

July 8, 2018

Dear Roddy,

Thank you giving us the opportunity to provide the facts and ACADIA's perspective. We have addressed your questions below. Please consider the below as on-the-record responses, attributed to ACADIA or an "ACADIA spokesperson."

For ease of reference, a few important takeaways include:

- ACADIA's top priority has always been, and continues to be, patient safety. ACADIA maintains strict protocols with its approach to scientific studies and the marketing of its product.
- NUPLAZID® (pimavanserin) is the only medicine approved in the United States to treat hallucinations and delusions associated with Parkinson's disease psychosis (PDP). NUPLAZID was approved by the FDA based on a pivotal Phase 3 study that demonstrated clinically robust and highly statistically significant efficacy, combined with other supportive studies.
- Additionally, we carefully monitor and analyze safety reports from clinical studies and post-marketing reporting to ensure the ongoing safety of NUPLAZID. The overall analysis of NUPLAZID's clinical and post-marketing safety database does not indicate an increased mortality risk associated with NUPLAZID.
- Based on the totality of available information, ACADIA is confident in NUPLAZID's efficacy and safety profile which remains unchanged and—as the FDA itself has stated—is appropriately described in the approved US NUPLAZID prescribing information. NUPLAZID has a very clear box warning—which includes specific language about patients with dementia-related psychosis—and ACADIA is committed to the safe use of NUPLAZID as indicated and in accordance with the FDA-approved prescribing information.
- ACADIA distributes its drug through specialty channels, which results in frequent contact with patients and caregivers. This, in turn, leads to more frequent adverse event reporting as compared to traditional antipsychotics or other drugs that are distributed through the retail channel and largely rely on spontaneous reporting.
 - To put that in perspective, while the vast majority of adverse events with traditional antipsychotics are reported spontaneously, only approximately 7 % of NUPLAZID adverse event reports are considered "spontaneous." The remaining 93 % come from the direct interaction through specialty channels, and therefore are considered "solicited."
- Since NUPLAZID first went to market, we've seen continued growth in the number of physicians prescribing NUPLAZID as well as more individual physicians prescribing NUPLAZID to a higher number of their patients. Importantly, despite the newness of the drug, less than 5% of prescriptions come from top 10 prescribers. In addition, a smaller percentage of ACADIA's business (approx. 30 to 35%) is in long term care (LTC) versus the percentage of LTC patients in the Parkinson's population as a whole (approx. 40%).
- While we consider the findings from the study Dr. Lon Schneider referenced in the Lancet Neurology to suggest potential efficacy and acceptable tolerability of pimavanserin for psychosis in Alzheimer's disease, we are currently conducting a well-controlled, confirmatory Phase 3 study in patients with Dementia Related Psychosis.

In summary, ACADIA continues to monitor all adverse events through robust pharmacovigilance activities and evaluates the benefit/risk profile of NUPLAZID on an ongoing basis. Based on the totality of available post-marketing and clinical trial information, our benefit/risk

assessment of NUPLAZID remains unchanged. ACADIA is committed to the safe use of NUPLAZID as indicated and in accordance with the FDA-approved prescribing information.

In addition to the above, which address your questions, we are providing further supporting information below. We are also providing supportive statements from physicians, caregivers, and advocacy organizations, as well as other information you may find helpful.

Best,
Elena Ridloff, CFA
Senior Vice President, Investor Relations
ACADIA Pharmaceuticals

NUPLAZID Safety, Efficacy and Distribution

ACADIA is committed to our mission of offering effective solutions to address serious medical conditions. As noted above, NUPLAZID® (pimavanserin) is the only medicine approved in the United States to treat hallucinations and delusions associated with Parkinson's disease psychosis. NUPLAZID was approved by the FDA based on a pivotal Phase 3 study that demonstrated clinically robust and highly statistically significant efficacy, combined with other supportive studies.

ACADIA's top priority has always been, and continues to be, patient safety. ACADIA maintains strict protocols with its approach to scientific studies and the marketing of its product.

