FDA Briefing Document

Psychopharmacologic Drugs Advisory Committee (PDAC)

June 17, 2022

Topic: Supplemental New Drug Applications 207318 & 210793

Pimavanserin for the treatment of hallucinations and delusions associated with Alzheimer's disease psychosis

FDA Briefing Document

NDA # 207318/S-011 and 210793/S-008 Resubmission

Drug name: Pimavanserin

Applicant: Acadia Pharmaceuticals, Inc.

Psychopharmacologic Drugs Advisory Committee Meeting

June 17, 2022

Division of Psychiatry/Office of Neuroscience

DISCLAIMER STATEMENT

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Glossary

AC	Advisory Committee
AD	Alzheimer's disease
ADCS-ADL	Alzheimer's Disease Cooperative Study-Activities of Daily Living
ADCS-CGIC	Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change
ADP	Alzheimer's disease psychosis
APA	American Psychiatric Association
CDER	Center for Drug Evaluation and Research
CGI-I	Clinical Global Impression-Improvement
CGI-S	Clinical Global Impression-Severity
CMAI-SF	Cohen-Mansfield Agitation Inventory-Short Form
CR	Complete Response
DB	double-blind
DLB	dementia with Lewy bodies
E-R	exposure-response
FAS	Full Analysis Set
FDA	Food and Drug Administration
FTD	frontotemporal dementia
HR	hazard ratio
IA	interim analysis
IAC	independent adjudication committee
ICF	informed consent form
IND	Investigational New Drug
ITT	Intent-To-Treat
LAR	legally authorized representative
LSM	least-squares mean
MMRM	mixed-effect model repeated measures
MMSE	Mini-Mental State Examination
NDA	New Drug Application
NPI-NH	Neuropsychiatric Inventory-Nursing Home Version
NPI-NH PS	Neuropsychiatric Inventory-Nursing Home Version Psychosis Score
OL	open-label
OSI	Office of Scientific Investigations
PDD	Parkinson's disease dementia
PDP	Parkinson's disease psychosis
REMS	risk evaluation and mitigation strategy
SAP	Statistical Analysis Plan
SAPS-H+D	Scale for the Assessment of Positive Symptoms Hallucinations+Delusions Score
SD	standard deviation
sNDA	supplemental New Drug Application
VaD	vascular dementia

1 Executive Summary/Draft Points for Consideration by the Advisory Committee

1.1 Purpose/Objective of the AC Meeting

FDA is convening this Advisory Committee meeting to discuss the evidence the Applicant has provided to establish the benefit of pimavanserin in the treatment of hallucinations and delusions associated with Alzheimer's disease psychosis (ADP).

1.2 Context for Issues to Be Discussed at the AC

Alzheimer's disease (AD) is the most common form of dementia in older adults in the United States. Hallucinations and delusions are among the neuropsychiatric symptoms that can occur in the context of the disease. These symptoms may cause distress and may be associated with a higher risk of rapid progression to severe dementia, death, and of out-of-home placement. There are currently no approved pharmacologic treatments for hallucinations and delusions that occur in individuals with AD. Pimavanserin is a serotonin-selective inverse agonist that preferentially targets the 5-HT2A receptor subtype. Pimavanserin is indicated for the treatment of hallucinations and delusions associated with Parkinson's disease psychosis (PDP). Acadia Pharmaceuticals (the Applicant) is seeking to broaden the indicated population to include patients with hallucinations and delusions associated with ADP.

In this submission, the Applicant presents data from two studies to provide support for pimavanserin as a treatment for ADP. Study ACP-103-019 (Study 019) evaluated the efficacy and safety of pimavanserin as a treatment of psychotic symptoms specifically in subjects with ADP. Study ACP-103-045 (Study 045) was conducted in subjects with psychosis related to several types of dementia, but included a large subgroup of subjects with AD. The Division seeks Advisory Committee input on the interpretation of the efficacy data submitted by the Applicant. The Division's review of the pimavanserin safety data will not be a focus of the discussion; the findings from the sNDA development program were largely consistent with the known safety profile of pimavanserin. The Advisory Committee's findings on the efficacy data will inform the Division's benefit-risk assessment.

1.3 Brief Description of Issues for Discussion at the AC

The application under review is a resubmission after a Complete Response (CR). In their original application, the Applicant was seeking an indication for the treatment of dementia-related psychosis. In this resubmission, the Applicant is seeking an indication for the treatment of hallucinations and delusions associated with ADP. Study 045, a relapse prevention study, was the primary source of effectiveness evidence in the original application; Study 019 was designed as a proof-of concept study and submitted as supportive evidence for the dementia-related psychosis indication. With the 2021 CR action, the Division noted that the results in the Parkinson's disease dementia (PDD) subgroup in Study 045 appeared to drive the overall study results. The Agency noted that the drug effect in this subgroup supports the effectiveness of pimavanserin as a treatment for hallucinations and delusions associated with PDD, but that the PDD population is already part of the current PDP indication (i.e., the broader PDP population includes individuals with Parkinson's disease with and without dementia). Study 045 was not powered to determine an effect in the included dementia subgroups; however, the ADP and PDD subgroups appeared to respond differently to pimavanserin. With123 subjects (63%), the AD subgroup

was the largest subgroup, yet the results in the PDD subgroup (n=35; 18%) in Study 045 appeared to drive the overall study results.

The current application cites Study 019 as the primary study providing evidence of effectiveness for the treatment of hallucinations and delusions associated with ADP, with additional supportive evidence provided from post hoc analyses of Study 045 data. In the first review cycle, the Agency concluded that Study 019 was not an adequate and well-controlled study, highlighting concerns related to trial design and conduct issues. The Applicant has asked the Agency to reconsider its conclusions regarding Study 019 and maintains that the study conforms to the statutory requirements outlined in 21CFR 314.126(b) for an adequate and well-controlled study. Study 019 was conducted in nursing homes in the United Kingdom and enrolled subjects ≥ 50 years of age who met criteria for possible or probable AD and psychotic symptoms. Pimavanserin demonstrated a statistically significant treatment effect, compared with placebo, on the primary efficacy endpoint, the change from baseline to Day 43 on the Neuropsychiatric Inventory – Nursing Home Version Psychosis Score (Delusions+Hallucinations) or NPI-NH-PS, with a treatment difference of -1.8 (95% CI: -3.64, -0.04; p=0.045). It is not clear from the Agency's review of Study 019 that the magnitude of improvement observed in this study–less than 2 points on a 24-point scale–reflects a clinically meaningful improvement. Of note, no notable separation from placebo occurred on any of the secondary endpoints, so secondary endpoints do not provide additional support for the improvement observed in the primary endpoint. It is also unclear from the results whether the improvement noted on the primary endpoint at Day 43 is durable.

Finally, the Applicant describes PDP and ADP as closely-related conditions and, thus, asserts the prior approval for PDP should be considered an additional source of evidence for the current application; the Division does not agree. The findings from Study 045 suggest a differential response to pimavanserin across dementia subtypes, and the Division noted this in the Complete Response to the prior submission. In the resubmission, the Applicant explored the subgroup results of Study 045 to support their hypothesis that the study demonstrated a consistent response to pimavanserin treatment in all subgroups, including a clinically meaningful effect in the AD subgroup. Study 045 was terminated early based on predetermined efficacy criteria. The Applicant hypothesizes that the robust response observed for patients with PDD was due to the concomitant use of dopaminergic medications resulting in a more rapid relapse in this subgroup and the appearance of a differential treatment effect compared to other subgroups. The Applicant has explored the interaction of treatment by dementia subgroup, examined the potential confounding effect of dopaminergic therapy in the PDD subgroup, conducted analyses of primary and exploratory efficacy endpoints in the AD subgroup, and performed a simulation to evaluate the potential impact on the final analysis if the effect in the PDD subgroup were attenuated. In addition, the Applicant believes that higher pimavanserin exposures were associated with greater efficacy and has conducted an analysis of the relationship between plasma pimavanserin concentration and the primary efficacy endpoint.

1.4 Draft Points for Consideration

Given the marked difference in response across dementia subgroups in Study 045, the Agency is not considering, and the Applicant has not requested, a broad dementia-related psychosis indication. The Agency is considering an indication for the treatment of ADP. Based upon this, the Agency requests that the Committee address the following:

1. Discuss whether the evidence supporting the effectiveness of pimavanserin for the treatment of hallucinations and delusions in the ADP population. In your discussion, comment on the strengths, limitations, and the extent to which each of the following potential sources of evidence contribute to your overall assessment of effectiveness:

    - Study 019
    - Study 045
    - The prior approval of pimavanserin for the treatment of hallucinations and delusions associated with Parkinson's disease psychosis

2. Does the available evidence support a conclusion that pimavanserin is effective for the treatment of hallucinations and delusions in the ADP population?

    - If yes, provide the rationale.
    - If no, provide your rationale and a recommendation for what further evidence should be generated.

2 Introduction and Background

2.1 Background of the Condition/Standard of Clinical Care

Alzheimer's disease (AD) is characterized by cognitive decline and impaired function, but also commonly involves neuropsychiatric symptoms, including hallucinations and delusions.[1-3] According to the Alzheimer's Association, more than 5.8 million Americans have AD.[4] A systematic review of patients with AD in various care settings reported a median prevalence of psychosis of 41.1% (range, 12.2 to 74.1%).[5] Scarmeas et al. reported an association between hallucinations and delusions and functional decline in patients with AD as well as between hallucinations and institutionalization and death.[6] Peters et al. reported an association between psychosis and rapid progression to severe dementia and death.[7] Lyketsos et al. noted that neuropsychiatric symptoms of dementia are associated with increased length of hospital stays, institutionalization, and greater caregiver stress and depression.[8]

No approved treatment exists for hallucinations and delusions associated with ADP. The currently approved antidementia medications for the treatment of AD target cognitive and functional endpoints. Generally, studies involving off-label use of medications for neuropsychiatric symptoms of AD have enrolled patients with presumed AD who have a variety of neuropsychiatric symptoms, including a combination of agitation, aggression, and psychosis. Published studies evaluating the effects of antipsychotics, antidementia drugs, antidepressants, and antiepileptics for these symptoms have largely had mixed results.[9-13]

Regarding off-label antipsychotic use, the 2016 American Psychiatric Association (APA) Practice Guideline on the Use of Antipsychotics to Treat Agitation or Psychosis in Patients With Dementia concluded that the benefits of antipsychotic medications observed in clinical trials were small at best.[3,14,15] Regarding risks associated with use of antipsychotics in this population, in 2005 the Agency issued a class-wide boxed warning for second generation (atypical) antipsychotics based on the results of a meta-analysis demonstrating an association between dementia-related psychosis and increased mortality for these drugs. In 2008, the boxed warning was extended to first generation (typical) antipsychotics based on additional analyses. Beyond mortality risk, other serious adverse events reported with off-label use of antipsychotics include stroke, cardiovascular events, metabolic effects (i.e., weight gain, diabetes, dyslipidemia, and metabolic syndrome), pneumonia, and venous thromboembolism. The APA Practice Guideline notes that evidence is variable for other adverse effects, including cognitive worsening, sedation/fatigue, anticholinergic effects, postural hypotension, prolonged QTc intervals, sexual dysfunction, and extrapyramidal symptoms (e.g., parkinsonism, dystonia, tardive dyskinesia).[3]

In summary, hallucinations and delusions in AD are a serious public health issue with an unmet treatment need.

2.2 Pertinent Drug Development and Regulatory History

Pimavanserin is a serotonin inverse agonist that preferentially targets the 5-HT2A receptor subtype. It was approved for the treatment of hallucinations and delusions associated with Parkinson's disease psychosis (PDP) in April 2016, under new drug application (NDA) 207318. The recommended dose for the treatment of PDP is 34-mg taken orally once daily (or 10-mg once daily when administered with

strong CYP3A4 inhibitors). Its mechanism of action in the treatment of hallucinations and delusions associated with PDP is unclear; however, the effect could be mediated through a combination of inverse agonist and antagonist activity at serotonin 5-HT2A receptors and, to a lesser extent, at serotonin 5-HT2C receptors.

This supplemental new drug application (sNDA) was originally submitted for the treatment of hallucinations and delusions associated with dementia-related psychosis. In 2008, during a pre-Investigational New Drug (IND) meeting, the Applicant outlined a plan to include a study of patients with psychosis secondary to Alzheimer's disease as part of a multi-study approach to support a "dementia-related psychosis" indication. In early discussions with the Agency, the Applicant indicated an intent for Study 019 to serve as one of the adequate and well-controlled trials in this planned multi-study program; however, based on Agency feedback, the Applicant redesigned the study to be more exploratory and evaluate potential functional co-primary endpoints for future phase 3 trials. Ultimately, the Agency did not require a functional co-primary for this indication. The Applicant submitted the topline results of Study 019 in 2017 in the context of an End of Phase 2 meeting request.

At a May 2017 End-Of-Phase 2 meeting, the Agency agreed that the treatment of hallucinations and delusions in "dementia-related psychosis" was a potentially approvable indication. However, the Agency expressed concerns about basing a regulatory decision on a single, randomized withdrawal study (e.g., the Agency pointed out that one of the strongest factors supporting the approval of pimavanserin for treatment of hallucinations and delusions in PDP was the number of complete responders compared with placebo—and this data would not be obtained with a randomized withdrawal study). The Applicant noted that the randomized withdrawal study design could provide data about the durability of pimavanserin's possible effect given the results of Study 019 and that it might ameliorate enrollment difficulties (with all patients initially offered active drug). After the discussion, the Agency agreed that the randomized withdrawal trial would be acceptable as a well-controlled trial for sNDA submission for the indication of hallucinations and delusions associated with dementia-related psychosis. The Agency agreed with the proposed Study 045 phase 3 randomized withdrawal study population as long as subjects were stratified by their current clinical diagnosis (i.e., dementia subtype), and noted that labeling would reflect the actual composition and response of subjects enrolled in the study.

- In October 2017, Breakthrough Therapy Designation was granted for the proposed indication of treatment of hallucinations and delusions associated with dementia-related psychosis. The Agency concluded that the data submitted at the time (largely the results of Study 019) provided preliminary evidence that pimavanserin had the potential to offer substantial improvement over existing therapies (i.e., early evidence of potential benefit in the context of no approved treatments).

- In June 2020, the Applicant submitted the original sNDA (210793-s008/207318-s011) for the treatment of hallucinations and delusions associated with dementia-related psychosis, supported by Study 045, Study 019, and resubmitted data from Study ACP-103-020 (Study 020), a phase 2 efficacy and safety study in subjects with PDP, a subset of whom had dementia.

- In April 2021, the Agency issued a Complete Response (CR) letter concluding that the sNDA did not provide substantial evidence of effectiveness for the requested indication of dementia-related psychosis, based on the following study observations:

    - The Agency noted that although Study 045 was not powered to demonstrate an effect in the subgroups of dementia included, an examination of dementia subgroups revealed the following study limitations:

        - Too few subjects with dementia with Lewy bodies (n= 10) or frontotemporal dementia (n=3) were included to adequately represent the response to pimavanserin for either subtype.

        - There was no difference on time-to-relapse between pimavanserin and placebo in subjects with vascular dementia (n=25).

        - Results for the AD subgroup were not nominally statistically significant, despite being the largest subgroup (n=123).

        - Results for Parkinson's disease dementia (PDD) were highly nominally statistically significant. Despite a relatively small size subgroup (n=35), the finding in this subgroup appeared to drive the overall study results. Patients with PDD are a subset of the Parkinson's disease population; the current indication of treatment of hallucinations and delusions associated with PDP includes all patients with PDP—with and without dementia. Therefore, the results were aligned with the approved indication.

    - The Agency did not consider Study 019 to be an adequate and well-controlled study, noting study design and study conduct concerns.

    - The Agency also noted that the findings from Study 045 suggested a differential response to pimavanserin across dementia subtypes. These findings called into question whether "dementia-related psychosis" is a useful construct for a potential indication.

- At a June 2021 Type A End-of-Review meeting, the Agency reiterated the issues outlined in the CR letter and advised the Applicant to study the effect of pimavanserin in a new study of specific populations of patients with dementia (e.g., AD). The Applicant provided an overview of their interpretation of the Study 045 subgroup data and maintained that there was a consistent response pattern in the subgroups. The Applicant asserted that they would be able to fully address the concerns raised in the CR letter by submitting new analyses of Study 045 subgroup data and additional information about the adequacy of Study 019.

- At a December 2021 Type B guidance meeting, the Applicant reviewed their plan for a resubmission based on new analyses of Study 045 data and additional information regarding the adequacy of Study 019. The Applicant notified the Division about a change in the proposed indication and described their intent to focus on hallucinations and delusions associated with ADP. The Agency noted that it would be prepared to consider the Applicant's arguments in a resubmission but

continued to advise the Applicant that an additional adequate and well-controlled study in subjects with ADP would likely provide the strongest data in support of a resubmission.

The current sNDA resubmission is for the treatment of hallucinations and delusions associated with ADP.

3 Summary of Issues for the AC

In this resubmission, the Applicant has positioned Study 019 to serve as the primary source of evidence (as an adequate and well-controlled study) for the effectiveness of pimavanserin in the treatment of hallucinations and delusions associated with ADP, with supportive evidence provided by Study 045. The Division is asking the Committee to opine about the strength of evidence in the application and whether the data in Applicant's sNDA resubmission provides evidence of a clinically meaningful benefit for pimavanserin as a treatment for ADP.

3.1 Study ACP-103-019

3.1.1 Overview of Design and Results

3.1.1.1 Study 019 Design

Study 019 was a phase 2, randomized, double-blind, placebo-controlled, 12-week, parallel-group study in 181 nursing home resident subjects (ages ≥50 years-old) from a 133-nursing home network in the United Kingdom, who met criteria for AD with psychosis and had a baseline Mini-Mental State Examination (MMSE) score ≥1 and ≤22. During the approximately 3-week screening period, subjects completed an antipsychotic washout (if necessary) and caregivers were trained to provide brief psychosocial therapy to the subject with a target of five times per week (minimum three times per week). Per the Applicant, the intention of the brief psychosocial therapy was to minimize placebo response prior to randomization and to assure that only subjects requiring pharmacologic therapy were randomized into the study. At baseline, subjects were randomized 1:1 to either oral pimavanserin tartrate 40 mg once daily (the equivalent of 34 mg free base pimavanserin) or placebo, stratified by baseline MMSE and NPI-NH PS scores. No dose adjustment was allowed. The primary endpoint was the change from baseline to Day 43 on the NPI-NH PS; secondary endpoints included change from baseline to Day 43 on the Alzheimer's Disease Cooperative Study – Clinical Global Impression of Change (ADCS-CGIC), other NPI-NH domains, and Cohen-Mansfield Agitation Inventory-Short Form (CMAI-SF) total and subdomain scores. Subjects had a 4-week safety follow-up telephone visit after the double-blind period; see the Appendix for the Applicant's detailed schedule of assessments.

Eligibility Criteria

In addition to the eligibility criteria described above, subjects were excluded for any psychotic symptoms that were likely part of a toxic, metabolic, or infection-induced delirium/encephalopathy; psychosis due to substance abuse; or psychosis associated with schizophrenia, bipolar disorder, or psychotic depression (subjects were also excluded for any prior or concomitant diagnosis of a significant psychotic disorder such as schizophrenia or bipolar disorder). Regarding prior or concomitant medications:

- Acetylcholinesterase inhibitors or memantine were required to be at a stable dose for at least 3 months prior to Baseline and during the study.

- Antipsychotics were prohibited and should have been tapered and discontinued at least five half-lives prior to Baseline.

