CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207318Orig1s000

SUMMARY REVIEW

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date	(electronic stamp)
From	Mitchell V. Mathis, MD
Subject	Division Director Summary Review
NDA/BLA #	207318
Applicant Name	Acadia Pharmaceuticals, Inc.
Date of Submission	September 1, 2015
PDAC Meeting Date	March 29, 2016
PDUFA Goal Date	May 1, 2016
Proprietary Name / Established (USAN) Name	Nuplazid/pimavanserin
Dosage Forms / Strength	Tablet, coated, 17 mg
Proposed Indication(s)	Hallucinations and Delusions Associated with Parkinson's Disease
Action/Recommended Action for NME:	Approval

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Paul Andreason, MD
Statistical Review	Eiji Ishida, MS Peiling Yang, Ph.D. H.M. James Hung, Ph.D.
Pharmacology Toxicology Review Supervisory	Amy M. Avila, PhD Aisar Atrakchi, PhD
CMC Review/OBP Review Application Technical Lead	David Claffey, PhD
Clinical Pharmacology Review	Kofi Kumi, PhD Di Zhou, PhD Kevin Krudys, PhD Hao Zhu, PhD
OPDP	Susannah O'Donnell, MPD
OSI	Cara Alfaro
OSE/DMEPA	Loretta Holmes, PharmD
Other	
Pediatrics and Maternal Health	Amy Taylor, MD
CSS	Martin Rusinowitz, M.D.

	Jovita Randal-Thompson, Ph.D.
QT-IRT	Li Zhang

OND=Office of New Drugs
OSE=Office of Surveillance and Epidemiology
OCP=Office of Clinical Pharmacology
OSI=Office of Scientific Investigation
OPDP=Office of Prescription Drug Promotion
DMEPA=Division of Medication Error Prevention and Analysis
CSS=Controlled Substance Staff
CMC=Chemistry, Manufacturing, and Controls

Benefit-Risk Assessment

Pimavanserin is a serotonin inverse agonist evaluated for the treatment of hallucinations and delusions associated with Parkinson's disease psychosis. As an antipsychotic, this drug is pharmacologically different from the approved antipsychotics because it appears to lack the usual dopamine blockade that other drugs in the class have. This relative lack of dopamine blockade is pharmacologically important in Parkinson's disease patients because these patients have a relative dopamine deficiency as part of their primary disease process.

The Parkinson's Disease Foundation estimates that 7-10 million people worldwide are living with Parkinson's disease (PD), and the incidence increases with age. Men are more than 1.5 times more likely to have PD than women. The hallucinations and delusions of PD affect nearly half of patients with PD, and there is no FDA-approved treatment. The hallucinations and delusions of PD are correlated with increased caregiver burden and nursing home placement, and nursing home placement is associated with increased mortality.

The primary clinical outcome variable to establish efficacy of pimavanserin was the 9-item Schedule for the Assessment of Positive Symptoms – Parkinson's Disease (SAPS-PD) scale. The mean difference from placebo for pimavanserin-treated subjects was approximately 3 points on this scale and was statistically significantly different than placebo. Differential response analyses were conducted by the Division staff and they too were impressive—a placebo-subtracted 13% complete response (no symptoms at endpoint) was most impressive to me.

The applicant evaluated worsening of the primary disease using the Unified Parkinson's Disease Rating Scale (UPDRS) Combined Part II (activities of daily living) and Part III (motor symptom examination). Using a pre-defined non-inferiority margin of 5, the applicant demonstrated no difference between drug and placebo.

The observed risk for serious adverse events including death (SAE) in the 6-week trials of pimavanserin was 2.38 (95% CI 1.00 to 5.73, p=0.05) for 34mg vs. placebo. SAEs occurred in 16/202 (7.9%) of patients taking pimavanserin and in 8/231 (3.5%) of patients taking placebo. There was no unifying mechanism of SAE or death identified from the clinical trial data. The approved antipsychotic drugs have a similar risk and are labeled to inform clinicians, but no unifying mechanism means that monitoring or mitigating the risk of SAEs are not possible.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Hallucinations and delusions of Parkinson's disease are disturbing and disabling symptoms associated with disruption of a patient's life. They often herald nursing home placement, which is a harbinger of death.	Safe and effective treatments for hallucinations and delusions associated with Parkinson's disease would provide treatment for a relatively large population with no approved treatment.
Current Treatment Options	• There are no approved treatments for the hallucinations and delusions of Parkinson's disease. • Clozapine and quetiapine have been recommended by several treatment organizations as acceptable drugs to use in PD patients with psychosis, but they have not been evaluated by FDA for this use, and have dopamine blocking properties (both drugs) and monitoring requirements (frequent blood draws, clozapine).	No drug has been approved to treat the hallucinations and delusions of Parkinson's disease. The drugs that are currently recommended by the treatment community have not been evaluated by FDA in clinical trials that were evaluated for inclusion in labeling.
Benefit	• Statistically significant reduction in symptoms as measured by the primary endpoint (SAPS-PD). Clinically meaningful secondary endpoints and multiple different responder analyses, including complete response.	Efficacy has been established.
Risk	• The observed risk in the controlled trial population of serious adverse events including death (SAE) occurred in 16/202 (7.9%) in patients taking pimavanserin 34mg versus 8/231 (3.5%) placebo treated patients. There were no individual adverse events that drove this difference. There was no unifying pathological mechanism that explained this difference. • A similar risk is seen with other drugs in the class.	Serious adverse events are known to occur in elderly patients on this class of medication, and pimavanserin is no exception. The risk can be elucidated in labeling but not mitigated because there is no unifying mechanism to explain the SAEs and therefore no way to monitor to prevent them.
Risk Management	• There is no unifying mechanism for the observed SAEs/deaths. Many of the SAEs including deaths were considered by the investigators to be unrelated or unlikely related to drug.	Pimavanserin treatment is associated with an increased risk of mortality and morbidity that is similar to other antipsychotic drugs when used in the elderly population.

Background and Summary

Pimavanserin tartrate is an oral atypical antipsychotic; this application was submitted by Acadia Pharmaceuticals for the treatment of psychosis associated with Parkinson's disease (PD). Pimavanserin is a New Molecular Entity (NME) that has not been approved elsewhere in the world for any indication.

