ACADIA Pharmaceuticals Submits Supplemental New Drug Application to U.S. FDA for NUPLAZID® (pimavanserin) for the Treatment of Hallucinations and Delusions Associated with Dementia-Related Psychosis

June 15, 2020

- Submission based on positive results from the Phase 3 HARMONY study which showed a statistically significant 2.8 fold reduction in the risk of relapse of psychosis

SAN DIEGO--(BUSINESS WIRE)--Jun. 15, 2020-- ACADIA Pharmaceuticals Inc. (Nasdaq: ACAD) announced today that the company submitted a supplemental New Drug Application (sNDA) to the U.S. Food and Drug Administration (FDA) to support a potential new indication for NUPLAZID® (pimavanserin) for the treatment of hallucinations and delusions associated with dementia-related psychosis (DRP). The FDA previously granted Breakthrough Therapy Designation for pimavanserin for the treatment of hallucinations and delusions associated with DRP.

"This is an important step forward for the approximately 2.4 million people in the U.S. who suffer from dementia-related hallucinations and delusions, representing a large unmet need with currently no approved treatment options," said Steve Davis, ACADIA's Chief Executive Officer. "Our pivotal HARMONY study showed a meaningful reduction of the symptoms and stabilization of psychosis and a nearly three-fold reduction in the risk of relapse of psychosis for patients continuing treatment on pimavanserin compared to placebo. We look forward to working with the FDA as it reviews our submission."

The sNDA is supported by results from the pivotal Phase 3 HARMONY study, which met its primary endpoint, demonstrating that pimavanserin significantly reduced the risk of relapse of psychosis by 2.8 fold compared to placebo (hazard ratio = 0.353; one-sided p=0.0023). The sNDA also includes positive efficacy results from two additional placebo-controlled studies, both of which met their respective primary endpoints: The Phase 2 (-019) study in patients with Alzheimer's disease psychosis and the Phase 3 (-020) study in patients with Parkinson's disease psychosis. The sNDA includes a large safety and tolerability database from completed and ongoing studies representing over 1500 patients with neurodegenerative disease.

Dementia is highly prevalent, affecting approximately 8 million people in the U.S., and is only expected to grow as the population ages. Approximately 30 percent, or 2.4 million people, experience dementia-related psychosis and only half, or 1.2 million, are diagnosed and treated[1,2].

NUPLAZID was approved in the U.S. in 2016 as the first and only treatment for hallucinations and delusions associated with Parkinson's disease psychosis. If approved by the FDA, NUPLAZID would be the first drug approved to treat the hallucinations and delusions associated with dementia-related psychosis and would be the second indication for NUPLAZID.

About HARMONY

HARMONY was a Phase 3 study designed to evaluate the efficacy and safety of pimavanserin for the treatment of hallucinations and delusions associated with dementia-related psychosis across a broad population of patients with the most common clinically diagnosed subtypes of dementia including: Alzheimer's disease, dementia with Lewy bodies, Parkinson's disease dementia, vascular dementia, and frontotemporal dementia spectrum disorders. A total of 392 patients were enrolled in the study, with an average age of 74.5 years and a mean Mini-Mental State Examination (MMSE) score of 16.7. The primary endpoint in the study was time to relapse in the double-blind period as represented by the Kaplan-Meier curve and the hazard ratio. Top-line results were presented at the 2019 Clinical Trials on Alzheimer's Disease (CTAD) Meeting in December 2019.

The HARMONY study included a 12-week open-label stabilization period during which patients with dementia-related psychosis began treatment with pimavanserin 34 mg once daily. In the open-label period, a significant majority (61.8%) of eligible subjects (N=351) met the sustained treatment response criteria at Week 8 and Week 12 and entered the double-blind period. Following the open-label period, patients who met pre-specified criteria for treatment response were then randomized into the double-blind period of the study to continue their pimavanserin dose (34 mg or 20 mg per day) or switched to placebo and followed for up to 26 weeks or until a relapse of psychosis occurred. Pimavanserin met its primary endpoint and was stopped at the pre-planned interim analysis for positive efficacy, demonstrating that pimavanserin significantly reduced the risk of relapse of psychosis by 2.8 fold compared to placebo (hazard ratio = 0.353; one-sided p=0.0023).

Pimavanserin was well-tolerated over the entire nine-month study duration, and pimavanserin treatment was not associated with a decline in cognition, as measured by the MMSE score, or the onset or worsening of extrapyramidal symptoms, as measured by the Extrapyramidal Symptom Rating Scale A (ESRS-A) score, compared to placebo. In the double-blind period, low rates of adverse events were observed, 41.0% of patients on pimavanserin and 36.6% on placebo. Discontinuations in the double-blind period due to adverse events were low, 2.9% for pimavanserin and 3.6% for placebo. Rates of serious adverse events were also low, 4.8% in the pimavanserin group and 3.6% in the placebo group. One death was reported in the open-label period and one death was reported in the pimavanserin group during the double-blind period. Investigators determined neither death was related to the study drug.

About Dementia-Related Psychosis

Approximately 8 million people in the United States are living with dementia, a condition with a core feature of declining cognition (changes in memory, decision-making abilities, language, etc.) resulting in functional impairment. Dementia is a manifestation of an underlying condition which is often progressive and neurodegenerative in nature.[3] In addition to cognitive decline, dementing illnesses almost universally lead to neuropsychiatric symptoms, including hallucinations, delusions, and changes in behavior.