- Antidepressants and anxiolytics (benzodiazepines) were required to be at a stable dose for at least 21 days prior to Baseline and during the study.

- Medications that can prolong the QT interval were either prohibited or restricted (following amendment 3); the antidepressants amitriptyline, clomipramine, desipramine, doxepin, fluoxetine, imipramine, mirtazapine, nortriptyline, paroxetine, sertraline, and trazodone were permitted if the subject's baseline electrocardiogram (ECG) demonstrated a corrected QT interval by Fridericia's formula (QTcF) <425 msec. In addition to the QTcF restriction, citalopram and escitalopram were restricted to a maximum dose of 20 mg daily and higher doses must have been tapered to that dose prior to Baseline.

Endpoints

- *Primary Endpoint*
  The primary endpoint was mean change from Baseline to Day 43 on the NPI-NH PS (delusions (domain A) + hallucinations (domain B)). The Neuropsychiatric Inventory was developed to evaluate 12 neuropsychiatric disturbances (domains) common in dementia: delusions, hallucinations, agitation, dysphoria, anxiety, apathy, irritability, euphoria, disinhibition, aberrant motor behavior, nighttime behavior disturbances, and appetite and eating abnormalities. The score of each item, if present, represents the product of symptom frequency (range 1 to 4) and severity (range 1 to 3), for a maximum score of 12 on each domain (with higher scores denoting more serious symptoms). Because the primary efficacy measure consisted of only two domains, A and B, the maximum possible score is 24. According to the Applicant, the nursing home version (NPI-NH) of this scale was designed to examine psychopathology in nursing home patients and has been validated for use in this population.[16]

  Although the NPI-NH is considered an adequate endpoint for exploratory purposes, this measure is supported by limited evidence of content validity as the Applicant has not provided a comprehensive review of the literature with a summary focused on how the items measure the targeted concept of interest (i.e., hallucinations and delusions) in the AD population. Nor has the Applicant undertaken research within their own development program to provide evidence of content validity due, in part, to an earlier focus on agitation and aggression. Nonetheless, the items of the NPI-NH PS are consistent with the classifications of hallucinations and delusions that may be experienced by patients with ADP and our primary concerns lie with the scoring and the interpretation of group and individual differences. In particular the scoring algorithm, which totals the product of severity and frequency item scores, yields a metric that is difficult to interpret. As an example, Fernandez et al. (2008)17 state, after a review of the available instruments in the context of Parkinson's disease, that frequency is a relevant aspect of measuring psychosis, but that frequency should not be scored with severity as a multiplicative score because products of scores are conceptually difficult to interpret. Understanding the clinical meaning of a within-patient change on the metric would be, arguably, even more difficult. For example, when attempting to establish the convergent validity of the NPI-NH PS by reviewing the relationship between two scores, the

nature of the relationship may not necessarily be evident in a correlation statistic (i.e., measure of linear association). In addition, because the assessment of items on the NPI-NH PS relies on report by the caregiver, evidence of standardized administration of the NPI-NH is important to assure appropriate interpretation of scores (e.g., Is there evidence that the caregiver spent enough hours per day with the patient to provide reliable observations?). In summary, the NPI-NH presents with limited evidence of content validity, as well as concerns regarding instrument administration; however, the most substantive issue is the limitation noted above on the interpretability of within-patient observed change.

- *Secondary Endpoints*
  - ADCS-CGIC rating on Day 43. Per the Applicant, the ADCS-CGIC scale was used to determine the subject's overall clinical condition as it relates to their psychosis and neuropsychiatric symptoms and to address the clinical significance of changes from baseline in other measures. After completion of the interview, the rater is asked to rate the subject's functioning relative to the baseline interview, using a standardized seven-point scale (1 = marked improvement to 7 = marked worsening).

  - Change from Baseline to Day 43 on the following:

    - NPI-NH Agitation/Aggression (Domain C).

    - NPI-NH Sleep and Nighttime Behavior Disorders (Domain K).

    - CMAI-SF total score. The CMAI-SF is a 14-item instrument assessing frequency of manifestations of agitation in the elderly based on directly observable behaviors including physically and verbally aggressive behaviors within the previous 2 weeks, with each item rated on a 1 (never) to 5 (a few times an hour or continuous for half an hour or more) scale. The CMAI-SF was to be completed at baseline and subsequent visits by a qualified rater with input solicited directly from staff carepersons. The score range is 14 to 70 points, with higher scores indicating more frequent agitation symptoms.

    - CMAI-SF Aggressive Behavior Subdomain score

    - CMAI-SF Physically Nonaggressive Behavior Subdomain score

    - CMAI-SF Verbally Agitated Behavior Subdomain score

- *Exploratory Endpoints*
  Exploratory endpoints relevant to the Applicant's resubmission included analysis of the primary and secondary endpoints at time points other than Day 43 (including the NPI-NH PS durability of response from Day 43 to Day 85), the change from Baseline to Day 43 on the NPI-NH PS by subgroups (including by baseline NPI-NH PS score <12 versus ≥12 and baseline MMSE <6 versus ≥6), and the Alzheimer's Disease Cooperative Study – Activities of Daily Living (ADCS-ADL) Instrument total score.

Statistical Considerations

The planned sample size was 212 subjects (106 per treatment group, 170 evaluable subjects with a dropout rate of 20%). Overall, 181 subjects were randomized to double-blind treatment (placebo, n=91; pimavanserin 40 mg, n=90). The Full Analysis Set (FAS) was defined as all randomized subjects treated with at least one dose of study drug and had both a Baseline and at least one post-Baseline NPI-NH PS. Subjects were classified according to their randomized treatment assignment. The FAS comprised 178 subjects (91 subjects, placebo; 87 subjects, pimavanserin 40 mg). Three subjects in the randomized analysis set were excluded from the FAS because they did not have a post-baseline NPI-NH PS. The FAS was used for the analysis of all efficacy endpoints.

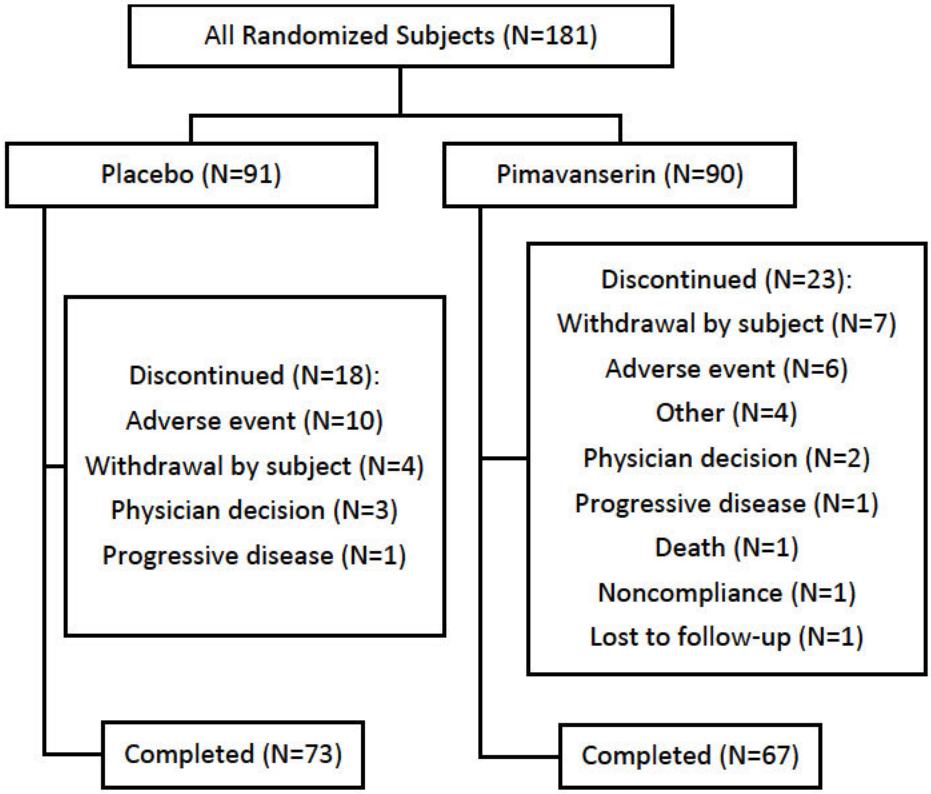
For the primary endpoint, the analysis was performed using the mixed-effect model repeated measures (MMRM) method in the FAS population. The model included the fixed effects of Baseline MMSE category (<6 and ≥6; 2 levels), Baseline NPI-NH PS (as a continuous covariate), treatment (placebo or pimavanserin 40 mg; two levels), visit (Days 15, 29, 43, 64, and 85; five levels), and treatment-by-visit interaction. An unstructured covariance matrix was used to model the variance-covariance matrix of the within-subject repeated measures (i.e., model within-subject errors). The Kenward-Roger approximation was used to estimate denominator degrees of freedom. The statistical analysis plan did not specify multiplicity adjustment for the secondary endpoints.

3.1.1.2 Study 019 Results

Disposition

See Figure 1 for a CONSORT diagram. Of the 181 subjects randomized to the DB period (91 to the placebo arm and 90 to the pimavanserin arm), 73 subjects (80.2%) in the placebo arm and 67 subjects (74.4%) in the pimavanserin arm completed 12 weeks of DB treatment. A total of 70 subjects in the placebo arm and 69 subjects in the pimavanserin arm had Day 85 NPI-NH PS scores. The most common cause for early termination for the total group was adverse events (10 subjects (11%) on placebo versus six subjects (6.7%) on pimavanserin), followed by withdrawal by subject (four subjects (4.4%) on placebo versus seven subjects (7.8%) on pimavanserin). A total of eight deaths were reported in the study (four in each arm); the term “death” was listed as the reason for early termination for one subject in the pimavanserin arm.

Figure 1. Study 019 CONSORT Diagram (All Randomized Subjects)



Source: Clinical reviewer-created from Study 019 Clinical Study Report, Figure 10-1, p. 68.

Demographics and Baseline Characteristics

Treatment arms were well-balanced by sex, age, race, and ethnicity (Table 1). Approximately 80% of subjects were female across both arms. The mean age of subjects was approximately 86 years across both arms. Race included 97.8% White subjects in the placebo arm and 93.3% White subjects in the pimavanserin arm. No subjects identified their ethnicity as Hispanic or Latino.

Table 1. Study 019 Demographic and Baseline Characteristics (All Randomized Subjects)

Demographic and Baseline Disease Parameters	Placebo (N=91) n (%)	Pimavanserin (N=90) n (%)
Sex		
Female	73 (80.2%)	73 (81.1%)
Male	18 (19.8%)	17 (18.9%)
Age (years)		
Mean (SD)	86.1 (6.0)	85.7 (7.1)
Range	64, 99	68, 99
Race		
White	89 (97.8%)	84 (93.3%)
Asian	0	3 (3.3%)
Black or African American	1 (1.1%)	3 (3.3%)
Other	1 (1.1%)	0
Ethnicity		
Not Hispanic or Latino	91 (100.0%)	90 (100.0%)
Hispanic or Latino	0	0
Duration of Alzheimer's disease [1] (months)		
Mean (SD)	55.5 (26.9)	68.0 (44.0)
Median	56.6	57.9
Range	9.0, 128.5	8.4, 232.9
Duration of ADP[2] (months)		
Mean (SD)	22.7 (19.1)	25.6 (27.0)
Range	1.7, 76.9	1.7, 182.0
NPI-NH psychosis score		
Mean (SD)	10.0 (5.6)	9.5 (4.8)
Range	4, 24	4, 24
NPI-NH total score		
Mean (SD)	32.9 (19.4)	33.5 (17.6)
Range	4, 99	4, 83
MMSE[3]		
Mean (SD)	9.8 (5.0)	10.2 (5.4)
Range	1, 22	1, 21
CMAI-SF total score[3]		
Mean (SD)	28.9 (8.9)	28.2 (8.6)
Range	14, 54	14, 50

Source: Clinical reviewer-adapted from Study 019 Clinical Study Report Table 11-1 and 11-2

Abbreviations: ADP = Alzheimer's disease psychosis, CMAI-SF = Cohen-Mansfield Agitation Inventory-Short Form, MMSE = Mini-Mental State Examination, NPI-NH = Neuropsychiatric Inventory-Nursing Home version

[1] N = 89 for placebo, N = 88 for pimavanserin

[2] N = 78 for placebo, N = 72 for pimavanserin

[3] N = 85 for placebo, N = 87 for pimavanserin

[4] N = 90 for placebo and pimavanserin each

Although the treatment arms were well-balanced by sex, age, race, and ethnicity, the study population was not representative of the U.S. population in terms of racial or ethnic characteristics, being almost entirely White and entirely non-Hispanic or Latino. It is unclear how these differences between the U.S.

population and the study population may affect the generalizability of the study results. Of particular note, multiple analyses have found a higher risk of dementia in Black and Hispanic/Latino populations than in White populations.[18,19] The study population was also majority female, which may reflect the predominance of AD in women[20] given longer life expectancy.

The treatment arms were also generally well-balanced with respect to duration of ADP and baseline NPI-NH total scores, NPI-NH PS, MMSE, and CMAI-SF total scores (Table 1). Subjects in the pimavanserin arm had a somewhat longer mean duration of AD (68 months versus 55.5 months for placebo) and standard deviation (44 months versus 26.9 months), although the medians were similar (approximately 57 months). Subjects in the pimavanserin arm had a longer maximum duration of AD (maximum 232.9 months versus 128.5 months for placebo).

Efficacy Results—Primary Endpoint

A statistically significant treatment effect for pimavanserin versus placebo was observed on Day 43 for the NPI-NH PS; the MMRM least squares mean (LSM) change from Baseline was -3.76 for the pimavanserin group versus -1.93 for the placebo group for a treatment difference of -1.84 (95% CI: -3.64, -0.04; p=0.0451; Table 2).

Table 2. Study 019 Primary Endpoint Results (Observed Cases, MMRM) Full Analysis Set

	Placebo (N=91)	Pimavanserin (N=87)
Mean NPI-NH PS score at Baseline (SD)	10.00 (5.584)	9.52 (4.839)
Mean NPI-NH PS score at Day 43 (SD)	7.88 (6.187)	6.14 (5.445)
LSM[1] Change from Baseline (SE)	-1.93 (0.634)	-3.76 (0.653)
Placebo-subtracted difference[2] (95% CI)[3]		-1.84 (-3.64, -0.04)
P-value[4]		0.0451

Source: Study 019 Clinical Study Report, Table 11-5, p. 84, confirmed by statistical reviewer Dr. Yang
Abbreviations: LSM = least squares mean, MMRM = mixed-effect model repeated measures, NPI-NH PS = Neuropsychiatric Inventory-Nursing Home Version Psychosis Score
[1] LSM from MMRM with fixed effects of baseline MMSE category (<6 and ≥6), planned treatment, study visit, treatment-by-visit interaction, and baseline NPI-NH psychosis score. An unstructured covariance matrix is used to model the within-subject errors. The denominator degrees of freedom are estimated by the Kenward-Roger approximation. LSMs are estimated using the observed margins.
[2] Difference between LSM changes for pimavanserin and placebo (pimavanserin-placebo) at the specified visit from MMRM analysis.
[3] 95% CI = 95% confidence interval without adjusting for multiple looks.
[4] 2-sided p-value for treatment difference at specified visit from MMRM analysis.

Various sensitivity analyses to explore the impact of missing outcomes yielded similar results to the primary analysis (Appendix 6.4.1). Although pimavanserin achieved statistical significance at the primary endpoint, the clinical significance of a -1.84 placebo-subtracted difference on the NPI-NH PS is unclear.

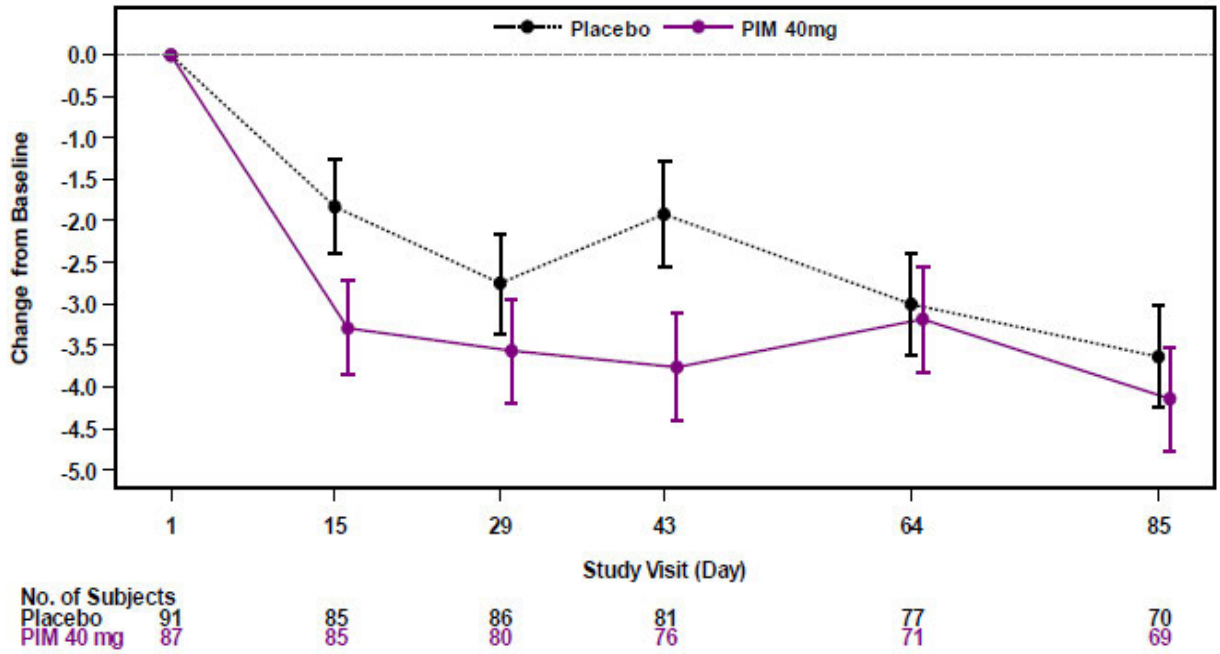
Efficacy Results—Secondary and Relevant Exploratory Endpoints

For the secondary and relevant exploratory endpoints, none of the between-group comparisons met nominal significance, and demonstrated no notable numerical separation (including the ADCS-CGIC,

CMAI-SF total score (Table 14), or the ADCS-ADL total score). Pimavanserin did not separate from placebo on the NPI-NH PS at Day 64 or Day 85 (Figure 2).

Figure 2 displays the LSM change from baseline in the primary efficacy measure over the 12-week treatment period. Separation between treatment groups was largest on the primary visit, Day 43, but this appears to be driven by the worsening in the placebo group at that visit.

Figure 2. Study 019 NPI-NH Psychosis Score Change from Baseline by Visit (LS Means ± SE; Observed Cases, MMRM), Full Analysis Set



Source: Study 019 Clinical Study Report, Figure 1.1, p. 85.
Abbreviations: LS = least squares, MMRM = mixed-effect model repeated measures, NPI-NH = Neuropsychiatric Inventory-Nursing Home Version

As noted above, although there was a statistically significant result on the primary efficacy endpoint, the clinical meaningfulness of the treatment difference is unclear. The lack of support from the secondary efficacy endpoints and the exploratory analyses that do not show discernable differences at D64 or D85 raise the question of whether the treatment difference at D43 is a chance finding (e.g., sudden one-time worsening in the placebo group) and/or about the durability of the effect.