PD is a debilitating degenerative disorder of the central nervous system (CNS) mainly affecting the motor system caused by death of dopaminergic neurons in the basal ganglia. The motor illness of PD is characterized by movement-related tremor, rigidity, slowness of movement and difficulty with walking/gait. The disease may progress to thinking and behavioral problems, and up to 40% of patients experience psychosis. In its advanced stages, PD patients may experience dementia, as well as sensory, sleep, and emotional problems.

Parkinson's disease psychosis (PDP) is characterized by hallucinations (most often visual), illusions, false sense of presence, and delusions in a patient with a clear sensorium and a diagnosis of PD. PDP affects an estimated 40% of patients who have PD, and is a debilitating part of the illness that is associated with increased rates of nursing home placement.

Treatments for PD replace the lost dopamine (L-DOPA and dopamine agonists), and are effective at relieving the motor symptoms early in the disease, but too much dopamine in the CNS can produce psychosis which is seen with the antiparkinson drugs used to treat PD. Therefore, the treatment of PD can exacerbate the PDP, and limit effective treatment of motor symptoms of PD.

No drug has been approved to treat PDP, but antipsychotics are used off-label to control the symptoms when reducing antiparkinson drugs is not a medical option for the patient. Antipsychotics approved for other indications (schizophrenia, bipolar mania, adjunct to antidepressants) primarily interfere with dopamine transmission, and they are therefore therapeutic for PDP, but blocking dopamine transmission worsens the motor symptoms that were being treated with the antiparkinson drugs in the first place. As a result, the treatment for PDP potentially exacerbates the movement symptoms of PD, making PDP a very difficult set of symptoms to treat in the PD patient without worsening the primary disease.

Atypical antipsychotics (primarily clozapine and quetiapine) are used to treat PDP, but neither is approved for this use. Clozapine and quetiapine are recommended in the treatment guidelines of the American Academy of Neurology for treating PDP. Pimavanserin is pharmacologically different than the other atypical antipsychotics in that it does not have prominent dopamine-blocking activity; it is primarily an inverse agonist at serotonin 5-HT2A receptors. As a result of this relative lack of dopamine blockade, the applicant has theorized that pimavanserin would block the psychosis of PDP without worsening the motor symptoms of PD. They have designed their study to test this theory.

As primary evidence of efficacy, the applicant submitted a single Phase 3 pivotal trial evaluating the safety and efficacy of pimavanserin in patients with PDP. The primary efficacy measure for this trial was the mean change on a psychosis rating scale modified for patients with the hallucinations and delusions of PD, and it was a statistically a positive trial by this measure. Motor symptoms were measured during treatment using usual PD motor symptom scales and, as was theorized from the pharmacology, motor symptoms were not made worse during treatment with pimavanserin. Although mean changes in the primary endpoint were statistically significant, analyses of response based upon 50% improvement or 100% improvement were clinically significant.

No atypical antipsychotic drug trial has been free of safety concerns, and this was the case with the pimavanserin trials. Dr. Andreason the primary reviewer, has identified an imbalance in the raw numbers of serious adverse events (SAEs) including death with these events in 7.9% of pimavanserin patients compared to 3.5% of placebo patients when combining data from all patients exposed in controlled trials of 6-weeks duration (the PDP6 population). As with the other atypical antipsychotics, all of which have been labeled as causing increased morbidity and mortality in elderly demented patients with psychosis, the SAEs and deaths in patients taking pimavanserin have no common pathological mechanism, and there are no signs or symptoms that can be routinely monitored clinically. Therefore, no monitoring requirements can be developed to include in labeling. The label can thus inform about, but not mitigate, these risks.

The Division's toxicologists have identified a finding of phospholipidosis and inflammation affecting the lung and other organs in animal models. This accumulation of phospholipids in the lung produced signs of respiratory distress in the preclinical models where animals were exposed to 5-10 times the maximum recommended human dose. Respiratory distress was not seen in the clinical trials, but is a monitorable set of symptoms and so can be included in labeling to alert prescribers of this potential risk of respiratory involvement.

The Division considers the hallucinations and delusions of PD to be a priority for drug development and had granted the applicant Breakthrough Status prior to submission. The NDA was given a Priority Review upon submission. The application was discussed at the Psychopharmacologic Drugs Advisory Committee (PDAC) and the Committee voted (12-2) that the benefits outweigh the risks. There has been a great deal of discussion within the Division and the Office about the risks and benefits of this drug to treat the hallucinations and delusions of PD, and I have concluded that the benefits do indeed outweigh the risks for this population. I have recommended that the Office Director approve pimavanserin for the treatment of hallucinations and delusions associated with PD and that we label risks of the drug as we have done for other drugs in the class.

Pharmacology
Pimavanserin is an atypical antipsychotic that would, if approved, be the first drug available in the class with no prominent dopamine antagonism as part of its binding profile. This lack of clinically meaningful dopamine blockade—the drug is primarily an inverse agonist at serotonin 5-HT2A receptors—was theorized by the applicant to allow for the treatment of PDP without worsening PD motor symptoms when treating patients with the hallucinations and delusions of PD.

Clinical
Dr. Andreason reviewed the application and recommended that it not be approved. This was based on his conclusion that efficacy was only minimally clinically significant, and not outweighed by significant safety concerns. Although Dr. Andreason agrees that even modest clinical improvement is important in this population, he was concerned about an increased signal for morbidity and mortality in the drug group. The safety profile of pimavanserin appears similar (but in a modest-sized database) to other atypical antipsychotics approved for treatment of psychosis but not approved for the treatment of dementia-related psychosis. All are labeled (Boxed Warning and Warnings and Precautions) to say that they cause increased mortality in patients with dementia-related psychosis.

I agree with Dr. Andreason that the mean change of 3 points on the SAPS-PD, while statistically strong, would represent a relatively modest improvement. However, even this small mean improvement in a disabling condition without an approved treatment is meaningful from a public health point-of-view. More important, patients have individual responses that can be smaller or greater than the mean. When different responder criteria are used to examine efficacy, clinically meaningful drug effects are apparent. The applicant and our reviewers conducted multiple differential response analyses, and each of them was helpful to understand efficacy, but the most impactful analysis, in my view, was the percent of patients on drug who had their hallucinations and delusions reduced to zero after having been at least moderately psychotically ill at enrollment. This analysis demonstrated that a placebo-subtracted 13% of patients on pimavanserin had no symptoms at trial endpoint; zero symptoms is an unusually impressive finding in a psychiatric drug trial. In addition, many patients had responses considerably greater than the 3 point mean change, e.g., response of 5 or 10 points.