Parkinson's disease psychosis is more typically seen in elderly patients with numerous medical comorbidities, and with an overall high risk of morbidity and mortality. In the FDA statement released to the media on April 10, 2018, the FDA stated, "The FDA continues to monitor adverse events reported with NUPLAZID that are submitted to the FDA Adverse Event Reporting System (FAERS). We have noted that the cases typically involve geriatric patients with advanced-stage Parkinson's disease, as well as numerous medical conditions, who are frequently taking concomitant medications with risks for serious adverse events, including death. Based on these data, the FDA has, at this time, not identified a specific safety issue that is not already adequately described in the product labeling."

Our confidence in the efficacy and safety of NUPLAZID is based on a number of key facts, including the following:

- Our post-marketing safety reviews and signal-detection analyses of serious and fatal adverse events did not identify the presence of any common etiology or underlying pathophysiological mechanism that would lead to the conclusion of a causal relationship to NUPLAZID. The reported deaths remain consistent with the patients' advanced age, medical conditions, and comorbidities.
- Placebo-controlled studies completed after NUPLAZID approval revealed no new or changed safety information. In addition, in controlled clinical studies in approximately 300 frail, elderly patients with Alzheimer's disease (average age between two studies was 82.5 years), there was no difference in the number of deaths reported between NUPLAZID and placebo.
- Pimavanserin is currently being evaluated in multiple, large clinical trials in over 1,300 patients with schizophrenia, major depressive disorder, and dementia-related psychosis. ACADIA utilizes independent safety data monitoring committees for many of these studies to perform regular assessments of safety and provide appropriate recommendations with respect to the conduct of clinical trials. To date, there have

been no issues identified by the independent safety data monitoring committees. The morbidity and mortality rates we observe in pimavanserin clinical studies and from the NUPLAZID post-marketing safety database are reassuring when contrasted to comparable literature data and large insurance datasets of other PD Psychosis patients.

Some recent media reports around NUPLAZID have incorrectly extrapolated a causal relationship between NUPLAZID and post-marketing adverse event information reported to the FDA, which is reflected in a database known as the FDA Adverse Event Reporting System or FAERS, for short.

The FAERS data alone are not an indicator of the safety profile of any drug or biologic. As the FDA explains on its website, while the FAERS database contains reports on adverse events that occur while a patient is on a particular drug or biologic, this does not mean that the drug or biologic caused the adverse event. The FAERS website also states, "...FAERS data does have limitations. First, there is no certainty that the reported event (adverse event or medication error) was due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event." Further, the FAERS database does not contain any information about underlying exposure to a particular drug or about adverse event collection methodology. So it is not possible to understand, draw reliable inferences or make appropriate comparisons between products based on this information alone.

It is important to note that ACADIA distributes its drug through specialty channels, which results in frequent contacts with patients and caregivers. This increased solicited interaction naturally leads to more frequent adverse event reporting.

- In contrast, traditional antipsychotics or other drugs that are distributed through the retail channel, which means the vast majority of adverse events with those products are reported spontaneously.
- Conversely, approximately 93 % of reported adverse events associated with NUPLAZID come from the direct interaction through specialty channels, and therefore are considered "solicited." Only approximately 7 % of NUPLAZID adverse event reports are voluntary reports originating spontaneously from consumers or healthcare professionals, and therefore are considered "spontaneous."
- Increased interaction with patients and caregivers results in a significantly higher number of adverse event reports, compared to products not distributed this way. As a result, it is not appropriate to compare the number of adverse event reports from regular interactions with patients, caregivers and physicians through our specialty distribution channels to spontaneous reporting occurring with other antipsychotics.

Based on the totality of available information, ACADIA is confident in NUPLAZID's efficacy and safety profile which remains unchanged and—as the FDA itself has stated—is appropriately described in the product labeling. NUPLAZID has a black box warning—which includes specific language about patients with dementia-related psychosis—and ACADIA is committed to the safe use of NUPLAZID as indicated and in accordance with the FDA-approved prescribing information.

Of the approximately one million individuals in the United States living with Parkinson's disease, over 50 % will experience hallucinations and delusions associated with Parkinson's disease psychosis (PDP) over the course of the disease. As the only drug currently approved by

the FDA for the treatment of hallucinations and delusions associated with PDP, NUPLAZID changes lives and addresses a previously unmet need.

Business Practices

ACADIA has a robust sales organization comprised of talented and highly qualified individuals with diverse backgrounds.