3.1.2 Resubmission

In the resubmission, the Applicant responded to the design and conduct concerns outlined in the Agency's CR letter regarding Study 019. At this time, the Agency has determined that the study was designed with features that could allow it to be considered an adequate and well-controlled trial suitable for regulatory decision making. However, questions remain related to whether the methods of assessment of subjects' response are well defined and reliable (see discussion of NPI-NH PS, above). Because of COVID-19 pandemic-related limitations on the Office of Scientific Investigation's (OSI's) ability to conduct on-site Good Clinical Practice inspections (particularly outside the United States), the Agency waived inspections of the site during the original sNDA submission. Instead, OSI conducted an

inspection of the Applicant. Based on the findings from the Applicant inspection, OSI had concerns about the reliability of Study 019 data because of the number of protocol deviations (Table 3). These violations principally involved subjects who did not have clear documentation that psychotic symptoms developed after AD diagnosis had been established or subjects who received exclusionary medications at the time of randomization. The Applicant has noted that the proportion of subjects with issues related to documentation of diagnosis or who received exclusionary medications was balanced between the treatment groups. The Applicant acknowledged that there were difficulties establishing the date of AD diagnosis for some subjects but pointed out that other eligibility criteria excluded subjects with psychosis caused by other underlying physical or psychiatric conditions (e.g., delirium, substance use, schizophrenia).

Table 3. Study 019 Major Protocol Deviations (Randomized Analysis Set)

Major Protocol Deviation	Placebo (N=91) n (%)	Pimavanserin (N=90) n (%)
Study procedures	60 (65.9%)	51 (56.7%)
Eligibility	39 (42.9%)	44 (48.9%)
Exclusionary medication use or change at time of randomization or within randomization window	20 (22.0%)	25 (27.8%)
Unable to confirm ADP onset after AD diagnosis	19 (20.1%)	20 (22.2%)
Informed consent	46 (50.5%)	39 (43.3%)
Investigational product compliance	8 (8.8%)	9 (10.0%)
Visit schedule	4 (4.4%)	8 (8.9%)
Concomitant medication	1 (1.1%)	4 (4.4%)
Serious adverse event reporting	1 (1.1%)	0
Other	1 (1.1%)	0

Source: Clinical reviewer-adapted from Study 019 ADDV dataset
Note: Subjects may have had multiple protocol deviations within each category and are counted once within each. Subjects with eligibility deviations in both listed subcategories appear in both subcategories.
Abbreviations: AD = Alzheimer's disease, ADP = Alzheimer's disease psychosis

The Applicant repeated the primary analysis on the pre-specified per-protocol analysis set[1] to assess the impact of protocol deviations (Table 4). The results were in favor of pimavanserin with a p-value 0.0064 and a treatment effect estimate of -3.31 as compared with the primary analysis result (p-value = 0.045 and treatment effect estimate of -1.84). Based on this analysis and on the nature and the balanced distribution of the deviations, the Agency anticipates that we will be able to rely upon the data from Study 019 for regulatory decision making. Regardless, the full analysis set should be used to assess treatment effect rather than the per-protocol set, given that exclusion of such a large number of randomized subjects from the analysis could lead to selection bias and exaggeration of treatment effect and the results of this subgroup may not be generalizable to the intended population.

The statistical reviewer repeated the primary analysis on the non-per-protocol analysis set (those who were randomized but were not in the per-protocol analysis set); the results showed a treatment effect estimate of -0.65 (nominal p-value 0.6474).

[1] The per-protocol analysis set was defined by the Applicant, based on blinded review of the protocol deviations, prior to unblinding the study for the final analysis. Subjects were to be excluded from the PP Analysis Set if they had a protocol deviation related to eligibility criteria. Subjects were also to be excluded if they had a protocol deviation that was judged to potentially impact the primary efficacy analysis.

Table 4. Study 019 Primary Endpoint Results (Observed Cases, MMRM) – Per-Protocol vs. Non-Per-Protocol Analysis Set

	Per-Protocol Analysis Set*		Non-Per-Protocol Analysis Set**	
	Placebo (N=50)	**Pimavanserin (N=45)**	**Placebo (N=41)**	**Pimavanserin (N=45)**
Mean NPI-NH PS score at Baseline (SD)	9.70 (6.02)	10.31 (5.5)	10.37 (5.05)	8.73 (3.91)
Mean NPI-NH PS score at Day 43 (SD)	7.85 (6.41)	4.82 (4.57)	7.91 (5.98)	7.47 (5.96)
LSM[1] Change from Baseline (SE)	-2.27 (0.79)	-5.57 (0.87)	-1.42 (1.01)	-2.07 (0.98)
Placebo-subtracted difference[2] (95% CI)[3]		-3.31 (-5.66, -0.96)		-0.65 (-2.17, 3.46)
P-value[4]		0.0064		0.6476

Source: Results for Per-Protocol analysis set are from Study 019 Clinical Study Report, Table 11-6, p. 87 and Study 019 Clinical Study Report- Addendum, Table 5-2, p. 14, confirmed by statistical reviewer Dr. Yang. Results for non-Per-Protocol analysis set are from statistical reviewer Dr. Yang.
Abbreviations: LSM = least squares mean, MMRM = mixed-effect model repeated measures, NPI-NH PS = Neuropsychiatric Inventory-Nursing Home Version Psychosis Score
* Subjects who had a protocol deviation related to eligibility criteria or a protocol deviation that was judged to potentially impact the primary efficcay analysis were excluded from the per-protoocl analysis set. This set included one subject randomized to pimavanserin who had no post-baseline score, so was excluded from the full analysis set.
** Non-Per-Protocol Analysis Set includes all randomized subjects excluded from the per-protocol analysis set. This set included 2 subjects randomized to pimavanserin who had no post-baseline scores, so were excluded from the full analysis set.
[1] LSM from MMRM with fixed effects of baseline MMSE category (<6 and ≥6), planned treatment, study visit, treatment-by-visit interaction, and baseline NPI-NH psychosis score. An unstructured covariance matrix is used to model the within-subject errors. The denominator degrees of freedom are estimated by the Kenward-Roger approximation. LSMs are estimated using the observed margins.
[2] Difference between LSM changes for pimavanserin and placebo (pimavanserin-placebo) at the specified visit from MMRM analysis.
[3] 95% CI = 95% confidence interval without adjusting for multiple looks.
[4] 2-sided p-value for treatment difference at specified visit from MMRM analysis.

3.2 Study ACP-103-045

3.2.1 Overview of Design and Results

3.2.1.1 Study 045 Design

Study 045 was a phase 3, double-blind, placebo-controlled, multicenter, randomized withdrawal study in subjects ages ≥50 to ≤90 years-old who met criteria for all-cause dementia with psychosis and clinical criteria for a dementia subtype. During a 3- to 35-day screening period, as in Study 019, caregivers were instructed to provide brief psychosocial therapy to the subject with a target of five times per week (minimum three times per week); per the Applicant, the intention of the brief psychosocial therapy was to assure that only subjects requiring pharmacologic therapy were randomized into the study. The study consisted of two periods (Figure 3):

- Open-label (OL) period: Eligible subjects received pimavanserin 34 mg once daily for 12 weeks. Subjects were to continue at that dose for the first week; after that, the dose could be decreased to 20 mg for tolerability (and returned to 34 mg for efficacy) at any scheduled or

unscheduled visit until Week 4, at which point the dose was to remain stable through the rest of the OL period and the double-blind (DB) period.

- DB period: Subjects who met both of the following response criteria at Weeks 8 and 12 and who remained otherwise eligible were permitted to enter the DB randomized withdrawal period of the study (if not, they were withdrawn and entered the safety follow-up period):

    - Subject experienced a ≥ 30% reduction (improvement) from Week 0 (OL Baseline) on the Scale for the Assessment of Positive Symptoms–Hallucinations and Delusions subscales (SAPS-H+D) total score, AND

    - Subject had a Clinical Global Impression–Improvement (CGI-I) score of 1 (very much improved) or 2 (much improved), relative to Week 0 (OL baseline)

Eligible subjects were randomized 1:1 at the DB Baseline visit (OL Week 12/DB Week 0) to continue their current pimavanserin dose or switch to placebo for up to 26 weeks. Randomization was stratified by designated dementia subtype and geographical region. Subjects were assessed for relapse of psychosis weekly for the first 2 weeks after randomization (Weeks 13 and 14 (DB Weeks 1 and 2)), every 2 weeks until Week 26 (DB Week 14), and then every 4 weeks through to Week 38 (DB Week 26), as well as at unscheduled visits and other unscheduled contacts. See the Appendix for the Applicant's detailed schedule of assessments.

The protocol-defined relapse criteria for psychosis were designed to identify subjects with an impending or actual relapse of psychosis:

- Subject experienced a ≥30% increase (worsening) from OL Week 12 (DB baseline) on the SAPS-H+D total score and had a CGI-I score of 6 (much worse) or 7 (very much worse), relative to the DB baseline. For subjects with an OL Week 12 (DB baseline) SAPS-H+D total score of "0," any increase in the SAPS-H+D total score at any visit after OL Week 12 was considered to satisfy the criteria for a ≥30% increase (worsening).

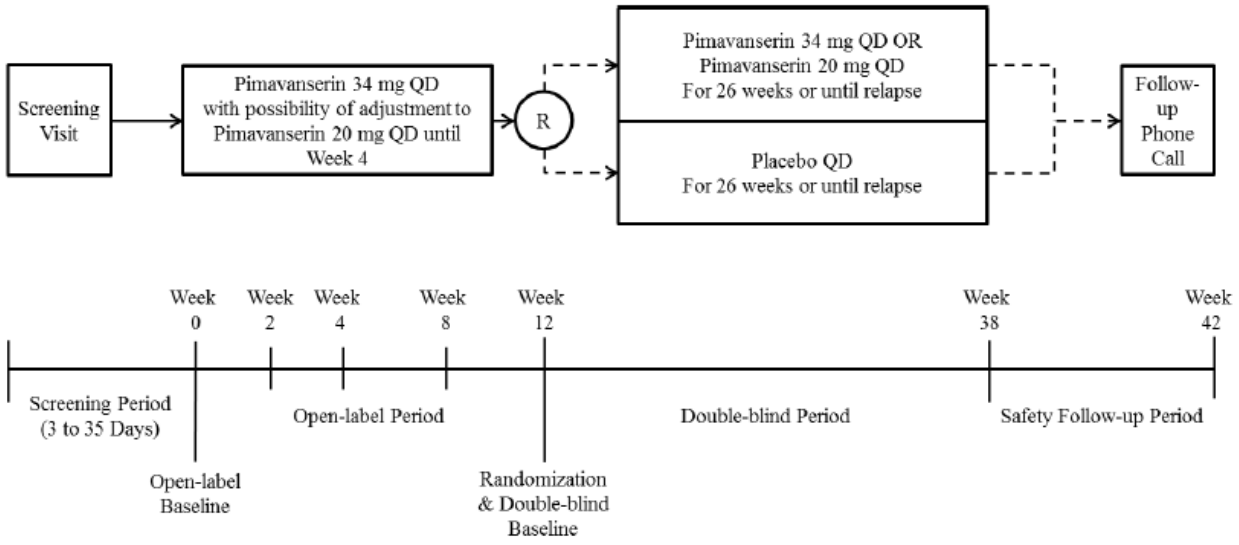
- Subject was treated with an antipsychotic (other than study drug) for dementia-related delusions or hallucinations.

- Subject stopped study drug or withdrew from the study for lack of efficacy (as reported by the subject or study partner/caregiver), or the Investigator discontinued the study drug due to lack of efficacy.

- Subject was hospitalized for worsening psychosis.

Any subject who met one or more of the protocol-defined relapse criteria after randomization was withdrawn from study drug and entered the safety follow-up period of the study. The Independent Adjudication Committee (IAC) reviewed all termination cases that occurred before the study discontinuation date to determine if protocol-defined relapse criteria were met.

Figure 3. Study ACP-103-045 Design Schematic



Source: Study ACP-103-045 Clinical Study Report, Figure 9-1, p. 49
Abbreviations: QD = once daily, R = randomization

Endpoints

- *Primary Endpoint*
  The primary endpoint was time from randomization to relapse in the DB period.

- *Secondary Endpoint*
  The secondary endpoint was time from randomization to discontinuation from the DB period for any reason.

- *Exploratory Endpoints*
  Exploratory endpoints relevant to the Applicant's resubmission included the SAPS-H+D total score and separate Hallucinations and Delusions domain scores. The SAPS was designed to measure hallucinations, delusions, abnormalities in language and behavior, and disordered thought processes. This study used the 20 items from the Hallucinations and Delusions subscales, which include global ratings of severity of both hallucinations (H7) and delusions (D13). Each item is rated on a six-point scale, from 0 (none) to 5 (severe), for a maximum score of 100 (with higher scores denoting more severe symptoms). See the Appendix for a copy of the SAPS-H+D.

Statistical Considerations

The sample size calculation was based on the following assumptions: a placebo relapse event rate of 60% over 26 weeks; a pimavanserin relapse event rate of 35% over 26 weeks (hazard ratio = 0.47); a dropout rate of 25% over 26 weeks; an overall two-sided alpha level of 0.05; use of a one-sided (0.025) O'Brien-Fleming stopping boundary to adjust for a single interim analysis that was to be performed when one half of the total planned number of post-randomization relapse events had occurred; and a power of 90%. The total number of post-randomization relapse events required at the final analysis was

75 and the calculated sample size was 89 in each of the two treatment groups (giving a total estimate of 178 subjects).

An interim analysis evaluating efficacy based on the primary efficacy endpoint was conducted by an independent statistical group when at least 38 adjudicated relapse events had been accrued. The O'Brien-Fleming stopping boundary was calculated based on the actual number of relapse events accrued at the interim analysis. The decision to stop or continue the study was made based on this recalculated boundary. For the planned interim analysis, if the observed one-sided p-value from the Cox regression analysis was less than the corresponding lower stopping boundary p-value, then the null hypothesis would be rejected with the conclusion that the study demonstrates superiority of pimavanserin compared to placebo. Conversely, if the observed one-sided p-value was greater than or equal to the lower stopping boundary p-value, the null hypothesis would not be rejected.

Because the study was stopped at the interim analysis, the primary efficacy analysis was based on the interim analysis dataset. The treatment effect was measured by the hazard ratio (HR). The pimavanserin group included all subjects taking pimavanserin irrespective of the dose (20 or 34 mg). The time from randomization to relapse in the DB period was compared between treatment groups using a Cox regression model, with covariates for treatment group, designated dementia subtype (three subtypes: AD or frontotemporal dementia-spectrum disorders, vascular dementia, and PDD or dementia with Lewy bodies), and region (four levels: North America, Western Europe, Eastern Europe, and Latin America).

The key secondary endpoint was time from randomization to discontinuation from the double-blind period for any reason (other than termination of the study by the Applicant). The key secondary efficacy endpoint was analyzed using the same Cox regression model described for the primary efficacy endpoint. Testing of the key secondary endpoint was to be conducted at most once either at the interim analysis or the final analysis provided that the primary endpoint reaches statistical significance. The one-sided p-value scale boundary for the key secondary efficacy endpoint at the interim analysis was given by the same type I error spent at the interim analysis for the primary efficacy endpoint.

3.2.1.2 Study 045 Results

Disposition

Of the 392 subjects enrolled in the OL period, 41 were ongoing in the OL period at the time of study discontinuation (following interim analysis) and 351 subjects (229 with AD, 59 with PDD, and 63 with other dementia subtypes) completed or discontinued from the OL period. The most common reason for early termination during the OL period was lack of response (70/351 subjects (19.9%)). Other common reasons contributing to early termination were AEs (27/351 subjects (7.7%)) and withdrawn consent (17/351 subjects (4.8%)).

Among those 351 subjects who completed or discontinued from the OL period, a total of 217 subjects (61.8%) met sustained response criteria (at Weeks 8 and 12) and were randomized to the DB period (Table 5). Among those randomized, 137 subjects had AD and 42 subjects had PDD.

Within each dementia subtype, 60% (137/229) of the subjects with AD who completed or discontinued from the OL period met the response criteria and were randomized, and 71% (42/59) of the subjects with PDD who completed the OL period met the response criteria and were randomized.

Table 5. Study 045 Response Rate in Open Label Phase at Week 12 (ITT Analysis Set)

	Sustained Response* % (n/N)	Complete Response+ % (n/N)
Overall	61.8 (217/351)	20.8 (73/351)
Alzheimer's disease	59.8 (137/229)	19.2 (44/229)
Parkinson's disease dementia	71.2 (42/59)	27.1 (16/59)
Other	60.3 (38/63)	20.6 (13/63)

Source: Study 045 Clinical Study Report - Addendum Table 6-1.

Abbreviations: ITT = Intent-To-Treat

*Sustained response is defined as ≥30% SAPS-H+D improvement and CGI-I very much or much improved at both Weeks 8 and 12. includes subjects in the OL phase who were randomized into the DB phase. Note that 2 subjects achieved sustained response but terminated from study before randomization.

+Complete response is defined as 100% Symptom Reduction in SAPS-H+D and CGI-I=1 or 2

Excluded 41 subjects who were ongoing in the open label period at the time of study discontinuation.

Demographics and Baseline Characteristics

In the OL period and both DB treatment arms, subjects included roughly 60% females and 40% males; mean age was roughly 74 years; race was almost entirely white; and ethnicity was roughly 76% not Hispanic or Latino. Generally, dementia subtype distribution was similar between OL and DB periods and DB treatment arms, with roughly two-thirds of subjects diagnosed with AD in the OL period, and slightly less upon moving to DB. DB Baseline mean MMSE scores were generally similar between the DB treatment arms (approximately 18). Mean SAPS-H+D scores improved from OL baseline (24.4), with similar DB baselines in both DB arms (5.0 for pimavanserin and 5.2 for placebo).

Efficacy Results—Primary Endpoint

The primary efficacy endpoint was time from randomization to relapse in the DB period. In accordance with the statistical analysis plan (SAP), an interim analysis (IA) was conducted by an Independent Statistical Group after 40 adjudicated relapse events had accrued. The prespecified stopping criterion was met at the IA (one-sided p-value less than the O'Brien-Fleming stopping boundary), and the independent Data Safety Monitoring Board recommended stopping the study for efficacy. The primary analysis result is summarized in Table 6.

Table 6. Study 045 Primary Analysis of Time from Randomization to Relapse in the Double-Blind Period Determined by the IAC – Interim Analysis (ITT Analysis Set)

	Placebo (n=99)	Pimavanserin (n=95)
Number of subjects having a relapse event, n (%)	28 (28.3)	12 (12.6)
Number of subjects censored, n (%)	71 (71.7)	83 (87.4)
Hazard Ratio[1] (pimavanserin/placebo) (95% CI)[2]		0.353 (0.172, 0.727)
One-sided p-value (vs placebo)		0.0023
O'Brien-Fleming stopping boundary (one-sided p-value scale)		0.0033

Source: Applicant's Analysis, Study 045 Clinical Study Report, Table 11-10, p. 125, confirmed by statistical reviewer Dr. Yang.

Abbreviations: IAC = independent adjudication committee, ITT = intent-to-treat

[1] The Cox regression model included effects for treatment group, designated dementia subtype, and region.

[2] 95% CI = 95% confidence interval without adjusting for multiple looks

Based on these results, Study 045 did meet its primary endpoint. However, exploratory subgroup analyses were also conducted to assess consistency across subgroups with respect to the primary analysis results. Only the treatment effect in the combined "PDD or dementia with Lewy body" subgroup or the PDD subgroup appears to separate from placebo – the confidence intervals excluded a hazard ratio of 1 (Table 7).