Regarding safety, it is true that this drug has the same unfortunate serious adverse events (SAEs) including death as the other atypical antipsychotics, although there were only 4 on-treatment deaths in the 6-week controlled trials database, and there is an imbalance (3 to 1) in the drug and the placebo groups. However, as with the other approved antipsychotics, there is no unifying mechanism of SAE or death that could help explain the pathophysiology of the safety signals; the causes of SAE, including death, were variable, and therefore are not monitorable or specifically preventable; they are also hard to attribute to pimavanserin and hard to interpret. Many of the SAEs identified in Dr. Andreason's review seem very unlikely to be related to drug, and the number of deaths is too small to draw definite drug-related conclusions. As with the other drugs in the class, an approval would require labeling that notes this risk: a Boxed Warning describing the risk with details in the first Warning and Precaution.

It is worth noting that the sponsor extensively explored the effects of the drug on the motor symptoms of Parkinson's disease and verified their pharmacological theory that motor symptoms are not made worse by pimavanserin. Although not a large part of the discussion within the Division or at the Advisory Committee, the lack of clinically relevant dopaminergic blockade in patients with a dopamine deficiency as their primary disease process (PD) is extremely relevant to this population and the movement disorder specialists who treat them.

Dr. Andreason does not agree that benefits outweigh risks for pimavanserin for the treatment of hallucinations and delusions of PD, but I disagree. I think that there is a clearly documented efficacy that is modest in mean change differences between drug and placebo, but substantial in the responder analyses, and pimavanserin has a safety profile that is similar to the other drugs in the class (drugs already used off-label to treat PDP). This drug has been clearly demonstrated not to make the primary motor symptoms of the disease worse and to improve the treatment-limiting hallucinations and delusions of PD. I think the risks can be well explained using language similar to that in the labeling for other drugs of the class. This drug is the first in the class specifically for a population that we know is more susceptible to serious adverse events including death, but it is also the first in the class with proven efficacy in the PD population with psychosis, a disease process which has its own risks of serious adverse outcomes, including death.

Efficacy

Efficacy in the treatment of the hallucinations and delusions of Parkinson's disease was demonstrated in a single US/Canadian study (Study 020) in patients with PD who had hallucinations and delusions

severe enough to warrant antipsychotic treatment. Study 020 was a six-week, multi-center, randomized, double-blind, placebo-controlled, centrally-rated trial with the Schedule for the Assessment of Positive Symptoms in Parkinson's disease (SAPS-PD) as the primary endpoint. The SAPS-PD was derived by the sponsor and is a collection of nine items from the original twenty item Schedule for the Assessment of Positive Symptoms (SAPS) scale. The nine items were selected by the sponsor (and agreed to by the Division) because they represent the symptoms of psychosis known to occur in patients with PD: hallucinations and delusions. The nine SAPS-PD items are made up of 4 hallucination items (plus a global severity of hallucinations rating) and 3 delusion items (plus a global severity rating of delusions). The results of the primary efficacy analysis are presented below.

Primary Efficacy Analysis Results—SAPS-PD Change from Baseline to Week Six

Pimavanserin Difference from Placebo in LS Mean of Change from Baseline score (Week 6)				
LS Mean Estimate		Difference from Placebo in LS Mean Estimate (SE)	95% Confidence Interval	P value
Pimavanserin (SE)	Placebo (SE)			
-5.79 (0.66)	-2.73 (0.67)	-3.06 (0.94)	(-4.91, -1.20)	0.0014

Note: A negative change from baseline indicates an improvement. LS (Least Square) Mean estimates were obtained from an application of the pre-specified MMRM.
Source: Medical and Statistical reviews

The discontinuations and reasons for discontinuation are presented below. As can be seen in the table, most discontinuations from the treatment group were due to adverse events, which occurred at a rate 5 times higher on drug than on placebo.

Primary Efficacy Assessment with Reason for Discontinuation

Treatment group (# Randomized subjects)	**Placebo** (N=94)	**Pimavanserin** (N=105)	**Total** (N=199)
Excluded from mITT population	4	10	14
Sponsor mITT population	90	95	185
SAPS-PD observed at Week 6	86	87	173
SAPS-PD observation missing at Week 6	4	8	12
# Discontinued Patients	7	16	23
Reason for Discontinuation from Study (Sponsor mITT population)			
Adverse event	2	10	12
Voluntary withdrawal of consent	2	3	5
At discretion of ACADIA	2	2	4
Subject fails to comply with protocol requirements	0	1	1
Investigator's decision	1	0	1

Source: Table 14.1.2.1.1 of the CSR and Reviewer's analysis

Multiple sensitivity analyses were conducted by the statistical review team to evaluate the effect of dropouts on efficacy conclusions. From the table below, imputation of WOCF (worst observation carried forward) was used to establish the least favorable calculations for efficacy of pimavanserin because this method carries forward the worst measure of efficacy for the drug to endpoint for any missing observations (dropouts) at endpoint. Also included below is the LOCF (last observation carried forward) analysis to use last data collected prior to missing data (dropout). From the results, the worst-case data and last data support the primary analysis; the impact of dropouts was assessed and did not change the efficacy conclusion.

SAPS-PD Primary Analysis and Sensitivity Analysis

	Method	LS Mean Change from Baseline at Week 6 (SE)		Difference from Placebo (pimavanserin – placebo)	95% Confidence Interval	p-value
		Pimavanserin	Placebo			
Primary Analysis	MMRM	-5.79 (0.66)	-2.73 (0.67)	-3.06 (0.94)	(-4.91, -1.20)	0.001
Sensitivity Analysis	ANCOVA (LOCF)	-5.56 (0.65)	-2.65 (0.67)	-2.91 (0.93)	(-4.76, -1.07)	0.002
	ANCOVA (WOCF)	-5.43 (0.65)	-2.65 (0.67)	-2.78 (0.94)	(-4.63, -0.93)	0.003

Note: LS (Least Square) Mean estimates were obtained from an application of the pre-specified MMRM. SE denotes standard error. Source: Table 13 of the CSR and Reviewer's analysis.

