March 7, 2019
RE: CNN inquiry, March 3, 2019

Blake and Melanie,

We would like to further clarify your understanding about the benefit/risk safety profile of NUPLAZID® (pimavanserin) as described in the drug's label and ACADIA's physician interactions. We hope you will agree with us that preventing misinformation and mischaracterization of data is in the **best interests of Parkinson's disease psychosis (PDP) patients and their caregivers**.

Nothing is more important to us than the well-being of the people who use NUPLAZID to treat hallucinations and delusions associated with PDP. We believe it is critical that the facts be clearly represented because patients with PDP and their caregivers have so much at stake.

To be frank, we are struggling to understand what news you are reporting. The DOJ investigation is ongoing and has been disclosed in our public filings. We have further responded to your statements regarding the Open Payments CMS data and the Boxed Warning below. Based on our further comments below, we find it difficult to see the 'story' here, unless you intend to again present data out of context, mischaracterize data, and present misleading statements.

Our concern is not unfounded. Previous reporting by CNN included misleading and unsupported statements and implications about NUPLAZID that raised unwarranted safety concerns among patients, their caregivers, and the medical community. Accurate, fair, and complete information is needed to educate the community about PDP and the availability of evidence-based treatments like NUPLAZID. Following a thorough Tracked Safety Issue (TSI) evaluation, the FDA's conclusion on September 20, 2018 clearly refutes your April 2018 article.

When you published your article last year, it was ultimately the patients and caregivers who suffered the most as many of them no longer sought, opted for or continued treatment with the only FDA-approved drug with a positive benefit/risk profile for hallucinations and delusions associated with PDP. As a result, a large number of patients were untreated or were left to decide whether to attempt to manage their PDP symptoms with off-label antipsychotic drugs without a proven positive benefit/risk profile.

The Movement Disorder Society (MDS) recently published an update to their recommendations for "Treatments for Non-Motor Symptoms of Parkinson's Disease." This update is important because NUPLAZID is the only treatment listed as both efficacious and having an acceptable level of safety risk without specialized monitoring for the treatment of psychosis. The guidelines list three additional antipsychotics, including clozapine (requires specialized monitoring), olanzapine (unacceptable risk), and quetiapine (insufficient evidence of efficacy), none of which are FDA-approved to treat PDP. We invite you to review the labels of these drugs carefully. Note that prior to the approval of NUPLAZID, physicians had no option for treating PDP other than the use of these unapproved antipsychotic drugs and others like them.

- NUPLAZID® (pimavanserin): (https://www.nuplazid.com/pdf/NUPLAZID_Prescribing_Information.pdf.)
- Clozaril® (clozapine): (https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/019758s073lbl.pdf)
- Zyprexa® (olanzapine): (https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/020592s062021086s040021253s048lbl.pdf)

3611 Valley Centre Drive, Suite 300 • San Diego, California 92130 • USA • www.acadia-pharm.com

- Seroquel XR® (quetiapine): (https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/022047s011s016s017s019s022lbl.pdf)

In regards to your inquiry about our general education grants for the Movement Disorder Society, ACADIA, as well as other supporters of this organization, have provided educational grants. Our grants are in accordance with the Accreditation Council for Continuing Medical Education (ACCME) guidelines and are unrelated to the Movement Disorder Society's published treatment recommendation. The recently published recommendation is an independent evidence-based medicine (EMB) review authored by 8 of the leading international movement disorders specialists. Please note as listed in this publication, "Relevant conflicts of interests/financial disclosures: Nothing to report."

In regards to your analysis of prescriber and payment data, we would like to reiterate that we are committed to responsible interactions with healthcare providers (HCPs) and educating the medical community about hallucinations and delusions associated with PDP, the importance of identifying these symptoms, and the benefits, risks, and appropriate use of NUPLAZID per its FDA-approved labeling. Since NUPLAZID's launch in 2016, more than 13,000 U.S. HCPs have prescribed NUPLAZID.