Table 7. Study 045 Subgroup Analysis: Analysis of Time from Randomization to Relapse Determined by the IAC by Subgroup (ITT Analysis Set)

	Subjects with a Relapse Event		Cox Regression Analysis[1]
Subgroup	**Placebo n/N (%)**	**Pimavanserin n/N (%)**	**Hazard Ratio (Pimavanserin/Placebo) (95% CI)[2]**
Designated dementia subtype			
AD or FTD-spectrum disorders	14/64 (21.9)	9/62 (14.5)	0.690 (0.295, 1.611)
PDD or DLB	12/23 (52.2)	1/21 (4.8)	0.034 (0.010, 0.116)
VaD	2/12 (16.7)	2/12 (16.7)	1.065 (0.159, 7.122)
Dementia subtype			
AD	14/62 (22.6)	8/61 (13.1)	0.618 (0.257, 1.487)
DLB	2/3 (66.7)	0/6	--
FTD-spectrum disorders	0/2	1/1 (100.0)	--
PDD	10/20 (50.0)	1/15 (6.7)	0.054 (0.017, 0.175)
VaD	2/12 (16.7)	2/12 (16.7)	1.065 (0.159, 7.122)

Source: Adapted from Applicant's analysis, Study 045 Clinical Study Report, Table 11–13, p. 130, confirmed by Statistical Reviewer Dr. Yang.

Abbreviations: AD = Alzheimer's disease, DLB = dementia with Lewy bodies, FTD = frontotemporal dementia, IAC = independent adjudication committee, ITT = intent-to-treat, PDD = Parkinson's disease dementia, VaD = vascular dementia

[1] The Cox regression model included effects for treatment group, designated dementia subtype, and region.

[2] 95% CI = 95% confidence interval without adjusting for multiple looks

The Statistical reviewer performed an additional analysis of the primary endpoint with exclusion of the PDD subset (Table 8).

Table 8. Study 045 Additional Subgroup Analysis: Analysis of Time from Randomization to Relapse Determined by the IAC, with PDD Subset Exclusion (ITT Analysis Set)

Analysis Type	Placebo n/N (%)	Pimavanserin n/N (%)	Cox Regression Analysis[1]		
			Hazard Ratio (Pimavanserin/ Placebo)	95% CI[2]	One-Sided P-Value
Primary: determined by the IAC interim analysis	28/99 (28.3)	12/95 (12.6)	0.353	0.172, 0.727	0.0023
Excluding subjects with PDD	18/79 (22.8)	11/80 (13.8)	0.600	0.281, 1.281	0.0935
Excluding subjects with PDD or DLB	16/76 (21.1)	11/74 (14.9)	0.719	0.333, 1.554	0.2008

Source: Statistical reviewer Dr. Yang's results.
Abbreviations: DLB = dementia with Lewy bodies, IAC = independent adjudication committee, ITT = intent-to-treat, PDD = Parkinson's disease dementia
[1] The Cox regression model included effects for treatment group, designated dementia subtype, and region.
[2] 95% CI = 95% confidence interval without adjusting for multiple looks
Note: The one-sided p-values from the interim analysis were compared with the O'Brien-Fleming stopping boundary 0.0033.

The key secondary efficacy endpoint was the time from randomization to discontinuation in the DB period for any reason (other than termination of the study by the Applicant). Pimavanserin statistically significantly reduced the risk of all-cause discontinuation compared with placebo based on the prespecified hierarchical algorithm to control overall type I error, tested at the one-sided 0.0033 significance level (HR=0.452, 95% CI: 0.261, 0.785; one-sided p=0.0024). Similar to the primary endpoint results, overall significance appears driven primarily by results in the PDD subgroup (HR=0.251, 95% CI: 0.086, 0.733), with a relatively wide confidence interval that includes 1 in the AD subgroup (HR=0.658, 95% CI: 0.326, 1.329).

The apparent differential effects of pimavanserin in the PDD subgroup relative to the other dementia subgroups was the primary reason for the complete response action in the first review cycle and the reason that a broad "dementia-related" psychosis indication is no longer being considered.

3.2.2 Resubmission Analyses

The Applicant asserts that there was consistency of response across dementia subtypes and that the PDD subgroup's smaller HR is an outlier caused by use of dopaminergic therapy to manage motor symptoms of Parkinson's disease, which can cause or worsen psychotic symptoms. According to the Applicant's hypothesis, withdrawal of pimavanserin and randomization to placebo during the DB may have contributed to a more rapid rate of relapse in subjects with PDD compared to subgroups who were not taking dopaminergic drugs. In the resubmission, the Applicant has provided several exploratory analyses to investigate these hypotheses. The Applicant has explored the interaction of treatment by dementia subgroup, examined the potential confounding effect of dopaminergic therapy in the PDD subgroup, conducted re-analyses of primary and exploratory efficacy endpoints in the AD subgroup, and performed simulations to evaluate the potential impact on the final analysis if the effect in the PDD subgroup were attenuated. The Applicant also believes that higher pimavanserin exposures are associated with greater efficacy and has compared efficacy results in subjects treated with pimavanserin

34 mg compared to those treated with 20 mg and has conducted an analysis of the relationship between plasma pimavanserin concentration and the primary efficacy endpoint.

3.2.2.1 *Post-hoc Analyses by Dementia Subtype*

Subgroup analysis by dementia subtype suggests differential results, including a particularly remarkable difference in placebo response across subgroups (Appendix 6.5.2). According to the Applicant's hypothesis, withdrawal of pimavanserin and randomization to placebo during the DB may have contributed to the more rapid rate of relapse in subjects with PDD compared to other subgroups who were not taking dopaminergic drugs. This is a reasonable hypothesis given that dopaminergic drugs may worsen psychotic symptoms. However, dopaminergic medication use was almost completely confounded with the dementia subtype because most subjects taking dopaminergic medication were in the PDD subgroup. Hence, it is not possible to statistically adjust for the dopaminergic medication effect for PDD subjects receiving placebo. Furthermore, it is unclear whether the effect of dopaminergic medication on the risk of relapse is the only explanation for possible difference in treatment effect between the AD and the PDD subgroups.

3.2.2.2 *Post-hoc Reanalysis of AD Subgroup Treatment Response*

The Applicant re-analyzed primary endpoint data in the AD subgroup by including a set of covariates, selected post hoc, in the analysis model. This led to a smaller hazard ratio estimate (0.475 compared to 0.618 from the pre-specified primary analysis model) and a smaller two-sided p-value (0.10 compared to 0.28 from the pre-specified primary analysis model). However, the choice of covariates for adjustment should be pre-specified and results of post-hoc, potentially data-driven analyses such as this are very challenging to interpret. Specifically, in the applicant's analysis, the OL baseline SAPS-H+D score was used as a covariate for the baseline severity of psychosis. However, there is no reason to use the OL baseline score instead of the DB baseline score when testing the treatment effect on relapse in the DB period. Additionally, the applicant's analysis excluded the stratified region variable pre-specified in the primary model without providing any reason. The reviewer conducted an analysis adjusting for the same covariates that the applicants selected, except that the OL baseline SAPS-H+D score was replaced with DB baseline score, with the addition of the stratified region covariate that was pre-specified. Regardless of which model is selected, the HR results are not statistically significant (Table 9; Appendix 6.5.3).

Table 9. Time from Randomization to Relapse in the Double-Blind Period—AD ITT Analysis Set

	HR	95% CI	p-value
Pre-specified Primary Cox Model	0.618	(0.257, 1.487)	0.28
Applicant's Refined Cox Model	0.475	(0.194, 1.162)	0.10
Reviewer's Refined Cox Model	0.638	(0.268, 1.516)	0.31

Source: Study 045 Clinical Study Report - Addendum Figure 7-9; Statistical reviewer Dr. Ling.
Abbreviations: AD = Alzheimer's disease, AIC = Akaike information criterion, CI = confidence interval, HR = hazard ratio, ITT = intent-to-treat

3.2.2.3 *Post-hoc Analysis of Exploratory Endpoint of SAPS-H+D Score*

The Applicant performed post-hoc analyses for exploratory endpoints. The most relevant exploratory endpoint for this study was the change from DB Baseline in SAPS-H+D score in the AD subgroup. The Applicant's post-hoc analyses of this exploratory endpoint were based on ranking the scores. Depending on the rank ordering, these post hoc analyses for SAPS-H+D could yield a nominally statistically significant treatment effect (p = 0.04). These analyses assigned the same best rank or the second-best

rank to over half of the subjects whose SAPS-H+D scores never worsened during the DB period. However, for these subjects, there were differences in terms of how much the SAPS-H+D score changed. The statistical reviewer conducted an exploratory analysis based on ranking on subjects' maximum changes of SAPS-H+D scores during the DB period. This approach assigned worse ranks to subjects who ever relapsed based on their time to relapse and better ranks to those who never relapsed based on their maximum change of SAPS-H+D score. This analysis (arguably more reasonable) yielded a nominal p-value of 0.14. Regardless, none of these analyses took the multiplicity issue into consideration. Results of the exploratory endpoint of SAPS-H+D score did not provide much additional support for efficacy (Table 10, Appendix 6.5.4).

Table 10. Analysis of SAPS-H+D - ADP ITT Analysis Set

	Placebo	Pimavanserin
Maximum change of SAPS-H+D		
n	61	60
Mean	3.9	1.8
SD	6.88	5.97
Median	2.0	0.0
Minimum, maximum	-7, 23	-10, 29
Sponsor's Van Elteren test p-value[a]		0.04
Reviewer's Van Elteren test p-value[b]		0.14

Source: Study 045 Clinical Study Report - Addendum Figure 7-4; Statistical reviewer Dr. Ling, using Van Elteren test stratified by region.

Abbreviations: ADP = Alzheimer's disease psychosis, ITT = intent-to-treat, SAPS-H+D = Scale for the Assessment of Positive Symptoms – Hallucinations and Delusions score

[a] Sponsor's Van Elteren test assigned the same best rank to subjects whose SAPS-H+D scores never worsened during the DB period and the ranks for other subjects based on their maximum change of SAPS-H+D score without considering relapse status.

[b] Reviewer's Van Elteren test assigned worse ranks to subjects who ever relapsed based on their time to relapse and better ranks to those who never relapsed based on their maximum change of SAPS-H+D score.

3.2.2.4 *Post-hoc Analyses by Post-baseline Dose*

The Applicant proposed to focus on the 34-mg daily dose level. During the OL period, eligible subjects began receiving pimavanserin 34 mg daily and dose adjustments to 20 mg daily were permitted until OL Week 4, after which the subject's dose remained fixed at either 34 or 20 mg daily. Subjects who met the response criteria at OL Weeks 8 and 12 and who remained otherwise eligible were randomly assigned 1:1 to continue their current pimavanserin dose (34 or 20 mg) or to receive matching placebo in the DB period. A total of 12 out of 194 subjects (6%) who were included in the IA ITT analysis set were on pimavanserin 20 mg. The results were numerically in favor of placebo against pimavanserin 20 mg in the AD subgroup. However, the randomization was not stratified by pimavanserin dose level and it was not pre-specified to analyze 34 mg alone. Focusing on 34 mg only after knowing the unfavorable results of the 20 mg would result in biased estimates (Appendix 6.5.5).

3.2.2.5 *Post-hoc Exposure-Response Analyses*

The Applicant also conducted an exposure-response (E-R) analysis to evaluate the relationship between pimavanserin plasma concentrations ($AUC_{0\text{-}24h}$) and time to relapse in Study 045 to provide supportive evidence for efficacy. The E-R analysis assessed whether the efficacy difference between AD and PDD subgroups was associated with $AUC_{0\text{-}24h}$ and its variability. The Applicant concluded that the risk of relapse decreased with higher $AUC_{0\text{-}24h}$. However, it should be noted that pimavanserin $AUC_{0\text{-}24}$ was

similar between AD and PDD subgroups. The risk of relapse decreased by 53% in AD versus 83% in PDD subgroup. These findings are consistent with the primary statistical analysis findings for AD and PDD subgroups. The analysis does not provide additional insights into efficacy difference between AD and PDD subgroups (Appendix 6.5.6).

3.2.2.6 *Overall Summary/Conclusion from Resubmission Analyses*

In summary, AD was the largest subgroup with only 22 relapse events observed at the interim analysis. The efficacy results of the AD subgroup showed a HR of 0.618 (nominal p=0.28) with a wide confidence interval (0.257, 1.487). The Agency would like the AC to consider whether these exploratory analyses inform our understanding of the treatment effect in the AD population.

4 Safety Summary

The Agency does not have a key safety issue to bring before the Advisory Committee. The findings from the sNDA development program were generally consistent with the known safety profile of pimavanserin. The most common adverse reactions (≥2% and twice the rate of placebo) include peripheral edema and confusional state. Approved labeling includes a warning about the risk of QT interval prolongation; use with drugs that also increase the QT interval and in patients with risk factors for prolonged QT interval should be avoided. A boxed warning advises of an increased risk of death for elderly patients with dementia-related psychosis treated with antipsychotic drugs.

5 References

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6 Appendix

6.1 Applicant's Assessment Schedules

Table 11. Study ACP-103-019 Applicant's Schedule of Assessments

Visit	Screening Visit 1 (SV1)	Screening Visit 2 (SV2)	Screening Visit 3 (SV3)	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7
	Screening (Day -21 - Day 1)			Day 1	Day 15 (±3 days)	Day 29 (±3 days)	Day 43 (±3 days)	Day 64 (±5 days)	Day 85 (±5 days)	Day 115 (±5 days)
Evaluation				Baseline[1]					or Early Term	Follow-up Visit[2]
Visit Type	On-site	Telephone	Telephone	On-site	On-site	On-site	On-site	On-site	On-site	Telephone
Informed Consent[3]	X[3]									
BPST	X[4]	X[4]	X[4]							
Demography	X									
Medical History	X									
AD History	X									
Inclusion/Exclusion	X			X						
Height and Weight				X					X[5]	
ECG[6]	X			X	X	X	X	X	X	
Vital Signs	X			X	X	X	X	X	X	
Physical Exam[7]	X			X	X	X	X	X	X	
Clinical Labs	X			X		X			X	
Pregnancy Test[8]	X			X					X	
MMSE	X			X	X	X	X	X	X	
UPDRS Part III				X	X	X	X	X	X	
NPI-NH[9]	X			X	X	X	X	X	X	
CMAI-SF				X	X	X	X	X	X	
ADCS-CGIC				X	X	X	X	X	X	
ADCS-ADL				X	X	X	X	X	X	
Adverse Events[10]	X	X	X	X	X	X	X	X	X	X
Prior/Con Meds	X			X	X	X	X	X	X	X
Randomization				X						
Investigational drug administration[11]				X	X	X	X	X		

Source: Source: Study ACP-103-019 Protocol, Table 1 (continued next page)

1. All assessments are to be performed PRIOR to investigational drug administration.
2. If participation of a patient in the study is terminated early then the follow-up telephone assessment visit will be performed 4 weeks after the last day of investigational drug administration.
3. It is not required to obtain informed consent within the 21 day screening period. However, informed consent must be completed prior to conduct of screening procedures.
4. Brief psycho-social therapy (BPST) will be administered during the 3-week screening period. Caregivers will be trained at the Screening Visit and will receive follow-up telephone contact at Week 2 and Week 3 of the screening period PRIOR to Baseline. Randomization prior to completion of the 3 week BPST screening period may occur for those patients who otherwise meet all eligibility requirements and whose psychotic symptoms worsen during the screening period at the discretion of the investigator upon consultation with the Medical Monitor.
5. Weight only.
6. 12-lead ECG required at Visits Day 1, Day 15, and Day 85; for other visits a 'rhythm strip' may be used unless 12-lead ECG is clinically indicated.
7. A full physical examination will be performed at Screening and on Day 1, and Day 85 (or early termination). The physical examination performed on Day 15, Day 29, Day 43, and Day 64 will be an abbreviated physical examination.
8. Serum pregnancy testing will be conducted in women of childbearing potential at Screening, Day 85 (or early termination). A dipstick urine pregnancy test will be conducted in these same patients at Baseline (Day 1).
9. NPI-NH full assessment will be completed at Screening, Baseline, Day 15, Day 29, Day 43, Day 64, and Day 85.
10. Adverse event collection begins upon signing of informed consent and should be assessed at each visit following Screening Visit 1.
11. The first dose of Investigational drug is to be taken within 24 hours of completion of all Baseline assessments (Day 1). Investigational drug is to be taken daily thereafter.

Source: Source: Study ACP-103-019 Protocol, Table 1 (including footnotes)

Table 12. Study ACP-103-045 Open-Label Period, Applicant's Schedule of Assessments

	Screening	Open-label Period				
Visit week	-4 to 0	0	2	4	8	12[a]
Allowable visit window (# days)			±3	±3	±3	+3
Visit Number	1	2	3	4	5	6
Informed consent	X					
Inclusion/exclusion criteria assessment	X	X				
Medical history and demographics	X					
Mini-Mental State Examination	X	X	X	X	X	X
MRI or CT[b]	X					
Psychosocial therapy training	X					
Physical and neurological examinations	X	X				X
Vital signs and weight	X	X	X	X	X	X
Height	X					
12-lead electrocardiogram[c]	X	X	X			X
Clinical laboratory tests	X	X				X
Pregnancy test[d]	X	X				X
SAPS-H+D	X	X	X	X	X	X
Clinical Global Impression-Improvement[e]			X	X	X	X
Clinical Global Impression-Severity	X	X	X	X	X	X
Zarit Burden Interview[f]		X				X
Karolinska Sleepiness Scale		X				X
EQ-5D-5L		X				X
Assessment for response criteria					X	X
Assessment for concomitant medications	X	X	X	X	X	X
Global Clinician Assessment of Suicidality	X	X	X	X	X	X
Extrapyramidal Symptom Rating Scale		X				X
Assessment for adverse events	X	X	X	X	X	X
Pharmacokinetic sample collection[g]		X			X	X
Pharmacogenomic sample collection[h]		X				
Drug dispensation		X	X	X	X	X[i]
Drug return and accountability			X	X	X	X
Randomization						X

Abbreviations: CT=computed tomography; MRI=magnetic resonance imaging; SAPS-H+D=Scale for the Assessment of Positive Symptoms, Hallucinations and Delusions subscales

Source: Study ACP-103-045 Protocol, Table S-1 (continued next page)

Note: Subjects who withdraw early, including those that do not meet relapse criteria at Visit 5 (Week 8) should complete Visit 17/ET assessments [as described here in Table 13]

[a] Visit 6 (Week 12) will serve as both the final visit of the open-label period and the Baseline visit of the double-blind period (Table S–2).

[b] A non-contrast brain MRI or non-contrast head CT will be completed if the subject has not had a CT or MRI scan completed (a) within the past 3 years AND (b) during or subsequent to the onset of dementia.

[c] The ECG will be completed in triplicate at Visit 1 (Screening). A single ECG will be completed at all other visits.

[d] A pregnancy test (serum at Visit 1 and urine at all other visits) is only required for women of child-bearing potential.

[e] The CGI-I should be scored relative to Visit 2, the subject's open-label Baseline.

[f] The ZBI should only be administered to study partners/caregivers who are family members.

[g] Pharmacokinetic samples will also be collected, if possible, at any ET visit (Table S-2) or the visit immediately following any SAE or following an AE leading to discontinuation.