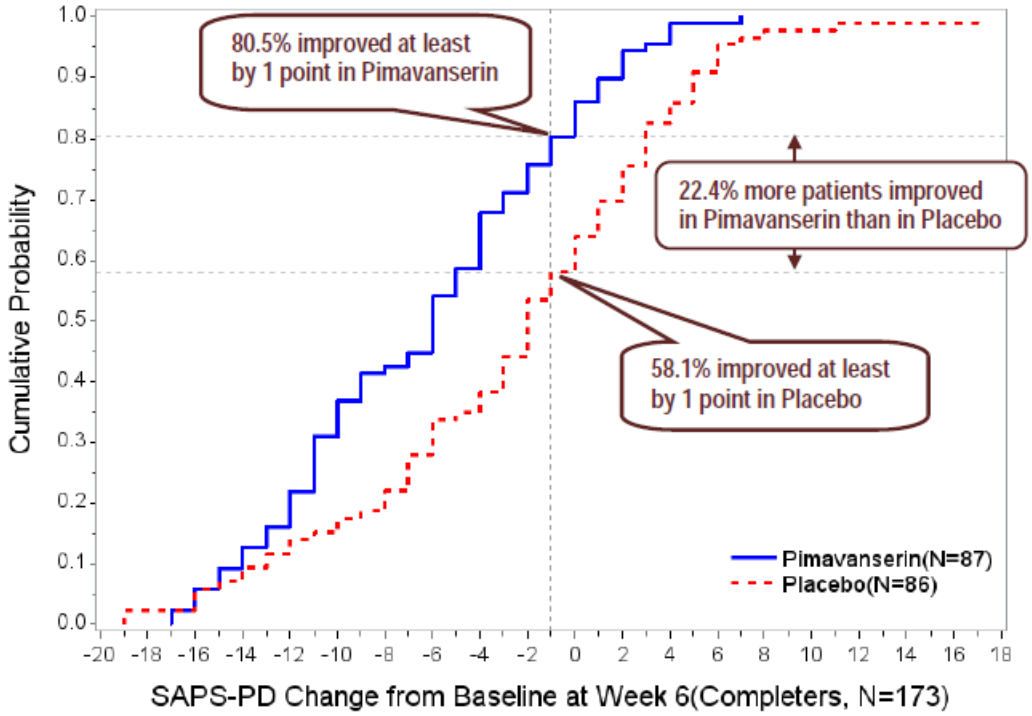
Source: Statistical review.

Exploratory Analyses of Primary Endpoint for Study 020

The Biometrics reviewers conducted several exploratory analyses to probe the study efficacy data. Although these analyses were conducted *post hoc*, they provide useful information to aid in interpreting the primary efficacy results.

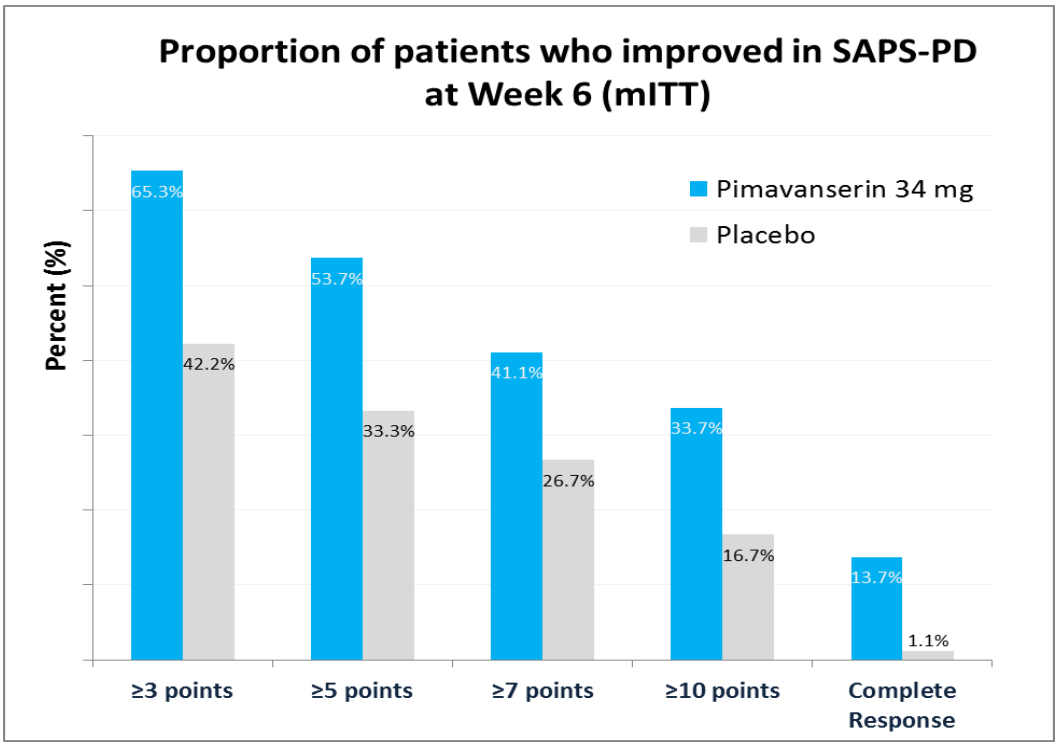
Cumulative distribution of SAPS-PD change from baseline was constructed to visualize the cumulative efficacy difference between drug and placebo at Week 6. As shown in the figure below, 81% of pimavanserin completers and 58% of placebo completers improved at Week 6.

