ACADIA Pharmaceuticals Announces Top-line Results from the Phase 3 CLARITY Study Evaluating Pimavanserin for the Adjunctive Treatment of Major Depressive Disorder

July 20, 2020

- The study did not achieve statistical significance on the primary endpoint

- Conference call and webcast to be held today at 4:30 p.m. Eastern Time

SAN DIEGO--(BUSINESS WIRE)--Jul. 20, 2020-- ACADIA Pharmaceuticals Inc. (Nasdaq: ACAD) today announced top-line results from its 298 patient Phase 3 CLARITY study which combined two identical, double-blind, placebo-controlled studies evaluating the efficacy, safety and tolerability of pimavanserin as an adjunctive treatment for major depressive disorder (MDD). The combined efficacy and safety analysis was pre-specified prior to data unblinding following feedback from the FDA.

The study did not achieve statistical significance on the primary endpoint which was the 17-item Hamilton Depression Rating Scale (HAMD-17) total score change from baseline to week 5. Pimavanserin 34 mg, given once-daily as an adjunctive treatment to standard antidepressant therapy was associated with a mean reduction of 9.0 in HAMD-17 total score compared to 8.1 for placebo as an adjunctive treatment (p=0.296).

Positive results were observed on the key secondary endpoint, the Clinical Global Impression – Severity (CGI-S) score, a clinician assessment of a patient's severity of depression (nominal p=0.042).

"We observed a consistent improvement of depressive symptoms over time with pimavanserin but, unfortunately, the robust positive results from our CLARITY-1 study were not replicated," said Serge Stankovic, ACADIA's President. "While these results do not support the product profile to pursue an additional Phase 3 study in adjunctive MDD, we will continue to analyze the data and the findings from our earlier positive depression studies as we assess next steps. All of us at ACADIA thank the patients, their families and the investigators who participated in the Phase 3 CLARITY study."

In the study, pimavanserin was generally well-tolerated when added to existing antidepressant therapy, and similar rates of adverse events were observed between pimavanserin (58.1%) and placebo (54.7%).

About the Phase 3 CLARITY Study

The Phase 3 CLARITY study is a combination of CLARITY-2 and CLARITY-3, which were both 6-week, parallel-designed, randomized, double-blind, placebo-controlled, multi-center studies designed to evaluate the efficacy and safety of pimavanserin as adjunctive treatment in patients with MDD who have an inadequate response to standard antidepressant therapy with either a selective serotonin reuptake inhibitor (SSRI) or a serotonin norepinephrine reuptake inhibitor (SNRI). A total of 298 patients were randomized to receive six weeks of oral treatment with either 34 mg of pimavanserin or placebo, once daily, in addition to their ongoing antidepressant. The primary endpoint was change from baseline on the HAMD-17 total score.

Phase 3 CLARITY Study Results:

Efficacy Analysis

- Statistical significance not achieved on the primary endpoint: HAMD-17 (p=0.296).
- Positive results observed on key secondary endpoint: CGI-S (nominal p=0.042).
- Positive results observed on Karolinska Sleepiness Scale (KSS) score (nominal p=0.005).
- Clinically meaningful separation was not achieved on the other secondary endpoints.

Safety and Tolerability

- Similar rates of adverse events were observed between pimavanserin (58.1%) and placebo (54.7%).
- Adverse events reported in greater than 5% of patients on pimavanserin and greater than placebo were diarrhea, dry mouth and headache.
- Discontinuations due to adverse events were 2.7% for both pimavanserin and placebo.
- Two subjects in each of the pimavanserin and placebo groups reported serious adverse events (SAEs). These SAEs were deemed not to be related to the study drug by the investigators.
- The adjunctive use of pimavanserin did not result in clinically significant differences in vital signs, metabolic parameters or extrapyramidal symptoms compared to placebo.

ACADIA previously announced plans to combine its CLARITY-2 and CLARITY-3 Phase 3 studies evaluating pimavanserin for the adjunctive treatment of MDD with a pre-specified statistical analysis plan. The two Phase 3 studies concluded with slightly more than 50% enrollment.

Patients who completed the Phase 3 study were eligible to participate in the ongoing 52-week open-label extension study to evaluate the long-term safety and tolerability of pimavanserin as adjunctive treatment to standard antidepressants in MDD.

About the CLARITY-1 Study

CLARITY-1 was a Phase 2, 10-week, randomized, double-blind, placebo-controlled, multi-center, 2-stage sequential parallel comparison design (SPCD) study that evaluated the safety, tolerability, and efficacy of pimavanserin (34 mg once daily) as an adjunctive treatment in patients with MDD who had an inadequate response to a stable dose of standard antidepressant therapy with either a SSRI or a SNRI. The study was conducted in collaboration with the Massachusetts General Hospital Clinical Trials Network & Institute and randomized 207 patients across 27 clinical research centers in the U.S. and was completed in 2018.