[h] A separate informed consent (or assent, if applicable) must be given for the pharmacogenomic component of the study. This consent may be obtained at any time during the study. If informed consent is given in time for sample collection at Visit 2, a pre-dose sample should be collected at Visit 2. If informed consent for pharmacogenomics is not given in time for sample collection at Visit 2, a sample may be collected any time after informed consent for pharmacogenomics is given.

[i] Blinded study drug will be dispensed after randomization at Visit 6 (Week 12).

Source: Study ACP-103-045 Protocol, Table S-1 (including footnotes)

Table 13. Study ACP-103-045 Double-Blind Period, Applicant's Schedule of Assessments

Visit week	13	14	16	18	20	22	24	26	30	34	38/EOT	42
Allowable visit window (# days)	±3	±3	±3	±3	±3	±3	±3	±3	±7	±7	+7	+3
Visit Number	7	8	9	10	11	12	13	14	15	16	17/ET	18
Visit Type (Clinic [C] or Telephone [T])	C	C	C	C	T	C	T	C	C	C	C	T
Mini-Mental State Examination	X	X	X	X		X		X	X	X	X	
Physical and neurological examinations						X					X	
Vital signs and weight	X	X	X	X		X		X	X	X	X	
12-lead electrocardiogram				X				X			X	
Clinical laboratory tests				X				X			X	
Pregnancy test[a]								X			X	
SAPS-H+D	X	X	X	X		X		X	X	X	X	
Clinical Global Impression-Improvement[b]	X	X	X	X		X		X	X	X	X	
Clinical Global Impression-Severity	X	X	X	X		X		X	X	X	X	
Zarit Burden Interview[c]				X				X			X	
Karolinska Sleepiness Scale				X				X			X	
EQ-5D-5L				X				X			X	
Assessment for protocol-defined relapse criteria	X	X	X	X	X	X	X	X	X	X	X	
Assessment for concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X
Global Clinician Assessment of Suicidality	X	X	X	X	X	X	X	X	X	X	X	
Extrapyramidal Symptom Rating Scale	X	X	X	X		X		X	X	X	X	
Assessment for adverse events	X	X	X	X	X	X	X	X	X	X	X	X
Pharmacokinetic sample collection[d]	X					X					X	
Drug dispensation		X	X	X		X		X	X	X		
Drug return and accountability	X[e]	X	X	X		X		X	X	X	X	

Source: Study ACP-103-045 Protocol, Table S-2 (continued next page)

Abbreviations: EOT=end-of-treatment; ET=early termination; SAPS-H+D=Scale for the Assessment of Positive Symptoms, Hallucinations and Delusions subscales

For additional details on study procedures, see Section 6.

[a] A urine pregnancy test is only required for women of child-bearing potential.

[b] CGI-I should be scored relative to Visit 12, the subject's double-blind Baseline.

[c] The ZBI should only be administered to study partners/caregivers who are family members.

[d] Pharmacokinetic samples will also be collected, if possible, at the visit immediately following any SAE or following an AE leading to discontinuation.

[e] Only drug accountability will be completed at this visit.

Source: Study ACP-103-045 Protocol, Table S-2 (including footnotes)

6.2 Neuropsychiatric Inventory-Nursing Home Version Psychosis Score

A. DELUSIONS **(NA)**

Does the resident have beliefs that you know are not true? For example, saying that people are trying to harm him/her or steal from him/her. Has he/she said that family members or staff are not who they say they are or that his/her spouse is having an affair? Has the resident had any other unusual beliefs?

☐ Yes (If yes, please proceed to subquestions)
☐ No (if no, please proceed to next screening question) ☐ N/A

1. Does the resident believe that he/her is in danger – that others are planning to hurt him/her or have been hurting him/her?	☐ Yes	☐ No
2. Does the resident believe that others are stealing from him/her?	☐ Yes	☐ No
3. Does the resident believe that his/her spouse is having an affair?	☐ Yes	☐ No
4. Does the resident believe that his/her family, staff members or others are not who they say they are?	☐ Yes	☐ No
5. Does the resident believe that television or magazine figures are actually present in the room? (Does he/she try to talk or interact with them?)	☐ Yes	☐ No
6. Does he/she believe any other unusual things that I haven't asked about?	☐ Yes	☐ No

Comments: _____

_____

If the screening question is confirmed, determine the frequency and severity of the delusions.

Frequency:

☐ 1. Rarely – less than once per week
☐ 2. Sometimes – about once per week
☐ 3. Often – several times per week but less than every day
☐ 4. Very often – once or more per day

Severity:

☐ 1. Mild – delusions present but seem harmless and does not upset the resident that much.
☐ 2. Moderate – delusions are stressful and upsetting to the resident and cause unusual or strange behavior.
☐ 3. Severe – delusions are very stressful and upsetting to the resident and cause a major amount of unusual or strange behavior.

Occupational Disruptiveness: How much does this behavior upset you and/or create more work for you?

☐ 0. Not at all
☐ 1. Minimally (almost no change in work routine)
☐ 2. Mildly (some change in work routine but little time rebudgeting required)
☐ 3. Moderately (disrupts work routine, requires time rebudgeting)
☐ 4. Severely (disruptive, upsetting to staff and other residents, major time infringement)
☐ 5. Very Severely or Extremely (very disruptive, major source of distress for staff and other residents, requires time usually devoted to other residents or activities)

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Source: Study ACP-103-019 Protocol, Appendix 3 (continued next page)

B. HALLUCINAIONS **(NA)**

Does the resident have hallucinations – meaning, does he/she see, hear, or experience things that are not present? (If "Yes," ask for an example to determine if in fact it is a hallucination). Does the resident talk to people who are not there?

☐ Yes (if yes, please proceed to subquestions)
☐ No (if no, please proceed to next screening question) ☐ N/A

1. Does the resident act as if he/she hears voices or describe hearing voices?	☐ Yes	☐ No
2. Does the resident talk to people who are not there?	☐ Yes	☐ No
3. Does the resident see things that are not present or act like he/she sees things that are not present (people, animals, lights, etc)?	☐ Yes	☐ No
4. Does the resident smell things that others cannot smell?	☐ Yes	☐ No
5. Does the resident describe feeling things on his/her skin or act like he/she is feeling things crawling or touching him/her?	☐ Yes	☐ No
6. Does the resident say or act like he/she tastes things that are not present?	☐ Yes	☐ No
7. Does the resident describe any other unusual sensory experiences?	☐ Yes	☐ No

Comments: _____

_____

If the screening question is confirmed, determine the frequency and severity of the hallucinations.

Frequency:

☐ 1. Rarely – less than once per week
☐ 2. Sometimes – about once per week
☐ 3. Often – several times per week but less than every day
☐ 4. Very often – once or more per day

Severity:

☐ 1. Mild – hallucinations are present but seem harmless and does not upset the resident that much.
☐ 2. Moderate – hallucinations are stressful and upsetting to the resident and cause unusual or strange behavior.
☐ 3. Severe – hallucinations are very stressful and upsetting to the resident and cause a major amount of unusual or strange behavior. (PRN medications may be required to control them).

Occupational Disruptiveness: How much does this behavior upset you and/or create more work for you?

☐ 0. Not at all
☐ 1. Minimally (almost no change in work routine)
☐ 2. Mildly (some change in work routine but little time rebudgeting required)
☐ 3. Moderately (disrupts work routine, requires time rebudgeting)
☐ 4. Severely (disruptive, upsetting to staff and other residents, major time infringement)
☐ 5. Very Severely or Extremely (very disruptive, major source of distress for staff and other residents, requires time usually devoted to other residents or activities)

9

Source: Study ACP-103-019 Protocol, Appendix 3

6.3 Scale for the Assessment of Positive Symptoms Hallucinations+Delusions Score

Scale for the Assessment of Positive Symptoms (SAPS)

Introduction

Investigators using this instrument will need to use a standard clinical interview in order to evaluate the subject's symptoms. In addition to using a clinical interview, the investigator should also draw on other sources of information, such as direct observation, reports from the subject's family, reports from nurses, and reports from the subject himself. In general, the subject can usually be considered a relatively reliable informant concerning delusions and hallucinations if he is able to communicate clearly and will comply with a clinical interview.

Hallucinations

Hallucinations represent an abnormality in perception. They may be false perceptions occurring in the absence of some identifiable external stimulus. They may be experienced in any of the sensory modalities, including hearing, touch, taste, smell, and vision. True hallucinations should be distinguished from illusions (which involve a misperception of an external stimulus), hypnogogic and hypnopompic experiences (which occur when the subject is falling asleep or waking up), or normal thought processes that are exceptionally vivid. If the hallucinations have a religious quality, then they should be judged within the context of what is normal for the subject's social and cultural background. Hallucinations occurring under the immediate influence of alcohol, drugs, or serious physical illness should not be rated as present. The subject should always be requested to describe the hallucination in detail.

1. Auditory Hallucinations

The subject has reported voices, noises, or sounds. The commonest auditory hallucinations involve hearing voices speaking to the subject or calling him names. The voices may be male or female, familiar or unfamiliar, and critical or complimentary. Typically, subjects suffering from schizophrenia experience the voices as unpleasant and negative. Hallucinations involving sounds rather than voices, such as noises or music, should be considered less characteristic and less severe.

"Have you ever heard voices or other sounds when no one is around?"

"What did they say?"

Check One			
0	☐	None	
1	☐	Questionable	
2	☐	Mild	Subject hears noises or single words; they occur only occasionally
3	☐	Moderate	Clear evidence of voices; they have occurred at least weekly
4	☐	Marked	Clear evidence of voices which occur almost every day
5	☐	Severe	Voices occur often every day.

Source: Study ACP-103-006 Protocol, Appendix 7 (continued next page)

2. Voices Commenting

Voices commenting are a particular type of auditory hallucination which phenomenologists as Kurt Schneider consider to be pathognomonic of schizophrenia, although some recent evidence contradicts this. These hallucinations involve hearing a voice that makes a running commentary on the subject's behavior or thought as it occurs. If this is the only type of auditory hallucination that the subject hears, it should be scored instead of auditory hallucinations (No. 1 above). Usually, however, voices commenting will occur in addition to other types of auditory hallucinations.

"Have you ever heard voices commenting on what you are thinking or doing?"
"What do they say?"

Check One			
0	☐	None	
1	☐	Questionable	
2	☐	Mild	Subject hears noises or single words; they occur only occasionally
3	☐	Moderate	Clear evidence of voices; they have occurred at least weekly
4	☐	Marked	Clear evidence of voices which occur almost every day
5	☐	Severe	Voices occur often every day.

3. Voices Conversing

Like voices commenting, voices conversing are considered a Schneiderian first-rank symptom. They involve hearing two or more voices talking with one another, usually discussing something about the subject. As in the case of voices commenting, they should be scored independently of other auditory hallucinations.

"Have you heard two or more voices talking with each other?"

"What did they say?"

Check One			
0	☐	None	
1	☐	Questionable	
2	☐	Mild	Subject hears noises or single words; they occur only occasionally
3	☐	Moderate	Clear evidence of voices; they have occurred at least weekly
4	☐	Marked	Clear evidence of voices which occur almost every day
5	☐	Severe	Voices occur often every day.

Source: Study ACP-103-006 Protocol, Appendix 7 (continued next page)

4. Somatic or Tactile Hallucinations

These hallucinations involve experiencing peculiar physical sensations in the body. They include burning sensations, tingling, and perceptions that the body has changed in shape or size.

"Have you ever had burning sensations or other strange feelings in your body?"

"What were they?"

"Did your body ever appear to change in shape or size?"

Check One			
0	☐	None	
1	☐	Questionable	
2	☐	Mild	Subject experiences peculiar physical sensations; they occur only occasionally
3	☐	Moderate	Clear evidence of somatic or tactile hallucinations; they have occurred at least weekly
4	☐	Marked	Clear evidence of somatic or tactile hallucinations which occur almost every day
5	☐	Severe	Hallucinations occur often every day.

5. Olfactory Hallucinations

The subject experiences unusual smells which are typically quite unpleasant. Sometimes the subject may believe that he himself smells. This belief should be scored here if the subject can actually smell the odor himself, but should be scored among delusions if he only believes that others can smell the odor.

"Have you ever experienced any unusual smells or smells that others did not notice?"

"What were they?"

Check One			
0	☐	None	
1	☐	Questionable	
2	☐	Mild	Subject experiences unusual smells; they occur only occasionally
3	☐	Moderate	Clear evidence of olfactory hallucinations; they have occurred at least weekly
4	☐	Marked	Clear evidence of olfactory hallucinations which occur almost every day
5	☐	Severe	Olfactory hallucinations occur often every day.

Source: Study ACP-103-006 Protocol, Appendix 7 (continued next page)

6. Visual Hallucinations

The subject sees shapes or people that are not actually present. Sometimes these are shapes or colors, but most typically they are figures of people or human-like objects. They may also be characters of a religious nature, such as the devil or Christ. As always, visual hallucinations involving religious themes should be judged within the context of the subject's cultural background. Hypnogogic and hypnopompic visual hallucinations (which are relatively common) should be excluded, as should visual hallucinations occurring when the subject has been taking hallucinogenic drugs.

"Have you had visions or seen things that other people cannot?"

"What did you see?"

"Did this occur when you were falling asleep or waking up?"

Check One			
0	☐	None	
1	☐	Questionable	
2	☐	Mild	Subject experiences visual hallucinations; they occur only occasionally
3	☐	Moderate	Clear evidence of visual hallucinations; they have occurred at least weekly
4	☐	Marked	Clear evidence of visual hallucinations which occur almost every day
5	☐	Severe	Hallucinations occur often every day.

7. Global Rating of Severity of Hallucinations

This global rating should be based on the duration and severity of hallucinations, the extent of the subject's preoccupation with the hallucinations, his degree of conviction, and their effect on his actions. Also consider the extent to which the hallucinations might be considered bizarre or unusual. Hallucinations not mentioned above, such as those involving taste, should be included in this rating.

Check One			
0	☐	None	
1	☐	Questionable	
2	☐	Mild	Hallucinations definitely present, but occur infrequently; at times the subject may question their existence
3	☐	Moderate	Hallucinations are vivid and occur occasionally; they may bother him to some extent
4	☐	Marked	Hallucinations are quite vivid, occur frequently, and pervade his life
5	☐	Severe	Hallucinations occur almost daily and are sometimes unusual or bizarre; they are very vivid and extremely troubling

Source: Study ACP-103-006 Protocol, Appendix 7 (continued next page)

DELUSIONS

Delusions

Delusions represent an abnormality in content of thought. They are false beliefs that cannot be explained on the basis of the subject's cultural background. Although delusions are sometimes defined as "fixed false beliefs," in their mildest form delusions may persist only for weeks to months, and the subject may question his beliefs or doubt them. The subject's behavior may or may not be influenced by his delusions. The rating of severity of individual delusions and of the global severity of delusional thinking should take into account their persistence, their complexity, the extent to which the subject acts on them, the extent to which the subject doubts them, and the extent to which the beliefs deviate from those that normal people might have. For each positive rating, specific examples should be noted in the margin.

1. Persecutory Delusions

People suffering from persecutory delusions believe that they are being conspired against or persecuted in some way. Common manifestations include the belief that one is being followed, that one's mail is being opened, that one's room or office is bugged, that the telephone is tapped, or that police, government officials, neighbors, or fellow workers are harassing the subject. Persecutory delusions are sometimes relatively isolated or fragmented, but sometimes the subject has a complex set of delusions involving both a wide range of forms of persecution and a belief that there is a well-designed conspiracy behind them. For example, a subject may believe that his house is bugged and that he is being followed because the government wrongly considers him a secret agent for a foreign government; this delusion may be so complex that it explains almost everything that happens to him. The ratings of severity should be based on duration and complexity.

"Have people been bothering you in any way?"

"Have you felt that people are against you?"

"Has anyone been trying to harm you in any way?"

"Has anyone been watching or monitoring you?"

Check One			
0	☐	None	
1	☐	Questionable	
2	☐	Mild	Delusional beliefs are simple and may be of several different types; subject may question them occasionally
3	☐	Moderate	Clear, consistent delusion that is firmly held
4	☐	Marked	Consistent, firmly-held delusion that the subject acts on
5	☐	Severe	Complex well-formed delusion that the subject acts on and that preoccupies him a great deal of the time; some aspects of the delusion or his reaction may seem quite bizarre

Source: Study ACP-103-006 Protocol, Appendix 7 (continued next page)

2. Delusions of Jealousy

The subject believes that his/her mate is having an affair with someone. Miscellaneous bits of information are construed as "evidence." The person usually goes to great effort to prove the existence of the affair, searching for hair in the bedclothes, the odor of shaving lotion or smoke on clothing, or receipts or checks indicating a gift has been bought for the lover. Elaborate plans are often made in order to trap the two together.

"Have you ever worried that your husband (wife) might be unfaithful to you?"

"What evidence do you have?"

Check One			
0	☐	None	
1	☐	Questionable	
2	☐	Mild	Delusion clearly present, but the subject may question it occasionally
3	☐	Moderate	Clear consistent delusion that is firmly held
4	☐	Marked	Consistent, firmly-held delusion that the subject acts on
5	☐	Severe	Complex, well-formed delusion that the subject acts on and that preoccupies him a great deal of the time; some aspects of the delusion or his reaction may seem quite bizarre

3. Delusions of Sin or Guilt

The subject believes that he has committed some terrible sin or done something unforgivable. Sometimes the subject is excessively or inappropriately preoccupied with things he did wrong as a child, such as masturbating. Sometimes the subject feels responsible for causing some disastrous event, such as a fire or accident, with which he in fact has no connection. Sometimes these delusions may have a religious flavor, involving the belief that the sin is unpardonable and that the subject will suffer eternal punishment from God. Sometimes the subject simply believes that he deserves punishment by society. The subject may spend a good deal of time confessing these sins to whomever will listen.

"Have you ever felt that you have done some terrible thing that you deserve to be punished for?"

Check One			
0	☐	None	
1	☐	Questionable	
2	☐	Mild	Delusional beliefs may be simple and may be of several different types; subject may question them occasionally
3	☐	Moderate	Clear, consistent delusion that is firmly held
4	☐	Marked	Consistent, firmly-held delusion that the subject acts on
5	☐	Severe	Complex, well-formed delusion that the subject acts on and that preoccupies him a great deal of the time; some aspects of the delusion or his reaction may seem quite bizarre

Source: Study ACP-103-006 Protocol, Appendix 7 (continued next page)

4. Grandiose Delusions

The subject believes that he has special powers or abilities. He may think he is actually some famous personage, such as a rock star, Napoleon, or Christ. He may believe he is writing some definitive book, composing a great piece of music, or developing some wonderful new invention. The subject is often suspicious that someone is trying to steal his ideas, and he may become quite irritable if his ideas are doubted.

"Do you have any special or unusual abilities or talents?"

"Do you feel you are going to achieve great things?"

Check One			
0	☐	None	
1	☐	Questionable	
2	☐	Mild	Delusional beliefs may be simple and may be of several different types; subject may question them occasionally
3	☐	Moderate	Clear, consistent delusion that is firmly held
4	☐	Marked	Consistent, firmly-held delusion that the subject acts on
5	☐	Severe	Complex, well-formed delusion that the subject acts on and that preoccupies him a great deal of the time; some aspects of the delusion or his reaction may seem quite bizarre

5. Religious Delusions

The subject is preoccupied with false beliefs of a religious nature. Sometimes these exist within the context of a conventional religious system, such as beliefs about the Second Coming, the Antichrist, or possession by the Devil. At other times, they may involve an entirely new religious system or a pastiche of beliefs from a variety of religions, particularly Eastern religions, such as ideas about reincarnation or Nirvana. Religious delusions may be combined with grandiose delusions (if the subject considers himself a religious leader), delusions of guilt, or delusions of being controlled. Religious delusions must be outside the range considered normal for the subject's cultural and religious background.