Cumulative Distribution Function by Treatment at Week 6 for Completers (N=173)



Note: A patient improves if the change from baseline score to Week 6 is less than 0.
Source: Reviewer's analysis

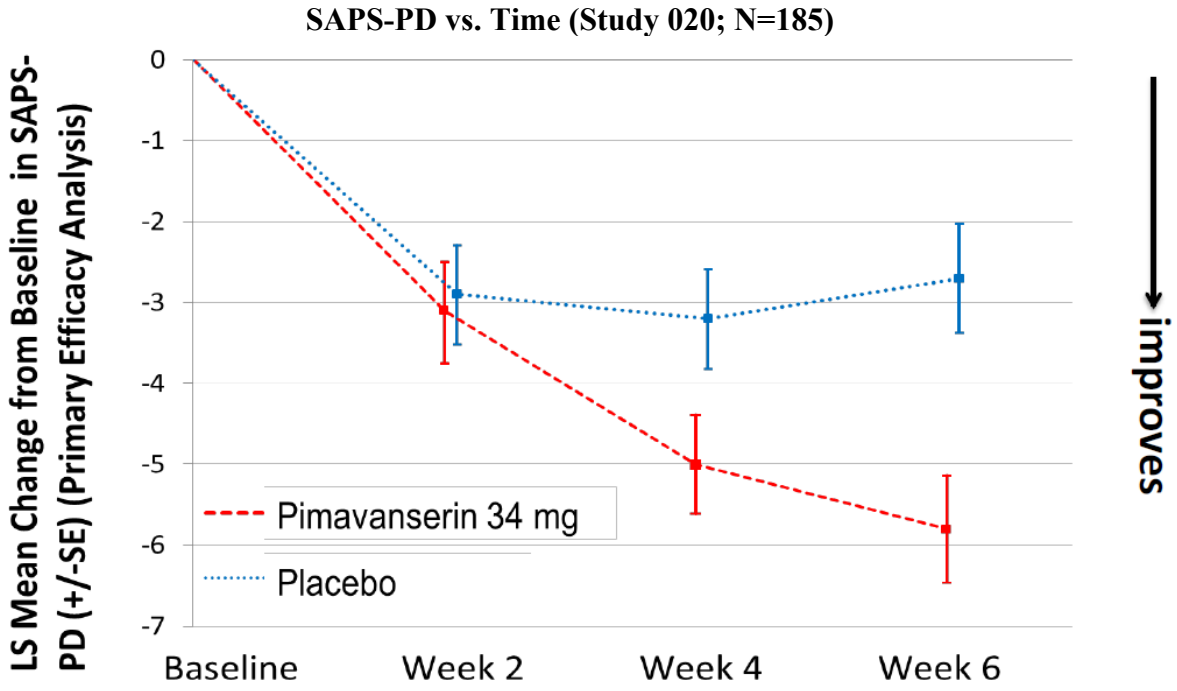
Primary efficacy conclusions were further explored using multiple different responder analyses, the most impressive of which was evaluation of complete response. Complete response is defined as no hallucinations or delusions (SAPS-PD of zero) at endpoint in patients who were at least moderately psychotically ill at the beginning of the trial. Although it can be argued in conducting these analyses that the definition of response is critical (must be clinically meaningful), it is hard to argue that reducing disabling symptoms to zero is not clinically meaningful. As can be seen from the figure below, approximately 14% of patients in the pimavanserin group achieved a complete response, compared to 1% of patients on placebo. A placebo-subtracted 13% complete response is an unusual finding in psychiatric drug trials.



Source: Biostatistics FDA

Time Course of Response

Change from baseline in the primary endpoint over time is depicted in the figure below. A separation from placebo was evident at Week 4 and continued until the end of the trial.



Source: Biostatistics FDA

Demographic Explorations
The applicant conducted subgroup analyses (summary statistics presented below) for sex, race, and age. The results of these subgroup analyses were consistent with the overall population and confirmed by our Biometrics team.

Subgroup Analysis Study 020

Observed (Raw) data Primary Endpoint (SAPS-PD)		Mean Change from Baseline at Week 6 (SD)				
		Pimavanserin		Placebo		Total Number of Subjects at Week 6
			#Subjects		#Subjects	
Primary Analysis Set mITT population (N=185)		-6.3 (5.88)	87	-2.7 (7.03)	86	173
Gender	Male	-7.3 (5.54)	56	-3.0 (6.82)	50	106
	Female	-4.7 (6.20)	31	-2.2 (7.38)	36	67
Race	White	-6.0 (5.81)	82	-2.3 (6.83)	81	163
	Non-white	-11.4 (5.18)	5	-7.8 (9.04)	5	10
Age Group	< 65 years of age	-5.0 (4.60)	10	-5.4 (5.14)	11	21
	≥ 65 and < 75 years of age	-6.5 (6.14)	47	-2.3 (6.77)	47	94
	> 75 years of age	-6.6 (5.96)	30	-5.4 (8.00)	28	58

SD denotes standard deviation.
Source: Tables 14.2.3.14 - 14.2.3.16 of the CSR

Secondary Endpoints
The sponsor has suggested, from the beginning of the development program, that the relative lack of dopamine blockade with pimavanserin would make it a pharmacologically more intelligent choice for treating psychosis in PD patients who have a relative dopamine deficiency and are being treated with dopaminergic drugs. They tested this hypothesis by evaluating, as their second comparison in the pre-specified testing sequence, the change in motor function for patients on drug versus placebo. This test was accomplished by comparing drug and placebo on the Unified Parkinson's Disease Rating Scale (UPDRS) Combined Part II (activities of daily living) and Part III (motor symptom examination).

The UPDRS is a commonly used measure of Parkinson's disease, and Parts II and III combined in Study 20 provide a measure of stability of the underlying PD symptoms in patients being treated with pimavanserin. The pre-specified plan was to show non-inferiority of pimavanserin to placebo in worsening of the underlying PD symptoms. A pre-specified non-inferiority margin of 5 was established with the Division prior to starting the study. The results are presented below.

Primary Analysis Results of Second Endpoint: Parkinson's Disease Status (UPDRS II+III) Change from Baseline to Week 6

ANCOVA (OC) LSM Estimate (SE)		Difference from Placebo in LSM Estimate (SE)	95% Confidence Interval	P value
Pimavanserin [N=92]	Placebo [N=88]			
-1.40 (0.86)	-1.69 (0.88)	0.29 (1.23)	(-2.14, 2.72)	0.8140

Note: A negative change from baseline indicates an improvement. The analysis result is based on ANCOVA (OC) model with treatment group as a factor and baseline score as a covariate. OC denotes Observed Cases. SE denotes standard error. N denotes the number of patients who had a baseline score and the endpoint score at Week 6.
Source: Reviewer's analysis

From the data in Study 020, this confirms the applicant's hypothesis that pimavanserin reduces the hallucinations and delusions of Parkinson's disease without worsening primary parkinsonian symptoms.

Exploratory Secondary Endpoints
Clinical Global Impression—Improvement (CGI-I) and Clinical Global Impression—Severity (CGI-S) were exploratory endpoints in the protocol and both were statistically significant in drug vs. placebo comparisons in Study 020. The Zarit Caregiver Burden Scale was also collected and statistically favored drug over placebo.