We disagree with the premise that ACADIA is pursuing a LTC-centric model. ACADIA has a multi-pronged strategy that reflects the needs of our patient population and the objectives of NUPLAZID. PDP is a debilitating disease with symptoms that can be extremely difficult to manage and that dramatically impact quality of life for both patients and their caregivers. Due to the nature of the disease, many patients with Parkinson's are in LTC and, accordingly, approximately 30 to 35% of patients who are prescribed NUPLAZID are in LTC.

Prescribing Physicians, Market Education and Pricing

NUPLAZID was approved and launched in 2016 as the first and only FDA-approved medicine for the treatment of the hallucinations and delusions associated with Parkinson's disease psychosis, a progressive and debilitating condition with serious and costly consequences to patients and families. It is a fairly new medicine addressing a previously unmet medical need and, as such, part of our efforts focus on raising awareness of PDP and NUPLAZID.

In 2017, NUPLAZID's first full year of launch, ACADIA focused on educating physicians about the hallucinations and delusions associated with PDP. This market education is important so that physicians who treat PDP also understand the importance of screening for PDP. These physician interactions play a critical role in advancing patient care and help ensure NUPLAZID is used as safely and effectively as possible. We have policies, procedures, training and Compliance monitoring in place to foster compliance with our policies, OIG guidance and provisions of the PhRMA Code governing speaker programs, including conducting periodic reviews of speakers to ensure they still meet the requisite qualifications.

ACADIA conducted studies to carefully evaluate and benchmark our pricing versus key competitors and took into account research costs, market education and Medicare and commercial plans to secure coverage of NUPLAZID. We also continue to invest in research and development in other CNS indications of high unmet need including dementia-related psychosis.

As physicians become increasingly familiar with NUPLAZID, they, along with patients and caregivers, witness first hand a reduction in the severity and frequency of the hallucinations and delusions in their PDP patients. Since NUPLAZID first went to market in 2016, we've seen:

- Continued growth in the number of patients taking NUPLAZID;
- Growth in the number of physicians prescribing NUPLAZID, including at academic centers, in community practices and in long-term care facilities;
- More individual physicians prescribing NUPLAZID to a higher number of their patients;
- Strong market research results that consistently demonstrate very high levels of physician and patient satisfaction with NUPLAZID, including increasing physician intent to prescribe

Importantly, despite the newness of the drug, less than 5% of prescriptions come from top 10 prescribers.

Post-marketing Commitments

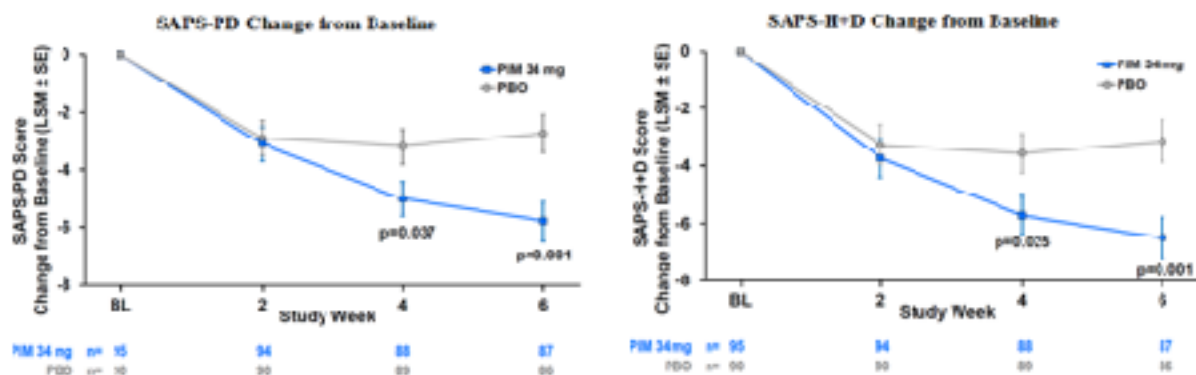
ACADIA is in the process of completing all of the post-marketing commitments included with the FDA's approval letter of NUPLAZID, in full compliance with the timelines defined by the FDA. ACADIA has completed two controlled clinical studies in an aggregate of approximately 300 patients with Alzheimer's disease, which are part of our post-marketing commitment. In these controlled studies in elderly patients with dementia, there was no difference in the number of deaths reported between pimavanserin and placebo.