"Are you a religious person?"
"Have you had any unusual religious experiences?"
"What was your religious training as a child?"

Check One			
0	☐	None	
1	☐	Questionable	
2	☐	Mild	Delusional beliefs may be simple and may be of several different types; subject may question them occasionally
3	☐	Moderate	Clear, consistent delusion that is firmly held
4	☐	Marked	Consistent, firmly-held delusion that the subject acts on
5	☐	Severe	Complex, well-formed delusion that the subject acts on and that preoccupies him a great deal of the time; some aspects of the delusion or his reaction may seem quite bizarre

Source: Study ACP-103-006 Protocol, Appendix 7 (continued next page)

6. Somatic Delusions

The subject believes that somehow his body is diseased, abnormal, or changed. For example, he may believe that his stomach or brain is rotting, that his hands or penis have become enlarged, or that his facial features are unusual (dysmorphobia). Sometimes somatic delusions are accompanied by tactile or other hallucinations, and when this occurs, both should be rated. (For example, the subject believes that he has ballbearings rolling around in his head, placed there by a dentist who filled his teeth, and can actually hear them clanking against one another.)

"Is there anything wrong with your body?"

"Have you noticed any change in your appearance?"

Check One			
0	☐	None	
1	☐	Questionable	
2	☐	Mild	Delusional beliefs may be simple and may be of several different types; subject may question them occasionally
3	☐	Moderate	Clear, consistent delusion that is firmly held
4	☐	Marked	Consistent, firmly-held delusion that the subject acts on
5	☐	Severe	Complex, well-formed delusion that the subject acts on and that preoccupies him a great deal of the time; some aspects of the delusion or his reaction may seem quite bizarre

7. Ideas and Delusions of Reference

The subject believes that insignificant remarks, statements, or events refer to him or have some special meaning for him. For example, the subject walks into a room, sees people laughing, and suspects that they were just talking about him and laughing at him. Sometimes items read in the paper, heard on the radio, or seen on television are considered to be special messages to the subject. In the case of ideas of reference, the subject is suspicious, but recognizes his idea is erroneous. When the subject actually believes that the statements refer to him, then this is considered a delusion of reference.

Source: Study ACP-103-006 Protocol, Appendix 7 (continued next page)

"Have you ever walked into a room and thought people were talking about you or laughing at you?"

"Have you seen things in magazines or on TV that seem to refer to you or contain a special message for you?"

"Have people communicated with you in any unusual ways?"

Check One			
0	☐	None	
1	☐	Questionable	
2	☐	Mild	Occasional ideas of reference
3	☐	Moderate	Have occurred at least weekly
4	☐	Marked	Occurs at least two to four times weekly
5	☐	Severe	Occurs frequently

8. Delusions of Being Controlled

The subject has a subjective experience that his feelings or actions are controlled by some outside force. The central requirement for this type of delusion is an actual strong subjective experience of being controlled. It does not include simple beliefs or ideas, such as that the subject is acting as an agent of God or that friends or parents are trying to coerce him to do something. Rather, the subject must describe, for example, that his body has been occupied by some alien force that is making it move in peculiar ways, or that messages are being sent to his brain by radio waves and causing him to experience particular feelings that he recognizes are not his own.

"Have you ever felt you were being controlled by some outside force?"

Check One			
0	☐	None	
1	☐	Questionable	
2	☐	Mild	Subject has experienced being controlled, but doubts it occasionally
3	☐	Moderate	Clear experience of control, which has occurred on two or three occasions in a week
4	☐	Marked	Clear experience of control, which occurs frequently; behavior may be affected
5	☐	Severe	Clear experience of control which occurs frequently, pervades the subject's life, and often affects his behavior

Source: Study ACP-103-006 Protocol, Appendix 7 (continued next page)

9. Delusions of Mind Reading

The subject believes that people can read his mind or know his thoughts. This is different than thought broadcasting (see below) in that it is a belief without a percept. That is, the subject subjectively experiences and recognizes that others know his thoughts, but he does not think that they can be heard out loud.

"Have you ever had the feeling that people could read your mind?"

Check One			
0	☐	None	
1	☐	Questionable	
2	☐	Mild	Subject has experienced mind reading, but doubts it occasionally
3	☐	Moderate	Clear experience of mind reading which has occurred on two or three occasions in a week
4	☐	Marked	Clear experience of mind reading which occurs frequently; behavior may be affected
5	☐	Severe	Clear experience of mind reading which occurs frequently, pervades the subject's life, and often affects his behavior

10. Thought Broadcasting

The subject believes that his thoughts are broadcast so that he or others can hear them. Sometimes the subject experiences his thoughts as a voice outside his head; this is an auditory hallucination as well as a delusion. Sometimes the subject feels his thoughts are being broadcast although he cannot hear them himself. Sometimes he believes that his thoughts are picked up by a microphone and broadcast on the radio or television.

"Have you ever heard your own thoughts out loud, as if they were a voice outside your head?"

"Have you ever felt your thoughts were broadcast so other people could hear them?"

Check One			
0	☐	None	
1	☐	Questionable	
2	☐	Mild	Subject has experienced thought broadcasting, but doubts it occasionally
3	☐	Moderate	Clear experience of thought broadcasting which has occurred on two or three occasions in a week
4	☐	Marked	Clear experience of thought broadcasting which occurs frequently; behavior may be affected
5	☐	Severe	Clear experience of thought broadcasting which occurs frequently, pervades the subject's life, and often affects his behavior

Source: Study ACP-103-006 Protocol, Appendix 7 (continued next page)

11. Thought Insertion

The subject believes that thoughts that are not his own have been inserted into his mind. For example, the subject may believe that a neighbor is practicing voodoo and planting alien sexual thoughts in his mind. This symptom should not be confused with experiencing unpleasant thoughts that the subject recognizes on his own, such as delusions of persecution or guilt.

"Have you ever felt that thoughts were being put into your head by some outside force?"

"Have you ever experienced thoughts that didn't seem to be your own?"

Check One			
0	☐	None	
1	☐	Questionable	
2	☐	Mild	Subject has experienced thought insertion, but doubts it occasionally
3	☐	Moderate	Clear experience of thought insertion which has occurred on two or three occasions in a week
4	☐	Marked	Clear experience of thought insertion which occurs frequently; behavior may be affected
5	☐	Severe	Thought insertion which occurs frequently, pervades the subject's life, and often affects behavior

12. Thought Withdrawal

The subject believes that thoughts have been taken away from his mind. He is able to describe the subjective experience of beginning a thought and then suddenly having it removed by some outside force. This symptom does not include the mere subjective recognition of alogia.

"Have you ever felt your thoughts were taken away by some outside force?"

Check One			
0	☐	None	
1	☐	Questionable	
2	☐	Mild	Subject has experienced thought withdrawal, but doubts it occasionally
3	☐	Moderate	Clear experience of thought withdrawal which has occurred on two or three occasions in a week
4	☐	Marked	Clear experience of thought withdrawal which occurs frequently; behavior may be affected
5	☐	Severe	Clear experience of thought withdrawal which occurs frequently, pervades the subject's life, and often affects behavior

Source: Study ACP-103-006 Protocol, Appendix 7 (continued next page)

13. Global Rating of Severity of Delusions

The global rating should be based on duration and persistence of delusions, the extent of the subject's preoccupation with the delusions, his degree of conviction, and their effect on his actions. Also consider the extent to which the delusions might be considered bizarre or unusual. Delusions not mentioned above should be included in this rating.

Check One			
0	☐	None	
1	☐	Questionable	
2	☐	Mild	Delusion definitely present but, at times, the subject questions the belief
3	☐	Moderate	The subject is convinced of the belief, but it may occur infrequently and have little effect on his behavior
4	☐	Marked	The delusion is firmly held; it occurs frequently and affects the subject's behavior
5	☐	Severe	Delusions are complex, well-formed, and pervasive; they are firmly held and have a major effect on the subject's behavior; they may be somewhat bizarre or unusual

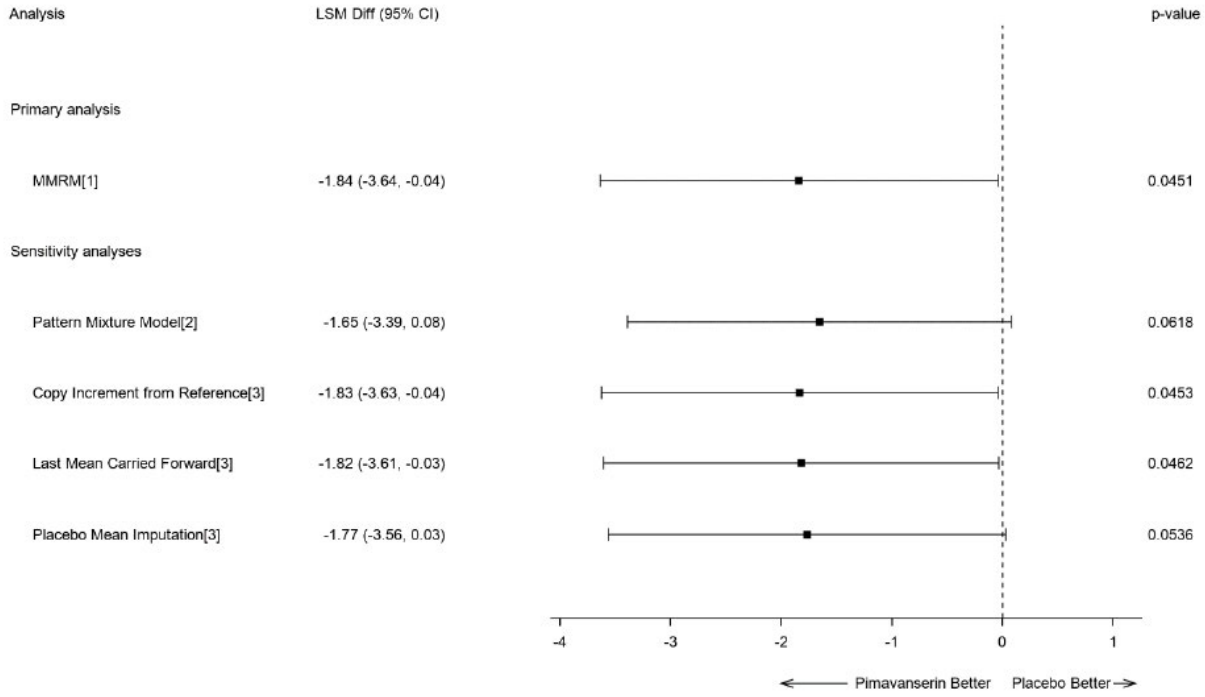
Source: Study ACP-103-006 Protocol, Appendix 7

6.4 Study 019 - Additional Analyses

6.4.1 Applicant's Sensitivity Analyses

Approximately 21% of subjects prematurely discontinued from the 12-week treatment period on the FAS set. To explore the impact of missing outcomes on the primary efficacy analysis, the Applicant conducted several sensitivity analyses using various multiple imputation methods that are a pattern mixture model analysis of covariance, copy increment from reference imputation, last mean carried forward imputation, and placebo mean imputation. All the sensitivity analyses results are consistent with the primary analysis results.

Figure 4. Primary and Sensitivity Analyses of NPI-NH Psychosis Score Change from Baseline at Week 6 (FAS)

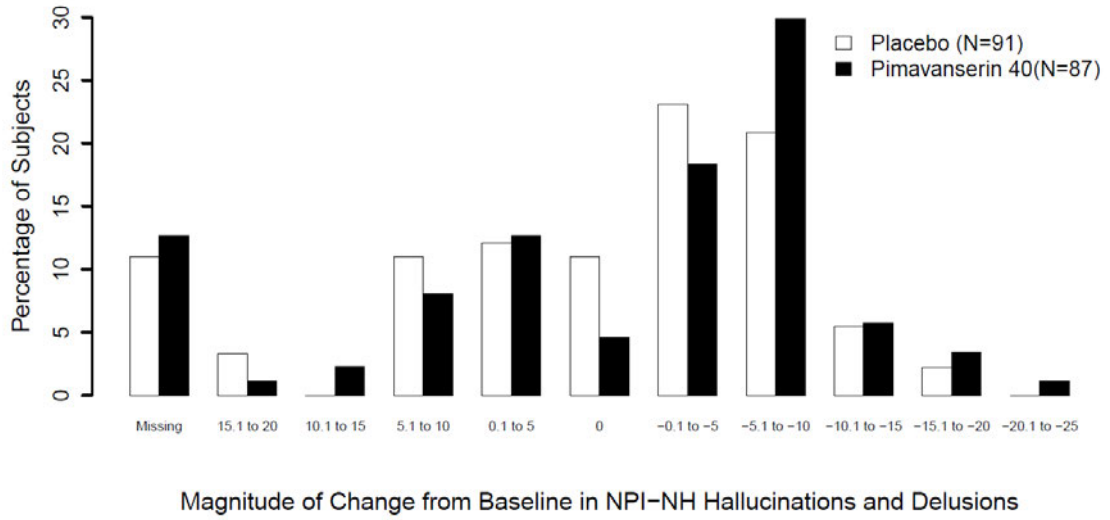


Source: Study 019 Clinical Study Report - Addendum, Figure 5-1, p. 10.
Abbreviations: CI = confidence interval, DIA = Drug Information Association, FAS = Full Analysis Set, LSM=least squares mean, MMRM = mixed-effect model repeated measures, NPI-NH = Neuropsychiatric Inventory–Nursing Home Version, SAP = statistical analysis plan
[1] Mixed-effect model for repeated measures.
[2] Multiple imputation analysis of covariance using pattern mixture model as specified in the SAP.
[3] Multiple imputation analysis of covariance using the macros developed by the DIA missing data working group.

6.4.2 Statistical Reviewer's Analysis: Histogram of Primary Efficacy Endpoint

The histogram displays the proportions of subjects who either improved or worsened on the primary score from baseline. The far left is the proportion of the subjects with missing data. Negative score represents improvement, and positive represents worsening. For subjects who had an improvement, the largest difference between the treatment groups was on the improvement interval of 5 to 10.

Figure 5. Change from Baseline to Day 43 in NPI-NH Hallucinations and Delusions – Full Analysis Set



Source: Statistical Reviewer Dr. Yang's Figure

6.4.3 Applicant's Secondary Analyses

The secondary efficacy endpoints are summarized in Table 14 below. Pimavanserin did not separate from placebo on any of secondary endpoints.

Table 14. Summary of Secondary Efficacy Endpoints – Change from Baseline to Day 43 (MMRM) – Full Analysis Set

Secondary Endpoint	Placebo (N=91)	Pimavanserin 40 mg (N=87)
ADCS-CGIC Rating on Day 43	n=82	n=77
MMRM LSM (SE)[1]	3.59 (0.135)	3.71 (0.139)
Difference in MMRM LSM (95% CI)		0.13 (-0.26, 0.51)
MMRM p-value		0.5140
Change from Baseline to Day 43:		
NPI-NH Agitation/Aggression (Domain C)	n=81	n=76
MMRM LSM (SE)[1]	-0.47 (0.401)	-1.13 (0.414)
Difference in MMRM LSM (95% CI)		-0.66 (-1.80, 0.48)
MMRM p-value		0.2544
NPI-NH Sleep and Nighttime Behavior Disorders (Domain K)	n=81	n=76
MMRM LSM (SE)[1]	-0.42 (0.309)	-0.84 (0.319)
Difference in MMRM LSM (95% CI)		-0.42 (-1.30, 0.46)
MMRM p-value		0.3442

CMAI-SF (14-item) Total Score	n=81	n=77
MMRM LSM (SE)[1]	-2.36 (0.825)	-2.07 (0.846)
Difference in MMRM LSM (95% CI)		0.30 (-2.04, 2.63)
MMRM p-value		0.8031
CMAI-SF Aggressive Behavior Subdomain Score	n=80	n=77
MMRM LSM (SE)[1]	-0.74 (0.289)	-0.45 (0.295)
Difference in MMRM LSM (95% CI)		0.30 (-0.52, 1.11)
MMRM p-value		0.114
CMAI-SF Physically Nonaggressive Behavior Subdomain Score	n=81	n=77
MMRM LSM (SE)[1]	-0.45 (0.371)	-0.27 (0.380)
Difference in MMRM LSM (95% CI)		0.18 (-0.87, 1.23)
MMRM p-value		0.7341
CMAI-SF Verbally Agitated Behavior Subdomain Score	n=81	n=77
MMRM LSM (SE)[1]	-1.18 (0.417)	-1.35 (0.428)
Difference in MMRM LSM (95% CI)		-0.17 (-1.35, 1.02)
MMRM p-value		0.7823

Source: Study 019 Clinical Study Report, Table 11-14, p. 101.

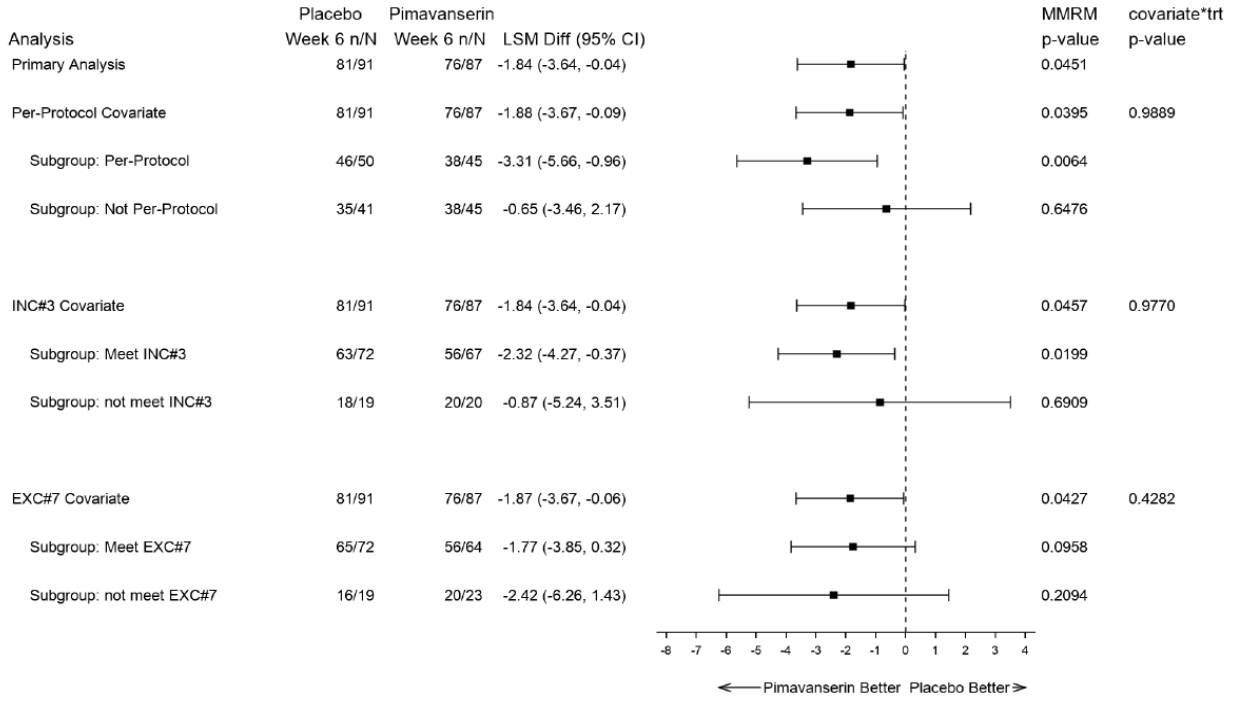
Abbreviations: ADCS-CGIC = Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change, CI = confidence interval, CMAI-SF = Cohen-Mansfield Agitation Inventory-Short Form, LSM = least squares mean, MMRM = mixed-effects model repeated measures, MMSE = Mini-Mental State Examination, NPI-NH = Neuropsychiatric Inventory-Nursing Home Version, OC = observed cases, SE=standard error

[1] LSM from MMRM with fixed categorical effects of baseline MMSE category (<6 and ≥6), baseline NPI-NH psychosis score category (<12 and ≥12), planned treatment, visit, and treatment-by-visit interaction. For all endpoints other than ADCS-CGIC the baseline value of the endpoint was included as a continuous covariate. An unstructured covariance matrix was used to model the within subject errors. The denominator degrees of freedom were estimated by the Kenward-Roger approximation. LSM was estimated using the observed margins.