Summary of Efficacy
Analysis of mean change data and responder analyses demonstrate efficacy for pimavanserin for the treatment of the hallucinations and delusions of Parkinson's disease psychosis. Dr. Andreason, the primary medical reviewer, agrees that efficacy has been demonstrated, but he maintains in his review that efficacy is modest and must be weighed against the safety signals for the drug. I agree that the mean change, while statistically robustly positive, is less impressive than the responder analyses our team conducted, but even a modest mean change is clinically meaningful in a disabling condition with no approved treatment. When mean change data are considered along with responder analyses, I conclude that the drug has demonstrated substantial evidence of effectiveness, and that the robustly positive single study 020 is sufficient to reach this conclusion.

The first secondary endpoint analysis supports that the primary disease process, PD, is not made worse by treatment with pimavanserin. Multiple exploratory endpoints confirm the finding on the primary endpoint.

Safety

Exposure
There were 1096 subjects exposed to pimavanserin during development; 338 for more than 6 months, 278 for more than 12 months, and 141 for more than 24 months. The longest exposure was for 8 years. Although these numbers are relatively small, and the ICH recommendation for total exposures has not been met, ICH recommendations for exposure at 6 and 12 months have been met. As Dr. Andreason points out, the exposure numbers were sufficient to detect the kind of safety signals already labeled for

other drugs in the class, and the Division has determined that the exposure numbers were adequate to evaluate initial safety.

Characteristics of the Study Population
The population of patients with PDP is medically vulnerable, and so death and serious adverse events are to be expected. We have evidence from other drugs in the antipsychotic class (used for, but not labeled to treat, elderly patients with psychosis) that adverse reactions and death are more common on drug, and this is unfortunately the case with pimavanserin as well. Because of the increased risk of morbidity and mortality in the PD population, open label safety data are difficult to interpret. Therefore, the controlled trial database is the only reliable source of data to compare the safety of drug to placebo.

Deaths
Among the 5 deaths seen in the 6 week study database, four were on drug and one was on placebo. The specifics for the deaths are presented below.

Deaths in Pimavanserin 6-Week Placebo-Controlled Trials

Study ID	Unique Subject ID	Age(yrs) Sex	Dose[1] (mg)	Time[2] (days)	Death Date	Last Dose Date	Study Termination Date	Verbatim	Preferred Term	Investigator Assigned Causality
ACP-103-020	ACP-103-020-028-101	85 Male	None/ Placebo	9/27	(b) (6)	2010-11-23	2010-11-23	Cardio pulmonary Arrest	Cardio-Respiratory Arrest	Unlikely Related
ACP-103-012	ACP-103-012-005-005	61 Male	PIM 10mg	46		Unknown	2008-07-26	Probable Myocardial Infarction	Myocardial Infarction	Unlikely Related
ACP-103-020	ACP-103-020-001-101	76 Male	None/ PIM 40mg	1/9		2010-12-30	2010-12-30	Septic Shock	Septic Shock	Unlikely Related
ACP-103-020	ACP-103-020-303-121	74 Male	None/ PIM 40mg	7/38		2012-09-13	2012-09-18	Septicemia	Sepsis	Not Related
ACP-103-012	ACP-103-012-118-001	84 Female	None/ PIM 40mg	32/29		2008-11-21	2008-12-23	Respiratory Distress	Respiratory Distress	Unlikely Related

Source: Dr. Andreason's review.

From the table above, the expected causes of death in the population are represented with no clear unifying underlying pathologic mechanism identified. Dr. Andreason agrees that there is no unified cause of death in these cases, and that the background rate of death is high in the PDP population, but the imbalance between drug and placebo groups concerned him. In my view, while it is true that there were more deaths in the patients on drug than in patients on placebo, the overall small number of deaths and the size of this database make meaningful interpretations difficult. We have labeled the other atypical antipsychotics for increased mortality in elderly demented patients, and we would do the same for this drug if it were approved.

Serious Adverse Events (SAEs)
When uniquely identifiable rare and serious events occur in a clinical trial at rates that are disproportionately higher than the background rate in a population, these events become a reason for regulatory concern. The pimavanserin development program has no rare and serious events occurring in

the controlled trials. There were two cases of rhabdomyolysis that occurred in the open-label extensions of controlled studies, but as Dr. Andreason points out, the physical stressors of PD itself make attributing rhabdomyolysis to drug difficult.

From the controlled trial data, there were more SAEs on 34 mg of drug (16/202; 8%) than placebo (8/231; 3.5%). As with the deaths, an examination of the SAEs does not identify an obvious unifying pathological mechanism, and many events are very unlikely to be related to drug, although one can never be absolutely certain (e.g., hemorrhoids, psychosis, Parkinson's disease).