NUPLAZID Efficacy in Treating the Hallucinations and Delusions associated with Parkinson's Disease Psychosis (Pivotal 020 Study)

The benefits that NUPLAZID offers to patients suffering from the debilitating symptoms of PD Psychosis were observed in our pivotal Phase 3 study that demonstrated clinically robust and highly statistically significant efficacy.

In Study 020, the efficacy analysis was performed using SAPS-PD and SAPS-H+D scale scores. The SAPS-PD is a 9-item scale derived from the SAPS H+D scale and captures those symptoms that are characteristic of the symptoms expressed in PDP. As cited in the FDA's Briefing Package supporting the 29 March 2016 Advisory Committee meeting, the FDA indicated its agreement that this modification appears to have improved clinical relevance and face validity and was appropriate for Study 020. Importantly, the same clinically meaningful and highly statistically significant results were obtained with both analyses. SAPS-PD analysis showed treatment difference of 3.06 points ($p=0.001$; effect size 0.50) and SAPS-H+D analysis showed treatment difference of 3.37 points ($p=0.001$; effect size 0.50), both in favor of pimavanserin.

For your convenience, the following graphs illustrate the consistency of results between the two scales from Study 020.



It is also important to note that Study 020 demonstrated robust efficacy across multiple scales by different raters. The SAPS-PD and SAPS-H+D were rated by centralized raters who were not affiliated with the study sites. The Clinical Global Impression of Severity (CGI-S) and

Improvement (CGI-I) were also statistically significantly positive (both with $p < 0.001$), as rated by the site Investigators. The Zarit Caregiver Burden, rated by the patients' caregivers, was also positive ($p = 0.002$). Also, patients reported improved sleep ($p = 0.045$) and reduced daytime sleepiness ($p = 0.012$). Thus, multiple scales rated by different raters were positive, giving evidence of the robustness of the overall benefit to patients.

Lastly, approximately 74% of patients saw improvement on psychosis and 14% experienced a complete response. In addition, NUPLAZID did not show an effect compared to placebo on motor function. The robustness of the NUPLAZID response seen in this responder analysis was the subject of a publication by the FDA's review staff responsible for the approval of NUPLAZID (Mathis et al 2017).

Lancet Neurology Article

Results from the study of pimavanserin in Alzheimer's disease psychosis (ADP), Study 019, were published in the March 2018 issue, Vol. 17 of Lancet Neurology under the title "Evaluation of the efficacy, tolerability, and safety of pimavanserin versus placebo in patients with Alzheimer's disease and psychosis: phase 2, randomized, placebo-controlled, double blind study". In the same issue, Dr. Lon Schneider published his commentary and interpretation of the study results. We strongly disagree with Dr. Schneider's characterization of the study results which contain a number of inaccuracies and personal viewpoints. For instance, Dr. Schneider's assertion that the results of this trial cannot be considered to be positive or clinically meaningful is not supported by facts. The Study 019 was positive on the basis of rigorous hypothesis testing with pre-specified primary endpoint at week 6. Clinical meaningfulness of the results is reflected in the effects size observed (Cohen's $d = -0.32$), comparatively larger than for most other antipsychotics. Additionally, there was an even larger effect favoring pimavanserin (Cohen's $d = -0.73$) and responder rates were considerably enhanced in the subgroup of subjects with more severe psychotic symptoms, providing the potential for pimavanserin to provide the greatest benefit to patients who are most in need of treatment (Ballard et al. 2018). Continued treatment beyond the primary endpoint at week 6 showed maintenance of effect (to week 12) in the pimavanserin group, but the separation from placebo was not maintained due to observed improvement in the placebo group between Week 6 and Week 12. This may not be surprising in the context of the remitting/relapsing course of psychosis in people with Alzheimer's Disease.

Overall, the findings from the Study 019 suggested potential efficacy and acceptable tolerability of pimavanserin for psychosis in Alzheimer's disease, and supported the FDA granting of breakthrough therapy designation and initiation of the Phase 3 HARMONY study in Dementia Related Psychosis. The results from the Study 019 were discussed in full with the FDA prior to initiation of the Phase 3 study in dementia related psychosis. The currently ongoing Phase 3 HARMONY study will evaluate maintenance of efficacy, safety, and tolerability of pimavanserin in the randomized-withdrawal study design with longer trial duration.