ACADIA Pharmaceuticals Announces Top-line Results from Phase 3 ENHANCE Trial of Pimavanserin as Adjunctive Treatment for Patients with Schizophrenia

July 22, 2019

- Pimavanserin did not achieve statistical significance on the primary endpoint, but showed a consistent trend in improvement of psychotic symptoms (p=0.0940)

- Significant improvements observed on secondary endpoint of PANSS negative symptoms scale sub-score (unadjusted p=0.0474)

- Conference call and webcast to be held today at 5:00 p.m. Eastern Time

SAN DIEGO--(BUSINESS WIRE)--Jul. 22, 2019-- ACADIA Pharmaceuticals Inc. (Nasdaq: ACAD), today announced top-line results from its Phase 3 ENHANCE study, which evaluated pimavanserin as an adjunctive treatment in adult schizophrenia patients with persistent inadequate response to their current antipsychotic therapy. A total of 396 patients with moderate-to-severe psychotic symptoms were randomized to receive either pimavanserin or placebo added to their current antipsychotic treatment. There is currently no FDA-approved adjunctive treatment for schizophrenia patients with inadequate response to existing therapies.

In the study, adding pimavanserin to existing antipsychotic treatment showed a consistent trend in improvement of psychotic symptoms, however the results did not achieve statistical significance on the primary endpoint, the Positive and Negative Syndrome Scale (PANSS) total score (p=0.0940). A positive trend was also observed on the key secondary endpoint, the Clinical Global Impression-Severity (CGI-S) score (p=0.0543). The majority of patients in the study were enrolled in Europe (>80%), in this pre-specified subgroup analysis by region, consistent positive results were observed on both the primary endpoint, PANSS total score (unadjusted p=0.0234), and the key secondary endpoint, CGI-S score (unadjusted p=0.0214).

Notably, in the full analysis set, pimavanserin showed significant improvements on two pre-specified measures of negative symptoms: the secondary endpoint PANSS negative symptoms scale sub-score (unadjusted p=0.0474) and the exploratory endpoint PANSS Marder negative factor score (unadjusted p=0.0362).

“I want to thank all the patients, their families, and the investigators who participated in our ENHANCE study. Unfortunately, we did not achieve a statistically significant reduction in the PANSS total score in this study,” said Serge Stankovic, M.D., M.S.P.H., ACADIA's President. “We are pleased with the improvement in negative symptoms observed in this study. We look forward to completing our ongoing ADVANCE trial evaluating pimavanserin in schizophrenia patients with predominant negative symptoms.”

Pimavanserin was well-tolerated with similar rates of adverse events between adjunctive pimavanserin (40.4%) and adjunctive placebo (36.9%). Adverse events reported in at least 5% of patients in the pimavanserin group included headache, somnolence, and insomnia. Additionally, the adjunctive use of pimavanserin did not result in clinically significant differences in vital signs, weight, metabolic syndrome, and extrapyramidal symptoms compared to adjunctive placebo. Approximately 88% of pimavanserin and 96% of placebo patients completed the study. 1% of patients in each arm reported serious adverse events. Discontinuations due to adverse events were low, 2.5% for pimavanserin and 0% for placebo.

In addition to the ENHANCE study, the Company is currently evaluating pimavanserin for adjunctive treatment of schizophrenia patients with predominant negative symptoms in the 26-week Phase 2 ADVANCE study. The primary endpoint of the study is change from baseline on the Negative Symptom Assessment-16 total score. Top-line results from this study are expected around year-end 2019. There are currently no FDA-approved therapies for the treatment of the negative symptoms of schizophrenia.

About ENHANCE

The Phase 3 ENHANCE study was a global, six-week, randomized, double-blind, placebo-controlled, multi-center, outpatient study designed to examine the efficacy and safety of adjunctive use of pimavanserin in patients with schizophrenia who have not achieved an adequate response to their current antipsychotic treatment. A total of 396 patients were randomized (1:1) to receive either pimavanserin, orally, once daily, in a flexible dosing regimen as an adjunctive treatment with a background antipsychotic or placebo, orally, once daily, with a background antipsychotic. The starting daily dose of 20 mg of pimavanserin or matching placebo at baseline could be adjusted to 34 mg or 10 mg during the first three weeks of treatment. The majority of patients completed the study at the highest dose-level (55%). Baseline characteristics were similar across two treatment arms. The most prevalent background antipsychotics in the study included risperidone (39.1%), olanzapine (35.7%), and aripiprazole (21.3%). The average age of patients in the study was 37.2 years.

Additional results from this study will be presented in the future.

Conference Call and Webcast Information

ACADIA will discuss top-line results from its Phase 3 trial of pimavanserin for adjunctive treatment of patients with schizophrenia via conference call and webcast today at 5:00 p.m. Eastern Time. The conference call can be accessed by dialing 855-638-4820 for participants in the U.S. or Canada and 443-877-4067 for international callers (reference passcode 9294551). A telephone replay of the conference call may be accessed through August 6, 2019 by dialing 855-859-2056 for callers in the U.S. or Canada and 404-537-3406 for international callers (reference passcode 9294551). The conference call will also be webcast live on ACADIA’s website, www.acadia-pharm.com, in the investors section and will be archived there until August 22, 2019.

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[1]. ACADIA is evaluating pimavanserin in an extensive clinical development program across multiple indications with significant unmet need including dementia-related psychosis, schizophrenia, and major depressive disorder. 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 the adjunctive treatment of patients with schizophrenia, dementia-related psychosis, or major depressive disorder.

About Schizophrenia

According to the National Mental Health Institute, approximately one percent of the U.S. population develops schizophrenia during their lifetime[2]. Schizophrenia is a chronic, debilitating and often progressive mental illness characterized by disturbances in thinking, emotional reaction, and behavior. These disturbances may include positive symptoms, such as hallucinations and delusions, and a range of negative symptoms, including loss of interest, emotional withdrawal and cognitive disturbances.

According to the American Psychiatric Association, about 30% of patients with schizophrenia have an inadequate response to antipsychotic medications, meaning that they exhibit some improvement, but continue to have significant psychotic symptoms. Given the high unmet need, physicians often try multiple different antipsychotics as monotherapy in search of better efficacy. In addition, it is common for patients to be treated with two or more antipsychotics concurrently which has been associated with increased dose-related side effects and complicated dosing regimens that can further contribute to poor treatment compliance and subsequent relapse in these patients[3].

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, 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: the potential benefits of pimavanserin for central nervous system disorders as well as the potential results of clinical trials of pimavanserin in other indications. 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, and the fact that past results of clinical trials may not be indicative of future trial results. 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, 2018 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)
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.

- **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 most 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.

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

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 see the full Prescribing Information including **Boxed WARNING** for NUPLAZID.

References

[1]ACADIA Pharmaceuticals Inc. NUPLAZID® [package insert]. San Diego, CA.
[2]NAMI, Mental Help, PsyCom, SAMHSA study, NIMH data consolidation.
[3]Freudenreich O, Goff DC. Acta Psychiatr Scand 2002;106:323–30.

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