Patients with SAEs (by Dose) in the Placebo-controlled 6-week Safety Database

Unique-Subject ID	Age/ Sex	Adverse Event Preferred Term	Study Days	Last Dose Day	Action Taken	Severity	Causality	Study DC Reason
Placebo								
012-011-004	79/F	Anaemia	31-35	44	Interrupted	Moderate	Not related	No
		Gastrointestinal ulcer haemorrhage	31-35	44	Interrupted	Moderate	Not related	No
012-019-004	82/F	Bronchitis	46-49	46	Interrupted	Severe	Not related	No
014-071-002	73/M	Mental status changes	14-19	14	DC	Moderate	Possibly	Yes
014-160-003	78/M	Gastroenteritis	36-44	28	Interrupted	Mild	Not related	No
		Delirium	36-44	28	DC	Moderate	Unlikely	Yes
020-010-112	77/F	Decubitus ulcer	40-Unk	47	No change	Moderate	Not related	No
020-028-101	85/M	Arrhythmia	13-Unk	27	DC	Severe	Unlikely	Yes
		Cardio-respiratory arrest	36-36	27	No change	Severe	Unlikely	Fatal
		Transient ischaemic attack	13-13	27	No change	Moderate	Unlikely	No
020-038-103	73/M	Urinary tract infection	22-33	23	DC	Moderate	Not Related	Yes
020-320-101	72/M	Spinal fracture	47-52	57	No change	Moderate	Not related	No
Pimavanserin 8.5 mg								
012-004-002	87/M	Dementia with Lewy bodies	5-Unk	3	No change	Mild	Not related	No
		Encephalopathy	3-7	3	DC	Moderate	Unlikely	Yes
020-011-103	61/M	Myocardial infarction	46-45	46	DC	Severe	Unlikely	Fatal
012-016-001	70/M	Syncope	6-7	6	DC	Moderate	Possibly	Yes
012-028-002	72/M	Cellulitis	32-36	4	No change	Moderate	Not related	No
		Sepsis	32-34	4	No change	Severe	Not related	No
012-116-007	67/M	Inguinal hernia repair	44-49	50	Interrupted	Mild	Not related	No
014-072-005	78/F	Fall	41-64	28	DC	Severe	Unlikely	Yes
		Hip fracture	41-64	28	DC	Severe	Unlikely	Yes
014-154-012	53/M	Psychotic disorder	42-81	41	No change	Severe	Unlikely	No
014-169-001	53/F	Delusion	27-42	16	No change	Moderate	Not related	No
		Delusion	3-7	16	DC	Moderate	Not related	Yes
Pimavanserin 17 mg								
014-068-003	68/M	Parkinson's disease	11-7	11	DC	Moderate	Not related	Yes
Pimavanserin 34 mg								
012-013-001	79/M	Mental status changes	3-4	2	DC	Severe	Possibly	Yes
012-106-001	72/M	Headache	51-58	36	DC	Moderate	Possibly	Yes
012-116-006	74/M	Confusional state	9-9	8	No change	Severe	Not related	No
		Hallucination	9-12	8	DC	Severe	Not related	Yes
012-117-002	77/F	Breast cancer	36-36	32	DC	Severe	Not related	Yes
012-118-001	84/F	Syncope [2]	-28 to -21	29	No change	Moderate	Not related	No
		Respiratory distress	32-61	29	DC	Severe	Unlikely	Fatal
020-001-101	76/M	Multi-organ failure	10-Unk	9	No change	Severe	Not related	No
		Septic shock	10-10	9	No change	Severe	Unlikely	Fatal

		Psychotic disorder	4-Unk	9	DC	Severe	Not related	Yes
		Sleep disorder	4-Unk	9	No change	Severe	Not related	No
020-011-103	82/M	Fall	2-2	15	No change	Moderate	Unlikely	No
		Mental status changes	2-6	15	No change	Moderate	Unlikely	No
020-013-102	69/M	Haemorrhoids	36-39	40	No change	Severe	Unlikely	No
020-019-105	80/F	Bronchitis	36-43	11	No change	Severe	Not related	No
		Septic shock [a]	48-82	11	No change	Severe	Not related	No
020-019-106	72/F	Atrial fibrillation	26-27	45	No change	Moderate	Not related	No
020-038-104	78/F	Urinary tract infection	2-36	1	DC	Mild	Not related	Yes
020-039-103	74/M	Asthenia	6-6	5	DC	Severe	Unlikely	Yes
		Fatigue	6-6	5	DC	Severe	Unlikely	Yes
		Urinary tract infection	6-12	5	DC	Severe	Not related	Yes
		Dehydration	6-6	5	DC	Severe	Unlikely	Yes
020-063-110	80/F	Urinary tract infection	12-15	43	No change	Moderate	Not related	No
020-303-121	74/M	Sepsis	42-45	38	No change	Severe	Not related	Fatal
		Psychotic disorder	38-Unk	38	DC	Severe	Possibly	Yes
020-308-103	74/M	Parkinson's disease	41-61	40	No change	Severe	Unlikely	No
020-327-105	79/M	Syncope [a]	-11 to -5	42	No change	Moderate	Not related	No
020-330-101	72/F	Hallucination	16-Unk	7	No change	Severe	Not related	No

Source: Dr. Andreason's review.

QT Prolongation

The QT review team examined the electrocardiographic data collected as part of the controlled trials and identified a mean increase in QTc interval of 5-8 msec in patients on 34 mg/day. They have provided labeling language that says that use of pimavanserin should be avoided in combination with other QT-prolonging drugs and in patients with prolonged QT for other reasons. The Division has negotiated this warning into labeling and the sponsor has accepted it.

Common Adverse Reactions

Common adverse events (defined as events reported in at least 2% of patients and occurring more than in placebo) have been included in draft labeling. Table one from the draft labeling is presented below.

Table 1. Adverse Reactions in Placebo-Controlled PDP Studies of 6-Week Treatment Duration and Reported in ≥2% and >Placebo

	Percentage of Subjects Reporting Adverse Reaction	
System Organ Class	**NUPLAZID 34 mg**	**Placebo**
Preferred Term	N=202	N=231
Gastrointestinal disorders		
Nausea	7%	4%
Constipation	4%	3%
General disorders		
Peripheral edema	7%	2%
Gait disturbance	2%	<1%
Psychiatric disorders		
Hallucination[a]	5%	3%
Confusional state	6%	3%

[a] Hallucination includes visual, auditory, tactile, and somatic hallucinations.

Source: Proposed draft labeling.

Potential for Pulmonary Toxicity

The preclinical development of pimavanserin identified phospholipidosis in rat at doses 5-10 times higher than human exposures, and this led to respiratory distress in some animals. Although we have no evidence of this problem in humans, the development program is relatively small and the team has decided to include the possibility of this effect in labeling so that prescribers and patients are aware of it (see preclinical section below).

Summary of Safety Findings
In summary, the disproportionate increased risk of serious morbidity/mortality without a known pathophysiologic mechanism has been the established norm in the antipsychotic drug class in elderly patients, including drugs not specifically approved to treat psychosis in elderly patients, and pimavanserin is no exception to this. As with the other drugs in this class, pimavanserin, if approved, will bear the Boxed Warning and Warnings and Precautions language about use in the demented elderly psychotic population—while there is no clear way to mitigate this risk, we can inform about it in labeling as we have done for the other drugs in the class.

Integrated Evaluation of Efficacy and Safety
Pimavanserin has been demonstrated to have efficacy for the treatment of the hallucinations and delusions of Parkinson's disease, a debilitating part of a disease with no FDA-approved treatment, and it has large effects in some patients. Pimavanserin has also been demonstrated to have risks that are consistent with the other drugs in the class (drugs recommended by treatment authorities in treatment guidelines for clinicians, although not labeled for this use), namely, increased morbidity and mortality in elderly patients. Pimavanserin did not worsen the underlying Parkinson's disease in Study 020.

