candidate NNZ-2591. In April of this year, Acadia launched trofinetide in the United States under the brand name DAYBUE as the first and only drug approved for the treatment of Rett syndrome.

"This expanded worldwide agreement solidifies Acadia's position as the global leader in addressing the unmet needs of people with Rett syndrome," said Steve Davis, Acadia's President and Chief Executive Officer. "We have successfully delivered DAYBUE, the first FDA-approved therapy that treats the core symptoms of Rett syndrome, and are deeply committed to broadening access to this important therapy for patients worldwide."

In addition to expanding access to trofinetide outside of North America, this agreement gives Acadia exclusive worldwide rights to NNZ-2591 in both Rett syndrome and Fragile X syndrome. NNZ-2591 is an investigational synthetic analogue of cyclo-glycyl-proline (cGP) which results from the breakdown of human insulin-like growth factor 1 (IGF-1). NNZ-2591 is currently under development by Neuren in four other rare neurodevelopmental syndromes.

Execution of this agreement advances Acadia's corporate strategy to expand our rare disease business. This deal also enables Acadia to leverage insights from our successful U.S. launch of DAYBUE in other global territories. In addition, this expansion will further advance the global potential of Acadia's current development portfolio.

Acadia intends to submit a New Drug Submission (NDS) for trofinetide in Canada in the next 18 months with plans for Europe, Asia and other regions to be announced at a later date.

Financial Terms

Under the terms of the expanded agreement, Neuren will receive an upfront payment of US $100 million and is eligible to receive additional potential downstream milestone and royalty payments earned separately for trofinetide and NNZ-2591.

Outside of North America, Neuren is eligible to receive additional payments for trofinetide upon the achievement of specified revenue milestones as follows:

	First Commercial Sales Milestones	Total Sales Milestones[(1)]
Europe	$35M (Rett); $10M (2nd indication)	Up to $170M
Japan	$15M (Rett); $4M (2nd indication)	Up to $110M
Rest of World	-0-	Up to $83M

(1) Each region's sales milestones are divided into four distinct milestones based upon escalating annual net sales thresholds as defined in the agreement.

Neuren will also receive tiered royalties from the mid-teens to low-twenties percent of trofinetide net sales outside of North America. In North America, all milestones and royalties for trofinetide remain unchanged from Acadia's previously existing North American license agreement with Neuren. Potential future payments to Neuren related to NNZ-2591 in Rett syndrome and Fragile X syndrome are identical to the payments for trofinetide in each of North America and outside North America.

Preliminary Second Quarter Revenues and Updated Guidance

DAYBUE

- DAYBUE 2Q 2023 preliminary net sales: $21 to $23 million.
- DAYBUE 3Q 2023 net sales guidance: $45 to $55 million.

NUPLAZID

- NUPLAZID 2Q 2023 preliminary net sales: $140 to $144 million.
- NUPLAZID Full Year 2023 net sales guidance: $530 to $545 million.

Conference Call and Webcast Information

Acadia will discuss the exclusive worldwide licensing of trofinetide and NNZ-2591 via conference call and webcast today at 4:30 p.m. Eastern Time. The conference call will be available on Acadia's website, www.acadia.com under the investors section and will be archived there until August 12, 2023. The conference call may also be accessed by registering for the call here. Once registered, participants will receive an email with the dial-in number and unique PIN number to use for accessing the call.

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] Worldwide, incidence rates for Rett syndrome are similar in countries across the globe, with prevalence varying according to population size, with the number of patients in Europe estimated to be larger and that of Japan's smaller. 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)

Trofinetide is a synthetic version of a naturally occurring molecule known as the tripeptide glycine-proline-glutamate (GPE). 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.[10,11]

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 Fragile X Syndrome

Fragile X syndrome is the most common inherited cause of intellectual disability and the most common known cause of autism. Fragile X syndrome is due to a gene mutation on the X chromosome that impacts the FMRP protein, which is responsible for regulating the synapses of nerve cells. The full mutation causes Fragile X syndrome. It is estimated that between one in 4,000 and one in 7,000 males and between one in 6,000 and one in 11,000 females have the full mutation. Generally, males are more severely affected, with approximately 50% of the females having some features of the syndrome. Clinically, Fragile X syndrome is characterized by intellectual handicap, hyperactivity and attentional problems, autistic symptoms, anxiety, emotional lability and epilepsy.[12,13] Currently, there are no medicines approved for the treatment of Fragile X syndrome.

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 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, Prader-Willi syndrome, 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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