In the trial, pimavanserin met the primary endpoint by significantly reducing the HAMD-17 total score compared to placebo (p=0.039). On the key secondary endpoint, pimavanserin demonstrated statistically significant reductions compared to placebo in the Sheehan Disability Scale score (p=0.004). Positive results were also observed for seven other secondary endpoints including the CGI-S score (p=0.008) and the KSS score (p=0.021).

In the parallel design portion (Stage 1) of this SPCD study, adding pimavanserin to SSRI or SNRI therapy also significantly reduced HAMD-17 scores compared to placebo (p=0.0003). On the key secondary endpoint, pimavanserin also demonstrated statistically significant reductions compared to placebo in the Sheehan Disability Scale score (p=0.004).

About the Open-Label Comorbid Parkinson's Disease and Depression Study

This was an 8-week, open-label, single-arm Phase 2 study evaluating the efficacy and safety of pimavanserin as an adjunct to a SSRI or a SNRI or as a monotherapy in adults with both Parkinson's disease and depression (n=47) and was completed in 2019. In the study, patients treated with pimavanserin had significant improvement on the primary endpoint, the HAMD-17 total score change in baseline to week 8 (p<0.0001), with significant improvement seen as early as week 2 (p<0.0001). Improvement of ≥50% on the HAMD-17 total score was observed in 60.0% of patients at week 8, with 44.4% of patients reaching remission (HAMD-17 ≤7).

Additional results from this study showed that Parkinson's disease patients treated with pimavanserin for depression also demonstrated improvement on multiple secondary endpoints compared to baseline, including the CGI-S score (p<0.0001) and the SCOPA-Global Sleep Quality scale (p<0.0001).

Conference Call and Webcast Information

ACADIA will provide a corporate update via conference call and webcast today at 4:30 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 1486597). A telephone replay of the conference call may be accessed through July 27, 2020 by dialing 855-859-2056 for callers in the U.S. or Canada and 404-537-3406 for international callers (reference passcode 1486597). 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 20, 2020.

About Major Depressive Disorder

According to the National Institute of Mental Health, MDD affects approximately 17 million adults in the U.S.[1], with approximately 2.5 million adults treated with adjunctive therapy.[2,3] MDD is a condition characterized by depressive symptoms such as a depressed mood or a loss of interest or pleasure in daily activities for more than two weeks, as well as impaired social, occupational, or other important functioning. Continuing depression has been consistently linked with greater economic burden, with higher rate of healthcare utilization and reduced work productivity.[4] The majority of people who suffer from MDD do not respond adequately to initial antidepressant therapy or discontinue due to side effects or safety concerns.[5,6]

About Pimavanserin

Pimavanserin is a selective serotonin inverse agonist and antagonist preferentially targeting 5-HT_{2A} receptors. The serotonin system is 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®. ACADIA submitted a supplemental new drug application (sNDA) for pimavanserin for the treatment of hallucinations and delusions associated with dementia-related psychosis on June 3, 2020. The FDA has accepted for filing the sNDA for DRP with a PDUFA date of April 3, 2021. NUPLAZID is not approved for dementia-related psychosis. In addition, ACADIA is developing pimavanserin in other neuropsychiatric conditions.

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's development efforts are focused on pimavanserin for additional neuropsychiatric conditions, trofinetide for Rett syndrome, and an early-stage muscarinic receptor program. 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 as adjunctive treatment for major depressive disorder or other 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, 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]National Institute of Mental Health. (2017). Major Depression. Retrieved from http://www.nimh.nih.gov/health/statistics/major-depression.shtml
[2]IMS NSP, NPA, NDTI MAT-24 month data through Aug 2017.
[3]PLOS One, Characterization of Treatment Resistant Depression Episodes in a Cohort of Patients from a US Commercial Claims Database, Oct 2013, Vol 8, Issue 10.
[4]Greenberg PE, Fournier AA, Sisitsky T, Pike CT, Kessler RC. The economic burden of adults with major depressive disorder in the United States (2005 and 2010). *J Clin Psych.* 2015;76(2):155-162. doi: 10.4088/JCP.14m09298.
[5]Rush AJ, et al. (2007) *Am J. Psychiatry* 163:11, pp. 1905-1917 (STAR*D Study).
[6]Sansone RA, Sansone LA. Antidepressant adherence: are patients taking their medications? *Innov Clin Neurosci*. 2012;9(5-6):41-46.

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