The New England Journal of Medicine Publishes Results from the Phase 3 HARMONY Study Evaluating Pimavanserin in Patients with Dementia-Related Psychosis

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- Pimavanserin met the primary endpoint of reduced risk of relapse of psychosis by 2.8 fold compared to placebo

- Pimavanserin met the secondary endpoint of significantly reducing trial discontinuation for any reason by 2.2 fold

SAN DIEGO--(BUSINESS WIRE)--Jul. 21, 2021-- Acadia Pharmaceuticals Inc. (Nasdaq: ACAD) announced today that the *New England Journal of Medicine* published results from the Phase 3 HARMONY study, an international, double-blind, placebo-controlled relapse prevention trial in 392 patients evaluating pimavanserin as an investigational treatment in patients with hallucinations and delusions associated with dementia-related psychosis (DRP). The study included patients across five subgroups of dementia: Alzheimer's disease, dementia with Lewy bodies, frontotemporal dementia, Parkinson's disease dementia, and vascular dementia.

The HARMONY study was stopped early due to positive efficacy at the pre-planned interim analysis upon recommendation of the trial's independent data safety monitoring board. HARMONY met its primary endpoint by significantly reducing the risk of relapse of psychosis by 2.8 fold compared to placebo in the double-blind period (hazard ratio (HR)=0.35, two-sided p=0.005; one-sided p=0.0023). The study also met its secondary endpoint by significantly reducing the time to trial discontinuation for any reason (HR=0.45, two-sided p=0.005; one-sided p=0.0024). The data from the HARMONY study demonstrates that patients with DRP who had responded to pimavanserin had a significantly lower risk of relapse of psychosis with continuation of pimavanserin compared to placebo up to 26 weeks.

"The relapse prevention design of the HARMONY study mirrors exactly what we do in clinical practice. This landmark trial showed that when patients responded to pimavanserin and then continued treatment, they were almost three times less likely to develop recurrence of their hallucinations and delusions than those patients who discontinued pimavanserin treatment," said the study's lead author, Dr. Pierre N. Tariot, Banner Alzheimer's Institute director. "This is a substantial finding and a significant advance for a critical public health need in our field. There is no FDA approved treatment for DRP, and the majority of antipsychotics currently used off-label have equivocal efficacy and may accelerate cognitive decline."

Pimavanserin was well-tolerated over the nine-month study duration. In a pre-specified analysis, pimavanserin was not associated with a decline in cognition as measured by Mini-Mental State Examination (MMSE) or the onset or worsening of motor symptoms as measured by Extrapyramidal Symptom Rating Scale A (ESRS-A).

"The HARMONY study findings demonstrated three important results. First, in the 12-week open-label period, pimavanserin treatment showed a sustained reduction of psychotic symptoms. Second, in the 26-week double-blind period, patients on pimavanserin had a nearly three-fold reduction of risk of psychosis relapse compared to patients on placebo. Third, pimavanserin was well-tolerated by elderly patients with DRP," said Steve Davis, Chief Executive Officer of Acadia. "We are very pleased that the *New England Journal of Medicine* has chosen to publish the important results of this study."

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. The study included patients with Alzheimer's disease, dementia with Lewy bodies, frontotemporal dementia, Parkinson's disease dementia, and vascular dementia. A total of 392 patients were enrolled in the study, with a mean age of 74.5 years and a mean MMSE score of 16.7. The primary endpoint in the study was time from randomization to relapse of psychosis in the double-blind period as represented by the Kaplan-Meier curve and the hazard ratio.

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 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 sustained treatment response were then randomized into the double-blind period of the study to continue their pimavanserin dose 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 (HR=0.35, p=0.005).

In the double-blind period, similar, low rates of adverse events were observed, 43 (41.0%) patients on pimavanserin (n=105) and 41 (36.6%) patients on placebo (n=112). 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 that 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.[1] In addition to cognitive decline, dementing illnesses almost universally lead to neuropsychiatric symptoms, which may include 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.[2,3] These

symptoms may be frequent and severe and may recur over time. 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. A delusion is defined as a false, fixed belief that is resolutely held despite evidence to the contrary. 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 neuropsychiatric disorders. In vitro, pimavanserin demonstrated no appreciable binding affinity for dopamine (including D2), histamine, muscarinic, or adrenergic receptors. 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. In addition, Acadia is developing pimavanserin in other neuropsychiatric conditions.

About Acadia Pharmaceuticals

Acadia is trailblazing breakthroughs in neuroscience to elevate life. For more than 25 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 therapy for hallucinations and delusions associated with Parkinson's disease psychosis. Our late-stage development efforts are focused on dementia-related psychosis, negative symptoms of schizophrenia and Rett syndrome, and in early-stage clinical research we are exploring novel approaches to pain management, and cognition and neuropsychiatric symptoms in central nervous system disorders. For more information, visit us at www.acadia-pharm.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, 2020 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]Dementia. (2019, September 19). Retrieved from https://www.who.int/news-room/fact-sheets/detail/dementia.

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

[3]2017 Alzheimer's Disease Facts and Figures and Acadia market research.

[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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