6.4.4 Applicant's Resubmission Analyses

The Applicant assessed the impact of per-protocol analysis set by including the interaction of treatment with the per-protocol status (i.e., whether in the per-protocol set or not) in the primary efficacy MMRM model. They then applied the same statistical analyses to assessing the impacts of protocol deviations with respect to inclusion criterion #3 and exclusion criterion #7. As displayed in Figure 6, the p-values of the interactions in all subgroups analyses are highly non-significant; all subgroups trend in the same direction. The size of treatment effect in per-protocol analysis set appears much larger than that in non-per-protocol analyses set, but there is no evidence (p-value for the interaction = 0.99) to conclude that there was a large difference in treatment effect between per-protocol and non-per-protocol sets.

Figure 6. Exploratory Analyses Evaluating the Impact of Protocol Deviations on Primary Efficacy Endpoint – Study 019



Source: Applicant's Figure AH1.4.PP of the Study Addendum in re-submission
Abbreviations: CI = confidence interval, EXC=exclusion criteria, INC = inclusion criteria, LSM = least squares mean, MMRM = mixed-effect model repeated measures, N = number of subjects in each group, n = number of subjects meeting the criterion, trt = treatment

The Division has concerns about the interpretability of the per-protocol analysis given that almost 83 subjects (47%) in the FAS were excluded. In the per-protocol analysis set, a statistically significant treatment effect for pimavanserin 40 mg versus placebo was observed on Day 43 for the NPI-NH PS; the MMRM LSM change with a treatment difference of -3.31 (95% CI: -5.66, -0.96; p=0.0064). However, exclusion of such a large number of randomized subjects from the analysis could lead to selection bias and exaggeration of treatment effect, and the results of this subgroup may not be generalizable to the intended population, and the results of this subgroup may not be generalizable to the intended population.

6.5 Study 045–Resubmission Analyses

6.5.1 Interaction of Treatment by Dementia Subgroup

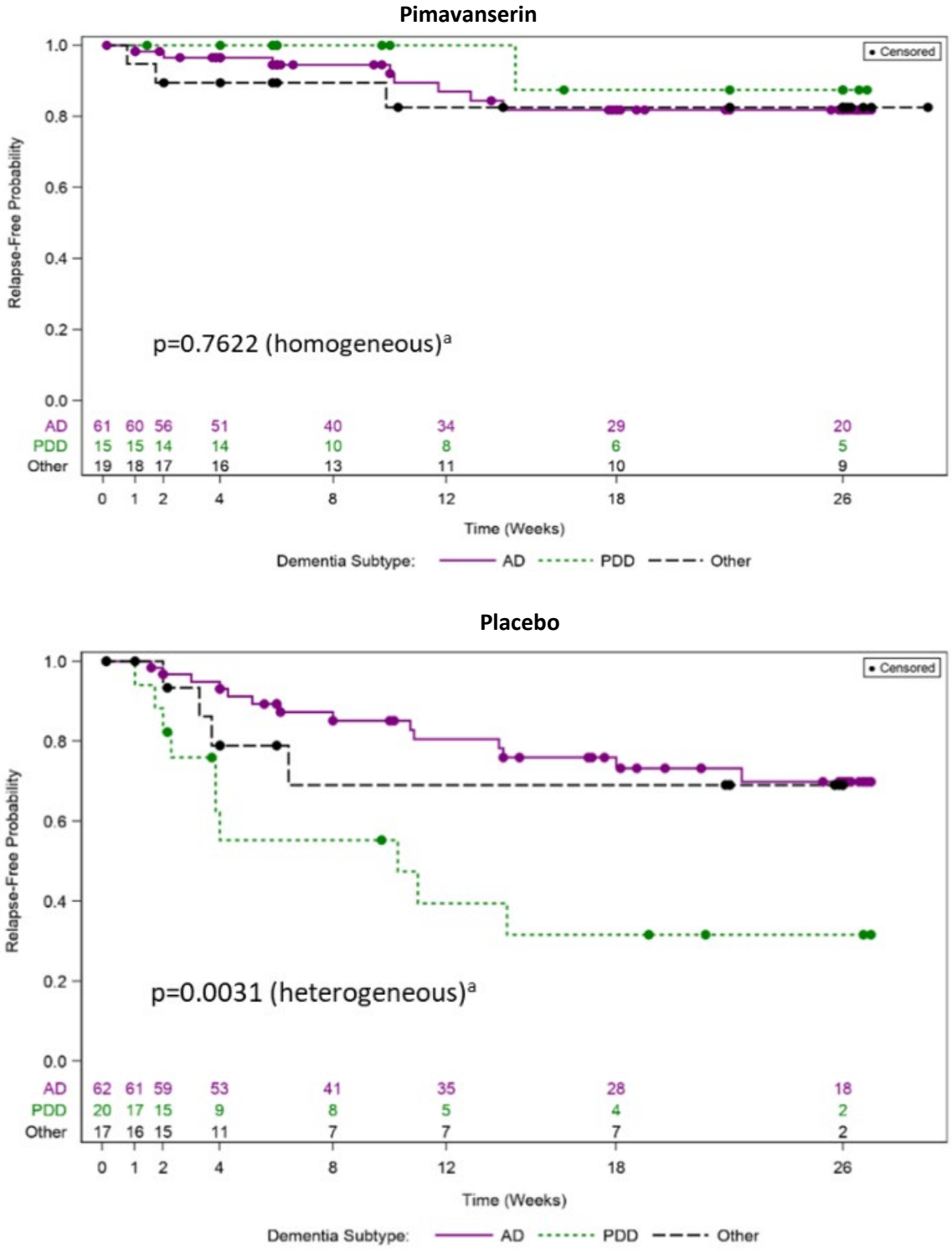
The Applicant asserted that there was no evidence of a qualitative (that is, cross-over) interaction in treatment effect on the risk of relapse across dementia subgroups (AD, PDD, Other; p=0.75 based on the Gail-Simon test) and that the treatment effects observed across different dementia subgroups were directionally consistent. The Gail-Simon test specifically tests for a qualitative or cross-over interaction, which occurs when one treatment is superior in some subsets of subjects, but the other treatment is superior in other subsets. This is not the case in Study 045; all dementia subgroups appear to trend numerically in one direction.

However, the lack of qualitative interaction does not mean that the treatment effects are consistent. There could be quantitative or non-crossover interaction (i.e., treatment effects differ in magnitude, but not direction, among subgroups). As shown in Table 7 the treatment effect estimates are very different between the AD subgroup and the PDD subgroup (HR 0.618, 95% CI (0.257, 1.487) in the AD group and HR 0.054, 95% CI (0.017, 0.175) in the PDD subgroup). Their 95% confidence intervals are distantly separated and the 95% confidence interval in the AD group is wide and contains no effect (i.e., HR=1). The Division's analysis that includes the interaction of treatment by dementia subgroup stratification factor in the primary analysis model appears to show strong evidence of a quantitative interaction, i.e., of a difference in the magnitude of treatment effects across the dementia subgroups (the interaction p = 0.0036). A similar analysis also shows a difference in the magnitude of treatment effects between the AD and PDD subgroups (the interaction p = 0.0020).

6.5.2 Potential Confounding of Dopaminergic Therapy in PDD Subgroup

Figure 7 displays the Kaplan-Meier curves for relapse events of psychosis by treatment group. The top panel of the figure suggests that pimavanserin slightly lowered the risk of relapse in subjects with PDD compared with those with other dementia subtypes, although the differences did not appear to be remarkable. The bottom panel suggests that in the placebo group subjects with PDD had a higher risk of relapse than those with other dementia subtypes. The Applicant asserts that "the withdrawal of an effective antipsychotic therapy of pimavanserin (i.e., randomization to placebo group during the DB period) may have contributed to the observed more rapid return of psychosis symptoms in subjects in the PDD subgroup compared with subjects in other dementia subgroups who were not taking dopaminergic therapies, resulting in higher relapse rate and faster time to relapse."

Figure 7. Relapse Pattern of Subjects by Dementia Subgroup – ITT Analysis Set



Source: Applicant's Addendum in re-submission, Figure 6-5

Abbreviations: AD = Alzheimer's dementia, ITT = intent-to-treat, PDD = Parkinson's disease dementia

Table 15 summarizes the number of subjects on dopaminergic therapies versus the number of subjects not on dopaminergic therapies. Most subjects did not take dopaminergic therapies. In the placebo group, those who took dopaminergic therapies seem to have rapid occurrence of relapse compared to those who did not, and most of those who took dopaminergic therapies were in the PDD subgroup.

Table 15. Proportion of Subjects with Relapse by Dementia Subtype and Dopaminergic Therapy – ITT Analysis Set

Dementia Subtype	Dopaminergic Therapy	# of Subjects Who Relapsed/ # of Subjects in the Subgroup	
		Placebo	Pimavanserin
Overall	Yes	11/21 (52.4%)	1/20 (5.0%)
	No	17/78 (21.8%)	11/75 (14.7)
PDD	Yes	9/19 (47.4%)	1/15 (6.7%)
	No	1/1 (100)	--
Non-PDD	Yes	2/2 (100%)	0/5 (5)
	No	16/77 (21.8)	11/75 (14.7)

Source: Statistical reviewer Dr. Ling.
Abbreviations: ITT = intent-to-treat, PDD = Parkinson's disease dementia

Although the preliminary findings may appear to explain the higher relapse rate in subjects receiving placebo in the PDD subgroup, it is unclear whether the effect of dopaminergic medication on the risk of relapse is the only explanation for possible difference in treatment effect between the AD and the PDD subgroups, given that dopaminergic medication use is almost completely confounded with the dementia subtype. Still, this does not affect the assessment of the treatment effect for the AD subgroup.

6.5.3 Re-analyses of Primary Endpoint in AD Subgroup

The pre-specified primary analysis for time to relapse was based on the Cox regression model with treatment, designated dementia subtype, and region as factors for the analysis of the overall population. Note that both the designated dementia subtype and region were stratification factors for randomization. The Applicant conducted a refined Cox regression analysis that included five factors selected post hoc: treatment, baseline severity of psychosis, baseline dementia severity, prior antipsychotic treatment and concomitant antidementia medications, but region was not included. The result showed a smaller HR of 0.475 and a smaller p-value of 0.10, compared to the prespecified primary Cox model. The Applicant provided several justifications (e.g., potential baseline imbalances) for using the refined model for the AD subgroup. However, there is no indication of significant baseline imbalances for the covariates selected (Table 16).

Table 16. Summary of Select Baseline Prognostic Factors–AD ITT Analysis Set

	Placebo (N=62)	Pimavanserin (N=61)
Dementia Severity, n (%)		
Mild	9 (14.5)	10 (16.4)
Non-mild	53 (85.5)	51 (83.6)
Antipsychotic Use within 14 Days of Screening, n (%)		
Yes	22 (35.5)	20 (32.8)
No	40 (64.5)	41 (67.2)
Antidementia Medication Use at Baseline, n (%)		
Yes	46 (74.2)	50 (82.0)
No	16 (25.8)	11 (18.0)
DB Baseline SAPS-H+D		
Mean (SD)	5.7 (5.67)	4.8 (4.48)
Median (Q1, Q3)	4.0 (0, 8)	4.0 (0, 9)

Source: Statistical reviewer Dr. Ling.
Abbreviations: AD = Alzheimer's disease, DB = double-blind, ITT = intent-to-treat, SAPS-H+D = Scale for the Assessment of Positive Symptoms – Hallucinations and Delusions score

The Applicant used OL baseline SAPS-H+D score as a covariate for the baseline severity of psychosis. However, there is no reason to use the OL baseline score instead of the DB baseline score when testing the treatment effect on relapse in the DB period. Additionally, there is no reason to exclude region which was a stratification factor and a prespecified covariate for the primary analysis. The Agency's statistical reviewer performed the refined Cox model analysis by using the DB baseline SAPS-H+D instead and adding back the region. The results are consistent with the results of the pre-specified primary model (Table 17). The Applicant stated that their refined model was supported by better model fitting statistics based on the Akaike information criterion (AIC).[2] However, the AIC values for the five models in the table were similar and the bottom one appears to fit best (smallest AIC value).

Regardless of which model is selected, the HR results are not statistically significant. In summary, the refined model proposed by the Applicant is not justified. Moreover, the choice of covariates for adjustment should be pre-specified and results of post-hoc, potentially data-driven analyses are very challenging to interpret. The study conclusion should be based on the primary Cox model.

[2] The Akaike information criterion (AIC) is an estimator of prediction error. AIC estimates the relative amount of information lost by a given model. A smaller value of AIC indicates better model fitting. In estimating the amount of information lost by a model, AIC deals with both the risk of overfitting and the risk of underfitting.

Table 17. Time from Randomization to Relapse in the Double-Blind Period—AD ITT Analysis Set

	HR	95% CI	p-value	AIC
Pre-specified Primary Cox Model (2 covariates: treatment and region)	0.618	(0.257, 1.487)	0.28	191.785
Refined Cox Model by Applicant (5 covariates including OL BL SAPS-H+D)	0.475	(0.194, 1.162)	0.10	191.368
Refined Cox Model by FDA Reviewer (5 covariates including DB BL SAPS-H+D)	0.566	(0.239, 1.341)	0.20	192.638
Refined Cox Model by FDA Reviewer (6 covariates including DB BL SAPS-H+D and Region)	0.638	(0.268, 1.516)	0.31	189.758

Source: Statistical reviewer Dr. Ling.

Abbreviations: AD = Alzheimer's disease, AIC = Akaike information criterion, CI = confidence interval, DB = double-blind, HR = hazard ratio, ITT = intent-to-treat, OL = open-label, SAPS-H+D = Scale for the Assessment of Positive Symptoms – Hallucinations and Delusions score

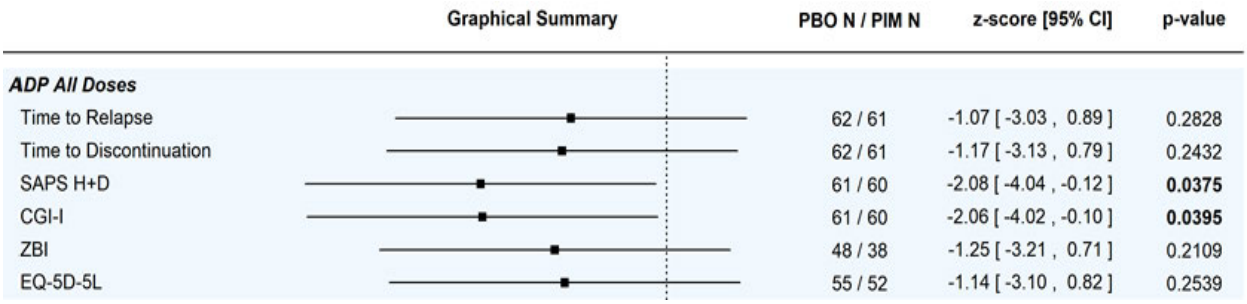
6.5.4 Analyses of Exploratory Endpoints in AD Subgroup

The most relevant exploratory endpoint for this study was the change from DB Baseline in SAPS-H+D score in the AD subgroup. For this endpoint, observed and change from DB baseline values at each DB analysis visit were summarized using descriptive statistics for each visit. Treatment comparisons were made using MMRM and ANCOVA as specified in SAP.

In the randomized withdrawal design, assessments of these scores could not be made for subjects who were withdrawn from the DB treatment following a relapse. The assumption of missing at random for the SAP specified analyses of MMRM and ANCOVA was violated. In addition, these exploratory analyses did not account for multiplicity adjustment. Thus, the SAP specified analyses for the exploratory endpoints are not discussed further.

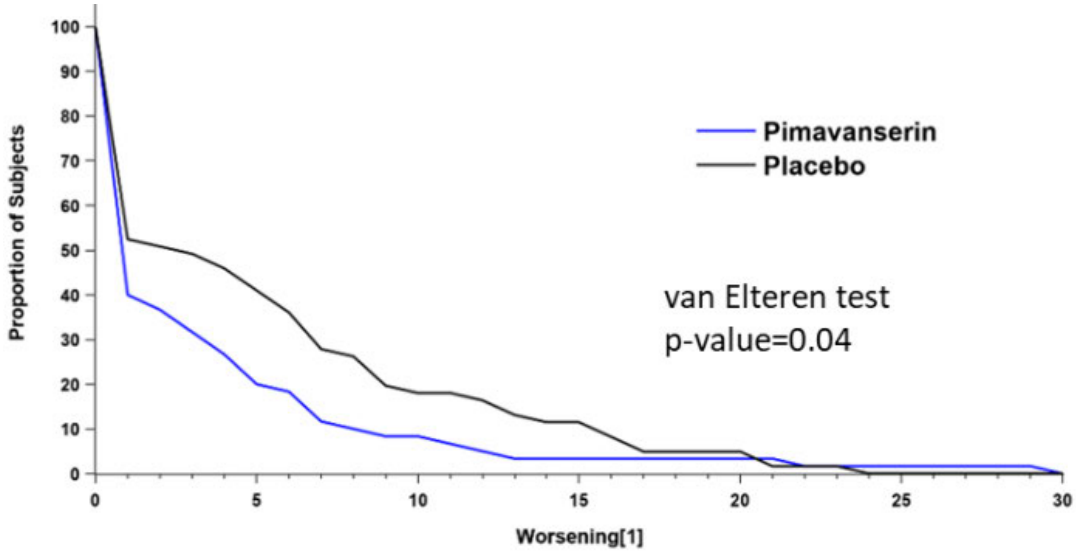
The Applicant used a forest plot to present the results in the AD subgroup across efficacy measures (Figure 8); post-hoc analyses for the exploratory endpoints were based on the Van Elteren test. The Van Elteren test conducted by the Applicant (post hoc) was a non-parametric test on ranked scores while adjusting for the stratification factor of region. Depending on the rank ordering, these post hoc analyses for SAPS-H+D could yield a nominal p-value of 0.0375 (Figure 8) or a nominal p-value of 0.04 (Figure 9). The Applicant's post hoc analyses of SAPS-H+D assigned the same highest rank (i.e., best ranking) or highest two ranks for over half of the subjects whose SAPS-H+D scores never worsened during the DB period. However, for these subjects, there were still differences in terms of how much the SAPS-H+D score changed. The statistical reviewer conducted an exploratory analysis using Van Elteren test by ranking subjects' maximum change of SAPS-H+D scores during the DB period regardless of whether they worsened or not and assigning worse ranks to subjects who ever relapsed based on their time to relapse and better ranks to those who never relapsed based on their maximum change of SAPS-H+D score. This analysis yielded a nominal p-value of 0.1355 (Table 18).