It is estimated that 2.4 million Americans (or 30% of people with dementia) experience dementia-related hallucinations and delusions[1,2]. These symptoms may be frequent and severe and may recur over time. A delusion is defined as a false, fixed belief that is resolutely held despite evidence to

the contrary. A hallucination is defined as a perception-like experience that occurs without an external stimulus and is sensory (seen, heard, felt, tasted, sensed) in nature. Dementia-related psychosis occurs in many types of dementia, including Alzheimer's disease, dementia with Lewy bodies, Parkinson's disease dementia, vascular dementia, and frontotemporal dementia. Serious consequences have been associated with psychosis in patients with dementia, such as repeated hospital admissions, increased likelihood of nursing home placement, faster progression of dementia, and increased risk of morbidity and mortality[4].

About Pimavanserin

Pimavanserin is a selective serotonin inverse agonist and antagonist preferentially targeting 5-HT_{2A} receptors. These receptors are thought to play an important role in psychosis, schizophrenia, depression and other neuropsychiatric disorders. In vitro, pimavanserin demonstrated no appreciable binding affinity for dopamine (including D2), histamine, muscarinic, or adrenergic receptors. ACADIA is evaluating pimavanserin in an extensive clinical development program in multiple indications with significant unmet need, including dementia-related psychosis, major depressive disorder, and negative symptoms of schizophrenia. Pimavanserin was approved for the treatment of hallucinations and delusions associated with Parkinson's disease psychosis by the U.S. Food and Drug Administration in April 2016 under the trade name NUPLAZID®. NUPLAZID is not approved for dementia-related psychosis, schizophrenia or major depressive disorder.

About ACADIA Pharmaceuticals

ACADIA is a biopharmaceutical company focused on the development and commercialization of innovative medicines to address unmet medical needs in central nervous system disorders. ACADIA has developed and commercialized the first and only medicine approved for the treatment of hallucinations and delusions associated with Parkinson's disease psychosis. ACADIA also has ongoing clinical development efforts in additional areas with significant unmet need, including dementia-related psychosis, the negative symptoms of schizophrenia, major depressive disorder, and Rett syndrome. This press release and further information about ACADIA can be found at: www.acadia-pharm.com.

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 related to pimavanserin as a potential treatment for the hallucinations and delusions associated with dementia-related psychosis and other statements that are not historical facts. 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, and 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, 2019 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.

Important Safety Information and Indication for NUPLAZID (pimavanserin)

Indication

NUPLAZID is indicated for the treatment of hallucinations and delusions associated with Parkinson's disease psychosis.

Important Safety Information

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

- **Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death.**
- **NUPLAZID is not approved for the treatment of patients with dementia-related psychosis unrelated to the hallucinations and delusions associated with Parkinson's disease psychosis.**

- **Contraindication:** NUPLAZID is contraindicated in patients with a history of a hypersensitivity reaction to pimavanserin or any of its components. Rash, urticaria, and reactions consistent with angioedema (e.g., tongue swelling, circumoral edema, throat tightness, and dyspnea) have been reported.
- **Warnings and Precautions:** QT Interval Prolongation
  - NUPLAZID prolongs the QT interval. The use of NUPLAZID should be avoided in patients with known QT prolongation or in combination with other drugs known to prolong QT interval including Class 1A antiarrhythmics or Class 3 antiarrhythmics, certain antipsychotic medications, and certain antibiotics.
  - NUPLAZID should also be avoided in patients with a history of cardiac arrhythmias, as well as other circumstances that may increase the risk of the occurrence of torsade de pointes and/or sudden death, including symptomatic bradycardia, hypokalemia or hypomagnesemia, and presence of congenital prolongation of the QT interval.
- **Adverse Reactions:** The common adverse reactions (≥2% for NUPLAZID and greater than placebo) were peripheral edema (7% vs 2%), nausea (7% vs 4%), confusional state (6% vs 3%), hallucination (5% vs 3%), constipation (4% vs 3%), and gait disturbance (2% vs <1%).
- **Drug Interactions:**
  - Coadministration with strong CYP3A4 inhibitors (e.g., ketoconazole) increases NUPLAZID exposure. Reduce NUPLAZID dose to 10 mg taken orally as one tablet once daily.
  - Coadministration with strong or moderate CYP3A4 inducers reduces NUPLAZID exposure. Avoid concomitant use of strong or moderate CYP3A4 inducers with NUPLAZID.

Dosage and Administration

Recommended dose: 34 mg capsule taken orally once daily, without titration.

NUPLAZID is available as 34 mg capsules and 10 mg tablets.

Please read the full Prescribing Information including **Boxed WARNING**.

References

[1]Plassman BL, et al. Prevalence of dementia in the United States: the Aging Demographics, and Memory study. Neuroepidemiology. 2007;29(1-2):125-132.

[2]2017 Alzheimer's Disease Facts and Figures and ACADIA market research.

[3]Dementia. (2019, September 19). Retrieved from https://www.who.int/news-room/fact-sheets/detail/dementia.

[4]Connors MH et al. Am J Geriatr Psychiatry 2018;26(3). Peters ME et al. Am J Psychiatry 2015;172(5). Haupt M et al. Int J Geriatr Psychiatry 1996;11(11). Naimark D et al. J Am Geriatr Soc 1996;44(3). Stern Y et al. Neurology 1994;44(12).

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