When reviewing ACADIA's CMS Medicare prescriber and Open Payment data, it is important to understand that a large number of prescribers account for the vast majority of prescriptions. For example, ACADIA has a database of known prescribers* from the Specialty Pharmacy channel, which accounted for approximately 70% of the total 2016 Medicare claims. From this database:

- In 2016, of these 1,448 HCPs who prescribed NUPLAZID for Medicare patients **95% received either no or a nominal transfer of value** ($125 or less) from ACADIA and these prescribers accounted for greater than 80% of the NUPLAZID Rx Medicare volume.
- In 2017, of these 3,168 HCPs who prescribed NUPLAZID for Medicare patients **85% received either no or a nominal transfer of value** ($125 or less) from ACADIA and these prescribers accounted for 70% of the NUPLAZID Rx Medicare volume.

**Note: We believe these known prescribers are representative of all prescribers of NUPLAZID. Prescribers in the Specialty Distribution channel (e.g. Long-term care, VA Health Benefits, TRICARE) typically are not captured in our known prescriber database, due to limited visibility of individual fulfillment of prescriptions in this channel. However, all physicians are captured in ACADIA's submitted Open Payment data.*

Transfers of value to HCPs can include items such as clinical reprints of peer reviewed articles, nominal meals and refreshments provided at exhibit booths, presentations, medical congresses or speaker programs. Our current spending limit for one physician dinner and ancillary costs is $125. That limit is considered to be a best practice by ACADIA and is a common industry benchmark.

You describe that 26 doctors received six-figure payments from the company with the highest physician receiving around $180,000 and you compare this to the approximately $3,000 national average for physicians. This is an apples-to-oranges comparison. The national average is, and we quote from the CMS website, "the mean general payment amount is $3,307.06 for all physicians in the United States in 2017, out of 624,621 physicians reported." The better comparison is ACADIA's average compensation per physician compared to the $3,307.06 national average:

- For ACADIA, the mean general payment amount was approximately $1,225 for physicians in the United States in 2017, out of approximately 7,060 physicians reported.
- For ACADIA, the mean general payment amount was approximately $380 for physicians in the United States in 2016, out of approximately 1,580 physicians reported.

3611 Valley Centre Drive, Suite 300 • San Diego, California 92130 • USA • www.acadia-pharm.com

The data clearly shows the vast majority of prescribing physicians received little to no payments from ACADIA. In addition, as we show below, the physicians receiving the highest amounts are involved in medical education of the PDP community.

Similar to the data we provided to you on the mean general payments, for ACADIA the median general payment amount is also below the national median.

In regards to your statement that "of the 170 top Medicare prescribers of Nuplazid in 2016, the drug's first year on the market, more than 25% were also company consultants", please refer to our recently filed 8-K (https://www.sec.gov/Archives/edgar/data/1070494/000119312519064601/d681058d8k.htm) which provides updated categorization detail for the 2016 and 2017 Open Payments data, this data is also referenced below. You will clearly note the total number of payment transactions related to consulting fees was 16 in 2016 for a total of approximately $18,000. This may impact the calculations of your previous statement quoted above. Other transfers of value to physicians were related to services other than consulting.

We also wish to underscore that transfers of value to physicians during the early launch period of a product are typically higher than average due to the need for medical education. Selectively comparing to the average of a select group of physicians heavily engaged in important medical education during the launch period versus a national average of physicians is not an appropriate comparison.

The need for education on PDP is profound. Approximately 50% of the roughly one million Parkinson's disease patients in the United States will experience hallucinations and delusions over the course of their disease. Prior to the launch of NUPLAZID, awareness among Parkinson's patients and caregivers of these potential non-motor symptoms was only 5%, according to a 2015 survey. We have focused on informing the community on the disease state, burden of illness, and clinical course of PDP.

Given the limited awareness of PDP, during 2017, the first full year of launch activities, ACADIA focused on educating physicians and other HCPs regarding PDP, the importance of identifying symptoms, and the benefits, risks, and appropriate uses of NUPLAZID. These early launch activities play a critical role in advancing patient care and ensuring that NUPLAZID is used in a safe and effective manner. In calendar year 2018, the second full year of marketing NUPLAZID, the company's aggregate general payments to physicians decreased to approximately $4.7 million, an approximate 46% reduction from 2017. ACADIA will submit payment information for 2018 to the Open Payments system by the annual deadline of March 31, 2019.