PDP itself, as acknowledged by Dr. Andreason, increases morbidity and mortality—psychotic patients are at risk of irrational behavior secondary to hallucinations or delusions, and they are at increased risk of being placed in a nursing facility if they become psychotic at home—admission to these facilities is often a harbinger of death.

In summary, I conclude that the drug has been proven to have efficacy in a disabling disease, and the safety risks of the drug are the same as other drugs in the class that, although recommended in treatment guidelines for off-label use in PDP, have a known pharmacology that can cause worsening of the primary symptoms of the underlying Parkinson's disease. While the risks of pimavanserin cannot be mitigated, they can be labeled along with the efficacy data to allow for rational decision-making by clinicians, patients, and family members struggling to manage the symptoms of PDP.

Office of Clinical Pharmacology (OCP)
The applicant submitted nine pharmacokinetic studies, three pharmacodynamic studies and thirty-one in vitro studies to support their application. The key findings from these studies are presented below.

OCP Key Findings
- The proposed dosing regimen of 34 mg once daily is acceptable.
- Pimavanserin can be taken with or without food and the immediate-release (IR) tablets may be crushed for patients who cannot swallow pills.
- Pimavanserin dose should be reduced to one-half the usual recommended dose when co-administered with strong CYP3A4 inhibitors.

- No dose adjustment is recommended for patients with mild or moderate renal impairment but use is not recommended for patients with severe renal impairment.
- Pimavanserin is not recommended in patients with hepatic impairment.
- No dose adjustment is recommended based upon weight, height, age, or sex.
- Pimavanserin is expected to increase the QT/QTc interval by approximately 8 msec at the recommended dose of 34 mg.

The Office of Clinical Pharmacology concluded that there is sufficient clinical pharmacology and biopharmaceutics information provided in the NDA original and resubmission to support approval.

General pharmacokinetic and biopharmaceutic features of pimavanserin:

- Relative bioavailability of the to-be-marketed product compared to the pimavanserin oral solution used in early studies is 99.7%.
- PK is dose-proportional between 20 mg and 300 mg.
- Elimination half-life of pimavanserin and its active metabolite (AC-279) are about 57 and 200 hours, respectively. The accumulation ratio is between 3.5 and 5.8.
- AC-279 makes up about 5% of the administered dose in plasma.
- Protein binding is approximately 91-97% with less than 2% excreted in urine or feces unchanged.
- Pimavanserin is a substrate of CYP3A, but not an inducer.

OCP determined that there are no significant issues with the clinical pharmacology that would prevent approval.

Chemistry, Manufacturing, and Controls (CMC)

The Office of New Drug Quality Assessment (ONDQA) evaluated the drug substance and drug product, and they have recommended approval. The only recommendation for the action letter is to grant the expiry at 24 months when stored at controlled conditions.

The Office of Compliance has issued an acceptable recommendation. Inspectional results for drug substance and drug product manufacturing were acceptable. There were no Phase 4 recommendations.

Pharmacology/Toxicology

Pimavanserin was evaluated for toxicity in three species (mouse, rat, and monkey) for up to 12 months of treatment. The drug is a cationic amphiphilic drug (CAD) and is known, as are all CADs, to cause phosopholipidosis (PLD) which is an excessive accumulation of phospholipids in cells. Pimavanserin caused widespread, multi-organ, systemic PLD in mice, rats, and monkeys after sub-chronic and chronic administration. The lung and the kidney were the most affected tissues in all species. Chronic inflammation occurred and was assessed by the applicant and by our reviewers to be secondary to prolonged PLD. Two internal expert pathologists from FDA-CFSAN (Center for Food Safety and Applied Nutrition) were involved, and they concluded that the fibrosis observed in lung was not a direct drug effect and not consistent with human pulmonary fibrosis. Pharmacology/Toxicology has recommended approval of the application and suggested that language be added to the label to advise clinicians about the possibility of respiratory symptoms being secondary to PLD accumulation in the lungs.

Advisory Committee

This application was presented to the Psychopharmacologic Drugs Advisory Committee (PDAC) on 29 March 2016. The PDAC voted 12 to 2 that the benefits of the drug outweighed the risks of treatment.

Controlled Substances Staff (CSS)
The conclusions of the CSS review team were that no abuse-related AEs were evident from the data and that the drug need not be scheduled under the Controlled Substance Act.

Office of Scientific Investigation (OSI)
OSI inspected three clinical investigator sites and found some violations but state that the data reported in the NDA appears to be reliable and reflects the source documentation at the sites inspected. There were several protocol violations that were identified, many related to concomitant medications not allowed by protocol. The biostatistics team analyzed the data excluding the patients with protocol violations data and found only negligible changes in the efficacy results.

Labeling/Medication Guide
The label for this drug has been negotiated with the applicant to include the usual Boxed Warning for increased risk of death in dementia-related psychosis. We have included phosopholipidosis in the label, and have edited the Indications section to read that the drug is indicated for the treatment of hallucinations and delusions associated with Parkinson's disease, since the primary endpoint specifically measured hallucinations and delusions.

Phase Four Requirements/Commitments
Multiple post-marketing commitments (PMCs) have been identified by the review team, including a randomized withdrawal trial, a commitment to study frail/elderly patients to collect more safety data at the 34 mg dose (not necessarily in Parkinson's disease patients), an *in vivo* drug-drug interaction study to evaluate the effect of strong CYP3A4 inducers on pimavanserin exposure, and a microscopic reevaluation of lung tissue samples using special stains to detect collagen from high dose animals.

Conclusions
I recommend an approval action. Pimavanserin has been demonstrated to be effective for the treatment of the hallucinations and delusions of Parkinson's disease and labeling has been negotiated to include the same safety warnings that are part of all drugs in the antipsychotic class concerning increased mortality in dementia-related psychosis. Although a member of the atypical antipsychotic class of drugs, pimavanserin has a different binding profile, which may explain why motor symptoms of Parkinson's disease did not worsen with pimavanserin treatment in Study 020. The applicant has agreed to labeling with FDA edits and has agreed to conduct each of the post-marketing studies listed above. This application should be approved by the PDUFA date.

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/s/

MITCHELL V Mathis
04/29/2016