Figure 8. Applicant's Analysis of Efficacy Endpoints–AD ITT Analysis Set



Source: Applicant Addendum in re-submission, Figure 7-8.
Abbreviations: AD = Alzheimer's disease, ADP = Alzheimer's disease psychosis, CGI-I = Clinical Global Impression-Improvement, EQ-5D-5L = 5-Level European Quality of Life 5-Dimensions Questionnaire, ITT = intent-to-treat, SAPS-H+D = Scale for the Assessment of Positive Symptoms – Hallucinations and Delusions score, ZBI = Zarit Burden Interview

Figure 9. Applicant's Post hoc Analysis of SAPS-H+D with Cumulative Relapse Curves–ADP ITT Analysis Set



Source: Applicant's Addendum in re-submission, Figure 7-4.
Abbreviations: ADP = Alzheimer's disease psychosis, ITT = intent-to-treat, SAPS-H+D = Scale for the Assessment of Positive Symptoms – Hallucinations and Delusions score

Table 18. Reviewer's Analysis of SAPS-H+D - ADP ITT Analysis Set

	Placebo	Pimavanserin
Maximum change of SAPS-H+D		
n	61	60
Mean	3.9	1.8
SD	6.88	5.97
Median	2.0	0.0
Minimum, maximum	-7, 23	-10, 29
p-value by Van Elteren test		0.1355

Source: Statistical reviewer Dr. Ling, using Van Elteren test stratified by region.
Abbreviations: ADP = Alzheimer's disease psychosis, ITT = intent-to-treat, SAPS-H+D = Scale for the Assessment of Positive Symptoms – Hallucinations and Delusions score

6.5.5 Pimavanserin Dose Levels

In the resubmission, the Applicant proposed to focus on the 34-mg daily dose level. During the OL period of Study 045, eligible subjects began receiving pimavanserin 34 mg daily and dose adjustments to 20 mg daily were permitted until OL Week 4, after which the subject's dose remained fixed at either 34 or 20 mg daily. Subjects who met the response criteria at OL Weeks 8 and 12 and who remained otherwise eligible were randomly assigned 1:1 to continue their current pimavanserin dose (34 or 20 mg) or to receive matching placebo in the DB period. A total of 12 out of 194 subjects (6%) who were included in the IA ITT analysis set were on pimavanserin 20 mg. The results were numerically in favor of placebo against pimavanserin 20 mg in the AD subgroup (Table 19). The randomization was not stratified by pimavanserin dose level.

Table 19. Relapse Rate in the Double-Blind Period by Dose Level and Disease Subgroup - ITT Analysis Set

	34 mg		20 mg	
	Placebo (N=93) n/N (%)	**Pimavanserin (N=89) n/N (%)**	**Placebo (N=6) n/N (%)**	**Pimavanserin (N=6) n/N (%)**
AD	14/59 (23.7)	6/57 (10.5)	0/3 (0.0)	2/4 (0.5)
PDD	9/17 (52.9)	1/13 (7.7)	1/3 (0.3)	0/2 (0.0)
Other	4/17 (23.5)	3/19 (15.8)	-	-

Source: Statistical reviewer Dr. Ling.
Abbreviations: AD = Alzheimer's disease, PDD = Parkinson's disease dementia, ITT = intent-to-treat

6.5.6 Relationships Between Pimavanserin Plasma Concentrations and Efficacy

The Applicant evaluated the relationship between pimavanserin plasma concentrations and efficacy in Study 045 (exposure-response (E-R) analysis). Pimavanserin plasma concentrations are represented as area under the plasma concentration-time profile during the dosing interval (AUC_{0-24}). The efficacy is defined as time from randomization to relapse during DB, which is the primary efficacy endpoint. Data from a total of 185 subjects were included in the E-R analysis. Nine subjects were excluded from the analysis due to missing pharmacokinetic (PK) exposures. Table 20 summarizes the number of subjects by dementia subgroup and dose. Twelve subjects (six in pimavanserin and six in placebo) stabilized on 20 mg were included in the analysis. Pimavanserin AUC_{0-24h} was calculated using information on daily dose from the start of DB period to the last dose in OL period.

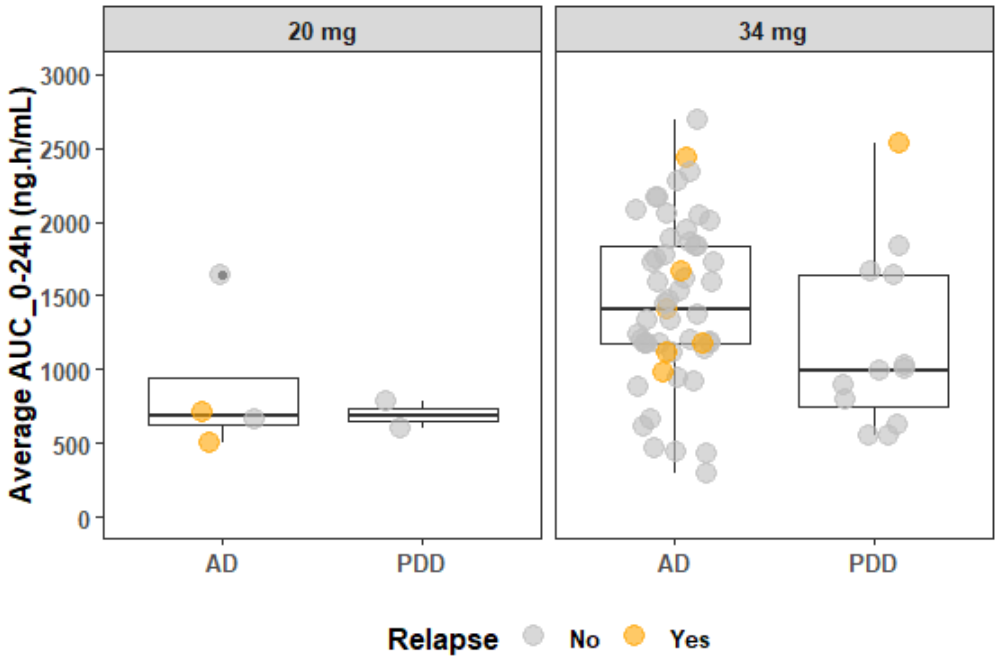
Table 20. Number of Subjects by Dementia Subgroups and Dose in ER analysis dataset

	Pimavanserin 34 mg [N=84]	**Pimavanserin 20 mg [N=6]**	**Placebo [N=95]**
Alzheimer's disease	53	4	58
Dementia with Lewy bodies	6	0	3
Frontotemporal dementia	1	0	2
Parkinson's disease	12	2	20
Vascular dementia	12	0	12

Source: Clinical pharmacology reviewer's analysis

Pimavanserin PK exposure comparison: Pimavanserin AUC_{0-24} was compared between AD and PDD subgroups by dose and relapse events to evaluate if PK exposure differences can explain the differential drug effect between these two subgroups. As shown in Figure 10 and Table 21, a wide range of AUC_{0-24} was observed after exposure to the 20 mg and 34 mg doses in the AD and PDD subgroups. Relapse events were well distributed over the wide AUC range. The findings suggest that differences in efficacy in AD and PDD subgroups is not likely associated with PK exposures.

Figure 10. Comparison of Average PK Exposure (AUC_{0-24h}) by Dose between AD and PDD Subgroups



Source: Clinical pharmacology reviewer
Abbreviations: AD = Alzheimer's disease, AUC_{0-24h} = area under the concentration-time curve from time 0 to 24 hours, PDD = Parkinson's disease dementia, PK = pharmacokinetic

Table 21. Comparison of AUC_{0-24} by Dose and Relapse Events between AD and PDD Subgroups

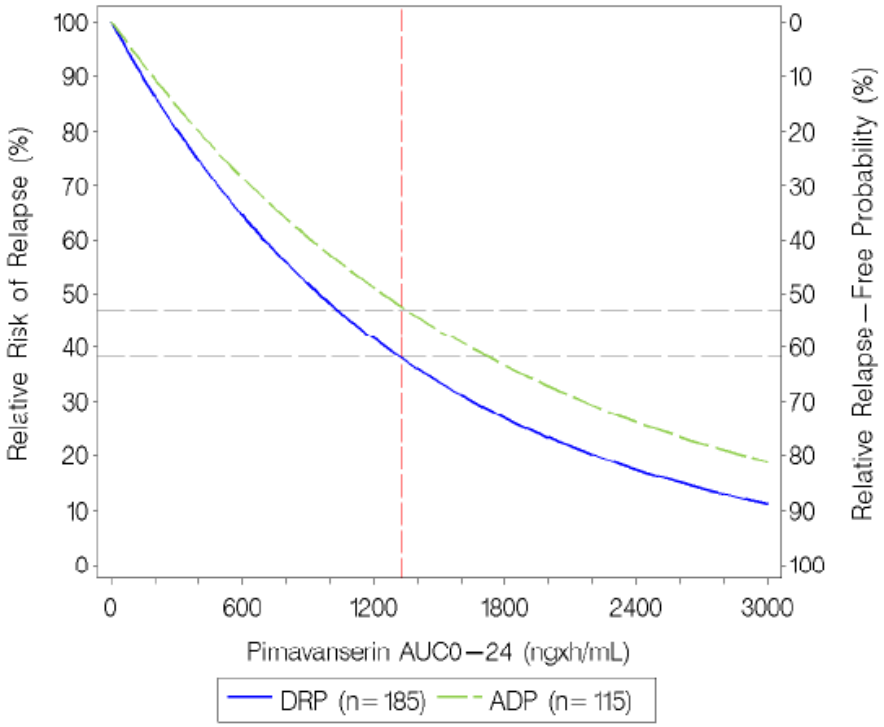
Population	Relapse	Dose 20 mg		Dose 34 mg	
		N	Median (Min, Max)	N	Median (Min, Max)
AD	Yes	2	608 (507, 710)	6	1290 (984, 2440)
	No	2	1150 (659,1640)	47	1440 (291, 2690)
PDD	Yes	0	--	1	2530
	No	2	690 (598, 781)	11	995 (546, 1840)

Source: Clinical pharmacology reviewer's analysis
Abbreviations: AD = Alzheimer's disease, PDD = Parkinson's disease dementia, Min = minimum, Max = maximum

Exposure-Response relationship comparison: Applicant compared E-R relationships between AD (N=115) and DRP (N=185) subgroups. Cox proportional hazard E-R model showed that the risk of relapse decreases with higher AUC_{0-24} (Hazard ratio: 0.48) in overall DRP population (Table 22). The analysis did not identify additional influence of baseline factors (age, sex, weight, race, dementia subgroup, baseline SAPS-H+D total score, baseline MMSE total score, region, antidementia medication, anticholinesterase use, and dementia severity) on the relationship between AUC_{0-24} and the risk of relapse. The Applicant

concluded that the E-R relationship observed in the AD subgroup was consistent in terms of direction and magnitude of risk reduction with that observed in subjects with DRP overall (Table 22).

Figure 11. Model-Predicted Relative Risk of Relapse versus Pimavanserin AUC, in All DRP Subjects and in AD Subgroup–Study 045



Source: Applicant's report ACP-103-MS-018
Abbreviations: ADP = Alzheimer's disease psychosis, $AUC_{0\text{-}24h}$ = area under the concentration-time curve from time 0 to 24 hours, DRP = dementia-related psychosis

Table 22. Summary of Exposure Response Analysis for Time to Relapse, by Population—Study 045

Population	Variable	Number of Patients	Parameter Estimate	*P*-value	Hazard Ratio (95% CI) for 1 Unit (1 µg×h/mL) $AUC_{0\text{-}24}$	Hazard Ratio (95% CI) at Median $AUC_{0\text{-}24}$ of 1.33 µg × h/mL	Reduction in Risk at Median Exposure[b]
All DRP patients	Continuous $AUC_{0\text{-}24}$	185	-0.7303	0.00293	0.4818[c] (0.2815, 0.8245)	0.3786 (0.2212, 0.6479)	62%[d]
AD subgroup	Continuous $AUC_{0\text{-}24}$	115	-0.5615	0.06566	0.5704[e] (0.2971, 1.0950)	0.4739 (0.2468, 0.9098)	53%[f]

Source: Applicant's report ACP-103-MS-018.
Abbreviations: AD = Alzheimer's disease, AUC0-24 = area under the concentration-time curve from time 0 to 24 hours, CI = confidence interval, DRP = dementia-related psychosis

Nominally statistically significant drug effect was only shown for PDD subgroups and not for other dementia subgroups. The PDD subgroup in DRP population is 18% (i.e., 34/185), and thus it has a lesser contribution for the E-R relationship in the DRP population. The estimated slope coefficient and hazard ratio for PDD and AD subgroups are given in Table 23**.** A greater reduction in relapse with higher AUC_{0-24} is reported in PDD subgroup relative to AD subgroup (Hazard ratio: 0.57 in AD versus 0.27 in PDD). These results are consistent with the primary statistical analysis (i.e., statistically significant effect on DRP population, nominally significant effect for PDD subgroup and not nominally significant effect on AD subgroups). The E-R relationship by dementia subgroup based on the model estimates overlaid with observed data was shown in Figure 12**.** It shows that higher PK exposures were associated with a higher relapse-free probability for both AD and PDD, but the drug effect for AD group is lower than PDD subgroup.

The Applicant states that efficacy results in the AD subgroup improved with the removal of the approximately 6% of subjects on 20 mg, consistent with the E-R analysis findings. The E-R analysis showed that the removal of seven subjects (four subjects in pimavanserin and three subjects in placebo) on 20 mg in the AD subgroup improved the hazard ratio by 3% (Table 23). Of note, the relapse events were observed in 2/4 (50%) subjects of the pimavanserin 20 mg group and 0/3 (0%) subject of the placebo group. Therefore, removing these seven subjects improves E-R slope coefficient as two relapse events at PK exposures higher than placebo have been removed from the analysis.

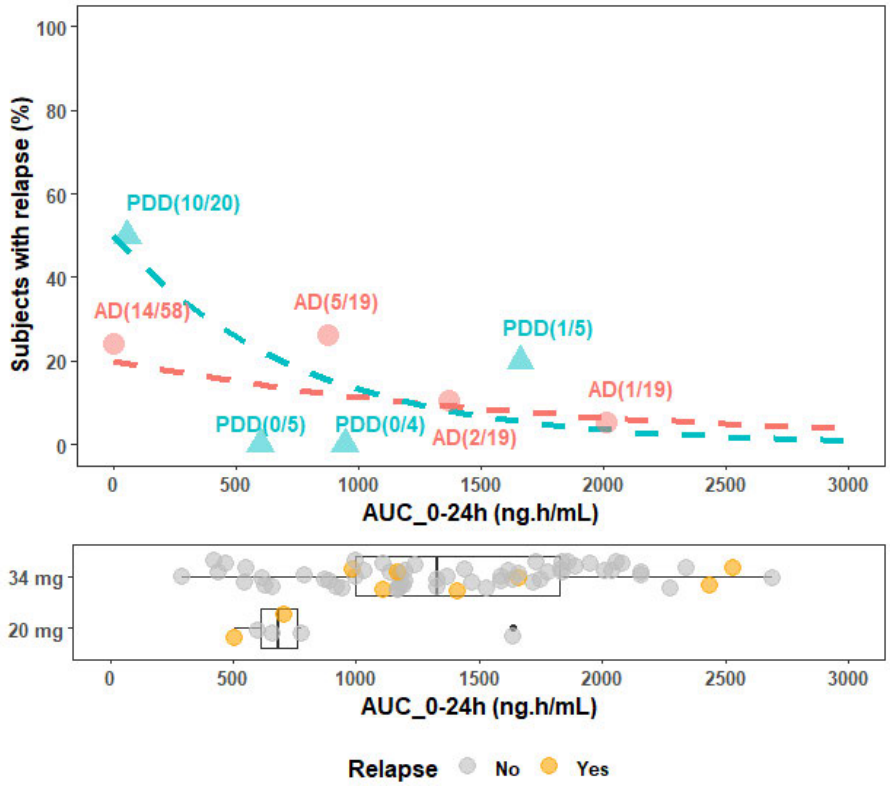
Table 23. Summary of Exposure-Response Models for Time to relapse, by Population - Study 045

Population	Variable	Number of Subjects	coefficients	P-value	Hazard Ratio for 1- unit (1 ug.h/mL) AUC_{0-24}	Hazard Ratio at median AUC_{0-24} of 1.33 ug.h/mL	Reduction in risk at median exposures
DRP	Continuous AUC_{0-24}	185	-0.7303	0.00293	0.48	0.38	62%
PDD	Continuous AUC_{0-24}	34	-1.327	0.032	0.27	0.17	83%
AD	Continuous AUC_{0-24}	115	-0.5615	0.06566	0.57	0.47	53%
AD 34 mg only	Continuous AUC_{0-24}	108	-0.6228	0.05151	0.54	0.44	56%

Source: Clinical pharmacology reviewer's analysis

Abbreviations: AD = Alzheimer's disease, AUC_{0-24h} = area under the concentration-time curve from time 0 to 24 hours, CI = confidence interval, DRP = dementia-related psychosis, PDD = Parkinson's disease dementia

Figure 12. Model-Predicted Placebo-Normalized Risk of Relapse versus Pimavanserin AUC Overlaid with Observed Data in PDD and AD Subgroups



Source: Clinical pharmacology reviewer's analysis
Abbreviations: AD = Alzheimer's disease, $AUC_{0\text{-}24h}$ = area under the concentration-time curve from time 0 to 24 hours, DRP = dementia-related psychosis, PDD = Parkinson's disease dementia
Note: Solid red circle and blue triangle represents PDD and AD subgroup. For each subgroup, four observed data points represents placebo and tertiles of pimavanserin treatment. Dashed colored line represents model-predicted placebo-normalized risk of relapse based on the cox-proportional hazard exposure-response model.

Conclusions based on the relationship between efficacy and pimavanserin exposure:

1. Differences in efficacy in AD and PDD subgroups are not due to PK exposures differences.

2. Higher PK exposures were associated with a higher relapse-free probability for both AD and PDD, but the drug effect for AD group is lower than PDD subgroup.

6.5.7 Applicant's Simulations to Explore Influence of PDD Subgroup

The Applicant conducted simulations to address the influence of the PDD subgroup on the primary efficacy findings. In the simulations, the effect size in the PDD subgroup was attenuated while the other subgroups were left untouched. The Applicant concluded that with events added to the pimavanserin arm of the PDD subgroup to the point where the effect is weaker in the PDD subgroup than in the overall study (i.e., if nine events were added to the pimavanserin arm in the PDD subgroup), the overall

study still had a large probability of success at the final analysis (conditional power for the overall population >75%, details not shown).

Conditional power (CP) is usually used for trial planning/modification purposes, such as sample size re-estimation or futility assessment for one or more treatment arms or the entire study. With a sufficiently large CP, the trial usually continues to the final analysis without the need to increase sample size. Even if the CP may predict a large probability of success at the final analysis, the study conclusion will need to be based on the final analysis using the actual data. If the trial is stopped earlier at the IA, then the study conclusion can only be based on the IA.

For this study, the CP calculated at the IA for the largest subgroup of AD is 19%, suggesting that even if the trial was not stopped early, the probability of showing a statistically significant result for the AD subgroup at the final analysis is low. The sample size for the AD group would need to be increased (and the final analysis needs to adjust for the midway adaptation of the study) in order to potentially obtain robust findings on the treatment effect for the AD group at the final analysis. Because the trial was terminated early at the IA, the conclusion for the AD population can only be based on the IA results; that is, the study failed to demonstrate a treatment effect in the AD population.