We recently submitted updated categorization detail to CMS. The update includes the reclassifying of certain categorization information regarding general payments provided to physician, as detailed in the tables below. Note that these amounts may be subject to minor changes post-submission as a result of routine, ongoing validation by CMS within the Open Payments system:

3611 Valley Centre Drive, Suite 300 • San Diego, California 92130 • USA • www.acadia-pharm.com

2016 (for the period from November 22 to December 31)			
Nature of Payment	**Total Payments**	**Total Amount**	**Total Amount (%)**
Consulting Fee	16	$18,031.75	3.0
Comp. for services other than consulting, including speaker/faculty fees for non-CME programs	166	$431,615.00	71.7
Honoraria	1	$2,300.00	0.4
Education	13	$210.29	0.0
Travel and Lodging	262	$84,572.16	14.0
Food and Beverage	1,927	$62,614.37	10.4
Grant	2	$2,700.00	0.4

2017 (full year)			
Nature of Payment	**Total Payments**	**Total Amount**	**Total Amount (%)**
Consulting Fee	154	$494,278.65	5.7
Comp. for services other than consulting, including speaker/faculty fees for non-CME programs	2,325	$6,667,785.00	77.1
Education	11	$276.40	0.0
Travel and Lodging	2,876	$740,151.98	8.6
Food and Beverage	23,629	$616,336.74	7.1
Grant	6	$132,855.00	1.5

Treatment of Parkinson's disease patients is concentrated at **Parkinson's Disease Centers of Excellence or Movement Disorders Clinics**. These are medical centers with specialized teams of neurologists, movement disorder specialists, physical and occupational therapists, mental health professionals and others who are up-to-date on the latest Parkinson's disease medications, therapies, and research to provide the best care for patients.

Of the prescribers responsible for 10% of the NUPLAZID Medicare volume:

- **80%** were associated with a Parkinson's Disease Center of Excellence or associated with a Movement Disorders Clinic in 2016.
- **86%** were associated with a Parkinson's Disease Center of Excellence or associated with a Movement Disorders Clinic in 2017.

Given that these centers are integral in providing disease education, it is not surprising that several of these prescribers engaged with ACADIA on our educational efforts.

In regards to your correspondence on the Boxed Warning for NUPLAZID, we agree that the label, including the Boxed Warning, applies to all patients who take NUPLAZID. The Boxed Warning has always been a part of the FDA-approved NUPLAZID label. The Boxed Warning and other important safety information, from the NUPLAZID label, are included with all our communications with the public, including physicians, patients, and their families when NUPLAZID is mentioned. In addition, the NUPLAZID label was assessed by the FDA on at least two separate occasions after an extensive review (i.e. at the time of approval and most recently in the context of the TSI evaluation) and each concluded that the label adequately describes the benefits and risks of NUPLAZID treatment and that no changes to the label are required.

3611 Valley Centre Drive, Suite 300 • San Diego, California 92130 • USA • www.acadia-pharm.com

We would like to reiterate that as part of our pharmacovigilance activities, we conduct ongoing surveillance and evaluation to identify potential safety risks. We have a robust governance process that determines what actions are needed to ensure patient safety, including communication of new risks in updated labeling. We submit periodic safety updates and proposed label changes to the FDA in a timely fashion.

This additional information should provide you with the appropriate context and understanding about NUPLAZID and ACADIA's corporate practices.

Finally, in light of CNN's prior reporting on NUPLAZID, which contained several misleading and unsupported statements and implications about the drug's safety and efficacy, we would appreciate the opportunity to **obtain an advance copy of the article.**

Additional resources for information on NUPLAZID® (pimavanserin):

- FDA Statement from September 20, 2018 (https://www.fda.gov/Drugs/DrugSafety/ucm621160.htm)
- Movement Disorder Society's Guidelines for Treatment of the Nonmotor Symptoms in PD (https://www.movementdisorders.org/MDS-Files1/Resources/PDFs/Seppi_et_al-2019-Movement_Disorders.pdf)
- NUPLAZID Home page (www.nuplazid.com)
- NUPLAZID Straight Talk (www.nuplazidstraighttalk.com)
- ACADIA Pharmaceuticals website product page (www.acadia-pharm.com/product/)

3611 Valley Centre Drive, Suite 300 • San Diego, California 92130 • USA • www.acadia-pharm.com